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REVIEW

The Role of Galectin-3 in Liver Inflammation and Fibrosis

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Abstract: Galectin-3, a β-galactoside–binding lectin encoded by *LGALS3*, is increasingly recognized as a central mediator in liver disease and inflammation. Galectin-3 has the unique ability to cross-link glycosylated molecules, resulting in a broad range of functions, from receptor clustering to influence downstream signaling, to extracellular matrix stabilization and the regulation of cell adhesion. In the liver, it regulates fibrogenesis through hepatic stellate cell activation, oxidative stress regulation, apoptosis, and extracellular matrix deposition. Immunologically, galectin-3 contributes to leukocyte infiltration, macrophage polarization, inflammasome activation and T cell regulation. Elevated circulating and hepatic galectin-3 levels are reported across different stages of liver disease, including metabolic dysfunction-associated liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated steatohepatitis (MASH), and cirrhosis, correlating with disease stage and the risk of hepatocellular carcinoma. Translational studies highlight galectin-3 as both a biomarker and a therapeutic target. Clinical trials of galectin-3 inhibitors, including GB1211 (Selvigaltin) and GR-MD-02 (Belapectin), demonstrate safety and preliminary efficacy signals in reducing liver fibrosis, portal hypertension, and systemic inflammation. Preclinical models reinforce its role in modulating fibrogenic and inflammatory signaling, supporting drug development efforts. This review synthesizes current evidence on galectin-3 in liver disease and inflammation, with emphasis on mechanisms, biomarker potential, the requirements for clinical investigation and translational opportunities. By bridging molecular insights with ongoing therapeutic trials, galectin-3 appears to be an important driver of liver pathology and a promising target for liver-directed antifibrotic and anti-inflammatory therapies.

Keywords: LGALS3, cirrhosis, fibrogenesis, inflammation, therapy, drug development

Introduction

Chronic liver diseases are highly prevalent worldwide and contribute to substantial global morbidity and mortality.[1] A key pathological process underlying many of these conditions is the progressive scarring of liver tissue, termed liver fibrosis. Fibrosis results from the excessive accumulation of extracellular matrix (ECM) proteins in response to persistent liver injury, while cirrhosis represents its advanced stage, characterized by extensive scarring with architectural distortion, hepatocellular loss, and, consequently, impaired liver function.[2] Inflammation is a major perpetrator of liver disease. Repeated liver injury triggers hepatocyte injury and death, which stimulates leucocyte recruitment and inflammatory polarization of infiltrating and resident immune cells.[3,4] This can drive a vicious cycle of renewed injury, wherein stimulated immune cells aggravate parenchymal injury through the release of mediators that stimulate hepatic stellate cells (HSCs) to transform into ECM-producing myofibroblasts and activate further cell types.[5] Furthermore, chronic liver disease is increasingly recognized as a multisystem disease involving the gut and its microbiome, adipose tissue and systemic lipids, as well as the bone marrow as the source of circulating immune cells.[6]

The most frequent etiologies include chronic viral hepatitis, metabolic dysfunction-associated steatotic liver disease (MASLD), and alcohol-associated liver disease (ALD).[7] At present, the majority of hepatitis B virus (HBV) and hepatitis

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C virus (HCV) infections worldwide remain undiagnosed, despite screening and eradication efforts.[8] Simultaneously, the prevalence of MASLD is increasing, now affecting more than 30% of Europeans and Americans.[9,10] Alongside mixed forms of MASLD with elevated alcohol consumption (MetALD) and cholestatic and autoimmune liver diseases, these etiologies represent the major causes for liver fibrosis and cirrhosis worldwide.[11]

The severe clinical burden of advanced fibrosis and cirrhosis underscores the urgent need for mechanistic understanding and effective antifibrotic therapies. The development of fibrolytic medication, however, remains challenging due to the complex interplay of hepatocellular injury, inflammation, and extracellular matrix remodeling.[12] Current therapeutic strategies primarily aim to halt or slow disease progression by targeting primary pathogenic triggers, such as viral replication,[13] lipotoxicity and metabolic dysregulation,[14] as well as alcohol consumption,[15] rather than directly targeting fibrogenesis or reversing established fibrosis, cirrhosis, or cirrhosis-associated complications.

Galectin-3 is a lectin, a glycoprotein without catalytic function, but with the ability to bind carbohydrate structures,[16,17] that has emerged as an important regulator of liver pathology. In the healthy liver, galectin-3 expression is restricted to macrophages and bile duct epithelial cells,[18] with low or absent expression in healthy hepatocytes.[19] Galectin-3 is upregulated in chronic liver injury[20] and engages in diverse interactions with cellular and extracellular partners, influencing both inflammation and fibrogenesis.[21] As a multifunctional regulator, it can direct the progression of liver disease. Its broad interaction profile complicates the dissection of its precise mechanistic role. Nevertheless, accumulating evidence suggests that galectin-3 not only serves as a biomarker of disease severity, but may also represent a promising therapeutic target. Indeed, early attempts to pharmacologically inhibit galectin-3 in preclinical and clinical studies highlight its potential as a novel antifibrotic strategy.[22]

Structure of Galectin-3

Galectin-3 is a 30 kDa glycoprotein belonging to the β-galactoside-binding lectin family. Like most mammalian galectins, it binds non-enzymatically to ubiquitous cell surface glycans, with strong affinity for poly-N-acetyllactosamine chains.[23] Oligomerized galectin-3 crosslinks glycosylated proteins and lipids on the cell surface to regulate signaling pathways and ligand endocytosis.[24] Additionally, it can bind non-carbohydrate ligands in the cytosol and nucleus.[25] This versatility underlies its involvement in diverse processes, including cell adhesion, cell growth and differentiation, cell cycle, cell signaling, apoptosis and angiogenesis.[17,26–29]

Galectins are evolutionarily ancient glycan-binding proteins (GBPs). At least 16 galectins have been identified in vertebrates, each containing a conserved carbohydrate recognition domain (CRD) of ~130 amino acids, responsible for the lectin activity.[30] Galectins are classified into three subgroups, based on their CRD organization: prototype galectins, tandem-repeat galectins and chimera-type galectins.[31] Prototype galectins contain one CRD that associates to form non-covalent homodimers and include galectin-1, −2, −5, −7, −10, −11, −13-16. Tandem-repeat galectins have two homologous CRD motifs separated by a peptide linker and comprise galectin-4, −6, −8, −9, −12.[32,33] Structurally unique, galectin-3 is the only mammalian representative of a chimera-type lectin, containing a single canonical CRD connected to a short N-terminal domain via an intermediary proline-rich collagen-α-like domain (Figure 1).

The CRD contains the β-galactoside-binding site and the NWGR amino acid sequence.[34] The N-terminal domain of galectin-3 mediates oligomerization,[24] nuclear-cytoplasmic translocation,[35] and extracellular secretion of galectin-3.[36] In the extracellular space, Galectin-3 can be cleaved in its collagen-α-like domain by matrix metalloproteinases 2 and 9, thus abrogating oligomerisation.[37,38]

Localization and Binding Partners of Galectin-3

The localization of galectin-3 depends on cell type, proliferation status and culture conditions.[32] It is predominantly a cytosolic protein,[39] but can shuttle between cytoplasm and nucleus.[39] While galectin-3 preferentially binds β-galactoside motifs, many intracellular ligands also bind to galectin-3 via protein-protein interactions instead of lectin-carbohydrate recognition.[39,40] This renders the functional profile of galectin-3 to be inherently flexible. Secreted galectin-3 can interact with a wide range of cell surface molecules, including immune receptors, integrins, adhesion molecules, and signalling receptors, or interact with soluble mediators and components of the ECM. Selected localization-dependent interactions of galectin-3 are illustrated in Figure 2.

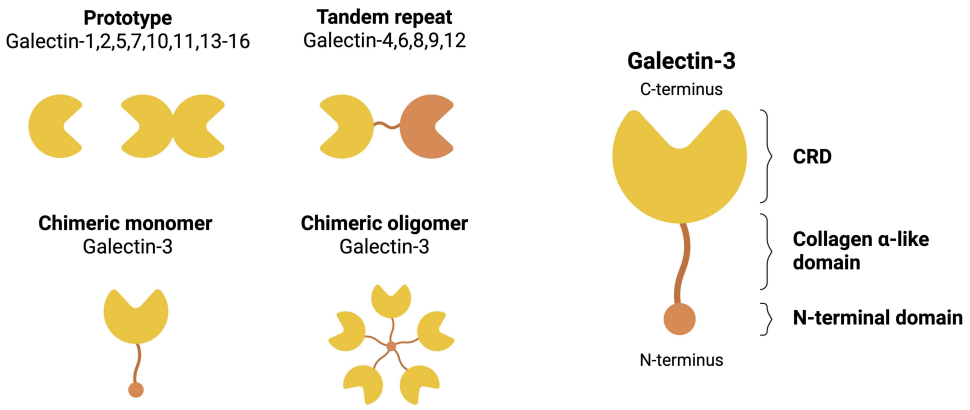

Figure 1 Structure of galectin family members. Galectins are classified into three groups based on the number and organization of their carbohydrate recognition domains (CRDs): prototype galectins, tandem-repeat galectins and chimera-type galectins. Galectin-3 is a structurally unique member of the galectin family as it contains a single CRD connected to a short N-terminal domain via an intermediary proline-rich collagen-α-like domain, which is required for oligomerisation. Figure adapted from Mukherjee MM, Biesbrock D, Hanover JA. Galectin-3: Integrator of Signaling via Hexosamine Flux. Biomolecules. 2025; 15(7):1028. https://doi.org/10.3390/biom15071028,[30] Created with https:BioRender.com. Hammerich, (L) (2025) https://BioRender.com/lracrq0.

Intracellular Functions

A key function of intracellular galectin-3 is the regulation of apoptosis, mediated through its interaction with several intracellular ligands that inhibit cell death, such as Bcl-2 and synexin (annexin VII).[41,42] The latter mediates the translocation of galectin-3 to the outer mitochondrial membrane to preserve mitochondrial integrity under apoptotic stimuli.[42] Galectin-3 can further stimulate survival in oncogenic settings, where activated k-Ras recruits galectin-3 from the cytosol to the plasma membrane. This leads to k-Ras stabilization and phosphoinositide 3-kinase (PI3-K) and Raf-1 activation.[43,44] In turn, galectin-3 facilitates micropinocytic nutrient uptake and redox balance in *KRAS*-mutated tumours.[45]

Beyond apoptosis, galectin-3 functions as a sensor of intracellular damage, detecting and responding to compromised cellular structures. Under homeostatic conditions, most glycoconjugates are restricted to the lumen of organelles.[46] In case of a loss of lysosomal integrity, induced by bacterial or viral damage, galectin-3 swiftly accumulates around lysed vesicles by binding to exposed β-galactosides on damaged membranes, where it associates with autophagy regulator tripartite motif 16 (TRIM16) to trigger autophagy and bacterial clearance.[47–49] Therefore, galectin-3 acts as a vacuolar damage sensor which coordinates lysosomal repair and removal.[50,51]

In leukocytes, intracellular galectin-3 plays an additional regulatory role, influencing both their functionality and polarization. In T cells, the interaction of galectin-3 with Alix/AIP-1 (ALG-2-interacting protein X or ALG-2 interacting protein-1) downregulates the T cell receptor (TCR) at the immunological synapse and inhibits its activation.[52] At the same time, the presence of intracellular galectin-3 is required for T cell polarization and long-term adaptive responses. While early $CD8^+$ T cell activation is independent of galectin-3, subsequent memory formation and survival in response to antigenic stimulation is dependent on intracellular galectin-3.[53] Through its expression in dendritic cells, galectin-3 attenuates Th17-type inflammatory polarization by reducing IL-23 secretion.[54]

Nuclear Function of Galectin-3

Within the nucleus, galectin-3 participates in RNA processing and transcriptional regulation. It interacts with Gemin4, a component of the survival of motor neuron (SMN) multiprotein complex, which facilitates pre-mRNA splicing.[55] Galectin-3 also directly interacts with β-catenin and Axin, a regulator of the Wnt pathway. It colocalizes with the β-catenin/T cell factor complex to the nucleus to enhance the Wnt/β-catenin signalling pathway and promotes cell cycle progression through cyclin D1 and c-myc.[56,57]

Secretion and Extracellular Functions of Galectin-3

Galectin-3 is secreted by activated HSCs, inflammatory macrophages, tumour-infiltrating lymphocytes, and stromal cells.[58–60] Like other galectins, it bypasses the endoplasmic reticulum-Golgi complex due to its lack of a signal peptide,[61] and is secreted through non-classical routes involving exosomes.[61,62]

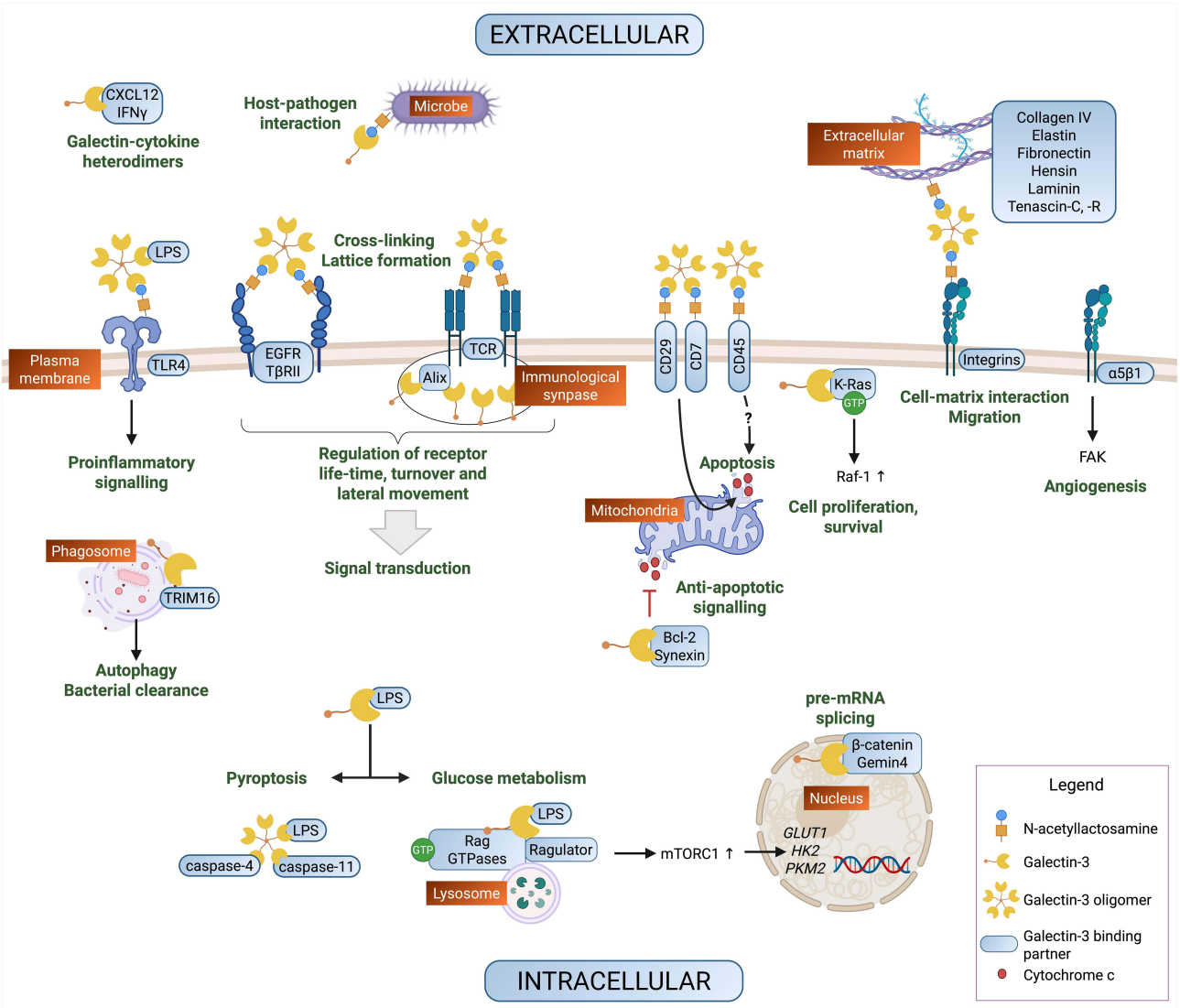

Figure 2 Localization, binding partners and physiological functions of galectin-3. Galectin-3 is involved in diverse cellular functions, as reflected by its broad distribution in different tissues and cellular compartments. Galectin-3 can exert inflammatory actions via binding to lipopolysaccharide (LPS) and enhancement of toll-like receptor 4 (TLR4) signalling and assembly of caspase-4/-11 oligomers, leading to noncanonical inflammasome activation and pyroptosis. It can also dampen inflammation by scavenging cytokines/chemokines. Intracellular LPS sensing by galectin-3 can activate mTORC1 signalling, resulting in enhanced glucose uptake and glycolysis, providing a link between chronic inflammation and diabetes. Depending on its localization, it can either protect from apoptosis or induce apoptosis in T cells via binding to several cell surface receptors. An important extracellular function of galectin-3 is to cross-link glycosylated receptors for regulation of receptor turnover and signal transduction. Galectin-3 governs T cell receptor (TCR) signalling by binding to ALG-2-interacting protein X (Alix) in the immunological synapse and by extracellular lattice formation which inhibits lateral movements of TCR and therefore uncontrolled activation. Galectin-3 mediates cell proliferation and cell cycle progression through enhancement of k-Ras and β-catenin signalling. Binding of galectin-3 to several extracellular matrix components modulates cell adhesion and motility. Galectin-3 is also involved in processes such as angiogenesis, pre-mRNA spliceosome assembly, Wnt signalling and autophagy. Created with https:BioRender. Hammerich, (L) (2025) https://BioRender.com/kl7lbpk.
Abbreviations: Bcl-2, B-cell lymphoma-2; CXCL12, CXC motif chemokine ligand 12; EGFR, epidermal growth factor receptor; FAK, focal adhesion kinase; GLUT1, glucose transporter 1; HK2, hexokinase 2; PKM2, pyruvate kinase M2; mTORC1, mechanistic target of rapamycin complex 1; TβRII, transforming growth factor β receptor; TRIM16, tripartite motif 16.

Galectin-3 plays a central extracellular role by interacting with the ECM. Due to the unique ability to form pentamers, galectin-3 can cross-link extracellular structures and stabilize their interaction. This includes the binding of glycosylated ECM components such as laminin, fibronectin, tenascin-C and -R, chondroitin sulfate, and Mac-2 binding protein.[63–67] By recruiting and activating α5β1 integrins in focal adhesions, galectin-3 promotes fibronectin fibrillogenesis, the assembly of fibronectin dimers into stable, fibrous networks in the ECM, and can facilitate tumour cell spreading.[68] In diabetes, galectin-3-integrin α5β1 interactions promote angiogenesis and wound healing, but excessive advanced glycation end products (AGEs) disrupt this interaction.[26] Depending on cell type, integrin subtype, and galectin-3 concentration, it can either promote adhesion by clustering integrins into focal adhesions,[69] or reduce adhesion via caveolae-like endocytosis of β1-integrins.[70,71]

At the external cell surface, galectin-3 oligomerises into lattices that regulate receptor diffusion, endocytosis and signalling, in both inhibitory and stimulatory ways.[72] Galectin-3 oligomers can engage membrane glycans in *cis* (on one cell) and in *trans* (between cells).[17] For example, galectin-3 cross-links Mgat5-modified glycans on epidermal growth factor receptor (EGFR) and transforming growth factor-β receptor (TGF-βR), delaying endocytosis,[73] while in T cells, lattice formation restricts TCR movement to fine-tune sensitivity, enhancing pathogen defence while limiting autoimmunity.[52,74–76] In contrast to its intracellular anti-apoptotic function, extracellular galectin-3 induces T cell apoptosis by cross-linking CD29 and CD7, although CD45 has also been proposed as the relevant receptor.[17,77,78] In the tumour microenvironment, galectin-3 modulates immune checkpoints by suppressing CD8+ T cells through binding to heavily glycosylated LAG-3.[60]

Extracellular galectin-3 contributes to the recognition of microbial structures, including bacteria, parasites, and fungi.[79–83] It binds lipopolysaccharides (LPS) through its CRD and N-terminal domains,[84] sequestering LPS and limiting macrophage signalling to protect the host from endotoxic shock.[85] Paradoxically, galectin-3 also contributes to immunopathology through LPS-induced galectin-3 oligomerisation, CD14 binding and amplified neutrophil-driven inflammation,[86] and exacerbates leukocyte infiltration in sepsis.[87]

Evidence from neuroinflammation shows a direct alarmin function of extracellular galectin-3, which is secreted by microglia and directly stimulates toll-like receptor 4 (TLR4)-dependent inflammation.[88] In addition, galectin-3 has been shown to bind cytokines, forming "galectokines" with CXC motif chemokine ligand (CXCL) 12 to dampen its signaling, and with interferon (IFN) γ to reduce T cell tumor infiltration.[89–91]

In sum, the broad spectrum of galectin-3 ligands and its context-dependent localization underlie its diverse, often opposing, extracellular functions. A representative list of localization-specific binding partners is summarized in Table 1.

Table 1 Selected Compartment-Specific Interaction Partners of Galectin-3

Extracellular		Cell Surface		Intracellular	
ECM Proteins	Laminin[63] Fibronectin[64] Tenascin-C[65] Tenascin-R[65] Mac-2 binding protein[67] Collagen IV[71] Elastin[97] Hensin[101] NG2 proteoglycan[103]	Immune receptors	CD3 (TCR)[52,75] CD7[17] CD45[77,92] CD66a/b[93] CD71 (transferrin receptor)[77] CD95 (APO-1/Fas)[95] IgE[98,99] LAG-3[60] Mucin-1[104]	Signalling and scaffold proteins	Axin[56] β-catenin[56] K-Ras[43,44] Rag GTPases[19] NLRP3[94] TTF-1[96]
				Stress regulators	Bcl-2[41,100] Nucling[102] TRIM16[48]
Cytokine/Chemokine	CXCL12[89] IFNγ[91]	Integrins and adhesion molecules	α1β1 integrin[71] α2β1 integrin[105] α5β1 integrin[26,68] CD146[107] CD98[108] CEA[109]	Structural proteins	Cytokeratins[40] Synexin (annexin VII)[42] Protocadherin-24[106]
PAMP	LPS[19,84]				
				RNA- and protein-processing	Gemin4[55] Alix/AIP1[52] hnRNP[25]
		Ligand signaling receptors	TβRII[73] Insulin receptor[110] EGFR[73] VEGF[111]		
		PRRs	TLR2[112] TLR4[88]		
		PAMPs	LPS[19,84] Fungal capsule[82]		

Abbreviations: Alix/AIP-1, ALG-2-interacting protein X/ALG-2 interacting protein-1; Bcl-2, B-cell lymphoma-2; CEA, carcinoembryonic antigen; CXCL12, CXC motif chemokine ligand 12; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; hnRNP, heterogeneous nuclear ribonucleoprotein; IFNγ, interferon gamma; IgE, immunoglobulin E; LAG-3, lymphocyte activation gene 3; LPS, lipopolysaccharide; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; TβRII, transforming growth factor β receptor II; TCR, T cell receptor; TLR, toll-like receptor; TRIM16, tripartite motif 16; TTF-1, thyroid transcription factor-1, VEGF, vascular endothelial growth factor.

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Galectin-3 as a Regulator of Hepatic Fibrogenesis

Galectin-3 as a Driver of Liver Disease

Galectin-3 occupies a central axis in the progression of liver disease, a hypothesis supported by two compelling lines of evidence. First, both hepatic and circulating levels of galectin-3 are significantly elevated in patients with liver fibrosis and cirrhosis.[20] Galectin-3 concentrations correlate with cirrhosis severity across alcohol-associated, metabolic dysfunction-associated, and toxic etiologies and are highest in cases of end-stage liver disease and hepatocellular carcinoma (HCC).[113] Second, deficiency for the gene encoding galectin-3 (*Lgals3*) in mice confers protection against liver fibrogenesis. In rodent models of fibrotic hepatic injury (eg, CCl_4-induced fibrosis or bile duct ligation), myofibroblast activation, soluble collagen deposition, and fibrosis are attenuated in *Lgals3*$^{-/-}$ strains, even when injury and inflammation levels are comparable to wild-type controls.[114] Disruption of galectin-3 in HSCs prevents their activation via TGF-β signaling, underscoring its essential role in stellate cell-mediated fibrogenesis.[114] Together, these observations support the notion that galectin-3 is an important driver of liver fibrosis.

Galectin-3 in Macrophages

Liver macrophages are tissue-resident and infiltrating immune cells with high plasticity.[115,116] Galectin-3 is expressed in hepatic macrophages and contributes to both inflammatory and fibrogenic responses in liver injury. During hepatotoxic insults, galectin-3 binds directly to and activates the NLRP3 inflammasome in hepatic macrophages (eg, in cholestatic liver injury), leading to caspase-1 activation and downstream induction of interleukin (IL)-1β.[94] This cascade triggers an IL-17 response that exacerbates liver inflammation and fibrotic progression.[94] In steatohepatitis, galectin-3 amplifies inflammatory signaling by promoting NLRP3 inflammasome activation through the engagement of TLR4.[117]

The traditional M1/M2 dichotomy, with M1 ("classical") macrophages described as proinflammatory and fibrolytic and M2 ("alternative") macrophages, viewed as regenerative and pro-fibrotic, has largely been replaced by the recognition of a continuum of macrophage activation states.[116] However, much of the evidence on macrophage biology in galectin-3-mediated liver disease was framed within this outdated dichotomy, and deeper insights into the full spectrum of macrophage phenotypes with regard to galectin-3 remain limited.

On the one hand, galectin-3 is necessary for the polarization of macrophages towards an IL-4 driven, pro-fibrotic phenotype. In turn, these "alternatively activated" macrophages can be characterized by increased galectin-3 expression and secretion.[108] On the other hand, while acute acetaminophen (APAP) intoxication increased intrahepatic galectin-3^{+} macrophages in mice, the CD11b^{+}/Ly6C^{hi} monocyte/macrophage population, functionally categorized as "classical", was reduced by galectin-3 knockout (*Lgals3*$^{-/-}$).[118] In turn, M2-like CD11b^{+}/Ly6C^{lo}, IL-10-producing monocytes/macrophages increased in *Lgals3*$^{-/-}$ mice 72h after APAP injury.[118] In the context of acute APAP-induced injury, *Lgals3*$^{-/-}$ animals exhibited less hepatotoxicity and improved hepatocyte recovery with a higher mitotic index than wildtype controls.[118,119]

As a modifier of the cell surface glycoproteome, galectin-3 regulates leukocyte adhesion, rolling and emigration.[120] Accordingly, *Lgals3*$^{-/-}$ mice exhibit restricted leucocyte rolling velocity and recruitment, while recombinant galectin-3 proportionally increases neutrophil and monocyte recruitment. These effects are mediated by defects in E-selectin-dependent adhesion in *Lgals3*$^{-/-}$ leucocytes, which display reduced lectin binding sites on their cell surface.[120] Consistent with these immunomodulatory roles, galectin-3 deficiency in the tumor vasculature of melanoma causes vascular remodeling and reduced infiltration of CD68^{+} macrophages.[121] However, in the CCl_4-induced liver fibrosis model, *Lgals3*$^{-/-}$ mice displayed no changes in overall leucocyte or T cell recruitment during the early injury phase (1 week),[114] although a more detailed characterization of leukocyte subsets was not performed. Thus, galectin-3 clearly shapes immune cell trafficking in several contexts, but its role in leukocyte recruitment during early liver fibrosis remains inconclusive.

Stimulation of Myofibroblasts

In the liver, HSCs are the main fibrogenic cell type, due to their ability to transform into ECM-producing myofibroblasts upon tissue injury.[2] Simultaneously, they also convey regenerative functions in liver regeneration and hepatocyte zonation.[122] Galectin-3 both directly and indirectly affects HSC transformation, transdifferentiation, and liver regeneration.[123] Profibrotic effects of galectin-3 in liver fibrosis are summarized in Figure 3.

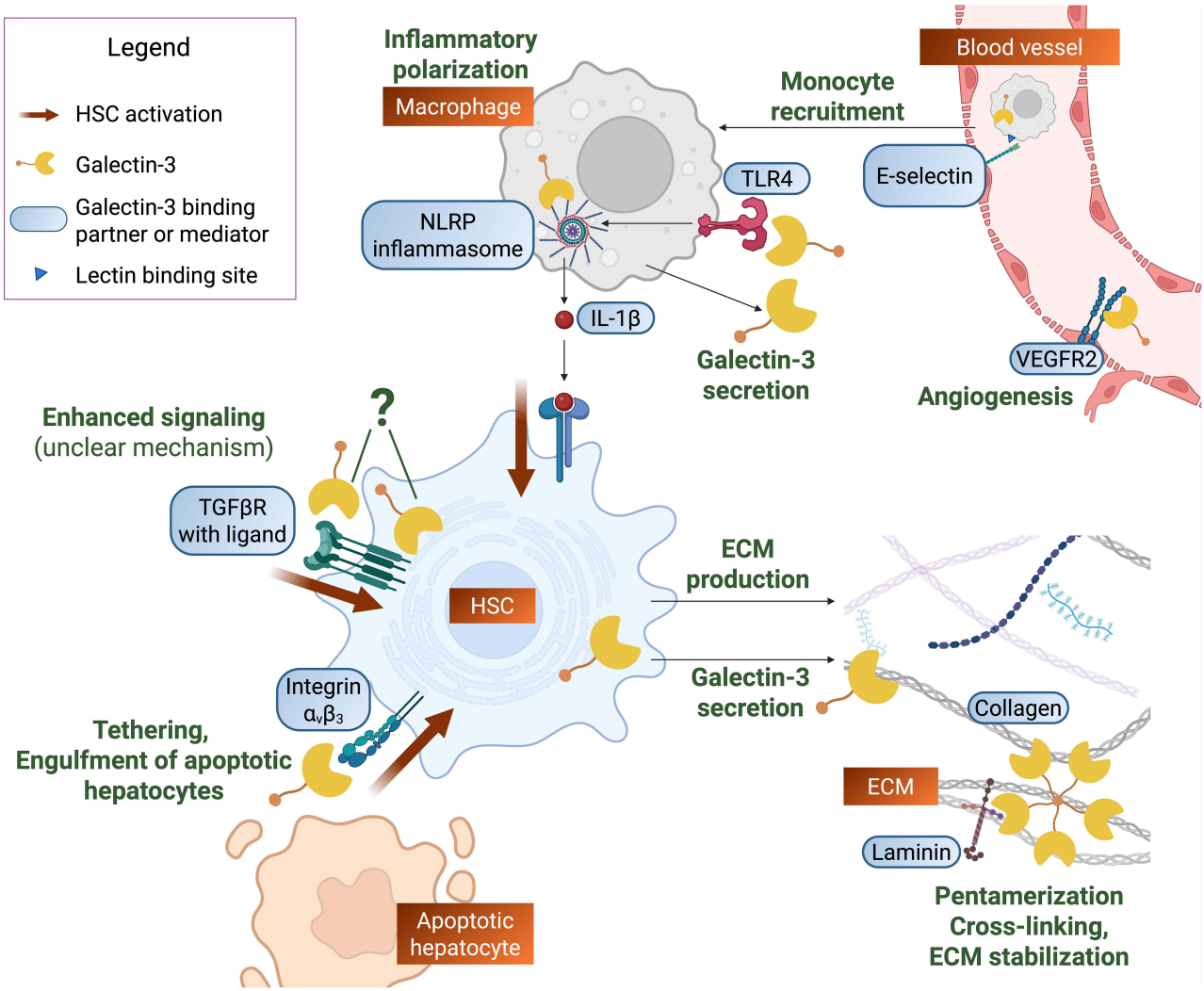

Figure 3 Profibrotic function of galectin-3 in chronic liver disease. HSCs are essential to the production of ECM in liver fibrogenesis. They are stimulated through hepatocyte apoptosis and engulf apoptotic bodies through galectin-3 mediated integrin interactions. The central profibrotic pathway involves TGFβ and is augmented through galectin-3. Galectin-3 recruits immune cells through endothelial/LSEC modifications, stimulates macrophages through TLR4 signaling and NLRP inflammasome activation, resulting in a proinflammatory phenotype that further stimulates HSCs. In the ECM, galectin-3 cross-links glycosylated components to form lattice structures by polymerization, stabilizing the ECM. Created with https:BioRender.com. *Hammerich, (L) (2025)* https://BioRender.com/dwyo3hk.
Abbreviations: ECM, extracellular matrix; HSC, hepatic stellate cell; IL, interleukin; LSEC, liver sinusoidal endothelial cell; TGF, Transforming Growth Factor; TLR, toll-like receptor; VEGF, vascular endothelial growth factor.

Although now almost two decades old, the seminal work by Henderson et al remains a cornerstone in our understanding of galectin-3 in liver fibrosis.[114] Their study was among the first to demonstrate that galectin-3 is upregulated in HSCs during fibrogenic activation and directly linked this lectin to the profibrotic response. Galectin-3 expression was temporally and spatially associated with fibrotic septae, with the expression regressing after fibrosis resolution. Hepatic collagen deposition was abrogated through galectin-3 deficiency (*Lgals3*$^{-/-}$) in mice and mediated through the galectin-3-dependent activation of HSCs. The authors observed that galectin-3 deficiency reduced the ability of TGF-β (a central fibrogenic mediator signaling via Smad2/3) to transactivate HSC, even though downstream Smad2/3 phosphorylation in response to TGF-β was similar between wild type and *Lgals3*$^{-/-}$ HSCs.[114] This suggests parallel or downstream effects of the galectin-3-TGF-β interplay that have not yet been fully clarified in liver fibrogenesis. In lung fibrosis, an intriguing mechanism has been described, in which extracellular galectin-3 induces fibrogenic signaling in lung fibroblasts by binding to av Integrins and to the TGFβRII subunit, thereby promoting receptor clustering and pathological TGF-β1 signaling.[124] Whether a similar mechanism operates in HCSs during liver fibrogenesis remains to be established.

The presence of extracellular galectin-3 further facilitates the interaction of HSCs with apoptotic cells through $\alpha_v\beta_3$ integrin-dependent tethering. During this process, galectin-3 expression and release are upregulated in activated HSCs, a response mediated by nuclear factor (NF)-κB signaling.[58]

In contrast, during liver regeneration, galectin-3 acts as an essential modifier of the ECM. Galectin-3-deficient mice failed to establish a regenerative niche for hepatic progenitor cells during 2-week models of dietary and biliary injury.[18] Hepatic progenitor cells and macrophages actively secrete galectin-3 in response to injury, enabling regenerative niche formation and the expansion of hepatic progenitor cells, as well as their adhesion to laminin.[18]

Modulation of Vascular Function

Galectin-3 shapes vascular responses that extend beyond its impact on leucocyte recruitment (detailed in III.I, "Galectin-3 in macrophages"). In particular, it contributes to processes such as neoangiogenesis and proliferative signaling within the vascular microenvironment.[111] Emerging clinical data suggest that galectin-3 inhibition may exert therapeutic benefits by attenuating pathological vascular remodeling and variceal formation, an endpoint that has gained increasing attention in recent clinical trials (detailed in IV, "Galectin-3 as a therapeutic target: evidence from clinical trials").[125] Experimental evidence indicates that treatment with the galectin-3 inhibitor GR-MD-02 not only reduced the degree of liver fibrosis and normalized liver architecture in thioacetamide-treated rats, but also significantly reduced portal venous pressure.[126] While the mechanistic basis of this hemodynamic improvement is not fully clear, accumulating evidence suggests that the hemodynamic benefits of galectin-3 inhibition in portal hypertension arise not solely from structural fibrosis remodeling, but also from direct effects on liver sinusoidal endothelial cells (LSECs), potentially involving improved endothelial phenotype and sinusoidal function.

Galectin-3 shapes vascular responses by stimulating vascular endothelial growth factor (VEGF)-signaling in endothelial cells. It induces the phosphorylation of the VEGF-2 receptor, resulting in increased plasma membrane retention and angiogenic function.[111] The notion of galectin-3-associated LSEC pathology in the setting of fibrosis and cirrhosis is supported by a high galectin-3 signature in liver sinusoidal endothelial cells, which has been linked to endothelial dysfunction.[127]

In breast cancer, MMP-2 and MMP-9-mediated cleavage of extracellular galectin-3 has been shown to induce angiogenesis, with galectin-3 fragments directly stimulating the migration and morphogenesis of endothelial cells.[128] While this mechanism has not yet been replicated in liver malignancies, both MMP-2 and MMP-9 are often upregulated in HCC, and their overexpression is associated with an inferior treatment prognosis.[129,130]

Barriers to Mechanistic Understanding

Although extensive liver disease models have been conducted in galectin-3 knockout mice (*Lgals3*$^{-/-}$), mechanistic interpretation remains challenging due to the protein's diverse subcellular localization and context-dependent functions. Much of today's understanding comes from murine Lgals3$^{-/-}$ knockout models, which lack cell- or compartment-specificity but nonetheless provide valuable directional insights. Intracellular galectin-3 mediates more cell-specific processes, while secreted galectin-3 contributes to intercellular communication, particularly in modulating ECM and regulating fibroblast activity. This functional and spatial heterogeneity makes it challenging to attribute observed phenotypes to specific interactions. A further limitation in the current literature is that we still lack direct evidence showing how structural modifications like cleavage or oligomerization of galectin-3 affect the injured liver. As a result, current models of the role of galectin-3 in liver disease remain largely inferential, highlighting the need for studies that directly map its biochemical states to specific mechanisms during hepatic inflammation and fibrosis. The following section further illustrates the diverse, and at times opposing roles of galectin-3 across the temporal progression of steatosis to steatohepatitis to cirrhosis.

Galectin-3 in Steatotic Liver Disease (MASLD/MASH)

The etiology of chronic liver disease shapes its clinical course, with distinct patterns of progression and outcomes noted in metabolic-associated causes. The trajectory of MASLD involves several key pathological processes, including hepatic steatosis driven by insulin resistance, elevated free fatty acids, and excessive lipid synthesis. These alterations contribute to oxidative stress, inflammation, and, ultimately, fibrosis.[131] The innate immune system, mainly liver-resident (ie Kupffer cells) and recruited macrophages, is a major contributor to the progression of MASLD, with inflammatory responses due to

metabolic injury as well as repair processes during disease regression.[4] More recently, MASLD has been associated with additional changes in the pathological hepatic microenvironment with autoreactive dendritic cells and CD8 T cells that drives disease and confers resistance to immune checkpoint inhibitors in case of malignancy.[132–135] Furthermore, series from America and Europe have noted inferior long-term survival in MASLD-related and ALD-related HCC compared to other etiologies,[136,137] underscoring the prognostic and therapeutic relevance of understanding disease origin.

Emerging evidence indicates that the role of galectin-3 in MASLD progression may vary depending on the disease stage and the predominant mechanism of injury, with differential effects on steatosis and inflammation.[21] *LGALS3* its dynamically regulated in response to diet/steatosis, as demonstrated by models of porcine dietary models. Hepatic *LGALS3* expression closely paralleled lipid droplet accumulation during steatosis induction and declined upon dietary reversal, highlighting its association with hepatic steatosis load.[138]

During the initial development of liver steatosis, galectin-3 appears to exert a protective role. *Lgals3*$^{-/-}$ mice spontaneously developed liver steatosis at 6 months of age and exhibited increased AGE and receptor for AGE (RAGE),[139] indicative of oxidative stress and metabolic dysfunction. Furthermore, galectin-3-deficient animals upregulated lipopolysaccharide-mediated and cancer-associated signaling in response to a choline-deficient L-amino-acid-defined (CDAA) diet.[140] The degree of steatohepatitis was higher between two and four weeks of dietary exposure, but reached similar levels of steatosis and inflammation as their wildtype counterparts after 8 weeks of feeding. Canonical pathway analysis revealed a hepatic upregulation of the platelet-derived growth factor (PDGF) signaling and IL-6 signaling pathways in *Lgals3*$^{-/-}$ animals after 8 weeks of CDAA-feeding.[140]

In contrast to the aggressive CDAA model, which swiftly induces not only steatosis, but also moderate weight loss, severe inflammation and fibrosis, the high-fat diet (HFD) model replicates obesogenic mechanisms and is also suitable for studying inflammatory activity over an extended experimental period.[141] In a murine HFD model, galectin-3 ablation aggravated hepatic steatosis by promoting adiposity and lipid accumulation, consistent with a protective role in early metabolic regulation. The loss of galectin-3 dampened immune activation and disrupted IL-33-dependent profibrotic signaling, thereby attenuating liver inflammation and fibrosis, underscoring its dual role in disease progression.[142] A human biopsy study in pediatric MASLD patients demonstrated an overall decrease of galectin-3-positive cells with rising severity of disease, while α-SMA^{+}/galectin-3^{+} cells, likely activated HSCs, increased, further suggesting stage-dependent expression and function across cell types.[143]

Treatment with a galectin-3 inhibitor (GR-MD-02) reduced MASH activity and fibrosis in rodents, both in early disease and after the establishment of liver fibrosis.[144] In a HFD-feeding rabbit model of MASLD/MASH, the galectin-3 inhibitor selvigaltin attenuated hepatic inflammation and fibrotic remodeling in a dose-dependent manner.[145]

Together, these findings underscore the context-dependent and stage-specific functions of galectin-3 in MASLD, highlighting it as both a potential protective factor (for steatosis), but also as a disease driver and a promising therapeutic target (for inflammation and fibrosis).

Human Studies and Clinical Relevance

Galectin-3 as a Biomarker of Liver Disease

Non-invasive biomarkers can support the detection, staging, and clinical management of chronic liver disease.[146] This need for biomarkers in liver disease is underscored by the high global prevalence of liver fibrosis and cirrhosis, the initial asymptomatic course, and the variable progression to decompensation and cancer.[147,148] In primary liver cancer, reliable biomarkers are essential not only for earlier diagnosis but also for pretreatment risk stratification and for monitoring therapeutic response and disease recurrence.[149,150] Galectin-3 has therefore gained attention as a candidate biomarker, as its systemic levels are elevated across chronic liver diseases and may reflect clinically relevant disease processes.

Serum galectin-3 levels are elevated across a wide range of diseases, such as renal,[151,152] cardiac,[153] and liver disease[154] and are associated with increased all-cause mortality.[151] Because of this, galectin-3 is considered a nonspecific biomarker. Its analysis further requires adaptation to age and biological sex, with females and older individuals presenting with intrinsically higher galectin-3 levels.[151,155]

Across multiple studies in subjects with chronic HCV infection, galectin-3 serum levels showed no significant correlation with viral load or serum ALT, and did not reliably predict liver fibrosis stage.[156,157] However, after successful HCV eradication, serum galectin-3 levels decline.[156] In patients with cirrhosis, galectin-3 levels had considerable discriminating power between compensated and advanced disease stages.[20]

In ALD, systemic galectin-3 levels are elevated,[158] and show good discriminative ability between compensated and de-compensated disease, reaching an area under the curve (AUC) of 0.95.[20] A potential mechanism for galectin-3 accumulation in this setting may be reduced hepatic galectin-3 clearance, as individuals with ALD cirrhosis had similar concentrations between portal vein and hepatic vein galectin-3 concentrations, unlike liver-healthy individuals, where portal venous concentrations were higher than in liver-effluent blood.[158]

Individuals with MASLD have elevated levels of galectin-3.[154] This is also the case across various MASLD-associated cardiometabolic conditions, with elevated galectin-3 serum levels noted in individuals with type II diabetes,[159] diabetes-associated vascular complications,[160] obesity,[161] impaired renal function,[151] elevated blood pressure,[151] and dysregulated serum lipids.[151,162] Serum galectin-3 levels were furthermore associated with elevated liver stiffness, indicative of fibrotic remodeling.[163] An Asian population-based analysis found that higher galectin-3 serum levels were associated significantly with an increased risk of moderate-to-severe liver steatosis.[164]

Cholestatic liver diseases are a heterogenous group of diseases, differing in etiology, pathomechanisms and patterns of injury, and experimental translation remains challenging.[165] In an exploratory cohort, patients with primary sclerosing cholangitis (PSC) had elevated galectin-3 levels, particularly in the presence of concomitant inflammatory bowel disease (IBD).[166] However, overall diagnostic and prognostic evidence on galectin-3 in cholestatic liver diseases is currently limited.

In HCC, galectin-3 is a prognostic marker indicative of aggressive tumor phenotype; patients with high galectin-3 protein or mRNA expression, as well as circulating galectin-3 had inferior overall survival across multiple patient cohorts.[167–170] High *LGALS3* mRNA expression further correlates with a high regulatory T cell signature and the expression of the inflammatory mediators CCL20 and CCR6 in the tumor microenvironment.[168] Gene ontology (GO) analyses demonstrated that *LGALS3*-high tumors are associated with an upregulation of several chemotaxis and leucocyte migration pathways.[170] *LGALS3*-overexpressing tumors had a higher presence of cancer-associated fibroblasts, as well as increased leucocyte infiltration, including enriched activated macrophage signatures, as well as neutrophils, dendritic cells, B cells, $CD8^+$ T cells and $CD4^+$ T cells. Furthermore, a higher expression of a range of checkpoint molecules was found in these tumors, suggesting a suppressive microenvironment, despite leucocyte abundance.[170]

Both protein and gene expression of galectin-3 and its binding partner galectin-3 binding protein (LGALS3BP) were identified as key dysregulated analytes in recurrent HCC compared to non-recurrent tumors,[169] highlighting the association with aggressive disease behavior. In line with this, overexpression of galectin-3 enhances the bone metastatic potential of HCC cells and drives skeletal-related events by fostering a pre-metastatic niche through promotion of osteoclast fusion and podosome formation.[171]

HCC shows overall low response rates to checkpoint inhibitor monotherapy, prompting the adoption of combination regimens to overcome immune resistance.[172] Targeting galectin-3, which contributes to this resistance by promoting immunosuppression, angiogenesis, and fibrosis, has been suggested as a monotherapy or to improve immunotherapy efficacy in HCC. A recent murine study used a subcutaneous cell line (H22) tumor model to study the combined liposomal delivery of the galectin-3 inhibitor GB1107, a PD1-inhibitor, and an androgen receptor antagonist. Monotherapy with GB1107 increased intratumoral $CD8^+$ T cell infiltration as well as IFN-γ and CXCL10 concentrations, and reprogrammed macrophages towards an antitumor phenotype. Importantly, the liposomes exhibited no direct cytotoxicity in vitro, indicating that the therapeutic benefit of galectin-3 inhibition predominantly arose from immune modulation rather than direct tumor cell killing.[173]

Pharmacology of Targeting Galectin-3

The central role of galectin-3 in driving chronic liver disease provides a strong rationale for its pharmacological targeting. However, targeting a molecule with physiologically broad expression throughout tissues, manifold intra- and extracellular interaction partners, and particularly across a progressing and chronic disease, is challenging. Furthermore, patient selection – shaped by factors such as disease stage (from early fibrosis to decompensated cirrhosis), underlying etiology, and the

availability of established treatments, including the recent regulatory approval of drugs like resmetirom for MASLD/MASH[174,175] – constitutes a challenge unique to liver disease. Therapeutic targeting in MASLD/MASH presents additional challenges in stage, population and endpoint selection, that are reviewed in detail elsewhere.[176] We therefore briefly outline the key considerations guiding the therapeutic targeting of galectin-3 (Table 2), before reviewing the human applications to date.

Table 2 Considerations Guiding Galectin-3 Targeting Drug Discovery

Requirement	Rationale	Key Assessments / Metrics	Design Considerations and Examples
I. Pharmacological & formulation requirements			
Pharmacokinetics & bioavailability	Ensure sufficient systemic and hepatic exposure to modulate galectin-3 (extracellular and/or intracellular pools), dose prediction	Oral bioavailability, AUC, Cmax, $t_{1/2}$, hepatic/plasma concentration ratio, Pharmacokinetics variability, PBPK	Conventional or AI-supported PBPK modeling[177] Optimize formulation (oral vs IV)[178] exploit first-pass hepatic uptake or use targeted carriers (eg, liposomes[173])
Tissue distribution	Demonstrate delivery to liver	Liver biopsy: target occupancy, galectin-3 staining	Liposomal or liver-targeted systems;[173] measure pharmacodynamics markers
Selectivity & off-target profile	Avoid cross-reactivity with other galectins or lectins that could reduce safety or efficacy.	KD/IC50 across galectin family, proteome-wide off-target screens, functional assays.	Prioritize molecules with high galectin-3 selectivity[173]
Potency and efficacy	Inhibit galectin-3 at concentrations achievable in vivo	HSC activation readouts, target occupancy	Prioritize molecules with high galectin-3 potency and efficacy
II. Safety/ toxicology			
Safety in chronic liver disease	Minimize infection risk and hepatotoxicity in patients with impaired liver function.	Toxicity studies, liver panels (transaminases, bilirubin), infection surveillance, histopathology.	Conservative dose escalation; include cohorts with cirhosis cautiously; monitor liver function closely; Utilize advanced in vitro models (eg organoids, spheroids).[179]
Drug-drug interactions (DDI)	Consider polypharmacy and DDI, particularly in patients with liver disease	CYP/UGT enzyme profiling, transporter assays (OATP, P-gp), clinical DDI studies versus common co-medications.	Investigate CYP induction, label DDI recommendations[180]
Immunogenicity (for biologicals)	Antibody/peptide therapeutics may elicit ADAs that affect pharmacokinetics, -distribution, and safety.	ADA incidence, neutralizing antibody assays, impact on pharmacokinetics, -distribution, safety and efficacy.	Humanized sequences, immunogenicity risk assessment, longitudinal ADA monitoring[181]
Dosing regimen and route	Chronic liver disease requires tolerable long-term regimens that promote adherence.	Dose-response, exposure-response modeling, trough levels, adherence measures.	Oral administration preferred if bioavailability is adequate;[182] otherwise infrequent parenteral dosing.
Special populations and contraindications	Dose/safety may differ in decompensated cirrhosis, pregnancy, renal impairment.	Pharmacokinetics in hepatic or renal impairment, reproductive toxicology, dose adjustment calculation.	Early attention to decompensating patients; consider pharmacokinetics in hepatic and renal impairment[177,180]
III. Efficacy & endpoints			
Efficacy endpoints (regulatory-relevant)	Demonstrate meaningful antifibrotic effects using accepted endpoints	Histologic steatosis/ fibrosis stage, collagen deposition, transient elastography, clinical outcomes (decompensation).	Combine noninvasive[183] and histologic[175] endpoints; include long-term decompensation and oncological endpoints.
Long-term effects and cancer risk	Chronic immune modulation may affect tumor surveillance and risk of malignancy.	Long-term animal carcinogenicity, cancer incidence surveillance in long-term studies.	Include oncological monitoring for high-risk populations in extensions and subsequent longitudinal observation studies[184]
IV. Manufacturing & regulatory approval			
Manufacturing, stability and formulation	Scalable, stable product meeting distribution requirements for chronic therapy.	Efficient production (high GMP yield), stability studies (shelf life), cold-chain needs, excipient compatibility with the drug for long-term stability	Ideally stable oral formats; liposomal biologics require specialized manufacturing[185]
Regulatory & reimbursement considerations	Align development program with regulatory expectations and payer value frameworks.	Agency feedback, selection of approval-relevant primary endpoints (FDA/EMA), health-economic modeling.	Early regulator engagement (FDA/EMA)[186]

Abbreviations: ADAs, anti-drug antibody; AUC, Area under the concentration-time curve; Cmax, Maximum plasma concentration; CYP, cytochrome P; DDI, drug-drug interactions; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GMP, Good Manufacturing Practice; HSC, Hepatic stellate cell; IV, intravenous; KD, Equilibrium dissociation constant; OATP, Organic Anion Transporting Polypeptides; PBPK, Physiologically based pharmacokinetic (model); P,glycoprotein; $t_{1/2}$, half-life; UGT, UDP-glucuronosyltransferase.

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Recent investigations have increasingly explored oral administration as a means of enhancing patient adherence. Combining the nanostructure Tetrahedral Framework DNA with galectin-3-targeted small interfering RNA (siRNA) succeeded in experimental hepatic drug delivery. As a result of silenced galectin-3 expression, fibrosis was reduced in murine models, and inflammatory macrophage polarization was attenuated.[182]

Galectin-3 as a Therapeutic Target: Evidence From Clinical Trials

Two main compounds are under clinical investigation in human trials of liver fibrosis, the galactopyranoside-derived small molecule GB1211 (Selvigaltin) and the polysaccharide-based GR-MD-02 (Belapectin). A key distinction between the two is their route of administration, with GB1211 given orally and GR-MD-02 delivered intravenously. Despite oral administration, GB1211 demonstrates a favorable bioavailability of approximately 68% in mice.[187] In humans, urinary excretion of GB1211 within 96 hours is higher with tablet formulations (30–36%) compared to capsules (~15%), but results show high interindividual variability, with no consistent differences between healthy participants and those with hepatic impairment (Table 3).[188,189]

The first human trial targeting galectin-3 in liver fibrosis was published in 2016,[190] yet to date, no drug directed against galectin-3 has received regulatory approval. Since then, several human trials have investigated different inhibitors, varying in phase, trial design, compound structure, route of administration, and other pharmacological aspects.

The GT-020 study was the first to evaluate a galectin-3 inhibitor in humans. GR-MD-02, a polysaccharide-based compound, was administered intravenously in three different dosing regimens and was reported as safe and tolerable.[190] Adverse events (AEs) occurred at similar frequencies across groups, were mostly mild, and did not correlate with dosage. GR-MD-02 did not lead to changes in laboratory or clinical parameters compared to placebo. Notably, in the third cohort (8 mg/kg) a significant reduction in FibroTest scores was observed, although this endpoint was not assessed in the other cohorts. To further explore this finding, Harrison et al examined imaging outcomes in patients who received 8 mg/kg biweekly for 16 weeks. No differences were observed between treatment and placebo in iron-corrected T1 (cT1) mapping, liver stiffness by magnetic resonance elastography (MRE), or shear-wave elastography (LSM). Histological validation by liver biopsy was not performed.[22]

In 2020, Chalasani et al published a multicenter, double-blind randomized controlled trial (RCT) conducted across 36 sites.[125] Patients received GR-MD-02 at 4 or 8 mg/kg biweekly for 52 weeks. The primary endpoint – change in hepatic venous pressure gradient (HVPG) – was not met in the overall cohort. However, subgroup analyses revealed reductions

Table 3 Comparing Two Prototypic Galectin-3 Inhibitors GB1211 and GR-MD-02

	GB1211 (Selvigaltin)	**GR-MD-02 (Belapectin)**
Structure	Small molecule from the group of galactopyranosides with additional non-natural aromatic structures[178,188]	Polysaccharide-based drug (galactoarabino-rhamnogalacturonate)[22,125,190]
Administration	Oral[178,188]	Intravenous[22,125,190]
Absolute bioavailability	68% in mice[187]	100%
Relative bioavailability	Higher with tablet formulation compared to capsule[189]	n.a.
Investigated doses	5, 20, 50, 100, 200 or 400 mg once daily as well as 50 or 100mg twice daily[178,188]	2, 4 and 8mg/kg weekly or biweekly[22,125,190]
Urine excretion	High variability in healthy participants and those with hepatic impairment[188] Variable data[178,188]	n.a.
AUC	Dose-dependent[178,188] Higher in patients with hepatic impairment[188]	Dose-dependent[125,190] Potential drug accumulation[190] No direct pharmacokinetic comparison of healthy and liver-impaired individuals
C_{max}	Dose-dependent[178,188] Higher in patients with Child-Pugh C cirrhosis[188]	Dose-dependent[125,190]
$T_{1/2}$	Higher in patients with hepatic impairment[188]	Higher when applied biweekly than weekly[125]

Abbreviations: AUC, Area under the concentration-time curve; C_{max}, maximum plasma concentration; n.a., not available; $T_{1/2}$, half-life.

in HVPG and a reduced incidence of new varices in patients without esophageal varices at baseline. These findings led to the ongoing NAVIGATE trial (NCT04365868), designed to evaluate GR-MD-02 in variceal prevention.[191] Secondary endpoints, including fibrosis stage, NAFLD activity score, and liver-related outcomes, showed no significant changes.[125]

GB1211 (Selvigaltin) represents the first orally available galectin-3 inhibitor, deemed safe and tolerable in healthy individuals.[178] A three-part clinical trial was initiated: parts one and three assessed single-dose pharmacokinetics in patients with hepatic impairment, as compared to healthy individuals (NCT05009680).[188] Part two (phase IIA) investigates repeated dosing in the same population, with results still pending.

Pharmacokinetics of both compounds were altered in the presence of liver disease. For GB1211, pharmacokinetic parameters such as AUC, maximum plasma concentration (C_{max}), and time to peak drug concentration (T_{max}) increased dose-dependently in healthy individuals.[178] Hepatic impairment (Child-Pugh B/C) led to ~60% higher AUC, with elevated C_{max} only in Child-Pugh C, and prolonged half-life.[188,189] GR-MD-02 likewise showed dose-dependent increases in AUC and C_{max} in patients with MASH, with evidence of drug accumulation at 8 mg/kg and a half-life extending beyond 24h with biweekly dosing.[125,190] Although no direct comparison between healthy and liver-impaired subjects has been made, early trials adjusted dosing intervals, underscoring the importance of careful pharmacokinetic monitoring and potential dose adaptation in diseased populations (Table 4).[190]

In conclusion, although galectin-3 inhibitors have progressed into clinical testing with acceptable safety profiles, effective translation remains complex, particularly in light of past trials that failed to meet primary liver-related endpoints.

Table 4 Overview of Published Human Clinical Trials Targeting Galectin-3

Study	Type of Trial	Intervention	n =	Inclusion Concerning Liver Disease	Primary Endpoint	Main Findings
Harrison et al 2016[190] NCT01899859	RCT Phase I study	Belapectin (GR-MD-02) intravenous either 2, 4 or 8mg/kg each four times	Cohort 1: 2mg/kg 4 vs 2 placebo-controls Cohort 2: 4mg/kg 8 vs 2 placebo-controls Cohort 3: 8mg/kg 7 vs 6 placebo-controls	Biopsy-proven NASH with advanced fibrosis (Brunt stage 3)	Safety, tolerability, and dose-limiting toxicity	No difference in incidence and severity of AE No difference in clinical and laboratory parameters (ECG, blood count, electrolytes, renal function, lipid parameters, fasted glucose, urine analysis) FibroTest Score significantly reduced in cohort 3 compared to placebo
Harrison et al 2018[22] NCT02421094	RCT Phase II study	Belapectin (GR-MD-02) intravenous 8 mg/kg Biweekly for 16 weeks	15 vs 15 placebo-controls	Biopsy-proven NASH with advanced fibrosis (Brunt stage 3)	Changes in liver inflammation and fibrosis measured by cT1 mapping Changes in liver stiffness in MRE or LSM	No difference in cT1 No difference in liver stiffness in MRE or LSM
Chalasani et al 2020[125] NCT02462967	RCT Phase IIB study	Belapectin (GR-MD-02) Intravenous 2 or 8 mg/kg biweekly for 52 weeks	54 (2mg/kg) vs 54 (8mg/kg) vs 54 placebo-controls	NASH, cirrhosis, and portal hypertension with a hepatic venous pressure gradient (HVPG) ≥ 6 mmHg	Changes in HVPG at the end of the 52-week period compared with baseline	No difference in changes in HVPG Subgroup analysis for patients without esophageal varices 2mg/kg Belapectin showed a reduction in HVPG (p=0.02) and development of new varices (p=0.03)
Aslanis et al 2023[178] NCT03809052	RCT Phase I study	Selvigaltin (GB1211) Oral 5, 20, 50, 100, 200 or 400 mg once daily or 50 or 100mg twice daily for 10 days	58 vs 20 placebo-controls	Healthy participants	Safety, tolerability and pharmacokinetic profile	No severe AEs Most frequent treatment-emergent AE were gastrointestinal disorders No difference in clinical laboratory evaluation, vital signs, ECG or physical examination

(*Continued*)

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Table 4 (Continued).

Study	Type of Trial	Intervention	n =	Inclusion Concerning Liver Disease	Primary Endpoint	Main Findings
Aslanis et al 2024[189] GALBA-1 trial NCT05747573	RCT crossover	Selvigaltin (GB1211) Oral Single dose 100mg tablet or two 50mg capsules in fasted or fed participants	13 with 1 drop-out	Healthy participants	Plasma and urine pharmacokinetic parameters	GB1211 tablet form shows higher relative bioavailability than capsule No relevant influence of food intake on pharmacokinetics
Aslanis et al 2024[188] GULLIVER-2 trial Part 1 and 3 (part 2 unpublished) NCT05009680	Matched control trial Phase IB study	Selvigaltin (GB1211) Oral Single dose 100mg four times	Parts 1 and 3: 6 individuals with hepatic impairment vs 6 healthy matched controls	Moderate (Child-Pugh B, Part 1) or severe (Child-Pugh C, Part 3) hepatic impairment	Safety, tolerability and pharmacokinetic profile	No adverse events reported No clinically significant changes Total plasma exposure was higher in participants with hepatic impairment than in matched controls

Abbreviations: AE, adverse events; cT1, iron-corrected T1; ECG, electrocardiogram; HVPG, hepatic venous pressure gradient; LSM, shear-wave ultrasonic elastography; MRE, magnetic resonance elastography; NASH, non-alcoholic steatohepatitis; RCT, randomized controlled trial.

Certain subgroups, eg with portal hypertension, may be more likely to benefit from anti-galectin-3 directed treatment, an observation under prospective investigation. However, until comprehensive predictive data will be available across trials and etiologies, it is only possible to speculate whether disease subgroups, eg those with active fibro-inflammatory signaling, elevated hepatic or circulating galectin-3 or with particular etiologies, will derive particular benefit. Therefore, future studies will need to explore potential predictive markers to identify responsive subpopulations and to guide targeted clinical trial designs for galectin-3-directed antifibrotic therapy.

Conclusions and Future Directions

Galectin-3 is a regulator of inflammation, fibrogenesis, and immune remodeling in chronic liver disease, with compelling preclinical evidence supporting its role as both a disease driver and a therapeutic target. Its biological functions are broad and context-dependent. In chronic liver disease, galectin-3 acts as an activator of monocytes and macrophages and drives fibrosis and ECM deposition through the activation of HSCs. Most experimental studies in MASLD indicate that galectin-3 is a driver of steatosis and fibrosis in this etiology, but these effects are likely dependent on disease stage and experimental models. A key experimental gap is the lack of direct evidence linking galectin-3 localization, structure and interaction partners, to liver injury.

Human studies have indicated the relevance of galectin-3 as a biomarker of disease severity, particularly in cirrhosis, MASLD, and HCC. Most cross-sectional analyses report elevated galectin-3 levels across these conditions, correlating with fibrosis burden, inflammation, and overall adverse outcomes. In the future, clinical value would depend on the ability to predict longitudinal changes in disease activity and prognosis. As such, prospective longitudinal analyses of galectin-3 dynamics over the course of chronic liver disease may be valuable to predict major events, such as fibrosis progression, decompensation, or cancerogenesis.

Several clinical studies advanced the translation of galectin-3 inhibition towards antifibrotic therapy. Current trials with GR-MD-02 and GB1211 demonstrate safety and pharmacological activity but have yet to establish consistent clinical efficacy across patient populations. While patients at risk of esophageal varices may derive particular benefit from galectin-3 inhibition, a refinement of predictive biomarkers through translational research is necessary to refine the group of patients who may benefit from galectin-3 inhibition. Possible approaches may include measurement of circulating or serum galectin-3, HSC or inflammatory markers. Several challenges continue to complicate drug development: the pleiotropic and compartment-specific functions of galectin-3, its dynamic and stage-dependent roles in liver disease, variability in pharmacokinetics for galectin-3 inhibitors in patients with impaired hepatic function, and the heterogeneity of underlying etiologies.

Addressing these uncertainties will require refined patient stratification, context-specific targeting strategies, and long-term trials integrating mechanistic biomarkers with clinically meaningful endpoints.

CRediT Statement

IL: Investigation, Visualization, Writing – original draft, DB: Investigation, Visualization, Writing – original draft, IWZ: Investigation, Visualization, Writing – original draft, FT: Conceptualization, Supervision, Writing – review and editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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