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Review

Galectin-3: A Multitasking Protein Linking Cardiovascular Diseases, Immune Disorders and Beyond

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Abstract

In recent decades, the novel role of Galectin-3 (Gal-3) in both physiological and pathological conditions has emerged. Gal-3 is a key protein involved in immunity, inflammation, cell adhesion, proliferation, differentiation, and apoptosis. Its physiological role is crucial for the regulation of these cellular functions. In pathological settings, elevated levels of Gal-3 are associated with diseases such as cancer, heart failure, and fibrotic diseases, making it an important diagnostic and prognostic biomarker in these conditions. It seems that Gal-3 acts as a bridge between different diseases. Because of its pro-inflammatory and pro-tumorigenic properties, it connects atherosclerosis and cancer, regulating inflammation, cell proliferation, immune evasion, angiogenesis and survival in both diseases. Specifically, in atherosclerosis, Gal-3 promotes plaque formation by driving inflammation, oxidative stress, lipid deposition, and vascular cell migration. In cancer, Gal-3 influences tumor growth and metastasis by modulating an immunosuppressive tumor microenvironment, increasing cell survival, and enhancing cell–matrix and cell–cell interactions. Moreover, by stimulating fibroblasts, Gal-3 favors matrix deposition and tissue fibrosis that together with the inflammatory properties contributes to adverse ventricular remodeling leading to heart failure. Finally, taking into account its role in pathogen recognition and immune cells (B and T cells) modulation, Gal-3 might be a critical factor in host defense, disease progression, and the development of autoimmune conditions. Thus, targeting Gal-3 might be a promising therapeutic strategy to pursue for management of different pathological scenarios.

Keywords: Galectin-3; immunity; inflammation; cardiovascular diseases

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1. Introduction

Galectin-3 (Gal-3) is a multifunctional protein belonging to the lectin family that specifically bind carbohydrates with various biological function [1]. This protein is of particular interest in the biomedical field due to its involvement in various physiological process, such as innate immunity, apoptosis, cell adhesion, proliferation, and cell differentiation [2,3], as well as pathological conditions, including cardiovascular diseases (CVD) [4], fibrosis [5], cancer [6], and chronic inflammation [7]. Thus, measurement of Gal-3 levels can provide valuable information about health status and disease progression, as demonstrated in heart failure (HF), liver fibrosis, and cancer, where elevated Gal-3 correlates with adverse clinical outcomes [4–6,8]. Different endogenous and exogenous factors can modulate its levels. Endogenous factors include the presence of inflammation and tissue damage [9]. During inflammatory processes, macrophages and other types of immune cells can release Gal-3, which contributes to tissue repair and modulation of the immune response [10]. Fibrosis is another process in which Gal-3 plays an important role, as it facilitates collagen accumulation and tissue remodeling, which is critical in diseases such as liver fibrosis and cardiac fibrosis leading to HF [5,11,12]. Among exogenous factors, lifestyle habits such as diet, exercise, and alcohol consumption can influence gal-3 levels. Oxidative stress and exposure to environmental toxins can also alter the expression of this protein [13]. Unrevealing the role of Gal-3 in the pathological pathways leading to diseases could open new avenues for the development of targeted therapies. Inhibiting Gal-3 is being explored as a potential therapeutic strategy to prevent or treat CVD such as HF by counteracting inflammation, oxidative stress, and fibrosis. In the present review, we aim at summarizing the role Gal-3 in CVD and beyond highlighting its immune-inflammatory properties.

2. Galectin-3: Starting from Bench

2.1. Molecular Mechanisms of Carbohydrate Recognition (N-/O-Glycosylation, CRD)

Gal-3 is a lectin highly conserved in animals that specifically recognizes N acetyllactosamine moieties present on both N-linked and O-linked of cell surface conjugates. Its architecture can be divided into three distinct domains:

- An N terminal region (~130 amino acids), rich in proline, glycine, tyrosine, and glutamine, including two possible phosphorylation sites; this segment enables Gal 3 to dimerize and to bind interacting partners such as CD147 (in keratinocytes) and Alix (in T cells) [14–16].
- The carbohydrate recognition domain (CRD) at the C terminus, also ~135 amino acids, forming a β sandwich fold of twelve β strands. Despite modest sequence homology (~20 25%) with Gal 1 and 2, its three-dimensional fold is strongly similar [17,18].
- A flexible, collagen like linker joining the N terminal domain with the CRD, which provides structural adaptability and supports multivalent ligand interactions [19]. Figure 1 provides a schematic overview of Gal-3 structural domains and their potential interactions with cell surface glycoconjugates, which underlie its diverse intra- and extracellular roles [20].

Gal-3 shows affinity for ligands like N acetyllactosamine (LacNAc), lactose, galactose, and polylactosamine [21,22]. The ligand-binding pocket is largely defined by β strands S4 through S6a/S6b within the CRD. Galactose hydroxyls at C 4 and C 6 engage in hydrogen bonds with residues such as His158, Arg162, Asn160, Glu184, and Asn174, assisted by water molecules [23]. For GlcNAc, the C 3 hydroxyl forms hydrogen bonds with Glu184 and Arg162; the N acetyl moiety participates via water mediated H bonding (to Glu165) and van der Waals contacts (to Arg186). These interactions lead to a substantially higher binding strength for LacNAc vs. lactose (≈fivefold) [1].

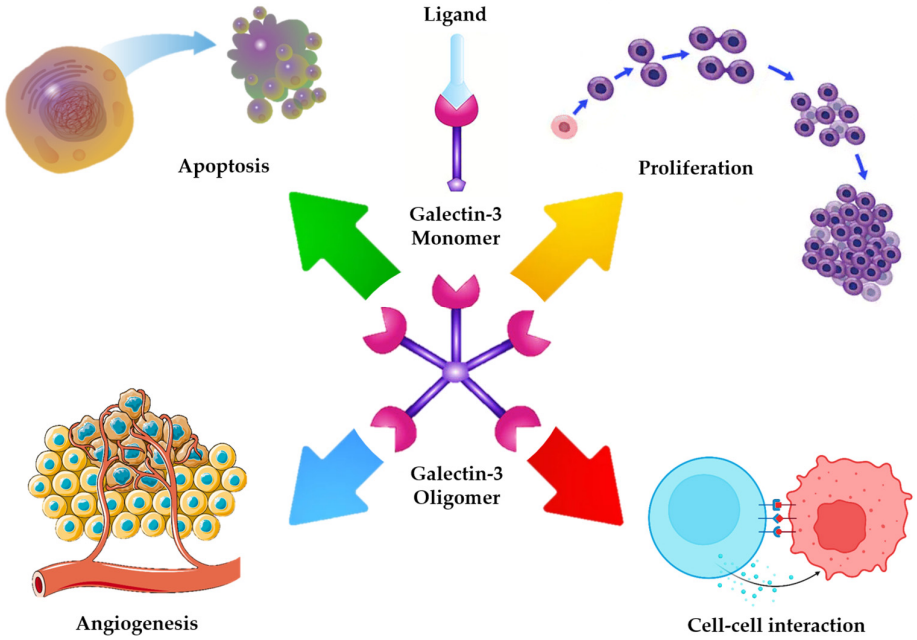

Figure 1. Galectin-3 structure and main biological pathway modulation.

2.2. Intracellular Functions: Regulation of Apoptosis and Survival Signals

Gal-3 exerts different roles depending on its cellular localization: inside cells, it often acts to inhibit cell death, whereas in extracellular or membrane-bound contexts it can promote apoptotic pathways [24]. It has been implicated in cancer biology—including effects on cell proliferation, differentiation, adhesion, metastatic spread—and plays a role in angiogenesis through enhancing migration of endothelial cells and promoting capillary formation [25,26]. Across many cell types, its anti-apoptotic action involves stabilization of mitochondria, translocation in response to apoptotic cues [27], interaction with proteins like Bcl-2, Bad modulation, and signaling via MAPK pathways; notably phosphorylation at Ser6 by casein kinase 1 facilitates relocation from the nucleus to perinuclear regions, aiding in inhibition of cytochrome c release and caspase activation [28–31].

Gal-3 also enhances cellular proliferation and adhesion: externally supplied Gal-3 increases lung fibroblast growth [32]; overexpression in breast carcinoma augments adhesion to extracellular matrix components such as vitronectin and fibronectin, potentially via integrin α3β1 upregulation [33,34]. In acute myeloid leukemia, higher Gal-3 levels correlate with reduced sensitivity to apoptosis induced by chemotherapy [35]. Conversely, under certain stimuli or via interactions such as CD29/CD7 or TCR CD3 complexes, and via death receptors like Fas (CD95), Gal-3 may promote apoptosis [36–39]. Outside immunological contexts, Gal-3 supports cell survival in tissues like testis: for example., in mice missing the protein Nucling (a pro-apoptotic regulator via NF-κB), Gal-3 is elevated and appears to protect testicular cells [40].

2.3. Extracellular Functions: Cell–Cell and Cell–Matrix Interactions

Gal-3 is produced by diverse cell types (vascular, bone, adipose, connective, tumor), and is secreted to reside in extracellular matrix (ECM), blood, and interstitial fluids [41]. When anchored in the ECM, it mediates cell binding through carbohydrate-dependent interactions [42]. In the nervous system, strong binding partners include MAG, laminin, tenascin R; these interactions can modulate signaling by altering receptor clustering or conformation and are sensitive to inhibition by lactose [43]. In colon carcinoma, Gal-3 binds mucins, LAMPs, and carcinoembryonic antigen (CEA), helping tumor cells adhere both to each other and to their microenvironment [6,44]. Gal-3 can both promote and inhibit

cell adhesion to the ECM [45]. It strengthens adhesion by binding integrin receptors and clustering them into focal adhesion sites, essential for cell attachment. Conversely, Gal-3 may reduce adhesion by promoting integrin internalization via endocytosis or causing steric hindrance when bound to integrins or ECM ligands [42]. This dual function likely depends on Gal-3 concentration, integrin type, and cell context. Gal-3 binds integrins such as CD11b/CD18 (Mac-1) on murine macrophages [45] and α1β1 [46], probably through its carbohydrate recognition domain (CRD) interacting with branched polylactosamine chains [47]. In tumors, low to moderate Gal-3 levels (~0.1–0.25 μM) enhance adhesion by promoting integrin clustering, whereas high levels (~5 μM) inhibit ECM binding and induce integrin internalization, particularly in cells with highly glycosylated integrins, suggesting therapeutic potential [42]. Normal epithelial cells generally show less modulation of adhesion by Gal-3 and secrete it apically [48].

Gal-3 also binds ECM proteins like fibronectin and laminin, which have polylactosamine chains serving as ligands [49]. Secreted by tumor cells and macrophages, Gal-3 enhances endothelial cell chemotaxis and migration during early angiogenesis. Different angiogenic factors regulate integrin expression: VEGF via αvβ5, bFGF via αvβ3, and TGFβ upregulates α2, α5, and β1 integrins [50]. Exogenous Gal-3 increases αvβ3 integrin expression, promoting endothelial motility during tube formation [51].

Angiogenic molecules generally either promote both proliferation and differentiation (e.g., bFGF, VEGF) or mainly differentiation (e.g., TNFα, angiogenin) [52]. Gal-3 falls into the latter group. Its angiogenic effects are carbohydrate-dependent and inhibited by specific inhibitors or antibodies [53].

Beyond vertebrates, Gal-3 also facilitates microbial adhesion. For example, *Trypanosoma cruzi* binds laminin in a lactose-dependent manner [54], and Gal-3 recognizes bacterial lipopolysaccharides, enhancing microbial interaction with ECM and host tissues [55]. A summary overview of Gal-3 structure and function is shown in Figure 1.

2.4. Role of Galectin-3 in Immune System Modulation: The Common Pathway Through Multiple Diseases

Gal-3 is a versatile protein whose function varies depending on its cellular location. Inside the cell, it plays roles in mRNA processing, apoptosis inhibition, and mast cell signaling regulation. Outside the cell—whether attached to the membrane or secreted—Gal-3 is involved in modulating immune defenses, managing inflammation, and recognizing pathogens [7]. It plays a key role in transitioning inflammation from an acute to a chronic phase, contributing to fibrosis, tissue remodeling, and scarring [56].

Notably, its effect differs by injury type. For example, lack of Gal-3 prevents fibrosis and myofibroblast buildup in obstructed kidneys. In other models, its expression mitigates inflammation and limits tissue damage without significant fibrosis [56]. This was demonstrated in the study by Iacobini et al., where Gal-3 acts in vivo as an AGE receptor involved in kidney disease and protects against AGE-dependent tissue injury [57].

Upon infection, Gal-3 reaches extracellular spaces either through active secretion by stimulated cells or passive release from damaged ones. In the extracellular milieu, it serves as a pattern-recognition receptor (PRR) for a wide range of pathogens—including parasites, bacteria, viruses, and fungi [2,58]. It can act as a damage-associated molecular pattern (DAMP) that influences innate immunity [59]. Its expression is increased in myeloid and epithelial cells responding to microbial or inflammatory triggers, for instance during monocyte differentiation into macrophages, or infections by Candida species and *Helicobacter pylori* [60,61]. Elevated Gal-3 levels are also detected in *Neisseria meningitidis* infection and chronic obstructive pulmonary disease, correlating with neutrophil infiltration [62,63]. Furthermore, in infections caused by intracellular bacteria like mycobacteria, Gal-3 modulates T cell-mediated immune responses [64].

Gal-3 interacts with lipopolysaccharides (LPS) from bacteria such as *Pseudomonas aeruginosa* and *Escherichia coli* through its carbohydrate-recognition domain and N-terminal region. This dual interaction promotes oligomerization and enhanced neutrophil activation [65]. Interestingly, it also acts to restrain LPS-driven inflammation, as Gal-3 deficient macrophages produce more pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β) [10]. In fungal infections, Gal-3 collaborates with Dectin-1 to recognize β-glucans and β-1,2-oligomannans, stimulating TNF-α release and fungal clearance [66]. In parasitic infection like *Trypanosoma cruzi*, Gal-3 enhances pathogen adhesion to host tissues, and its blockade reduces invasion [54].

Gal-3's immunomodulatory effects extend to key innate immune cells including neutrophils, macrophages, and dendritic cells [67,68]. In neutrophils, it induces L-selectin shedding and IL-8 secretion, while cleaved Gal-3 further amplifies NADPH oxidase activity [69]. Macrophages are highly plastic and can switch between pro-inflammatory M1 and tissue-repairing M2 states. Gal-3 is essential for M2 polarization, which promotes anti-inflammatory activity and tissue repair. IL-4 increases Gal-3 expression, which supports this alternative activation. Macrophages lacking Gal-3 show impaired M2 differentiation [70]. In monocytes, Gal-3 triggers superoxide release. It can also inhibit their maturation into dendritic cells [71]. Dendritic cells use Gal-3 to regulate cytokine production. This can influence T helper cell responses to Th1 or Th17 depending on the infectious context [72,73].

Gal-3 belongs to a family of galectins that share carbohydrate-binding properties, whereas they differ in immune functions. Unlike Galectin-1 (Gal-1), which generally suppresses inflammation and induces apoptosis of activated T cells, Gal-3 tends to sustain and amplify inflammatory responses [74]. Similarly, Galectin-9 (Gal-9) modulates T cell apoptosis and antiviral immunity via distinct pathways [75]. The interplay among galectins is complex and can be synergistic or antagonistic; for example, Gal-3 can counteract Gal-1's immunosuppressive effects, highlighting its unique role in prolonging inflammation and tissue repair [74]. This balance among galectins is critical for shaping immune outcomes in infection, autoimmunity, and chronic inflammation.

In autoimmune diseases, Gal-3's impact is complex and context-dependent, displaying both protective and harmful roles. For instance, it may limit apoptosis and thus autoantigen availability in systemic lupus erythematosus but can also heighten type I interferon responses. The balance between intracellular and extracellular Gal-3 further affects its immunological role, and abnormal Gal-3 expression is noted in many cancers, suggesting connections between autoimmunity and tumor development [76,77].

Gal-3 is also a critical player in cardiovascular pathology. It exerts several functions by linking immune activation to fibrosis and structural heart changes, contributing to endothelial dysfunction, promoting lipid buildup in macrophages, and driving cardiac fibrosis. As final end of these actions, Gal-3 influences diseases such as HF, atrial fibrillation (AF), hypertension, aortic stenosis, and plaque instability [4,78–80]. In acute coronary syndrome and myocardial infarction, Gal-3 levels correlate with inflammation and tissue remodeling, being especially elevated in STEMI patients. Secreted by macrophages, it amplifies immune cell recruitment and fibrosis, impairing cardiac function and increasing HF risk [81–85]. Gal-3 overexpression is also linked to cirrhotic cardiomyopathy. Its inhibition improves heart contractility and reduces pro-inflammatory mediators in this condition [86,87]. Several studies have reported that Gal-3 concentrations in serum or plasma positively correlate with disease severity and with systemic inflammatory markers such as CRP and CCL2 [78,88]. The contribution of Gal-3 to monocyte-driven atherogenesis extends beyond its ability to enhance monocyte adhesion through endothelial activation [89]. In ApoE$^{-/-}$ mice fed a high-fat diet, a direct relationship between plaque Gal-3 content and macrophage accumulation has been reported [90]. Moreover, phorbol

myristate acetate (PMA)-stimulated monocytes and macrophages as major sources of Gal-3, which is secreted via an exosome-dependent pathway [91]. More recently, Gal-3–positive macrophages subset within atherosclerotic plaques has been shown to exert protective effects by modulating macrophage polarization and invasiveness, ultimately contributing to slower plaque progression [92]. Taken together, these observations highlight the complex and context-dependent role of Gal-3, which may exert both pro- and anti-atherogenic actions that warrant further investigation.

Myocarditis is an inflammatory disorder of the heart that can arise from autoimmune reactions, drug toxicity, or infections by viruses and parasites. Macrophages have been identified as the main producers of Gal-3 during both the acute and chronic phases of myocarditis [93]. This observation is consistent with other studies showing that Gal-3–positive cells in inflamed cardiac tissue predominantly correspond to macrophages [94,95]. In viral myocarditis, Gal-3 has been consistently associated with a pro-inflammatory profile. Gal-3–expressing macrophages and dendritic cells infiltrate the myocardium, and elevated Gal-3 levels correlate with the extent of fibrosis [96]. Evidence from in vivo models supports that Gal-3 knockout mice show reduced leukocyte infiltration, lower expression of inflammatory mediators such as CCL2, and decreased fibrotic markers including proCol I mRNA and α-smooth muscle actin [97]. These findings collectively point to a pro-inflammatory and pro-fibrotic role of Gal-3 in virus-induced myocarditis. A comparable pattern has been observed also in aldosterone-induced myocarditis, where pharmacological inhibition of Gal-3 led to reduced cardiac inflammation and fibrosis in rats [97]. Interestingly, Gal-3 may also exert an opposite, protective role in autoimmune myocarditis. In experimental autoimmune myocarditis (EAM), Gal-3 deficiency resulted in exacerbated disease, with increased $CD45^+$ leukocyte infiltration in cardiac tissue [98]. This effect appears to involve enhanced Th2-mediated immune responses and elevated IgG production, which may promote cardiomyocyte damage through antibody-dependent cytotoxic mechanisms [98]. Since Gal-3 suppresses plasma cell differentiation [99], its absence may thus favor antigen-specific antibody generation and aggravate myocardial injury. Gal-3, produced by endothelial cells, cardiomyocytes, and macrophages, facilitates the recruitment of neutrophils and macrophages to the injured myocardium following infarction [100]. In Gal-3 knockout mice, a marked reduction in macrophage accumulation within the infarct area was observed seven days after myocardial infarction, together with a shift toward an M2-dominant macrophage phenotype [100].

During infectious diseases like COVID-19, Gal-3 levels rise in lung epithelial and immune cells in severe cases, paralleling increased inflammatory cytokines and chemokines. This amplification of immune responses contributes to lung inflammation and damage, highlighting Gal-3's potential as both a biomarker of severity and a therapeutic target [101–104]. A schematic view of immune cells regulation by Gal-3 in several diseases is provided in Figure 2.

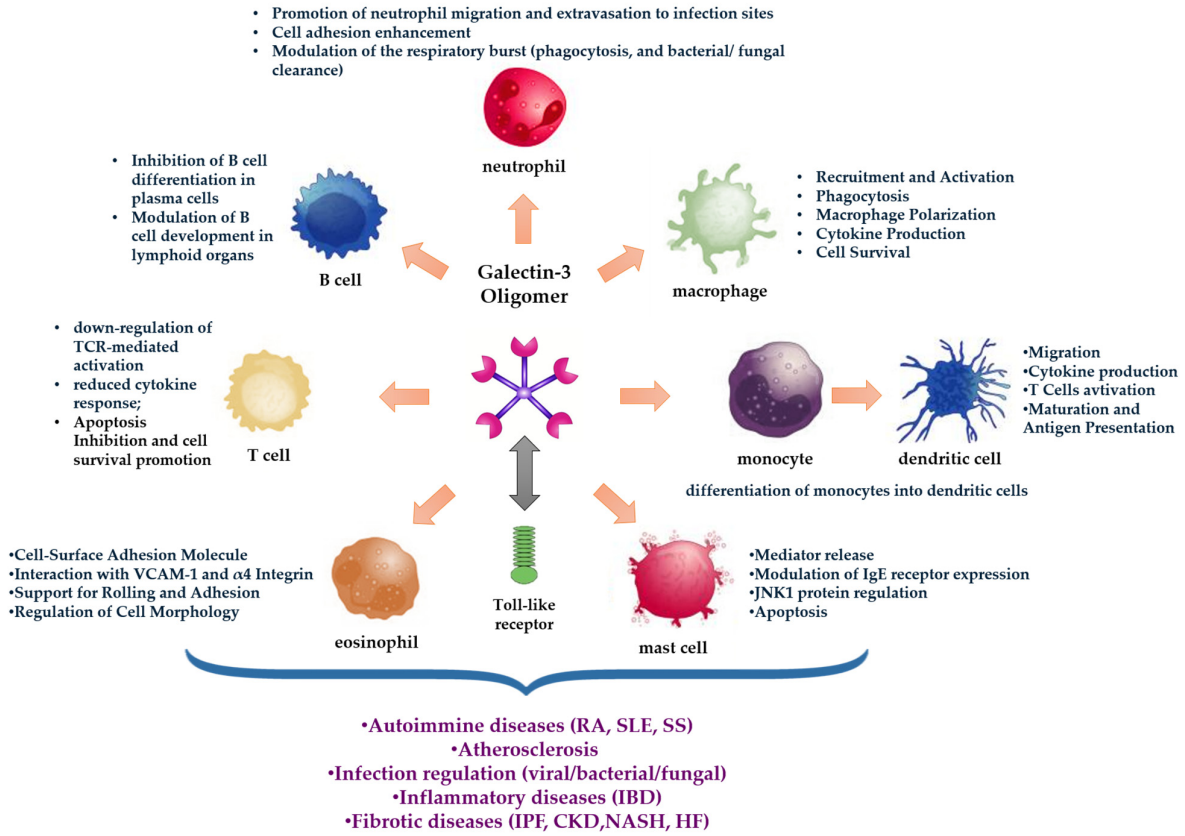

Figure 2. Summary overview of Gal-3 effect on the immune system: the possible link for multiple diseases (RA: rheumatoid arthritis; SLE: Systemic Lupus Erythematosus; SS: systemic sclerosis; IBD: intestinal bowel diseases; IPF: idiopathic pulmonary fibrosis; CKD: chronic kidney disease; NASH: non-alcoholic steatohepatitis; HF: heart failure).

3. Galectin-3 in Cardiovascular Pathophysiology: Not Only Atherogenesis

Gal-3 contributes to atherosclerosis by promoting monocyte infiltration, local inflammation, and plaque progression. Elevated Gal-3 levels correlate with unstable lesions, higher mortality in acute coronary syndrome, and ischemic stroke severity, supporting its role as a biomarker of advanced disease [82]. Recent evidence links Gal-3–mediated immune activation with endothelial dysfunction, suggesting that macrophage-derived Gal-3 promotes endothelial-to-mesenchymal transition through IL-6–STAT3 signaling and contributes to vascular remodeling and plaque instability [82,105].

Moreover, several studies have shown that genetic or pharmacologic inhibition of Gal-3 reduces atherosclerosis and slows plaque progression in mouse models [106].

Gal-3 also promotes the osteogenic differentiation of vascular smooth muscle cells, leading to calcium deposition and increased type I collagen synthesis, which contribute to vascular remodelling [82].

Gal-3 mediates the formation of lattice complexes that interact with TGF-β, increasing fibroblast activity and extracellular matrix synthesis. Initially, Gal-3 may exert cardioprotective effects via anti-apoptotic and anti-necrotic actions; however, chronically elevated Gal-3 levels drive tissue remodelling and fibrosis, in part by inhibiting matrix metalloproteinases that normally degrade the extracellular matrix. Gal-3 further promotes fibrosis through nuclear translocation of transcription factors such as β-catenin, which upregulates collagen synthesis [82]. These mechanisms form the pathophysiological basis of HF and atrial fibrosis and are implicated in the initiation of AF [4,82]. Accordingly, the 2017 AHA Guidelines emphasise the prognostic and risk-stratification role of Gal-3 in HF. Gal-3 is used as a biomarker for risk stratification in HF patients, with a reported cut-off value of

17.8 ng/mL to distinguish low from high risk. While NT-proBNP levels increase in patients with renal insufficiency regardless of HF status, Gal-3 is more specific because its levels are less influenced by eGFR [82]. A recent study found that adult male rats receiving Gal-3 infusion into the pericardial sac developed inflammation, ventricular remodelling, and dysfunction [4,106]. Finally, Gal-3 contributes to thrombosis through interactions with inflammatory mediators such as interleukin-6 (IL-6) [82]. It also interacts with von Willebrand factor and factor VIII influencing hemostasis activity and platelets aggregation [107].

4. The Bing-Bang of Cardiovascular Diseases: Galectin-3 and Endothelial Function

4.1. Interaction with Inflammatory Cytokines (IL-6, TNF-α, Etc.)

Gal-3 functions not only as a biomarker of endothelial activation but also as an active modulator of vascular inflammation. In endothelial cell cultures, Gal-3 stimulates the release of IL-6 and other pro-inflammatory cytokines, potentially establishing an autocrine loop that sustains inflammatory signaling and endothelial activation [108].

At the molecular level, Gal-3 interacts with the surface glycoprotein CD146 (MCAM), promoting receptor dimerization and triggering downstream signaling pathways including AKT. This interaction is critical for Gal-3–mediated cytokine secretion, as inhibition of CD146 markedly reduces the release of IL-6 and G-CSF [109].

These observations underscore Gal-3's role as an active amplifier of endothelial inflammation rather than a passive indicator, highlighting its potential as a therapeutic target in conditions driven by IL-6 and TNF-α–mediated endothelial activation.

4.2. Modulation of Adhesion Molecules (ICAM, VCAM)

Endothelial activation is characterized by the upregulation of adhesion molecules such as ICAM-1 and VCAM-1, which facilitate leukocyte adhesion and transmigration. Experimental evidence suggests that Gal-3 contributes to this pro-inflammatory phenotype by promoting the expression of these adhesion molecules in endothelial cells [108].

Although the precise transcriptional mechanisms require further investigation, the ability of Gal-3 to enhance ICAM-1 and VCAM-1 expression provides a mechanistic link to leukocyte recruitment and the amplification of vascular inflammation.

4.3. Regulation of the NF-κB Pathway

Gal-3 has been implicated in the modulation of NF-κB signaling, a central pathway controlling inflammation and immune responses in endothelial cells. Through interactions with receptors such as Toll-like receptor 4 (TLR4), Gal-3 can activate MyD88-dependent NF-κB signaling, leading to the transcription of pro-inflammatory cytokines, chemokines, and adhesion molecules [110,111].

Additionally, Gal-3 promotes the generation of reactive oxygen species (ROS) and activates p38 MAPK signaling, further enhancing NF-κB nuclear translocation and inflammatory gene expression [53]. These interconnected events are summarized schematically in Figure 2, illustrating the proposed Gal-3–mediated pathway in endothelial cells.

4.4. Tissue Factor Expression and Thrombotic Risk: Experimental Evidence in Cellular Models

Gal-3 influences multiple aspects of endothelial cell behavior, including activation, migration, and angiogenesis [53]. While direct evidence linking Gal-3 to tissue factor (TF) expression is limited, experimental studies indicate that Gal-3 can indirectly promote a pro-thrombotic phenotype through enhanced endothelial activation [53,112].

In HUVECs, Gal-3 stimulates migration and capillary tubule formation, reflecting heightened endothelial responsiveness [53,112]. It also upregulates ICAM-1, reinforcing leukocyte adhesion and potentially contributing to thrombosis [112].

Collectively, these findings support the concept that Gal-3 primes endothelial cells toward a pro-thrombotic state by integrating inflammatory and adhesion signaling pathways. This reinforces its role as an active mediator in vascular dysfunction and underscores its potential as a therapeutic target in CVD associated with IL-6–driven inflammation. The pleiotropic effects of Gal-3 integrate shared mechanisms across distinct pathological settings. In Figure 3 is summarized the converging and diverging molecular pathways through which Gal-3 modulates tumor progression and cardiovascular remodeling.

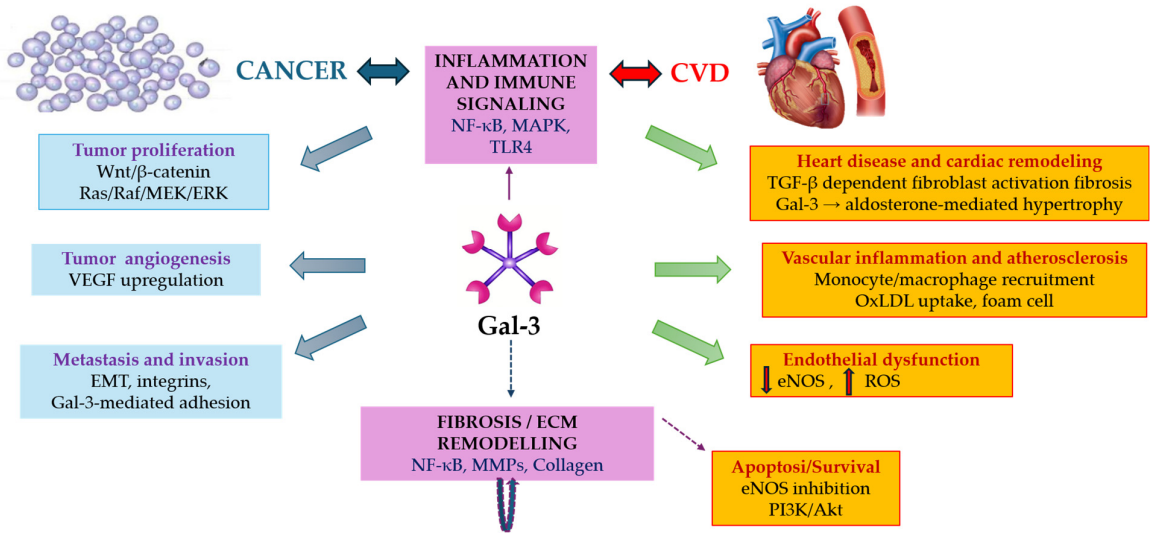

Figure 3. Schematic overview of Galectin-3 (Gal-3)-mediated molecular pathways in cancer (**left**) and cardiovascular diseases (CVD, **right**). Gal-3 acts as a convergence hub linking inflammatory, fibrotic, and survival signaling. In cancer, Gal-3 promotes tumor proliferation (Wnt/β-catenin, Ras/Raf/MEK/ERK), angiogenesis (VEGF up-regulation), and metastasis/invasion (EMT, integrins, Gal-3-mediated adhesion). In CVD, Gal-3 contributes to cardiac remodeling and fibrosis (TGF-β-dependent fibroblast activation, aldosterone-mediated hypertrophy), vascular inflammation and atherosclerosis (monocyte/macrophage recruitment, oxLDL uptake, foam-cell formation), and endothelial dysfunction (reduced eNOS activity, increased ROS). The central axis depicts shared inflammatory and fibrotic signaling (NF-κB, MAPK, TLR4, PI3K/Akt). Solid arrows indicate direct activation or causal interactions, dashed arrows denote indirect modulation or downstream effects, and the curved dashed arrow represents a feedback loop in which fibrosis and ECM remodeling further amplify inflammatory signaling.

5. Galectin-3 Beyond the Observable Universe of Cardiovascular System

In recent years, Gal-3 has emerged as a key mediator in cardiovascular, metabolic, oncological, and immune-inflammatory diseases [10,113,114].

In metabolic syndrome, the role of Gal-3 has become increasingly evident over the past decade, with human studies consistently reporting its higher circulating levels in individuals with obesity and type 2 diabetes [113,115]. The combination of severe obesity and elevated Gal-3 was found linked to a >4-fold higher risk of HF than the combination of normal weight and low Gal-3 [115]. Gal-3 levels also correlate positively with markers of insulin resistance (HOMA-IR) in the general population, but research has shown as, within diabetic populations, higher Gal-3 is sometimes associated with better insulin sensitivity and lower HbA1c, suggesting a potential compensatory or protective effect [113]. The study of Menini et al. [113], revealed that a Gal-3 cut-off value of 803.55 pg/mL can diagnose diabetes with a sensitivity of 80.7% and a specificity of 85.5%. However, the role of Gal-3 in

obesity and metabolic syndrome is complex and context-dependent, with animal studies showing both protective [116], and promoting effects, whereas human studies consistently find elevated Gal-3 in metabolic disease, even if cannot establish causality. These results highlight the need for further research to clarify Gal-3 role and therapeutic potential in metabolic disorders.

As indicated above, Gal-3 has also long been recognized for its overexpression in a wide range of cancers. Its strong correlation with disease progression is indicative of a crucial involvement in tumorigenesis and metastasis, operating through both intracellular and extracellular pathways [20,117,118]. Functionally, Gal-3 interacts with glycoproteins and glycolipids, forming lattices on the cell surface that facilitate cancer cell survival, migration, and resistance to apoptosis. Its expression is notably upregulated in response to common tumor microenvironment (TME) stressors, such as hypoxia and nutrient deprivation, enhancing cancer cell adaptation and invasiveness [119,120]. Targeting Gal-3 has shown promising in preclinical models, where its inhibition enhances anti-tumor immunity, reduces metastasis, and augments responses to immunotherapies such as PD-1/PD-L1 blockade [114,121,122]. Additionally, simultaneous inhibition of Gal-3 and TREM2 seems to be a potent therapeutic approach for lung cancer therapy [122].

Recent researches have also identified Gal-3 role as a multifunctional regulator deeply involved in both innate and adaptive immunity, orchestrating pathogen recognition, inflammation modulation, and immune cell differentiation (monocytes, macrophages, dendritic cells, T and B lymphocytes) [10,123]. Gal-3, interacting with receptors like TLR4 and NLRP3, is able to promote inflammatory signaling (e.g., NF-κB activation), and can directly bind pathogens, influencing infection outcomes [124,125].

Gal-3 has been recently implicated as a potential marker of lung damage, and a predictor of poor outcomes, in COVID-19 patients [104,126]. Accumulating evidence suggests that Gal-3 is involved in the promotion of various viral infections, and the enhancement of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α [126,127].

Furthermore, recent studies have also shown how Gal-3 is able to promote inflammation in models of multiple sclerosis, uveitis, lupus, and myopathies, often correlating with disease activity and tissue damage. Its inhibition reduces disease severity in animal models [124,128]. Additionally, the accumulating body of evidence underscores Gal-3 as a crucial, multifunctional mediator deeply implicated in a broad spectrum of severe pathological processes, such as tumorigenesis, metastasis, chronic inflammation, and metabolic dysfunction. On the other side, Gal-3 is also highlighted as a promising tool, both as a diagnostic or prognostic biomarker (e.g., for diabetes diagnosis or poor outcomes in COVID-19) and as a potential therapeutic target (e.g., through inhibition to enhance anti-tumor immunity or reduce disease severity) across these critical medical domains [129].

6. Galectin: Going to Bedside for A Possible Therapeutic Target

Given the strong experimental evidence that Gal-3 amplifies IL-6–driven endothelial activation and pro-thrombotic responses, pharmacological inhibition of Gal-3 emerges as a rational strategy to mitigate vascular inflammation and thrombogenicity in CVD.

6.1. Pharmacological Inhibitors (e.g., TD139, Modified Citrus Pectin)

TD139 (GB0139), a selective Gal-3 inhibitor administered via inhalation, has shown encouraging efficacy in both preclinical and clinical contexts. In a phase Ib/IIa trial involving patients with idiopathic pulmonary fibrosis (IPF), TD139 was well tolerated and demonstrated dose-dependent reductions in Gal-3 expression and circulating biomarkers of fibrosis [11]. In vitro, Gal-3 enhances TGF-β1 activation and upregulates fibrotic markers

in human lung fibroblasts, whereas its inhibition attenuates these profibrotic responses [5]. Additional investigations report that Gal-3 blockade confers neuroprotection in ocular hypertensive glaucoma models [130], reduces placental inflammation and fibrosis in gestational diabetes models [131], and improves functional recovery while limiting fibrotic scarring after spinal cord injury in mice [132]. Although these studies are not directly cardiovascular, they consistently highlight the anti-inflammatory and anti-fibrotic potential of Gal-3 inhibition, supporting its translational relevance to vascular pathology. Mechanistically, this aligns with its documented effects on endothelial activation, adhesion molecule expression, and pro-thrombotic signaling (Section 4).

6.2. Antisense Oligonucleotides and Monoclonal Antibodies

While antisense oligonucleotides targeting Gal-3 remain mostly in preclinical or theoretical stages, monoclonal antibodies have provided more tangible results. For instance, the monoclonal antibody 14D11 inhibited tumor growth and downstream AKT/ERK signaling in MUC16-expressing ovarian and breast cancer models [133]. Experimental evidence further indicates that Gal-3 blockade via monoclonal antibodies reduces medial hypertrophy, vascular inflammation, and fibrosis, reinforcing the therapeutic promise of Gal-3 inhibition in cardiovascular contexts [134]. These biologics illustrate the feasibility of targeting Gal-3 therapeutically, with potential applicability to thrombotic and vascular conditions.

6.3. Preclinical Evidence in Cardiovascular and Fibrotic Models

Preclinical models consistently demonstrate that Gal-3 drives organ fibrosis and cardiovascular dysfunction. Pharmacological inhibition reduces collagen deposition, fibroblast activation, and tissue stiffness. In cardiac models, Gal-3 modulation improves myocardial performance and attenuates remodeling, suggesting a role in managing fibrotic cardiomyopathy and related vascular complications [12]. These findings corroborate the mechanistic links between Gal-3 and thrombosis discussed in Section 4, where Gal-3 promotes endothelial activation and a pro-thrombotic phenotype.

6.4. Preclinical Evidence in Reducing Thrombogenicity and Endothelial Inflammation

Recent studies further support the pro-thrombotic and pro-inflammatory role of Gal-3 at the endothelial level. Its inhibition reduces leukocyte adhesion, the expression of adhesion molecules (VCAM-1, ICAM-1), and platelet activation in models of vascular inflammation [112]. These observations reinforce Section 4 findings, confirming that Gal-3, in synergy with IL-6, primes endothelial cells toward a pro-thrombotic and pro-inflammatory state. Collectively, these data provide a mechanistic rationale for pharmacologically targeting Gal-3 to mitigate endothelial activation and thrombogenicity in CVD.

6.5. Current Status of Clinical Trials

TD139 has been investigated in a phase Ib/IIa trial in IPF patients, yielding promising results [11]. The ongoing phase IIb GALACTIC-1 trial (NCT03832946) is evaluating 426 IPF patients over 52 weeks to assess long-term safety and efficacy (https://clinicaltrials.gov/study/NCT03832946) (accessed on 15 September 2025). Simultaneously, the DEFINE study examines inhaled GB0139 in hospitalized COVID-19 patients, aiming to reduce viral load, inflammatory markers, and disease progression [135]. Recent clinical investigations have shown that inhaled Gal-3 inhibitors can achieve target engagement with an acceptable safety and tolerability profile in early-phase studies, although their efficacy in chronic fibrotic disorders remains uncertain. In a phase 1/2a study, TD139 (GB0139) demonstrated favourable pharmacokinetics, pharmacodynamics, and target engagement in patients with idiopathic pulmonary fibrosis, and was generally well tolerated [11]. A subsequent multicenter program advanced GB0139 to larger trials, including the 52-week

phase 2b GALACTIC-1 study (https://clinicaltrials.gov/study/NCT03832946) (accessed on 15 September 2025); however, preliminary results indicated that the primary endpoint was not met, highlighting the complexity of translating molecular target inhibition into consistent clinical benefit. Parallel exploratory work in acute severe respiratory disease (DEFINE trial) showed that inhaled GB0139 reached pharmacologically relevant plasma concentrations, modulated inflammation and fibrotic biomarkers, and maintained a good safety profile [135]. These results support further evaluation but do not yet confirm efficacy. Important limitations of current Gal-3-targeting strategies include uncertainty regarding systemic specificity, potential off-target or dose-dependent effects, variability in patient selection and endpoints, and analytical inconsistencies in Gal-3 assays due to comorbidities such as renal impairment [136]. To enhance translational relevance, future cardiovascular trials should focus on well-defined patient phenotypes, harmonized biomarker methodologies, clinically meaningful outcomes, and robust safety monitoring to clarify the therapeutic potential of Gal-3 inhibition.

7. Challenges and Future Perspectives

Despite the growing interest in Gal-3 as a key factor in cardiovascular health, many questions remain unanswered. It is essential to deeply understand its biological role, clarify how it contributes to pathological mechanisms, and evaluate its real clinical applicability. Current research must address the complexity of Gal-3's involvement in inflammatory, fibrotic, and thrombotic processes, aiming to bridge the gaps between preclinical and clinical findings. Moreover, it is crucial to determine whether Gal-3 is merely a biomarker of tissue damage or an active mediator of disease [82,137,138].

7.1. Biomarker or Pathological Mediator? An Open Question

The role of Gal-3 in human diseases remains a topic of discussion, particularly regarding its function: is it just a disease marker or does it play an active role in disease progression? Its expression is increased in many cardiovascular, oncological, and inflammatory conditions [139]. However, recent studies suggest that Gal-3 may be directly involved in tissue remodeling, immune recruitment, and fibrosis processes [140]. This opens the door to using Gal-3 not only for diagnostic purposes but also as a potential therapeutic target, especially as a marker of systemic immuno-inflammation [82,138]. Compared to other galectins, such as Gal-1 and Gal-9, Gal-3 exhibits unique structural and functional characteristics. While the former tend to play immunosuppressive roles, Gal-3 stands out for its pro-inflammatory and pro-fibrotic activity, due to its single CRD structure and ability to form lattices with extracellular glycans [141]. To be considered a clinically useful biomarker, Gal-3 must be validated in terms of specificity and sensitivity, standardized assay methods must be implemented, and reliable diagnostic thresholds defined. Some studies suggest plasma levels above 17.8 ng/mL as predictive for HF, but a universally accepted clinical cut-off is still lacking [142].

7.2. Limitations of In Vitro Research Compared to In Vivo Studies

One of the main challenges in studying Gal-3 is translating results obtained in vitro to in vivo models. Experiments on cell cultures have helped uncover some of the molecular mechanisms regulated by this lectin, such as cell adhesion, cytokine signaling, and extracellular matrix remodeling. However, these simplified systems fail to replicate the complex physiological conditions of a living organism. Animal models are essential to understand how Gal-3 interacts with immune cells, vascular endothelium, and extracellular matrix in real pathological situations. Additionally, studies in models of hyperaldosteronism and hypertension have shown that Gal-3 inhibition reduces inflammation and fibrosis,

highlighting the importance of validating preclinical data in complex environments [143]. However, the choice of model, disease stage, and method of Gal-3 inhibition significantly influence the results obtained [144].

7.3. Clinical Impact: From Atherosclerosis to Heart Failure

Evidence links Gal-3 to CVD through its role in endothelial dysfunction, leukocyte recruitment, and plaque progression [145]. In thrombotic situations, Gal-3 stimulates coagulation system activation through inflammatory mechanisms, suggesting its direct involvement in thrombogenesis [146]. Furthermore, numerous clinical studies have associated elevated Gal-3 levels with an increased risk of HF, mainly due to its profibrotic activity and progressive impairment of ventricular function [137,138]. At the molecular level, Gal-3 can bind to surface receptors such as TLR4, CD36, and CD98, activating intracellular pathways including TGF-β/Smad, NF-κB, and PI3K/Akt, which respectively contribute to fibrosis, inflammation, and cell survival—worsening myocardial dysfunction [147,148].

7.4. Galectin-3 and IL-6: A Combined Therapeutic Target

A new research perspective focuses on the synergistic action between Gal-3 and interleukin-6 (IL-6), two key mediators in the immuno-inflammatory process. IL-6 is a pro-inflammatory cytokine involved in many chronic diseases, including cardiovascular ones. Gal-3, also involved in inflammatory and fibrotic mechanisms, can amplify IL-6 activity or activate similar signaling pathways, thus intensifying the pathological response [146]. Preclinical studies suggest that a dual inhibition approach targeting both Gal-3 and IL-6 could more effectively reduce systemic inflammation and organ damage compared to therapies targeting only one mediator [82].

7.5. New Therapeutic Perspectives

Recent research is investigating targeted inhibition of Gal-3 using small molecules (such as TD139), modified polysaccharides, or monoclonal antibodies. These therapeutic approaches aim to reduce fibrosis and chronic inflammation in various pathological conditions, including cardiovascular, hepatic, pulmonary, and oncological diseases [139,146]. At the same time, new biological agents are being developed to interfere with the carbohydrate-binding domain of Gal-3, aiming to selectively block its pathological functions [144]. With growing knowledge of its mechanisms of action, Gal-3 is increasingly recognized as a key therapeutic target in chronic immuno-inflammatory processes. However, despite promising results in preclinical models, several clinical challenges remain. TD139, for instance, is currently under evaluation in clinical trials for idiopathic pulmonary fibrosis (NCT05240131), but its cardiovascular efficacy has yet to be demonstrated [149]. Furthermore, systemic bioavailability, tissue selectivity, toxicity profiles, and interindividual variability represent major hurdles to its clinical implementation [150].

8. Conclusions

The available evidence support the emerging role of Gal-3 as diagnostic and prognostic biomarker in several diseases. Because of its key involvement in cell signaling in various biochemical pathways Gal-3 might be a promising tool to develop innovative therapeutic strategy for management of CVD and beyond. However, research must go on since several issues need to be solved such as type of Gal-3 modulation, timing of administration and systemic effect. Improvement of our knowledge of the complex intracellular and extracellular signaling in which Gal-3 in involved in the different cell types will help to better understand its modulation in different clinical scenarios. Looking ahead, future studies should aim to clarify how dynamic changes in circulating Gal-3 levels relate to disease onset, progression, and treatment response. Combining Gal-3 inhibition with

existing anti-fibrotic or anti-inflammatory therapies could offer synergistic benefits, while targeted or tissue-specific modulation may help preserve its physiological roles in immune regulation and tissue repair. Continued translational and clinical research will be essential to fully define the therapeutic and diagnostic potential of Gal-3 and to move this multifaceted molecule closer to clinical application.

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