

Review

Transcription Factors as Drivers of Gallbladder Cancer: Mechanisms, Dysregulation, and Therapeutic Prospects

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Abstract

Gallbladder cancer (GBC), an aggressive malignancy of the biliary tract, is characterized by pronounced geographical variation and a poor prognosis, with a five-year survival rate below 20%. Despite its low global incidence, it ranks as the fifth most prevalent gastrointestinal cancer. The aim of this review is to provide a comprehensive understanding of the molecular mechanisms underpinning GBC progression, with a particular focus on the pivotal role of transcription factors (TFs) in its pathogenesis. This review delineates how aberrant regulation of TFs contributes to tumor initiation, progression, and therapeutic resistance, and to discuss the translational potential of targeting these factors for clinical benefit. Tumor suppressor TFs such as p53 and p16 frequently undergo genetic alterations, including mutations, deletions, or epigenetic silencing, leading to impaired cell cycle control, DNA repair, and apoptosis. Conversely, oncogenic TFs including TCF4, MYBL2, NF-κB, AP-1, Snail, c-MYC, SP1, FOXK1, KLF-5, STAT3 and BIRC7 are often upregulated in GBC, promoting unchecked proliferation, epithelial–mesenchymal transition (EMT), metastasis, and therapeutic resistance. This review aims to bridge current molecular insights with emerging therapeutic approaches, with particular emphasis on innovative interventions such as proteolysis-targeting chimeras (PROTACs), RNA-based therapeutics, CRISPR-driven genome editing, and epigenetic modulators, which collectively represent promising strategies for achieving more effective and personalized treatment outcomes in patients with GBC.

Keywords: transcription factors; cell cycle progression; biliary duct; gastrointestinal cancer; EMT; metastasis



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1. Introduction

Gallbladder cancer (GBC), a malignancy of the biliary tract, remains a formidable challenge in oncology due to its aggressive nature, late diagnosis, and limited treatment options. It exhibits a striking geographical variation in incidence, underscoring its complex etiology and regional risk factors. Globally, GBC is associated with a dismal prognosis and its association with a high mortality rate, with a median five-year overall survival rate of 5% [1]. The reported number of new cases of GBC worldwide in 2022 was 122,462 with 89,031 death cases, as per Globocan, 2022 [2]. In India, GBC is highly prevalent, accounting for nearly 10% of the global disease burden [3]. There are notable regional

variations, with significantly higher incidence rates in the northern and northeastern regions than in the southern states of India. Despite continued research, the underlying molecular mechanisms for GBC pathogenesis in the Indian population remain largely unexplored [4]. The development of GBC is multifactorial, involving a complex interplay of genetic predisposition, chronic inflammation, gallstone disease or cholelithiasis (especially when left untreated), infections (such as *Helicobacter* or *Salmonella* species), and lifestyle choices, which all work together to increase the likelihood of GBC tumorigenesis. Central to this pathogenesis is the dysregulation of transcription factors (TFs), key regulators of gene expression. As essential conductors of gene expression, these TFs regulate a broad variety of cellular processes including proliferation, differentiation, DNA repair, immune response and programmed cell death (Figure 1). Disruption in TF activity is a common molecular event across many cancers, including GBC, and contributes to aberrant transcriptional programs of the downstream cellular programs that drive tumorigenesis. An understanding of the altered expression of these upstream regulatory factors may shed light on the core causes of GBC malignancy [5,6].

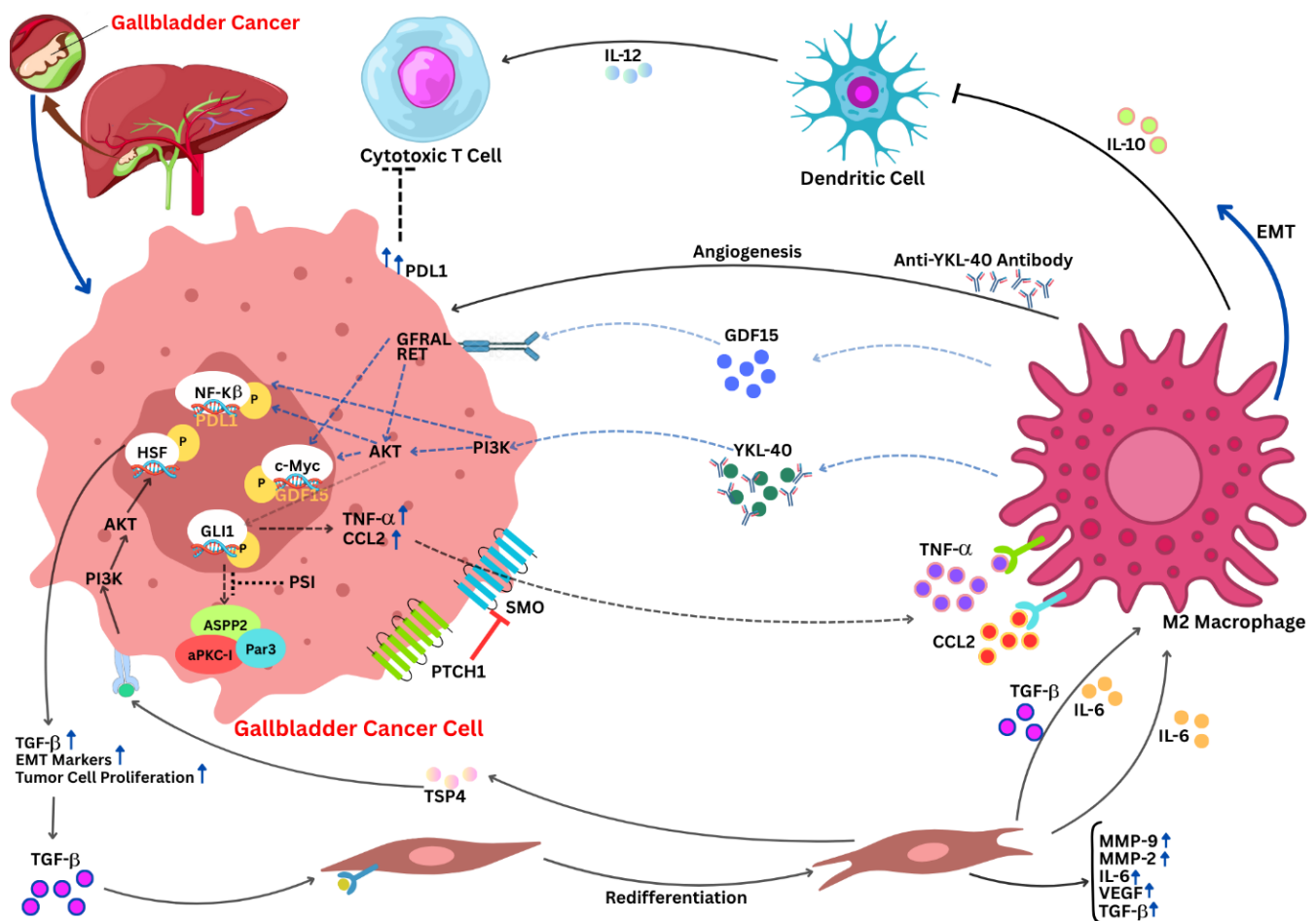


Figure 1. Oncogenic pathway in gallbladder cancer: an interplay. The tumor microenvironment and signaling factors have an interconnection, and they play in a rhythm to promote tumor progression in GBC. M2 macrophages contribute to immune evasion by secreting chitinase-3-like protein 1 (YKL-40), a chitinase-like glycoprotein that has been linked to increased tumor angiogenesis, immune suppression, and malignancy in a variety of cancers, as well as increased PD-L1 expression on tumor cells. M2 macrophages promote extracellular matrix remodeling and EMT by secreting IL-10 and modulating tumor growth, invasion, and lymph node metastasis via anti-YKL-40 antibodies. Additionally, they upregulate IL-6, TGF- β , and MMPs. Through TGF- β and CCL2 signaling, CAFs aid

in tumor cell proliferation and increase EMT markers. Integrin $\alpha 2$ and the PI3K/AKT axis both enhance metastatic behavior. Elevated PD-L1 expression on tumor cells implies immune evasion by suppressing cytotoxic T cell activity, and GDF15-GFRAL interactions may control metabolic reprogramming. The upward blue arrows represent the upregulation; dotted blue arrows represent the activation pathways; curved blue arrows represent directional signaling; black arrows represent the flow of molecular process; and the hammer-headed arrows represent inhibition. AKT, protein kinase B; CAF, cancer-associated fibroblast; CCL2, C-C motif chemokine ligand 2; EMT, epithelial–mesenchymal transition; GBC, gallbladder cancer; GDF15, growth differentiation factor 15; GFRAL, glial cell-derived neurotrophic factor receptor alpha-like; IL-6, interleukin-6; IL-10, interleukin-10; IL-12, interleukin-12; MMP, matrix metalloproteinase; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PTCH1, patched 1; SMO, smoothened; TGF- β , transforming growth factor-beta; TNF- α , tumor necrosis factor-alpha; YKL-40, chitinase 3-like protein 1 (adapted from Tang et al., 2025 [7]).

This review delves into the dysregulation of TFs and highlights their vital roles in GBC development. It focuses specifically on the TFs that exhibit strong associations with GBC pathogenesis and hold promise as future diagnostic markers or therapeutic targets. Through the analysis of these transcription factors across a wide variety of datasets, ranging from transcriptomic analysis to protein expression and gene copy analysis, it has been observed that GBC emerges not just as the sum of various gene mutations, but as a breakdown of a fine-tuned and essential transcription-control mechanism orchestrated by TFs. Despite the advances, the precise mechanisms linking epidemiology to pathogenesis remain elusive, necessitating integrated studies to develop prevention and early detection strategies. Understanding these risk profiles is foundational to unraveling GBC's transcriptional dysregulation, as explored in subsequent sections.

2. Transcriptional Factors and Their Roles in GBC

Through their modulation of gene expression patterns, transcription factors significantly contribute to the development and advancement of GBC as depicted in Figure 2 and listed along with their functions in Table 1. These factors impact cell proliferation, metastasis, and survival. Importantly, GBC tissues show a marked increase in Transcription Factor 4 (TCF4) compared to chronic cholecystitis, which is associated with higher tumor grades and advanced stages [8]. TCF4 is a critical component of the Wnt/ β -catenin signaling pathway. The overexpression of Forkhead box K1 (FOXK1) in GBC also activates the AKT/mTOR signaling pathway, which in turn promotes tumor growth and metastasis. Increased invasiveness of GBC cells is caused by the interaction of Histone Deacetylase 1 (HDAC1) and Transcription Factor 12 (TCF12), which further promotes epithelial–mesenchymal transition (EMT). Furthermore, Forkhead box O3 (FOXO3) is a tumor suppressor that, when activated, causes GBC cell death and proliferation inhibition, especially through the Janus kinase2/signal transducer and activators of transcription 3 (JAK2/STAT3) pathway. These results demonstrate the possible therapeutic intervention targets and emphasize the intricate regulatory networks involving transcription factors in GBC [9,10].

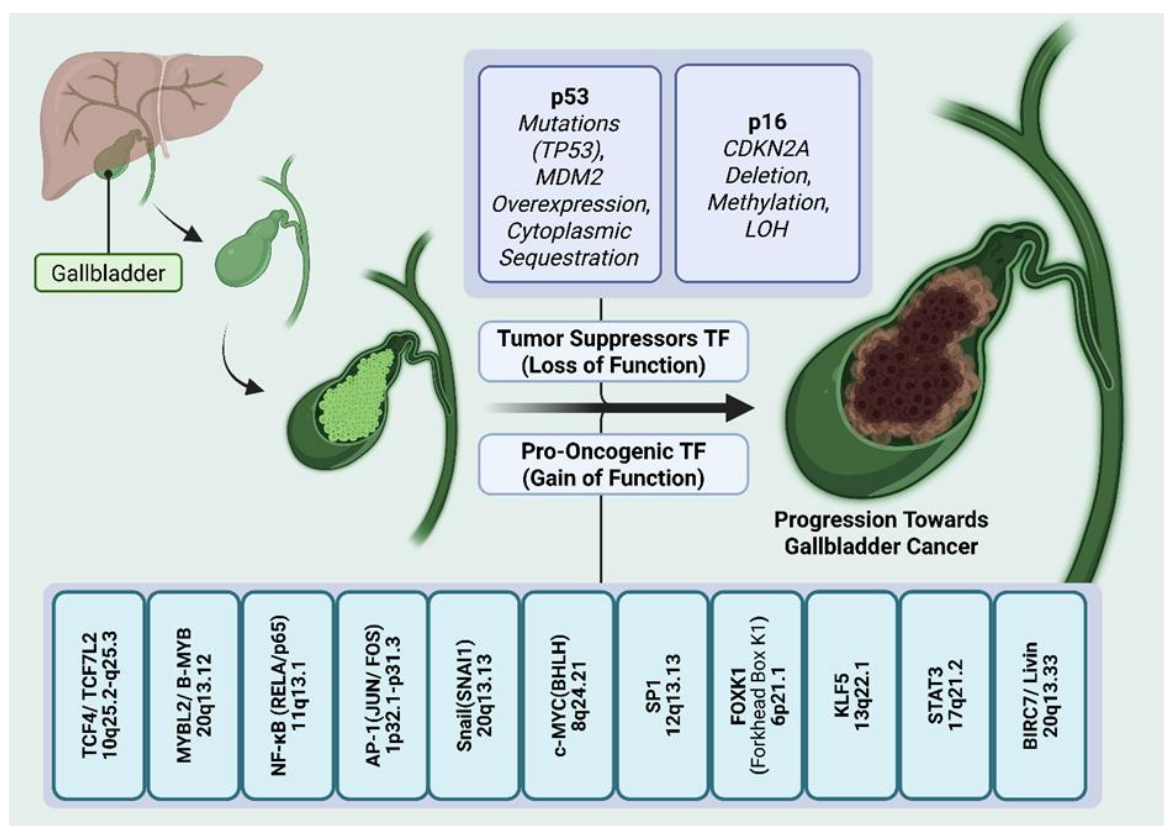


Figure 2. Role of transcription factors in the progression of gallbladder cancer. Transcriptional disparities in gallbladder cancer involving tumor suppressor and pro-oncogenic transcription factors compounding the process of epithelial–mesenchymal transition and tumor metastasis. Loss of function or mutation in tumor suppressor TFs (top panel), such as p53 and p16, along with MDM2 overexpression and cytoplasmic sequestration of p53 result in cell cycle dysregulation, impaired apoptosis and uncontrolled proliferation. Gain of function or hyperactivation of pro-oncogenic TFs (bottom panel), such as TCF4, MYBL2, NF-κB, AP-1, Snail, c-MYC, SP1, FOXK1, KLF5, STAT3, Livin, etc., drives tumorigenesis by activating various signaling pathways, promoting inflammation, cell proliferation, dedifferentiation, metastasis, angiogenesis, etc.

Table 1. Transcription factors and their role in GBC development.

Transcription Factor Family	Transcription Co/Factor	Role in GBC Progression	Experimental Model	Current Therapeutics Targets	References
SNAIL (Zinc-finger)	SNAIL1 (Snail)	It binds to E-cadherin promoter, repressing epithelial genes while inducing mesenchymal ones. It drives EMT, invasiveness, dedifferentiation, metastasis, and poor prognosis in GBC patients.	In vitro and in vivo	Snail degradation, EMT inhibitors	[11–19]
SNAIL	SNAIL2 (Slug)	It also stimulates EMT binding to the E-cadherin promoter. MMP-19 upregulates it and activates Axl, maintaining EMT and tumor aggressiveness.	In vitro	MMP 19/Axl inhibitors	[12,16,20]
SNAIL	Smuc	Promote cancer progression by binding to the E-cadherin promoter to initiate EMT	In vitro	EMT pathway inhibition	[12]

Table 1. Cont.

Transcription Factor Family	Transcription Co/Factor	Role in GBC Progression	Experimental Model	Current Therapeutics Targets	References
ZEB (Zinc-finger and E-box-binding proteins)	Homeobox 1 (ZEB1)	It binds to the E-cadherin promoter, represses epithelial cadherin and promotes mesenchymal markers to drive EMT. FOX L1 restores E-Cadherin and reduces invasion.	In vitro and in vivo	ZEB1 inhibitors, FOX L1 restoration	[12,17,21–23]
ZEB	ZEB2	Promote cancer progression by binding to the E-cadherin promoter, suppressing epithelial genes, and activating mesenchymal genes to initiate EMT	In vitro	EMT inhibitors	[12]
Twist (bHLH)	Twist1	Drives EMT by binding to the E-cadherin promoter, suppressing epithelial genes, and activating mesenchymal genes.	In vitro and in vivo	BH3 mimetics, EMT inhibitors	[12,24]
Twist (bHLH)	Twist2	Promote cancer progression by binding to the E-cadherin promoter, suppressing epithelial genes, and activating mesenchymal genes to initiate EMT	In vitro	EMT inhibitors	[12]
E-protein (bHLH)	TCF4	Cip1-interacting zinc-finger protein-1 promotes GBC cell growth and migration by activating β -catenin/TCF target genes (<i>c-Myc</i> , <i>Snail</i> , <i>Cyclin D1</i>) via interaction with TCF4.	In vitro	Wnt/ β catenin inhibitors, CIZ1 blockade	[25]
AP-1	JunB	Overexpressed in GBC and linked to poor prognosis, Promotes EMT by reducing E-cadherin expression via PDK1	In vitro	PDK1 inhibitors	[26–28]
FAD-dependent amine oxidase superfamily	LSD1/KDM1A	Upregulated in GBC and linked to poor prognosis. It promotes EMT by demethylating H3K4 at the E-cadherin promoter (recruited by Snail), suppressing E-cadherin, and enhancing invasion. It also cooperates with c-Myc to drive GBC proliferation and invasion.	In vitro	LSD1 inhibitors, c Myc suppressors	[29–32]
TCF/LEF family (HMG-box)	TCF4 (TCF7L2)	Interacts with β -catenin upon Wnt activation, drives expression of targets (<i>c-Myc</i> , <i>Cyclin D1</i> , <i>Snail</i>), promotes EMT, proliferation, cell growth, and migration in GBC [via Ciz1 co-factor].	In vitro	Wnt inhibitors, TCF4 silencing	[15,33]
Zinc-finger TF (Matrin-3 family)	CIZ1	Binds TCF4, activates Wnt/ β -catenin–TCF signaling in GBC; increases proliferation, migration, EMT, tumorigenesis in vitro/in vivo. Acts as oncogenic transcription co-factor	In vitro and in vivo	CIZ1 inhibitors	[25]
AP-1 family (bZIP)	c-Jun	Represses WIF-1 via promoter hypermethylation (via DNMT1 recruitment); leads to Wnt pathway derepression-increased GBC proliferation, invasion, decreased apoptosis.	In vitro	DNMT1 inhibitors, epigenetic modulators	[34,35]

Table 1. Cont.

Transcription Factor Family	Transcription Co/Factor	Role in GBC Progression	Experimental Model	Current Therapeutics Targets	References
Bromodomain (BRD)-containing protein family	BRD9	Upregulated in GBC and regulates the expression of cystatin 1 (CST1) by binding to FOXP1 TF to <i>CST1</i> promoter. It also activates CST1/PI3K/AKT pathway to induce hyperproliferation.	In vitro and in vivo	BRD9 inhibitor I-BRD9	[36]
Tumor Suppressor Gene family	<i>TP53</i> (p53)	<i>TP53</i> mutations (in 27–70% of GBC cases, especially in exons 5–9) lead to loss of tumor-suppressive function, promoting carcinogenesis.	In situ and in vivo	p53 reactivation molecules, gene therapy	[37–47]
Tumor Suppressor Gene family	Rb (Retinoblastoma)	pRb, TF co-factor regulating E2F TFs, is deleted in 18–67% of GBC cases. Loss of pRb promotes cancer progression, higher stage/grade, and poor survival.	In situ	CDK4/6 inhibitors	[48]

Abbreviations: AP-1, Activator Protein-1; bHLH, basic helix–loop–helix; CIZ1, Cip7-interacting zinc-finger protein-1; DNMT1, DNA methyltransferase 1; EMT, epithelial–mesenchymal transition; FOX L1, forkhead box L1; HMG, high-mobility group; H3K4, histone 3 lysine 4; KDM1A, lysine-specific demethylase 1A; LSD1, lysine-specific demethylase 1; NF-κB, nuclear factor-kappa B; PI3K, phosphatidylinositol 3-kinase; PDK1, phosphoinositide-dependent kinase 1; PROTAC, proteolysis-targeting chimera; Rb, retinoblastoma protein; Snail, zinc-finger protein SNAIL; Smuc, snail family zinc-finger protein Smuc; STAT3, signal transducer and activator of transcription 3; TCF, T-cell factor; TCF4, transcription factor 4; TWIST, twist-related protein; WIF-1, Wnt inhibitory factor 1; ZEB, zinc-finger E-box-binding homeobox.

3. Loss of Function of Tumor Suppressor Genes

The loss of tumor suppressor genes contributes significantly to the development and progression of gallbladder cancer (GBC). A dysfunctional p53 protein that fails to regulate genomic integrity is the result of mutations and loss of heterozygosity (LOH), which affect more than half of all cases and often occur early in carcinogenesis. Loss of p16 is found in approximately 61% to 75% of gallbladder tumors and is strongly linked to a poor prognosis. This inactivation of the CDKN2A/p16 locus at chromosome 9p21 can occur as a result of point mutations, promoter hypermethylation, loss of heterozygosity (LOH), homozygous deletions, or a mix of these factors. Furthermore, in around 30% of cases, PTEN, a crucial negative regulator of the PI3K/AKT pathway, is downregulated through promoter methylation, LOH, or protein loss, which adds to unregulated proliferative signaling. While SMAD4/DPC4 and pRB are less commonly impacted genes, their inactivation further disturbs cell cycle regulation and tumor differentiation in some tumor types. The aggressive pathobiology of GBC is fueled by the loss of these tumor suppressors, which together dismantle critical checkpoints against cell proliferation and survival [49,50]. The genes associated with loss of tumor function in GBC are given below.

3.1. p53

p53, also known as the tumor protein p53 (*TP53*), is a potent transcription factor and a well-established tumor suppressor protein. Encoded by the *TP53* gene, often dubbed as “Guardian of the genome,” p53 plays a critical role in preserving genomic integrity by orchestrating cellular responses to various stress signals. These stressors include, but are not limited to, DNA damage (from sources like UV radiation or chemotherapeutic agents), hypoxia, and oncogene activation [51]. While p53 protein is exclusively located within the nucleus, executing its transcriptional regulatory functions, it can also be found in the cytoplasm in an inactive state [51,52]. A crucial regulator, Mdm2, is intimately involved in controlling p53’s subcellular localization. It binds to p53, promoting its export

from the nucleus to the cytoplasm, where p53 is subsequently targeted for proteasomal degradation [51,52]. Under basal conditions, p53 protein levels are kept low due to rapid degradation primarily mediated by Mdm2. However, upon exposure to cellular stress, such as DNA damage, p53 undergoes post-translational modifications (such as phosphorylation and acetylation) that lead to its stabilization and accumulation in the nucleus [53]. Once activated and accumulated, p53 orchestrates a variety of cellular responses aimed at preserving cellular integrity. p53 can induce cell cycle arrests, often mediated through the transcriptional activation of genes like *CDKN1A* (which encodes p21), a potent inhibitor of cyclin-dependent kinases (CDKs) [51].

Aberrant p53 activity, whether through mutation or altered expression, is a common finding in GBC. Some evidence also suggests increased prevalence [54]. The implications of p53 deregulation for GBC are multifaceted, encompassing aspects of disease severity, prognosis, and therapeutic response [51]. High levels of p53 protein are a common finding in GBC tumors, reflecting a disruption of normal p53 regulatory mechanisms, which could result due to DNA alterations that can affect the p53 [55,56]. Multiple studies employing immunohistochemistry have reported p53 overexpression in a significant proportion of GBC cases, suggesting an early and frequent event in tumorigenesis [56]. Mutations in the *TP53* gene, particularly missense point mutations and loss of heterozygosity (LOH) at the *TP53* locus, are prevalent mechanisms leading to impaired p53 function. Mutations in *TP53* are frequently observed in GBC, with a systematic review of 3893 GBC samples reporting a weighted average mutation frequency of 38.4%, ranging from 13.2% to 66.7% across studies [57]. Geographical variations in mutation rates and spectra have been noted, highlighting potential roles for environmental or genetic factors [58]. Studies showed varied co-relations from positive and negative findings between patients' survivability and prognosis, after chemotherapy, radiotherapy, and other treatments [59]. This data can be used with others in the search for a better treatment approach, such as Mdm2 [52], an inhibitor which could have beneficial effects by inducing p53, which is impaired from damage, mutations, etc. [51]. In certain cases, p53 status in GBC has been linked to poor prognosis. Higher p53 expression, reflecting p53 dysfunction, often correlates with more aggressive tumor behavior, higher tumor grade, advanced disease stage, shorter patient survival times, increased rates of metastasis and reduced responsiveness to certain therapies. Also, some other factors such as *K-ras* mutations can potentially worsen patient state [58]. Takagi and Ohashi suggest differential p53 levels, via tests like IHC and other more accurate tests such as sequencing, to create a better analysis of which biomarkers should be screened, for differential or risk stages, to implement the most effective approach. While the focus is on GBC, it is worth noting that p53's role is consistent with its function in other cancers, such as of the bladder, lung, and colon, where mutations are also common and linked to poor survival. For instance, combined deletion of p53 and PTEN in bladder epithelium leads to invasive cancer, mirroring findings in GBC [60]. In some cases, even with lower percentages of p53 expression, the risk for metastasis is observed to be greater because of the alteration. In summary, p53 dysregulation is a critical event in GBC development. Its multifaceted roles as a tumor suppressor, a regulator of cellular stress responses, and a potential therapeutic target highlight its importance. A dissection of the precise molecular mechanisms by which p53 is altered and how those alterations contribute to the aggressive nature of GBC is given in Figure 3. Such studies may, one day, inform both prevention strategies and better tailored therapies.

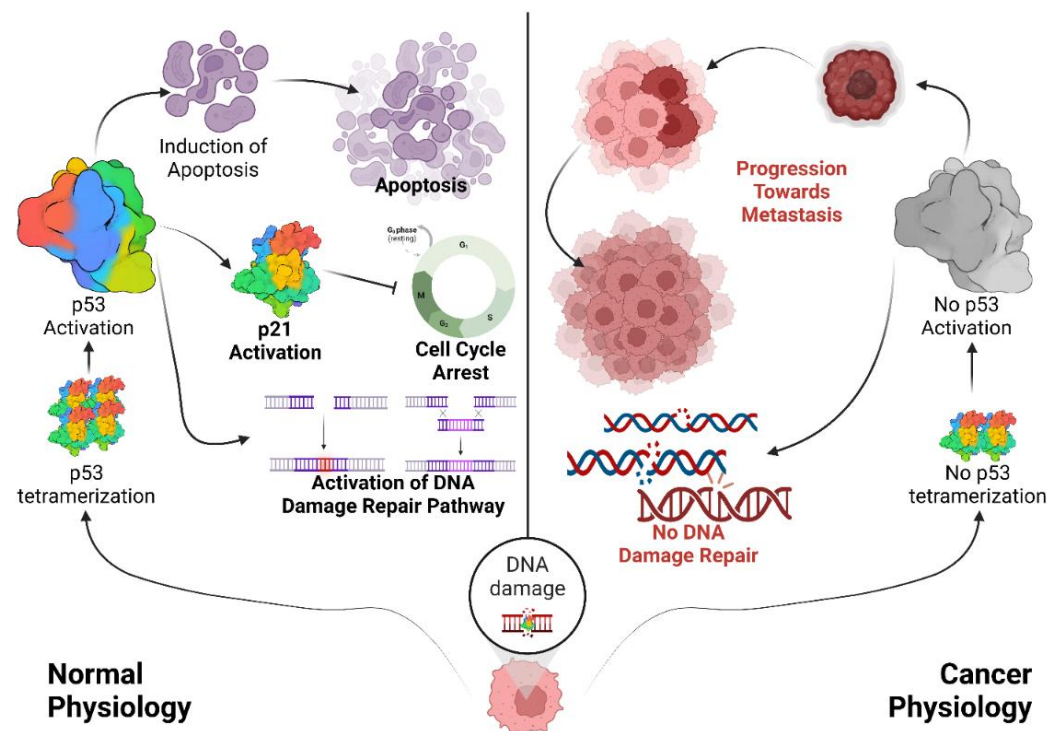


Figure 3. Role of p53 in regulating the cell cycle to maintain genomic integrity. Under normal conditions, p53 is maintained at low levels. In response to cellular stresses such as DNA damage, p53 accumulates and functions as a tetrameric transcription factor, inducing either cell cycle arrest or apoptosis. DNA damage stimulates p53 tetramerization and activation, which facilitates cell cycle regulation and the maintenance of genomic integrity. Activated p53 binds to specific response elements upstream of target genes such as p21, leading to cell cycle arrest and activation of the DNA repair machinery, primarily via ATR/ATM kinase pathways. When DNA damage is irreparable, p53 triggers the expression of pro-apoptotic genes such as Bax and Bak to initiate apoptosis. In contrast, under carcinogenic conditions, mutations in various domains of p53 impede its stabilization and tetramer formation, resulting in p53 inactivation. Some p53 mutants with a functional tetramerization domain can form mixed tetramers with wild-type p53, exerting dominant-negative effects (DNE) that further inactivate p53, ultimately contributing to genomic instability and metastasis. Black arrows represent the flow of molecular process; and the hammer-headed arrows represent inhibition.

3.2. $p16^{INK4a}$

$p16^{INK4a}$, encoded by the *CDKN2A* gene on chromosome 9p21, stands as a critical gatekeeper-like suppressive regulator of cell cycle progression, and its deregulation is a frequent hallmark of gallbladder cancer (GBC) [61–66]. As a potent cyclin-dependent kinase inhibitor (CDKI), $p16^{INK4a}$ normally exerts its tumor-suppressive function by binding to CDK4 and CDK6, preventing their association with D-type cyclins and thereby inhibiting phosphorylation of the retinoblastoma protein (RB) [67,68], a key event required for the G1-S transition of cell cycle. By maintaining RB in its hyperphosphorylated, active state, $p16^{INK4a}$ sequesters E2F transcription factors, preventing the expression of genes essential for DNA replication and cell cycle progression [68,69]. Thus, functional $p16^{INK4a}$ serves as a crucial brake on uncontrolled cellular proliferation [70]. Dysfunctional p16 fails to inhibit Cyclin/CDK activity, allowing unchecked entry into the S phase of DNA synthesis. This leads to Rb pathway disruption, triggering continuous activation of downstream signals that drive uncontrolled cell proliferation [5].

In GBC, this brake is frequently released, contributing significantly to tumorigenesis. In contrast to other cancers where *RB* mutations are prevalent, GBC often exhibits alterations that target $p16^{INK4a}$ itself [71]. The most common mechanisms leading to $p16^{INK4a}$ inactivation in GBC are homozygous deletion of the *CDKN2A* gene, and epigenetic silenc-

ing via promoter hypermethylation [69,72,73]. Loss of heterozygosity (LOH) at 9p21-22 also provided further evidence from a study in 2007, which found homozygous deletions in 26.0% (13/50) of cases, LOH in 56.9% (29/51), and promoter hypermethylation in 72.5% (37/51), with loss of p16 protein expression in 62.7% (32/51) of cases [74]. Although some studies find a significant correlation with loss and/or alterations of p16 with other factors [69], mutations in p16 have been shown to be only secondary events in GBC tumorigenesis [5]. While several molecular methods show similar results, PCR analysis proved more practical when evaluating bile in an endoscopic retrograde study. The consequence of p16^{INK4a} loss is profound. Without functional p16^{INK4a}, CDK4/6 are free to complex with D-type cyclins, leading to RB hyperphosphorylation, E2F release, and ultimately, uncontrolled cell cycle progression [68].

The relationship between p16^{INK4a} alterations and clinicopathological features in GBC remains under debate. Studies report a prevalence in the range of promoter hypermethylation [5,75]. Also, studies have provided conflicting evidence for such an interaction; while some studies suggest that loss of p16^{INK4a} expression correlates with poor prognosis, advanced tumor stage, and increased invasiveness [69,76], others have found no significant association with clinicopathological parameters [5]. These discrepancies may arise from differences in study populations, sample sizes, methodologies (e.g., immunohistochemistry versus methylation-specific PCR), and the inclusion of different histological subtypes of GBC. It is also present in “patients with PSC”, showing similarity with other frank biliary tract cancers [75]. It is believed that hypermethylation occurs before homozygous deletion [74,77–79]. Importantly, the *in vitro* and preclinical data strongly support p16^{INK4a}'s role as a tumor suppressor in the biliary tract. Furthermore, the development of selective CDK4/6 inhibitors (e.g., palbociclib, abemaciclib, LEE011) has provided a powerful therapeutic approach that, in essence, restores p16^{INK4a}-like function by blocking the downstream consequences of its loss [68,80–85]. Clinical trials with these agents, particularly in combination with other targeted therapies or hormone therapy, are yielding encouraging results, highlighting the importance of the p16^{INK4a}/CDK4/6/RB pathway in GBC and other cancers. However, the response to these agents is likely influenced by other gene alterations like methylation and its effectiveness is further proven in combination therapies [5]. Further assessments with larger patient populations can bring valuable inputs to our understanding of its involvement.

4. Gain of Function of Pro-Oncogenic Transcription Factors

The growth, invasion, and metastasis of tumors are driven by various pro-oncogenic transcription factors, which are frequently upregulated in gallbladder cancer. Approximately 83% of tumors have overexpressed STAT3, a critical effector of the JAK/STAT pathway; increased levels of STAT3 are associated with advanced tumor stage, poor differentiation, early recurrence, and enhanced VEGF-driven angiogenesis and epithelial–mesenchymal transition (EMT) [8]. The GPRC5A-JAK2-STAT3-TNS4 axis enhances metastatic potential, and inflammatory cytokine loops like IL-11/STAT3 and IL-6/JAK-STAT3 via fibroblasts maintain this activation. Furthermore, there is an upregulation of FOXK1, a forkhead-box transcription factor, in GBC [86]. This upregulation promotes cell cycle progression, EMT, and AKT/mTOR signaling. It is closely linked to poorly differentiated cells, liver metastasis, advanced TNM stage, and decreased survival. Furthermore, TCF4, an important transcription factor in the *Wnt/β-catenin* pathway, is found to be overexpressed in more than 80% of GBC samples. Its levels are even higher in late-stage and high-grade tumors, suggesting that it is involved in the growth and advancement of tumors. These abnormalities in STAT3, FOXK1, and TCF4 function, when combined, form a

transcriptional network that promotes aggressive behavior and may be therapeutic targets for gallbladder cancer [87,88].

4.1. TCF4

Transcription factor 4, alternatively termed as transcription factor 7-like 2 (TCF7L2), is encoded by the TCF 4 gene, spanning 442 Kb (approx.) across chromosomal region 18q21.2 [89,90]. As a pivotal mediator of the *Wnt*/ β -catenin signaling cascade, TCF4 has dual functionality as a transcriptional repressor or activator, depending on its interaction with Groucho/TLE family members, while β -catenin association enables transcriptional activation [91]. In the absence of Wnt signaling, phosphorylation by GSK3 β directs β -catenin to undergo ubiquitin-mediated degradation in the β -catenin destruction complex (DC). Activity of GSK3 β is inhibited by Wnt signaling. Following this, β -catenin builds up in the nucleus, where it attaches to TCF family members and changes these WNT effectors from transcriptional repressors to activators [92]. Since TCF4 is widely expressed, it binds to the consensus sequence CANNTG (“Ephrussi box or E-box”) either as homo- or heterodimers [93] and is classified under the class I HLH (helix–loop–helix) group often referred to as E-proteins [94]. It has been reported in regulation of hematopoiesis [95], myogenesis [96], neurogenesis [97], melanogenesis [98], and osteogenesis [99], as well as the differentiation of endothelial [100], mammary gland [101], placental [102], and Sertoli cells [103].

TCF4-driven dysregulation of *Wnt*/ β -catenin signaling is implicated in cancer stem cell maintenance in cancers like colorectal cancer [92], lung cancer [104], hepatocellular carcinoma [105] and GBC [10]. Neogi et al. used RT-qPCR and immunohistochemistry (IHC) to demonstrate that the mRNA levels of TCF4 and β catenin in GBC tissues were considerably ($p < 0.05$) higher than chronic cholecystitis [10]. Furthermore, TCF4 overexpression was associated with an increased chance of advanced disease state, as seen by the fact that TCF4 expression was higher in high tumor grades than low grades and higher in stages 2 and 3 than stage 1. These outcomes suggested that specific inhibitors of the β catenin/TCF4 interaction or downregulation of *Wnt*/ β catenin signaling may be effective treatments for GBC.

4.2. MYBL-2 (B-MYB)

A member of the myb transcription factor family, *MYBL2* (B-myb, v-Myb avian myeloblastosis viral oncogene homolog-like 2) is found on chromosome 20q13.12 and is frequently expressed in embryonic stem cells (ESC). Structurally this protein consists of multiple domains (DNA-binding domain and C-terminal domain) allowing it to regulate multiple crucial cellular pathways like cell proliferation, differentiation, DNA damage repair and apoptosis including various phases of the cell cycle. Dysregulation of the *MYBL-2* gene is reported in several cancers (breast, ovarian, liver, colorectal, blood, neural and bladder) [106], often arising from deregulation of DREAM complex assembly or aberrant regulation at the post-transcriptional level via microRNAs [4–9,107,108]. Notably, the p53-p21-DREAM pathway suppresses *MYBL2* expression, particularly in response to DNA damage (cellular stress). *MYBL2* is also disproportionately elevated in a number of p53-mutant cancers [109,110]. Moreover, the oncoprotein HPV16 E7 can induce *MYBL2* expression by deregulating the assembly of the DREAM complex [111].

Surprisingly, downregulation of *MYBL2* is often linked with certain types of hematological malignancies [112,113], whereas in solid tumors, expression is elevated [106]. Using RT-qPCR and immunohistochemistry (IHC), Liang et al. reported that *MYBL2* is increased in GBC compared to cholecystitis tissue and promotes DNA replication and GBC cell proliferation [114]. Using Cell Counting Kit-8 (CCK-8) and colony formation

assays, they demonstrated that *MYBL2* overexpression promotes cell growth, but RNA interference-based *MYBL2* knockdown markedly inhibits cell proliferation. Additionally, *MYBL2* promotes passage through the S and G2/M phases by controlling the GBC cell cycle. Its function in cell division was suggested by the fact that overexpression promoted cell cycle progression, whereas knockdown trials caused G1-phase arrest. Using xenograft tumor models in mice, the oncogenic potential of *MYBL2* was confirmed in vivo. *MYBL2*-overexpressing cells induced tumors that were bigger than controls, but knockdown cells produced tumors that were noticeably smaller [114]. This suggests a prospective alternative for future clinical treatments meant to act as both a prognostic marker and as a possible therapeutic target in GBC.

4.3. NF-kappa B

NF-κB is a family of related protein complexes that function as hetero- and homodimers. It can produce up to 15 NF-κB complexes by selecting from a pool of five monomers (p50, p52, Rel A (p65), Rel B, and c-Rel) [115]. Hundreds of genes incorporate NF-κB within their enhancers or promoters due to variations of the palindromic κB site, which follows the consensus sequence 5'-GGGRNWYYCC-3' (where N represents any base, R denotes purines, W signifies adenine or thymine, and Y corresponds to pyrimidines) (<https://www.bu.edu/nf-kb/gene-resources/target-genes/>, accessed on 13 April 2025). NF-κB is widely distributed and inhibited by IκBs in the cytoplasm. A variety of cancers like breast cancer [116], melanoma [117], lung cancer [118], colon cancer [119], multiple myeloma [120], pancreatic cancer [121], esophageal adenocarcinoma [122], leukemia and lymphoma [123] are associated with overexpression of NF-κB, which is typically measured by the presence of nuclear RelA. Bao et al. reported that human immortalized normal biliary epithelial cells (H69) had higher levels of lncRNA MEG3 expression than GBC cell lines (EH-GB1, GBC-SD, and OCU-1; $p < 0.05$) [124]. When compared to the negative control (NC) group, the overexpression of lncRNA MEG3 dramatically decreased the proliferation rate and colony formation capacity of GBC-SD cells, as determined by the CCK-8 and colony formation assays. Furthermore, the lncRNA MEG3 overexpression sample exhibited higher levels of apoptosis than the NC group. This implies that MEG3 had the capacity to inhibit tumors [124]. Additionally, they discovered that overexpression of lncRNA MEG3 significantly increased the amount of NF-κB protein in the nucleus, suggesting that lncRNA MEG3 overexpression triggers the NF-κB signal. Moreover, they also suggest that the tumor suppressor ability of MEG3 is facilitated by NF-κB expression by using NF-κB inhibitor SN50 on lncRNA MEG3 transfected GBC cells.

4.4. AP-1

The AP-1 (activating protein-1) family of transcription factors consists of homodimers and heterodimers of Jun (v-Jun, c-Jun, JunB, JunD), Fos (v-Fos, c-Fos, FosB, Fra1, Fra2) or activating transcription factor (ATF2, ATF3/LRF1, B-ATF) bZIP (basic region leucine zipper) proteins [125]. Dimerization between members of the AP-1 family occurs through a structure known as a leucine zipper, which can dimerize with another α-helix via the formation of a coiled-coil structure with contacts between hydrophobic leucine zipper domains. Jun-Jun and Jun-Fos dimers preferentially bind to the phorbol 12-O-tetradecanoate-13-acetate (TPA)-responsive element (TRE). On the other hand, Jun-ATF dimers or ATF homodimers prefer to bind to the cAMP-responsive element (CRE) [126]. MAF (c-MAF, MAFA, -B, -F, -G, -K, and Nrl) multigene families bind either to the MARE I or MARE II motifs that are the extension of TRE and CRE motifs respectively [26,127]. It is found that AP-1 plays a very significant role in T-cell activation and the differentiation of naïve T-cells to T helper cells by using the MAPK (Mitogen-activated protein kinase) pathway and also controls

the expression of the cytokines TNF- α , IL-1, interleukin 2 (IL-2), IFN γ , and GM-CSF as well as matrix-degrading matrix metalloproteases (MMPs) such as collagenase 1 and stromelysin [128]. AP-1 is necessary for skin homeostasis and differentiation. It modulates the activity of the human distal regulatory enhancer [129].

Cancer is undoubtedly the most documented pathology involving AP-1 dysregulation, which leads to cell transformation and tumor progression [26,27]. It acts as a tumor suppressor or oncogene and is a crucial effector of the upstream oncogenic events [130]. c-JUN-deficient cells were found to undergo premature senescence as a result of spontaneous DNA damage, suggesting that c-JUN plays a role in stimulating DNA [131]. C-JUN acts as a proliferating agent by inhibiting p53 and stimulating cyclin D1. A reduction in levels of p53 leads to the dampening of the cyclin-dependent kinase inhibitor (CDKI) p21, leading to the transition from the G1 to the S phase [132,133]. JUN-B suppresses the proliferation by the activation of CDKI p^{16INK4a} and repression of cyclin D1 and leads to inhibition of progression into the S phase. In various cancers the AP-1 component level is upregulated, for example in breast cancer, endometrial carcinoma, colorectal cancer, acute myeloid leukemia, Hodgkin's, and anaplastic large cell lymphoma [134].

Fos-like antigen-1 (FOSL1) is a member of the AP-1 complex and it exerts oncogenic effects like proliferation, invasion, and epithelial–mesenchymal transition (EMT) [135]. It was confirmed that the miR-195-5p/FOSL1 regulatory axis is closely related to GBC by using bioinformatics and qRT-PCR analysis. FOSL1 is the direct target of miR-195-5p and the overexpression of miR-195-5p leads to the inhibition of the proliferation, migration, and invasion ability of GBC. It was found that the GBC cells were blocked in the Go/G1 phase by directly targeting FOSL1 and regulating the *Wnt*/ β -catenin signaling pathway [136]. Further research is required to know the interaction mechanism between FOSL1 and the *Wnt*/ β -catenin signaling pathway. Studies on malignant melanoma and ovarian cancer found that the decoy oligodeoxynucleotides act as the therapeutic drug against c-JUN. This leads to the decrease in proliferation ability of the cancer as well as an increase in the apoptosis inside the cancerous cell by inhibition of downstream targets like cyclin D1, p53, BCL3 and matrix metalloproteinase 9. Given these findings, similar strategies may be applicable for GBC treatment, though further research is required to validate their efficacy [137,138].

4.5. Snail

Snail is a zinc-finger transcription factor that which is highly conserved in *Drosophila* and higher vertebrates. The highly conserved C₂H₂-type zinc-finger domain helps in the binding to the E-box motif-containing CANNTG-specific nucleotide sequence. Snail is the transcription repressor that plays a very important role in various cell differentiation processes, mainly in the epithelial–mesenchymal transition (EMT). Studies have shown that the Snail promoter is directly regulated by different growth factors like TGF-beta, FGF-2, and EGF along with different signaling molecules like integrin-linked kinase (ILK), H-ras, v-Akt and NF-KappaB/p65 [139–141]. Research studies indicate that the human Snail (hSnail) modulates epithelial-specific cytokeratin leading to the EMT. It is one of the major structural proteins in the epithelial cells forming a cytoplasmic network of intermediate filaments [139,141].

In cancer, EMT dysregulation can be triggered by various molecules, promoting carcinoma cell invasion and metastasis [142]. Findings from colorectal cancer studies revealed that the human Snail leads to morphologic changes and plays a crucial role in promoting cancer invasion [142]. In ovarian cancer, high expression of the Snail transcription factor is seen and provides resistance to apoptosis [143]. In cases of GBC, the Snail transcription factor is a tumor-promoting factor. The expression of Snail is higher in gallbladder adeno-

carcinoma as compared to peritumoral tissues and cholecystitis [11]. Through the screening process, a novel lncRNA, HOXA-AS2, is identified to be highly expressed in GBC and promotes GBC cells' migration by sponging miR-6867-5p which targets YAP (overexpressed in GBC) [144–146]. lncRNA HOXA-AS2 in GBC cells upregulates YAP1, which plays a role in EMT and potentially impacts the Snail transcription factor [147]; however, further research is required for better understanding of the mechanism.

4.6. *c-MYC*

c-MYC is a protooncogene present in the cell, playing a role in cellular growth, differentiation and apoptosis [148]. It is a DNA-binding protein containing the helix–loop–helix and leucine zipper protein dimerization domain. The basic region in the C-terminal acts as the major DNA contact surface [149]. The complete binding site of the *c-MYC* is GAC-CACGTGGTC [149]. Max is another bHLHZip protein that forms a heterodimer with *c-MYC* and they have a common DNA target (Ebox) site [150,151]. Studies have shown that the MYC-Max transcription factor complex regulates the target genes mediating the multiple effects of MYC [152–154]. This heterodimer promotes Cyclin D1, D2, E1, A2, and Cyclin-Dependent Kinase 4 for cell cycle progression and represses transcription of cell cycle checkpoint genes like GADD45 and GADD153 as well as cyclin-dependent kinase inhibitor p15 and p21 [155–158].

In cancer, *c-MYC* is frequently dysregulated and exhibits overexpression in the majority of human malignancies [159]. Recent studies have revealed that small nucleolar RNAs (SNORNs), a class of non-coding RNA about 60–300 nucleotides long located in the nucleolus, play a crucial role in cancer. For instance, SNORA42 is significantly overexpressed in non-small-cell lung cancer (NSCLC) and colorectal cancer [160,161]. qRT-PCR analysis has revealed that SNORA21 is significantly downregulated in GBC. Studies indicate that SNORA21 overexpression induces G1-G0-phase cell cycle arrest, thereby inhibiting proliferation, migration, and invasion of GBC cells. This effect is further supported by a reduction in cyclin D1 and *c-MYC* levels, along with an increase in p21 expression. Given these findings, SNORA21 holds potential as a therapeutic target for GBC, though further research is required [162].

4.7. *Sp1*

Sp1 is a transcription factor that is necessary for the transcription of several “house-keeping genes” involved in metabolism, cell growth and proliferation and cell death [163]. The majority of *Sp1*'s transcriptional activity is supported by its two primary transactivation domains, A and B, which work in tandem with the DNA-binding domain *Sp1* to function as an activator or as a part of a repressor complex [164]. *Sp1* expression is closely associated with patient survival in most cancers, with elevated levels often indicating a poor prognosis. Numerous studies have investigated the potential of targeting *Sp1* to eliminate cancer cells or enhance their sensitivity to treatment [165–168].

Sp1 regulates a broad range of target genes, including proto-oncogenes such as *c-MYC* and tumor suppressors like *TP53*, which are critical for controlling cell proliferation and oncogenesis. Additionally, *Sp1* modulates the expression of both pro- and anti-angiogenic factors involved in invasion and metastasis, as well as pro- and anti-apoptotic genes that influence genomic stability. It also governs key regulators of the cell cycle, such as cyclins, thereby impacting cell cycle progression and arrest [169]. *Sp1* is also a key transcriptional regulator of the *hTERT* gene, which encodes the catalytic subunit of telomerase. Activation of *hTERT* promotes telomere maintenance, enabling replicative immortality—a hallmark of cancer. *Sp1* binding sites within the *hTERT* promoter are essential for its transcriptional activation, and overexpression of *Sp1* has been linked to increased *hTERT* expression

in various cancers [170]. In addition, Sp1 collaborates with other transcription factors and epigenetic modifiers to regulate *hTERT* expression through chromatin remodeling and histone modifications, further contributing to tumorigenesis [171]. Multiple Sp1 binding sites are also present in the gene that codes for the RNA component of telomerase, human telomerase RNA component (hTERC). Additionally, Sp1 controls acetylation and other histone modifications to control the expression of *hTERT* [172]. Sp1 is also known to regulate the long non-coding RNA, LINC00152, by directly binding to its promoter region and upregulates its expression in GBC cells, NOZ. Elevated LINC00152, in turn, activates the PI3K/AKT signaling pathway, thereby promoting tumor growth, invasion, and metastasis. This Sp1–LINC00152–PI3K/AKT regulatory axis underscores a potential therapeutic target in GBC. Additionally, arsenic trioxide (As_2O_3) has been reported to inhibit GBC cell proliferation by downregulating *Cyclin D1* expression in an Sp1-dependent manner, although the exact mechanism of Sp1 modulation in this context remains to be properly explored [173].

4.8. FOXK1

FOXK1 is a member of the Human Forkhead-box (FOX) gene family [174]. The characteristic of FOX proteins is their conserved forkhead DNA-binding domain (DBD). In order to modify gene expression, this domain permits certain interactions with DNA sequences [175]. Human genetic illnesses, cancer, and/or aging are caused by genetic changes or dysregulation of FOX genes [176]. In stem cell populations and cancer, FOXK1 plays a crucial role in regulating cell division, proliferation, and quiescence [177]. In gastric cancer, increased FOXK1 expression was shown to suppress autophagy via the PI3K/AKT/mTOR pathway [178]. Similarly, FOXK1 is found upregulated in several cancers and is thought to participate in tumorigenesis [179,180]. FOXK1 is reported to be overexpressed in GBC cells. The overexpression of FOXK1 increases the ability of GBC cells to migrate and invade by initiating EMT and promoting cell proliferation through cell cycle regulation [87]. Furthermore, the activation of the Akt/mTOR axis may be partially linked to the tumor-promoting impact of FOXK1. Mechanistic studies confirmed that FOXK1 knockdown could result in G1/S cell cycle arrest by downregulating CDK4, CDK6, cyclin D1, and cyclin E1 [87]. Additionally, FOXK1 may control the expression of proteins linked to the epithelial–mesenchymal transition (EMT), including vimentin, N-cadherin, and E-cadherin. FOXK1 stimulates GBC cells to proliferate in vitro, while the inactivation of FOXK1 induces G1/S arrest [87]. In GBC patients, FOXK1 may therefore be a viable prognosis biomarker and therapeutic target.

4.9. KLF5

Kruppel-like factor 5 (*KLF5*) is a zinc-finger transcription factor encoded on chromosome 13q21 and consists of 457 amino acid residues [181]. It contains three C_2H_2 -type zinc-finger motifs at its C-terminus which facilitate the binding to GC-rich promoter regions [182]. *KLF5* plays a crucial role in the regulation of multiple genes, such as *Cyclin D1*, *p27*, *Nanog* and *Slug* [181], and is implicated in numerous cellular processes such as proliferation, apoptosis, stemness, autophagy, cell cycle progression, metabolism and cellular homeostasis. Functionally, *KLF5* exhibits context-dependent behavior, acting as either a tumor suppressor or an oncogene across different cancer types [183]. Its dysregulation is associated with various pathological conditions, including cancer and cardiovascular diseases. Post-translational modifications such as phosphorylation and acetylation enhance *KLF5* transcriptional activity [184,185]. *KLF5* is expressed in multiple tissues and plays diverse context-dependent roles. In breast cancer cells, enhanced *KLF5* expression increases the expression of many genes, such as Cyclin A, chromatin licensing and DNA

replication factor 1 (*cdc-10* dependent transcript 1; CDT1), and E2F transcription factor 3 (E2F3), progesterone and progesterone receptor (PR) thereby promote the proliferation of cells [186]. Additionally, KLF5 maintains the stemness in mammary cells by promoting the transcription of the *Slug* gene, a known regulator of stemness and epithelial–mesenchymal transition [187].

KLF5 is implicated in multiple signaling pathways and has been increasingly recognized for its oncogenic potential. In non-small-cell lung cancer (NSCLC), KLF5 is thought to promote tumorigenesis by activating the PI3K/AKT signaling pathway [188]. According to various studies, KLF5 triggers NF- κ B signaling. For instance, in thyroid cancer cells, KLF5 enhances the nuclear translocation of p65 and promotes phosphorylation of IKK β and I κ B α [189]. Also, KLF5 has been demonstrated to increase Sox4 expression, which in turn promotes lung cancer cell proliferation and tumor progression [190]. According to recent research, KLF5 promotes tumor growth in gallbladder cancer. GBC progression is suppressed when KLF5 is silenced, likely through the downregulation of *PDGFA*, which affects cell proliferation, metastasis, angiogenesis, and apoptosis of GBC cells [191]. Given its central role in modulating key oncogenic transcriptional networks, targeting KLF5 may offer therapeutic potential not only in GBC but across a wide spectrum of cancers.

4.10. STAT3

Signal Transducer and Activator of Transcription 3 (STAT3) is a transcription factor and signal transducer protein which can be activated by a variety of cytokines, growth factors and intracellular kinases, particularly through the JAK/STAT signaling pathway. It is an 89 kDa (770-amino-acid) latent cytoplasmic protein characterized by several distinct structural protein domains, including N-terminal, coiled-coil, DNA binding, linker, SH2 (Src homology) and transcriptional-activation domains [192]. STAT3 expression and activity are tightly regulated through alternative splicing, post-translational modification and subcellular localization. One key splice variant of the mammalian STAT3 with deletion of a 50-nucleotide sequence near the C-terminus codes for an 80 kDa STAT3 isomer (STAT3 β) that functions as a negative regulator of canonical STAT3 α isoform [192]. Unlike STAT3 α , which primarily promotes oncogenic transcriptional programs, STAT3 β is associated with pro-apoptotic functions and exerts context-dependent roles in tumor suppression, thus playing a role distinct from STAT3 α . Despite the different mechanism, STAT3 activation through phosphorylation or acetylation can facilitate tumorigenesis synergistically. STAT3 shuttles between the cytoplasm, nucleus, mitochondria and other possible organelles, and exerts its diverse functions in transcriptional regulation, cellular respiration, proliferation and apoptosis. A variety of animal models reveal that STAT3 is essential for embryo development, pluripotency of stem cells, embryo implantation and decidualization. Among the seven members of the STAT protein family, STAT3 is arguably the most important for tumor progression [193]. In cancer, STAT3 dysregulation leads to its prolonged activation, resulting in cell proliferation, invasion, angiogenesis, decreased apoptosis, and immune evasion [194].

STAT3 is highly expressed in various cancer types, such as endometrial cancer [195], glioma of the brain [196], breast cancer [197], lung cancer [198], and gall bladder cancer [199]. Higher expression of STAT3 was correlated with clinical stage and positively associated with early postoperative recurrence of the GBC malignancy. This overexpression is closely linked to the formation of vasculogenic mimicry (VM), a process where tumor cells form vessel-like structures independent of endothelial cells. VM is a tumor vascular model that differs from angiogenesis that has been detected in melanoma, inflammatory breast cancer, liver cancer and other malignant tumor types with highly invasive characteristics [200]. In GBC, VM was observed in over 92% of tumors with high STAT3 expression, and statistical

analysis confirmed a significant positive correlation between STAT3 levels and VM presence. Furthermore, both high STAT3 expression and VM formation were strongly associated with postoperative recurrence [201]. Specifically, patients with high STAT3 expression had a mean time to recurrence (TTR) of 17.35 months, compared to 35.65 months in those with low STAT3 expression. Similarly, VM-positive tumors recurred at a mean of 22.38 months, versus 36.00 months in VM-negative cases [201]. These findings suggest that STAT3 not only contributes to GBC cell proliferation and invasion but also promotes alternative vascularization through VM, underscoring its potential as a therapeutic target for antitumor angiogenesis therapy and metastasis inhibition in gallbladder carcinoma.

4.11. *BIRC7*

Baculoviral IAP repeat-containing 7 (*BIRC7*), commonly referred to as Livin, encodes a member of the inhibitor of apoptosis protein (IAP) family. The *BIRC7* gene is localized in the cytoplasm and is situated on the long arm of chromosome 20, specifically at the cytogenetic band 20q13.33. The Livin gene, spanning approximately 4.6 kilobases, is located on chromosome 20 at cytogenetic band q13. This gene consists of six introns and seven exons. The Livin protein comprises 298 amino acids with a molecular weight of approximately 32.8 kDa. It is characterized by the presence of a single baculovirus IAP repeat (BIR) domain and a RING-type zinc-finger domain. The BIR domain plays a critical role in mediating interactions with caspases and inhibiting apoptosis. The BIR domain, approximately 70 amino acids in length, is characterized by zinc-binding residues. Its core structure is enriched with conserved cysteine and histidine residues, which play a pivotal role in anti-apoptotic activity. Structurally, the BIR domain exhibits a globular architecture formed by four α -helices and a three-stranded anti-parallel β -sheet, along with specific residues contributing to its hydrophobic core. In contrast, the RING finger domain may enhance anti-apoptotic activity in certain contexts but is insufficient to inhibit apoptosis independently. The RING finger motif, found at the carboxyl terminus, is defined by seven cysteine residues and one histidine residue that coordinates two zinc atoms. This motif facilitates interactions with the cellular ubiquitination machinery, thereby regulating the degradation of key cellular proteins [202].

The Livin gene encodes two splice variants, Livin- α and Livin- β . These variants are almost identical except for a 54-base-pair truncation at the 5' end of exon 6 in Livin- β . The open reading frames for Livin- α and Livin- β encode proteins consisting of 298 and 280 amino acids, respectively. Both variants share the N-terminal BIR domain and the C-terminal RING domain. However, Livin- β lacks 18 amino acids in the region linking the BIR and RING domains, which may influence its structural and functional properties [202]. Livin plays a pivotal role in the inhibition of apoptosis. Studies have demonstrated that Livin directly interacts with caspase-3 and caspase-7 in vitro, as well as with caspase-9 in vivo, through its Baculovirus IAP Repeat (BIR) domain [203]. Its anti-apoptotic activity is regulated by Smac/DIABLO, a mitochondrial protein that antagonizes IAPs. The anti-apoptotic function of Livin is primarily attributed to its singular BIR domain. This domain enables Livin to bind to and inhibit caspase-9, effectively preventing the activation of apoptotic pathways. Mutations in the BIR domain significantly impair Livin's ability to inhibit caspase-9, thereby diminishing its overall anti-apoptotic activity. Furthermore, Smac/DIABLO interacts physically with Livin and neutralizes its ability to inhibit apoptosis, underscoring the regulatory dynamics between Livin and pro-apoptotic factors [203]. In addition to its role in apoptosis inhibition, evidence indicates that Livin is also implicated in the regulation of cell proliferation. It was reported that in human malignant melanoma LiBr cells, silencing of Livin significantly induces apoptosis, arrests the cell cycle at the G0/G1 phase, and inhibits cellular proliferation [204]. These findings suggest that Livin expression

is closely linked to cell cycle regulation and may play a critical role in maintaining cell proliferation dynamics [205].

The BIRC7 protein (Livin) has been implicated in the pathogenesis of gallbladder cancer (GBC), contributing to tumor progression through its anti-apoptotic functions. By inhibiting caspases via its BIR domain, BIRC7 effectively suppresses apoptosis, allowing malignant cells to evade programmed cell death and sustain unchecked growth. Furthermore, the RING-type zinc-finger domain may augment the anti-apoptotic effects, promoting cancer cell survival and resistance to therapy. In GBC, overexpression of BIRC7 has been associated with poor prognosis, increased tumor aggressiveness, and resistance to chemotherapeutic agents [206]. This highlights its potential as a biomarker for disease progression and a therapeutic target. Targeting BIRC7 through specific inhibitors could restore apoptotic pathways, thereby enhancing the efficacy of conventional treatments, and may improve patient outcomes.

5. Clinical Implications of Transcription Factors Targeting Signaling Pathways in Gallbladder Cancer

There are substantial therapeutic implications of transcription factors in GBC as diagnostic and prognostic biomarkers and as possible therapeutic targets (Tables 1 and 2). Several small-molecule inhibitors targeting key molecular and/or signaling pathways are currently under clinical investigation for suppressing tumorigenesis in GBC as therapeutic developments (Figure 4). Studies have demonstrated that dysregulation of specific TFs correlates with tumor aggressiveness, progression, and patient outcomes. The *Wnt*/ β -catenin pathway's essential effector, TCF4, has been found to be associated with higher tumor grade and stage, suggesting that it could be used as a biomarker to track disease progression and a possible target for personalized molecular therapies. Overexpression of certain tumor factors is associated with a worse prognosis for patients; for example, FOXK1 has been found to activate AKT/mTOR signaling, which in turn promotes proliferation and metastasis in GBC. The roles of tumor-suppressing TFs such as SMAD4 and p53 are highlighted by dysregulation of these proteins. Mutations in SMAD4 have been associated with disrupted TGF- β signaling in around 6% of GBC cases, while mutations in p53 are prevalent in over 40%. Detection of mutant p53 protein could help with early diagnosis or risk stratification [207].

These transcription factors are not only becoming potential therapeutic vulnerabilities, but they are also used as biomarkers. Master regulators orchestrating super-enhancer-driven programs, like SOX9, TCF7L2, and other components of colorectal cancer, display “transcriptional addiction” in GBC cells. Key oncogenic TF networks can be suppressed and tumor growth can be impaired through transcription inhibition, as demonstrated in preclinical models, especially with CDK7 inhibitors. Additionally, a reasonable anti-cancer strategy involves targeting downstream effectors of TF pathways, such as blocking AKT/mTOR signaling in tumors overexpressing FOXK1. Potentially better early detection, risk assessment, and treatment results for GBC patients might result from additional research into transcription-focused therapies and the ongoing integration of TF profiling into clinical practice [208,209]. Some of the relevant clinical trials are listed in Table 2.

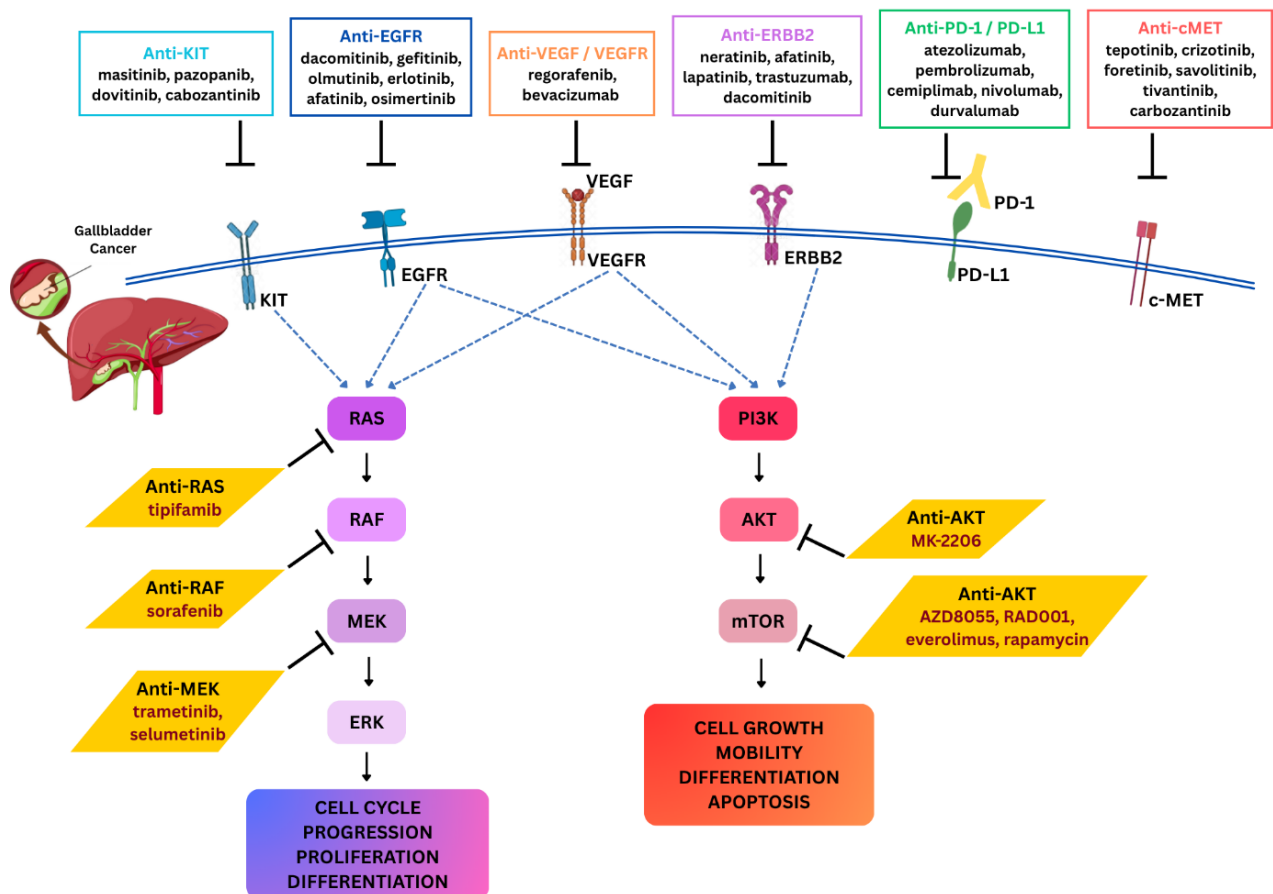


Figure 4. Targeted therapeutic strategies and key signaling pathways in gallbladder cancer. Schematic illustration of major receptor tyrosine kinases (KIT, EGFR, VEGFR, ERBB2, PD-1/PD-L1, and c-MET) and their downstream signaling cascades implicated in GBC progression. Activation of these receptors drives the RAS signaling and AKT signaling regulating cell cycle progression, proliferation, differentiation, cell growth, mobility, differentiation, and apoptosis. Various inhibitors belonging to anti-KIT, anti-EGFR, anti-VEGF/VEGFR, anti-PD-1/PD-L1, and anti-c-MET directly target these tyrosine kinase receptors. Additionally, small-molecule inhibitors against intracellular signaling components like anti-RAS, anti-RAF, anti-MEK, and anti-AKT/mTOR directly target the downstream targets of these signaling pathways. Together, these therapeutic approaches highlight potential avenues for targeted and immune-based interventions in GBC. Doted blue arrows represent the activation pathways; black arrows represent the flow of molecular process; and the hammer-headed arrows represent inhibition.

Table 2. Clinical drug trials and molecular targets of GBC along with their clinical phases [210].

Drug Investigated	Molecular Target	Clinical Phase
Sorafenib	Multitargeted TKI	2/3
Afatinib	EGFR, HER2	2
Apatinib	EGFR, HER2	2
Trametinib	MEK	2
Guadecitabine	DNMT	1
Pembrolizumab	PD-1 (Immune checkpoint inhibitor)	2
Nivolumab + Ipilimumab	PD-1 + CTLA-4 (Immunotherapy combo)	2

Table 2. *Cont.*

Drug Investigated	Molecular Target	Clinical Phase
Zanidatamab (Ziihera)	HER2 (bispecific antibody)	2
Neratinib	Pan-HER (HER2, EGFR)	2
Pertuzumab + Trastuzumab	HER2 (dual antibody therapy)	2
Trastuzumab deruxtecan	HER2 (antibody-drug conjugate)	2
Crelosidenib (LY3410738)	IDH1 mutation	1
Ponatinib	FGFR1–4 (pan-FGFR inhibitor)	2
Erdafitinib (JNJ-42756493)	FGFR1–4	2
Atezolizumab + CDX-1127 (Varlilumab) ± Cobimetinib	PD-L1 + CD27 (immunotherapy) ± MEK inhibitor	2
Sintilimab + Bevacizumab + Gemcitabine + Nab-paclitaxel	PD-1 + VEGF + chemotherapy	2

Abbreviations: TKI, Tyrosine kinase inhibitor; EGFR, Epidermal growth factor receptor; HER2, Human epidermal growth factor receptor 2; MEK, Mitogen-activated protein kinase; DNMT, DNA methyltransferase; PD-1, Programmed cell death protein 1; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; FGFR, Fibroblast growth factor receptor; IDH1, Isocitrate dehydrogenase 1; PD-L1, Programmed cell death ligand 1; CD27, Cluster of Differentiation 27; VEGF, Vascular endothelial growth factor.

6. Emerging Trends and Future Directions

Although various drugs targeting the dysregulated TFs in GBC are under clinical trial, effective treatment of GBC remains a significant challenge. This is largely due to the tumor heterogeneity, non-specificity, immunogenic response and chemo-resistivity arising from diverse genetic and epigenetic alterations, as well as the dynamic rewiring of TF networks and cell cycle pathways within cancer cells. Therefore, there is a need for more precise, effective and advanced therapy to deal with this lethal malignancy.

6.1. Proteolysis-Targeting Chimeras (PROTACs)

Over the past two decades, proteolysis-targeting chimeras (PROTACs) have emerged as a novel class of therapeutic molecules that exploit the ubiquitin–proteasome system (UPS) to selectively degrade target proteins. Structurally, PROTACs are bifunctional molecules composed of two ligands: one that binds the protein of interest and another that recruits an E3 ubiquitin ligase, thereby facilitating ubiquitination and subsequent proteasomal degradation [211,212]. Recent studies have demonstrated the feasibility of PROTACs in targeting transcription factors (TFs) across multiple cancer types. Notably, two small-molecule PROTACs—ARV-110, an androgen receptor (AR) degrader, and ARV-471, an estrogen receptor (ER) degrader—have advanced into clinical trials [213]. ARV-110 has shown therapeutic efficacy in prostate cancers harboring both wild-type and mutant AR, while ARV-471 has produced promising clinical responses in breast cancer patients with wild-type or mutant ER [214]. PROTAC techniques could be transferred to the treatment of GBC by leveraging their unique ability to target and degrade oncogenic proteins, specifically, transcription factors and signaling molecules that are often considered “undruggable” by conventional therapies. Identifying key oncogenic transcription factors (e.g., *MYBL2*, NF-κB, TCF4) that are consistently dysregulated in GBC and contribute to tumor progression, EMT, and therapy resistance could provide a more specific and precise therapy to manage the oncogenesis and progression of this cancer.

6.2. RNA-Based Therapeutics

RNA-based therapies represent an emerging class of treatments that harness or modulate RNA molecules to achieve therapeutic effects. They often exploit non-coding RNAs,

including microRNAs (miRNAs), circular RNAs (circRNAs), and long non-coding RNAs (lncRNAs) [215]. A recent study demonstrated that miR-145-5p, frequently downregulated in GBC, restores tumor-suppressive signaling by activating Signal Transducer and Activator of Transcription 1 (STAT1) through direct targeting of the oncogenic regulator Protein Tyrosine Phosphatase Receptor Type F (PTPRF) [216]. Similarly, an lncRNA ZEB2-NAT binds to TF Zeb2 and masks the splicing site of internal ribosome entry sites (IRES), resulting in the enhanced expression of Zeb2, which activates EMT in colon cancer cells [217]. RNA-based therapeutics present a promising approach towards regulation of TFs and the better management of GBC.

6.3. CRISPR-Based Gene Editing

Clustered regularly interspaced palindromic repeats (CRISPR) is a genome-editing platform composed of a guide RNA that directs the system to a specific target sequence and the Cas endonuclease, which introduces a double-stranded DNA break to enable precise genetic modifications in the target sequence [218]. By employing the CRISPR/Cas system, the expression of oncogenic or tumor-suppressive TFs can be edited in order to manage the cancer progression [219]. In addition to this, recently the new concept of artificial transcription factors (ATFs) emerged for cancer drug repurposing and increased chemosensitivity. ATFs are small molecules with the ability to modulate the transcriptional ability of a gene. Among the various types of ATFs, CRISPR/dCas9 (deactivated Cas9) is the most advanced one. CRISPR/dCas9-based ATFs have an effector domain that interacts with the DNA-binding domain to either activate or repress the transcription of target gene [220]. It was observed that lung adenocarcinoma (LAD) and lung cancer, with overexpressed lncRNA KCNQ1OT1, were resistant to paclitaxel. When the drug was used in combination with CRISPR/dCas9-based ATFs, the chemosensitivity of the LAD cells significantly increased [221]. Developing these target-specific CRISPR-based gene editing strategies to directly modulate the expression of dysregulated TFs in GBC could offer a highly specific and effective therapeutic avenue, addressing a critical un-met need in the management of this malignancy.

7. Conclusions

GBC remains a highly aggressive malignancy with poor prognosis, largely due to the dysregulation of transcription factors that govern key cellular processes. This review highlights the critical role of both tumor-suppressor and oncogenic transcription factors in GBC pathogenesis, emphasizing how their altered expression drives uncontrolled proliferation, metastasis, and therapeutic resistance. While this review underscores the critical role of both oncogenic and tumor-suppressor transcription factors in GBC pathogenesis, the translation of innovative molecular therapies like PROTACs, RNA-based therapeutics, and CRISPR-based gene editing into clinical practice remains at an early but promising stage. Key milestones for translating these molecular therapies into clinical practice for GBC include comprehensive target validation in preclinical models, development of high-affinity ligands and effective delivery systems tailored to gallbladder tissue, rigorous safety and off-target profiling, early-phase clinical trials to establish safety and efficacy, integration of precision oncology tools for patient stratification, and exploration of combination therapies with existing treatments to overcome resistance. These focused efforts are essential to bridge molecular findings and enable effective targeted interventions that improve patient outcomes in this aggressive cancer.

Emerging technologies such as single-cell transcriptomics, artificial intelligence-driven drug discovery, and multi-omics integration will further enhance our understanding of transcription factor networks in GBC. Future research should also focus on identifying reliable

biomarkers for early detection. Moving forward, a multidisciplinary approach incorporating genomics, immunotherapy, and personalized medicine will be key to translating these molecular insights into effective clinical interventions. While significant challenges remain, ongoing research and novel therapeutic strategies offer hope for improved diagnosis, treatment, and survival outcomes in GBC patients.

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