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Review

Immune Checkpoints and the Immunology of Liver Fibrosis

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Abstract: Liver fibrosis is a very complicated dynamic process where several immune cells are involved. Both innate and adaptive immunity are implicated, and their interplay is always present. Multi-directional interactions between liver macrophages, hepatic stellate cells (HSCs), immune cells, and several cytokines are important for the induction and perpetuation of liver fibrosis. Detailed studies of proteomics and transcriptomics have produced new evidence for the role of individual cells in the process of liver fibrosis and cirrhosis. Most of these cells are controlled by the various immune checkpoints whose main function is to maintain the homeostasis of the implicated immune cells. Recent evidence indicates that several immune checkpoints are involved in liver fibrosis. In particular, the role of the programmed cell death protein 1 (PD-1), the programmed death-ligand 1 (PD-L1), and the role of the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) have been investigated, particularly after the availability of checkpoint inhibitors. Their activation leads to the exhaustion of CD4+ve and CD8+ve T cells and the promotion of liver fibrosis. In this review, the current pathogenesis of liver fibrosis and the immunological abnormalities are discussed. The recent data on the involvement of immune checkpoints are identified as possible targets of future interventions.

Keywords: liver fibrosis; macrophages; hepatic stellate cells; innate immunity cells; adaptive immunity cells; immune checkpoints

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1. Introduction

The development of liver fibrosis (LF) is characterized by the deposition of extracellular matrix (ECM) proteins produced by myofibroblasts (MFs) of various origins including epithelial cells, mesenchymal stromal cells (MSCs), and HSCs [1]. Hepatocyte damage, irrespective of etiology, leads to the recruitment of immune cells in the liver. Quiescent HSCs (qHSCs) are activated and transformed into MFs, which are the main producers of connective tissue elements. If the insult is short term, the pro-fibrotic and anti-fibrotic mechanisms of the liver are in balance, and LF is not likely to occur. The continuous activation of the heterogenous population of hepatic MFs, mostly driven by liver macrophages, is the hallmark of chronic liver disease (CLD), but several other cells of the innate and adaptive immunity are also implicated [2,3]. The advancement of liver fibrosis leads to the final stage of cirrhosis. The pathological characteristics of cirrhosis are extensive fibrosis, the development of regenerative nodules, and the distortion of the hepatic architecture leading to overt clinical manifestations [4].

Global epidemiological data [5,6] reveal that almost 1.5 billion people suffer from CLD, leading to approximately 20,000 annual deaths, half of which are direct complica-

tions of liver cirrhosis. The overall mortality from cirrhosis has increased by 47.15% in recent years [7]. The WHO's Global Burden of Diseases reports indicate that 560.4 age-standardized disability-adjusted life-years (DALYs) per 100,000 population worldwide were due to cirrhosis. In comparison, only 151.1 DALYs were due to liver cancer [8]. The most frequent causes of CLD are viral hepatitis, alcoholic liver disease, and metabolic-associated fatty liver disease (MAFLD/MASH) with heterogeneity across geographical regions [9]. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the underlying etiology of more than 60% of cirrhotic cases worldwide [10]. Less frequent etiologies that lead to fibrosis and cirrhosis include, among others, genetic diseases of iron or copper overload, cholestatic syndromes, and autoimmune diseases [4]. An important step in the clarification of the immune modulation and the therapeutic potential of the inhibition of certain immune checkpoints practically started when James Allison described the cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and Tasuku Honjo described the programmed cell death protein 1 (PD-1). They were awarded the Nobel Prize for Physiology or Medicine in 2018 [11,12]. Immune checkpoint molecules are ligand–receptor pairs that exert inhibitory or stimulatory effects on immune responses. Most of the immune checkpoint molecules that have been described so far are expressed on cells of the innate and adaptive immune system, particularly on natural killer (NK) cells and T cells, respectively. They maintain the self-tolerance and modulate the immune responses of effectors in different tissues to minimize the tissue damage. Immune checkpoint proteins (ICPs) trigger the exhaustion, senescence, or apoptosis of effector immune cells [13].

It is, therefore, imperative to delineate the mechanisms implicated in the process of fibrosis. The present review will focus on the current data on the pathogenesis of liver fibrosis with emphasis on the immunological aspects and the emerging roles of the immune checkpoints.

2. A Pathogenetic Overview of Liver Fibrosis

2.1. The Fibrotic Process

For descriptive reasons, four pathological stages of fibrosis can be identified. Initially, exogenous or endogenous elements cause damage to the local liver cells and induce inflammation, followed by the large recruitment of immune cells at the site of the initial damage, thus aggravating the inflammatory response. Damaged hepatocytes or activated sinusoidal cells, by whatever cause, produce cytokines such as tumor necrosis factor-alpha (TNF-α) and IL-1, which are responsible for the recruitment of extrahepatic immune cells. In addition, they secrete pro-fibrotic factors, generating the background for the third stage. Quiescent hepatic stellate cells (HSCs) are transformed into myofibroblast-like HSCs [14,15] that lead to the fourth stage, the deposition of large amounts of ECM, and the remodeling of the liver architecture [16–18].

The ECM is composed of collagens, including type I (the most abundant protein) and type III collagens, fibronectin, elastin, and smaller amounts of several other proteins. The important components of the ECM are the basement membrane proteins such as laminin. It should be noted that myofibroblasts first secrete procollagen into the tissue, while mature collagen fibers evolve at a later extra-cellular stage through modification and cross-linking [19].

An important mechanism of fibrosis is the Epithelial-to-Mesenchymal Transition (EMT). It implies the differentiation of epithelial non-mesenchymal cells that acquire a fibroblast phenotype. Their participation in liver fibrosis has been extensively studied [20–23]. Epithelial cells undergo EMT under the influence of certain stimuli. An important one is the snail family transcriptional repressor 1 (Snail1). Hepatocytes with the deletion of the snail1 gene showed a significant decrease in EMT. Snail1 affected genes

known to contribute to the progression of liver fibrosis, increasing the expression of pro-fibrotic genes such as those involved in collagen and vimentin production in the liver [24]. Moreover, the expression of Snail1 increased during the TGF-β1-induced EMT in murine hepatocytes, while the expression of the miR-30 family members was significantly down-regulated. miR-30 inhibited the EMT transformation in hepatocyte by targeting Snail1 [25]. Studies of cholestatic liver diseases have demonstrated the participation of EMT transformation in experimental and in human cholangiopathies such as biliary atresia. Cholangiocytes acquire mesenchymal markers and lose their epithelial characteristics [26–28]. The involvement of liver macrophages in EMT hepatocyte trans-differentiation has not been conclusively proved. Data from extrahepatic cancers indicate that the involvement of liver macrophages cannot be ruled out [29,30].

Recent evidence has indicated a significant role of non-coding RNAs in liver fibrosis. Myofibroblast activation is positively or negatively modulated by a number of non-coding RNAs [31]. They act on either EMT or through the ECM. ECM deposition can suppress miR-29, an important negative regulator of pro-fibrotic genes. Consequently, many such genes are recruited in the ribosomes and sustain the deposition of ECMs even in the absence of the initial stimulus. On the other hand, increased ECM stiffness activates the Hippo pathway effector Yes-associated protein 1 (YAP1), which also increases ECM deposition, thus initiating another positive feedback loop mediated by miR-21 [32]. miRNAs are implicated in liver fibrosis and stellate cell activation by targeting SMAD proteins [33]. MiR-199a promotes EMT transformation and fibrosis by increasing the expression of genes encoding procollagens and the tissue inhibitor of metalloproteinase-1 (TIMP1) [34]. MiR-32 is also pro-fibrotic in hyperglycemia in experimental conditions. Its inhibition attenuated EMT-induced liver fibrosis [35]. Several other miRNAs increase fibrosis in liver damage, affecting fibrotic pathways such as transforming growth factor-β/Smad, Wnt/β-catenin, and snail [36,37].

HSCs activation is also influenced by several anti-fibrotic miRNAs such as miR-16 and miR-19b among others that retain the quiescence of HSCs or induce either apoptosis or the de-differentiation of activated HSCs [37]. In more detail, miR-30a attenuates the EMT process by reducing TGF-β1. There is an inverse relation between mir30 and snail1, indicating that snail1 is a possible target of mir30, as mentioned before [38]. In addition, miR-30a can repress fibrosis by suppressing beclin-mediated autophagy [39].

Long non-coding RNAs (lncRNAs) are also implicated in liver fibrosis. An upregulation of lncRNA H19 in murine fibrosis activated the EMT pathway [40]. GAS5 acts as a sponge platform for miR-23a, a fact that ameliorates the progression of fibrosis [41]. The overexpression of Meg8 lncRNA was noticed during the activation of HSCs. Meg8 repressed the pro-fibrotic genes in activated HSCs and EMT, while its knockdown induced the expression of mesenchymal markers in hepatocytes [42].

In murine MASH models, the circRNA_29981 was identified as a possible regulator of HSC transformation [43]. Moreover, the mitochondrial circRNA SCAR can close the mitochondrial permeability transition pores, repressing the activation of MFs by inhibiting the mitochondrial ROS output [44].

A third important mechanism implicated in the regulation of liver fibrosis is the involvement of transcription factors such as the nuclear receptors (NRs) [45]. They mediate anti-inflammatory effects through direct interaction with other transcription factors, such as NF-κB [46,47]. They also have a fundamental role in liver regeneration and HSC activation [48,49]. The farnesoid X receptor (FXR) is better studied, and the use of FXR agonists repressed liver fibrosis in animal models by reducing HSC activation [50–52]. The details of nuclear receptors on liver fibrosis are found in recent extensive reviews [53,54].

A fourth and very important factor modulating liver fibrosis, and other forms of organ fibrosis, is the epigenetic modification of genes. They may lead to either the activation or repression of downstream proteins. Non-coding RNAs may act as epigenetic regulators. Other epigenetic modifications include DNA methylation, histone modification, and chromatin remodeling [55,56]. The DNA methylation pattern is critical in liver fibrosis [57] as it is in the activation of HSCs. The downregulation of the gene coding for the DNA methyl transferases DNMT3a and DNMT3b decreased DNA methylation followed by the suppression of HSC activation [58]. The activation of the hedgehog (Hh) pathway triggers liver EMT. The hypermethylation of the negative regulator of Hh, patched 1 (PTCH1), leads to its downregulation and an increase in liver fibrosis. Recent studies have established the anti-fibrotic efficacy of Salvianolic acid B (Sal B) that inhibits the Hh-mediated EMT [59]. In Sal B-treated cells, PTCH1 was increased due to the inhibition of DNA methyltransferase 1 (DNMT1), followed by a decrease in DNA methylation. The observed upregulation of miR-152 led to the hypomethylation of PTCH1, as DNMT1 was the direct target of miR-152 [60].

2.2. Cells Involved in Liver Fibrosis

2.2.1. Kupffer Cells and Liver Macrophages

Traditionally, Kupffer cells (KCs) included all macrophages in the liver, expressing surface markers such as F4/80 in mice or CD68 in humans. However, hepatic macrophages are a heterogeneous population, particularly after liver injury, and can be broadly divided into embryonic tissue resident KCs and monocyte-derived macrophages [61].

KCs are, therefore, liver resident macrophages initially generated in the embryo but also during adulthood [62,63]. Embryo-derived KCs (Em-KCs) persist in the liver throughout life by self-renewal [64]. In normal adulthood, bone marrow (BM)-derived monocytes can enrich the KC pool when Em-KCs are exhausted [65]. Monocyte-derived macrophages are recruited and accumulated in the liver after a damaging insult [66]. Em-KCs are CD49a+, a fact that distinguishes them from BM monocytes [67]. Em-KCs have a dual role in liver inflammation as they express both pro-inflammatory cytokines such as TNFa and anti-inflammatory cytokines such as IL-10. Em-KCs seem to be operational during normal homeostasis and promote tolerance, participating only in early liver injury, while BM-KCs act in chronic inflammation and fibrosis [68]. In the murine liver, only a few macrophages originate from BM monocytes under normal conditions [69]. Murine monocytes are divided into two phenotypes based on the presence of the lymphocyte antigen 6 complex, locus C (Ly6C). Ly6Chigh monocytes are recruited to the liver in liver injury and differentiated into BM-derived macrophages that are responsible for chronic inflammation and fibrosis. On the other hand, Ly-6Clow BM-derived macrophages promote damage resolution [70]. During early liver injury, damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), produced by the injured hepatocytes, interact with the Toll-like receptors (TLRs) on KCs. The activated KCs in turn recruit Ly-6Chigh macrophages through the release of chemokines such as CCL2 and CXCL1. Ly-6Chi macrophages sustain the activation and survival of HSCs [71], producing pro-fibrogenic mediators such as TGFβ, PDGF, and CCL2 [72]. Galectin-3 is also a lectin secreted by macrophages, which promotes HSC activation [73]. Liver macrophages also express receptors that bind the alarmin high-mobility group box 1 (HMGB1), released from injured hepatocytes. HMGB1 also activates HSC and stimulates the phenotypic responses of liver MFs [74].

The initial classification of KCs included classically activated pro-inflammatory M1 cells and alternatively activated anti-inflammatory M2 cells. LPS and IFNγ polarize KCs into M1 cells expressing inflammatory molecules such as IL-1, IL-12, TNFa, inducible nitric

oxide synthase (iNOS), and a group of CXCL chemokines. On the other hand, Th2 helper T cells and IL-4 polarize KCs into M2-type expressing Arginase 1, IL-10, and PDL-1 and CCR2, CXCR1, and CXCR2 chemokines [75]. The M1/M2 balance is also dependent on production by the M2 cells of IL-10 that promotes M1 apoptosis [76,77]. M2 macrophages are additionally classified into distinct subtypes expressing different genes [78]. The M2 phenotype predominantly mediates tissue repair, but when the liver injury persists, M2 macrophages acquire a pro-fibrotic capacity [79].

In the diseased liver, macrophages frequently express both inflammation and regenerative markers with phenotypes that may change according to the local conditions and, therefore, the traditional model may not be relevant in liver damage [80,81]. A complex classification goes beyond the traditional distinction between M1 and M2 polarization [82,83]. It has been proposed that instead of the classical classification, a more detailed description should be made based on the activation stage, such as M (IL-10) or M (TGF-β) [84]. This classification is compatible with the changing roles of macrophages in liver disease that may be completely different or even opposite [19]. The fact that most macrophages do not comply with the M1/M2 model was recently verified. Two cytokines, the macrophage colony stimulating factor (M-CSF) and the granulocyte macrophage stimulating factor (GM-CSF) involved in the differentiation of KCs, indicate that the situation is more complex. In general, GM-CSF leads to M1 polarization and M-CSF to M2 polarization, but their combination with other cytokines may lead to a spectrum of macrophages expressing both M1 and M2 markers [85,86]. The murine models of liver fibrosis have shown an additional factor that participates in macrophage activation. The Notch signaling pathway is a significant regulator of macrophage differentiation. The suppression of the Notch1/Jagged1 signaling pathway may reverse M2 polarization [87]. In another model, the repression of the Notch signaling reduced the activation of HSCs and the polarization of macrophages into the M1 phenotype with the upregulation of anti-inflammatory genes and the reduction in liver fibrosis [88]. Several other macrophage-specific signaling pathways such as c-Jun N-terminal kinase (JNK), nuclear factor kappa-B (NF-kB), Janus kinase (JAK), and the signal transducer and activation of transcription (STAT) participate in liver fibrosis progression. On the opposite side, the activation of the Wnt/β-catenin signaling pathway in macrophages favors the resolution of liver fibrosis [19]. Murine studies, using single-cell RNA sequencing, identified a distinct type of hepatic bone marrow-derived macrophage with an inflammatory profile, particularly prominent in MASH [89].

The definition problem is far from being solved. Recently, in the murine livers, two types of KCs were characterized by single-cell RNA sequencing. KC1 represents the majority of KCs and is an endothelial cell-selective adhesion molecule (ESAM) negative with a low expression of CD 206. Functionally, it is tolerogenic, while KC2 (CD206hi) has pro-inflammatory potential [19]. An additional pro-fibrogenic subset of liver macrophages was characterized by the presence of the triggering receptor expressed on the myeloid cells 2 (TREM2+) CD9 + marker and was prominent in liver fibrosis, particularly in MAFLD/MASH patients [90,91]. In patients with liver fibrosis, findings analogous to the Ly6C murine macrophages were described.

The exact role of each of the described macrophage subtypes in individual liver diseases is not fully clarified. Murine alcohol-related liver disease (ALD) is exacerbated by infiltration of chemokine receptor positive macrophages, such as CCR2+ or CCR5+ [92]. Moreover, activated liver macrophages secrete vasoconstrictive agents that lead to the induction of portal hypertension and the development of liver fibrosis as they enhance HSCs transformation into MFs [64]. In addition, the activation of KCs and liver macrophages is metabolically re-programmed by endoplasmic reticulum (ER) stress present in MAFLD/MASH [93]. The additional implications of macrophage subtypes in MASH have been mentioned above.

2.2.2. Hepatic Stellate Cells

Under normal conditions, they contain retinoids and are the only site of vitamin A storage. Activated HSCs (aHSC) secrete more pro-fibrotic factors and a positive loop is operative, aggravating fibrosis [94,95]. aHSC may proliferate, produce ECM proteins, and generate inflammatory signals [31]. ECM accumulation is the outcome of the synthesis and degradation of ECM proteins. Matrix metalloproteinases (MMPs), including collagenase (MMP1) and Gelatinase B (MMP9) are zinc-dependent enzymes that degrade ECM components. The deposition of ECM in fibrosis depends on the balance between the MMPs and tissue inhibitors of metalloproteinases (TIMPs) [96]. An imbalance in the activity of MMPs and TIMPs can promote either the progression or the resolution of liver fibrosis [97]. Upon activation, HSCs lose vitamin A droplets and have different characteristics compared to quiescent HSCs such as increased expressions of alpha-smooth muscle actin and collagen type 1 alpha 1. The expression of the peroxisome proliferator-activated receptor γ (PPARγ) is reduced [1]. aHSCs are the main, but not the only, progenitors of MFs [98]. MFs may also originate from portal fibroblasts and bone marrow-derived cells [99] and by the already discussed EMT [100,101] or the complementary endothelial-to-mesenchymal (EndoTM) transition [102,103]. The activation of HSCs is mediated by either several extracellular growth factors, including the platelet-derived growth factor (PDGF), the transforming growth factor-β (TGFβ), the connective tissue growth factor (CTGF), the Wnt/β catenin pathway, chemokines, lipolysaccharide (LPS), DAMPs and PAMPs, or by nuclear mechanisms through the actions of miRNAs. Epigenetic mechanisms may also be implicated, as mentioned before, as well as a number of cellular factors such as oxidative stress and reactive oxygen species (ROS), ER stress, and the autophagic pathway [104,105].

Autophagy has attracted attention as it provides the necessary energy through a specialized form of autophagy called lipophagy that metabolizes the lipid droplets to maintain the activation of HSCs [106–108]. However, there is evidence that autophagy may also protect from liver fibrosis, acting as a double-edged sword [109–112]. Thus, PDGF inhibited autophagy, inducing the release of multivesicular body-derived exosomes and microvesicles from HSCs. Therefore, increased autophagy in HSCs represses liver fibrosis by inhibiting the release of fibrogenic extracellular vesicles [113].

HSCs are by no means a homogeneous population as believed in the past. Studies in the livers of rodents identified two transcriptomes from different populations. One was located in the portal area and the other was associated with the central vein. Interestingly, the latter was responsible for the production of collagen during centrilobular liver damage [114]. The HSC subtype of zone 1 is not transformed into MFs in liver injury but behaves as a capillary pericyte, participating in the process of sinusoidal capillarization [115]. In aging livers, HSCs with a "mixed" phenotype have been identified. They have lipid droplets indicating quiescence together with the markers of senescence and activation such as aSMA. ScRNAseq analysis indicated that even MFs are also a heterogeneous population with distinct functions [101,116].

2.2.3. The Interplay Between KCs and HSCs

As mentioned above, damaged hepatocytes release reactive oxygen species (ROS) and DAMPs. DAMPs activate Toll-like receptors (TLRs), TNFa receptors, and IL1R. The binding of DAMPs to their ligands initiates the myeloid differentiation 88 (MYD88) pathway, followed by the activation of nuclear factor kB (NF-κB) in Kupffer cells, and the transcription of the NLRP3 inflammasome. The resultant inflammatory response is due to the transcription of procaspase-1, pro-IL-18, and pro-IL-1β. ROS also initiate the transcription of NLRP3. Activated inflammasomes induce the production of IL-1β and IL-18, which in turn differentiates HSCs into myofibroblasts, promoting the development of liver

fibrosis [117–119]. TNFa produced by Kupffer cells may promote fibrosis as it inhibits the apoptosis of HSCs and increases the production of TIMPs by activated HSCs [113,120].

Kupffer cells and HSCs in the murine fibrotic liver were able to recruit Ly6Chi monocytes by secreting CCL2, after the hepatocyte-specific deletion of NF-κB. Recruited monocytes further activated HSCs and aggravated fibrosis [121]. The deletion of CCL2 inhibited monocyte recruitment and attenuated liver fibrosis [121]. In addition, activated HSCs produced tissue inhibitors of metalloproteinases (TIMPs), which aggravated fibrosis by inhibiting the degradation of ECM by metalloproteinases [122].

MCP-1 secreted by macrophages increases fibrosis, interfering with macrophages and HSCs. CCR2, the receptor of MCP-1, is expressed on both Kupffer cells and HSCs. In Kupffer cells, the stimulation of CCR2 increases liver infiltration by macrophages, inducing early liver inflammation [123]. In HSCs, the stimulation of CCR2 causes an overexpression of fibrosis genes [124]. CXCL6 was found to be an initiator of TGF-β production by Kupffer cells [125]. In addition, the production of CCL2 and CCL5 by macrophages induced the fibrotic phenotype of HSC and initiated their movement toward the damaged area via their matching receptors in HSCs [126,127]. Stimulated HSCs also express CCL2 and CCL5, which participate in a positive feedback loop and aggravate liver fibrosis [128,129]. Increased levels of CXCL6 were demonstrated in the serum and liver of patients with advanced fibrosis. In vitro cell experiments indicated that HSCs were only indirectly stimulated by CXCL6, which induced TGF-β secretion by KCs [125]. Furthermore, the binding of PDGF produced by activated KCs transforms quiescent HSCs into activated HSCs [130].

Table 1 presents a synopsis of macrophage cytokines and chemokines involved in the interactions with HSCs.

Table 1. Macrophage cytokines and chemokines involved in the interaction with HSCs.

Molecules	Functions	References
TGF-β	Primarily produced by macrophages. Enhances ECM production in HSCs through Smad-dependent pathways and Smad-independent pathways.	[131,132]
PDGF	Produced by macrophages. It contributes to fibrosis progression through HSC activation.	[133]
TNF-α	Upregulates TIMP-1 production, prevents HSC apoptosis.	[134,135]
IL-1β,IL-18	Produced by pro-inflammatory macrophages through activation of the NLRP3 inflammasome. Activates HSCs, upregulates TIMP production.	[136,137]
IL-13, IL-4	Produced by M2 macrophages. Promotes the activation of HSCs.	[138]
MCP1	Activates CCR2 in Kupffer cells and HSCs.	[139,140]
CCL2 CCL5	Produced by macrophages and HSCs. Increases macrophage infiltration and fibrotic phenotype of HSCs.	[141,142]
CXCL6	Induces TGF β production by KCs and indirectly promotes fibrosis.	[143]

HSCs secrete anti-inflammatory cytokines such as IL-10 and TGF-β that initiate the polarization of macrophages toward an anti-inflammatory phenotype, leading to fibrosis resolution. However, the same anti-inflammatory macrophages can also produce cytokines such as IL-13 and IL-4, which favor the differentiation of HSCs into myofibroblasts [144]. IL-6 from either KCs or HSCs may also differentiate HSCs toward myofibroblasts [145,146]. In a murine model of ALD, the extracellular vehicles from alcohol-damaged hepatocytes increased IL1β and IL-17 expression in macrophages followed by the activation of HSCs and the exacerbation of liver fibrosis [147].

An additional mechanism of macrophage–HSC interaction was recently proposed. Cadherin-11 (CDH11) induced intercellular junctions between activated HSCs and macrophages, forming a fibrotic niche. As a result, TGF-β that is produced by macrophages activates the connected HSC, thus inducing their prolonged activation. The repression of CDH11 could derange this niche and promote fibrosis resolution [148].

2.2.4. Liver Sinusoidal Endothelial Cells (LSECs)

Liver sinusoidal endothelial cells are liver endothelial cells with the unique characteristic of the presence of fenestrae. An additional characteristic is the minimal presence of basement membrane. LSECs maintain hepatic cell-to-cell communication and are regulators of signal transduction among cells [134]. The presence of fenestrations is a distinguishing feature useful for the distinction of LSECs from other liver endothelial populations [149]. LSECs are considered to be the actual gatekeepers of the liver microenvironment [150]. Any impairment of the intercellular communications of LSECs may lead to the development of liver fibrosis [151]. Thus, vascular cell adhesion molecule 1 (VCAM1) deletion from LSECs reduces macrophage accumulation in the liver and ameliorates fibrosis, as VCAM1 is an important mediator of LSEC capillarization and hence of liver fibrosis [152].

SECs also have loose cell junctions [136]. In analogy with Kupffer cells and HSCs, LSECs are not a homogeneous population in the normal mouse liver. Their phenotype is variable in the different zones of the liver acinus. Zone 1 LSECs are CD36hi and lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1) low, whereas zone 2 and zone 3 LSECs are CD36low, LYVE1hi, and CD32hi [153]. In the cirrhotic liver, seven different subpopulations of LSECs were identified by scRNA analysis [91]. The increased expression of atypical chemokine receptor 1 (ACKR1) + ve and plasmalemma vesicle-associated protein (PLVAP) + ve were described in LSECs, which are restricted to the fibrotic niche and increase the trans-migration of leucocytes [91,137]. In addition, LSECs may be transformed into endothelial–mesenchymal transition (EndMT), acquiring the phenotype of mesenchymal cells. They start producing ECM proteins that further accumulate in the sinusoids, aggravating capillarization [154,155]. The impairment of autophagy, as observed in MAFLD, increases the EndMT of LSECs and induces the inflammatory response and finally liver fibrosis [139]. The underlying molecular mechanisms involve the stimulation of Twist1 by the transcriptional regulator megakaryocytic leukemia 1 (MKL1) and the signal transducer and activator of transcription 3 (STAT3), leading to an amplification of EndMT in LSECs by TGF-β [140]. The implication of LSECs in liver fibrosis is mostly indirect through the loss of the capacity of LSECs to suppress the activation of the HSCs. This is due to the capillarization of the sinusoids that prevent secretory factors from LSECs to inhibit the activation of HSCs [31].

2.2.5. Cytokines Involved in Liver Fibrosis

Fundamental fibrogenic cytokines, such as the transforming growth factor-β (TGF-β), the platelet-derived growth factor (PDGF), the vascular endothelial growth factor (VEGF), and the connective tissue growth factor (CTGF), all act through specific receptors and participate in advanced liver fibrogenesis [16].

a. TGF-β and IL-10.

TGF-β belongs to a superfamily of 33 cytokines, including among others the isoforms of TGF-β (TGF-β1/2/3), the bone morphogenetic proteins (BMPs), the growth and differentiation factor (GDF), and activins [143].

Activated TGF-β molecules are liberated from a latent complex after liver injury. TGF-β then binds to the TGF-β type II receptor (TβRII), resulting in the recruitment of the TGF-β type I receptor (TβRI). Then, TβRII phosphorylates TβRI that in turn phospho-

rylates SMAD2 and SMAD3 proteins which are complexed with SMAD4, which translocate to the nucleus and regulate the transcription of target genes such as αSMA and CTGF [141,142]. TGF-β also activates non-canonical SMAD-independent pathways, such as MAPK, mTOR, PI3K/AKT, and Rho/GTPase. SMAD7 negatively regulates TGF-β, competing with SMAD3 and SMAD4 for TβRI binding [156].

There has been plenty of evidence that TGF-β is a crucial factor in liver fibrosis. The deletion or suppression of TGF-β attenuated liver fibrosis in mice, whereas the induced overexpression of TGF-β increased liver fibrosis [72,133,157]. The internalization of the type II receptor (TGFβRII) is dependent on the protein diaphanous homolog 1 (Diaph1) as the first step for the transformation of HSCs into MFs. The inactivation of Diaph1 inhibited the endocytosis and intracellular trafficking of TβRII, reducing Smad 3 phosphorylation [138]. The activation of the focal adhesion kinase (FAK) is also a vital component in TGFβ signaling. FAK protects TGFβRII from lysosomal degradation and promotes TGFβ-mediated HSC activation [158]. Almost all the secreted TGF-β1 is found in a latent form bound to the ECM, and the activation of TGF-β1 during fibrosis is site-specific [159]. The better-studied activation mechanism for TGF-β1 is the interaction of the latent complex with the αv-containing subset of integrins. Specifically, the integrins αvβ1, αvβ3, αvβ5, αvβ6, and αvβ8 bind to the latency-associated peptide (LAP) that inhibits the active molecule from binding to its receptors [160–162]. The deletion or blockade of the αvβ6 integrin protected mice from biliary fibrosis in the bile duct-ligated model [163,164]. Also, the blocking of αv-containing integrins by a small molecule ameliorated liver fibrosis, even after the establishment of fibrosis [165]. There is evidence that all TGF-β subtypes are involved in liver fibrosis. The increased levels of TGF-β1 have been found in the murine models of liver fibrosis [166], while increased mRNA levels of TGF-β1 have also been observed in fibrotic patients [143,166,167]. Both TGF-β1 and TGF-β2 induced EMT and fibrogenesis in isolated cell experiments. The upregulation of miR-200a downregulated smad-3 activity and mitigated the TGF-β-dependent EMT. TGF-β1 and TGF-β2 were shown to downregulate the expression of miR-200a. miR-200a also downregulated the expression of TGF-β2 via direct interaction with the 3′ untranslated region of TGF-β2 [168]. Interestingly, the serum levels of the TGF-β subtypes are different according to disease etiology. Serum TGF-β2 was significantly higher in viral cirrhosis but not in primary biliary cholangitis (PBC) patients compared to healthy controls. TGFβ-3 was increased in early and late PBC and decreased in viral cirrhosis. Hepatic vein subtype levels were similar to those in peripheral blood. All TGF-β subtypes were identified by immunocytochemistry in portal tract lymphocytes, sinusoidal cells, and cholangiocytes. TGF-β3 was only overexpressed in hepatocytes from PBC patients [169].

TGFβ and IL-10 regulate the induction of and prolongation of T cell exhaustion. IL-10 is often overproduced in chronic infections such as HIV, HBV, and HCV. The inhibition of IL-10 may prevent or even restore T cell exhaustion. IL-10 acts either directly on T cells through STAT-3 or indirectly by inducing APCs to increase T cell exhaustion and viral persistence. On the other hand, the inhibition of IL-10 in combination with PD-1 leads to the preservation of effector T cell responses, and the effective control of viral replication. Moreover, the use of neutralizing IL-10 antibodies along with therapeutic vaccination promoted CD8+ and CD4+ T cell responses, decreasing viral load [170].

TGF-β is also a suppressive cytokine involved in T cell exhaustion. TGF-β can ameliorate immune cell activation by activating downstream SMAD transcription factors. In acute viral infections, TGF-β is a negative regulator of effector function through the repression of T-bet (T-box expressed in T cells) leading to the upregulation of the pro-apoptotic factor Bim. In chronic viral infections, TGF-β expression and/or downstream SMAD2 activation lead to T cell exhaustion, thus promoting fibrosis [170,171]. HBV initiates the production

of TGF-β and IL-10 by macrophages and inhibits TNF-α production [172]. Similarly, in chronic HBV (CHB) patients, monocytes produce more IL-10 and TGF-β and express high levels of PD-L1. Studies have demonstrated that HBsAg and HBV DNA directly promote PD-L1 expression and anti-inflammatory cytokines production from the monocytes of healthy people [173].

b. Activin A is expressed in murine hepatocytes, HSCs, and LSECs but not in KCs. Different activin receptor combinations are expressed in liver cells. HSCs do not respond to activin A due to the downregulation of type II activin receptors, while KCs respond by increasing the production of TNFα και TGFβ1. Conditioned medium from activin A-treated KCs led to HSC transformation into a pro-fibrogenic phenotype, expressing collagen and αSMA [174]. In addition, TGF-β itself stimulates the production of activin A by fibroblasts [131].

c. Other cytokines are implicated in the fibrotic process in the liver [132,175]. IL-1β has fibrogenic effects similar to TGF-β by inducing EMT, which can be blocked by a monoclonal antibody [176]. It should be noted that IL-6, TNFa, and IL-1-β synergistically act with TGF-β, because the deletion of these cytokines attenuates liver fibrosis [177–180]. Mechanistically, IL-1-β, and TNFa enhance TGF-β actions by downregulating the BMP activin membrane-bound inhibitor (BAMBI), which is a pseudo-receptor for the TGF-β type I receptor and a negative regulator of TGF-β signaling [120].

Whatever the mechanism of liver fibrosis might be, the end result is due to the balance of synthesis over the degradation of ECM, particularly collagens. This in turn is the balance between collagen-synthesizing enzymes and degradative factors such as collagenases and MMPs. The balance may be different according to the etiology of fibrosis. In alcoholic fibrosis and primary biliary cholangitis, it is the synthesis that predominates, while in viral fibrosis, it is the reduced degradation that is mainly responsible [181].

2.3. Resolution of Liver Fibrosis

The resolution of liver fibrosis requires a reduction in the number of activated HSCs and other MFs. This can be achieved through three mechanisms: the regression of activated HSCs to quiescence, the induction of senescence, and the elimination of activated HSCs and MFs through apoptosis and ferroptosis [2,31].

Activated HSCs can de-differentiate back to an inactivated phenotype by upregulating transcription factors such as peroxisome proliferator-activated receptor-γ (PPARγ), GATA-binding factors 4 and 6, and transcription factor 21 (TCF21) [182]. They may also enter senescence or may be eliminated by cell death. Both HSC apoptosis mediated by NK and CD8+ T cells [183] and ferroptosis have been reported during the resolution of liver fibrosis [116]. The induction of apoptosis is often mediated by natural killer cells (NK cells) through the production of interferon-γ (IFNγ) [184,185]. NK cells may also kill senescent MFs, in addition to activated HSCs [186]. The implication of natural killer T cells (NKT cells) in the induction of apoptosis is still controversial [187]. In that respect, it was recently reported that Artesunate (an ester from Artemisin) induced ferroptosis in HSCs and attenuated liver fibrosis in a murine model [188]. Another way to reduce liver fibrosis is the change in the phenotypes of liver macrophages [189]. This has been clearly demonstrated in murine models, as mentioned before. Pro-fibrogenic Ly-6Chi macrophages can change into Ly-6Clow anti-fibrotic macrophages, releasing anti-inflammatory cytokines such as IL- 10, restorative growth factors such as HGF, and ECM-degrading MMPs [61,72,83,190] including MMP12 and MMP13 [82,191]. Partial resolution is still feasible even if the fibrosis is advanced. The appearance of Ly-6Clow macrophages is associated with either the apoptosis of MFs induced by the macrophage production of TNF-related apoptosis-inducing ligands (TRAIL) [192] or by reversion to quiescent HSCs [193].

Many traditional Chinese medications (TCMs) have been reported to be effective in treating liver fibrosis. Single herbal extracts and TCM formulas may prevent or treat hepatic fibrosis. HSCs and oxidative stress, which are implicated in liver fibrosis, are common targets of TCMs [194,195]. However, caution should be exercised in the interpretation of the results as many papers on the clinical trials of TCMs do not comply with the acceptable design of trials [196].

Figure 1 summarizes the mechanisms of liver fibrosis.

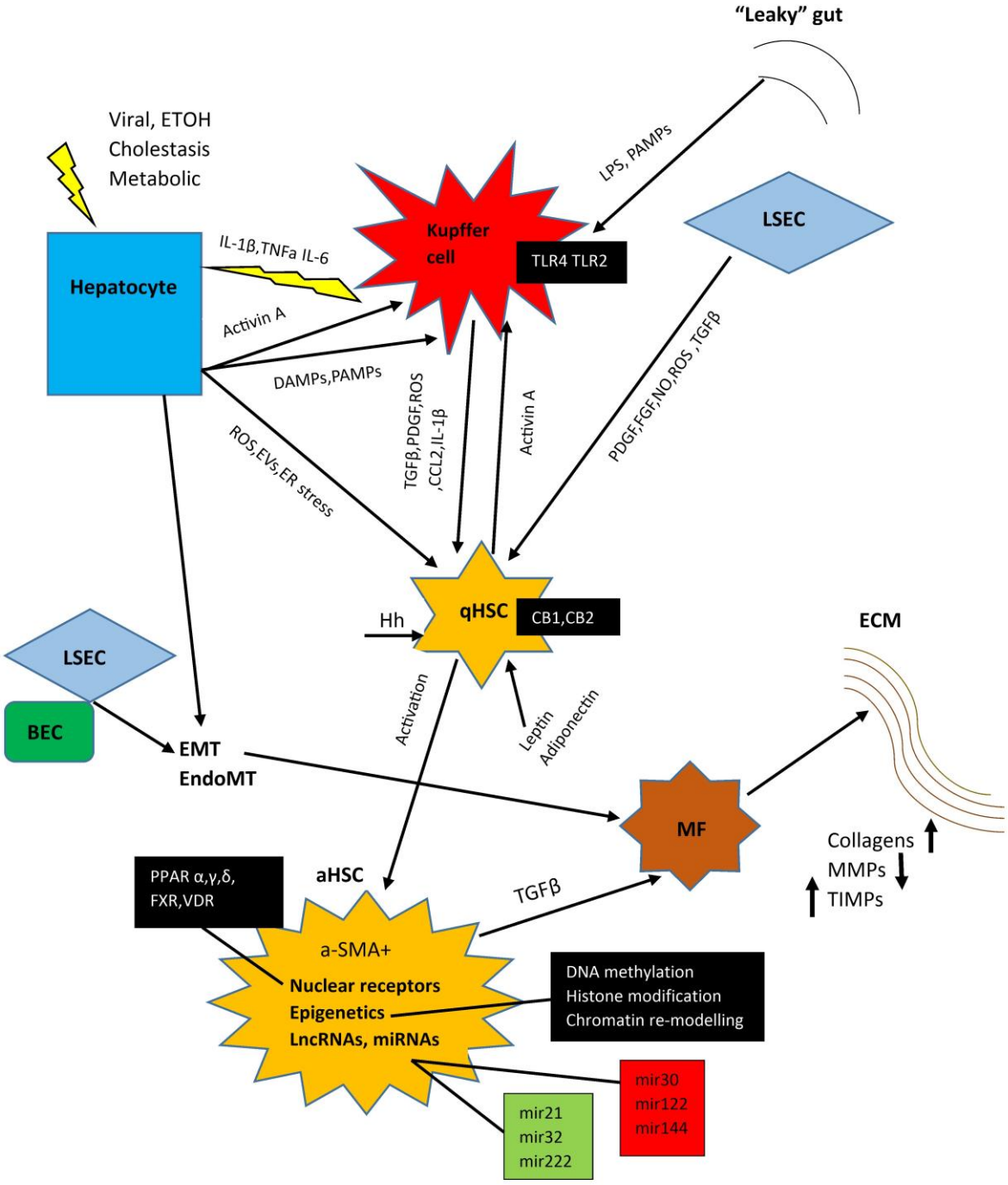

Figure 1. Cellular and molecular pathogenesis of liver fibrosis. Some elements have been omitted for clarity. For details, see text. Green box miRNAs indicate enhancement of fibrosis. Red box indicates inhibition.

BEC: Biliary epithelial cells; CB1 and 2: cannabinoid receptors 1 and 2; DAMPs: damage-associated molecular patterns; EM: epithelial-to-mesenchymal transition; EndoMT: endothelial-to-mesenchymal transition; EVs: extracellular vesicles; FGF: fibroblast growth factor; FXR: farnesoid X receptor; FGF: fibroblast growth factor; Hh: hedgehog ligand; LSECs: liver sinusoidal endothelial cells; LncRNA: long non-coding RNA; miRNA: microRNA; MMPs: matrix metalloproteinases; PAMPs: pathogen-associated molecular patterns; PDGF: platelet-derived growth factor; PPAR: peroxisome proliferator activated receptor; TIMPs: tissue inhibitors of metalloproteases; VDR: vitamin D receptor.

3. Immunology of Liver Fibrosis

3.1. The Liver as an Immune Organ

The liver, in addition to its central metabolic role, is also a significant immune organ [197,198]. It contains several components implicated in both innate and adaptive immunity. Some of them are not strictly immune cells, such as hepatocytes [199] and LSECs, but express Toll-like receptors (TLRs) and major histocompatibility complex (MHC) molecules, and participate in the maintenance of tolerance [200–203] or the biliary epithelial cells (BECs) and HSCs, which are also tolerogenic and may present antigens to T lymphocytes [135,198,204]. These cells are implicated in both innate and adaptive responses. On the contrary, liver sinusoids contain the proper cells of innate immunity such as KCs, dendritic cells, myeloid-derived suppressor cells, or lymphoid-derived cells (NKs and innate lymphoid cells). Certain cells do not comply with either the innate or adaptive immunity criteria and are defined as "innate-like", or "unconventional" lymphocytes. They include mucosal-associated invariant T (MAIT) cells, natural killer T (NKT) cells, and γδ-T cells. In addition, the normal liver also houses the conventional T and B lymphocytes of adaptive immunity [198].

Tolerance is a main function of the liver. An important mechanism of hepatic tolerance is the expression by several liver cells of MHC molecules not accompanied by co-stimulatory molecules. Other, equally important tolerogenic mechanisms, are the secretion of suppressor cytokines such as IL-10 and TGF-β, the inhibition of professional antigen-presenting cells (APCs), and the subjection of immune cells to programmed cell death-ligand 1 (PD-L1) [205–207]. Liver-draining lymph nodes (LNs) are also important components of the liver immune system. Portal LNs are an area of regulatory T cells (Tregs) induction, while celiac LNs are an area of T cell responses [205,208]. Moreover, cellular metabolism is associated with immune responses. A glycolytic metabolism is involved in the effector function of T lymphocytes, while fatty acid oxidation is used by non-inflammatory immune cells such as Tregs [209]. Glycolysis induced by hypoxia-inducible factor 1-alpha (HIF-1a) and oxidative metabolism induced by IL-4/STAT6 are used by either pro-inflammatory or anti-inflammatory macrophages, respectively [210–212].

3.2. Immune Factors Implicated in Liver Fibrosis

Liver fibrosis is closely linked to impaired hepatic immune responses [213]. Several experimental data indicate that the immune cells can regulate both the progression and reversal of liver fibrosis [214]. Excessive alcohol consumption, viruses, western dietary habits, or MAMPs and PAMPS originating from the microbiota of a leaky gut, may impair hepatic immune homeostasis leading to liver inflammation, fibrosis, and cirrhosis. The liver must handle antigens arriving at the sinusoids from the systemic circulation and the intestinal tract. These antigens are processed by the liver through a series of pattern recognition receptors (PRRs), such as TLRs and nucleotide-binding oligomeric domain-like receptors (NOD-like receptors), which induce either a tolerogenic response or inflammation and fibrosis [215–218].

Early in the course of chronic liver disease, damaged hepatocytes release inflammatory mediators that recruit and activate inflammatory cells, such as macrophages, lymphocytes, and NK cells [183,190,219]. Inflammation leads to a disordered crosstalk between hepatic immune cells, which drives the induction and progress of fibrosis [189,220,221]. TLRs are expressed on various hepatic cells like KCs, dendritic cells, hepatic stellate cells, endothelial cells, and hepatocytes [222]. Changes to the liver immune system leading to fibrosis include a decrease in CD8+ T cells and NK cells and an increase in CD4+ T cells infiltration accompanied by the expression of certain immune-regulatory genes [223,224].

Innate and Adaptive Immunity

Innate and adaptive immune cells are involved in hepatic inflammation, fibrosis, cirrhosis, and HCC. They have distinct roles, but at the same time, they affect each other. Adaptive immunity depends on the activation signals and cytokines secreted by the innate immune system. PAMPs from damaged hepatocytes lead to the activation of intrahepatic innate cells that initiate the recruitment of circulating immunocytes to the liver. The infiltrating cells stimulate other parenchymal and non-parenchymal cells in the liver, thus creating a perpetuating circle. The induction of pro-fibrogenic mediators such as IL-10 and TGF-β encourage liver fibrosis by activating quiescent hepatic stellate cells. The continuous supplementation of these fibrogenic stimuli promotes further disease progression toward fibrosis and cirrhosis [225].

3.3. Innate Immunity in Liver Fibrosis

As mentioned above, DAMPs activate innate immunity that induces fibrosis. The NLR family pyrin domain-containing 3 (NLRP3) inflammasome is a major element of the innate immunity, which functions as PRR, recognizing both PAMPs and DAMPs [226]. Kupffer cells are rich in NLRP3, and its activation leads to the secretion of several pro-inflammatory cytokines, such as IL- 1b and IL-18 [227]. Human and murine data indicate that NLRP3 activation induces caspase-1-mediated pyroptotic death and the liberation of inflammasomes that are engulfed by HSCs, leading to their activation and liver fibrosis [228].

3.3.1. Cells Involved in Innate Immunity

a. Hepatocytes. Hepatocytes may induce innate immunity as they express immune receptors that recognize PAMPs. These receptors include surface receptors such as TLR4, endosomal receptors such as TLR3, cytoplasmic receptors such as the stimulators of the IFN gene (STING) and the members of the NOD family [199,229,230]. Hepatocytes can also induce adaptive immunity. During inflammation, certain hepatocytes express MHC-II molecules and activate T lymphocytes [206,231], but as they do not express co-stimulatory molecules such as CD80 and CD86, they are not capable of generating the long-lasting activation of T cells. Importantly, hepatocytes express PD-L1 either after viral infection or under the influence of type I and type II IFN, thus mediating the apoptosis of T cells [232]. Activated hepatocytes may also induce the transformation of BM-derived monocytes into pro-inflammatory macrophages, upregulating the Yes-associated protein (YAP) and the transcriptional coactivator with a PDZ-binding motif (TAZ) [233]. YAP/TAZ is the effector in the Hippo pathway, which is a regulator of the TGF-β2-mediated fibrogenesis as indicated by data from other organs [234]. The increased expression of the transcription factor Fork head box M1 (FoxM1), and the subsequent overexpression of the CCL2 chemokine, induce hepatocyte death, leading to liver inflammation and fibrosis through macrophage recruitment [235,236].

Most of the data mentioned above come from animal experiments. However, there is evidence from liver disease patients that hepatocytes are indeed involved in inflammation and fibrosis. MHC-II molecules are expressed in the hepatocytes of alcoholic hepatitis,

and activate CD4+ T cells, inducing positive lymphocytes [237]. Lipid-laden hepatocytes are more susceptible to apoptosis in patients with MASH [238]. Exosomes derived from HBV-infected hepatocyte contain miR-222 and increase fibrosis by inhibiting the transferrin receptor (TFRC) and TFRC-induced ferroptosis [239].

The autophagy pathway within the hepatocytes is also implicated in immune-mediated liver fibrosis. Autophagy protects hepatocytes from death signals [199,240] and is implicated in most chronic liver diseases [241–244]. The vitamin D receptor (VDR) promotes autophagy by regulating beclin-1, bcl-2, the mTOR elements of the autophagy pathway, and lysosomal maturation [245]. The VDR was decreased in the hepatocytes of cirrhotic patients [246]. In murine models and human cirrhosis, hepatocyte autophagy was inhibited by the miR-125a/VDR axis, leading to increased liver fibrosis [247].

Endoplasmic reticulum (ER) stress and hepatocyte senescence are two additional factors that implicate hepatocytes in the process of liver fibrosis. The accumulation of misfolded proteins in the ER activates the unfolded protein response (UPR), mediated by three ER sensors, namely PKR-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme 1 (IRE1) to counteract the protein-folding defect [248]. Massive ER stress overcomes UPR and leads to hepatocyte steatosis and death [93,249]. ER stress can trigger C/EBP Homologous Protein (CHOP) transcription factor-dependent NLRP3 inflammasome activation and the activation of IRE1A in hepatocytes, both leading to the release of pro-inflammatory cytokines and inflammatory extracellular vesicles (EVs), therefore promoting fibrosis [199]. A strong positive correlation between senescent hepatocytes and liver fibrosis severity has been described in MASH and alcoholic liver disease patients [250,251]. In chronic viral hepatitis patients, senescence is associated with telomere shortening and the absence of telomerase in hepatocytes, favoring virus replication and liver cirrhosis [252,253]. An additional confirmation that senescent hepatocytes are directly involved in liver fibrosis was recently reported. PDGF is a potent activator of HSCs, as mentioned before. PDGF levels were significantly higher in the media from cultured senescent hepatocytes compared to control hepatocytes, and similar findings were demonstrated in serum samples from patients with cirrhosis compared to healthy controls [254].

b. Kupffer cells and liver macrophages. KCs are probably the most important cells in liver innate immunity. They are professional antigen-presenting cells (APCs) to T cells and therefore participate in the initiation of adaptive immunity [83,255]. In MASH, there is a positive correlation between the severity of inflammation and fibrosis and the number of pro-inflammatory macrophages in the periportal zone [256]. As mentioned before, early liver damage activates hepatic macrophages including the KCs. In turn, they secrete several cytokines such as TGF-β1, PDGF, TNF-α, IL-1, IL-6, and IL-10, and cytokines such as CXCL1, CCL2, and CCL5. KCs produce mediators such as ROS that induce HSC transformation and attract BM monocytes and neutrophils [183,191]. Liver macrophages, irrespective of origin, are the main sources of TGFβ and one of the leading causes of increased ECM deposition in liver fibrosis. They also maintain the survival of MFs by activating NF-kB through the secretion of IL-1β and TNFa [183,189,191,219]. In addition to these functions, Kupffer cells activated by DAMPs and PAMPs, as mentioned above, induce an increased expression of vascular adhesion molecules on LSECs [82,257].

Recruited bone marrow-derived macrophages differentiate into a Kupffer cell-like phenotype [65], approximately 60 days of repopulation after liver damage [258]. It is not clear if the newly recruited macrophages live long or whether their functional role is comparable to the original Kupffer cells [65,259].

KCs have a dual role in the immune regulation of liver inflammation and fibrosis. Depending on the microenvironment, they can acquire a pro-inflammatory phenotype (referred to as M1). M1 KCs are activated by IFNγ and lipopolysaccharide (LPS) and are

characterized by the ability to present antigens and produce inflammatory cytokines such as TNFα, IL-1, IL-6, IL-12, and IL-23, promoting antiviral activity. Alternatively, KCs can acquire an anti-inflammatory phenotype (referred to as M2) characterized by their ability to balance inflammatory responses and facilitate tissue repair through the release of IL-10, IL-4, IL-13, and TGF-β and the low production of IL-12, IL-6, and TNF-α [260,261]. Furthermore, IL-17 activates Kupffer cells and lead to the upregulation of pro-fibrotic cytokines like IL-6, IL-1β, and TGF- β1 [262].

KCs differentiation into the M2 phenotype upregulates PD-L1 and galectin-9 expression in the presence of HBeAg. HBcAg upregulates TLR-2 on the surface of KCs and increases IL-10 secretion, thus upregulating CD8+ T cell exhaustion [263]. The activation of the TLR4 signaling pathway promotes M1 inflammatory differentiation that leads to the upregulation of the clearance of HBV [264]. The stimulator of interferon genes (STING) is a key adaptor in DNA-initiated innate immune activation [265]. The stimulation of KCs by STING increases the hepatic expression of interferon-inducible protein 16 (IFI 16), which binds to HBV cccDNA, inhibiting cccDNA transcription and leading to its silencing [266].

In human cirrhosis, KC numbers are similar to the normal liver [91,267], in contrast to the murine liver where extensive fibrosis and cirrhosis is accompanied by a reduction in the number of KCs [268]. The presence of KCs and the differentiation of other macrophages is influenced by stromal cells through the inhibition of monocyte maturation. This is achieved by the production of IL-6 from the stromal cells. Interestingly, the local IL-6 levels are diminished in early-stage human liver injury, implicating a protective role of IL-6 [269]. Apart from the production of TGF-β and the maintenance of the viability of MFs, KCs may be transformed into fibroblast-like cells, contributing to ECM production [270]. The KCs also promote collagen cross-linking that stabilizes collagen through the action of Lysyl-oxidase (LOX) and Lysyl oxidase-like protein-2 (LOXL2) [271]. On the opposite side, KCs produce MMP9, leading to collagen degradation [272]. KC infusion attenuated liver fibrosis in a murine model [273]. Interestingly, the T-cell immunoglobulin domain and mucin domain-4 (TIM-4) expression by KCs represses liver fibrosis [274].

Although fibrosis is the final common result in all liver diseases irrespective of etiology, the underlying participation of the involved cells may be different. Hepatitis B and hepatitis C viruses (HBVs, HCVs) activate human macrophages, but the response is different in the two viral diseases. Macrophages respond to HBV by the production of inflammatory cytokines and the stimulation of NK cells [275,276]. The response to HCV proteins is the activation of inflammasomes mediated through TLR2 activation [277,278]. HBV and HCV infection lead human macrophages to secrete immunomodulatory mediators such as IL-10, TGFβ1, PD-L1, and PD-L2 that eventually mitigate antiviral T cell response [279]. In MASH, the accumulation of fat in the macrophage [280] production of EVs from fat-containing hepatocytes, [281,282] or histidine rich glycoprotein [283,284], induces an inflammatory phenotype in liver macrophages. In ALD patients, macrophages have a fundamental role in the inflammatory response during severe alcoholic hepatitis [285,286]. In murine ALD models, increased gut permeability contributes to the recruitment of pro-inflammatory macrophages [279,287,288]. In cholestatic conditions, BM-derived macrophages are influenced by the concentration and the composition of the bile acids in the liver [289]. Chenodeoxycholic acid (CDCA) activates the NLRP3 inflammasome in the macrophages of cholestatic animals with fibrosis [290]. On the contrary, KCs have the G-protein-coupled bile acid receptor 1 (TGR5), which is a sensor for bile acids, leading to the inhibition of inflammasomes [291] and the emergence of an anti-inflammatory phenotype [292,293].

c. The role of HSCs. The multiple factors implicated in the activation of HSCs are further complicated due to the interaction of HSCs with the cells of the immune microenvironment during liver fibrosis. All cells involved in both innate and adaptive immunity are

communicating with HSCs either directly or indirectly [90,294]. aHSCs, apart from their fundamental contribution as ECM producers, are also pro-inflammatory cells. They produce several cytokines and chemokines such as IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1). They also recruit monocytes and hematopoietic stem cells [15]. Inflammatory mediators produced by HSCs target the nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB), the central regulator of the inflammatory response [295,296]. Therefore, NF-κB is a critical molecule in the inflammation and resultant fibrosis but also in the apoptosis or survival of HSCs after liver injury. Indeed, NF-κB activation is associated with an increased resistance to the apoptosis of activated HSCs [104,297].

The activation of HSCs is important in the pathogenesis of MASH. There is experimental evidence that free cholesterol accumulation in HSCs leads to their activation [298–301]. Free cholesterol in hepatocytes indirectly affects HSC activation through the stabilization of the transcriptional coactivator with the PDZ-binding motif (TAZ) with subsequent over-secretion of the pro-fibrotic factor Indian Hedgehog [302]. In chronic hepatitis B, a different mechanism is operative. aHSCs recruit large numbers of Th17 cells and promote the secretion of IL-12A and IL-22 that contribute to fibrosis [303]. On the other hand, HSCs may favor the development of tolerance in mice as they favor the expansion of FoxP3+ve Tregs or myeloid-derived suppressor cells [304,305].

HSCs also influence B-cell activity. HSCs inhibit the increased expression of activation markers on B cells and immunoglobulin production. Interestingly, blocking the interaction of PD-L1 with PD-1 mitigated the inhibition of B cells by HSCs [306].

HSCs are also implicated in inflammation and fibrosis by their involvement with the adipokines leptin and adiponectin, which act through binding to their receptors on HSCs [307–309]. Leptin is a pro-fibrotic factor that suppresses the sterol regulatory element-binding protein-1c (SREBP-1c) and activates HSCs through the β-catenin pathway [310]. Adiponectin, on the other hand, ameliorates liver fibrosis through the induction of nitric oxide (NO) and TIMP-1 production, leading to the suppression and inactivation of aHSCs [311–315]. Currently, it is not yet clear under which conditions hepatic stellate cells are pro-inflammatory and under which conditions they are tolerogenic [219].

The details of the immune regulation of fibrosis by HSCs have been extensively reviewed [2].

d. The role of liver sinusoidal endothelial cells. LSECs express TLRs and MHC molecules and are implicated in the maintenance of tolerance either through the direct inhibition of T lymphocytes by PDL1 expression or through the so-called "veto" effect, consisting of inhibiting other APCs such as dendritic cells to activate T lymphocytes by physical contact without the need for the presence of MHC [200–203,316]. The early stages of MAFLD are a clear example of the immunological role of LSECs in liver fibrosis. Lipotoxicity, adipokines, and gut-derived PAMPS lead to LSECs' de-differentiation and sinusoidal capillarization. Capillarized LSECs are transformed into a pro-inflammatory and pro-fibrotic phenotype, recruiting immune cells that cannot support the quiescence of HSCs and KCs [151,317]. Specifically, the quantity and size of LSEC fenestrae are lost, and in advanced stages they even disappear. The blood filtration in the sinusoids is impaired, and harmful components are not adequately removed, and the risk of liver injury is increased [200]. Human studies reported that the expression level of the scavenger receptor Fc gamma receptor IIb (FcγRIIb) in LSECs is negatively correlated with fibrosis and inflammation in patients with MASH. FcγRIIb is involved in the elimination of small immune complexes from sinusoids [318]. A study on patients with chronic hepatitis C showed that LSEC capillarization was observed even at the initial stages of fibrosis [319]. Moreover, there is evidence that capillarization is the result of the impaired differentiation of the bone marrow-derived LSECs [320]. An important regulator of LSECs fenestration is

the bone morphogenetic protein 9 (BMP9). The role of BMP9 in liver fibrosis is controversial. The deletion of BMP9 in murine models increased liver fibrosis [321,322]. On the other hand, liver biopsies from fibrotic patients showed increased levels of BMP9 in advanced fibrosis. In murine models, BMP9 overexpression accelerated liver fibrosis, and BMP9 knockdown ameliorated fibrosis. BMP9 directly stimulated hepatic stellate cell activation via the SMAD signaling pathway to upregulate hepatic fibrosis [323]. The details of the effects of BMP9 on liver fibrosis were recently reviewed [324].

In addition to capillarization, hepatic neo-angiogenesis was also strongly related to LSECs and was associated with the development of liver fibrosis [149], possibly mediated through the vascular endothelial growth factor (VEGF) [325]. This is supported from the alterations of LSEC phenotypes made by certain drugs such as Vatalanib, a VEGFR1 and VEGFR2 inhibitor, or Lenvatinib, an inhibitor of VEGF1, VEGF2, and VEGF-A. They decreased both sinusoidal capillarization and liver fibrosis [326,327]. The beta-blocker carvedilol repressed the expression of VEGF and angiopoietin-2, leading to the attenuation of sinusoidal capillarization [328]. Moreover, HIF-1α is also implicated in LSEC capillarization and angiogenesis. MiR322/424 upregulated the expression of the HIF-1α protein in LSECs and promoted neo-angiogenesis and liver fibrosis [329]. LSECs can also directly stimulate neo-angiogenesis through the secretion of angiogenic factors. Interestingly, LSEC capillarization is a process that starts before the activation of macrophages and HSCs in liver fibrosis [134]. A detailed description of the participation of LSECs-dependent angiogenesis in liver fibrosis was recently reported [134].

LSECs are involved in the progression of liver fibrosis by two additional mechanisms. Reduced NO bioavailability has been observed in LSECs from cirrhotic rodent livers [330] due to the ROS scavenger effect of NO via the superoxide anion (O2-) and the ERK1/2-AKT axis [331]. ERK1/2 shifted the balance toward NO, favoring LSEC homeostasis, while AKT could shift the balance toward ROS, promoting liver fibrosis. A second mechanism by which NO modulates liver fibrosis is the induction of autophagy. Autophagy in LSECs increases the bioavailability of NO and eliminates the accumulation of ROS [332]. This protective action of autophagy is not sufficient at the later stages of chronic liver [333]. Autophagy acts the opposite way as well by degrading Caveolin-1 (Cav-1), leading to LECs defenestration [334]. Moreover, LSECs mediate in the transformation of macrophages into KCs. The interactions of the Notch ligand delta-like ligand 4 (DLL4) produced by LSECs binding to the Notch receptor found in macrophages is required for the induction of the KC identity. Ligands such as ICAM-1 and vascular cell adhesion protein 1 (VCAM-1) in LSECs interact with the integrins on KCs and participate in the direct interplay between KCs and LSECs [335,336].

The central role of LSECs in the regulation of liver immunology and their effects in liver fibrosis is clearly exemplified in viral diseases. In murine adenovirus infection, 90% of the virus is rapidly taken up by LSECs and only 10% is found in KCs [337]. HIV-like particles are also taken up by mouse LSECs at a rate of 100 million viral particles per minute [338]. In the duck hepatitis B virus (DHBV) model, viral particles are mostly taken up by LSECs before passing on to further infect hepatocytes [339]. In HCV, the innate sensing of the virus by LSECs leads to the release of paracrine molecules such as the pro-viral molecule bone morphogenetic protein 4 (BMP4), which promotes the viral infection of hepatocytes [340,341]. On the other hand, the direct sensing of HCV RNA in LSECs produce type I and type III interferon-containing exosomes that inhibit HCV replication [342]. The balance of the two opposite responses determines whether the HCV virus will be eliminated or will cause a sustained infection.

e. Mesenchymal stromal cells (MSCs) are fibroblast-like cells with immunomodulatory ability, as they regulate both innate and adaptive immunity and have the potential to

differentiate into hepatocyte-like cells (HLCs) [343–346]. MSCs express a specific set of surface markers, such as CD73, CD90, and CD105 [347]. MSCs produce the hepatocyte growth factor (HGF) and IL-6, which inhibit monocyte differentiation into dendritic cells and the activation of KCs. They also secrete a variety of other growth factors that help the proliferation of healthy cells and protect the destruction of other cells [348–350]. They also produce IL-10 and mitigate the activation of T cells [351]. MSCs secrete prostaglandin E2 (PGE2) to transform M1 macrophages into M2 macrophages [352]. MSCs repress the proliferation of CD8+ T lymphocyte and promote Th1-to-Th2 conversion [353]. It should be noted that the anti-fibrotic potential of MSCs is dependent on autophagy and senescence. Intact autophagy maintains anti-fibrotic activity, while reduced autophagy that coincides with advanced age is associated with a reduction in MSC numbers and function, promoting liver fibrosis [354]. The scRNA analysis of cirrhotic human livers identified four subpopulations of mesenchymal cells. Mes (1) was identified as vascular smooth muscle cells, Mes (4) expressed mesothelial markers, Mes (2) resembled HSCs, but they were not present in the cirrhotic niche, and Mes (3) distinguished by PDGFRA were pro-fibrogenic. Mes (3) cells were increased in cirrhotic livers [91,137]. Extensive reviews on MSCs were recently published [355–357].

f. Natural killer (NK) cells. They bear the activating receptor NKG2D and are capable of HSC elimination, inducing apoptosis and IFNγ secretion [358–360]. IFNγ secreted by NK cells directly inhibits HSC activation and ECM synthesis [361] and amplifies the killing capacity of NK cells against HSCs by increasing the expression of the NKG2D receptor [362]. The decreased numbers and function of NKs have been demonstrated in the murine models of cirrhosis [363] and cirrhotic patients [364–366]. These findings confirmed the anti-fibrotic effects of NK cells. Four immunity-related genes in NK cells, including interferon regulatory factor 8 (IRF8) and REL, are involved in liver fibrogenesis [224].

NK cells are classified into two subpopulations. The vast majority, over 90%, express low levels of CD56 (CD56dim), while the minority express high levels of CD56 (CD56bright). The first is more cytotoxic and a better immunomodulator [367]. In acute viral hepatitis, they both exhibit an antiviral effect either by the direct killing of infected cells or by the activation of viral-specific T cells secreting IFN-γ and TNF-a [368]. NK cell function is defective in patients with chronic hepatitis B (CHB), participating in persistent HBV infection and the development of fibrosis [172]. A further mechanism of NK dysfunction in the particular group of HBeAg+ve patients with CHB is the induction by HBeAg of IL-10 secretion from Tregs, leading to an increased expression of the inhibitory receptor NKG2A on NK cells [369]. Among the many immune abnormalities found in MAFLD, a reduction in CD56bright NK cells and an elevation in CD56dim with less expression in the activating receptor NKG2D was described in patients, offering an additional explanation for the progress of liver fibrosis in MAFLD [370]. A recent observation shed more light on the role of NK cells in MAFLD. Uncoupling protein 1 (UCP1) participates in the leak of protons from the mitochondrial inner membrane. Reduced levels were found in NK cells from patients with MAFLD. Sustained high-lipid administration in mice decreased UCP1 expression and promoted NK cell necroptosis and was involved in the progression to fibrosis [371]. Patients with primary sclerosing cholangitis (PSC) showed considerably higher serum levels of IFNγ and elevated numbers of hepatic CD56bright NK cells. Murine knockout experiments confirmed that increased IFNγ turned the phenotype of hepatic NK cells into increased cytotoxicity, while its absence ameliorated liver fibrosis in PSC [372].

g. Neutrophils. There are very few resident neutrophils in the healthy liver, but there is a rapid recruitment from the circulation in the diseased liver [373]. Neutrophils participate in the liver inflammatory response through the secretion of pro-inflammatory cytokines and the production of extracellular neutrophil traps (NETs). They activate KCs and recruit other

types of immune cells [374–376]. In mice, the elimination of neutrophils ameliorates the development of hepatic fibrosis [377]. The characteristic neutrophil infiltration into the liver during alcoholic hepatitis is associated with the upregulation of the glycoprotein lipocalin-2 (LCN2) in the neutrophils. A deficiency of bactericidal activity and myeloperoxidase secretion was also found in these patients [92]. The liver-infiltrating neutrophils are also implicated in the immune response in the fibrotic progression in MASH [378,379].

3.3.2. LSECs as Gatekeepers of Innate and Adaptive Immunity

LSECs have a central role in the regulation of both the innate and adaptive immunity being the gatekeepers of the overall liver immune response. Thus, in normal livers, LSECs prevent HSC activation through vascular endothelial growth factor (VEFG)-induced nitric oxide (NO) production. In addition, normal LSECs can reverse activated HSCs back to quiescence through unidentified mechanisms. Decapillarized LSECs isolated from normal rat livers can suppress HSC activation, but capillarized LSECs from cirrhotic rats lose this function. The interaction between LSECs and Kupffer cells is not clarified so far. However, in the fibrosis model, there is evidence that the crosstalk between LSECs and Kupffer cells results in a loss of fenestration and increased CD31 expression [380]. In addition, fenestrated LSECs inhibit liver inflammation by having antioxidant activity. In contrast, capillarized or defenestrated LSECs caused by factors such as ROS production or through lipotoxicity have low antioxidant activity and can induce liver inflammation and promote HSC activation.

It should be noted that the fenestrations of LSECs allow for effector CD8+ T cells to recognize viral antigens expressed in hepatocytes and produce antiviral cytokines by cellular protrusions that extend through the fenestration in a diapedesis-independent manner. This mechanism is obviously lost along with the fenestrae in liver fibrosis, and the effector function of antigen-specific T cells is decreased [381].

Furthermore, LSEC death produces PAMPS that can promote liver inflammation, fibrosis, and cirrhosis acting on KCs and macrophages [317]. LSECs are also implicated in adaptive immunity. They can restrict the entry of immune complexes and leucocytes into liver tissue. Most importantly, LSECs can act as antigen-presenting cells (APCs) and regulate lymphocyte action because they constitutively express MHC class I and II, CD54 (ICAM-1), CD4, CD11, and CD106 (VCAM-1) molecules as well as co-stimulatory molecules CD40, CD80, and CD86, which are necessary for the antigen presentation to T cells. LSECs express MHC- I receptors and present antigens to CD8+ cytotoxic T cells. At low antigen concentrations, this presentation leads to the tolerogenic deletion of CD8+ T cells, but at high antigen concentration, leads to a memory effector T cell phenotype. In HBV infection, CD8+ T cells attach to the sinusoids and then search for infected hepatocytes through LSEC fenestrae. CD8 T cells actively cross the LECS barrier once they sense an infected hepatocyte and release TNFa that in turn eliminates the infected hepatocyte. Moreover, LSECs also present antigens to CD4+ T cells through MHC class II receptors, inducing suppressor Treg cells [200,382].

3.4. Adaptive Immunity T Cells

Cells of adaptive immunity are the many subpopulations of the T lymphocyte family and the B cells. Virtually all lymphocytes originating from naive CD4+ cells participate in the regulation of liver fibrosis. T cells are classified into conventional T cells and innate-like T cells (unconventional T cells). Unconventional T cells consist of natural killer T (NKT) cells, γδ T cells, and mucosal-associated invariant T (MAIT) cells [383,384]. Conventional T cells can be further subdivided into CD8+ cytotoxic T lymphocytes (CTLs), regulatory T (Treg) cells, T follicular regulatory (Tfr) cells, and CD4+ T helper cells, including Th1,

Th2, Th9, Th17, Th22, and T follicular helper (Tfh) cells [385,386]. TNF-α-producing CD4+ T cells are dominant in HBV infection, participating in the progression of liver damage. A sequential increase in IFNγ-producing CD4 T cells characterizes patients with elevated levels of viral clearance [387].

A distinct type of T cell is the tissue resident memory (TRM) T cell that is important as a first-line defense in the liver. These consist of CD8+ and CD4+ cells and they do not circulate [385]. Their storing effector ability of hepatic TRM cells makes them critical in chronic liver diseases. The proliferation of liver TRMs is modulated by cytokines such as interleukin IL-2, IL- 15, IL-10, and TGF-β. Liver TRM cells are antiviral in chronic viral hepatitis. Importantly, the number of liver TRMs positively correlates with inflammation in patients with obesity [388]. A detailed description of the role of the T cell subclasses in liver fibrosis has been published [386].

APCs are classified into professional and non-professional. All professional APCs express the MHC-II molecules and include macrophages, dendritic cells (DCs), and B-lymphocytes. The MHC family consists of MHC-I and MHC-II receptors. MHC-I presents antigens to CD8+ cytotoxic T cells, while the MHC-II molecules induce CD4+ T cell activation [213]. Hepatocytes express MHC-II molecules and co-stimulators, and they may act as an atypical APC to promote T cell activation [389,390]. This has been demonstrated in the liver samples of patients with alcoholic hepatitis (AH) and MASH, where increased levels of MHC-II were observed in close association with MHC-II-producing hepatocytes [237]. Although DCs belong to the cells of innate immunity, they connect the innate and the adaptive immunity [391]. Hepatic DCs (HDCs) are less than 1% of total liver myeloid cells and are subdivided into plasmacytoid and myeloid subpopulations. Myeloid HDCs are further classified as type 1 and type 2 [392,393]. In the healthy liver, HDCs are tolerogenic [394], but they stimulate CD4 +T cells during liver diseases [393]. The majority of HDCs are localized at the portal vein area, with a few localized at the central vein area [395], while their numbers are significantly increased in MASH patients [396]. In the murine models of liver diseases, HDCs have no effect on the survival of HSCs in contrast to macrophages [71]. Animal and human data indicate that other cell types express the MHC-II molecules and act as atypical APCs. They include mast cells, basophils, eosinophils, neutrophils, and innate lymphoid cells (ILCs) [397].

T cell response after the presentation of antigens involves the recognition of the antigen by the T cell receptors (TCRs) on the surface of either CD4+ or CD8+ cells acting in collaboration with the CD3 co-receptor [398]. Other co-stimulatory molecules such as OX40L are required for proper antigen recognition by the T cells [399–401]. TCRs comprise two different heterodimers: TCRα/TCRβ or TCRγ/TCRδ [402]. A reduction in TCR subtypes was found in the liver of fibrotic animals, while the deletion of TCRβ aggravated liver fibrosis [403].

Current evidence indicates that T cell immunity influences the fibrosis process [386]. Earlier studies reported that the transfer of CD8+ve T cells contributed to liver fibrosis. CD8+ve T cells directly activated HSCs in murine models [404]. IL-21 promotes the antiviral activity of HBV-specific CD8+ T cells by promoting the production of IFNγ, granzyme B, and CD107a and decreasing PD-1 and TIM-3 production [405]. In addition, IL-2 promotes the proliferation of CD8+ T cells by activating the mTOR pathway to restore dysfunctional CD8+ T cells [406]. IL-33 initiates the proliferation of HBV-specific CD8+ T cells and upregulates PD-1 production, promoting HBV clearance. Not unexpectedly, the plasma levels of IL-33 are low in patients with CHB [407].

The severity of liver fibrosis was positively correlated with intrahepatic CD4+ve T cell apoptosis [408]. CD4+ve T cell activity is involved in the progression of liver fibrosis, by secreting cytokines such as IL-4, IL-10, and IFN-γ, and by stimulating other immune

cells such as NK cells [224,366,409]. An analysis of T cell distribution in a small number of viral cirrhosis patients found that CD4+ve T cells, but not CD8+ve cells, were decreased in cirrhotic tissue. This is in contrast to a larger and more detailed study, which reported that a reduction in CD8+ve and NK cells and an infiltration of CD4+ve memory T cells contributed to immune changes in cirrhosis [224,366,409]. The impairment of CD4+ve T cells is implicated in the evolution of liver fibrosis in MASH. An accumulation of liver CD4+ve T cells was demonstrated in human disease and murine MASH models [410–412]. CD4+ve T cells were critical in the progression of liver fibrosis after the transfer of human T cells to a specific murine model of MASH. Moreover, the depletion of human CD4+ve T cells attenuated fibrosis in the humanized MASH mice, confirming the significance of these cells in the pathogenesis of MASH [410].

As mentioned before, the group of CD4+ve T lymphocytes includes different subgroups without a uniform behavior in liver fibrosis.

T helper 1 (Th1) cells are pro-fibrotic, producing cytokines such as IFN-γ, IL-2, and TNF-a [413]. An indirect support for the role of Th1 cells in liver fibrosis came from an INFγ knockout murine model of MASH, where the attenuation of fibrosis was observed [414]. These results are in line with the clinical observations that MASH patients have increased hepatic IFNγ-producing CD4+ve T cells [415,416].

Th2 cells are anti-inflammatory, eliciting a protective immune response [417]. Th2 cells produce cytokines such as IL-4, IL-5, and IL-13 [418,419]. Increased serum levels of IL-13, accompanied by the increased hepatic expression of its receptor IL-13Ra2, were reported in MASH patients. Moreover, the IL-13-mediated killing of IL-13Ra2+ve cells suppressed liver fibrosis in a rat model of MASH, supporting the involvement of the IL-13/IL-13Ra2 pathway in MASH [420]. Paradoxically, the administration of IL-33 increased liver fibrosis in a murine model of MASH, despite the fact that IL-33 promotes a Th2 response [421].

Th1 and Th2 cells communicate with LSECs through different adhesion molecules to exert opposite effects in liver fibrosis. The interaction of Th1 cells and LSECs facilitates the reduction in LSEC fenestrae and increases LSEC angiogenesis, finally aggravating liver fibrosis, while the interaction of Th2 cells and LSECs attenuates fibrosis [422,423].

TGF-β and IL-6 are the mediators of the differentiation of T cells into Th17 cells [179,424]. The IL-17 cytokine family consists of six members, namely IL-17A-F [425]. Murine Th17 cells have strong pro-fibrogenic and pro-inflammatory potentials [183,426–428]. Th17 cells can trigger hepatic inflammation possibly due to the recruitment of macrophages by the IL-17-dependent upregulation of the chemokine CXCL10 [429,430]. However, the role of Th17 cells in liver fibrosis is not clear. There are reports supporting the pro-fibrotic potential of IL-17 [417,431–433]. Other studies support an opposite effect after blocking IL-17 [429,434]. Th17 cells play a crucial role in inflammation, hepatic fibrosis, and HCC development. Th17 cells secrete IL-17 in the presence of IL-6, IL-1β, IL-12, and IL-23, acting through binding to its receptor [435]. Almost all liver cells including hepatocytes, HSCs, BECs, KCs, and LSECs express IL-17R [436]. Moreover, Th17 cells also secrete IL-22 and granulocyte macrophage colony-stimulating factors. These cytokines increase the production and recruitment of neutrophils. Increased numbers of Th17 cells in HBV patients are associated with fibrosis and cirrhosis [437,438]. IL-17 activates MDCs and monocytes to release inflammatory cytokines and recruit neutrophils to the liver [439]. Moreover, there is a negative correlation between disease severity and the methylation level of the IL-17 promoter [440]. The Th17/Treg cell ratio increases and positively correlates with liver injury in patients with a chronic HBV infection [441].

T helper 22 cells are characterized by the production of IL-22 in the absence of IL-17 [442]. The differentiation of the Th22 cell is mediated by IL-6 and TNFa and is inhibited by TGF-β. Evidence supports an anti-fibrotic effect for IL-22 that would be beneficial

in MASH [443,444]. However, there is a concern that IL-22 treatment may be a risk for hepatocellular carcinoma development through the activation of STAT3 [445].

There is an interaction of the different cytokines produced by several sources in the modulation of liver fibrosis [446]. For example, the pro-fibrotic cytokine IL-17A was also produced by neutrophils and mast cells [427,447,448]. Th17A promotes the secretion of TGF-β but also promotes the expression of TGF-βRII on fibroblasts, therefore increasing the effect of TGF-β [426,428,449], a similar effect with the Th17-associated cytokine IL-22 [447]. TGF-β in turn induces the expression of IL-17A in collaboration with the IL-1, IL-6, or TNFa [450]. The cytokines IL-4 and IL-13 are also important inducers of fibrosis in association with an eosinophil and M2 macrophage environment [451]. IL-13 induces the production of TGF-β by macrophages [452], but it may increase fibrosis independently of TGF-β [452,453] by a direct effect on myofibroblasts [454].

One should remember that the immune mechanisms of liver fibrosis vary according to the underlying etiology, and results are often contradictory. T cells are no exception. Thus, in MAFLD, activated NK cells attenuate fibrosis progression [455–457]. Single-cell transcriptome analysis showed that CD4+ve T cells, CD8+ve T cells, and γδ T cells are increased in the liver with MASH [458]. Alcohol exposure impairs the balance between different T cell subpopulations, leading to a reduction in naïve CD4+ve T cells and CD8+ve T cells [459]. CD8+ve T cell activation and infiltration are considered as the effector mediators of bile duct damage in PBC. Research has demonstrated that specific cytotoxic CD8+ T cells are indeed increased in PBC patients [460,461]. A comprehensive review on the role of Th cells in liver fibrosis has been recently published [430].

One of the most important players in the process of inflammation and fibrosis is a subset of CD4+ve cells originating from the thymus and peripheral organs that are called ***regulatory T cells (Tregs).*** They suppress the proliferation and activity of CD4+ve and CD8+ve T cells through co-inhibitory molecules such as the cytotoxic T lymphocyte antigen 4 (CTLA-4) or by secreting suppressor cytokines such as IL-10 and TGF-β [462,463]. Tregs express the transcription factor Fork head box protein 3 (FOXP3). Within the liver, both myeloid and plasmacytoid HDCs are responsible to transform naive CD4+ve T cells into Tregs by expressing the membrane checkpoint programmed cell death 1 ligand 1 (PD- L1) and by releasing IL-10 and kynurenine [462].

In hepatic steatosis, increased oxidative stress leads to the apoptosis and reduction in hepatic Treg cells, and leads to a lowered suppression of inflammatory responses [464]. Moreover, Tregs were reported to be more sensitive to apoptosis in steatohepatitis [412]. Decreased numbers of hepatic Tregs were described in the animal models of MAFLD [411,464–466]. An additional explanation is that in fatty livers, adipokines affect Treg cells. Increased leptin production from adipose tissue reduces Treg differentiation, stimulating dendritic cells to polarize CD4+ve cells into Th1 and Th17 cells instead of Tregs [467]. In disagreement with these findings, a recent study found increased numbers of Tregs in the livers of high fat- and high carbohydrate-fed mice. Moreover, the elimination of Tregs inhibited the progression of MASH [468]. In another model of MASH, increased intrahepatic Tregs were found, but when Tregs were transferred, they aggravated MASH, indicating that Tregs increase the metabolic inflammation [469]. In the bile duct ligation model, the elimination of Tregs aggravated liver fibrosis in association with the decreased production of IL-10 [470]. However, Tregs also secrete TGF-β, a well-known promoter of liver fibrosis [142]. To make things more complicated, Tregs were increased in chronic HCV and repressed liver fibrosis [471] but promoted fibrosis in another study of chronic HCV [472]. Despite these contradictory findings, most available evidence indicates that Treg cells are anti-fibrotic, secreting the immunosuppressive IL-10 [419]. An earlier study may offer some explanation. In chronic HBV, it is the significance of the balance between

Tregs and Th17 cells that is important and not the absolute number of the individual cells. Both Tregs and Th17 cells in the peripheral blood were increased, but it was the ratio of Treg/Th17 that was correlated with liver fibrosis. Moreover, experiments with isolated human HSCs indicated that Tregs from HBV patients inhibited the activation of HSCs, while recombinant IL-17 increased HSC activation [473].

Tregs are increased during persistent HBV infection [474], downregulating the effector T cells and recruiting innate immune cells to the infected liver, leading to incomplete viral clearance. IL-1β upregulates Treg activation and produces inhibitory cytokines such as IL-10, IL-35, and TGF-β, which are key mediators of Treg function. IL-10 inhibits host anti-HBV activity, leading to the increased replication of HBV. Increased IL-10 levels are correlated with HBV DNA and liver inflammation [475]. HLA-DQ promotes the suppressive function of Tregs [476], while decreased PD-1 expression mitigates the immunosuppressive ability of Tregs and promotes the antiviral activity of effector T cells [477].

HBsAg-specific Tregs intervene with Tfh-dependent HBsAb dysregulation by limiting the differentiation of HBsAg-specific Tfh cells, resulting in insufficient HBsAb production [478]. Tfh cells are implicated in B cell response. They participate in the development of germinal centers from which high-affinity memory B and long-lived plasma cells originate. B cells and plasma cells are required for a protective antibody response [479].

IL-35 is mainly secreted by regulatory T cells and regulatory B cells, which contribute to immune tolerance and viral persistence during chronic HBV infection [480]. IL-35 modulates CD4+ and CD8+ T cells, and induces immunosuppression in chronic HBV infection and non-viral hepatitis-related HCC [481,482]. IL-35 increases PD-1 expression through the JAK1/TYK2/STAT1/STAT4 pathway [483].

In summary, it is clear that Tregs are implicated in the development of liver fibrosis. Tregs activity may either be protective or promotive at different stages of fibrosis development or at different combinations with other interleukins, acting as a two-edged sword. Signaling through the mammalian target of the rapamycin (mTOR) pathway is involved in the protective function of Tregs [484].

Liver B cells are also involved in the immunological response during liver fibrosis through the production of antibodies and the presentation of antigens [485]. It seems that B cells favor the induction and progression of liver fibrosis [484], but most data are derived from pulmonary fibrosis. However, the elimination of B cells attenuated CCl4-induced fibrosis progression in mice [486], while B cell accumulation in the livers of MASH patients correlates to hepatic inflammation and fibrosis [487].

A particular subset of B cells are the ***B regulatory cells***. Bregs in patients with CHB are high, reaching a peak at the immune-active stage. There is a negative correlation with the levels of IL-17 and IFN-γ-secreting Th1 and Th17 cells and CD8+ cells, and a positive correlation with IL-4-producing Th2 cells [488,489]. Bregs can dysregulate T cell function through IL-10, TGF-β, and IL-35. IL-35 levels correlate with the deterioration of liver cirrhosis. The progression of inflammation favors the elevation of Bregs to prevent excessive immune responses, but this may prove detrimental contributing to the persistence of HBV [480,490,491].

Table 2 presents a synopsis of cytokines involved in immune responses in liver diseases.

Table 2. A synopsis of cytokines involved in immune responses in liver diseases.

Cytokines	Functions	References
TNF-α	Inhibit HBV replication, provide antiviral immunity, induce inflammation.	[432,461]
TGF-β	Impair NK cell function, promote fibrosis and HCC.	[131,132,177]
IL-10	Inhibit cytokine production, regulate T cell immunity, develop persistence of HBV infection.	[481,482,484]
IL-13	Induce inflammation, liver fibrosis. and cirrhosis.	[471,472]
IL-6	Produced by macrophages. Induce inflammation and fibrosis. Inhibit HBV replication; inhibits HBV entry.	[200,202,203]
IL-18, IL-1β	Pro-inflammatory. Activate HSCs. IL-1β induces the phosphorylation of Smad2/3 to promote the transformation of hepatocytes to EMT. IL-18 rs187238 GG genotype increases the risk of HCC in a healthy population and the risk of cirrhosis in CHB carriers.	[137,199,202]
IL-17	Exacerbate inflammation, induce liver fibrosis and cirrhosis.	[436,450,451]
IL-21	Produced by activated CD4+ T cells. Activate T and B cells. Maintenance of specific CD8+ T-cell functions and control of viremia. Increased levels may promote cirrhosis and exacerbate liver injury.	[424]
IL-22	Inhibit liver inflammation and fibrosis.	[462,463]
IL-27	Higher levels in patients with liver cirrhosis or hepatocellular carcinoma. Compensate the function of IL-21 by supporting Tfh-B cell function, required for protective antibody response.	[424]
IL-33	Induce liver damage and fibrosis, activate Tfh cells, and enhance humoral immunity; suppress HBV replication.	[426,433,440]
IL-35	Development of fibrosis, cirrhosis, and HCC. Inhibit HBV-specific CD8 T cells cytotoxicity. Inhibit cytokines and induce antiviral immunity.	[492–494]
IFN-γ	Antiviral immunity. Inhibit HBV replication; induce inflammation.	[432,434]

3.5. Unconventional T Cells

They are a heterogeneous group of lymphocytes belonging to the immune system of the liver. The better-studied subpopulations of unconventional T cells include mucosal-associated invariant T (MAIT) cells, γδ T cells, and NKT cells. In the peripheral circulation, they represent almost 10% of T cells. In the liver, however, they are the majority of T cells [379,495]. There are plenty of MAIT cells in the human liver (15–45% of the total T cells), but they are scarce in the liver of mice. On the other hand, invariant NKT (iNKT) cells are <1% of the total T cells in the human liver as opposed to 30–50% in the murine liver [68]. From a functional point of view, NKT cells can be considered as the murine equivalent of human MAIT cells [496].

NKT cells are subdivided into type I NKT (iNKT) cells and type II NKT cells [497], with the former being important in the pathogenesis of several liver diseases [367,498]. In HBV-related cirrhosis, peripheral iNKTs are over-activated and may be partly responsible for the progression of fibrosis [499]. High cholesterol uptake destroys the function of NKT cells through lipid oxidation during the evolution of MAFLD toward cirrhosis. At the early stages of MASH, a reduction in NKT cells has been reported, while in advanced MASH, NKT cells are anti-fibrotic [500,501]. Patients with PBC have increased numbers of Il-17A-producing iNKT cells. The levels of 17A correlate with fibrosis severity [492]. However, this suggestion has been recently disputed in a murine model of PBC, where it was IL-21 and not IL-17A that was associated with disease progression [502]. But again,

one should remember the differences in liver NKT cells between humans and mice in every effort to explain these differences.

γδ-T cells have a TCR with two γ and δ chains instead of α and β and comprise 15–25% of all intrahepatic T cells. They are mostly located in portal tracts and areas of bile duct fibrogenesis [493,495]. The activation of γδ T cells does not require an antigen presentation by MHC molecules in contrast to αβ T cells. Therefore, they are referred to as MHC-unrestricted, which may not be absolutely true as some targets of γδ-TCR include the class I MHC molecules [494]. These cells are IL17A producers [503]. γδ-T cells were increased in the liver of the murine models of MAFLD, and their deletion or depletion ameliorated steatohepatitis and accelerated damage repair [504,505]. Interestingly, the gut microbiota may act synergistically with γδ-T IL17+ve cells in disease progression [506]. In contrast to these findings, a transfer of normal γδ T cells ameliorated liver inflammation by increasing the apoptosis of activated HSCs in the methionine–choline-deficient diet of chronic liver disease [507].

Innate lymphoid cells (ILCs). They are subdivided into three groups based on cell surface markers, the transcription factors that regulate their function, and the production of characteristic cytokines [508]. ILC1s consist of IFNγ-producing cells, and they are T-bet dependent, while ILC2s express type 2 cytokines such as IL-5 and IL-13 and are dependent on GATA-binding protein 3 (GATA3) for their function. ILC3s produce IL-17 and IL-22 and depend on the transcription factor retinoic acid receptor-related orphan receptor γt (RORγt) for their function [508–511]. Recently, a revision has been proposed to include conventional NK (cNK) cells and lymphoid tissue-inducer cells [512,513]. An intrahepatic accumulation of ILC3 cells with pro-fibrotic activity was reported in the CCl4-induced liver fibrosis model. The transfer of ILC3s after the elimination of resident ILC3s increased ECM deposition and liver fibrosis, indicating a pro-fibrogenic role of ILC3 [119,510,512,514]. In addition, a positive relation between the severity of liver fibrosis and the proportion of intrahepatic ILC2 was described. The pro-fibrotic effect of ILC2 was mediated by the overproduction of IL-13, which in turn was induced by IL-33 production from hepatocytes and Kupffer cells [515].

Mucosal-associated invariant T (MAIT) cells in circulation vary between 1 and 10% of total T cells but in the liver may increase up to 45% of intrahepatic T lymphocytes [516]. In patients with either alcohol-related or MAFLD cirrhosis, circulating MAIT cells were reduced, but they were increased in the fibrous septa. Most MAIT cells (80%) from both healthy controls and cirrhotics were CD8+ve, while 20% were double negative (CD8−CD4−). In animal models, the enrichment of mice with MAIT cells promoted liver fibrosis. MAIT cells also enhanced the fibrogenic functions of MFs and MB-derived macrophages [517]. Decreased peripheral MAIT cells with an impaired production of IFN-γ and TNF-α were also described in MAFLD patients. MAIT cells were also increased in the liver and were positively correlated with MAFLD severity. But in contrast to the previous findings, a protective role of MAITs was suggested, as activated MAIT cells in vitro induced M2 macrophage phenotype, and in MAIT-deficient animals, steatosis and inflammation was aggravated [518].

3.6. Extrahepatic Factors

The first and most important extrahepatic factor that is implicated in inflammation and fibrosis is the lymphocyte and monocyte recruitment in the liver. This is dependent on an adhesion cascade influenced by intercommunications between parenchymal and non- parenchymal cells. An example is the liberation of DAMPs by damaged hepatocytes leading to the overproduction of pro-inflammatory mediators by Kupffer cells, which increase adhesion molecule expression by LSECs. Lymphocyte recruitment across activated

LSECs involves a firm adhesion on the LSEC surface. Lymphocytes then move along the luminal endothelium until a signal makes them migrate through LSECs through either a paracellular or a transcellular route. Chemotactic factors secreted from activated HSCs direct lymphocytes into the final position within the liver tissue [200].

The dysfunctional gut–liver axis is the second extrahepatic factor that is seriously involved in liver fibrosis. It leads to a "leaky gut" through which bacterial products obtain access to the portal blood and activate liver macrophages, leading to fibrosis. The intestinal barrier is the first line of defense against human intestinal microbiota. The translocation of bacteria is further inhibited by the junctional complex of the intestinal epithelium and by immune cells infiltrating the lamina propria. In gut dysbiosis, as found in chronic liver diseases, all these elements are compromised, allowing abnormal translocations to the liver [519,520]. Different receptors expressed in liver cells can discriminate between gut commensal and pathological antigens. When dangerous signals are detected, APCs, including hepatocytes, recruit immune cells to eliminate pathogen,s maintaining immune homeostasis. On the other hand, when the massive translocation of PAMPs and DAMPs from the impaired intestinal barrier reach the liver, tolerance is replaced by an inflammatory and fibrogenic microenvironment. Innate immunity has the leading role, while adaptive immunity may sometimes be protective. Most relevant research has been based on investigations contacted in relation to MAFLD/MASH [519,521,522]. Other extrahepatic factors include the regulation of liver immunity by other organs. Thus, the spleen affects the composition of liver immune cells. Spleen lipocalin-2 represses the macrophage-induced activation of HSCs. The lung may also affect liver immune regulation, possibly via TNFa modulation of the inadequately studied lung–liver axis. The role of adipose tissue has already been presented. Activated adipose macrophages can migrate to the liver in MASH. Finally, the brain regulates liver immune responses through the liberation of catecholamine and acetylcholine from efferent sympathetic and vagus nerve fibers. They respond to hepatic inflammatory signals transmitted to the central nervous system [523].

3.7. The Interaction of Innate and Adaptive Immunity

The extensive interaction between innate and adaptive immunity was already mentioned in the subchapters of individual cells. However, there are certain discrete bridges that mediate the interplay between innate and adaptive immunity in liver fibrosis.

A first bridge is the activation of γδT cells acting as a connecting point between the innate and adaptive immunity, as they express TCRγδ that recognizes antigens and also produce inflammatory cytokines such as IL- 17A after stimulation [524]. The second bridge of the interplay between innate and adaptive immunity became evident in MASH investigations. Lipid toxicity and oxidative stress damage the hepatocytes, as mentioned before. Both innate immune response and adaptive immunity contribute to MASH-associated inflammation. Innate immunity may lead to fibrosis via PRRs, including TLRs and NLPR3 inflammasomes, that recognize PAMPs and DAMPs. T cell-mediated adaptive immunity also promotes fibrosis in MASH via cytotoxicity and cytokines. KCs are the bridge between the innate and the adaptive responses here. The third bridge is provided by hepatocytes, which, in addition to their functions as innate cells, also express MHC-II molecules and co-stimulators, acting as atypical APCs to induce CD4+ve T cell activation and their Th1 or Th17 cell polarization [213]. IFNγ and other Th1 cell cytokines provide the fourth bridge, as they increase the stimulation of liver macrophages to release M1 pro- inflammatory cytokines and chemokines that further increase the recruitment of monocytes and lymphocytes. Macrophages and dendritic cells release B cell-stimulating cytokines, such as the B cell-activating factor (BAFF), which are fundamental for B cell maturation into plasma cells. The fifth bridge is the secretion by both the hepatocytes and macrophages of IL-15

that improves the survival of CD8+ve T cells and in association with CXCL16, promotes liver NKT cell survival [412,484,525].

Figure 2 summarizes the immune mechanisms implicated in liver fibrosis.

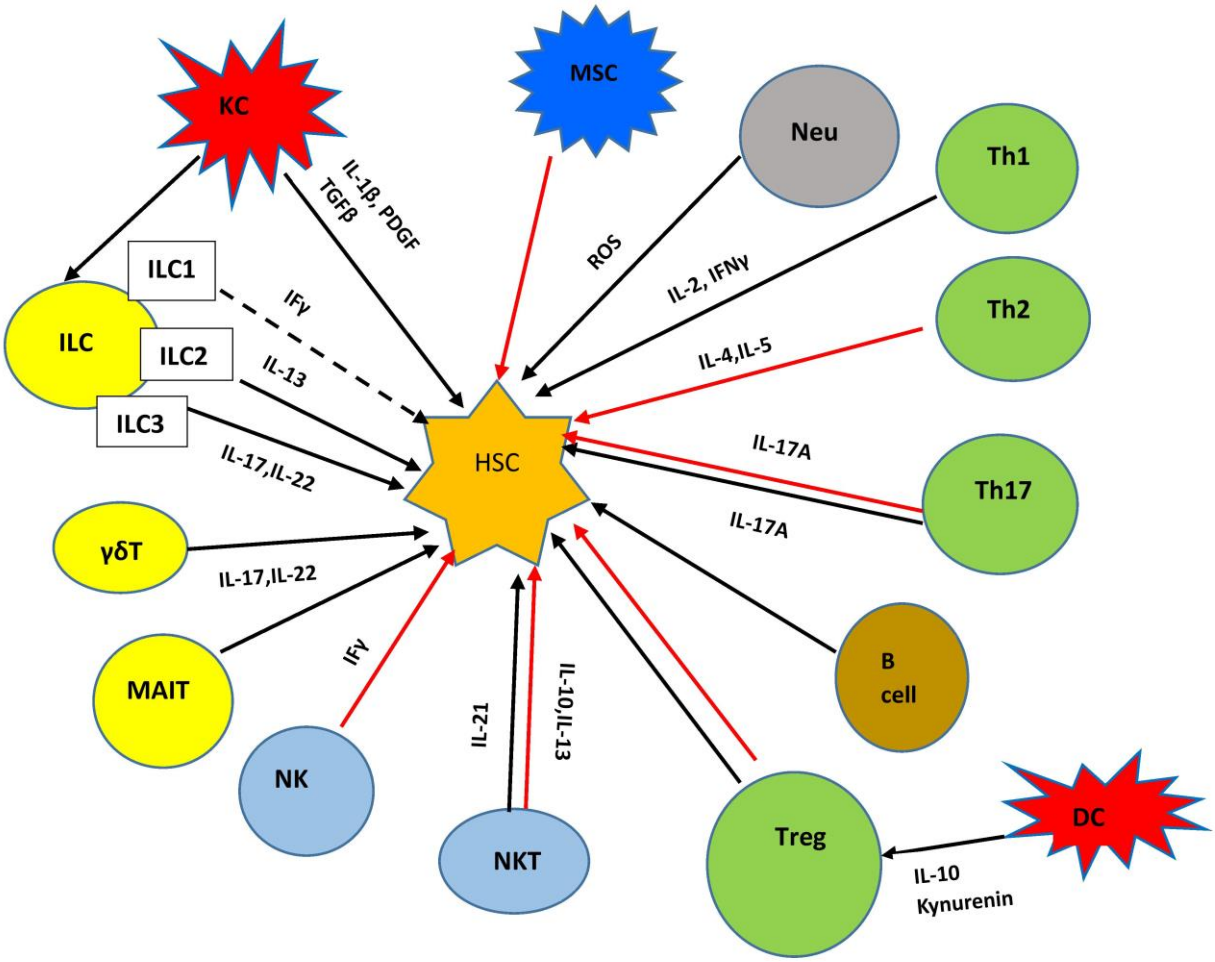

Figure 2. Immune cells and mediators involved in the pathogenesis of liver fibrosis. For details, see text. Black arrows: activation of HSCs. Red arrows: inhibition of HSCs. Dotted arrow: Not investigated. DCs: dendritic cells; ILCs: innate lymphoid cells; KCs: Kupffer cells; MAITs: Mucosal-associated invariant T cells; MSCs: Mesenchymal stromal cells; Neu: Neutrophils; ROS: reactive oxygen species.

4. Immune Checks in Liver Fibrosis

4.1. Immune Checkpoint

Immune checkpoint proteins (ICPs) have attracted extensive interest, as they are critical suppressors of the immune responses in a variety of tumors. However, they have a wider potential because they maintain immune tolerance in health by repressing T cell activation and proliferation [526–529]. ICPs which are expressed in tumor cells trigger the exhaustion, senescence, or apoptosis of effector immune cells [530,531]. The best-studied inhibitory immune checkpoints are CTLA-4, PD-1, and PD-L1. CTLA-4 is a molecule that is upregulated on the surface of activated T cells to break their over-stimulation by the TCRs. CTLA-4, also known as CD152, is a strong competitor of the TCR co-stimulatory molecule CD28 and binds to CD80 (B7-1)/CD86 (B7-2) with a stronger binding affinity compared to CD28, thus inhibiting T-cell activation [532]. CTLA-4 is mostly located in intracellular vesicles and is translocated to the cell membrane after T cell activation [533].

The upregulation of PD-1 has also been reported on activated T cells. PD-1 is mostly located at the membrane of cells [533] and binds to its ligand, PD-L1, transmitting inhibitory co-stimulatory signals that prevent T cell activation. The pro-oncogenic and immunosuppressive phenotype of the tumor microenvironment is characterized by the overexpression of PD-L1 by cancer cells and the overexpression of PD-1 and CTLA-4 by T cells [534,535]. Anti-PD-1 and anti-CTLA-4 monoclonal antibodies are two types of extensively used inhibitors of immune checkpoints (ICBs) [536].

PD-1 is expressed in several immune cells, including almost all subtypes of T cells, B cells, NK cells, macrophages, DCs, and monocytes [537–540]. High levels of PD-1 were an important characteristic of T cell exhaustion [537]. Resting effector T cells do not express PD-1, but after stimulation by antigens, there is a strong expression of PD-1 [541]. PD-1 downregulation follows the elimination of stimulation signals, otherwise the high levels are maintained [542]. Cytokines such as IL-10 and TGF-β also initiate the expression of PD-1 [543,544]. In addition, PD-L1 is induced by several inflammatory mediators such as IFN-γ, a fact that links PD-L1 expression with persistent inflammation [545,546]. The binding of PD-L1 to PD-1 inhibits the proliferation and differentiation of T cells into inflammatory populations, including Th1, Th2, and Th17 cells. This interaction also inhibits the function of CD8+ve cells. Moreover, this interaction upregulates the differentiation of T cells into Tregs [547].

CTLA-4 molecules were upregulated in CD4+ve and CD8+ve T cells in CHB according to recent studies, while the constitutive expression of CLTA-4 was reported in Tregs. CTLA-4 inhibition produced inconclusive results, as T cell proliferation and cytokine production were upregulated in some studies, while others confirmed this only after the inhibition of CTLA-4 in combination with other inhibitory receptors. CTLA-4 is also involved in T cell exhaustion in CHB, but the existing evidence is inadequate at this moment [548].

Macrophages are also modulated by ICPs. PD-1 expression in macrophages is negatively correlated with the presence of M1-polarized tumor-associated macrophages (TAMs) and their phagocytic capacity against tumor cells [549,550].

An important aspect of ICP function is the effect of post-translational modification by glycosylation. During glycosylation, glycan molecules are covalently attached to proteins or lipids by an enzymatic site-specific mechanism that affects the functions of ICPs such as biosynthesis and interactions [551]. No studies have addressed the significance of the glycosylation of ICPs in liver fibrosis and cirrhosis, but there is evidence that this may be important. Epithelial–mesenchymal transition (EMT) is a process that is involved in liver fibrosis, as mentioned before. The glycosylation of PD-1 has been studied in cancer stem cells, where the roles of EMT and N-glycosyl-transferase STT3 were explored. EMT upregulated PD-L1 expression in cancer stem cells by the EMT/β-catenin/STT3/PD-L1 signaling axis. The elimination of both STT3 isoforms suppressed EMT-mediated PD-L1 induction [552].

4.2. Association of Immune Checkpoints with Liver Fibrosis

4.2.1. The PD-1/PD-L1 Axis and CTLA-4

In recent years, the role of the PD-1/PD-L1 axis in liver fibrosis has attracted attention, but the data are still scarce and not conclusive. Most data are coming from the fibrosis progression in other organs, mainly the lung. However, they confirm that a close relationship exists between PD-1/PD-L1 signaling and liver fibrosis. The PD-1/PD-L1 interaction increases fibrosis by promoting important fibrogenic mechanisms such as macrophage polarization, T cell activation, and the trans-differentiation of epithelial cells. The upregulation of PD-L1 induces EMT, and signals that initiate EMT can also promote the expression of PD-L1, creating a positive loop [553]. Recent data indicated that an immune dysregulation

of the PD1/PD-L1 immune checkpoint may be implicated in liver fibrosis [554]. There is evidence that PD-L1 inhibitors, such as pembrolizumab and nivolumab, used to treat several cancers, have a potential effect on fibrosis treatment as they reduce fibroblast activation and ECM deposition [555]. Murine studies reported that the Golgi membrane protein 1 (GOLM1) is highly upregulated in carbon tetrachloride-induced liver fibrosis. GOML1 triggered PD-L1 expression and increased fibrosis by activating the EGFR/AKT/STAT3 signaling pathway [556]. The above data indicate that the PD-1/PD-L1 signaling favors the progression of liver fibrosis. On the other hand, reports have suggested that the indirect activation of PD-L1 signaling attenuates liver fibrosis [557].

Blocking PD-L1 inhibits the production of IL-10 and differentiation into Tregs and restores in part the function of CD4+ T cells [558] and HBV-specific CD8 T cells [559]. Continuous HBsAg and HBeAg exposure led to the exhaustion of many CD8+ve T cells and a gradual upregulation of PD-L1 and CTLA-4 expression. PD-1 inhibition alone could not completely restore the exhaustion, which was achieved only after a combined PD-1/CTLA-4 inhibition [559,560]. Interestingly, lower TLR2+ve monocytes and increased PD1 + CD8 + T cell proportions may contribute to viral breakthrough (VBT) in HBV patients switched to IFNa after the failure of nucleoside/tide (NUC) analogs. The combination of TLR2 activation and the PD1/PDL1 pathway blockade may repress HBV replication and prevent VBT through increased cytokine production and the recovering of CD8 T-cell function [561]. PD-L1 antagonists may block HBV replication by initiating cytokine production and by promoting the cytotoxic effects of CD8+ T cells, mostly in patients with low HBV DNA and negative HBeAg [562].

The investigation of specific disease entities offered more evidence that ICPs are implicated in liver fibrosis. In acute viral hepatitis, PD-1 and CTLA-4 are increased during the symptomatic phase, and decreased during recovery. PD-1 and CTLA-4 have protective effects as inhibitory molecules to stop the destruction by cytotoxic T cells in self-limited viral hepatitis. In HBeAg-negative chronic asymptomatic HBV carriers, ICPs are highly expressed on Th1, Th2, Th17, and Tregs [439,563].

Moreover, in chronic HCV, hepatocytes express high levels of PD-L1, leading to the generation of Tregs and follicular regulatory T cells and the liberation of extracellular vesicles rich in TGF-β [564]. The T cell response to chronic infection is suppressed, and liver fibrosis is promoted [565]. In addition, PD-L1 expression mediates the transformation of M2 macrophages in liver fibrosis [566]. A recent clinical study demonstrated that serum PD-1 levels were higher in patients with HCV infection compared to normal controls and gradually increased along with the severity of liver fibrosis [567]. In another clinical study, peripheral blood and splenic CD4+ve and CD8+ve T-cells expressed higher levels of PD-1, mucin domain-containing protein 3 (Tim-3), and CTLA-4 in HCV patients with cirrhosis and portal hypertension compared to normal [568].

Investigations in other organs confirm the association of checkpoints with the process of fibrosis. Several findings link the PD-1/PD-L1 axis with idiopathic pulmonary fibrosis (IPF), as abnormalities of this axis were reported in many cells implicated in IPF pathogenesis [569]. Interestingly, a recent report indicated that anti-PD-L1 antibodies mitigated the ECM deposition of TGF-β1-induced lung fibroblasts by downregulating the PI3K/Akt/mTOR signaling pathway, which is critical in autophagy regulation [570]. These findings are important as the mechanism of PD-L1 in hepatic fibrosis has many similarities with pulmonary fibrosis, mainly in connection with EMT induction in the lung and the liver. PDL1 can induce the production of TGF-β in liver fibrosis. In agreement with pulmonary fibrosis, EMT pathways involving TGF-β, such as Smad and PI3K/AKT, are also active in liver fibrosis [156,571–573]. PDL1 also activates HSCs, leading to the production of several factors involved in hepatic fibrosis, as presented above [574]. Finally, PD-L1 favors the

transformation into M2 macrophages, which in turn suppresses E cadherin and increases vimentin in hepatocytes, thus promoting EMT [575] in direct analogy with drug-induced pulmonary fibrosis, where the upregulation of PD-L1 promoted fibrosis through the inhibition of vimentin degradation [576]. Mechanistically, PD-L1 directly upregulated the serum and glucocorticoid kinase 2 (SGK2) and activated the SGK2/β-catenin signaling pathway to induce EMT and the transformation of liver cancer cells into a stem cell phenotype [577].

However, there are differences between liver and pulmonary fibrosis. PD-L1 on liver fibrosis is mostly immunomodulatory. Thus, in an earlier paper on chronic persistent HCV disease, it was demonstrated that HCV-specific CD8 T cells from the liver expressed high levels of PD-1 and a significant impairment of their function. CTLA-4 was also upregulated in PD-1+ve T cells from the liver but not from the blood of persistently infected HCV patients. Interestingly, the impaired function of CD8+ve cells was synergistically reversed by a combined PD-1/CTLA-4 blockade, but not by blocking PD-1 or CTLA-4 alone, indicating that both PD-1 and CTLA-4 pathways participate in the virus-specific T cell exhaustion in chronic HCV [578]. Although reported data suggests a similar role of CTLA-4 in T cell exhaustion, the documentation is weak to support the role of CTLA-4 in T cell exhaustion in chronic HBV infection, as mentioned above [548].

Another approach to clarify the role of ICPs in liver fibrosis is to delineate the association of ICPs with the functions proved to participate in the fibrotic process. ICPs are implicated in the function of critical cells in the regulation of liver fibrosis such as MCS, macrophages, and HSCs.

Thus, PD-L1 expression is involved in the immunomodulation mediated by the mesenchymal stromal/stem cells (MSCs) as well. PD-L1 on the surface of MSCs interacts with PD-1 on the surface of T cells through direct cell-to-cell communication, inhibiting the functions of T cells. PD-L1 may also be secreted, inhibiting T cell function without the close contact of cells. MSCs may transfer PD-L1 in extracellular vesicles, again affecting T cells from a distance. Signal transmissions from MSC PD-1 create a positive loop, enhancing their immunomodulatory potential. On the other hand, anti-PD-L1 antibodies can reduce immunomodulation mediated by MSCs [579].

Further immunomodulation by IPCs in liver fibrosis may be mediated via PD-1 induction in monocytes and macrophages through TLR signaling and cytokines such as TNF-α, IL-1β, and IL-6 [580,581]. Furthermore, PD-1 expression in macrophages may repress innate inflammatory responses [582,583]. PD-L1 activation sends negative signals to macrophages, inducing an immunosuppressor cell phenotype [584]. The overexpression of PD-L1 in macrophages and peripheral monocytes has been demonstrated in chronic viral infections in the liver [232,585]. A study of patients with cirrhosis showed that liver macrophages overexpressed the immune-suppressive proteins PD-L1, MARCO, and CD163. Monocytes from patients also overexpressed PD-L1, which was related to disease severity and the presence of infections. A blockade of PD-L1 with anti-PD- L1 antibodies restored liver macrophage functions [267]. These findings have been confirmed in an acetaminophen-induced acute liver injury murine model. Reduced bacterial clearance by KCs expressing PD-1 was observed during liver injury. During resolution, KCs expressed higher levels of PD-1 and lymphocytes expressed higher levels of PD-L1. The suppression of PD-1 expression by anti-PD-1 improved KC bacterial clearance. Increased PD-1 expression in monocytes and increased PD-L1 expression in lymphocytes of peripheral blood were found in patients with acute liver failure. Moreover, PD-L1 plasma levels were positively correlated with sepsis and mortality. Interestingly, PD-1 in vitro blockade restored monocyte functionality [586,587].

Activated hepatic stellate cells from human livers induce the apoptosis of activated T cells through the expression of PD-L1. Human HSCs have strong immunoregulatory

activity via the B7-H1-mediated induction of apoptosis in activated T cells [588]. Murine HSCs suppressed the upregulation of activation markers on B cells together with the repression of their proliferation and their cytokine production. Interestingly, the elimination of the interaction of PD-L1 with PD-1 decreased the ability of HSCs to suppress B cell activation [306]. Several recent reports have clearly demonstrated that senescent HSCs display an increased expression of PD-1/PD-L1 proteins. An increase in the level of the PD-L1 protein in senescent cells is able to suppress their immune surveillance and inhibit their elimination by cytotoxic CD8+ve T cells and NK cells [186,589–592]. ICPs also affect TGF-β function. PD-L1, produced by HSCs, is necessary for HSC activation by protecting the two TGF-β receptors from degradation. The extracellular domain of PD-L1 protects the TβRII protein, while the 260-RLRKGR-265 motif on PD-L1 protects the TβRI mRNA [593].

4.2.2. Other ICPs Involved in Liver Fibrosis

Apart from the better-studied PD-1/PD-L1 and CTLA-4, additional ICPs have the potential to be involved in fibrosis, although the data are inadequate.

The B7 homolog 3 protein (B7-H3), also designated as CD276, is a critical ICP of the B7 immunoglobin superfamily [594]. B7-H3 is expressed on APCs and is involved in T-cell-mediated immunity. The aberrant expression of B7-H3 in several cancers is associated with a poor prognosis and increased angiogenesis [595]. B7-H4 is also a member of the same B7 superfamily. It was also found on professional APC, preventing T cell activation and was also associated with poor prognosis [596,597].

ICPs such as LAG-3, TIM-3, and CD39 on CD8+ve T cells were increased in patients with chronic HBV. The ability of CD8+ve cells to secrete TNFa, IFNγ, and perforin was downregulated [598]. TIM-3 levels positively correlated with HBV DNA levels [599]. Lymphocyte activation gene 3 (LAG-3), also designated as CD223, has been a promising target in the treatment of hepatocellular carcinoma (HCC). In patients with HCC, LAG-3 expression in Tregs and NK cells is implicated in tumor immune evasion by interacting with MHC-II molecules. Its overexpression is associated with T cell exhaustion in synergy with PD-1 and increased angiogenesis [600].

The increased expression of TIM-3 and galectin-9 also led to the inhibition and apoptotic deletion of T cells. Th cells expressing TIM-3 have a limited production of IFN-γ and TNF-α after the recognition of HBV peptides and are sensitive to galectin-9-initiated cell death. The expression of TIM-3 on peripheral T cells parallels disease progression and markers of liver damage including increases in ALT, AST, bilirubin, and international normalized ratio (INR) [600]. The inhibition of TIM-3 initiated the proliferation of HBV-specific CD8 T cells and upregulated antiviral cytokine secretion [601].

Kynurenine (Kyn) is another important IPC modulator of immune responses via its aryl hydrocarbon receptor (Ahr). For Kyn synthesis, two enzymes are implicated, the indoleamine 2,3-dioxygenase (Ido) and the tryptophan 2,3-dioxygenase (Tdo). Ido is responsible for 90% of tryptophan catabolism. Although Kyn is increased in various liver disorders, the exact involvement of Kyn in liver damage has not been clarified as Ido1, Ido2, and Tdo are activated in several cell types. However, Ido1 deficiency aggravated liver fibrosis in the CCL4-induced liver injury murine model [602]. Moreover, liver fibrosis in the same model was mitigated in Ido2−/−, indicating that the inhibition of kyn or ido 2 may ameliorate hepatic fibrosis [603].

4.3. Therapeutic Implications of Checkpoint Inhibitors in Liver Fibrosis

Despite the increasing evidence that checkpoint inhibitors are involved in the regulation of inflammation and liver fibrosis, there are very few clinical data and some experimental observations on their use in these two conditions.

A blockade of inhibitory checkpoints including PD-1, CTLA-4, 2B4, TIM-3, and galectin-9 alone or in combination has emerged as a potential therapeutic approach to restore T and B cell functions in CHB [478,558,604–607]. In studies of HBV-infected mice and blood from patients with a chronic HBV infection, a Tfh cell response to HBsAg was required for HBV clearance, and this response was blocked by Treg cells. Inhibiting Treg cell activity using neutralizing antibody against CTLA4 restored the ability of Tfh cells to clear HBV infection. This approach might be used in future clinical trials for the treatment of patients with chronic HBV infection [478].

However, there are sufficient data from the extensive use of ICPs in the treatment of HCC. It is known that the great majority of HCC cases have a background of fibrosis and cirrhosis. Therefore, data on HCC treatment may offer an overview of the use of these drugs in advanced liver disease. The results of clinical trials for HCC may be extrapolated in the future treatment of liver fibrosis, at least as far as safety is concerned.

The published results of anti-PD1/PD-L1 monotherapy for HCC with nivolumab, pembrolizumab, durvalumab, and camrelizumab indicate a non-impressive overall survival of 13.2–16.9 months. More favorable were the results of the combinations of ICPs with tyrosine kinase inhibitors. Atezolizumab, a PD-L1 inhibitor, combined with bevacizumab showed a 56% reduced risk of death compared to sorafenib. Camriezumab combined with alpatinib had an overall survival of 22.1 months compared to 15.2 months for sorafenib [608]. The Himalaya trial evaluated the STRIDE regimen consisting of a single dose of tremelimumab with a dose of durvalumab every 4 wks. A significant but again not impressive increase in overall survival of 16.4 months vs. 13.8 months for sorafenib was reported [609]. Other combination treatments of anti-PD-1 with ipilimumab and tremelimumab (CTLA-4 IPCs inhibitors) are in progress [610].

Interestingly, a systematic review of systemic therapies in HCC from 2002 to 2020 revealed that immunotherapies were more effective in viral etiologies as compared to non-viral etiologies, possibly because the immune responses are more vigorous in viral infections compared to non-viral etiologies [611].

An additional interesting approach was recently reported. Coagulation factor Xa (FXa) and its receptor proteinase-activated receptor-2 (PAR-2) promote tumor metastasis in several forms of cancer. The combination of the anti-coagulation drug rivaroxaban and an anti-PD-1 antibody induced synergistic antitumor effects in experimental models. Most importantly, rivaroxaban improved the objective response rate of HCC patients and prolonged the overall survival time [612].

Whatever the survival benefits might be, adverse events (AEs) do happen, including immune-related adverse events (irAEs) such as rash and pruritus, diarrhea and colitis, hypothyroidism and hypophysitis, pneumonitis, and psychiatric disorders [613,614]. The reactivation of HBV has also been observed [615]. ICP inhibitors combined with angiogenesis inhibitors may reduce incidence and mortality for most irAEs [616].

5. Conclusions

Liver fibrosis is the end result of almost all chronic liver diseases. However, the underlying mechanisms are different in many respects according to etiology. There has been great progress in the cellular and molecular biology of liver fibrosis, and it is now accepted that the sinusoids are a fundamental field in fibrosis induction and progress. Kupffer cells and the hepatic stellate cells are the most important cells of innate immune response implicated in fibrosis. They are the masterminds of the immune regulation of fibrosis as they interact with each other, assisted by other immune cells such as lymphocytes and liver endothelial cells. Kupffer cells are implicated in the activation of HSCs that in turn are the producers of ECM through a complex network of cytokines and chemokines. At the same

time, both Kupffer cells and HSCs are responsible for the resolution of fibrosis through a network of inhibitory cytokines and the production of degrading metalloproteases. It is also well documented that adaptive immunity and its very many cells are critical components in the regulation of fibrosis as are cells of an intermediate nature such as MAIT cells and γδ T cells that interact with elements of both innate and adaptive immunity. Recently, a hotspot of research is the role of the immune checkpoints (ICPs), as they are the main controllers of the excessive immune responses, and their inhibition is currently in clinical use in an effort to overcome the immune evasion masterminded by several cancers. There is increasing evidence that ICPs are involved in the regulation of liver fibrosis; therefore, a new chapter in anti-fibrotic therapy may start as many new ICPs are described and the role of the better-studied PD-1/PD-L1 and CTLA-4 is intensively researched. They are effective in non-fibrotic viral liver disease as well, but their application will be limited. The current antivirals are very effective and more cost-efficient, and it is not reasonable to replace them. There are sufficient data on the safety of ICP inhibitors, alone or in combination with other drugs, from extensive trials on the treatment of HCC, indicating that trials on the treatment of liver fibrosis are justified, and possibly a new era on immunotherapy of this difficult-to-treat liver disease is ahead.

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References

1. Kisseleva, T. The origin of fibrogenic myofibroblasts in fibrotic liver. *Hepatology* **2017**, *65*, 1039–1043. [CrossRef] [PubMed]
2. Higashi, T.; Friedman, S.L.; Hoshida, Y. Hepatic stellate cells as key target in liver fibrosis. *Adv. Drug Deliv. Rev.* **2017**, *121*, 27–42. [CrossRef] [PubMed]
3. Koyama, Y.; Brenner, D.A. Liver inflammation and fibrosis. *J. Clin. Investig.* **2017**, *127*, 55–64. [CrossRef]
4. Ginès, P.; Krag, A.; Abraldes, J.G.; Solà, E.; Fabrellas, N.; Kamath, P.S. Liver cirrhosis. *Lancet* **2021**, *398*, 1359–1376. [CrossRef]
5. Devarbhavi, H.; Asrani, S.K.; Arab, J.P.; Nartey, Y.A.; Pose, E.; Kamath, P.S. Global burden of liver disease: 2023 update. *J. Hepatol.* **2023**, *79*, 516–537. [CrossRef]
6. Moon, A.M.; Singal, A.G.; Tapper, E.B. Contemporary Epidemiology of Chronic Liver Disease and Cirrhosis. *Clin. Gastroenterol. Hepatol.* **2020**, *18*, 2650–2666. [CrossRef]
7. Ye, F.; Zhai, M.; Long, J.; Gong, Y.; Ren, C.; Zhang, D.; Lin, X.; Liu, S. The burden of liver cirrhosis in mortality: Results from the global burden of disease study. *Front. Public. Health* **2022**, *10*, 909455. [CrossRef]
8. Jepsen, P.; Younossi, Z.M. The global burden of cirrhosis: A review of disability-adjusted life-years lost and unmet needs. *J. Hepatol.* **2021**, *75*, 3–13. [CrossRef]
9. Smith, A.; Baumgartner, K.; Bositis, C. Cirrhosis: Diagnosis and Management. *Am. Fam. Physician.* **2019**, *100*, 759–770.
10. Alberts, C.J.; Clifford, G.M.; Georges, D.; Negro, F.; Lesi, O.A.; Hutin, Y.J.; de Martel, C. Worldwide prevalence of hepatitis B virus and hepatitis C virus among patients with cirrhosis at country, region, and global levels: A systematic review. *Lancet Gastroenterol. Hepatol.* **2022**, *7*, 724–735. [CrossRef]
11. Dobosz, P.; Dzieciątkowski, T. The Intriguing History of Cancer Immunotherapy. *Front. Immunol.* **2019**, *10*, 2965. [CrossRef] [PubMed]
12. Kroemer, G.; Zitvogel, L. Immune checkpoint inhibitors. *J. Exp. Med.* **2021**, *218*, 20201979. [CrossRef] [PubMed]
13. Zhang, Y.; Zheng, J. Functions of Immune Checkpoint Molecules Beyond Immune Evasion. *Adv. Exp. Med. Biol.* **2020**, *1248*, 201–226.

14. Pinheiro, D.; Dias, I.; Ribeiro Silva, K.; Stumbo, A.C.; Thole, A.; Cortez, E.; de Carvalho, L.; Weiskirchen, R.; Carvalho, S. Mechanisms Underlying Cell Therapy in Liver Fibrosis: An Overview. *Cells* **2019**, *8*, 1339. [CrossRef]
15. Bourebaba, N.; Marycz, K. Hepatic stellate cells role in the course of metabolic disorders development—A molecular overview. *Pharmacol. Res.* **2021**, *170*, 105739. [CrossRef]
16. Zhang, D.; Zhang, Y.; Sun, B. The Molecular Mechanisms of Liver Fibrosis and Its Potential Therapy in Application. *Int. J. Mol. Sci.* **2022**, *23*, 12572. [CrossRef]
17. Weiskirchen, R.; Weiskirchen, S.; Tacke, F. Recent advances in understanding liver fibrosis: Bridging basic science and individualized treatment concepts. *F1000Res.* **2018**, *7*, 921. [CrossRef]
18. Rockey, D.C.; Bell, P.D.; Hill, J.A. Fibrosis--a common pathway to organ injury and failure. *N. Engl. J. Med.* **2015**, *372*, 1138–1149. [CrossRef]
19. Gao, C.C.; Bai, J.; Han, H.; Qin, H.Y. The versatility of macrophage heterogeneity in liver fibrosis. *Front. Immunol.* **2022**, *13*, 968879. [CrossRef]
20. Zhao, Y.L.; Zhu, R.T.; Sun, Y.L. Epithelial-mesenchymal transition in liver fibrosis. *Biomed. Rep.* **2016**, *4*, 269–274. [CrossRef]
21. Park, J.H.; Park, B.; Park, K.K. Suppression of Hepatic Epithelial-to-Mesenchymal Transition by Melittin via Blocking of TGFβ/Smad and MAPK-JNK Signaling Pathways. *Toxins* **2017**, *9*, 138. [CrossRef] [PubMed]
22. Li, T.Z.; Kim, S.M.; Hur, W.; Choi, J.E.; Kim, J.H.; Hong, S.W.; Lee, E.B.; Lee, J.H.; Yoon, S.K. Elk-3 Contributes to the Progression of Liver Fibrosis by Regulating the Epithelial-Mesenchymal Transition. *Gut Liver.* **2017**, *11*, 102–111. [CrossRef] [PubMed]
23. Di Gregorio, J.; Robuffo, I.; Spalletta, S.; Giambuzzi, G.; De Iuliis, V.; Toniato, E.; Martinotti, S.; Conti, P.; Flati, V. The Epithelial-to-Mesenchymal Transition as a Possible Therapeutic Target in Fibrotic Disorders. *Front. Cell Dev. Biol.* **2020**, *8*, 607483. [CrossRef] [PubMed]
24. Rowe, R.G.; Lin, Y.; Shimizu-Hirota, R.; Hanada, S.; Neilson, E.G.; Greenson, J.K.; Weiss, S.J. Hepatocyte-derived Snail1 propagates liver fibrosis progression. *Mol. Cell Biol.* **2011**, *31*, 2392–2403. [CrossRef]
25. Zhang, J.; Zhang, H.; Liu, J.; Tu, X.; Zang, Y.; Zhu, J.; Chen, J.; Dong, L.; Zhang, J. miR-30 inhibits TGF-β1-induced epithelial-to-mesenchymal transition in hepatocyte by targeting Snail1. *Biochem. Biophys. Res. Commun.* **2012**, *417*, 1100–1105. [CrossRef]
26. Zhan, J.; Liu, S.; Meng, Y.; Yang, Q.; Wang, Z.; Zhang, S.; Ge, L.; Zhao, L.; Xu, X.; Zhao, Y.; et al. Systematic review of the mechanism and assessment of liver fibrosis in biliary atresia. *Pediatr. Surg. Int.* **2024**, *40*, 205. [CrossRef]
27. Rygiel, K.A.; Robertson, H.; Marshall, H.L.; Pekalski, M.; Zhao, L.; Booth, T.A.; Jones, D.E.; Burt, A.D.; Kirby, J.A. Epithelial-mesenchymal transition contributes to portal tract fibrogenesis during human chronic liver disease. *Lab. Investig.* **2008**, *88*, 112–123. [CrossRef]
28. Harada, K.; Sato, Y.; Ikeda, H.; Isse, K.; Ozaki, S.; Enomae, M.; Ohama, K.; Katayanagi, K.; Kurumaya, H.; Matsui, A.; et al. Epithelial-mesenchymal transition induced by biliary innate immunity contributes to the sclerosing cholangiopathy of biliary atresia. *J. Pathol.* **2009**, *217*, 654–664. [CrossRef]
29. Zhang, J.; Yao, H.; Song, G.; Liao, X.; Xian, Y.; Li, W. Regulation of epithelial-mesenchymal transition by tumor-associated macrophages in cancer. *Am. J. Transl. Res.* **2015**, *7*, 1699–1711.
30. Yang, M.; Ma, B.; Shao, H.; Clark, A.M.; Wells, A. Macrophage phenotypic subtypes diametrically regulate epithelial-mesenchymal plasticity in breast cancer cells. *BMC Cancer.* **2016**, *16*, 419. [CrossRef]
31. Tsuchida, T.; Friedman, S.L. Mechanisms of hepatic stellate cell activation. *Nat. Rev. Gastroenterol. Hepatol.* **2017**, *14*, 397–411. [CrossRef] [PubMed]
32. Herrera, J.; Henke, C.A.; Bitterman, P.B. Extracellular matrix as a driver of progressive fibrosis. *J. Clin. Investig.* **2018**, *128*, 45–53. [CrossRef] [PubMed]
33. Xu, F.; Liu, C.; Zhou, D.; Zhang, L. TGF-β/SMAD Pathway and Its Regulation in Hepatic Fibrosis. *J. Histochem. Cytochem.* **2016**, *64*, 157–167. [CrossRef] [PubMed]
34. Murakami, Y.; Toyoda, H.; Tanaka, M.; Kuroda, M.; Harada, Y.; Matsuda, F.; Tajima, A.; Kosaka, N.; Ochiya, T.; Shimotohno, K. The progression of liver fibrosis is related with overexpression of the miR-199 and 200 families. *PLoS ONE* **2011**, *6*, 16081. [CrossRef]
35. Li, Q.; Li, Z.; Lin, Y.; Che, H.; Hu, Y.; Kang, X.; Zhang, Y.; Wang, L.; Zhang, Y. High glucose promotes hepatic fibrosis via miR-32/MTA3-mediated epithelial-to-mesenchymal transition. *Mol. Med. Rep.* **2019**, *19*, 3190–3200. [CrossRef]
36. Gao, Y.; Li, L.; Zhang, S.N.; Mang, Y.Y.; Zhang, X.B.; Feng, S.M. HepG2.2.15-derived exosomes facilitate the activation and fibrosis of hepatic stellate cells. *World J. Gastroenterol.* **2024**, *30*, 2553–2563. [CrossRef]
37. Ezhilarasan, D. MicroRNA interplay between hepatic stellate cell quiescence and activation. *Eur. J. Pharmacol.* **2020**, *885*, 173507. [CrossRef]
38. Zheng, J.; Wang, W.; Yu, F.; Dong, P.; Chen, B.; Zhou, M.T. MicroRNA-30a Suppresses the Activation of Hepatic Stellate Cells by Inhibiting Epithelial-to-Mesenchymal Transition. *Cell Physiol. Biochem.* **2018**, *46*, 82–92. [CrossRef]
39. Chen, J.; Yu, Y.; Li, S.; Liu, Y.; Zhou, S.; Cao, S.; Yin, J.; Li, G. MicroRNA-30a ameliorates hepatic fibrosis by inhibiting Beclin1-mediated autophagy. *J. Cell Mol. Med.* **2017**, *21*, 3679–3692. [CrossRef]

40. Xu, W.; Mo, W.; Han, D.; Dai, W.; Xu, X.; Li, J.; Xu, X. Hepatocyte-derived exosomes deliver the lncRNA CYTOR to hepatic stellate cells and promote liver fibrosis. *J. Cell Mol. Med.* **2024**, *28*, 18234. [CrossRef]
41. Dong, Z.; Li, S.; Wang, X.; Si, L.; Ma, R.; Bao, L.; Bo, A. lncRNA GAS5 restrains CCl4-induced hepatic fibrosis by targeting miR-23a through the PTEN/PI3K/Akt signaling pathway. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2019**, *316*, 539–550. [CrossRef] [PubMed]
42. Chen, T.; Lin, H.; Chen, X.; Li, G.; Zhao, Y.; Zheng, L.; Shi, Z.; Zhang, K.; Hong, W.; Han, T. LncRNA Meg8 suppresses activation of hepatic stellate cells and epithelial-mesenchymal transition of hepatocytes via the Notch pathway. *Biochem. Biophys. Res. Commun.* **2020**, *521*, 921–927. [CrossRef] [PubMed]
43. Ou, Q.; Zhao, Y.; Zhou, J.; Wu, X. Comprehensive circular RNA expression profiles in a mouse model of nonalcoholic steatohepatitis. *Mol. Med. Rep.* **2019**, *19*, 2636–2648. [CrossRef] [PubMed]
44. Zhao, Q.; Liu, J.; Deng, H.; Ma, R.; Liao, J.Y.; Liang, H.; Hu, J.; Li, J.; Guo, Z.; Cai, J.; et al. Targeting Mitochondria-Located circRNA SCAR Alleviates NASH via Reducing mROS Output. *Cell* **2020**, *183*, 76–93. [CrossRef]
45. Zollner, G.; Trauner, M. Nuclear receptors as therapeutic targets in cholestatic liver diseases. *Br. J. Pharmacol.* **2009**, *156*, 7–27. [CrossRef]
46. Wang, Y.D.; Chen, W.D.; Wang, M.; Yu, D.; Forman, B.M.; Huang, W. Farnesoid X receptor antagonizes nuclear factor kappaB in hepatic inflammatory response. *Hepatology* **2008**, *48*, 1632–1643. [CrossRef]
47. Wagner, M.; Zollner, G.; Trauner, M. Nuclear bile acid receptor farnesoid X receptor meets nuclear factor-kappaB: New insights into hepatic inflammation. *Hepatology* **2008**, *48*, 1383–1386. [CrossRef]
48. Tran, M.; Liu, Y.; Huang, W.; Wang, L. Nuclear receptors and liver disease: Summary of the 2017 basic research symposium. *Hepatol Commun.* **2018**, *2*, 765–777. [CrossRef]
49. Jin, L.; Li, Y. Structural and functional insights into nuclear receptor signaling. *Adv. Drug Deliv. Rev.* **2010**, *62*, 1218–1226. [CrossRef]
50. Wu, W.B.; Chen, Y.Y.; Zhu, B.; Peng, X.M.; Zhang, S.W.; Zhou, M.L. Excessive bile acid activated NF-kappa B and promoted the development of alcoholic steatohepatitis in farnesoid X receptor deficient mice. *Biochimie* **2015**, *115*, 86–92. [CrossRef]
51. Kong, B.; Luyendyk, J.P.; Tawfik, O.; Guo, G.L. Farnesoid X receptor deficiency induces nonalcoholic steatohepatitis in low-density lipoprotein receptor-knockout mice fed a high-fat diet. *J. Pharmacol. Exp. Ther.* **2009**, *328*, 116–122. [CrossRef] [PubMed]
52. Baghdasaryan, A.; Claudel, T.; Gumhold, J.; Silbert, D.; Adorini, L.; Roda, A.; Vecchiotti, S.; Gonzalez, F.J.; Schoonjans, K.; Strazzabosco, M.; et al. Dual farnesoid X receptor/TGR5 agonist INT-767 reduces liver injury in the Mdr2-/- (Abcb4-/-) mouse cholangiopathy model by promoting biliary HCO^{-}_{3} output. *Hepatology* **2011**, *54*, 1303–1312. [CrossRef] [PubMed]
53. Sinha, R.A. Targeting nuclear receptors for NASH/MASH: From bench to bedside. *Liver Res.* **2024**, *8*, 34–45. [CrossRef] [PubMed]
54. Königshofer, P.; Brusilovskaya, K.; Petrenko, O.; Hofer, B.S.; Schwabl, P.; Trauner, M.; Reiberger, T. Nuclear receptors in liver fibrosis. *Biochim. Biophys. Acta Mol. Basis Dis.* **2021**, *1867*, 166235. [CrossRef]
55. Wang, X.C.; Song, K.; Tu, B.; Sun, H.; Zhou, Y.; Xu, S.S.; Lu, D.; Sha, J.M.; Tao, H. New aspects of the epigenetic regulation of EMT related to pulmonary fibrosis. *Eur. J. Pharmacol.* **2023**, *956*, 175959. [CrossRef]
56. Sisto, M.; Lisi, S. Epigenetic Regulation of EMP/EMT-Dependent Fibrosis. *Int. J. Mol. Sci.* **2024**, *25*, 2775. [CrossRef]
57. Liu, Y.; Wen, D.; Ho, C.; Yu, L.; Zheng, D.; O'Reilly, S.; Gao, Y.; Li, Q.; Zhang, Y. Epigenetics as a versatile regulator of fibrosis. *J. Transl. Med.* **2023**, *21*, 164. [CrossRef]
58. Liu, R.; Li, Y.; Zheng, Q.; Ding, M.; Zhou, H.; Li, X. Epigenetic modification in liver fibrosis: Promising therapeutic direction with significant challenges ahead. *Acta Pharm. Sin. B* **2024**, *14*, 1009–1029. [CrossRef]
59. Tao, S.; Duan, R.; Xu, T.; Hong, J.; Gu, W.; Lin, A.; Lian, L.; Huang, H.; Lu, J.; Li, T. Salvianolic acid B inhibits the progression of liver fibrosis in rats via modulation of the Hedgehog signaling pathway. *Exp. Ther. Med.* **2022**, *23*, 116. [CrossRef]
60. Yu, F.; Lu, Z.; Chen, B.; Wu, X.; Dong, P.; Zheng, J. Salvianolic acid B-induced microRNA-152 inhibits liver fibrosis by attenuating DNMT1-mediated Patched1 methylation. *J. Cell Mol. Med.* **2015**, *19*, 2617–2632. [CrossRef]
61. Guillot, A.; Tacke, F. Liver Macrophages: Old Dogmas and New Insights. *Hepatol. Commun.* **2019**, *3*, 730–743. [CrossRef] [PubMed]
62. Hoeffel, G.; Chen, J.; Lavin, Y.; Low, D.; Almeida, F.F.; See, P.; Beaudin, A.E.; Lum, J.; Low, I.; Forsberg, E.C.; et al. C-Myb(+) erythro-myeloid progenitor-derived fetal monocytes give rise to adult tissue-resident macrophages. *Immunity* **2015**, *42*, 665–678. [CrossRef] [PubMed]
63. Gomez Perdiguero, E.; Klapproth, K.; Schulz, C.; Busch, K.; Azzoni, E.; Crozet, L.; Garner, H.; Trouillet, C.; de Bruijn, M.F.; Geissmann, F.; et al. Tissue-resident macrophages originate from yolk-sac-derived erythro-myeloid progenitors. *Nature* **2015**, *518*, 547–551. [CrossRef]
64. Li, W.; Chang, N.; Li, L. Heterogeneity and Function of Kupffer Cells in Liver Injury. *Front. Immunol.* **2022**, *13*, 940867. [CrossRef]
65. Scott, C.L.; Zheng, F.; De Baetselier, P.; Martens, L.; Saeys, Y.; De Prijck, S.; Lippens, S.; Abels, C.; Schoonooghe, S.; Raes, G.; et al. Bone marrow-derived monocytes give rise to self-renewing and fully differentiated Kupffer cells. *Nat. Commun.* **2016**, *7*, 10321. [CrossRef]
66. Park, M.D.; Silvin, A.; Ginhoux, F.; Merad, M. Macrophages in health and disease. *Cell* **2022**, *185*, 4259–4279. [CrossRef]

67. Martrus, G.; Goebels, H.; Langeneckert, A.E.; Kah, J.; Flomm, F.; Ziegler, A.E.; Niehrs, A.; Löbl, S.M.; Russu, K.; Hess, L.U.; et al. CD49a Expression Identifies a Subset of Intrahepatic Macrophages in Humans. *Front. Immunol.* **2019**, *10*, 1247. [CrossRef]
68. Heymann, F.; Tacke, F. Immunology in the liver--from homeostasis to disease. *Nat. Rev. Gastroenterol. Hepatol.* **2016**, *13*, 88–110. [CrossRef]
69. Fogg, D.K.; Sibon, C.; Miled, C.; Jung, S.; Aucouturier, P.; Littman, D.R.; Cumano, A.; Geissmann, F. A clonogenic bone marrow progenitor specific for macrophages and dendritic cells. *Science* **2006**, *311*, 83–87. [CrossRef]
70. Tacke, F.; Zimmermann, H.W. Macrophage heterogeneity in liver injury and fibrosis. *J. Hepatol.* **2014**, *60*, 1090–1096. [CrossRef]
71. Pradere, J.P.; Kluwe, J.; De Minicis, S.; Jiao, J.J.; Gwak, G.Y.; Dapito, D.H.; Jang, M.K.; Guenther, N.D.; Mederacke, I.; Friedman, R.; et al. Hepatic macrophages but not dendritic cells contribute to liver fibrosis by promoting the survival of activated hepatic stellate cells in mice. *Hepatology* **2013**, *58*, 1461–1473. [CrossRef] [PubMed]
72. Ramachandran, P.; Pellicoro, A.; Vernon, M.A.; Boulter, L.; Aucott, R.L.; Ali, A.; Hartland, S.N.; Snowdon, V.K.; Cappon, A.; Gordon-Walker, T.T.; et al. Differential Ly-6C expression identifies the recruited macrophage phenotype, which orchestrates the regression of murine liver fibrosis. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 3186–3195. [CrossRef]
73. Traber, P.G.; Chou, H.; Zomer, E.; Hong, F.; Klyosov, A.; Fiel, M.I.; Friedman, S.L. Regression of fibrosis and reversal of cirrhosis in rats by galectin inhibitors in thioacetamide-induced liver disease. *PLoS ONE* **2013**, *8*, 75361. [CrossRef] [PubMed]
74. Khambu, B.; Yan, S.; Huda, N.; Yin, X.M. Role of High-Mobility Group Box-1 in Liver Pathogenesis. *Int. J. Mol. Sci.* **2019**, *20*, 5314. [CrossRef] [PubMed]
75. Tian, Z.; Hou, X.; Liu, W.; Han, Z.; Wei, L. Macrophages and hepatocellular carcinoma. *Cell Biosci.* **2019**, *9*, 79. [CrossRef]
76. Wan, J.; Benkdane, M.; Teixeira-Clerc, F.; Bonnafous, S.; Louvet, A.; Lafdil, F.; Pecker, F.; Tran, A.; Gual, P.; Mallat, A.; et al. M2 Kupffer cells promote M1 Kupffer cell apoptosis: A protective mechanism against alcoholic and nonalcoholic fatty liver disease. *Hepatology* **2014**, *59*, 130–142. [CrossRef]
77. Shapouri-Moghaddam, A.; Mohammadian, S.; Vazini, H.; Taghadosi, M.; Esmaeili, S.A.; Mardani, F.; Seifi, B.; Mohammadi, A.; Afshari, J.T.; Sahebkar, A. Macrophage plasticity, polarization, and function in health and disease. *J. Cell Physiol.* **2018**, *233*, 6425–6440. [CrossRef]
78. Spiller, K.L.; Wrona, E.A.; Romero-Torres, S.; Pallotta, I.; Graney, P.L.; Witherel, C.E.; Panicker, L.M.; Feldman, R.A.; Urbanska, A.M.; Santambrogio, L.; et al. Differential gene expression in human, murine, and cell line-derived macrophages upon polarization. *Exp. Cell Res.* **2016**, *347*, 1–13. [CrossRef]
79. Braga, T.T.; Agudelo, J.S.; Camara, N.O. Macrophages During the Fibrotic Process: M2 as Friend and Foe. *Front. Immunol.* **2015**, *6*, 602. [CrossRef]
80. Xue, J.; Schmidt, S.V.; Sander, J.; Draffehn, A.; Krebs, W.; Quester, I.; De Nardo, D.; Gohel, T.D.; Emde, M.; Schmidleithner, L.; et al. Transcriptome-based network analysis reveals a spectrum model of human macrophage activation. *Immunity* **2014**, *40*, 274–288. [CrossRef]
81. Murray, P.J.; Allen, J.E.; Biswas, S.K.; Fisher, E.A.; Gilroy, D.W.; Goerdt, S.; Gordon, S.; Hamilton, J.A.; Ivashkiv, L.B.; Lawrence, T.; et al. Macrophage activation and polarization: Nomenclature and experimental guidelines. *Immunity* **2014**, *41*, 14–20. [CrossRef] [PubMed]
82. Tacke, F. Targeting hepatic macrophages to treat liver diseases. *J. Hepatol.* **2017**, *66*, 1300–1312. [CrossRef] [PubMed]
83. Krenkel, O.; Tacke, F. Liver macrophages in tissue homeostasis and disease. *Nat. Rev. Immunol.* **2017**, *17*, 306–321. [CrossRef]
84. Ritz, T.; Krenkel, O.; Tacke, F. Dynamic plasticity of macrophage functions in diseased liver. *Cell Immunol.* **2018**, *330*, 175–182. [CrossRef]
85. Trus, E.; Basta, S.; Gee, K. Who's in charge here? Macrophage colony stimulating factor and granulocyte macrophage colony stimulating factor: Competing factors in macrophage polarization. *Cytokine* **2020**, *127*, 154939. [CrossRef]
86. Petrina, M.; Alothaimeen, T.; Bouzeineddine, N.Z.; Trus, E.; Banete, A.; Gee, K.; Basta, S. Granulocyte macrophage colony stimulating factor exerts dominant effects over macrophage colony stimulating factor during macrophage differentiation in vitro to induce an inflammatory phenotype. *Inflamm. Res.* **2024**, *73*, 253–262. [CrossRef]
87. Zheng, S.; Zhang, P.; Chen, Y.; Zheng, S.; Zheng, L.; Weng, Z. Inhibition of Notch Signaling Attenuates Schistosomiasis Hepatic Fibrosis via Blocking Macrophage M2 Polarization. *PLoS ONE* **2016**, *11*, e0166808. [CrossRef]
88. Bansal, R.; van Baarlen, J.; Storm, G.; Prakash, J. The interplay of the Notch signaling in hepatic stellate cells and macrophages determines the fate of liver fibrogenesis. *Sci. Rep.* **2015**, *5*, 18272. [CrossRef]
89. Krenkel, O.; Hundertmark, J.; Abdallah, A.T.; Kohlhepp, M.; Puengel, T.; Roth, T.; Branco, D.P.P.; Mossanen, J.C.; Luedde, T.; Trautwein, C.; et al. Myeloid cells in liver and bone marrow acquire a functionally distinct inflammatory phenotype during obesity-related steatohepatitis. *Gut* **2020**, *69*, 551–563. [CrossRef]
90. Xiong, X.; Kuang, H.; Ansari, S.; Liu, T.; Gong, J.; Wang, S.; Zhao, X.Y.; Ji, Y.; Li, C.; Guo, L.; et al. Landscape of Intercellular Crosstalk in Healthy and NASH Liver Revealed by Single-Cell Secretome Gene Analysis. *Mol. Cell.* **2019**, *75*, 644–660. [CrossRef]

91. Ramachandran, P.; Dobie, R.; Wilson-Kanamori, J.R.; Dora, E.F.; Henderson, B.E.P.; Luu, N.T.; Portman, J.R.; Matchett, K.P.; Brice, M.; Marwick, J.A.; et al. Resolving the fibrotic niche of human liver cirrhosis at single-cell level. *Nature* **2019**, *575*, 512–518. [CrossRef] [PubMed]
92. Xu, W.; Wu, M.; Chen, B.; Wang, H. Myeloid cells in alcoholic liver diseases: Mechanism and prospect. *Front. Immunol.* **2022**, *13*, 971346. [CrossRef] [PubMed]
93. Zhou, L.; Shen, H.; Li, X.; Wang, H. Endoplasmic reticulum stress in innate immune cells—A significant contribution to non-alcoholic fatty liver disease. *Front. Immunol.* **2022**, *13*, 951406. [CrossRef]
94. Mentink-Kane, M.M.; Cheever, A.W.; Wilson, M.S.; Madala, S.K.; Beers, L.M.; Ramalingam, T.R.; Wynn, T.A. Accelerated and progressive and lethal liver fibrosis in mice that lack interleukin (IL)-10, IL-12p40, and IL-13Rα2. *Gastroenterology* **2011**, *141*, 2200–2209. [CrossRef]
95. Li, F.; Li, Q.H.; Wang, J.Y.; Zhan, C.Y.; Xie, C.; Lu, W.Y. Effects of interferon-gamma liposomes targeted to platelet-derived growth factor receptor-beta on hepatic fibrosis in rats. *J. Control Release.* **2012**, *159*, 261–270. [CrossRef]
96. Naim, A.; Pan, Q.; Baig, M.S. Matrix Metalloproteinases (MMPs) in Liver Diseases. *J. Clin. Exp. Hepatol.* **2017**, *7*, 367–372. [CrossRef]
97. Robert, S.; Gicquel, T.; Bodin, A.; Lagente, V.; Boichot, E. Characterization of the MMP/TIMP Imbalance and Collagen Production Induced by IL-1β or TNF-α Release from Human Hepatic Stellate Cells. *PLoS ONE* **2016**, *11*, 0153118. [CrossRef]
98. Mederacke, I.; Hsu, C.C.; Troeger, J.S.; Huebener, P.; Mu, X.; Dapito, D.H.; Pradere, J.P.; Schwabe, R.F. Fate tracing reveals hepatic stellate cells as dominant contributors to liver fibrosis independent of its aetiology. *Nat. Commun.* **2013**, *4*, 2823. [CrossRef]
99. Hernandez-Gea, V.; Friedman, S.L. Pathogenesis of liver fibrosis. *Annu. Rev. Pathol.* **2011**, *6*, 425–456. [CrossRef]
100. Pinzani, M. Epithelial-mesenchymal transition in chronic liver disease: Fibrogenesis or escape from death? *J. Hepatol.* **2011**, *55*, 459–465. [CrossRef]
101. Chen, Y.; Fan, Y.; Guo, D.Y.; Xu, B.; Shi, X.Y.; Li, J.T.; Duan, L.F. Study on the relationship between hepatic fibrosis and epithelial-mesenchymal transition in intrahepatic cells. *Biomed. Pharmacother.* **2020**, *129*, 110413. [CrossRef] [PubMed]
102. Ribera, J.; Pauta, M.; Melgar-Lesmes, P.; Córdoba, B.; Bosch, A.; Calvo, M.; Rodrigo-Torres, D.; Sancho-Bru, P.; Mira, A.; Jiménez, W.; et al. A small population of liver endothelial cells undergoes endothelial-to-mesenchymal transition in response to chronic liver injury. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2017**, *313*, 492–504. [CrossRef]
103. Piera-Velazquez, S.; Li, Z.; Jimenez, S.A. Role of endothelial-mesenchymal transition (EndoMT) in the pathogenesis of fibrotic disorders. *Am. J. Pathol.* **2011**, *179*, 1074–1080. [CrossRef] [PubMed]
104. Parola, M.; Pinzani, M. Liver fibrosis: Pathophysiology, pathogenetic targets and clinical issues. *Mol. Aspects Med.* **2019**, *65*, 37–55. [CrossRef] [PubMed]
105. Novo, E.; Bocca, C.; Foglia, B.; Protopapa, F.; Maggiora, M.; Parola, M.; Cannito, S. Liver fibrogenesis: Un update on established and emerging basic concepts. *Arch. Biochem. Biophys.* **2020**, *689*, 108445. [CrossRef]
106. Thoen, L.F.; Guimarães, E.L.; Dollé, L.; Mannaerts, I.; Najimi, M.; Sokal, E.; van Grunsven, L.A. A role for autophagy during hepatic stellate cell activation. *J. Hepatol.* **2011**, *55*, 1353–1360. [CrossRef]
107. Ni, H.M.; Woolbright, B.L.; Williams, J.; Copple, B.; Cui, W.; Luyendyk, J.P.; Jaeschke, H.; Ding, W.X. Nrf2 promotes the development of fibrosis and tumorigenesis in mice with defective hepatic autophagy. *J. Hepatol.* **2014**, *61*, 617–625. [CrossRef]
108. Hernández-Gea, V.; Ghiassi-Nejad, Z.; Rozenfeld, R.; Gordon, R.; Fiel, M.I.; Yue, Z.; Czaja, M.J.; Friedman, S.L. Autophagy releases lipid that promotes fibrogenesis by activated hepatic stellate cells in mice and in human tissues. *Gastroenterology* **2012**, *142*, 938–946. [CrossRef]
109. Mullan, L.A.; Mularczyk, E.J.; Kung, L.H.; Forouhan, M.; Wragg, J.M.; Goodacre, R.; Bateman, J.F.; Swanton, E.; Briggs, M.D.; Boot-Handford, R.P. Increased intracellular proteolysis reduces disease severity in an ER stress-associated dwarfism. *J. Clin. Investig.* **2017**, *127*, 3861–3865. [CrossRef]
110. Hidvegi, T.; Ewing, M.; Hale, P.; Dippold, C.; Beckett, C.; Kemp, C.; Maurice, N.; Mukherjee, A.; Goldbach, C.; Watkins, S.; et al. An autophagy-enhancing drug promotes degradation of mutant alpha1-antitrypsin Z and reduces hepatic fibrosis. *Science.* **2010**, *329*, 229–232. [CrossRef]
111. González-Rodríguez, A.; Mayoral, R.; Agra, N.; Valdecantos, M.P.; Pardo, V.; Miquilena-Colina, M.E.; Vargas-Castrillón, J.; Lo Iacono, O.; Corazzari, M.; Fimia, G.M.; et al. Impaired autophagic flux is associated with increased endoplasmic reticulum stress during the development of NAFLD. *Cell Death Dis.* **2014**, *5*, 1179. [CrossRef] [PubMed]
112. Bridle, K.R.; Popa, C.; Morgan, M.L.; Sobbe, A.L.; Clouston, A.D.; Fletcher, L.M.; Crawford, D.H. Rapamycin inhibits hepatic fibrosis in rats by attenuating multiple profibrogenic pathways. *Liver Transpl.* **2009**, *15*, 1315–1324. [CrossRef] [PubMed]
113. Gao, J.; Wei, B.; de Assuncao, T.M.; Liu, Z.; Hu, X.; Ibrahim, S.; Cooper, S.A.; Cao, S.; Shah, V.H.; Kostallari, E. Hepatic stellate cell autophagy inhibits extracellular vesicle release to attenuate liver fibrosis. *J. Hepatol.* **2020**, *73*, 1144–1154. [CrossRef]
114. Dobie, R.; Wilson-Kanamori, J.R.; Henderson, B.E.P.; Smith, J.R.; Matchett, K.P.; Portman, J.R.; Wallenborg, K.; Picelli, S.; Zagorska, A.; Pendem, S.V.; et al. Single-Cell Transcriptomics Uncovers Zonation of Function in the Mesenchyme during Liver Fibrosis. *Cell Rep.* **2019**, *29*, 1832–1847. [CrossRef]

115. Khan, M.A.; Fischer, J.; Harrer, L.; Schwiering, F.; Groneberg, D.; Friebe, A. Hepatic stellate cells in zone 1 engage in capillarization rather than myofibroblast formation in murine liver fibrosis. *Sci. Rep.* **2024**, *14*, 18840. [CrossRef]
116. Du, K.; Jun, J.H.; Dutta, R.K.; Diehl, A.M. Plasticity, heterogeneity, and multifunctionality of hepatic stellate cells in liver pathophysiology. *Hepatol. Commun.* **2024**, *8*, 0411. [CrossRef]
117. Zhang, W.J.; Chen, S.J.; Zhou, S.C.; Wu, S.Z.; Wang, H. Inflammasomes and Fibrosis. *Front. Immunol.* **2021**, *12*, 643149. [CrossRef]
118. Ramos-Tovar, E.; Muriel, P. Molecular Mechanisms That Link Oxidative Stress, Inflammation, and Fibrosis in the Liver. *Antioxidants* **2020**, *9*, 1279. [CrossRef]
119. Knorr, J.; Wree, A.; Tacke, F.; Feldstein, A.E. The NLRP3 Inflammasome in Alcoholic and Nonalcoholic Steatohepatitis. *Semin. Liver Dis.* **2020**, *40*, 298–306. [CrossRef]
120. Liu, C.; Chen, X.; Yang, L.; Kisseleva, T.; Brenner, D.A.; Seki, E. Transcriptional repression of the transforming growth factor β (TGF-β) Pseudoreceptor BMP and activin membrane-bound inhibitor (BAMBI) by Nuclear Factor κB (NF-κB) p50 enhances TGF-β signaling in hepatic stellate cells. *J. Biol. Chem.* **2014**, *289*, 7082–7091. [CrossRef]
121. Bartneck, M.; Koppe, C.; Fech, V.; Warzecha, K.T.; Kohlhepp, M.; Huss, S.; Weiskirchen, R.; Trautwein, C.; Luedde, T.; Tacke, F. Roles of CCR2 and CCR5 for Hepatic Macrophage Polarization in Mice With Liver Parenchymal Cell-Specific NEMO Deletion. *Cell Mol. Gastroenterol. Hepatol.* **2021**, *11*, 327–347. [CrossRef] [PubMed]
122. Iredale, J.P.; Thompson, A.; Henderson, N.C. Extracellular matrix degradation in liver fibrosis: Biochemistry and regulation. *Biochim. Biophys. Acta* **2013**, *1832*, 876–883. [CrossRef] [PubMed]
123. Seki, E.; de Minicis, S.; Inokuchi, S.; Taura, K.; Miyai, K.; van Rooijen, N.; Schwabe, R.F.; Brenner, D.A. CCR2 promotes hepatic fibrosis in mice. *Hepatology* **2009**, *50*, 185–197. [CrossRef]
124. Baeck, C.; Wehr, A.; Karlmark, K.R.; Heymann, F.; Vucur, M.; Gassler, N.; Huss, S.; Klussmann, S.; Eulberg, D.; Luedde, T.; et al. Pharmacological inhibition of the chemokine CCL2 (MCP-1) diminishes liver macrophage infiltration and steatohepatitis in chronic hepatic injury. *Gut* **2012**, *61*, 416–426. [CrossRef]
125. Cai, X.; Li, Z.; Zhang, Q.; Qu, Y.; Xu, M.; Wan, X.; Lu, L. CXCL6-EGFR-induced Kupffer cells secrete TGF-β1 promoting hepatic stellate cell activation via the SMAD2/BRD4/C-MYC/EZH2 pathway in liver fibrosis. *J. Cell Mol. Med.* **2018**, *22*, 5050–5061. [CrossRef]
126. Roehlen, N.; Crouchet, E.; Baumert, T.F. Liver Fibrosis: Mechanistic Concepts and Therapeutic Perspectives. *Cells* **2020**, *9*, 875. [CrossRef]
127. Sasaki, R.; Devhare, P.B.; Steele, R.; Ray, R.; Ray, R.B. Hepatitis C virus-induced CCL5 secretion from macrophages activates hepatic stellate cells. *Hepatology* **2017**, *66*, 746–757. [CrossRef]
128. Roh, Y.S.; Seki, E. Chemokines and Chemokine Receptors in the Development of NAFLD. *Adv. Exp. Med. Biol.* **2018**, *1061*, 45–53.
129. Matsuda, M.; Seki, E. Hepatic Stellate Cell-Macrophage Crosstalk in Liver Fibrosis and Carcinogenesis. *Semin. Liver Dis.* **2020**, *40*, 307–320. [CrossRef]
130. Kocabayoglu, P.; Lade, A.; Lee, Y.A.; Dragomir, A.C.; Sun, X.; Fiel, M.I.; Thung, S.; Aloman, C.; Soriano, P.; Hoshida, Y.; et al. β-PDGF receptor expressed by hepatic stellate cells regulates fibrosis in murine liver injury, but not carcinogenesis. *J. Hepatol.* **2015**, *63*, 141–147. [CrossRef]
131. Hedger, M.P.; de Kretser, D.M. The activins and their binding protein, follistatin-Diagnostic and therapeutic targets in inflammatory disease and fibrosis. *Cytokine Growth Factor. Rev.* **2013**, *24*, 285–295. [CrossRef] [PubMed]
132. Youssef, S.S.; Mostafa, A.; Saad, A.; Omran, M.H.; El Zanaty, T.; Mohamed Seif, S. Impact of IL12B gene rs 3212227 polymorphism on fibrosis, liver inflammation, and response to treatment in genotype 4 Egyptian hepatitis C patients. *Dis. Markers* **2013**, *35*, 431–437. [CrossRef] [PubMed]
133. Minutti, C.M.; Modak, R.V.; Macdonald, F.; Li, F.; Smyth, D.J.; Dorward, D.A.; Blair, N.; Husovsky, C.; Muir, A.; Giampazolias, E.; et al. A Macrophage-Pericyte Axis Directs Tissue Restoration via Amphiregulin-Induced Transforming Growth Factor Beta Activation. *Immunity* **2019**, *50*, 645–654. [CrossRef] [PubMed]
134. Qu, J.; Wang, L.; Li, Y.; Li, X. Liver sinusoidal endothelial cell: An important yet often overlooked player in the liver fibrosis. *Clin. Mol. Hepatol.* **2024**, *30*, 303–325. [CrossRef] [PubMed]
135. Schildberg, F.A.; Wojtalla, A.; Siegmund, S.V.; Endl, E.; Diehl, L.; Abdullah, Z.; Kurts, C.; Knolle, P.A. Murine hepatic stellate cells veto CD8 T cell activation by a CD54-dependent mechanism. *Hepatology* **2011**, *54*, 262–272. [CrossRef]
136. Géraud, C.; Evdokimov, K.; Straub, B.K.; Peitsch, W.K.; Demory, A.; Dörflinger, Y.; Schledzewski, K.; Schmieder, A.; Schemmer, P.; Augustin, H.G.; et al. Unique cell type-specific junctional complexes in vascular endothelium of human and rat liver sinusoids. *PLoS ONE* **2012**, *7*, 34206. [CrossRef]
137. Jophlin, L.L.; Cao, S.; Shah, V.H. The Transcriptome of Hepatic Fibrosis Revealed by Single-Cell RNA Sequencing. *Hepatology* **2020**, *71*, 1865–1867. [CrossRef]
138. Liu, D.; Fu, X.; Wang, Y.; Wang, X.; Wang, H.; Wen, J.; Kang, N. Protein diaphanous homolog 1 (Diaph1) promotes myofibroblastic activation of hepatic stellate cells by regulating Rab5a activity and TGFβ receptor endocytosis. *FASEB J.* **2020**, *34*, 7345–7359. [CrossRef]

139. Hammoutene, A.; Biquard, L.; Lasselin, J.; Kheloufi, M.; Tanguy, M.; Vion, A.C.; Mérian, J.; Colnot, N.; Loyer, X.; Tedgui, A.; et al. A defect in endothelial autophagy occurs in patients with non-alcoholic steatohepatitis and promotes inflammation and fibrosis. *J. Hepatol.* **2020**, *72*, 528–538. [CrossRef]
140. Li, Z.; Chen, B.; Dong, W.; Kong, M.; Fan, Z.; Yu, L.; Wu, D.; Lu, J.; Xu, Y. MKL1 promotes endothelial-to-mesenchymal transition and liver fibrosis by activating TWIST1 transcription. *Cell Death Dis.* **2019**, *10*, 899. [CrossRef]
141. Derynck, R.; Budi, E.H. Specificity, versatility, and control of TGF-β family signaling. *Sci. Signal.* **2019**, *12*, eaav5183. [CrossRef] [PubMed]
142. Fabregat, I.; Moreno-Càceres, J.; Sánchez, A.; Dooley, S.; Dewidar, B.; Giannelli, G.; Ten Dijke, P.; IT-LIVER Consortium. TGF-β signalling and liver disease. *FEBS J.* **2016**, *283*, 2219–2232. [CrossRef] [PubMed]
143. Wang, X.L.; Yang, M.; Wang, Y. Roles of transforming growth factor-β signaling in liver disease. *World J. Hepatol.* **2024**, *16*, 973–979. [CrossRef]
144. Carter, J.K.; Friedman, S.L. Hepatic Stellate Cell-Immune Interactions in NASH. *Front. Endocrinol.* **2022**, *13*, 867940. [CrossRef]
145. Xiang, D.M.; Sun, W.; Ning, B.F.; Zhou, T.F.; Li, X.F.; Zhong, W.; Cheng, Z.; Xia, M.Y.; Wang, X.; Deng, X.; et al. The HLF/IL-6/STAT3 feedforward circuit drives hepatic stellate cell activation to promote liver fibrosis. *Gut* **2018**, *67*, 1704–1715. [CrossRef]
146. Kou, K.; Li, S.; Qiu, W.; Fan, Z.; Li, M.; Lv, G. Hypoxia-inducible factor 1α/IL-6 axis in activated hepatic stellate cells aggravates liver fibrosis. *Biochem. Biophys. Res. Commun.* **2023**, *653*, 21–30. [CrossRef]
147. Eguchi, A.; Yan, R.; Pan, S.Q.; Wu, R.; Kim, J.; Chen, Y.; Ansong, C.; Smith, R.D.; Tempaku, M.; Ohno-Machado, L.; et al. Comprehensive characterization of hepatocyte-derived extracellular vesicles identifies direct miRNA-based regulation of hepatic stellate cells and DAMP-based hepatic macrophage IL-1β and IL-17 upregulation in alcoholic hepatitis mice. *J. Mol. Med.* **2020**, *98*, 1021–1034. [CrossRef]
148. Lodyga, M.; Cambridge, E.; Karvonen, H.M.; Pakshir, P.; Wu, B.; Boo, S.; Kiebalo, M.; Kaarteenaho, R.; Glogauer, M.; Kapoor, M.; et al. Cadherin-11-mediated adhesion of macrophages to myofibroblasts establishes a profibrotic niche of active TGF-β. *Sci Signal.* **2019**, *12*, eaao3469. [CrossRef]
149. Poisson, J.; Lemoinne, S.; Boulanger, C.; Durand, F.; Moreau, R.; Valla, D.; Rautou, P.E. Liver sinusoidal endothelial cells: Physiology and role in liver diseases. *J. Hepatol.* **2017**, *66*, 212–227. [CrossRef]
150. McConnell, M.J.; Kostallari, E.; Ibrahim, S.H.; Iwakiri, Y. The evolving role of liver sinusoidal endothelial cells in liver health and disease. *Hepatology* **2023**, *78*, 649–669. [CrossRef]
151. Du, W.; Wang, L. The Crosstalk Between Liver Sinusoidal Endothelial Cells and Hepatic Microenvironment in NASH Related Liver Fibrosis. *Front. Immunol.* **2022**, *13*, 936196. [CrossRef] [PubMed]
152. Guo, Q.; Furuta, K.; Islam, S.; Caporarello, N.; Kostallari, E.; Dielis, K.; Tschumperlin, D.J.; Hirsova, P.; Ibrahim, S.H. Liver sinusoidal endothelial cell expressed vascular cell adhesion molecule 1 promotes liver fibrosis. *Front. Immunol.* **2022**, *13*, 983255. [CrossRef] [PubMed]
153. Strauss, O.; Phillips, A.; Ruggiero, K.; Bartlett, A.; Dunbar, P.R. Immunofluorescence identifies distinct subsets of endothelial cells in the human liver. *Sci. Rep.* **2017**, *7*, 44356. [CrossRef]
154. Wei, M.; Zhang, Y.; Zhang, H.; Huang, Z.; Miao, H.; Zhang, T.; Lu, B.; Ji, L. HMGB1 induced endothelial to mesenchymal transition in liver fibrosis: The key regulation of early growth response factor 1. *Biochim. Biophys. Acta Gen. Subj.* **2022**, *1866*, 130202. [CrossRef]
155. Ruan, B.; Duan, J.L.; Xu, H.; Tao, K.S.; Han, H.; Dou, G.R.; Wang, L. Capillarized liver sinusoidal endothelial cells undergo partial endothelial-mesenchymal transition to actively deposit sinusoidal ECM in liver fibrosis. *Front. Cell Dev. Biol.* **2021**, *9*, 671081. [CrossRef]
156. Dewidar, B.; Meyer, C.; Dooley, S.; Meindl-Beinker, A.N. TGF-β in Hepatic Stellate Cell Activation and Liver Fibrogenesis-Updated 2019. *Cells* **2019**, *8*, 1419. [CrossRef]
157. de Gouville, A.C.; Boullay, V.; Krysa, G.; Pilot, J.; Brusq, J.M.; Loriolle, F.; Gauthier, J.M.; Papworth, S.A.; Laroze, A.; Gellibert, F.; et al. Inhibition of TGF-beta signaling by an ALK5 inhibitor protects rats from dimethylnitrosamine-induced liver fibrosis. *Br. J. Pharmacol.* **2005**, *145*, 166–177. [CrossRef]
158. Chen, Y.; Li, Q.; Tu, K.; Wang, Y.; Wang, X.; Liu, D.; Chen, C.; Liu, D.; Yang, R.; Qiu, W.; et al. Focal Adhesion Kinase Promotes Hepatic Stellate Cell Activation by Regulating Plasma Membrane Localization of TGFβ Receptor 2. *Hepatol Commun.* **2019**, *4*, 268–283. [CrossRef]
159. Robertson, I.B.; Rifkin, D.B. Regulation of the Bioavailability of TGF-β and TGF-β-Related Proteins. *Cold Spring Harb. Perspect. Biol.* **2016**, *8*, a021907. [CrossRef]
160. Dong, X.; Zhao, B.; Iacob, R.E.; Zhu, J.; Koksal, A.C.; Lu, C.; Engen, J.R.; Springer, T.A. Force interacts with macromolecular structure in activation of TGF-β. *Nature* **2017**, *542*, 55–59. [CrossRef]
161. Reed, N.I.; Jo, H.; Chen, C.; Tsujino, K.; Arnold, T.D.; DeGrado, W.F.; Sheppard, D. The αvβ1 integrin plays a critical in vivo role in tissue fibrosis. *Sci. Transl. Med.* **2015**, *7*, 288ra79. [CrossRef] [PubMed]

162. Wipff, P.J.; Rifkin, D.B.; Meister, J.J.; Hinz, B. Myofibroblast contraction activates latent TGF-beta1 from the extracellular matrix. *J. Cell Biol.* **2007**, *179*, 1311–1323. [CrossRef]
163. Peng, Z.W.; Ikenaga, N.; Liu, S.B.; Sverdlov, D.Y.; Vaid, K.A.; Dixit, R.; Weinreb, P.H.; Violette, S.; Sheppard, D.; Schuppan, D.; et al. Integrin αvβ6 critically regulates hepatic progenitor cell function and promotes ductular reaction, fibrosis, and tumorigenesis. *Hepatology* **2016**, *63*, 217–232. [CrossRef] [PubMed]
164. Wang, B.; Dolinski, B.M.; Kikuchi, N.; Leone, D.R.; Peters, M.G.; Weinreb, P.H.; Violette, S.M.; Bissell, D.M. Role of alphavbeta6 integrin in acute biliary fibrosis. *Hepatology* **2007**, *46*, 1404–1412. [CrossRef] [PubMed]
165. Henderson, N.C.; Arnold, T.D.; Katamura, Y.; Giacomini, M.M.; Rodriguez, J.D.; McCarty, J.H.; Pellicoro, A.; Raschperger, E.; Betsholtz, C.; Ruminski, P.G.; et al. Targeting of αv integrin identifies a core molecular pathway that regulates fibrosis in several organs. *Nat. Med.* **2013**, *19*, 1617–1624. [CrossRef]
166. Braunersreuther, V.; Viviani, G.L.; Mach, F.; Montecucco, F. Role of cytokines and chemokines in non-alcoholic fatty liver disease. *World J. Gastroenterol.* **2012**, *18*, 727–735. [CrossRef]
167. Ahmed, H.; Umar, M.I.; Imran, S.; Javaid, F.; Syed, S.K.; Riaz, R.; Hassan, W. TGF-β1 signaling can worsen NAFLD with liver fibrosis backdrop. *Exp. Mol. Pathol.* **2022**, *124*, 104733. [CrossRef]
168. Wang, B.; Koh, P.; Winbanks, C.; Coughlan, M.T.; McClelland, A.; Watson, A.; Jandeleit-Dahm, K.; Burns, W.C.; Thomas, M.C.; Cooper, M.E.; et al. *miR*-200a Prevents renal fibrogenesis through repression of TGF-β2 expression. *Diabetes* **2011**, *60*, 280–287. [CrossRef]
169. Voumvouraki, A.; Koulentaki, M.; Tzardi, M.; Sfakianaki, O.; Manousou, P.; Notas, G.; Kouroumalis, E. Increased TGF-β3 in primary biliary cirrhosis: An abnormality related to pathogenesis? *World J. Gastroenterol.* **2010**, *16*, 5057–5064. [CrossRef]
170. McLane, L.M.; Abdel-Hakeem, M.S.; Wherry, E.J. CD8 T Cell Exhaustion During Chronic Viral Infection and Cancer. *Annu. Rev. Immunol.* **2019**, *37*, 457–495. [CrossRef]
171. Kurachi, M. CD8+ T cell exhaustion. *Semin. Immunopathol.* **2019**, *41*, 327–337. [CrossRef] [PubMed]
172. Li, T.Y.; Yang, Y.; Zhou, G.; Tu, Z.K. Immune suppression in chronic hepatitis B infection associated liver disease: A review. *World J. Gastroenterol.* **2019**, *25*, 3527–3537. [CrossRef] [PubMed]
173. Li, H.; Zhai, N.; Wang, Z.; Song, H.; Yang, Y.; Cui, A.; Li, T.; Wang, G.; Niu, J.; Crispe, I.N.; et al. Regulatory NK cells mediated between immunosuppressive monocytes and dysfunctional T cells in chronic HBV infection. *Gut* **2018**, *67*, 2035–2044. [CrossRef]
174. Kiagiadaki, F.; Kampa, M.; Voumvouraki, A.; Castanas, E.; Kouroumalis, E.; Notas, G. Activin-A causes Hepatic stellate cell activation via the induction of TNFα and TGFβ in Kupffer cells. *Biochim. Biophys. Acta Mol. Basis Dis.* **2018**, *1864*, 891–899. [CrossRef]
175. Tsuda, M.; Zhang, W.; Yang, G.X.; Tsuneyama, K.; Ando, Y.; Kawata, K.; Park, O.; Leung, P.S.; Coppel, R.L.; Ansari, A.A.; et al. Deletion of interleukin (IL)-12p35 induces liver fibrosis in dominant-negative TGFβ receptor type II mice. *Hepatology* **2013**, *57*, 806–816. [CrossRef]
176. Masola, V.; Carraro, A.; Granata, S.; Signorini, L.; Bellin, G.; Violi, P.; Lupo, A.; Tedeschi, U.; Onisto, M.; Gambaro, G.; et al. In vitro effects of interleukin (IL)-1 beta inhibition on the epithelial-to-mesenchymal transition (EMT) of renal tubular and hepatic stellate cells. *J. Transl. Med.* **2019**, *17*, 12. [CrossRef]
177. Sudo, K.; Yamada, Y.; Moriwaki, H.; Saito, K.; Seishima, M. Lack of tumor necrosis factor receptor type 1 inhibits liver fibrosis induced by carbon tetrachloride in mice. *Cytokine* **2005**, *29*, 236–244. [CrossRef]
178. Seki, E.; De Minicis, S.; Osterreicher, C.H.; Kluwe, J.; Osawa, Y.; Brenner, D.A.; Schwabe, R.F. TLR4 enhances TGF-beta signaling and hepatic fibrosis. *Nat. Med.* **2007**, *13*, 1324–1332. [CrossRef]
179. Miura, K.; Kodama, Y.; Inokuchi, S.; Schnabl, B.; Aoyama, T.; Ohnishi, H.; Olefsky, J.M.; Brenner, D.A.; Seki, E. Toll-like receptor 9 promotes steatohepatitis by induction of interleukin-1beta in mice. *Gastroenterology* **2010**, *139*, 323–334. [CrossRef]
180. Kulkarni, A.B.; Karlsson, S. Inflammation and TGF beta 1: Lessons from the TGF beta 1 null mouse. *Res. Immunol.* **1997**, *148*, 453–456. [CrossRef]
181. Tsomidis, I.; Notas, G.; Xidakis, C.; Voumvouraki, A.; Samonakis, D.N.; Koulentaki, M.; Kouroumalis, E. Enzymes of Fibrosis in Chronic Liver Disease. *Biomedicines* **2022**, *10*, 3179. [CrossRef] [PubMed]
182. Akkız, H.; Gieseler, R.K.; Canbay, A. Liver Fibrosis: From Basic Science towards Clinical Progress, Focusing on the Central Role of Hepatic Stellate Cells. *Int. J. Mol. Sci.* **2024**, *25*, 7873. [CrossRef] [PubMed]
183. Hammerich, L.; Tacke, F. Hepatic inflammatory responses in liver fibrosis. *Nat. Rev. Gastroenterol. Hepatol.* **2023**, *20*, 633–646. [CrossRef] [PubMed]
184. Jeong, W.I.; Park, O.; Suh, Y.G.; Byun, J.S.; Park, S.Y.; Choi, E.; Kim, J.K.; Ko, H.; Wang, H.; Miller, A.M.; et al. Suppression of innate immunity (natural killer cell/interferon-γ) in the advanced stages of liver fibrosis in mice. *Hepatology* **2011**, *53*, 1342–1351. [CrossRef]
185. Glässner, A.; Eisenhardt, M.; Krämer, B.; Körner, C.; Coenen, M.; Sauerbruch, T.; Spengler, U.; Nattermann, J. NK cells from HCV-infected patients effectively induce apoptosis of activated primary human hepatic stellate cells in a TRAIL-, FasL- and NKG2D-dependent manner. *Lab. Investig.* **2012**, *92*, 967–977. [CrossRef]

186. Krizhanovsky, V.; Yon, M.; Dickins, R.A.; Hearn, S.; Simon, J.; Miething, C.; Yee, H.; Zender, L.; Lowe, S.W. Senescence of activated stellate cells limits liver fibrosis. *Cell* **2008**, *134*, 657–667. [CrossRef]
187. Wang, H.; Yin, S. Natural killer T cells in liver injury, inflammation and cancer. *Expert. Rev. Gastroenterol. Hepatol.* **2015**, *9*, 1077–1085. [CrossRef]
188. Wang, Y.; Li, Y.; Qiu, Y.; Shen, M.; Wang, L.; Shao, J.; Zhang, F.; Xu, X.; Zhang, Z.; Guo, M.; et al. Artesunate Induces Ferroptosis in Hepatic Stellate Cells and Alleviates Liver Fibrosis via the ROCK1/ATF3 Axis. *J. Clin. Transl. Hepatol.* **2024**, *12*, 36–51. [CrossRef]
189. Kisseleva, T.; Brenner, D. Molecular and cellular mechanisms of liver fibrosis and its regression. *Nat. Rev. Gastroenterol. Hepatol.* **2021**, *18*, 151–166. [CrossRef]
190. Campana, L.; Esser, H.; Huch, M.; Forbes, S. Liver regeneration and inflammation: From fundamental science to clinical applications. *Nat. Rev. Mol. Cell Biol.* **2021**, *22*, 608–624. [CrossRef]
191. Vonderlin, J.; Chavakis, T.; Sieweke, M.; Tacke, F. The Multifaceted Roles of Macrophages in NAFLD Pathogenesis. *Cell Mol. Gastroenterol. Hepatol.* **2023**, *15*, 1311–1324. [CrossRef] [PubMed]
192. Tacke, F.; Puengel, T.; Loomba, R.; Friedman, S.L. An integrated view of anti-inflammatory and antifibrotic targets for the treatment of NASH. *J. Hepatol.* **2023**, *79*, 552–566. [CrossRef] [PubMed]
193. Campana, L.; Iredale, J.P. Regression of Liver Fibrosis. *Semin. Liver Dis.* **2017**, *37*, 1–10.
194. Zhang, L.; Schuppan, D. Traditional Chinese Medicine (TCM) for fibrotic liver disease: Hope and hype. *J. Hepatol.* **2014**, *61*, 166–168. [CrossRef]
195. Li, Z.; Zhu, J.F.; Ouyang, H. Progress on traditional Chinese medicine in improving hepatic fibrosis through inhibiting oxidative stress. *World J. Hepatol.* **2023**, *15*, 1091–1108. [CrossRef]
196. Dai, Z.; Liao, X.; Wieland, L.S.; Hu, J.; Wang, Y.; Kim, T.H.; Liu, J.P.; Zhan, S.; Robinson, N. Cochrane systematic reviews on traditional Chinese medicine: What matters-the quantity or quality of evidence? *Phytomedicine* **2022**, *98*, 153921. [CrossRef]
197. Schulze, R.J.; Schott, M.B.; Casey, C.A.; Tuma, P.L.; McNiven, M.A. The cell biology of the hepatocyte: A membrane trafficking machine. *J. Cell Biol.* **2019**, *218*, 2096–2112. [CrossRef]
198. Kubes, P.; Jenne, C. Immune Responses in the Liver. *Annu. Rev. Immunol.* **2018**, *36*, 247–277. [CrossRef]
199. Gong, J.; Tu, W.; Liu, J.; Tian, D. Hepatocytes: A key role in liver inflammation. *Front. Immunol.* **2023**, *13*, 1083780. [CrossRef]
200. Shetty, S.; Lalor, P.F.; Adams, D.H. Liver sinusoidal endothelial cells—Gatekeepers of hepatic immunity. *Nat. Rev. Gastroenterol. Hepatol.* **2018**, *15*, 555–567. [CrossRef]
201. Schildberg, F.A.; Hegenbarth, S.I.; Schumak, B.; Scholz, K.; Limmer, A.; Knolle, P.A. Liver sinusoidal endothelial cells veto CD8 T cell activation by antigen-presenting dendritic cells. *Eur. J. Immunol.* **2008**, *38*, 957–967. [CrossRef] [PubMed]
202. Diehl, L.; Schurich, A.; Grochtmann, R.; Hegenbarth, S.; Chen, L.; Knolle, P.A. Tolerogenic maturation of liver sinusoidal endothelial cells promotes B7-homolog 1-dependent CD8+ T cell tolerance. *Hepatology* **2008**, *47*, 296–305. [CrossRef] [PubMed]
203. Crispe, I.N.; Giannandrea, M.; Klein, I.; John, B.; Sampson, B.; Wuensch, S. Cellular and molecular mechanisms of liver tolerance. *Immunol. Rev.* **2006**, *213*, 101–118. [CrossRef] [PubMed]
204. Harada, K.; Isse, K.; Sato, Y.; Ozaki, S.; Nakanuma, Y. Endotoxin tolerance in human intrahepatic biliary epithelial cells is induced by upregulation of IRAK-M. *Liver Int.* **2006**, *26*, 935–942. [CrossRef]
205. Zheng, M.; Tian, Z. Liver-Mediated Adaptive Immune Tolerance. *Front. Immunol.* **2019**, *10*, 2525. [CrossRef]
206. Jenne, C.N.; Kubes, P. Immune surveillance by the liver. *Nat. Immunol.* **2013**, *14*, 996–1006. [CrossRef]
207. Horst, A.K.; Neumann, K.; Diehl, L.; Tiegs, G. Modulation of liver tolerance by conventional and nonconventional antigen-presenting cells and regulatory immune cells. *Cell Mol. Immunol.* **2016**, *13*, 277–292. [CrossRef]
208. Yu, J.; Chen, Y.; Wu, Y.; Ye, L.; Lian, Z.; Wei, H.; Sun, R.; Tian, Z. The differential organogenesis and functionality of two liver-draining lymph nodes in mice. *J. Autoimmun.* **2017**, *84*, 109–121. [CrossRef]
209. Michalek, R.D.; Gerriets, V.A.; Jacobs, S.R.; Macintyre, A.N.; MacIver, N.J.; Mason, E.F.; Sullivan, S.A.; Nichols, A.G.; Rathmell, J.C. Cutting edge: Distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets. *J. Immunol.* **2011**, *186*, 3299–3303. [CrossRef]
210. Vats, D.; Mukundan, L.; Odegaard, J.I.; Zhang, L.; Smith, K.L.; Morel, C.R.; Wagner, R.A.; Greaves, D.R.; Murray, P.J.; Chawla, A. Oxidative metabolism and PGC-1beta attenuate macrophage-mediated inflammation. *Cell Metab.* **2006**, *4*, 13–24. [CrossRef]
211. Jung, J.; Zeng, H.; Horng, T. Metabolism as a guiding force for immunity. *Nat. Cell Biol.* **2019**, *21*, 85–93. [CrossRef] [PubMed]
212. Cramer, T.; Yamanishi, Y.; Clausen, B.E.; Förster, I.; Pawlinski, R.; Mackman, N.; Haase, V.H.; Jaenisch, R.; Corr, M.; Nizet, V.; et al. HIF-1alpha is essential for myeloid cell-mediated inflammation. *Cell* **2003**, *112*, 645–657. [CrossRef] [PubMed]
213. Zhou, Y.; Zhang, H.; Yao, Y.; Zhang, X.; Guan, Y.; Zheng, F. CD4+ T cell activation and inflammation in NASH-related fibrosis. *Front. Immunol.* **2022**, *13*, 967410. [CrossRef]
214. Alegre, F.; Pelegrin, P.; Feldstein, A.E. Inflammasomes in Liver Fibrosis. *Semin. Liver Dis.* **2017**, *37*, 119–127. [CrossRef]
215. Zhou, Y.; Wu, R.; Wang, X.; Bao, X.; Lu, C. Roles of necroptosis in alcoholic liver disease and hepatic pathogenesis. *Cell Prolif.* **2022**, *55*, 13193. [CrossRef]
216. Bataller, R.; Arab, J.P.; Shah, V.H. Alcohol-Associated Hepatitis. *N. Engl. J. Med.* **2022**, *387*, 2436–2448. [CrossRef]

217. Arab, J.P.; Arrese, M.; Shah, V.H. Gut microbiota in non-alcoholic fatty liver disease and alcohol-related liver disease: Current concepts and perspectives. *Hepatol. Res.* **2020**, *50*, 407–418. [CrossRef]
218. Albillos, A.; Martin-Mateos, R.; Van der Merwe, S.; Wiest, R.; Jalan, R.; Álvarez-Mon, M. Cirrhosis-associated immune dysfunction. *Nat. Rev. Gastroenterol. Hepatol.* **2022**, *19*, 112–134. [CrossRef]
219. Wiering, L.; Subramanian, P.; Hammerich, L. Hepatic Stellate Cells: Dictating Outcome in Nonalcoholic Fatty Liver Disease. *Cell Mol. Gastroenterol. Hepatol.* **2023**, *15*, 1277–1292. [CrossRef]
220. Zhangdi, H.J.; Su, S.B.; Wang, F.; Liang, Z.Y.; Yan, Y.D.; Qin, S.Y.; Jiang, H.X. Crosstalk network among multiple inflammatory mediators in liver fibrosis. *World J. Gastroenterol.* **2019**, *25*, 4835–4849. [CrossRef]
221. Berumen, J.; Baglieri, J.; Kisseleva, T.; Mekeel, K. Liver fibrosis: Pathophysiology and clinical implications. *WIREs Mech. Dis.* **2021**, *13*, 1499. [CrossRef] [PubMed]
222. Nakamoto, N.; Kanai, T. Role of toll-like receptors in immune activation and tolerance in the liver. *Front. Immunol.* **2014**, *5*, 221. [CrossRef] [PubMed]
223. Torre, P.; Motta, B.M.; Sciorio, R.; Masarone, M.; Persico, M. Inflammation and Fibrogenesis in MAFLD: Role of the Hepatic Immune System. *Front. Med.* **2021**, *8*, 781567. [CrossRef]
224. Liu, Y.; Dong, Y.; Wu, X.; Wang, X.; Niu, J. Identification of Immune Microenvironment Changes and the Expression of Immune-Related Genes in Liver Cirrhosis. *Front. Immunol.* **2022**, *13*, 918445. [CrossRef]
225. Khanam, A.; Chua, J.V.; Kottilil, S. Immunopathology of Chronic Hepatitis B Infection: Role of Innate and Adaptive Immune Response in Disease Progression. *Int. J. Mol. Sci.* **2021**, *22*, 5497. [CrossRef]
226. Martinon, F. Detection of immune danger signals by NALP3. *J. Leukoc. Biol.* **2008**, *83*, 507–511. [CrossRef]
227. Swanson, K.V.; Deng, M.; Ting, J.P. The NLRP3 inflammasome: Molecular activation and regulation to therapeutics. *Nat. Rev. Immunol.* **2019**, *19*, 477–489. [CrossRef]
228. Gaul, S.; Leszczynska, A.; Alegre, F.; Kaufmann, B.; Johnson, C.D.; Adams, L.A.; Wree, A.; Damm, G.; Seehofer, D.; Calvente, C.J.; et al. Hepatocyte pyroptosis and release of inflammasome particles induce stellate cell activation and liver fibrosis. *J. Hepatol.* **2021**, *74*, 156–167. [CrossRef]
229. Kong, F.; You, H.; Zheng, K.; Tang, R.; Zheng, C. The crosstalk between pattern-recognition receptor signaling and calcium signaling. *Int. J. Biol. Macromol.* **2021**, *192*, 745–756. [CrossRef]
230. Wree, A.; Holtmann, T.M.; Inzaugarat, M.E.; Feldstein, A.E. Novel Drivers of the Inflammatory Response in Liver Injury and Fibrosis. *Semin. Liver Dis.* **2019**, *39*, 275–282. [CrossRef]
231. Jiang, Y.; Que, W.; Zhu, P.; Li, X.K. The Role of Diverse Liver Cells in Liver Transplantation Tolerance. *Front. Immunol.* **2020**, *11*, 1203. [CrossRef] [PubMed]
232. Mühlbauer, M.; Fleck, M.; Schütz, C.; Weiss, T.; Froh, M.; Blank, C.; Schölmerich, J.; Hellerbrand, C. PD-L1 is induced in hepatocytes by viral infection and by interferon-alpha and -gamma and mediates T cell apoptosis. *J. Hepatol.* **2006**, *45*, 520–528. [CrossRef] [PubMed]
233. Mooring, M.; Fowl, B.H.; Lum, S.Z.C.; Liu, Y.; Yao, K.; Softic, S.; Kirchner, R.; Bernstein, A.; Singhi, A.D.; Jay, D.G.; et al. Hepatocyte Stress Increases Expression of Yes-Associated Protein and Transcriptional Coactivator With PDZ-Binding Motif in Hepatocytes to Promote Parenchymal Inflammation and Fibrosis. *Hepatology* **2020**, *71*, 1813–1830. [CrossRef] [PubMed]
234. Futakuchi, A.; Inoue, T.; Wei, F.Y.; Inoue-Mochita, M.; Fujimoto, T.; Tomizawa, K.; Tanihara, H. YAP/TAZ Are Essential for TGF-β2-Mediated Conjunctival Fibrosis. *Investig. Ophthalmol. Vis. Sci.* **2018**, *59*, 3069–3078. [CrossRef] [PubMed]
235. Filliol, A.; Schwabe, R.F. FoxM1 Induces CCl2 Secretion From Hepatocytes Triggering Hepatic Inflammation, Injury, Fibrosis, and Liver Cancer. *Cell Mol. Gastroenterol. Hepatol.* **2020**, *9*, 555–556. [CrossRef]
236. Kurahashi, T.; Yoshida, Y.; Ogura, S.; Egawa, M.; Furuta, K.; Hikita, H.; Kodama, T.; Sakamori, R.; Kiso, S.; Kamada, Y.; et al. Forkhead Box M1 Transcription Factor Drives Liver Inflammation Linking to Hepatocarcinogenesis in Mice. *Cell Mol. Gastroenterol. Hepatol.* **2020**, *9*, 425–446. [CrossRef]
237. Lu, J.G.; Iyasu, A.; French, B.; Tillman, B.; French, S.W. Overexpression of MHCII by hepatocytes in alcoholic hepatitis (AH) compared to non-alcoholic steatohepatitis (NASH) and normal controls. *Alcohol* **2020**, *84*, 27–32. [CrossRef]
238. Huby, T.; Gautier, E.L. Immune cell-mediated features of non-alcoholic steatohepatitis. *Nat. Rev. Immunol.* **2022**, *22*, 429–443. [CrossRef]
239. Zhang, Q.; Qu, Y.; Zhang, Q.; Li, F.; Li, B.; Li, Z.; Dong, Y.; Lu, L.; Cai, X. Exosomes derived from hepatitis B virus-infected hepatocytes promote liver fibrosis via miR-222/TFRC axis. *Cell Biol. Toxicol.* **2023**, *39*, 467–481. [CrossRef]
240. Francis, H.; Wu, N.; Alpini, G.; Meng, F. Hepatocyte Autophagy: Maintaining a Toxic-Free Environment. *Hepatology* **2020**, *72*, 371–374. [CrossRef]
241. Kim, Y.S.; Kim, S.G. Endoplasmic reticulum stress and autophagy dysregulation in alcoholic and non-alcoholic liver diseases. *Clin. Mol. Hepatol.* **2020**, *26*, 715–727. [CrossRef] [PubMed]
242. Kouroumalis, E.; Voumvouraki, A.; Augoustaki, A.; Samonakis, D.N. Autophagy in liver diseases. *World J. Hepatol.* **2021**, *13*, 6–65. [CrossRef]

243. Shiode, Y.; Hikita, H.; Tanaka, S.; Shirai, K.; Doi, A.; Sakane, S.; Kai, Y.; Nakabori, T.; Yamada, R.; Kodama, T.; et al. Hepatitis C virus enhances Rubicon expression, leading to autophagy inhibition and intracellular innate immune activation. *Sci. Rep.* **2020**, *10*, 15290. [CrossRef] [PubMed]
244. Sir, D.; Tian, Y.; Chen, W.L.; Ann, D.K.; Yen, T.S.; Ou, J.H. The early autophagic pathway is activated by hepatitis B virus and required for viral DNA replication. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 4383–4388. [CrossRef]
245. Tavera-Mendoza, L.E.; Westerling, T.; Libby, E.; Marusyk, A.; Cato, L.; Cassani, R.; Cameron, L.A.; Ficarro, S.B.; Marto, J.A.; Klawitter, J.; et al. Vitamin D receptor regulates autophagy in the normal mammary gland and in luminal breast cancer cells. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 2186–2194. [CrossRef]
246. Barchetta, I.; Carotti, S.; Labbadia, G.; Gentilucci, U.V.; Muda, A.O.; Angelico, F.; Silecchia, G.; Leonetti, F.; Fraioli, A.; Picardi, A.; et al. Liver vitamin D receptor, CYP2R1, and CYP27A1 expression: Relationship with liver histology and vitamin D3 levels in patients with nonalcoholic steatohepatitis or hepatitis C virus. *Hepatology* **2012**, *56*, 2180–2187. [CrossRef]
247. He, W.; Ni, W.; Zhao, L.; Wang, X.; Liu, L.; Fan, Z. MicroRNA-125a/VDR axis impaired autophagic flux and contributed to fibrosis in a CCL4-induced mouse model and patients with liver cirrhosis. *Life Sci.* **2021**, *264*, 118666. [CrossRef]
248. Malhi, H.; Kaufman, R.J. Endoplasmic reticulum stress in liver disease. *J. Hepatol.* **2011**, *54*, 795–809. [CrossRef]
249. Mollica, M.P.; Lionetti, L.; Putti, R.; Cavaliere, G.; Gaita, M.; Barletta, A. From chronic overfeeding to hepatic injury: Role of endoplasmic reticulum stress and inflammation. *Nutr. Metab. Cardiovasc. Dis.* **2011**, *21*, 222–230. [CrossRef]
250. Aravinthan, A.; Pietrosi, G.; Hoare, M.; Jupp, J.; Marshall, A.; Verrill, C.; Davies, S.; Bateman, A.; Sheron, N.; Allison, M.; et al. Hepatocyte expression of the senescence marker p21 is linked to fibrosis and an adverse liver-related outcome in alcohol-related liver disease. *PLoS ONE* **2013**, *8*, 72904. [CrossRef]
251. Aravinthan, A.; Scarpini, C.; Tachtatzis, P.; Verma, S.; Penrhyn-Lowe, S.; Harvey, R.; Davies, S.E.; Allison, M.; Coleman, N.; Alexander, G. Hepatocyte senescence predicts progression in non-alcohol-related fatty liver disease. *J. Hepatol.* **2013**, *58*, 549–556. [CrossRef] [PubMed]
252. Barnard, A.; Moch, A.; Saab, S. Relationship between Telomere Maintenance and Liver Disease. *Gut Liver.* **2019**, *13*, 11–15. [CrossRef] [PubMed]
253. Nault, J.C.; Ningarhari, M.; Rebouissou, S.; Zucman-Rossi, J. The role of telomeres and telomerase in cirrhosis and liver cancer. *Nat. Rev. Gastroenterol. Hepatol.* **2019**, *16*, 544–558. [CrossRef]
254. Wijayasiri, P.; Astbury, S.; Kaye, P.; Oakley, F.; Alexander, G.J.; Kendall, T.J.; Aravinthan, A.D. Role of Hepatocyte Senescence in the Activation of Hepatic Stellate Cells and Liver Fibrosis Progression. *Cells* **2022**, *11*, 2221. [CrossRef]
255. Cai, J.; Zhang, X.J.; Li, H. The Role of Innate Immune Cells in Nonalcoholic Steatohepatitis. *Hepatology* **2019**, *70*, 1026–1037. [CrossRef] [PubMed]
256. Krenkel, O.; Puengel, T.; Govaere, O.; Abdallah, A.T.; Mossanen, J.C.; Kohlhepp, M.; Liepelt, A.; Lefebvre, E.; Luedde, T.; Hellerbrand, C.; et al. Therapeutic inhibition of inflammatory monocyte recruitment reduces steatohepatitis and liver fibrosis. *Hepatology* **2018**, *67*, 1270–1283. [CrossRef]
257. Lee, Y.S.; Seki, E. In Vivo and In Vitro Models to Study Liver Fibrosis: Mechanisms and Limitations. *Cell Mol. Gastroenterol. Hepatol.* **2023**, *16*, 355–367. [CrossRef]
258. David, B.A.; Rezende, R.M.; Antunes, M.M.; Santos, M.M.; Freitas Lopes, M.A.; Diniz, A.B.; Sousa Pereira, R.V.; Marchesi, S.C.; Alvarenga, D.M.; Nakagaki, B.N.; et al. Combination of Mass Cytometry and Imaging Analysis Reveals Origin, Location, and Functional Repopulation of Liver Myeloid Cells in Mice. *Gastroenterology* **2016**, *15*, 1176–1191. [CrossRef]
259. Devisscher, L.; Scott, C.L.; Lefere, S.; Raevens, S.; Bogaerts, E.; Paridaens, A.; Verhelst, X.; Geerts, A.; Guilliams, M.; Van Vlierberghe, H. Non-alcoholic steatohepatitis induces transient changes within the liver macrophage pool. *Cell Immunol.* **2017**, *322*, 74–83. [CrossRef]
260. Ait Ahmed, Y.; Lafdil, F.; Tacke, F. Ambiguous Pathogenic Roles of Macrophages in Alcohol-Associated Liver Diseases. *Hepat. Med.* **2023**, *15*, 113–127. [CrossRef]
261. Wang, Z.; Du, K.; Jin, N.; Tang, B.; Zhang, W. Macrophage in liver Fibrosis: Identities and mechanisms. *Int. Immunopharmacol.* **2023**, *120*, 110357. [CrossRef] [PubMed]
262. An, S.Y.; Petrescu, A.D.; DeMorrow, S. Targeting Certain Interleukins as Novel Treatment Options for Liver Fibrosis. *Front. Pharmacol.* **2021**, *12*, 645703. [CrossRef] [PubMed]
263. Liu, J.; Yu, Q.; Wu, W.; Huang, X.; Broering, R.; Werner, M.; Roggendorf, M.; Yang, D.; Lu, M. TLR2 Stimulation Strengthens Intrahepatic Myeloid-Derived Cell-Mediated T Cell Tolerance through Inducing Kupffer Cell Expansion and IL-10 Production. *J. Immunol.* **2018**, *200*, 2341–2351. [CrossRef]
264. Wang, Q.; Zhang, H.; Chen, Z.; Chen, L.; Pan, F.; Zhou, Q. Proliferation of CD11b+ myeloid cells induced by TLR4 signaling promotes hepatitis B virus clearance. *Cytokine* **2022**, *153*, 155867. [CrossRef]
265. Li, Y.; He, M.; Wang, Z.; Duan, Z.; Guo, Z.; Wang, Z.; Gong, R.; Chu, T.; Cai, J.; Gao, B. STING signaling activation inhibits HBV replication and attenuates the severity of liver injury and HBV-induced fibrosis. *Cell Mol. Immunol.* **2022**, *19*, 92–107. [CrossRef]

266. Yang, Y.; Zhao, X.; Wang, Z.; Shu, W.; Li, L.; Li, Y.; Guo, Z.; Gao, B.; Xiong, S. Nuclear Sensor Interferon-Inducible Protein 16 Inhibits the Function of Hepatitis B Virus Covalently Closed Circular DNA by Integrating Innate Immune Activation and Epigenetic Suppression. *Hepatology* **2020**, *71*, 1154–1169. [CrossRef]
267. Pose, E.; Coll, M.; Martínez-Sánchez, C.; Zeng, Z.; Surewaard, B.G.J.; Català, C.; Velasco-de Andrés, M.; Lozano, J.J.; Ariño, S.; Fuster, D.; et al. Programmed Death Ligand 1 Is Overexpressed in Liver Macrophages in Chronic Liver Diseases, and Its Blockade Improves the Antibacterial Activity Against Infections. *Hepatology* **2021**, *74*, 296–311. [CrossRef]
268. Lough, J.; Rosenthall, L.; Arzoumanian, A.; Goresky, C.A. Kupffer cell depletion associated with capillarization of liver sinusoids in carbon tetrachloride-induced rat liver cirrhosis. *J. Hepatol.* **1987**, *5*, 190–198. [CrossRef]
269. Buonomo, E.L.; Mei, S.; Guinn, S.R.; Leo, I.R.; Peluso, M.J.; Nolan, M.A.; Schildberg, F.A.; Zhao, L.; Lian, C.; Xu, S.; et al. Liver stromal cells restrict macrophage maturation and stromal IL-6 limits the differentiation of cirrhosis-linked macrophages. *J. Hepatol.* **2022**, *76*, 1127–1137. [CrossRef]
270. Li, X.; Hollingshead, N.; Lampert, S.; Truong, C.D.; Li, W.; Niu, J.; Crispe, I.N.; Soysa, R. A conserved pathway of transdifferentiation in murine Kupffer cells. *Eur. J. Immunol.* **2021**, *51*, 2452–2463. [CrossRef]
271. Vadasz, Z.; Kessler, O.; Akiri, G.; Gengrinovitch, S.; Kagan, H.M.; Baruch, Y.; Izhak, O.B.; Neufeld, G. Abnormal deposition of collagen around hepatocytes in Wilson's disease is associated with hepatocyte specific expression of lysyl oxidase and lysyl oxidase like protein-2. *J. Hepatol.* **2005**, *43*, 499–507. [CrossRef] [PubMed]
272. Feng, M.; Ding, J.; Wang, M.; Zhang, J.; Zhu, X.; Guan, W. Kupffer-derived matrix metalloproteinase-9 contributes to liver fibrosis resolution. *Int. J. Biol. Sci.* **2018**, *14*, 1033–1040. [CrossRef] [PubMed]
273. Li, W.; He, F. Infusion of Kupffer Cells Expanded in Vitro Ameliorated Liver Fibrosis in a Murine Model of Liver Injury. *Cell Transplant.* **2021**, *30*, 9636897211004090. [CrossRef]
274. Wu, H.; Chen, G.; Wang, J.; Deng, M.; Yuan, F.; Gong, J. TIM-4 interference in Kupffer cells against CCL4-induced liver fibrosis by mediating Akt1/Mitophagy signalling pathway. *Cell Prolif.* **2020**, *53*, 12731. [CrossRef] [PubMed]
275. Tu, Z.; Bozorgzadeh, A.; Pierce, R.H.; Kurtis, J.; Crispe, I.N.; Orloff, M.S. TLR-dependent cross talk between human Kupffer cells and NK cells. *J. Exp. Med.* **2008**, *205*, 233–244. [CrossRef] [PubMed]
276. Boltjes, A.; van Montfoort, N.; Biesta, P.J.; Op den Brouw, M.L.; Kwekkeboom, J.; van der Laan, L.J.; Janssen, H.L.; Boonstra, A.; Woltman, A.M. Kupffer cells interact with hepatitis B surface antigen in vivo and in vitro, leading to proinflammatory cytokine production and natural killer cell function. *J. Infect. Dis.* **2015**, *211*, 1268–1278. [CrossRef]
277. Hosomura, N.; Kono, H.; Tsuchiya, M.; Ishii, K.; Ogiku, M.; Matsuda, M.; Fujii, H. HCV-related proteins activate Kupffer cells isolated from human liver tissues. *Dig. Dis. Sci.* **2011**, *56*, 1057–1064. [CrossRef]
278. Chang, S.; Dolganiuc, A.; Szabo, G. Toll-like receptors 1 and 6 are involved in TLR2-mediated macrophage activation by hepatitis C virus core and NS3 proteins. *J. Leukoc. Biol.* **2007**, *82*, 479–487. [CrossRef]
279. Ju, C.; Tacke, F. Hepatic macrophages in homeostasis and liver diseases: From pathogenesis to novel therapeutic strategies. *Cell Mol. Immunol.* **2016**, *13*, 316–327. [CrossRef]
280. Jindal, A.; Bruzzì, S.; Sutti, S.; Locatelli, I.; Bozzola, C.; Paternostro, C.; Parola, M.; Albano, E. Fat-laden macrophages modulate lobular inflammation in nonalcoholic steatohepatitis (NASH). *Exp. Mol. Pathol.* **2015**, *99*, 155–162. [CrossRef]
281. Hirsova, P.; Ibrahim, S.H.; Krishnan, A.; Verma, V.K.; Bronk, S.F.; Werneburg, N.W.; Charlton, M.R.; Shah, V.H.; Malhi, H.; Gores, G.J. Lipid-Induced Signaling Causes Release of Inflammatory Extracellular Vesicles From Hepatocytes. *Gastroenterology* **2016**, *150*, 956–967. [CrossRef] [PubMed]
282. Cannito, S.; Morello, E.; Bocca, C.; Foglia, B.; Benetti, E.; Novo, E.; Chiazza, F.; Rogazzo, M.; Fantozzi, R.; Povero, D.; et al. Microvesicles released from fat-laden cells promote activation of hepatocellular NLRP3 inflammasome: A pro-inflammatory link between lipotoxicity and non-alcoholic steatohepatitis. *PLoS ONE* **2017**, *12*, e0172575. [CrossRef] [PubMed]
283. Morello, E.; Sutti, S.; Foglia, B.; Novo, E.; Cannito, S.; Bocca, C.; Rajsky, M.; Bruzzì, S.; Abate, M.L.; Rosso, C.; et al. Hypoxia-inducible factor 2α drives nonalcoholic fatty liver progression by triggering hepatocyte release of histidine-rich glycoprotein. *Hepatology* **2018**, *67*, 2196–2214. [CrossRef]
284. Bartneck, M.; Fech, V.; Ehling, J.; Govaere, O.; Warzecha, K.T.; Hittatiya, K.; Vucur, M.; Gautheron, J.; Luedde, T.; Trautwein, C.; et al. Histidine-rich glycoprotein promotes macrophage activation and inflammation in chronic liver disease. *Hepatology* **2016**, *63*, 1310–1324. [CrossRef]
285. Suraweera, D.B.; Weeratunga, A.N.; Hu, R.W.; Pandol, S.J.; Hu, R. Alcoholic hepatitis: The pivotal role of Kupffer cells. *World J. Gastrointest. Pathophysiol.* **2015**, *6*, 90–98. [CrossRef]
286. Ju, C.; Mandrekar, P. Macrophages and Alcohol-Related Liver Inflammation. *Alcohol Res.* **2015**, *37*, 251–262.
287. Wang, M.; You, Q.; Lor, K.; Chen, F.; Gao, B.; Ju, C. Chronic alcohol ingestion modulates hepatic macrophage populations and functions in mice. *J. Leukoc. Biol.* **2014**, *96*, 657–665. [CrossRef]
288. Petrasek, J.; Bala, S.; Csak, T.; Lippai, D.; Kodys, K.; Menashy, V.; Barrieau, M.; Min, S.Y.; Kurt-Jones, E.A.; Szabo, G. IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. *J. Clin. Investig.* **2012**, *122*, 3476–3489. [CrossRef]

289. Calmus, Y.; Poupon, R. Shaping macrophages function and innate immunity by bile acids: Mechanisms and implication in cholestatic liver diseases. *Clin. Res. Hepatol. Gastroenterol.* **2014**, *38*, 550–556. [CrossRef]
290. Gong, Z.; Zhou, J.; Zhao, S.; Tian, C.; Wang, P.; Xu, C.; Chen, Y.; Cai, W.; Wu, J. Chenodeoxycholic acid activates NLRP3 inflammasome and contributes to cholestatic liver fibrosis. *Oncotarget* **2016**, *7*, 83951–83963. [CrossRef]
291. Guo, C.; Xie, S.; Chi, Z.; Zhang, J.; Liu, Y.; Zhang, L.; Zheng, M.; Zhang, X.; Xia, D.; Ke, Y.; et al. Bile Acids Control Inflammation and Metabolic Disorder through Inhibition of NLRP3 Inflammasome. *Immunity* **2016**, *45*, 802–816. [CrossRef] [PubMed]
292. Keitel, V.; Donner, M.; Winandy, S.; Kubitz, R.; Häussinger, D. Expression and function of the bile acid receptor TGR5 in Kupffer cells. *Biochem. Biophys. Res. Commun.* **2008**, *372*, 78–84. [CrossRef] [PubMed]
293. Duwaerts, C.C.; Gehring, S.; Cheng, C.W.; van Rooijen, N.; Gregory, S.H. Contrasting responses of Kupffer cells and inflammatory mononuclear phagocytes to biliary obstruction in a mouse model of cholestatic liver injury. *Liver Int.* **2013**, *33*, 255–265. [CrossRef] [PubMed]
294. Chang, J.; Hisamatsu, T.; Shimamura, K.; Yoneno, K.; Adachi, M.; Naruse, H.; Igarashi, T.; Higuchi, H.; Matsuoka, K.; Kitazume, M.T.; et al. Activated hepatic stellate cells mediate the differentiation of macrophages. *Hepatol. Res.* **2013**, *43*, 658–669. [CrossRef]
295. Xiao, C.; Ghosh, S. NF-kappaB, an evolutionarily conserved mediator of immune and inflammatory responses. *Adv. Exp. Med. Biol.* **2005**, *560*, 41–45.
296. Pahl, H.L. Activators and target genes of Rel/NF-kappaB transcription factors. *Oncogene* **1999**, *18*, 6853–6866. [CrossRef]
297. Luedde, T.; Schwabe, R.F. NF-κB in the liver--linking injury, fibrosis and hepatocellular carcinoma. *Nat. Rev. Gastroenterol. Hepatol.* **2011**, *8*, 108–118. [CrossRef]
298. Twu, Y.C.; Lee, T.S.; Lin, Y.L.; Hsu, S.M.; Wang, Y.H.; Liao, C.Y.; Wang, C.K.; Liang, Y.C.; Liao, Y.J. Niemann-Pick Type C2 Protein Mediates Hepatic Stellate Cells Activation by Regulating Free Cholesterol Accumulation. *Int. J. Mol. Sci.* **2016**, *17*, 1122. [CrossRef]
299. Tomita, K.; Teratani, T.; Suzuki, T.; Shimizu, M.; Sato, H.; Narimatsu, K.; Usui, S.; Furuhashi, H.; Kimura, A.; Nishiyama, K.; et al. Acyl-CoA:cholesterol acyltransferase 1 mediates liver fibrosis by regulating free cholesterol accumulation in hepatic stellate cells. *J. Hepatol.* **2014**, *61*, 98–106. [CrossRef]
300. Tomita, K.; Teratani, T.; Suzuki, T.; Shimizu, M.; Sato, H.; Narimatsu, K.; Okada, Y.; Kurihara, C.; Irie, R.; Yokoyama, H.; et al. Free cholesterol accumulation in hepatic stellate cells: Mechanism of liver fibrosis aggravation in nonalcoholic steatohepatitis in mice. *Hepatology* **2014**, *59*, 154–169. [CrossRef]
301. Teratani, T.; Tomita, K.; Suzuki, T.; Oshikawa, T.; Yokoyama, H.; Shimamura, K.; Tominaga, S.; Hiroi, S.; Irie, R.; Okada, Y.; et al. A high-cholesterol diet exacerbates liver fibrosis in mice via accumulation of free cholesterol in hepatic stellate cells. *Gastroenterology* **2012**, *142*, 152–164. [CrossRef] [PubMed]
302. Wang, X.; Cai, B.; Yang, X.; Sonubi, O.O.; Zheng, Z.; Ramakrishnan, R.; Shi, H.; Valenti, L.; Pajvani, U.B.; Sandhu, J.; et al. Cholesterol Stabilizes TAZ in Hepatocytes to Promote Experimental Non-alcoholic Steatohepatitis. *Cell Metab.* **2020**, *31*, 969–986. [CrossRef] [PubMed]
303. Zhang, H.; Yan, X.; Yang, C.; Zhan, Q.; Fu, Y.; Luo, H.; Luo, H. Intrahepatic T helper 17 cells recruited by hepatitis B virus X antigen-activated hepatic stellate cells exacerbate the progression of chronic hepatitis B virus infection. *J. Viral Hepat.* **2020**, *27*, 1138–1149. [CrossRef]
304. Chou, H.S.; Hsieh, C.C.; Yang, H.R.; Wang, L.; Arakawa, Y.; Brown, K.; Wu, Q.; Lin, F.; Peters, M.; Fung, J.J.; et al. Hepatic stellate cells regulate immune response by way of induction of myeloid suppressor cells in mice. *Hepatology* **2011**, *53*, 1007–1019. [CrossRef]
305. Jiang, G.; Yang, H.R.; Wang, L.; Wildey, G.M.; Fung, J.; Qian, S.; Lu, L. Hepatic stellate cells preferentially expand allogeneic CD4+ CD25+ FoxP3+ regulatory T cells in an IL-2-dependent manner. *Transplantation* **2008**, *86*, 1492–1502. [CrossRef]
306. Li, Y.; Lu, L.; Qian, S.; Fung, J.J.; Lin, F. Hepatic Stellate Cells Directly Inhibit B Cells via Programmed Death-Ligand 1. *J. Immunol.* **2016**, *196*, 1617–1625. [CrossRef]
307. Ding, X.; Saxena, N.K.; Lin, S.; Xu, A.; Srinivasan, S.; Anania, F.A. The roles of leptin and adiponectin: A novel paradigm in adipocytokine regulation of liver fibrosis and stellate cell biology. *Am. J. Pathol.* **2005**, *166*, 1655–1669. [CrossRef]
308. Ouchi, N.; Parker, J.L.; Lugus, J.J.; Walsh, K. Adipokines in inflammation and metabolic disease. *Nat. Rev. Immunol.* **2011**, *11*, 85–97. [CrossRef]
309. Saxena, N.K.; Anania, F.A. Adipocytokines and hepatic fibrosis. *Trends Endocrinol. Metab.* **2015**, *26*, 153–161. [CrossRef]
310. Zhai, X.; Yan, K.; Fan, J.; Niu, M.; Zhou, Q.; Zhou, Y.; Chen, H.; Zhou, Y. The β-catenin pathway contributes to the effects of leptin on SREBP-1c expression in rat hepatic stellate cells and liver fibrosis. *Br. J. Pharmacol.* **2013**, *169*, 197–212. [CrossRef]
311. Dong, Z.; Su, L.; Esmaili, S.; Iseli, T.J.; Ramezani-Moghadam, M.; Hu, L.; Xu, A.; George, J.; Wang, J. Adiponectin attenuates liver fibrosis by inducing nitric oxide production of hepatic stellate cells. *J. Mol. Med.* **2015**, *93*, 1327–1339. [CrossRef] [PubMed]
312. Kumar, P.; Smith, T.; Rahman, K.; Mells, J.E.; Thorn, N.E.; Saxena, N.K.; Anania, F.A. Adiponectin modulates focal adhesion disassembly in activated hepatic stellate cells: Implication for reversing hepatic fibrosis. *FASEB J.* **2014**, *28*, 5172–5183. [CrossRef] [PubMed]

313. Ramezani-Moghadam, M.; Wang, J.; Ho, V.; Iseli, T.J.; Alzahrani, B.; Xu, A.; Van der Poorten, D.; Qiao, L.; George, J.; Hebbard, L. Adiponectin reduces hepatic stellate cell migration by promoting tissue inhibitor of metalloproteinase-1 (TIMP-1) secretion. *J. Biol. Chem.* **2015**, *290*, 5533–5542. [CrossRef]
314. Tardelli, M.; Moreno-Viedma, V.; Zeyda, M.; Itariu, B.K.; Langer, F.B.; Prager, G.; Stulnig, T.M. Adiponectin regulates aquaglyceroporin expression in hepatic stellate cells altering their functional state. *J. Gastroenterol. Hepatol.* **2017**, *32*, 253–260. [CrossRef] [PubMed]
315. Wang, H.; Zhang, H.; Zhang, Z.; Huang, B.; Cheng, X.; Wang, D.; la Gahu, Z.; Xue, Z.; Da, Y.; Li, D.; et al. Adiponectin-derived active peptide ADP355 exerts anti-inflammatory and anti-fibrotic activities in thioacetamide-induced liver injury. *Sci. Rep.* **2016**, *6*, 19445. [CrossRef]
316. Carambia, A.; Freund, B.; Schwinge, D.; Heine, M.; Laschtowitz, A.; Huber, S.; Wraith, D.C.; Korn, T.; Schramm, C.; Lohse, A.W.; et al. TGF-β-dependent induction of $CD4^+CD25^+Foxp3^+$ Tregs by liver sinusoidal endothelial cells. *J. Hepatol.* **2014**, *61*, 594–599. [CrossRef]
317. Yang, M.; Zhang, C. The role of liver sinusoidal endothelial cells in cancer liver metastasis. *Am. J. Cancer Res.* **2021**, *11*, 1845–1860.
318. Ishikawa, T.; Yokoyama, H.; Matsuura, T.; Fujiwara, Y. Fc gamma RIIb expression levels in human liver sinusoidal endothelial cells during progression of non-alcoholic fatty liver disease. *PLoS ONE* **2019**, *14*, 0211543. [CrossRef]
319. Baiocchini, A.; Del Nonno, F.; Taibi, C.; Visco-Comandini, U.; D'Offizi, G.; Piacentini, M.; Falasca, L. Liver sinusoidal endothelial cells (LSECs) modifications in patients with chronic hepatitis C. *Sci. Rep.* **2019**, *9*, 8760, Erratum in: *Sci. Rep.* **2020**, *10*, 1420. [CrossRef]
320. Maretti-Mira, A.C.; Wang, X.; Wang, L.; DeLeve, L.D. Incomplete Differentiation of Engrafted Bone Marrow Endothelial Progenitor Cells Initiates Hepatic Fibrosis in the Rat. *Hepatology* **2019**, *69*, 1259–1272. [CrossRef]
321. Desroches-Castan, A.; Tillet, E.; Ricard, N.; Ouarné, M.; Mallet, C.; Belmudes, L.; Couté, Y.; Boillot, O.; Scoazec, J.Y.; Bailly, S.; et al. Bone Morphogenetic Protein 9 Is a Paracrine Factor Controlling Liver Sinusoidal Endothelial Cell Fenestration and Protecting Against Hepatic Fibrosis. *Hepatology* **2019**, *70*, 1392–1408. [CrossRef] [PubMed]
322. Desroches-Castan, A.; Tillet, E.; Ricard, N.; Ouarné, M.; Mallet, C.; Feige, J.J.; Bailly, S. Differential Consequences of Bmp9 Deletion on Sinusoidal Endothelial Cell Differentiation and Liver Fibrosis in 129/Ola and C57BL/6 Mice. *Cells* **2019**, *8*, 1079. [CrossRef] [PubMed]
323. Li, P.; Li, Y.; Zhu, L.; Yang, Z.; He, J.; Wang, L.; Shang, Q.; Pan, H.; Wang, H.; Ma, X.; et al. Targeting secreted cytokine BMP9 gates the attenuation of hepatic fibrosis. *Biochim. Biophys. Acta Mol. Basis Dis.* **2018**, *1864*, 709–720. [CrossRef] [PubMed]
324. Chen, H.; Li, Y.Y.; Nio, K.; Tang, H. Unveiling the Impact of BMP9 in Liver Diseases: Insights into Pathogenesis and Therapeutic Potential. *Biomolecules* **2024**, *14*, 1013. [CrossRef]
325. Wang, L.; Feng, Y.; Xie, X.; Wu, H.; Su, X.N.; Qi, J.; Xin, W.; Gao, L.; Zhang, Y.; Shah, V.H.; et al. Neuropilin-1 aggravates liver cirrhosis by promoting angiogenesis via VEGFR2-dependent PI3K/Akt pathway in hepatic sinusoidal endothelial cells. *EBioMedicine* **2019**, *43*, 525–536. [CrossRef]
326. Kong, L.J.; Li, H.; Du, Y.J.; Pei, F.H.; Hu, Y.; Zhao, L.L.; Chen, J. Vatalanib, a tyrosine kinase inhibitor, decreases hepatic fibrosis and sinusoidal capillarization in CCl4-induced fibrotic mice. *Mol. Med. Rep.* **2017**, *15*, 2604–2610. [CrossRef]
327. Ogawa, H.; Kaji, K.; Nishimura, N.; Takagi, H.; Ishida, K.; Takaya, H.; Kawaratani, H.; Moriya, K.; Namisaki, T.; Akahane, T.; et al. Lenvatinib prevents liver fibrosis by inhibiting hepatic stellate cell activation and sinusoidal capillarization in experimental liver fibrosis. *J. Cell Mol. Med.* **2021**, *25*, 4001–4013. [CrossRef]
328. Wu, Y.; Li, Z.; Xiu, A.Y.; Meng, D.X.; Wang, S.N.; Zhang, C.Q. Carvedilol attenuates carbon tetrachloride-induced liver fibrosis and hepatic sinusoidal capillarization in mice. *Drug Des. Devel Ther.* **2019**, *13*, 2667–2676. [CrossRef]
329. Wang, Q.; Zhang, F.; Lei, Y.; Liu, P.; Liu, C.; Tao, Y. microRNA-322/424 promotes liver fibrosis by regulating angiogenesis through targeting CUL2/HIF-1α pathway. *Life Sci.* **2021**, *266*, 118819. [CrossRef]
330. Meyer, J.; Balaphas, A.; Fontana, P.; Morel, P.; Robson, S.C.; Sadoul, K.; Gonelle-Gispert, C.; Bühler, L. Platelet Interactions with Liver Sinusoidal Endothelial Cells and Hepatic Stellate Cells Lead to Hepatocyte Proliferation. *Cells* **2020**, *9*, 1243. [CrossRef]
331. Zheng, Y.; Wang, J.; Zhao, T.; Wang, L.; Wang, J. Modulation of the VEGF/AKT/eNOS signaling pathway to regulate liver angiogenesis to explore the anti-hepatic fibrosis mechanism of curcumol. *J. Ethnopharmacol.* **2021**, *280*, 114480. [CrossRef] [PubMed]
332. Ruart, M.; Chavarria, L.; Campreciós, G.; Suárez-Herrera, N.; Montironi, C.; Guixé-Muntet, S.; Bosch, J.; Friedman, S.L.; Garcia-Pagán, J.C.; Hernández-Gea, V. Impaired endothelial autophagy promotes liver fibrosis by aggravating the oxidative stress response during acute liver injury. *J. Hepatol.* **2019**, *70*, 458–469. [CrossRef] [PubMed]
333. Li, Y.; Liu, R.; Wu, J.; Li, X. Self-eating: Friend or foe? The emerging role of autophagy in fibrotic diseases. *Theranostics* **2020**, *10*, 7993–8017. [CrossRef]
334. Luo, X.; Wang, D.; Zhu, X.; Wang, G.; You, Y.; Ning, Z.; Li, Y.; Jin, S.; Huang, Y.; Hu, Y.; et al. Autophagic degradation of caveolin-1 promotes liver sinusoidal endothelial cells defenestration. *Cell Death Dis.* **2018**, *9*, 576. [CrossRef]

335. Kohara, S.; Ogawa, K. Eph/Ephrin Promotes the Adhesion of Liver Tissue-Resident Macrophages to a Mimicked Surface of Liver Sinusoidal Endothelial Cells. *Biomedicines* **2022**, *10*, 3234. [CrossRef]
336. Sakai, M.; Troutman, T.D.; Seidman, J.S.; Ouyang, Z.; Spann, N.J.; Abe, Y.; Ego, K.M.; Bruni, C.M.; Deng, Z.; Schlachetzki, J.C.M.; et al. Liver-Derived Signals Sequentially Reprogram Myeloid Enhancers to Initiate and Maintain Kupffer Cell Identity. *Immunity* **2019**, *51*, 655–670. [CrossRef]
337. Ganesan, L.P.; Mohanty, S.; Kim, J.; Clark, K.R.; Robinson, J.M.; Anderson, C.L. Rapid and efficient clearance of blood-borne virus by liver sinusoidal endothelium. *PLoS Pathog.* **2011**, *7*, 1002281. [CrossRef]
338. Mates, J.M.; Yao, Z.; Cheplowitz, A.M.; Suer, O.; Phillips, G.S.; Kwiek, J.J.; Rajaram, M.V.; Kim, J.; Robinson, J.M.; Ganesan, L.P.; et al. Mouse Liver Sinusoidal Endothelium Eliminates HIV-Like Particles from Blood at a Rate of 100 Million per Minute by a Second-Order Kinetic Process. *Front. Immunol.* **2017**, *8*, 35. [CrossRef]
339. Breiner, K.M.; Schaller, H.; Knolle, P.A. Endothelial cell-mediated uptake of a hepatitis B virus: A new concept of liver targeting of hepatotropic microorganisms. *Hepatology* **2001**, *34*, 803–808. [CrossRef]
340. Cormier, E.G.; Tsamis, F.; Kajumo, F.; Durso, R.J.; Gardner, J.P.; Dragic, T. CD81 is an entry coreceptor for hepatitis C virus. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 7270–7274. [CrossRef]
341. Rowe, I.A.; Galsinh, S.K.; Wilson, G.K.; Parker, R.; Durant, S.; Lazar, C.; Branza-Nichita, N.; Bicknell, R.; Adams, D.H.; Balfe, P.; et al. Paracrine signals from liver sinusoidal endothelium regulate hepatitis C virus replication. *Hepatology* **2014**, *59*, 375–384. [CrossRef] [PubMed]
342. Giugliano, S.; Kriss, M.; Golden-Mason, L.; Dobrinskikh, E.; Stone, A.E.; Soto-Gutierrez, A.; Mitchell, A.; Khetani, S.R.; Yamane, D.; Stoddard, M.; et al. Hepatitis C virus infection induces autocrine interferon signaling by human liver endothelial cells and release of exosomes, which inhibits viral replication. *Gastroenterology* **2015**, *148*, 392–402. [CrossRef] [PubMed]
343. Gao, F.; Chiu, S.M.; Motan, D.A.; Zhang, Z.; Chen, L.; Ji, H.L.; Tse, H.F.; Fu, Q.L.; Lian, Q. Mesenchymal stem cells and immunomodulation: Current status and future prospects. *Cell Death Dis.* **2016**, *7*, 2062. [CrossRef] [PubMed]
344. Lee, K.D.; Kuo, T.K.; Whang-Peng, J.; Chung, Y.F.; Lin, C.T.; Chou, S.H.; Chen, J.R.; Chen, Y.P.; Lee, O.K. In vitro hepatic differentiation of human mesenchymal stem cells. *Hepatology* **2004**, *40*, 1275–1284. [CrossRef]
345. Li, W.; Ren, G.; Huang, Y.; Su, J.; Han, Y.; Li, J.; Chen, X.; Cao, K.; Chen, Q.; Shou, P.; et al. Mesenchymal stem cells: A double-edged sword in regulating immune responses. *Cell Death Differ.* **2012**, *19*, 1505–1513. [CrossRef]
346. Shi, Y.; Wang, Y.; Li, Q.; Liu, K.; Hou, J.; Shao, C.; Wang, Y. Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases. *Nat. Rev. Nephrol.* **2018**, *14*, 493–507. [CrossRef]
347. Viswanathan, S.; Shi, Y.; Galipeau, J.; Krampera, M.; Leblanc, K.; Martin, I.; Nolta, J.; Phinney, D.G.; Sensebe, L. Mesenchymal stem versus stromal cells: International Society for Cell & Gene Therapy (ISCT®) Mesenchymal Stromal Cell committee position statement on nomenclature. *Cytotherapy* **2019**, *21*, 1019–1024.
348. Costa, L.A.; Eiro, N.; Fraile, M.; Gonzalez, L.O.; Saá, J.; Garcia-Portabella, P.; Vega, B.; Schneider, J.; Vizoso, F.J. Functional heterogeneity of mesenchymal stem cells from natural niches to culture conditions: Implications for further clinical uses. *Cell Mol. Life Sci.* **2021**, *78*, 447–467. [CrossRef]
349. Han, Y.; Yang, J.; Fang, J.; Zhou, Y.; Candi, E.; Wang, J.; Hua, D.; Shao, C.; Shi, Y. The secretion profile of mesenchymal stem cells and potential applications in treating human diseases. *Signal Transduct. Target. Ther.* **2022**, *7*, 92. [CrossRef]
350. Murakami, J.; Ishii, M.; Suehiro, F.; Ishihata, K.; Nakamura, N.; Nishimura, M. Vascular endothelial growth factor-C induces osteogenic differentiation of human mesenchymal stem cells through the ERK and RUNX2 pathway. *Biochem. Biophys. Res. Commun.* **2017**, *484*, 710–718. [CrossRef]
351. Deng, Y.; Zhang, Y.; Ye, L.; Zhang, T.; Cheng, J.; Chen, G.; Zhang, Q.; Yang, Y. Umbilical Cord-derived Mesenchymal Stem Cells Instruct Monocytes Towards an IL10-producing Phenotype by Secreting IL6 and HGF. *Sci. Rep.* **2016**, *6*, 37566. [CrossRef] [PubMed]
352. Prockop, D.J. Concise review: Two negative feedback loops place mesenchymal stem/stromal cells at the center of early regulators of inflammation. *Stem Cells* **2013**, *31*, 2042–2046. [CrossRef] [PubMed]
353. Ezquer, F.; Ezquer, M.; Contador, D.; Ricca, M.; Simon, V.; Conget, P. The antidiabetic effect of mesenchymal stem cells is unrelated to their transdifferentiation potential but to their capability to restore Th1/Th2 balance and to modify the pancreatic microenvironment. *Stem Cells* **2012**, *30*, 1664–1674. [CrossRef]
354. Tao, H.; Liu, Q.; Zeng, A.; Song, L. Unlocking the potential of Mesenchymal stem cells in liver Fibrosis: Insights into the impact of autophagy and aging. *Int. Immunopharmacol.* **2023**, *21*, 110497. [CrossRef]
355. Giacomini, C.; Granéli, C.; Hicks, R.; Dazzi, F. The critical role of apoptosis in mesenchymal stromal cell therapeutics and implications in homeostasis and normal tissue repair. *Cell Mol. Immunol.* **2023**, *20*, 570–582. [CrossRef]
356. Li, P.; Ou, Q.; Shi, S.; Shao, C. Immunomodulatory properties of mesenchymal stem cells/dental stem cells and their therapeutic applications. *Cell Mol. Immunol.* **2023**, *20*, 558–569. [CrossRef]
357. Zhou, J.; Shi, Y. Mesenchymal stem/stromal cells (MSCs): Origin, immune regulation, and clinical applications. *Cell Mol. Immunol.* **2023**, *20*, 555–557. [CrossRef]

358. Abel, A.M.; Yang, C.; Thakar, M.S.; Malarkannan, S. Natural Killer Cells: Development, Maturation, and Clinical Utilization. *Front. Immunol.* **2018**, *9*, 1869. [CrossRef]
359. Melhem, A.; Muhanna, N.; Bishara, A.; Alvarez, C.E.; Ilan, Y.; Bishara, T.; Horani, A.; Nassar, M.; Friedman, S.L.; Safadi, R. Anti-fibrotic activity of NK cells in experimental liver injury through killing of activated HSC. *J. Hepatol.* **2006**, *45*, 60–71. [CrossRef]
360. Radaeva, S.; Sun, R.; Jaruga, B.; Nguyen, V.T.; Tian, Z.; Gao, B. Natural killer cells ameliorate liver fibrosis by killing activated stellate cells in NKG2D-dependent and tumor necrosis factor-related apoptosis-inducing ligand-dependent manners. *Gastroenterology* **2006**, *130*, 435–452. [CrossRef]
361. Baroni, G.S.; D'Ambrosio, L.; Curto, P.; Casini, A.; Mancini, R.; Jezequel, A.M.; Benedetti, A. Interferon gamma decreases hepatic stellate cell activation and extracellular matrix deposition in rat liver fibrosis. *Hepatology* **1996**, *23*, 1189–1199. [CrossRef] [PubMed]
362. Jeong, W.I.; Park, O.; Radaeva, S.; Gao, B. STAT1 inhibits liver fibrosis in mice by inhibiting stellate cell proliferation and stimulating NK cell cytotoxicity. *Hepatology* **2006**, *44*, 1441–1451. [CrossRef] [PubMed]
363. Choi, W.M.; Ryu, T.; Lee, J.H.; Shim, Y.R.; Kim, M.H.; Kim, H.H.; Kim, Y.E.; Yang, K.; Kim, K.; Choi, S.E.; et al. Metabotropic Glutamate Receptor 5 in Natural Killer Cells Attenuates Liver Fibrosis by Exerting Cytotoxicity to Activated Stellate Cells. *Hepatology* **2021**, *74*, 2170–2185. [CrossRef] [PubMed]
364. Kawarabayashi, N.; Seki, S.; Hatsuse, K.; Ohkawa, T.; Koike, Y.; Aihara, T.; Habu, Y.; Nakagawa, R.; Ami, K.; Hiraide, H.; et al. Decrease of CD56(+)T cells and natural killer cells in cirrhotic livers with hepatitis C may be involved in their susceptibility to hepatocellular carcinoma. *Hepatology* **2000**, *32*, 962–969. [CrossRef]
365. Morishima, C.; Paschal, D.M.; Wang, C.C.; Yoshihara, C.S.; Wood, B.L.; Yeo, A.E.; Emerson, S.S.; Shuhart, M.C.; Gretch, D.R. Decreased NK cell frequency in chronic hepatitis C does not affect ex vivo cytolytic killing. *Hepatology* **2006**, *43*, 573–580. [CrossRef]
366. Muhanna, N.; Doron, S.; Wald, O.; Horani, A.; Eid, A.; Pappo, O.; Friedman, S.L.; Safadi, R. Activation of hepatic stellate cells after phagocytosis of lymphocytes: A novel pathway of fibrogenesis. *Hepatology* **2008**, *48*, 963–977. [CrossRef]
367. Gan, J.; Mao, X.R.; Zheng, S.J.; Li, J.F. Invariant natural killer T cells: Not to be ignored in liver disease. *J. Dig. Dis.* **2021**, *22*, 136–142. [CrossRef]
368. Sajid, M.; Liu, L.; Sun, C. The Dynamic Role of NK Cells in Liver Cancers: Role in HCC and HBV Associated HCC and Its Therapeutic Implications. *Front. Immunol.* **2022**, *13*, 887186. [CrossRef]
369. Ma, Q.; Dong, X.; Liu, S.; Zhong, T.; Sun, D.; Zong, L.; Zhao, C.; Lu, Q.; Zhang, M.; Gao, Y.; et al. Hepatitis B e Antigen Induces NKG2A+ Natural Killer Cell Dysfunction via Regulatory T Cell-Derived Interleukin 10 in Chronic Hepatitis B Virus Infection. *Front. Cell Dev. Biol.* **2020**, *8*, 421. [CrossRef]
370. Diedrich, T.; Kummer, S.; Galante, A.; Drolz, A.; Schlicker, V.; Lohse, A.W.; Kluwe, J.; Eberhard, J.M.; Schulze Zur Wiesch, J. Characterization of the immune cell landscape of patients with NAFLD. *PLoS ONE* **2020**, *15*, 0230307. [CrossRef]
371. Gu, M.; Zhang, Y.; Lin, Z.; Hu, X.; Zhu, Y.; Xiao, W.; Jia, X.; Chen, W.; Lu, G.; Gong, W. Decrease in UCP1 by sustained high lipid promotes NK cell necroptosis to exacerbate nonalcoholic liver fibrosis. *Cell Death Dis.* **2024**, *15*, 518. [CrossRef] [PubMed]
372. Ravichandran, G.; Neumann, K.; Berkhout, L.K.; Weidemann, S.; Langeneckert, A.E.; Schwinge, D.; Poch, T.; Huber, S.; Schiller, B.; Hess, L.U.; et al. Interferon-γ-dependent immune responses contribute to the pathogenesis of sclerosing cholangitis in mice. *J. Hepatol.* **2019**, *71*, 773–782. [CrossRef] [PubMed]
373. Siwicki, M.; Kubes, P. Neutrophils in host defense, healing, and hypersensitivity: Dynamic cells within a dynamic host. *J. Allergy Clin. Immunol.* **2023**, *151*, 634–655. [CrossRef] [PubMed]
374. Brinkmann, V.; Reichard, U.; Goosmann, C.; Fauler, B.; Uhlemann, Y.; Weiss, D.S.; Weinrauch, Y.; Zychlinsky, A. Neutrophil extracellular traps kill bacteria. *Science* **2004**, *303*, 1532–1535. [CrossRef]
375. Koyama, Y.; Wang, P.; Liang, S.; Iwaisako, K.; Liu, X.; Xu, J.; Zhang, M.; Sun, M.; Cong, M.; Karin, D.; et al. Mesothelin/mucin 16 signaling in activated portal fibroblasts regulates cholestatic liver fibrosis. *J. Clin. Investig.* **2017**, *127*, 1254–1270. [CrossRef]
376. Mridha, A.R.; Wree, A.; Robertson, A.A.B.; Yeh, M.M.; Johnson, C.D.; Van Rooyen, D.M.; Haczeyni, F.; Teoh, N.C.; Savard, C.; Ioannou, G.N.; et al. NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice. *J. Hepatol.* **2017**, *66*, 1037–1046. [CrossRef]
377. Moles, A.; Murphy, L.; Wilson, C.L.; Chakraborty, J.B.; Fox, C.; Park, E.J.; Mann, J.; Oakley, F.; Howarth, R.; Brain, J.; et al. A TLR2/S100A9/CXCL-2 signaling network is necessary for neutrophil recruitment in acute and chronic liver injury in the mouse. *J. Hepatol.* **2014**, *60*, 782–791. [CrossRef]
378. Peiseler, M.; Kubes, P. More friend than foe: The emerging role of neutrophils in tissue repair. *J. Clin. Investig.* **2019**, *129*, 2629–2639. [CrossRef]
379. Peiseler, M.; Schwabe, R.; Hampe, J.; Kubes, P.; Heikenwälder, M.; Tacke, F. Immune mechanisms linking metabolic injury to inflammation and fibrosis in fatty liver disease—Novel insights into cellular communication circuits. *J. Hepatol.* **2022**, *77*, 1136–1160. [CrossRef]
380. Wan, Y.; Li, X.; Slevin, E.; Harrison, K.; Li, T.; Zhang, Y.; Klaunig, J.E.; Wu, C.; Shetty, A.K.; Dong, X.C.; et al. Endothelial dysfunction in pathological processes of chronic liver disease during aging. *FASEB J.* **2022**, *36*, e22125. [CrossRef]

381. Inverso, D.; Iannacone, M. Spatiotemporal dynamics of effector CD8+ T cell responses within the liver. *J. Leukoc. Biol.* **2016**, *99*, 51–55. [CrossRef] [PubMed]
382. Wohlleber, D.; Knolle, P.A. The role of liver sinusoidal cells in local hepatic immune surveillance. *Clin. Transl. Immunol.* **2016**, *5*, 117. [CrossRef] [PubMed]
383. Pennington, D.J.; Vermijlen, D.; Wise, E.L.; Clarke, S.L.; Tigelaar, R.E.; Hayday, A.C. The integration of conventional and unconventional T cells that characterizes cell-mediated responses. *Adv. Immunol.* **2005**, *87*, 27–59. [PubMed]
384. Godfrey, D.I.; Uldrich, A.P.; McCluskey, J.; Rossjohn, J.; Moody, D.B. The burgeoning family of unconventional T cells. *Nat. Immunol.* **2015**, *16*, 1114–1123. [CrossRef]
385. Nguyen, Q.P.; Deng, T.Z.; Witherden, D.A.; Goldrath, A.W. Origins of CD4+ circulating and tissue-resident memory T-cells. *Immunology* **2019**, *157*, 3–12. [CrossRef]
386. Zhang, M.; Zhang, S. T Cells in Fibrosis and Fibrotic Diseases. *Front. Immunol.* **2020**, *11*, 1142. [CrossRef]
387. Wang, H.; Luo, H.; Wan, X.; Fu, X.; Mao, Q.; Xiang, X.; Zhou, Y.; He, W.; Zhang, J.; Guo, Y.; et al. TNF-α/IFN-γ profile of HBV-specific CD4 T cells is associated with liver damage and viral clearance in chronic HBV infection. *J. Hepatol.* **2020**, *72*, 45–56. [CrossRef]
388. Li, Y.; You, Z.; Tang, R.; Ma, X. Tissue-resident memory T cells in chronic liver diseases: Phenotype, development and function. *Front. Immunol.* **2022**, *13*, 967055. [CrossRef]
389. Herkel, J.; Jagemann, B.; Wiegard, C.; Lazaro, J.F.; Lueth, S.; Kanzler, S.; Blessing, M.; Schmitt, E.; Lohse, A.W. MHC class II-expressing hepatocytes function as antigen-presenting cells and activate specific CD4 T lymphocyutes. *Hepatology* **2003**, *37*, 1079–1085. [CrossRef]
390. Koch, K.S.; Leffert, H.L. Hypothesis: Targeted Ikkβ deletion upregulates MIF signaling responsiveness and MHC class II expression in mouse hepatocytes. *Hepat. Med.* **2010**, *2010*, 39–47. [CrossRef]
391. Cabeza-Cabrerizo, M.; Cardoso, A.; Minutti, C.M.; Pereira da Costa, M.; Reis e Sousa, C. Dendritic Cells Revisited. *Annu. Rev. Immunol.* **2021**, *39*, 131–166. [CrossRef] [PubMed]
392. Eckert, C.; Klein, N.; Kornek, M.; Lukacs-Kornek, V. The complex myeloid network of the liver with diverse functional capacity at steady state and in inflammation. *Front. Immunol.* **2015**, *6*, 179. [CrossRef] [PubMed]
393. Rahman, A.H.; Aloman, C. Dendritic cells and liver fibrosis. *Biochim. Biophys. Acta* **2013**, *1832*, 998–1004. [CrossRef] [PubMed]
394. Doherty, D.G. Immunity, tolerance and autoimmunity in the liver: A comprehensive review. *J. Autoimmun.* **2016**, *66*, 60–75. [CrossRef]
395. Guilliams, M.; Bonnardel, J.; Haest, B.; Vanderborght, B.; Wagner, C.; Remmerie, A.; Bujko, A.; Martens, L.; Thoné, T.; Browaeys, R.; et al. Spatial proteogenomics reveals distinct and evolutionarily conserved hepatic macrophage niches. *Cell* **2022**, *185*, 379–396. [CrossRef]
396. Haas, J.T.; Vonghia, L.; Mogilenko, D.A.; Verrijken, A.; Molendi-Coste, O.; Fleury, S.; Deprince, A.; Nikitin, A.; Woitrain, E.; Ducrocq-Geoffroym, L.; et al. Transcriptional Network Analysis Implicates Altered Hepatic Immune Function in NASH development and resolution. *Nat. Metab.* **2019**, *1*, 604–614. [CrossRef]
397. Kambayashi, T.; Laufer, T.M. Atypical MHC class II-expressing antigen-presenting cells: Can anything replace a dendritic cell? *Nat. Rev. Immunol.* **2014**, *14*, 719–730. [CrossRef]
398. Alcover, A.; Alarcón, B.; Di Bartolo, V. Cell Biology of T Cell Receptor Expression and Regulation. *Annu. Rev. Immunol.* **2018**, *36*, 103–125. [CrossRef]
399. Elhai, M.; Avouac, J.; Hoffmann-Vold, A.M.; Ruzehaji, N.; Amiar, O.; Ruiz, B.; Brahiti, H.; Ponsoye, M.; Fréchet, M.; Burgevin, A.; et al. OX40L blockade protects against inflammation-driven fibrosis. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 3901–3910. [CrossRef]
400. Sun, G.; Jin, H.; Zhang, C.; Meng, H.; Zhao, X.; Wei, D.; Ou, X.; Wang, Q.; Li, S.; Wang, T.; et al. OX40 Regulates Both Innate and Adaptive Immunity and Promotes Nonalcoholic Steatohepatitis. *Cell Rep.* **2018**, *25*, 3786–3799. [CrossRef]
401. Webb, G.J.; Hirschfield, G.M.; Lane, P.J. OX40, OX40L and Autoimmunity: A Comprehensive Review. *Clin. Rev. Allergy Immunol.* **2016**, *50*, 312–332. [CrossRef] [PubMed]
402. Shah, K.; Al-Haidari, A.; Sun, J.; Kazi, J.U. T cell receptor (TCR) signaling in health and disease. *Signal Transduct. Target. Ther.* **2021**, *6*, 412. [CrossRef] [PubMed]
403. Liang, Q.; Hu, Y.; Zhang, M.; Lin, C.; Zhang, W.; Li, Y.; Zhu, P.; Xue, P.; Chen, Y.; Li, Q.; et al. The T Cell Receptor Immune Repertoire Protects the Liver From Reconsitution. *Front. Immunol.* **2020**, *11*, 584979. [CrossRef] [PubMed]
404. Safadi, R.; Ohta, M.; Alvarez, C.E.; Fiel, M.I.; Bansal, M.; Mehal, W.Z.; Friedman, S.L. Immune stimulation of hepatic fibrogenesis by CD8 cells and attenuation by transgenic interleukin-10 from hepatocytes. *Gastroenterology* **2004**, *127*, 870–882. [CrossRef]
405. Tang, L.; Chen, C.; Gao, X.; Zhang, W.; Yan, X.; Zhou, Y.; Guo, L.; Zheng, X.; Wang, W.; Yang, F.; et al. Interleukin 21 Reinvigorates the Antiviral Activity of Hepatitis B Virus (HBV)-Specific CD8+ T Cells in Chronic HBV Infection. *J. Infect. Dis.* **2019**, *219*, 750–759. [CrossRef]

406. Liu, H.; Hu, B.; Huang, J.; Wang, Q.; Wang, F.; Pan, F.; Chen, L. Endoplasmic Reticulum Aminopeptidase 1 Is Involved in Anti-viral Immune Response of Hepatitis B Virus by Trimming Hepatitis B Core Antigen to Generate 9-Mers Peptides. *Front. Microbiol.* **2022**, *13*, 829241. [CrossRef]
407. Li, C.; Yu, T.; Shi, X.; Yu, J. Interleukin-33 Reinvigorates Antiviral Function of Viral-Specific CD8+ T Cells in Chronic Hepatitis B Virus Infection. *Viral Immunol.* **2022**, *35*, 41–49. [CrossRef]
408. Roger, P.M.; Chaillou, S.; Breittmayer, J.P.; Dahman, M.; St Paul, M.C.; Chevallier, P.; Benzaken, S.; Ticchioni, M.; Bernard, A.; Dellamonica, P.; et al. Intrahepatic CD4 T-Cell apoptosis is related to METAVIR score in patients with chronic hepatitis C virus. *Scand. J. Immunol.* **2005**, *62*, 168–175. [CrossRef]
409. Glässner, A.; Eisenhardt, M.; Kokordelis, P.; Krämer, B.; Wolter, F.; Nischalke, H.D.; Boesecke, C.; Sauerbruch, T.; Rockstroh, J.K.; Spengler, U.; et al. Impaired $CD4^+$ T cell stimulation of NK cell anti-fibrotic activity may contribute to accelerated liver fibrosis progression in HIV/HCV patients. *J. Hepatol.* **2013**, *59*, 427–433. [CrossRef]
410. Her, Z.; Tan, J.H.L.; Lim, Y.S.; Tan, S.Y.; Chan, X.Y.; Tan, W.W.S.; Liu, M.; Yong, K.S.M.; Lai, F.; Ceccarello, E.; et al. CD4+ T Cells Mediate the Development of Liver Fibrosis in High Fat Diet-Induced NAFLD in Humanized Mice. *Front. Immunol.* **2020**, *11*, 580968. [CrossRef]
411. Rau, M.; Schilling, A.K.; Meertens, J.; Hering, I.; Weiss, J.; Jurowich, C.; Kudlich, T.; Hermanns, H.M.; Bantel, H.; Beyersdorf, N.; et al. Progression from Nonalcoholic Fatty Liver to Nonalcoholic Steatohepatitis Is Marked by a Higher Frequency of Th17 Cells in the Liver and an Increased Th17/Resting Regulatory T Cell Ratio in Peripheral Blood and in the Liver. *J. Immunol.* **2016**, *196*, 97–105. [CrossRef] [PubMed]
412. Sutti, S.; Albano, E. Adaptive immunity: An emerging player in the progression of NAFLD. *Nat. Rev. Gastroenterol. Hepatol.* **2020**, *17*, 81–92. [CrossRef] [PubMed]
413. O'Garra, A.; Robinson, D. Development and function of T helper 1 cells. *Adv. Immunol.* **2004**, *83*, 133–162. [PubMed]
414. Luo, X.Y.; Takahara, T.; Kawai, K.; Fujino, M.; Sugiyama, T.; Tsuneyama, K.; Tsukada, K.; Nakae, S.; Zhong, L.; Li, X.K. IFN-γ deficiency attenuates hepatic inflammation and fibrosis in a steatohepatitis model induced by a methionine- and choline-deficient high-fat diet. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2013**, *305*, 891–899. [CrossRef]
415. Ferreyra Solari, N.E.; Inzaugarat, M.E.; Baz, P.; De Matteo, E.; Lezama, C.; Galoppo, M.; Galoppo, C.; Cherñavsky, A.C. The role of innate cells is coupled to a Th1-polarized immune response in pediatric nonalcoholic steatohepatitis. *J. Clin. Immunol.* **2012**, *32*, 611–621. [CrossRef]
416. Inzaugarat, M.E.; Ferreyra Solari, N.E.; Billordo, L.A.; Abecasis, R.; Gadano, A.C.; Cherñavsky, A.C. Altered phenotype and functionality of circulating immune cells characterize adult patients with nonalcoholic steatohepatitis. *J. Clin. Immunol.* **2011**, *31*, 1120–1130. [CrossRef]
417. Rolla, S.; Alchera, E.; Imarisio, C.; Bardina, V.; Valente, G.; Cappello, P.; Mombello, C.; Follenzi, A.; Novelli, F.; Carini, R. The balance between IL-17 and IL-22 produced by liver-infiltrating T-helper cells critically controls NASH development in mice. *Clin. Sci.* **2016**, *130*, 193–203. [CrossRef]
418. Nakayama, T.; Hirahara, K.; Onodera, A.; Endo, Y.; Hosokawa, H.; Shinoda, K.; Tumes, D.J.; Okamoto, Y. Th2 Cells in Health and Disease. *Annu. Rev. Immunol.* **2017**, *35*, 53–84. [CrossRef]
419. Zhang, C.; Li, L.; Feng, K.; Fan, D.; Xue, W.; Lu, J. 'Repair' Treg Cells in Tissue Injury. *Cell Physiol. Biochem.* **2017**, *43*, 2155–2169. [CrossRef]
420. Shimamura, T.; Fujisawa, T.; Husain, S.R.; Kioi, M.; Nakajima, A.; Puri, R.K. Novel role of IL-13 in fibrosis induced by nonalcoholic steatohepatitis and its amelioration by IL-13R-directed cytotoxin in a rat model. *J. Immunol.* **2008**, *181*, 4656–4665. [CrossRef]
421. Gao, Y.; Liu, Y.; Yang, M.; Guo, X.; Zhang, M.; Li, H.; Li, J.; Zhao, J. IL-33 treatment attenuated diet-induced hepatic steatosis but aggravated hepatic fibrosis. *Oncotarget* **2016**, *7*, 33649–33661. [CrossRef] [PubMed]
422. Lafoz, E.; Ruart, M.; Anton, A.; Oncins, A.; Hernández-Gea, V. The Endothelium as a Driver of Liver Fibrosis and Regeneration. *Cells* **2020**, *9*, 929. [CrossRef] [PubMed]
423. Zhong, Y.; Xu, M.; Hu, J.; Huang, X.; Lin, N.; Deng, M. Inhibiting Th1/2 cells influences hepatic capillarization by adjusting sinusoidal endothelial fenestrae through Rho-ROCK-myosin pathway. *Aging* **2021**, *13*, 5069–5086. [CrossRef] [PubMed]
424. Kremer, M.; Hines, I.N.; Milton, R.J.; Wheeler, M.D. Favored T helper 1 response in a mouse model of hepatosteatosis is associated with enhanced T cell-mediated hepatitis. *Hepatology* **2006**, *44*, 216–227. [CrossRef]
425. Molina, M.F.; Abdelnabi, M.N.; Fabre, T.; Shoukry, N.H. Type 3 cytokines in liver fibrosis and liver cancer. *Cytokine* **2019**, *124*, 154497. [CrossRef]
426. Fabre, T.; Kared, H.; Friedman, S.L.; Shoukry, N.H. IL-17A enhances the expression of profibrotic genes through upregulation of the TGF-β receptor on hepatic stellate cells in a JNK-dependent manner. *J. Immunol.* **2014**, *193*, 3925–3933. [CrossRef]
427. Meng, F.; Wang, K.; Aoyama, T.; Grivennikov, S.I.; Paik, Y.; Scholten, D.; Cong, M.; Iwaisako, K.; Liu, X.; Zhang, M.; et al. Interleukin-17 signaling in inflammatory, Kupffer cells, and hepatic stellate cells exacerbates liver fibrosis in mice. *Gastroenterology* **2012**, *143*, 765–776. [CrossRef]

428. Tan, Z.; Qian, X.; Jiang, R.; Liu, Q.; Wang, Y.; Chen, C.; Wang, X.; Ryffel, B.; Sun, B. IL-17A plays a critical role in the pathogenesis of liver fibrosis through hepatic stellate cell activation. *J. Immunol.* **2013**, *191*, 1835–1844. [CrossRef]
429. Giles, D.A.; Moreno-Fernandez, M.E.; Stankiewicz, T.E.; Cappelletti, M.; Huppert, S.S.; Iwakura, Y.; Dong, C.; Shanmukhappa, S.K.; Divanovic, S. Regulation of Inflammation by IL-17A and IL-17F Modulates Non-Alcoholic Fatty Liver Disease Pathogenesis. *PLoS ONE* **2016**, *11*, 0149783. [CrossRef]
430. Van Herck, M.A.; Weyler, J.; Kwanten, W.J.; Dirinck, E.L.; De Winter, B.Y.; Francque, S.M.; Vonghia, L. The Differential Roles of T Cells in Non-alcoholic Fatty Liver Disease and Obesity. *Front. Immunol.* **2019**, *10*, 82. [CrossRef]
431. Gomes, A.L.; Teijeiro, A.; Burén, S.; Tummala, K.S.; Yilmaz, M.; Waisman, A.; Theurillat, J.P.; Perna, C.; Djouder, N. Metabolic Inflammation-Associated IL-17A Causes Non-alcoholic Steatohepatitis and Hepatocellular Carcinoma. *Cancer Cell.* **2016**, *30*, 161–175. [CrossRef] [PubMed]
432. Tang, Y.; Bian, Z.; Zhao, L.; Liu, Y.; Liang, S.; Wang, Q.; Han, X.; Peng, Y.; Chen, X.; Shen, L.; et al. Interleukin-17 exacerbates hepatic steatosis and inflammation in non-alcoholic fatty liver disease. *Clin. Exp. Immunol.* **2011**, *166*, 281–290. [CrossRef] [PubMed]
433. Xu, R.; Tao, A.; Zhang, S.; Zhang, M. Neutralization of interleukin-17 attenuates high fat diet-induced non-alcoholic fatty liver disease in mice. *Acta Biochim. Biophys. Sin.* **2013**, *45*, 726–733. [CrossRef]
434. Harley, I.T.; Stankiewicz, T.E.; Giles, D.A.; Softic, S.; Flick, L.M.; Cappelletti, M.; Sheridan, R.; Xanthakos, S.A.; Steinbrecher, K.A.; Sartor, R.B.; et al. IL-17 signaling accelerates the progression of nonalcoholic fatty liver disease in mice. *Hepatology* **2014**, *59*, 1830–1839. [CrossRef] [PubMed]
435. Zhong, S.; Zhang, T.; Tang, L.; Li, Y. Cytokines and Chemokines in HBV Infection. *Front. Mol. Biosci.* **2021**, *8*, 805625. [CrossRef]
436. Ge, D.; You, Z. Expression of interleukin-17RC protein in normal human tissues. *Int. Arch. Med.* **2008**, *1*, 19. [CrossRef]
437. Lemmers, A.; Moreno, C.; Gustot, T.; Maréchal, R.; Degré, D.; Demetter, P.; de Nadai, P.; Geerts, A.; Quertinmont, E.; Vercruysse, V.; et al. The interleukin-17 pathway is involved in human alcoholic liver disease. *Hepatology* **2009**, *49*, 646–657. [CrossRef]
438. Paquissi, F.C. Immunity and Fibrogenesis: The Role of Th17/IL-17 Axis in HBV and HCV-induced Chronic Hepatitis and Progression to Cirrhosis. *Front. Immunol.* **2017**, *8*, 1195. [CrossRef]
439. Buschow, S.I.; Jansen, D.T.S.L. CD4+ T Cells in Chronic Hepatitis B and T Cell-Directed Immunotherapy. *Cells* **2021**, *10*, 1114. [CrossRef]
440. Zhu, L.; Li, J.; Xu, J.; Chen, F.; Wu, X.; Zhu, C. Significance of T-Cell Subsets for Clinical Response to Peginterferon Alfa-2a Therapy in HBeAg-Positive Chronic Hepatitis B Patients. *Int. J. Gen. Med.* **2022**, *15*, 4441–4451. [CrossRef] [PubMed]
441. Liu, B.; Gao, W.; Zhang, L.; Wang, J.; Chen, M.; Peng, M.; Ren, H.; Hu, P. Th17/Treg imbalance and increased interleukin-21 are associated with liver injury in patients with chronic severe hepatitis B. *Int. Immunopharmacol.* **2017**, *46*, 48–55. [CrossRef] [PubMed]
442. Jiang, Q.; Yang, G.; Xiao, F.; Xie, J.; Wang, S.; Lu, L.; Cui, D. Role of Th22 Cells in the Pathogenesis of Autoimmune Diseases. *Front. Immunol.* **2021**, *12*, 688066. [CrossRef] [PubMed]
443. Wang, X.; Ota, N.; Manzanillo, P.; Kates, L.; Zavala-Solorio, J.; Eidenschenk, C.; Zhang, J.; Lesch, J.; Lee, W.P.; Ross, J.; et al. Interleukin-22 alleviates metabolic disorders and restores mucosal immunity in diabetes. *Nature* **2014**, *514*, 237–241. [CrossRef]
444. Yang, L.; Zhang, Y.; Wang, L.; Fan, F.; Zhu, L.; Li, Z.; Ruan, X.; Huang, H.; Wang, Z.; Huang, Z.; et al. Amelioration of high fat diet induced liver lipogenesis and hepatic steatosis by interleukin-22. *J. Hepatol.* **2010**, *53*, 339–347. [CrossRef]
445. Jiang, R.; Tan, Z.; Deng, L.; Chen, Y.; Xia, Y.; Gao, Y.; Wang, X.; Sun, B. Interleukin-22 promotes human hepatocellular carcinoma by activation of STAT3. *Hepatology.* **2011**, *54*, 900–909. [CrossRef]
446. Barron, L.; Wynn, T.A. Fibrosis is regulated by Th2 and Th17 responses and by dynamic interactions between fibroblasts and macrophages. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2011**, *300*, 723–728. [CrossRef]
447. Fabre, T.; Molina, M.F.; Soucy, G.; Goulet, J.P.; Willems, B.; Villeneuve, J.P.; Bilodeau, M.; Shoukry, N.H. Type 3 cytokines IL-17A and IL-22 drive TGF-β-dependent liver fibrosis. *Sci. Immunol.* **2018**, *3*, 7754. [CrossRef]
448. Zhang, S.; Huang, D.; Weng, J.; Huang, Y.; Liu, S.; Zhang, Q.; Li, N.; Wen, M.; Zhu, G.; Lin, F.; et al. Neutralization of Interleukin-17 Attenuates Cholestatic Liver Fibrosis in Mice. *Scand. J. Immunol.* **2016**, *83*, 102–108. [CrossRef]
449. Hara, M.; Kono, H.; Furuya, S.; Hirayama, K.; Tsuchiya, M.; Fujii, H. Interleukin-17A plays a pivotal role in cholestatic liver fibrosis in mice. *J. Surg. Res.* **2013**, *183*, 574–582. [CrossRef]
450. Wree, A.; McGeough, M.D.; Inzaugarat, M.E.; Eguchi, A.; Schuster, S.; Johnson, C.D.; Peña, C.A.; Geisler, L.J.; Papouchado, B.G.; Hoffman, H.M.; et al. NLRP3 inflammasome driven liver injury and fibrosis: Roles of IL-17 and TNF in mice. *Hepatology* **2018**, *67*, 736–749. [CrossRef]
451. Gieseck, R.L., 3rd; Wilson, M.S.; Wynn, T.A. Type 2 immunity in tissue repair and fibrosis. *Nat. Rev. Immunol.* **2018**, *18*, 62–76. [CrossRef] [PubMed]
452. Lee, C.G.; Homer, R.J.; Zhu, Z.; Lanone, S.; Wang, X.; Koteliansky, V.; Shipley, J.M.; Gotwals, P.; Noble, P.; Chen, Q.; et al. Interleukin-13 induces tissue fibrosis by selectively stimulating and activating transforming growth factor beta(1). *J. Exp. Med.* **2001**, *194*, 809–821. [CrossRef] [PubMed]

453. Kaviratne, M.; Hesse, M.; Leusink, M.; Cheever, A.W.; Davies, S.J.; McKerrow, J.H.; Wakefield, L.M.; Letterio, J.J.; Wynn, T.A. IL-13 activates a mechanism of tissue fibrosis that is completely TGF-beta independent. *J. Immunol.* **2004**, *173*, 4020–4029. [CrossRef]
454. Gieseck, R.L., 3rd; Ramalingam, T.R.; Hart, K.M.; Vannella, K.M.; Cantu, D.A.; Lu, W.Y.; Ferreira-González, S.; Forbes, S.J.; Vallier, L.; Wynn, T.A. Interleukin-13 Activates Distinct Cellular Pathways Leading to Ductular Reaction, Steatosis, and Fibrosis. *Immunity* **2016**, *45*, 145–158. [CrossRef]
455. Fan, Y.; Zhang, W.; Wei, H.; Sun, R.; Tian, Z.; Chen, Y. Hepatic NK Cells Attenuate Fibrosis Progression of Non-Alcoholic Steatohepatitis in Dependent of CXCL10-Mediated Recruitment. *Liver Int.* **2020**, *40*, 598–608. [CrossRef]
456. Hart, K.M.; Fabre, T.; Sciurba, J.C.; Gieseck, R.L., 3rd; Borthwick, L.A.; Vannella, K.M.; Acciani, T.H.; de Queiroz Prado, R.; Thompson, R.W.; White, S.; et al. Type 2 immunity is protective in metabolic disease but exacerbates NAFLD collaboratively with TGF-β. *Sci. Transl. Med.* **2017**, *9*, 3694.
457. Tosello-Trampont, A.C.; Krueger, P.; Narayanan, S.; Landes, S.G.; Leitinger, N.; Hahn, Y.S. NKp46(+) natural killer cells attenuate metabolism-induced hepatic fibrosis by regulating macrophage activation in mice. *Hepatology* **2016**, *63*, 799–812. [CrossRef]
458. Zhang, H.; Meadows, G.G. Chronic alcohol consumption in mice increases the proportion of peripheral memory T cells by homeostatic proliferation. *J. Leukoc. Biol.* **2005**, *78*, 1070–1080. [CrossRef]
459. Zuluaga, P.; Sanvisens, A.; Teniente-Serra, A.; El Ars, O.; Fuster, D.; Quirant-Sánchez, B.; Martínez-Cáceres, E.; Muga, R. Loss of naive T lymphocytes is associated with advanced liver fibrosis in alcohol use disorder. *Drug Alcohol Depend.* **2020**, *213*, 108046. [CrossRef]
460. Kita, H.; Matsumura, S.; He, X.S.; Ansari, A.A.; Lian, Z.X.; Van de Water, J.; Coppel, R.L.; Kaplan, M.M.; Gershwin, M.E. Quantitative and functional analysis of PDC-E2-specific autoreactive cytotoxic T lymphocytes in primary biliary cirrhosis. *J. Clin. Investig.* **2002**, *109*, 1231–1240. [CrossRef]
461. Zhang, W.; Ono, Y.; Miyamura, Y.; Bowlus, C.L.; Gershwin, M.E.; Maverakis, E. T cell clonal expansions detected in patients with primary biliary cirrhosis express CX3CR1. *J. Autoimmun.* **2011**, *37*, 71–78. [CrossRef] [PubMed]
462. Crispe, I.N. Immune tolerance in liver disease. *Hepatology* **2014**, *60*, 2109–2117. [CrossRef] [PubMed]
463. Zhu, J.; Paul, W.E. CD4 T cells: Fates, functions, and faults. *Blood* **2008**, *112*, 1557–1569. [CrossRef] [PubMed]
464. Ma, X.; Hua, J.; Mohamood, A.R.; Hamad, A.R.; Ravi, R.; Li, Z. A high-fat diet and regulatory T cells influence susceptibility to endotoxin-induced liver injury. *Hepatology* **2007**, *46*, 1519–1529. [CrossRef]
465. He, B.; Wu, L.; Xie, W.; Shao, Y.; Jiang, J.; Zhao, Z.; Yan, M.; Chen, Z.; Cui, D. The imbalance of Th17/Treg cells is involved in the progression of nonalcoholic fatty liver disease in mice. *BMC Immunol.* **2017**, *18*, 33. [CrossRef]
466. Ma, C.; Kesarwala, A.H.; Eggert, T.; Medina-Echeverz, J.; Kleiner, D.E.; Jin, P.; Stroncek, D.F.; Terabe, M.; Kapoor, V.; ElGindi, M.; et al. NAFLD causes selective CD4(+) T lymphocyte loss and promotes hepatocarcinogenesis. *Nature* **2016**, *531*, 253–257. [CrossRef]
467. Francisco, V.; Pino, J.; Campos-Cabaleiro, V.; Ruiz-Fernández, C.; Mera, A.; Gonzalez-Gay, M.A.; Gómez, R.; Gualillo, O. Obesity, Fat Mass and Immune System: Role for Leptin. *Front. Physiol.* **2018**, *9*, 640. [CrossRef]
468. Wang, H.; Zhang, H.; Wang, Y.; Brown, Z.J.; Xia, Y.; Huang, Z.; Shen, C.; Hu, Z.; Beane, J.; Ansa-Addo, E.A.; et al. Regulatory T-cell and neutrophil extracellular trap interaction contributes to carcinogenesis in non-alcoholic steatohepatitis. *J. Hepatol.* **2021**, *75*, 1271–1283. [CrossRef]
469. Dywicki, J.; Buitrago-Molina, L.E.; Noyan, F.; Davalos-Misslitz, A.C.; Hupa-Breier, K.L.; Lieber, M.; Hapke, M.; Schlue, J.; Falk, C.S.; Raha, S.; et al. The Detrimental Role of Regulatory T Cells in Nonalcoholic Steatohepatitis. *Hepatol. Commun.* **2022**, *6*, 320–333. [CrossRef]
470. Katz, S.C.; Ryan, K.; Ahmed, N.; Plitas, G.; Chaudhry, U.I.; Kingham, T.P.; Naheed, S.; Nguyen, C.; Somasundar, P.; Espat, N.J.; et al. Obstructive jaundice expands intrahepatic regulatory T cells, which impair liver T lymphocyte function but modulate liver cholestasis and fibrosis. *J. Immunol.* **2011**, *187*, 1150–1156. [CrossRef]
471. Claassen, M.A.; de Knegt, R.J.; Tilanus, H.W.; Janssen, H.L.; Boonstra, A. Abundant numbers of regulatory T cells localize to the liver of chronic hepatitis C infected patients and limit the extent of fibrosis. *J. Hepatol.* **2010**, *52*, 315–321. [CrossRef] [PubMed]
472. Langhans, B.; Krämer, B.; Louis, M.; Nischalke, H.D.; Hüneburg, R.; Staratschek-Jox, A.; Odenthal, M.; Manekeller, S.; Schepke, M.; Kalff, J.; et al. Intrahepatic IL-8 producing $Foxp3^{+}CD4^{+}$ regulatory T cells and fibrogenesis in chronic hepatitis C. *J. Hepatol.* **2013**, *59*, 229–235. [CrossRef] [PubMed]
473. Li, J.; Qiu, S.J.; She, W.M.; Wang, F.P.; Gao, H.; Li, L.; Tu, C.T.; Wang, J.Y.; Shen, X.Z.; Jiang, W. Significance of the balance between regulatory T (Treg) and T helper 17 (Th17) cells during hepatitis B virus related liver fibrosis. *PLoS ONE* **2012**, *7*, 39307. [CrossRef]
474. Liu, C.; Zeng, X.; Yu, S.; Ren, L.; Sun, X.; Long, Y.; Wang, X.; Lu, S.; Song, Y.; Sun, X.H.; et al. Up-regulated DNA-binding inhibitor Id3 promotes differentiation of regulatory T cell to influence antiviral immunity in chronic hepatitis B virus infection. *Life Sci.* **2021**, *285*, 119991. [CrossRef]
475. Trehanpati, N.; Vyas, A.K. Immune Regulation by T Regulatory Cells in Hepatitis B Virus-Related Inflammation and Cancer. *Scand. J. Immunol.* **2017**, *85*, 175–181. [CrossRef]

476. Zeng, X.; Bahabayi, A.; Tuerhanbayi, B.; Zheng, M.; Liu, T.; Xu, L.; Long, Y.; Xia, C.; Lu, S.; Song, Y.; et al. The altered HLA-DQ expression in peripheral blood T cells of chronic hepatitis B patients characterizes the function of T cells. *J. Viral Hepat.* **2022**, *29*, 340–351. [CrossRef]
477. Liu, F.; Zhang, S.; Wong, D.K.; Huang, F.Y.; Cheung, K.S.; Mak, L.Y.; Fung, J.; Yuen, M.F.; Seto, W.K. Phenotypic Changes of PD-1 and GITR in T Cells Are Associated With Hepatitis B Surface Antigen Seroclearance. *J. Clin. Gastroenterol.* **2022**, *56*, e31–e37. [CrossRef]
478. Wang, X.; Dong, Q.; Li, Q.; Li, Y.; Zhao, D.; Sun, J.; Fu, J.; Meng, F.; Lin, H.; Luan, J.; et al. Dysregulated Response of Follicular Helper T Cells to Hepatitis B Surface Antigen Promotes HBV Persistence in Mice and Associates With Outcomes of Patients. *Gastroenterology* **2018**, *154*, 2222–2236. [CrossRef]
479. Tangye, S.G.; Ma, C.S. Regulation of the germinal center and humoral immunity by interleukin-21. *J. Exp. Med.* **2020**, *217*, e20191638. [CrossRef]
480. Liu, Y.; Cheng, L.S.; Wu, S.D.; Wang, S.Q.; Li, L.; She, W.M.; Li, J.; Wang, J.Y.; Jiang, W. IL-10-producing regulatory B-cells suppressed effector T-cells but enhanced regulatory T-cells in chronic HBV infection. *Clin. Sci.* **2016**, *130*, 907–919. [CrossRef]
481. Yang, L.; Shao, X.; Jia, S.; Zhang, Q.; Jin, Z. Interleukin-35 Dampens CD8+ T Cells Activity in Patients With Non-viral Hepatitis-Related Hepatocellular Carcinoma. *Front. Immunol.* **2019**, *10*, 1032. [CrossRef]
482. Zhang, Q.; Yang, L.; Liu, S.; Zhang, M.; Jin, Z. Interleukin-35 Suppresses Interleukin-9-Secreting CD4+ T Cell Activity in Patients With Hepatitis B-Related Hepatocellular Carcinoma. *Front. Immunol.* **2021**, *12*, 645835. [CrossRef]
483. Tang, Y.; Ma, T.; Jia, S.; Zhang, Q.; Liu, S.; Qi, L.; Yang, L. The Mechanism of Interleukin-35 in Chronic Hepatitis B. *Semin. Liver Dis.* **2021**, *41*, 516–524. [CrossRef] [PubMed]
484. Huang, E.; Peng, N.; Xiao, F.; Hu, D.; Wang, X.; Lu, L. The Roles of Immune Cells in the Pathogenesis of Fibrosis. *Int. J. Mol. Sci.* **2020**, *21*, 5203. [CrossRef] [PubMed]
485. Fillatreau, S. B cells and their cytokine activities implications in human diseases. *Clin. Immunol.* **2018**, *186*, 26–31. [CrossRef] [PubMed]
486. Novobrantseva, T.I.; Majeau, G.R.; Amatucci, A.; Kogan, S.; Brenner, I.; Casola, S.; Shlomchik, M.J.; Koteliansky, V.; Hochman, P.S.; Ibraghimov, A. Attenuated liver fibrosis in the absence of B cells. *J. Clin. Investig.* **2005**, *115*, 3072–3082. [CrossRef]
487. Bruzzì, S.; Sutti, S.; Giudici, G.; Burlone, M.E.; Ramavath, N.N.; Toscani, A.; Bozzola, C.; Schneider, P.; Morello, E.; Parola, M.; et al. B2-Lymphocyte responses to oxidative stress-derived antigens contribute to the evolution of nonalcoholic fatty liver disease (NAFLD). *Free Radic. Biol. Med.* **2018**, *124*, 249–259. [CrossRef]
488. Gong, Y.; Zhao, C.; Zhao, P.; Wang, M.; Zhou, G.; Han, F.; Cui, Y.; Qian, J.; Zhang, H.; Xiong, H.; et al. Role of IL-10-Producing Regulatory B Cells in Chronic Hepatitis B Virus Infection. *Dig. Dis. Sci.* **2015**, *60*, 1308–1314. [CrossRef]
489. Jin, X.; Yan, Z.H.; Lu, L.; Lu, S.; Zhang, G.; Lin, W. Peripheral Immune Cells Exhaustion and Functional Impairment in Patients With Chronic Hepatitis B. *Front. Med.* **2021**, *8*, 759292. [CrossRef]
490. Liu, Y.; Luo, Y.; Zhu, T.; Jiang, M.; Tian, Z.; Tang, G.; Liang, X. Regulatory B Cells Dysregulated T Cell Function in an IL-35-Dependent Way in Patients With Chronic Hepatitis B. *Front. Immunol.* **2021**, *12*, 653198. [CrossRef]
491. Zheng, P.; Dou, Y.; Wang, Q. Immune response and treatment targets of chronic hepatitis B virus infection: Innate and adaptive immunity. *Front. Cell Infect. Microbiol.* **2023**, *13*, 1206720. [CrossRef] [PubMed]
492. Jia, H.; Chen, J.; Zhang, X.; Bi, K.; Zhou, H.; Liu, T.; Xu, J.; Diao, H. IL-17A produced by invariant natural killer T cells and CD3+ CD56+ αGalcer-CD1d tetramer- T cells promote liver fibrosis in patients with primary biliary cholangitis. *J. Leukoc. Biol.* **2022**, *112*, 1079–1087. [CrossRef]
493. Hammerich, L.; Tacke, F. Role of gamma-delta T cells in liver inflammation and fibrosis. *World J. Gastrointest. Pathophysiol.* **2014**, *5*, 107–113. [CrossRef] [PubMed]
494. Bartish, M.; Del Rincón, S.V.; Rudd, C.E.; Saragovi, H.U. Aiming for the Sweet Spot: Glyco-Immune Checkpoints and γδ T Cells in Targeted Immunotherapy. *Front. Immunol.* **2020**, *11*, 564499. [CrossRef]
495. Pellicci, D.G.; Koay, H.F.; Berzins, S.P. Thymic development of unconventional T cells: How NKT cells, MAIT cells and γδ T cells emerge. *Nat. Rev. Immunol.* **2020**, *20*, 756–770. [CrossRef]
496. Kurioka, A.; Walker, L.J.; Klenerman, P.; Willberg, C.B. MAIT cells: New guardians of the liver. *Clin. Transl. Immunology.* **2016**, *5*, 98. [CrossRef]
497. Bandyopadhyay, K.; Marrero, I.; Kumar, V. NKT cell subsets as key participants in liver physiology and pathology. *Cell Mol. Immunol.* **2016**, *13*, 337–346. [CrossRef]
498. Ibidapo-Obe, O.; Bruns, T. Tissue-resident and innate-like T cells in patients with advanced chronic liver disease. *JHEP Rep.* **2023**, *5*, 100812. [CrossRef]
499. Wei, X.; Qian, J.; Yao, W.; Chen, L.; Guan, H.; Chen, Y.; Xie, Y.; Lu, H.; Zhang, Z.; Shi, L.; et al. Hyperactivated peripheral invariant natural killer T cells correlate with the progression of HBV-relative liver cirrhosis. *Scand. J. Immunol.* **2019**, *90*, 12775. [CrossRef]

500. Tang, W.; Zhou, J.; Yang, W.; Feng, Y.; Wu, H.; Mok, M.T.S.; Zhang, L.; Liang, Z.; Liu, X.; Xiong, Z.; et al. Aberrant cholesterol metabolic signaling impairs antitumor immunosurveillance through natural killer T cell dysfunction in obese liver. *Cell Mol. Immunol.* **2022**, *19*, 834–847. [CrossRef]
501. Zheng, S.; Yang, W.; Yao, D.; Tang, S.; Hou, J.; Chang, X. A comparative study on roles of natural killer T cells in two diet-induced non-alcoholic steatohepatitis-related fibrosis in mice. *Ann. Med.* **2022**, *54*, 2233–2245. [CrossRef] [PubMed]
502. Chan, C.W.; Chen, H.W.; Wang, Y.W.; Lin, C.I.; Chuang, Y.H. IL-21, not IL-17A, exacerbates murine primary biliary cholangitis. *Clin. Exp. Immunol.* **2024**, *215*, 137–147. [CrossRef] [PubMed]
503. Chen, Y.; Tian, Z. Roles of Hepatic Innate and Innate-Like Lymphocytes in Nonalcoholic Steatohepatitis. *Front. Immunol.* **2020**, *11*, 1500. [CrossRef]
504. Torres-Hernandez, A.; Wang, W.; Nikiforov, Y.; Tejada, K.; Torres, L.; Kalabin, A.; Adam, S.; Wu, J.; Lu, L.; Chen, R.; et al. γδ T Cells Promote Steatohepatitis by Orchestrating Innate and Adaptive Immune Programming. *Hepatology* **2020**, *71*, 477–494. [CrossRef] [PubMed]
505. Wang, X.; Gao, B. γδT Cells and CD1d, Novel Immune Players in Alcoholic and Nonalcoholic Steatohepatitis? *Hepatology* **2020**, *71*, 408–410. [CrossRef] [PubMed]
506. Li, F.; Hao, X.; Chen, Y.; Bai, L.; Gao, X.; Lian, Z.; Wei, H.; Sun, R.; Tian, Z. The microbiota maintain homeostasis of liver-resident γδT-17 cells in a lipid antigen/CD1d-dependent manner. *Nat. Commun.* **2017**, *7*, 13839. [CrossRef]
507. Hammerich, L.; Bangen, J.M.; Govaere, O.; Zimmermann, H.W.; Gassler, N.; Huss, S.; Liedtke, C.; Prinz, I.; Lira, S.A.; Luedde, T.; et al. Chemokine receptor CCR6-dependent accumulation of γδ T cells in injured liver restricts hepatic inflammation and fibrosis. *Hepatology* **2014**, *59*, 630–642. [CrossRef]
508. Spits, H.; Artis, D.; Colonna, M.; Diefenbach, A.; Di Santo, J.P.; Eberl, G.; Koyasu, S.; Locksley, R.M.; McKenzie, A.N.; Mebius, R.E.; et al. Innate lymphoid cells—A proposal for uniform nomenclature. *Nat. Rev. Immunol.* **2013**, *13*, 145–149. [CrossRef]
509. Vivier, E.; Artis, D.; Colonna, M.; Diefenbach, A.; Di Santo, J.P.; Eberl, G.; Koyasu, S.; Locksley, R.M.; McKenzie, A.N.J.; Mebius, R.E.; et al. Innate Lymphoid Cells: 10 Years On. *Cell* **2018**, *174*, 1054–1066. [CrossRef]
510. Wang, S.; Li, J.; Wu, S.; Cheng, L.; Shen, Y.; Ma, W.; She, W.; Yang, C.; Wang, J.; Jiang, W. Type 3 innate lymphoid cell: A new player in liver fibrosis progression. *Clin. Sci.* **2018**, *132*, 2565–2582. [CrossRef]
511. Wang, Y.; Zhang, C. The Roles of Liver-Resident Lymphocytes in Liver Diseases. *Front. Immunol.* **2019**, *10*, 1582. [CrossRef] [PubMed]
512. Liedtke, C.; Nevzorova, Y.A.; Luedde, T.; Zimmermann, H.; Kroy, D.; Strnad, P.; Berres, M.L.; Bernhagen, J.; Tacke, F.; Nattermann, J.; et al. Liver Fibrosis-From Mechanisms of Injury to Modulation of Disease. *Front. Med.* **2022**, *8*, 814496. [CrossRef] [PubMed]
513. Seillet, C.; Brossay, L.; Vivier, E. Natural killers or ILC1s? That is the question. *Curr. Opin. Immunol.* **2021**, *68*, 48–53. [CrossRef] [PubMed]
514. Ebbo, M.; Crinier, A.; Vély, F.; Vivier, E. Innate lymphoid cells: Major players in inflammatory diseases. *Nat. Rev. Immunol.* **2017**, *17*, 665–678. [CrossRef] [PubMed]
515. Forkel, M.; Berglin, L.; Kekäläinen, E.; Carlsson, A.; Svedin, E.; Michaëlsson, J.; Nagasawa, M.; Erjefält, J.S.; Mori, M.; Flodström-Tullberg, M.; et al. Composition and functionality of the intrahepatic innate lymphoid cell-compartment in human nonfibrotic and fibrotic livers. *Eur. J. Immunol.* **2017**, *47*, 1280–1294. [CrossRef]
516. Godfrey, D.I.; Koay, H.F.; McCluskey, J.; Gherardin, N.A. The biology and functional importance of MAIT cells. *Nat. Immunol.* **2019**, *20*, 1110–1128. [CrossRef]
517. Hegde, P.; Weiss, E.; Paradis, V.; Wan, J.; Mabire, M.; Sukriti, S.; Rautou, P.E.; Albuquerque, M.; Picq, O.; Gupta, A.C.; et al. Mucosal-associated invariant T cells are a profibrogenic immune cell population in the liver. *Nat. Commun.* **2018**, *9*, 2146. [CrossRef]
518. Li, Y.; Huang, B.; Jiang, X.; Chen, W.; Zhang, J.; Wei, Y.; Chen, Y.; Lian, M.; Bian, Z.; Miao, Q.; et al. Mucosal-Associated Invariant T Cells Improve Nonalcoholic Fatty Liver Disease Through Regulating Macrophage Polarization. *Front. Immunol.* **2018**, *9*, 1994. [CrossRef]
519. Guan, H.; Zhang, X.; Kuang, M.; Yu, J. The gut-liver axis in immune remodeling of hepatic cirrhosis. *Front. Immunol.* **2022**, *13*, 946628. [CrossRef]
520. Tranah, T.H.; Edwards, L.A.; Schnabl, B.; Shawcross, D.L. Targeting the gut-liver-immune axis to treat cirrhosis. *Gut* **2021**, *70*, 982–994. [CrossRef]
521. Koda, Y.; Teratani, T.; Chu, P.S.; Hagihara, Y.; Mikami, Y.; Harada, Y.; Tsujikawa, H.; Miyamoto, K.; Suzuki, T.; Taniki, N.; et al. CD8+ tissue-resident memory T cells promote liver fibrosis resolution by inducing apoptosis of hepatic stellate cells. *Nat. Commun.* **2021**, *12*, 4474. [CrossRef] [PubMed]
522. Vallianou, N.G.; Kounatidis, D.; Psallida, S.; Vythoulkas-Biotis, N.; Adamou, A.; Zachariadou, T.; Kargioti, S.; Karampela, I.; Dalamaga, M. NAFLD/MASLD and the Gut-Liver Axis: From Pathogenesis to Treatment Options. *Metabolites* **2024**, *14*, 366. [CrossRef] [PubMed]
523. Zhang, S.; Lu, S.; Li, Z. Extrahepatic factors in hepatic immune regulation. *Front. Immunol.* **2022**, *13*, 941721. [CrossRef] [PubMed]

524. Bonneville, M.; O'Brien, R.L.; Born, W.K. Gammadelta T cell effector functions: A blend of innate programming and acquired plasticity. *Nat. Rev. Immunol.* **2010**, *10*, 467–478. [CrossRef]
525. Yang, F.; Li, H.; Li, Y.; Hao, Y.; Wang, C.; Jia, P.; Chen, X.; Ma, S.; Xiao, Z. Crosstalk between hepatic stellate cells and surrounding cells in hepatic fibrosis. *Int. Immunopharmacol.* **2021**, *99*, 108051. [CrossRef]
526. Guo, Z.; Zhang, R.; Yang, A.G.; Zheng, G. Diversity of immune checkpoints in cancer immunotherapy. *Front. Immunol.* **2023**, *14*, 1121285. [CrossRef]
527. Qin, W.; Hu, L.; Zhang, X.; Jiang, S.; Li, J.; Zhang, Z.; Wang, X. The Diverse Function of PD-1/PD-L Pathway Beyond Cancer. *Front. Immunol.* **2019**, *10*, 2298. [CrossRef]
528. Sharpe, A.H.; Pauken, K.E. The diverse functions of the PD1 inhibitory pathway. *Nat. Rev. Immunol.* **2018**, *18*, 153–167. [CrossRef]
529. Zhong, Z.; Vong, C.T.; Chen, F.; Tan, H.; Zhang, C.; Wang, N.; Cui, L.; Wang, Y.; Feng, Y. Immunomodulatory potential of natural products from herbal medicines as immune checkpoints inhibitors: Helping to fight against cancer via multiple targets. *Med. Res. Rev.* **2022**, *42*, 1246–1279. [CrossRef]
530. Chow, A.; Perica, K.; Klebanoff, C.A.; Wolchok, J.D. Clinical implications of T cell exhaustion for cancer immunotherapy. *Nat. Rev. Clin. Oncol.* **2022**, *19*, 775–790. [CrossRef]
531. Zhao, Y.; Shao, Q.; Peng, G. Exhaustion and senescence: Two crucial dysfunctional states of T cells in the tumor microenvironment. *Cell Mol. Immunol.* **2020**, *17*, 27–35. [CrossRef] [PubMed]
532. Schwartz, J.C.; Zhang, X.; Fedorov, A.A.; Nathenson, S.G.; Almo, S.C. Structural basis for co-stimulation by the human CTLA-4/B7-2 complex. *Nature* **2001**, *410*, 604–608. [CrossRef] [PubMed]
533. Linsley, P.S.; Bradshaw, J.; Greene, J.; Peach, R.; Bennett, K.L.; Mittler, R.S. Intracellular trafficking of CTLA-4 and focal localization towards sites of TCR engagement. *Immunity* **1996**, *4*, 535–543. [CrossRef] [PubMed]
534. Marin-Acevedo, J.A.; Kimbrough, E.O.; Lou, Y. Next generation of immune checkpoint inhibitors and beyond. *J. Hematol. Oncol.* **2021**, *14*, 45. [CrossRef]
535. Seidel, J.A.; Otsuka, A.; Kabashima, K. Anti-PD-1 and Anti-CTLA-4 Therapies in Cancer: Mechanisms of Action, Efficacy, and Limitations. *Front. Oncol.* **2018**, *8*, 86. [CrossRef]
536. Ruff, S.M.; Pawlik, T.M. Emerging data on immune checkpoint inhibitors in the neoadjuvant and adjuvant setting for patients with hepatocellular carcinoma. *Hepatoma Res.* **2024**, *10*, 22. [CrossRef]
537. Baldanzi, G. Immune Checkpoint Receptors Signaling in T Cells. *Int. J. Mol. Sci.* **2022**, *23*, 3529. [CrossRef]
538. Cai, J.; Qi, Q.; Qian, X.; Han, J.; Zhu, X.; Zhang, Q.; Xia, R. The role of PD-1/PD-L1 axis and macrophage in the progression and treatment of cancer. *J. Cancer Res. Clin. Oncol.* **2019**, *145*, 1377–1385. [CrossRef]
539. Gianchecchi, E.; Delfino, D.V.; Fierabracci, A. Recent insights into the role of the PD-1/PD-L1 pathway in immunological tolerance and autoimmunity. *Autoimmun. Rev.* **2013**, *12*, 1091–1100. [CrossRef]
540. Keir, M.E.; Butte, M.J.; Freeman, G.J.; Sharpe, A.H. PD-1 and its ligands in tolerance and immunity. *Annu. Rev. Immunol.* **2008**, *26*, 677–704. [CrossRef]
541. Agata, Y.; Kawasaki, A.; Nishimura, H.; Ishida, Y.; Tsubata, T.; Yagita, H.; Honjo, T. Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. *Int. Immunol.* **1996**, *8*, 765–772. [CrossRef] [PubMed]
542. Barber, D.L.; Wherry, E.J.; Masopust, D.; Zhu, B.; Allison, J.P.; Sharpe, A.H.; Freeman, G.J.; Ahmed, R. Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature* **2006**, *439*, 682–687. [CrossRef] [PubMed]
543. Park, B.V.; Freeman, Z.T.; Ghasemzadeh, A.; Chattergoon, M.A.; Rutebemberwa, A.; Steigner, J.; Winter, M.E.; Huynh, T.V.; Sebald, S.M.; Lee, S.J.; et al. TGFβ1-Mediated SMAD3 Enhances PD-1 Expression on Antigen-Specific T Cells in Cancer. *Cancer Discov.* **2016**, *6*, 1366–1381. [CrossRef] [PubMed]
544. Sun, Z.; Fourcade, J.; Pagliano, O.; Chauvin, J.M.; Sander, C.; Kirkwood, J.M.; Zarour, H.M. IL10 and PD-1 Cooperate to Limit the Activity of Tumor-Specific CD8+ T Cells. *Cancer Res.* **2015**, *75*, 1635–1644. [CrossRef]
545. Sun, C.; Mezzadra, R.; Schumacher, T.N. Regulation and Function of the PD-L1 Checkpoint. *Immunity* **2018**, *48*, 434–452. [CrossRef]
546. Yamazaki, T.; Akiba, H.; Iwai, H.; Matsuda, H.; Aoki, M.; Tanno, Y.; Shin, T.; Tsuchiya, H.; Pardoll, D.M.; Okumura, K.; et al. Expression of programmed death 1 ligands by murine T cells and APC. *J. Immunol.* **2002**, *169*, 5538–5545. [CrossRef]
547. Li, K.; Yuan, Z.; Lyu, J.; Ahn, E.; Davis, S.J.; Ahmed, R.; Zhu, C. PD-1 suppresses TCR-CD8 cooperativity during T-cell antigen recognition. *Nat. Commun.* **2021**, *12*, 2746. [CrossRef]
548. Apol, Á.D.; Winckelmann, A.A.; Duus, R.B.; Bukh, J.; Weis, N. The Role of CTLA-4 in T Cell Exhaustion in Chronic Hepatitis B Virus Infection. *Viruses* **2023**, *15*, 1141. [CrossRef]
549. Gordon, S.R.; Maute, R.L.; Dulken, B.W.; Hutter, G.; George, B.M.; McCracken, M.N.; Gupta, R.; Tsai, J.M.; Sinha, R.; Corey, D.; et al. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. *Nature* **2017**, *545*, 495–499. [CrossRef]

550. Qorraj, M.; Bruns, H.; Böttcher, M.; Weigand, L.; Saul, D.; Mackensen, A.; Jitschin, R.; Mougiakakos, D. The PD-1/PD-L1 axis contributes to immune metabolic dysfunctions of monocytes in chronic lymphocytic leukemia. *Leukemia* **2017**, *31*, 470–478. [CrossRef]
551. Liu, J.; Xu, X.; Zhong, H.; Yu, M.; Abuduaini, N.; Zhang, S.; Yang, X.; Feng, B. Glycosylation and Its Role in Immune Checkpoint Proteins: From Molecular Mechanisms to Clinical Implications. *Biomedicines* **2024**, *12*, 1446. [CrossRef] [PubMed]
552. Hsu, J.M.; Xia, W.; Hsu, Y.H.; Chan, L.C.; Yu, W.H.; Cha, J.H.; Chen, C.T.; Liao, H.W.; Kuo, C.W.; Khoo, K.H.; et al. STT3-dependent PD-L1 accumulation on cancer stem cells promotes immune evasion. *Nat. Commun.* **2018**, *9*, 1908. [CrossRef] [PubMed]
553. Zhao, Y.; Qu, Y.; Hao, C.; Yao, W. PD-1/PD-L1 axis in organ fibrosis. *Front. Immunol.* **2023**, *14*, 1145682. [CrossRef]
554. Aoki, T.; Nishida, N.; Kudo, M. Current Perspectives on the Immunosuppressive Niche and Role of Fibrosis in Hepatocellular Carcinoma and the Development of Antitumor Immunity. *J. Histochem. Cytochem.* **2022**, *70*, 53–81. [CrossRef]
555. Zhang, Y.C.; Zhang, Y.T.; Wang, Y.; Zhao, Y.; He, L.J. What role does PDL1 play in EMT changes in tumors and fibrosis? *Front Immunol.* **2023**, *14*, 1226038. [CrossRef]
556. Ke, M.Y.; Xu, T.; Fang, Y.; Ye, Y.P.; Li, Z.J.; Ren, F.G.; Lu, S.Y.; Zhang, X.F.; Wu, R.Q.; Lv, Y.; et al. Liver fibrosis promotes immune escape in hepatocellular carcinoma via GOLM1-mediated PD-L1 upregulation. *Cancer Lett.* **2021**, *513*, 14–25. [CrossRef]
557. Xiang, M.; Liu, T.; Tian, C.; Ma, K.; Gou, J.; Huang, R.; Li, S.; Li, Q.; Xu, C.; Li, L.; et al. Kinsenoside attenuates liver fibro-inflammation by suppressing dendritic cells via the PI3K-AKT-FoxO1 pathway. *Pharmacol. Res.* **2022**, *177*, 106092. [CrossRef]
558. Dong, Y.; Li, X.; Zhang, L.; Zhu, Q.; Chen, C.; Bao, J.; Chen, Y. CD4+ T cell exhaustion revealed by high PD-1 and LAG-3 expression and the loss of helper T cell function in chronic hepatitis B. *BMC Immunol.* **2019**, *20*, 27. [CrossRef]
559. Ye, B.; Liu, X.; Li, X.; Kong, H.; Tian, L.; Chen, Y. T-cell exhaustion in chronic hepatitis B infection: Current knowledge and clinical significance. *Cell Death Dis.* **2015**, *6*, e1694. [CrossRef]
560. Cho, H.; Kang, H.; Lee, H.H.; Kim, C.W. Programmed Cell Death 1 (PD-1) and Cytotoxic T Lymphocyte-Associated Antigen 4 (CTLA-4) in Viral Hepatitis. *Int. J. Mol. Sci.* **2017**, *18*, 1517. [CrossRef]
561. Huang, D.; Yan, W.; Han, M.; Yuan, W.; Wang, P.; Chen, Y.; Wan, X.; Luo, X.; Wu, D.; Ning, Q. Insufficient immunity led to virologic breakthrough in NAs-treated chronic hepatitis B patients switching to Peg-IFN-α. *Antiviral Res.* **2022**, *197*, 105220. [CrossRef] [PubMed]
562. Ferrando-Martinez, S.; Huang, K.; Bennett, A.S.; Sterba, P.; Yu, L.; Suzich, J.A.; Janssen, H.L.A.; Robbins, S.H. HBeAg seroconversion is associated with a more effective PD-L1 blockade during chronic hepatitis B infection. *JHEP Rep.* **2019**, *1*, 170–178. [CrossRef] [PubMed]
563. Cui, D.; Jiang, D.; Yan, C.; Liu, X.; Lv, Y.; Xie, J.; Chen, Y. Immune Checkpoint Molecules Expressed on CD4+ T Cell Subsets in Chronic Asymptomatic Hepatitis B Virus Carriers With Hepatitis B e Antigen-Negative. *Front. Microbiol.* **2022**, *13*, 887408. [CrossRef] [PubMed]
564. Salem, M.L.; El-Badawy, A. Programmed death-1/programmed death-L1 signaling pathway and its blockade in hepatitis C virus immunotherapy. *World J. Hepatol.* **2015**, *7*, 2449–2458. [CrossRef]
565. Park, S.J.; Hahn, Y.S. Hepatocytes infected with hepatitis C virus change immunological features in the liver microenvironment. *Clin. Mol. Hepatol.* **2023**, *29*, 65–76. [CrossRef]
566. Liu, X.; Zhou, J.; Wu, H.; Chen, S.; Zhang, L.; Tang, W.; Duan, L.; Wang, Y.; McCabe, E.; Hu, M.; et al. Fibrotic immune microenvironment remodeling mediates superior anti-tumor efficacy of a nano-PD-L1 trap in hepatocellular carcinoma. *Mol. Ther.* **2023**, *31*, 119–133. [CrossRef]
567. Zhou, L.; Li, X.; Huang, X.; Chen, L.; Gu, L.; Huang, Y. Soluble programmed death-1 is a useful indicator for inflammatory and fibrosis severity in chronic hepatitis B. *J. Viral Hepat.* **2019**, *26*, 795–802. [CrossRef]
568. Huang, N.; Zhou, R.; Chen, H.; Zhang, S.; Li, J.; Wei, W.; Sun, J.; Ren, S.; Li, B.; Deng, H.; et al. Splenic CD4+ and CD8+ T-cells highly expressed PD-1 and Tim-3 in cirrhotic patients with HCV infection and portal hypertension. *Int. J. Immunopathol. Pharmacol.* **2021**, *35*, 20587384211061051. [CrossRef]
569. Jiang, A.; Liu, N.; Wang, J.; Zheng, X.; Ren, M.; Zhang, W.; Yao, Y. The role of PD-1/PD-L1 axis in idiopathic pulmonary fibrosis: Friend or foe? *Front. Immunol.* **2022**, *13*, 1022228. [CrossRef]
570. Lu, Y.; Zhong, W.; Liu, Y.; Chen, W.; Zhang, J.; Zeng, Z.; Huang, H.; Qiao, Y.; Wan, X.; Meng, X.; et al. Anti-PD-L1 antibody alleviates pulmonary fibrosis by inducing autophagy via inhibition of the PI3K/Akt/mTOR pathway. *Int. Immunopharmacol.* **2022**, *104*, 108504. [CrossRef]
571. Paskeh, M.D.A.; Ghadyani, F.; Hashemi, M.; Abbaspour, A.; Zabolian, A.; Javanshir, S.; Razzazan, M.; Mirzaei, S.; Entezari, M.; Goharrizi, M.A.S.B.; et al. Biological impact and therapeutic perspective of targeting PI3K/Akt signaling in hepatocellular carcinoma: Promises and Challenges. *Pharmacol. Res.* **2023**, *187*, 106553. [CrossRef] [PubMed]
572. Song, L.; Chen, T.Y.; Zhao, X.J.; Xu, Q.; Jiao, R.Q.; Li, J.M.; Kong, L.D. Pterostilbene prevents hepatocyte epithelial-mesenchymal transition in fructose-induced liver fibrosis through suppressing miR-34a/Sirt1/p53 and TGF-β1/Smads signalling. *Br. J. Pharmacol.* **2019**, *176*, 1619–1634. [CrossRef] [PubMed]

573. Yang, Y.Z.; Zhao, X.J.; Xu, H.J.; Wang, S.C.; Pan, Y.; Wang, S.J.; Xu, Q.; Jiao, R.Q.; Gu, H.M.; Kong, L.D. Magnesium isoglycyrrhizinate ameliorates high fructose-induced liver fibrosis in rat by increasing miR-375-3p to suppress JAK2/STAT3 pathway and TGF-β1/Smad signaling. *Acta Pharmacol. Sin.* **2019**, *40*, 879–894. [CrossRef]
574. Zhou, W.C.; Zhang, Q.B.; Qiao, L. Pathogenesis of liver cirrhosis. *World J. Gastroenterol.* **2014**, *20*, 7312–7324. [CrossRef]
575. Ye, Y.; Xu, Y.; Lai, Y.; He, W.; Li, Y.; Wang, R.; Luo, X.; Chen, R.; Chen, T. Long non-coding RNA cox-2 prevents immune evasion and metastasis of hepatocellular carcinoma by altering M1/M2 macrophage polarization. *J. Cell Biochem.* **2018**, *119*, 2951–2963. [CrossRef]
576. Li, Q.; Deng, M.S.; Wang, R.T.; Luo, H.; Luo, Y.Y.; Zhang, D.D.; Chen, K.J.; Cao, X.F.; Yang, G.M.; Zhao, T.M.; et al. PD-L1 upregulation promotes drug-induced pulmonary fibrosis by inhibiting vimentin degradation. *Pharmacol. Res.* **2023**, *187*, 106636. [CrossRef]
577. Kong, X.; Peng, H.; Liu, P.; Fu, X.; Wang, N.; Zhang, D. Programmed death ligand 1 regulates epithelial-mesenchymal transition and cancer stem cell phenotypes in hepatocellular carcinoma through the serum and glucocorticoid kinase 2/β-catenin signaling pathway. *Cancer Sci.* **2023**, *114*, 2265–2276. [CrossRef]
578. Nakamoto, N.; Cho, H.; Shaked, A.; Olthoff, K.; Valiga, M.E.; Kaminski, M.; Gostick, E.; Price, D.A.; Freeman, G.J.; Wherry, E.J.; et al. Synergistic reversal of intrahepatic HCV-specific CD8 T cell exhaustion by combined PD-1/CTLA-4 blockade. *PLoS Pathog.* **2009**, *5*, 1000313. [CrossRef]
579. Hazrati, A.; Malekpour, K.; Khorramdelazad, H.; Rajaei, S.; Hashemi, S.M. Therapeutic and immunomodulatory potentials of mesenchymal stromal/stem cells and immune checkpoints related molecules. *Biomark. Res.* **2024**, *12*, 35. [CrossRef]
580. Bally, A.P.; Lu, P.; Tang, Y.; Austin, J.W.; Scharer, C.D.; Ahmed, R.; Boss, J.M. NF-κB regulates PD-1 expression in macrophages. *J. Immunol.* **2015**, *194*, 4545–4554. [CrossRef]
581. Said, E.A.; Dupuy, F.P.; Trautmann, L.; Zhang, Y.; Shi, Y.; El-Far, M.; Hill, B.J.; Noto, A.; Ancuta, P.; Peretz, Y.; et al. Programmed death-1-induced interleukin-10 production by monocytes impairs CD4+ T cell activation during HIV infection. *Nat. Med.* **2010**, *16*, 452–459. [CrossRef]
582. Huang, X.; Venet, F.; Wang, Y.L.; Lepape, A.; Yuan, Z.; Chen, Y.; Swan, R.; Kherouf, H.; Monneret, G.; Chung, C.S.; et al. PD-1 expression by macrophages plays a pathologic role in altering microbial clearance and the innate inflammatory response to sepsis. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 6303–6308. [CrossRef] [PubMed]
583. Shen, L.; Gao, Y.; Liu, Y.; Zhang, B.; Liu, Q.; Wu, J.; Fan, L.; Ou, Q.; Zhang, W.; Shao, L. PD-1/PD-L pathway inhibits M.tb-specific CD4+ T-cell functions and phagocytosis of macrophages in active tuberculosis. *Sci. Rep.* **2016**, *6*, 38362. [CrossRef] [PubMed]
584. Hartley, G.P.; Chow, L.; Ammons, D.T.; Wheat, W.H.; Dow, S.W. Programmed Cell Death Ligand 1 (PD-L1) Signaling Regulates Macrophage Proliferation and Activation. *Cancer Immunol. Res.* **2018**, *6*, 1260–1273. [CrossRef] [PubMed]
585. Kassel, R.; Cruise, M.W.; Iezzoni, J.C.; Taylor, N.A.; Pruett, T.L.; Hahn, Y.S. Chronically inflamed livers up-regulate expression of inhibitory B7 family members. *Hepatology* **2009**, *50*, 1625–1637. [CrossRef]
586. Triantafyllou, E.; Gudd, C.L.; Mawhin, M.A.; Husbyn, H.C.; Trovato, F.M.; Siggins, M.K.; O'Connor, T.; Kudo, H.; Mukherjee, S.K.; Wendon, J.A.; et al. PD-1 blockade improves Kupffer cell bacterial clearance in acute liver injury. *J. Clin. Investig.* **2021**, *131*, 140196. [CrossRef]
587. Triantafyllou, E.; Woollard, K.J.; McPhail, M.J.W.; Antoniades, C.G.; Possamai, L.A. The Role of Monocytes and Macrophages in Acute and Acute-on-Chronic Liver Failure. *Front. Immunol.* **2018**, *9*, 2948. [CrossRef]
588. Charles, R.; Chou, H.S.; Wang, L.; Fung, J.J.; Lu, L.; Qian, S. Human hepatic stellate cells inhibit T-cell response through B7-H1 pathway. *Transplantation* **2013**, *96*, 17–24. [CrossRef]
589. Onorati, A.; Havas, A.P.; Lin, B.; Rajagopal, J.; Sen, P.; Adams, P.D.; Dou, Z. Upregulation of PD-L1 in Senescence and Aging. *Mol. Cell Biol.* **2022**, *42*, 0017122. [CrossRef] [PubMed]
590. Salminen, A. Inhibitory immune checkpoints suppress the surveillance of senescent cells promoting their accumulation with aging and in age-related diseases. *Biogerontology* **2024**, *25*, 749–773. [CrossRef]
591. Salminen, A. The role of the immunosuppressive PD-1/PD-L1 checkpoint pathway in the aging process and age-related diseases. *J. Mol. Med.* **2024**, *102*, 733–750. [CrossRef] [PubMed]
592. Wang, T.W.; Johmura, Y.; Suzuki, N.; Omori, S.; Migita, T.; Yamaguchi, K.; Hatakeyama, S.; Yamazaki, S.; Shimizu, E.; Imoto, S.; et al. Blocking PD-L1-PD-1 improves senescence surveillance and ageing phenotypes. *Nature* **2022**, *611*, 358–364. [CrossRef] [PubMed]
593. Sun, L.; Wang, Y.; Wang, X.; Navarro-Corcuera, A.; Ilyas, S.; Jalan-Sakrikar, N.; Gan, C.; Tu, X.; Shi, Y.; Tu, K.; et al. PD-L1 promotes myofibroblastic activation of hepatic stellate cells by distinct mechanisms selective for TGF-β receptor I versus II. *Cell Rep.* **2022**, *38*, 110349. [CrossRef] [PubMed]
594. Kontos, F.; Michelakos, T.; Kurokawa, T.; Sadagopan, A.; Schwab, J.H.; Ferrone, C.R.; Ferrone, S. B7-H3: An Attractive Target for Antibody-based Immunotherapy. *Clin. Cancer Res.* **2021**, *27*, 1227–1235. [CrossRef]
595. Picarda, E.; Ohaegbulam, K.C.; Zang, X. Molecular Pathways: Targeting B7-H3 (CD276) for Human Cancer Immunotherapy. *Clin. Cancer Res.* **2016**, *22*, 3425–3431. [CrossRef]

596. Podojil, J.R.; Miller, S.D. Potential targeting of B7-H4 for the treatment of cancer. *Immunol. Rev.* **2017**, *276*, 40–51. [CrossRef]
597. Sica, G.L.; Choi, I.H.; Zhu, G.; Tamada, K.; Wang, S.D.; Tamura, H.; Chapoval, A.I.; Flies, D.B.; Bajorath, J.; Chen, L. B7-H4, a molecule of the B7 family, negatively regulates T cell immunity. *Immunity.* **2003**, *18*, 849–861. [CrossRef]
598. Jiang, D.; Chen, C.; Yan, D.; Zhang, X.; Liu, X.; Yan, D.; Cui, D.; Yang, S. Exhausted phenotype of circulating CD8+ T cell subsets in hepatitis B virus carriers. *BMC Immunol.* **2022**, *23*, 18. [CrossRef]
599. Mohammadizad, H.; Shahbazi, M.; Hasanjani Roushan, M.R.; Soltanzadeh-Yamchi, M.; Mohammadnia-Afrouzi, M. TIM-3 as a marker of exhaustion in CD8+ T cells of active chronic hepatitis B patients. *Microb. Pathog.* **2019**, *128*, 323–328. [CrossRef]
600. Arvanitakis, K.; Papadakos, S.P.; Vakadaris, G.; Chatzikalil, E.; Stergiou, I.E.; Kalopitas, G.; Theocharis, S.; Germanidis, G. Shedding light on the role of LAG-3 in hepatocellular carcinoma: Unraveling immunomodulatory pathways. *Hepatoma Res.* **2024**, *10*, 21. [CrossRef]
601. Heim, K.; Neumann-Haefelin, C.; Thimme, R.; Hofmann, M. Heterogeneity of HBV-Specific CD8+ T-Cell Failure: Implications for Immunotherapy. *Front. Immunol.* **2019**, *10*, 2240. [CrossRef] [PubMed]
602. Ogiso, H.; Ito, H.; Ando, T.; Arioka, Y.; Kanbe, A.; Ando, K.; Ishikawa, T.; Saito, K.; Hara, A.; Moriwaki, H.; et al. The Deficiency of Indoleamine 2,3-Dioxygenase Aggravates the CCl4-Induced Liver Fibrosis in Mice. *PLoS ONE* **2016**, *11*, 0162183. [CrossRef] [PubMed]
603. Hoshi, M.; Osawa, Y.; Nakamoto, K.; Morita, N.; Yamamoto, Y.; Ando, T.; Tashita, C.; Nabeshima, T.; Saito, K. Kynurenine produced by indoleamine 2,3-dioxygenase 2 exacerbates acute liver injury by carbon tetrachloride in mice. *Toxicology* **2020**, *438*, 152458. [CrossRef]
604. Nebbia, G.; Peppa, D.; Schurich, A.; Khanna, P.; Singh, H.D.; Cheng, Y.; Rosenberg, W.; Dusheiko, G.; Gilson, R.; ChinAleong, J.; et al. Upregulation of the Tim-3/galectin-9 pathway of T cell exhaustion in chronic hepatitis B virus infection. *PLoS ONE* **2012**, *7*, e47648. [CrossRef]
605. Fisicaro, P.; Valdatta, C.; Massari, M.; Loggi, E.; Biasini, E.; Sacchelli, L.; Cavallo, M.C.; Silini, E.M.; Andreone, P.; Missale, G.; et al. Antiviral intrahepatic T-cell responses can be restored by blocking programmed death-1 pathway in chronic hepatitis B. *Gastroenterology* **2010**, *138*, 682–693. [CrossRef]
606. Wu, W.; Shi, Y.; Li, S.; Zhang, Y.; Liu, Y.; Wu, Y.; Chen, Z. Blockade of Tim-3 signaling restores the virus-specific $CD8^+$ T-cell response in patients with chronic hepatitis B. *Eur. J. Immunol.* **2012**, *42*, 1180–1191. [CrossRef]
607. Zong, L.; Peng, H.; Sun, C.; Li, F.; Zheng, M.; Chen, Y.; Wei, H.; Sun, R.; Tian, Z. Breakdown of adaptive immunotolerance induces hepatocellular carcinoma in HBsAg-tg mice. *Nat. Commun.* **2019**, *10*, 221. [CrossRef]
608. Li, Q.; Han, J.; Yang, Y.; Chen, Y. PD-1/PD-L1 checkpoint inhibitors in advanced hepatocellular carcinoma immunotherapy. *Front. Immunol.* **2022**, *13*, 1070961. [CrossRef]
609. Abou-Alfa, G.K.; Chan, S.L.; Kudo, M.; Lau, G.; Kelley, R.K.; Furuse, J.; Sukeepaisarnjaroen, W.; Kang, Y.K.; Dao, T.V.; De Toni, E.N.; et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. *J. Clin. Oncol.* **2022**, *40*, 379. [CrossRef]
610. Gupta, T.; Jarpula, N.S. Hepatocellular carcinoma immune microenvironment and check point inhibitors-current status. *World J. Hepatol.* **2024**, *16*, 353–365. [CrossRef]
611. Haber, P.K.; Puigvehí, M.; Castet, F.; Lourdusamy, V.; Montal, R.; Tabrizian, P.; Buckstein, M.; Kim, E.; Villanueva, A.; Schwartz, M.; et al. Evidence-Based Management of Hepatocellular Carcinoma: Systematic Review and Meta-analysis of Randomized Controlled Trials (2002–2020). *Gastroenterology* **2021**, *161*, 879–898. [CrossRef]
612. Li, X.; Gao, L.; Wang, B.; Hu, J.; Yu, Y.; Gu, B.; Xiang, L.; Li, X.; Li, H.; Zhang, T.; et al. FXa-mediated PAR-2 promotes the efficacy of immunotherapy for hepatocellular carcinoma through immune escape and anoikis resistance by inducing PD-L1 transcription. *J. Immunother. Cancer* **2024**, *12*, e009565. [CrossRef] [PubMed]
613. Oliveira, C.; Mainoli, B.; Duarte, G.S.; Machado, T.; Tinoco, R.G.; Esperança-Martins, M.; Ferreira, J.J.; Costa, J. Immune-related serious adverse events with immune checkpoint inhibitors: Systematic review and network meta-analysis. *Eur. J. Clin. Pharmacol.* **2024**, *80*, 677–684. [CrossRef] [PubMed]
614. Liang, X.; Xiao, H.; Li, H.; Chen, X.; Li, Y. Adverse events associated with immune checkpoint inhibitors in non-small cell lung cancer: A safety analysis of clinical trials and FDA pharmacovigilance system. *Front. Immunol.* **2024**, *15*, 1396752. [CrossRef] [PubMed]
615. Godbert, B.; Petitpain, N.; Lopez, A.; Nisse, Y.E.; Gillet, P. Hepatitis B reactivation and immune check point inhibitors. *Dig. Liver Dis.* **2021**, *53*, 452–455. [CrossRef] [PubMed]
616. Ren, X.; Wang, H.; Deng, L.; Wang, W.; Wang, Y. Immune-related adverse events of immune checkpoint inhibitors combined with angiogenesis inhibitors: A real-world pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database (2014–2022). *Int. Immunopharmacol.* **2024**, *136*, 112301. [CrossRef]