Role of extracellular matrix in liver fibrosis regression and regeneration (Review)

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Abstract. The extracellular matrix (ECM), a critical component of the cellular microenvironment, is intimately linked to normal physiological functions and pathological alterations in tissues. In the liver, ECM homeostasis governs key processes including fibrogenesis, fibrosis regression and regeneration. These processes are not only influenced by ECM dynamics but also interconnected through ECM remodeling. These processes are closely related to Hepatic stellate cells and matrix metalloproteinases to a large extent. They are influenced by various pathways such as transforming growth factor-β, hepatocyte growth factor, integrin-linked kinase, Yes-associated protein, regulating their activation, cellular senescence and functional processes. Elucidating the mechanisms regulating ECM alterations holds significant implications for developing therapies targeting liver fibrosis regression and regenerative enhancement. Currently, multiple drugs under research have been shown to affect the progression of liver fibrosis through these related mechanisms. Furthermore, such insights may contribute substantially to preventing malignant lesions, including hepatocellular carcinoma.

Contents

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1. Introduction

The extracellular matrix (ECM), a structural component found in all tissues, provides essential mechanical support while undergoing continuous dynamic remodeling (1). Composed of ~300 core matrisome proteins, together with ECM-modifying enzymes and ECM-associated growth factors (2), the ECM interacts closely with surrounding cells to establish a microenvironment that is critical for maintaining tissue homeostasis (3).

The focus of the present review is on the role of the ECM in liver fibrosis, a condition characterized by a disruption in the balance between ECM synthesis and degradation. Fibrosis develops when ECM deposition exceeds its rate of degradation following liver injury, a process driven primarily by the activation of hepatic stellate cells (HSCs). Several signaling pathways, including Hedgehog, Hippo/YAP and transforming growth factor-β (TGF-β), promote pathological ECM accumulation through their involvement in HSC activation. In addition, matrix proteins themselves contribute directly to fibrogenesis. Conversely, fibrosis regression is associated with HSC inactivation and enhanced ECM degradation, highlighting two complementary therapeutic approaches: Inhibiting excessive ECM production and promoting the removal of accumulated matrix. Although most current antifibrotic therapies target HSCs, the development of effective pharmacological treatments remains at an early stage.

The role of the ECM in liver regeneration was further examined, which is mediated primarily through hepatocyte growth factor (HGF)- and integrin-linked kinase (ILK)-dependent signaling pathways. In this context, the ECM functions predominantly as a structural scaffold and signaling intermediary rather than as a primary regulatory factor. Nevertheless, modulation of ECM composition and architecture represents a promising therapeutic strategy for enhancing liver regeneration. Notably, the physical properties of the ECM and their dynamic alterations may provide important biomechanical cues during the regenerative process, although cytokine-mediated signaling pathways ultimately govern its execution.

In summary, investigating ECM dynamics is essential for advancing our understanding of fibrogenesis and developing

strategies to limit fibrosis progression, elucidating the role of mechano-signaling in liver regeneration, and harnessing ECM-mediated signaling to improve outcomes following liver injury or partial hepatectomy (PHx). These insights may offer significant long-term benefits in preventing the progression of chronic liver diseases and guiding the development of therapeutic approaches for liver malignancies, including hepatocellular carcinoma (HCC).

2. Relationship between ECM and liver injury

Extensive research has demonstrated that the liver is the only solid organ capable of regenerating to restore the liver-to-body weight ratio to the level required for physiological homeostasis following injury or other forms of insult (4). This remarkable regenerative capacity is critical for re-establishing tissue integrity and functional homeostasis after hepatic damage. In response to injury, whether caused by physical trauma, disease, or surgical resection, the liver initiates a complex regenerative program involving both cellular responses, such as hepatocyte proliferation and extracellular alterations, including extensive ECM remodeling. The two-thirds PHx model first established by Higgins and Anderson remains a cornerstone of liver regeneration research (5) and continues to hold substantial clinical relevance for surgical procedures such as hepatectomy (6).

The ECM, which is primarily composed of water, proteins and proteoglycans, provides both physical scaffolding and positional cues that regulate cell adhesion and migration (7). It plays a fundamental role in tissue morphogenesis, cellular differentiation and the maintenance of tissue homeostasis (8). These functions are mediated through a complex network of matrix proteins, including collagen I, elastin, and various proteases, as well as a wide range of cytokines. ECM proteins comprise more than 300 core matrisome components, numerous of which contain multiple independently folded domains. These proteins provide structural support, facilitate cell-matrix adhesion through interactions with integrin receptors, and mediate the transduction of extracellular signals that regulate cellular behavior (9). Cytokines, which are small signaling proteins produced by a variety of cell types, bind to specific cell-surface receptors and activate intracellular signaling cascades that modulate protein activity and gene expression (10). Two major types of ECM have been identified. The first is the basement membrane, which consists primarily of collagen IV, laminins, heparan sulfate proteoglycans, nidogen, and entactin and serves as a specialized supporting structure for epithelial and endothelial cells (Fig. 1). The second is the interstitial ECM, which is secreted predominantly by fibroblasts and provides structural support for connective tissues. During fibrosis, the ECM acquires a more interstitial-like composition characterized by the excessive accumulation of fibrillar collagens I and III, fibronectin, hyaluronan, elastin and proteoglycans (11). A close interplay exists among ECM composition, structural organization, remodeling processes and biological function (12). This highly dynamic microenvironment plays a central role in the pathological and physiological responses that occur following chronic liver injury caused by diverse etiologies, including viral hepatitis, alcohol abuse, drug-induced liver injury, obesity, insulin resistance, metabolic disorders and autoimmune diseases (13).

Studies employing relevant experimental models have demonstrated that liver injury is accompanied by profound alterations in ECM composition and organization. Wound healing and tissue remodeling constitute protective responses that are activated following stress or injury to preserve the structural and functional integrity of the liver. Moderate hepatocellular necrosis and ECM damage typically initiate tissue repair processes, during which hepatocytes restore physiological liver mass through self-replication, replacing necrotic and apoptotic cells (14). Following liver injury, ECM accumulation results from a disruption in the dynamic balance between matrix synthesis and degradation. In cases of acute or self-limiting injury, this accumulation is generally transient and facilitates the restoration of normal tissue architecture. However, persistent injury promotes chronic inflammation, sustained ECM deposition, and the progressive replacement of functional parenchyma with fibrotic scar tissue. This process ultimately culminates in cirrhosis, a condition associated with poor clinical outcomes and high mortality rates (15). Numerous studies have identified viral and parasitic infections, excessive alcohol consumption, and non-alcoholic steatohepatitis (NASH) as major causes of liver fibrosis. A central event in hepatic fibrogenesis is the activation of classical myofibroblast (MF)-like cells, which may originate from HSCs, portal fibroblasts (PFs), or vascular smooth muscle cells (16). In hepatotoxic, viral and alcoholic liver diseases, HSCs represent the predominant source of collagen production. During hepatitis C virus (HCV) infection, HSCs are indirectly activated by TGF-β, C-C motif chemokine ligand 5 (CCL5), and exosomes containing miR-19a and miR-192 released from infected hepatocytes and macrophages (13,17). Under these conditions, the ECM is composed predominantly of type I and type III fibrillar collagens and is characterized by a marked increase in fibronectin deposition. This form of fibrosis exhibits a relatively high potential for regression. Following the cessation of liver injury or successful viral eradication, activated HSCs may undergo apoptosis, senescence, or reversion to a quiescent-like phenotype. Concurrently, matrix metalloproteinase (MMP) activity increases, promoting ECM degradation. However, prolonged injury can induce extensive covalent cross-linking of ECM components, thereby rendering fibrosis increasingly resistant to reversal. By contrast, during cholestatic liver disease, PFs are the first mesenchymal cells to respond to injury and differentiate into MFs, although HSCs also contribute as the disease progresses (18). The ECM in cholestatic fibrosis is enriched in basement membrane-associated proteins, including collagen type IV, collagen type XVIII, laminin and perlecan, and exhibits elevated elastin expression. Regression of this fibrotic phenotype is generally limited because the ECM contains high levels of cross-linking-associated proteins, such as lysyl oxidase-like 1 and latent TGF-β-binding protein 4. These proteins promote the formation of dense, highly stable fibrotic scars that remain largely refractory to degradation, even after removal of the underlying etiological factor. In metabolic liver diseases, including non-alcoholic fatty liver disease and NASH, HSCs likewise serve as the principal source of ECM production. Their activation is driven by free fatty acids, insulin resistance, lipotoxicity and a variety of pro-inflammatory cytokines. ECM remodeling in these disorders is characterized initially by the deposition

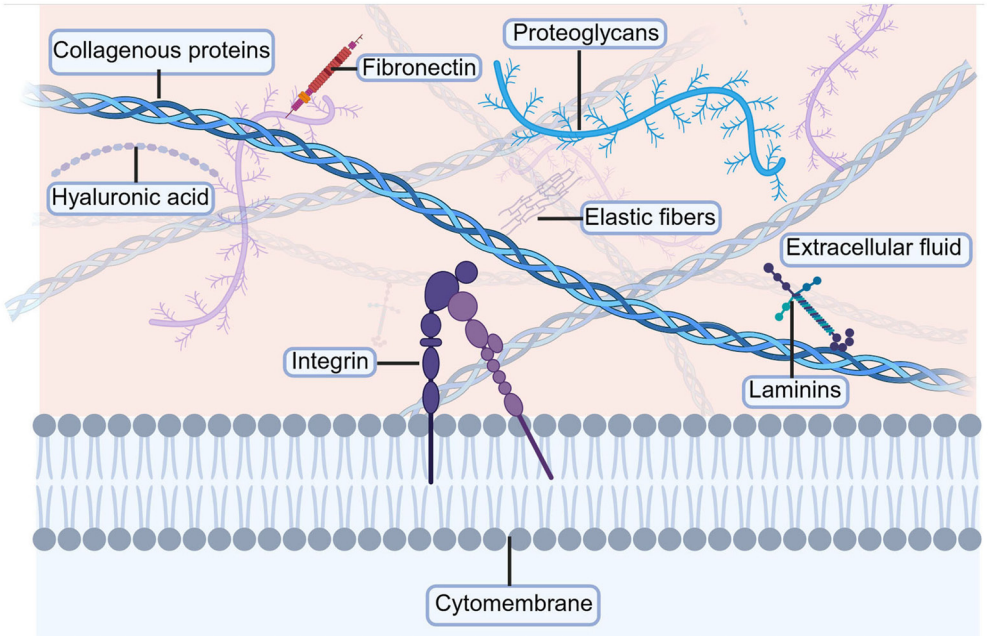

Figure 1. Schematic representation of major components within the ECM. Key structural and functional elements are depicted, including fibrous proteins (collagens, elastic fibers), adhesive glycoproteins (fibronectin, laminins), glycosaminoglycans/proteoglycans (for example, hyaluronic acid), and the cell-ECM linker protein integrin. The schematic also highlights the presence of extracellular fluid. ECM, extracellular matrix.

of type I and type III fibrillar collagens and subsequently by the development of sinusoidal capillarization during advanced disease stages. Although extensive ECM cross-linking limits fibrosis regression in advanced NASH, early-stage fibrosis can be substantially improved and, in some cases, reversed through lifestyle interventions, particularly sustained weight loss (19). It is also noteworthy that the CCl_4 model primarily simulates toxic injury, and its HSC activation trajectories and ECM deposition patterns (predominantly type I/III collagen) differ significantly from those in cholestatic models (enriched in basement membrane proteins) and metabolic models (often accompanied by lipotoxicity). Therefore, caution should be exercised when extrapolating mechanistic conclusions derived from a single model to clinical settings. This also explains why numerous drugs that show efficacy in animal models (for example, CCl_4) frequently fail in humans (for example, NASH/HBV). Hence, appropriate animal models should be selected when investigating corresponding diseases. Therefore, while the CCl_4 model provides valuable mechanistic insights, extrapolating these findings to other etiologies, particularly metabolic or cholestatic liver diseases, requires caution and validation using disease-specific models.

The preceding sections provide a general overview of the ECM and its role in liver fibrosis. For a deeper understanding of the molecular mechanisms underlying ECM remodeling during fibrogenesis, single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics have emerged as powerful investigative tools. One area of particular interest is the heterogeneity of HSCs and their differentiated subpopulations during ECM remodeling. In metabolic dysfunction-associated steatohepatitis (MASH)-related fibrosis, HSCs transdifferentiate into MFs, which serve as the primary source of excessive ECM deposition. Single-cell and spatial transcriptomic analyses have identified an ADAMTSL2$^+$ MF subpopulation that is enriched within fibrotic regions and is involved in the regulation of tumor necrosis factor (TNF) signaling and ECM structural organization (20). Importantly, HSCs exhibit distinct activation trajectories and functional phenotypes across different experimental models of fibrosis. For example, in the carbon tetrachloride (CCl_4) model, activated HSCs are primarily associated with ECM remodeling, whereas in the thioacetamide (TAA) model, they display a more pronounced immune-related activation profile (21). These findings highlight the context-dependent nature of HSC activation and suggest that different fibrogenic stimuli may drive distinct cellular programs. Immune cells, particularly macrophages, also play critical roles in shaping the ECM microenvironment. Multiple macrophage subpopulations have been identified in the liver, including C1QA$^+$, CXCL3$^+$, CXCL10$^+$, scar-associated macrophages (SAMacs) and SPP1$^+$ macrophages, all of which undergo dynamic changes during disease progression (22). Among these populations, SPP1$^+$ macrophages are enriched in HCC and may influence the tumor microenvironment through interactions with T lymphocytes. Distinct macrophage phenotypes are also observed across fibrosis models. In NASH models, immune-associated macrophage subtypes predominate, whereas lipid metabolism-related macrophage populations are more prevalent in CCl_4- and bile duct ligation (BDL)-induced fibrosis. These observations suggest the existence of model-specific immuno-metabolic mechanisms that contribute to ECM remodeling. Spatial transcriptomic analyses have further identified discrete fibrotic niches within liver tissues from patients with MASH. These regions exhibit significant enrichment of ECM-receptor interactions, glycosaminoglycan-binding pathways, and integrin-mediated signaling. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analyses have further demonstrated that these fibrotic regions are strongly associated with ECM structural components and activation of the nuclear factor kappa-B (NF-κB) signaling pathway. Moreover, high-resolution spatial

transcriptomic studies of healthy and fibrotic human liver tissues have revealed a continuous hepatocyte gene-expression gradient along the portal-central axis. ECM-related genes, including collagen type I alpha 1 chain and platelet-derived growth factor receptor beta, were found within newly emerged, non-zonally distributed cellular populations in fibrotic livers, suggesting that ECM remodeling is accompanied by alterations in hepatocyte identity and functional state. The integration of single-cell and spatial transcriptomic datasets using analytical platforms such as CellPhoneDB has enabled the identification of model-specific ligand-receptor interactions among HSCs, macrophages and hepatocytes. For example, vascular cell adhesion molecule, intercellular adhesion molecule and Semaphorins 4 signaling pathways are significantly enhanced in the BDL model, whereas thrombospondin (THBS), tenascin, and macrophage migration inhibitory factor signaling pathways are markedly altered in the CCl_4 model. In the healthy liver, communication among hepatocytes, macrophages and HSCs exhibits pronounced spatial specificity. Portal-zone hepatocytes communicate with macrophages primarily through the TGF-β3-TGF-βR1 signaling axis, whereas central-zone hepatocytes interact with HSCs through the THBS1-CD36 signaling pathway (23).

Liver fibrosis was once considered an irreversible process; however, accumulating evidence from both experimental and clinical studies has challenged this traditional view (24,25). MFs, the principal ECM-producing cells within fibrotic lesions, display characteristics of both smooth muscle cells and fibroblasts. These cells are characterized by abundant rough endoplasmic reticulum, prominent stress fibers, enlarged nucleoli, and expression of α-smooth muscle actin and other contractile proteins (26). Consequently, three major strategies have been proposed to promote fibrosis regression: Rapid elimination of the underlying etiological factor (27), degradation of excess ECM (28) and selective removal of fibrogenic MFs (25). Although these approaches are supported by substantial experimental evidence, most investigations remain limited to animal studies and preclinical drug development. Further research is required to confirm the extent of fibrosis regression in humans and to translate these findings into effective clinical therapies. Despite the potential for fibrosis regression, a portion of the ECM may become effectively irreversible. Following collagen synthesis, extensive enzymatic cross-linking occurs through the activity of enzymes such as LOX, resulting in the formation of highly stable ECM networks (29). In addition, cross-linking mediated by advanced glycation end products substantially alters the structural and biomechanical properties of collagen fibers, thereby exacerbating pathological ECM remodeling (30). The composition of irreversible ECM also undergoes profound qualitative changes. Increased accumulation of insoluble ECM components is strongly associated with progressive liver stiffness (31), while cross-linked elastin becomes highly resistant to degradation and further stabilizes fibrotic scar tissue. Other ECM constituents, including fibronectin, also exhibit alterations in composition and function, collectively contributing to fibrosis progression and the persistence of chronic liver disease.

The liver exhibits a remarkable regenerative capacity, which is one of its defining physiological characteristics. As discussed in the context of fibrosis and the ECM, fibrotic tissue formation and regression, along with ECM remodeling, represent key tissue repair mechanisms that are inherently associated with liver regeneration. However, the outcomes of repair vary considerably depending on the severity and type of injury, as well as regulation by the local microenvironment. Liver regeneration is more precisely described as compensatory hyperplasia, in which the remaining functional tissue expands to restore metabolic demands (32). Evidence suggests that ECM synthesis during the regenerative process contributes to the re-establishment of hepatocyte quiescence and differentiation (33-35). ECM components play essential roles in regulating the initiation, progression and termination of liver regeneration. For example, fibronectin and vitronectin can bind HGF, forming complexes with the Met receptor (HGF receptor) and integrins (ECM receptors), thereby enhancing cell migration (36). In addition, vascular endothelial growth factor interacts with specific fibronectin type III domains within fibronectin and tenascin-C, thereby promoting cellular proliferation (37). Beyond these ECM components, liver regeneration is also tightly regulated by proteolytic enzymes, including MMPs, ADAMs and ADAMTS, which are secreted by various cell types and stored within the ECM (38).

In summary, research on the role of the ECM in liver fibrosis, fibrosis regression and liver regeneration has accumulated over several decades, leading to a relatively comprehensive understanding of its core mechanisms. More recently, advances in experimental technologies and analytical methodologies have enabled increasingly detailed insights into underlying molecular and cellular pathways. These developments are essential for further elucidating the complex functional network regulated by the ECM and for refining current mechanistic models.

3. Relationship between ECM and liver fibrosis

Hepatic fibrosis represents a dynamic pathological process that is frequently initiated as part of the reparative response following liver injury. Although it initially serves as a protective healing mechanism, progressive fibrotic remodeling can significantly compromise hepatic function and contribute to disease advancement (39). Liver fibrosis research relies predominantly on animal models, among which the CCl_4 mouse model is the most widely used toxic-induced system worldwide. A clear understanding of the CCl_4 model requires an appreciation of its metabolic pathway (Fig. 2). CCl_4 is metabolized by the cytochrome P450 superfamily of monooxygenases (CYP enzymes) into the trichloromethyl radical ($\bullet CCl_3$). This highly reactive radical disrupts lipid metabolism, as evidenced by fatty degeneration and hepatic steatosis, and concurrently impairs protein synthesis. Subsequently, trichloro-methyl-peroxy radicals ($\bullet CCl_3OO$), generated through oxygenation of $\bullet CCl_3$, initiate lipid peroxidation and the degradation of polyunsaturated fatty acids. These cascading events reduce membrane integrity across multiple cellular compartments, including mitochondria, the endoplasmic reticulum and the plasma membrane, ultimately leading to hepatic injury characterized by inflammation, fibrosis, cirrhosis and HCC (40). Collectively, this model provides critical mechanistic insights into the pathogenesis of liver fibrosis.

Dissecting the cellular underpinnings of hepatic fibrosis requires examination at the cellular level. HSCs, located in the perisinusoidal space between hepatocytes and sinusoidal endothelial cells, serve as central effectors in liver fibrogenesis. These cells form the primary cellular basis of ECM expansion and represent a direct source of fibrotic tissue formation (41). Under physiological conditions, HSCs remain in a quiescent state; however, following liver injury, they become activated in response to signals released by damaged hepatocytes, immune cells and HSCs themselves, which collectively initiate the fibrogenic cascade (42). Upon stimulation by multiple signaling pathways and cytokines (13,43,44), HSCs transdifferentiate into proliferative, contractile MF-like cells. These activated cells produce and secrete large amounts of fibrogenic mediators and ECM components, including collagens I, III and IV, proteoglycans, glycoproteins, fibronectin and laminin, thereby contributing to tissue repair. However, sustained activation leads to excessive collagen deposition, ultimately driving the progression of hepatic fibrosis and associated functional impairment (41). The key mechanisms linking ECM remodeling and liver fibrosis are summarized in Fig. 3.

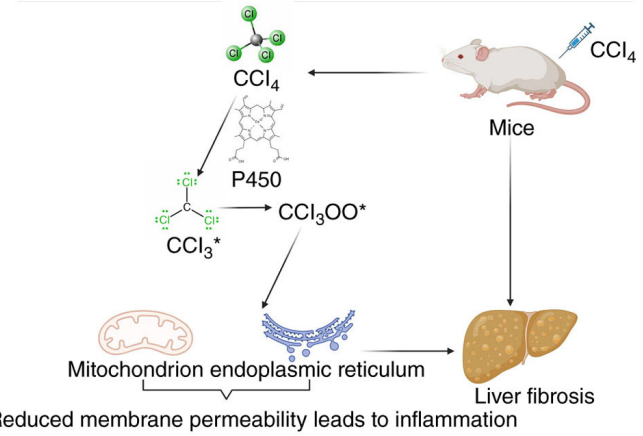

Figure 2. Proposed mechanism of CCl_4-induced hepatotoxicity leading to liver inflammation and fibrosis. CCl_4 is metabolized primarily in hepatocytes by cytochrome P450 monooxygenases (CYP450, predominantly CYP2E1) into the highly reactive trichloromethyl radical (CCl_3). Subsequent oxygenation generates the trichloromethyl peroxyl radical (CCl_3OO), which initiates lipid peroxidation and oxidative damage within key organelles involved in protein/lipid metabolism. Mitochondrial dysfunction and endoplasmic reticulum stress ensue, triggering inflammatory cascades and activating hepatic stellate cells, ultimately promoting fibrogenesis.

Hippo/yap and hedgehog pathways. The Hippo signaling pathway is a critical tumor suppressor pathway that regulates organ size by controlling cell proliferation, survival and differentiation (45). Yes-associated protein (YAP), its central downstream effector, plays a pivotal role in modulating organ size, stem cell renewal and tissue regeneration (46). Differential transcriptional activity of YAP in hepatocytes influences cell fate decisions (47), and its non-cell-autonomous effects may alter the hepatic microenvironment, thereby contributing to chronic inflammation, fibrosis, cirrhosis and carcinogenesis (48). YAP activity is regulated not only by the canonical Hippo pathway but also through crosstalk with other signaling cascades, most notably the Hedgehog pathway (49). Hedgehog signaling regulates cell proliferation, activation and differentiation, and plays a critical role in HSC activation (50). Functional interactions between these pathways occur through Hedgehog effector Gli1 and the Hippo pathway components YAP1 and TEA domain (TEAD) transcription factors (51). Mechanistically, Hedgehog signaling promotes HSC trans-differentiation by activating YAP1 and inducing a shift toward aerobic glycolysis, thereby facilitating the transition from quiescent HSCs to MFs-like cells. This metabolic reprogramming supports HSC activation by providing essential nutrients, including glutamine. Glutamine uptake is mediated by transporters such as the sodium-coupled neutral amino acid transporters SNAT1 and SNAT2 and is subsequently metabolized by glutaminase isoforms glutaminase 1 (GLS1; 'kidney-type') and glutaminase 2 (GLS2; 'liver-type') (49). In activated HSCs, elevated expression of myofibroblastic markers is observed, while inhibition of YAP reduces GLS1 expression, suggesting that Hedgehog signaling regulates GLS1 through YAP-dependent mechanisms (52). Collectively, these findings underscore a critical role for the YAP axis in HSC activation and the progression of liver fibrosis.

TGF-β signaling. TGF-β is a well-established profibrotic cytokine and one of the most potent drivers of fibrogenesis. Following liver injury, its expression is significantly elevated within the fibrotic microenvironment, where it activates SMAD2/3 signaling through TGF-β receptors 1 and 2 (53). This downstream signaling cascade exerts broad regulatory effects on multiple cell types and cytokine networks, thereby contributing to both the promotion and context-dependent modulation of fibrosis progression (54). HSCs, which express multiple TGF-β receptor subtypes (55), represent the primary cellular targets of TGF-β signaling. Mechanistically, TGF-β induces the degradation of tyrosine kinase receptor B (TrkB) in HSCs via the E3 ubiquitin ligase Nedd4-2. Notably, TrkB overexpression suppresses TGF-β/SMAD signaling and attenuates hepatic fibrosis both *in vitro* and *in vivo* (54), indicating a functional antagonistic relationship between TrkB signaling and TGF-β-mediated fibrogenesis. In addition, several bioactive compounds have been shown to interfere with this pathway. Physalin D inhibits TGF-β-induced activation of HSCs (56). Similarly, polysaccharides derived from *Ganoderma lucidum* suppress TGF-β/SMAD signaling and related fibrogenic pathways in CCl_4-induced liver fibrosis models (57). Collectively, these findings underscore the central role of TGF-β signaling in HSC activation and the progression of hepatic fibrosis (58).

Activin A, a member of the TGF-β superfamily (59), exists as homo- or heterodimers, including activins A, B and AB, which are composed of inhibin β-subunits (βA and βB) (60). Fibronectin, a major ECM component associated with both hepatocytes and HSCs (61), is synthesized during HSC activation and contributes to early fibrogenic remodeling. Activin A has been shown to positively regulate fibronectin synthesis in HSCs, although it does not directly promote collagen production (62). In addition, activin A-treated Kupffer cells (KCs) acquire a pro-inflammatory phenotype characterized by increased secretion of TGF-β1 and TNF-α. Elevated activin A levels derived from hepatocytes, liver sinusoidal endothelial cells, or HSCs can activate KCs via paracrine signaling. Subsequently, activated KCs release TGF-β1, TNF-α and other profibrotic mediators, which in turn promote the activation of

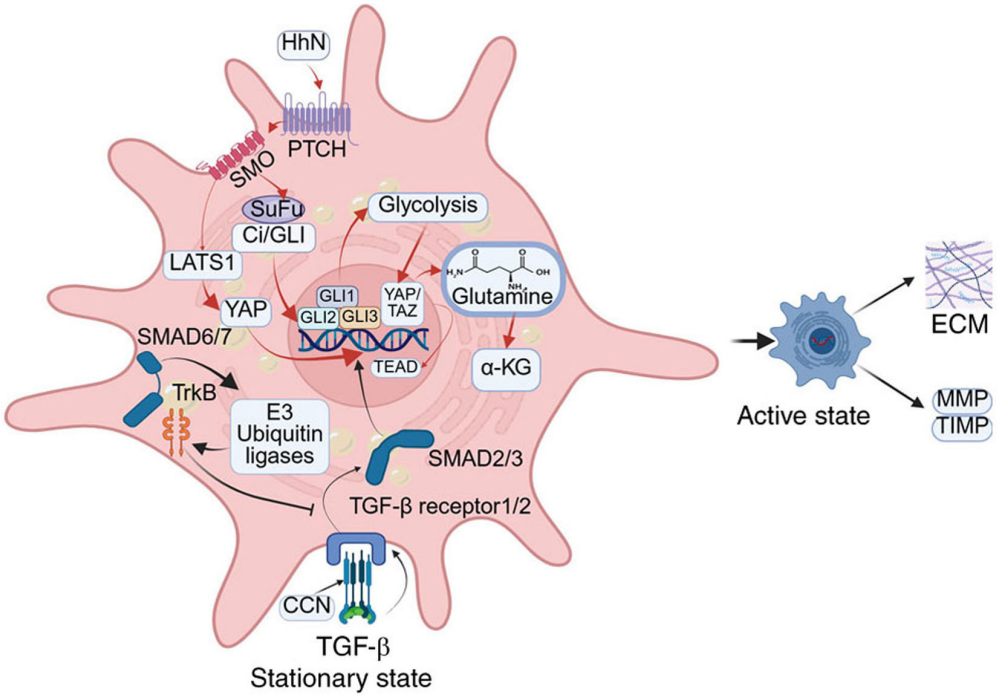

Figure 3. Molecular mechanisms of HSCs activation and ECM production. Quiescent (static) HSCs transition to activated myofibroblasts that produce ECM components (collagen fibers, fibronectin) and matrix proteases (MMPs/TIMPs). Three key regulatory pathways are shown. Hedgehog signaling: HhN ligand binding to PTCH triggers SMO release and GLI activator dissociation from SUFU. Nuclear GLI induces target genes (GLI1/2/3, PTCH), modulating HSC metabolism through glycolysis regulation, HIPPO pathway inhibition (via LATS1 suppression), YAP/TAZ-TEAD signaling blockade, and glutaminolysis promotion yielding α-KG. TGF-β signaling: TGF-β receptor activation differentially regulates pro-fibrotic SMADs (activate fibrogenic genes) and anti-fibrotic SMADs (for example, blocking Nedd4-2-mediated TrkB degradation). Matrix protease pathway: Factors (for example, CCN family) mediate HSC activation via TGF-β-dependent mechanisms. HSCs, hepatic stellate cells; ECM, extracellular matrix; α-KG, α-ketoglutarate; MMP, matrix metalloproteinase; TIMPs, tissue inhibitors of metalloproteinases; CCN, Cyr61/CTGF/Nov.

neighboring HSCs (63). Collectively, these findings highlight the role of activin A in amplifying TGF-β-mediated HSC activation and fibrogenic signaling in the liver.

Matrix proteins and other proteins. Matrix proteins play a pivotal role in the regulation of liver fibrosis. MMPs are key mediators that dynamically regulate cellular state transitions and ECM remodeling during fibrogenesis (64). The Cyr61/CTGF/Nov (CCN) protein family consists of six multifunctional matricellular proteins characterized by conserved structural domains, including insulin-like growth factor binding (IGF), von Willebrand factor type C (vWF), THBS type 1 (TSP1) and a C-terminal (CT) domain (65). Within this family, CCN2 and CCN4 exhibit predominantly profibrotic activity, whereas CCN1, CCN3, CCN5 and CCN6 are generally associated with antifibrotic effects in the context of chronic liver injury. CCN2 overexpression increases hepatic susceptibility to fibrosis (66), and its secretion via extracellular vesicles facilitates the propagation of profibrotic signaling within the hepatic microenvironment (67). Similarly, CCN4 promotes fibrogenesis through integrin-dependent cytoskeletal reprogramming of MF-like cells (68).

CCN1 exhibits context-dependent functional roles in liver fibrosis. It is produced by HSCs as part of the senescence-associated secretory phenotype. In this context, CCN1 binds to integrin α6β1 and induces reactive oxygen species (ROS) accumulation through activation of the Ras-related C3 botulinum toxin substrate 1-NADPH oxidase 1 complex, thereby promoting HSC senescence (69). By contrast, CCN1 can also exert pro-fibrotic effects. It functions as a molecular bridge between phosphatidylserine on apoptotic cells and integrin αVβ3 on phagocytic cells, facilitating apoptotic cell clearance. This process is associated with the release and activation of TGF-β1, which in turn promotes the differentiation of HSCs into MF-like cells (70).

Additional matricellular and regulatory proteins also contribute to HSC activation. For instance, autocrine collagen triple helix repeat containing-1 promotes HSC activation through the TGF-β signaling pathway (71). Similarly, bromodomain-containing protein 4, a member of the BET protein family, drives HSC activation via the P300/H3K27ac/PLK1 signaling axis (72). Collectively, these findings underscore the critical roles of both signaling pathways and ECM-associated proteins in the progression of liver fibrosis, primarily through the regulation of HSC activation and differentiation. A comprehensive understanding of these molecular mechanisms is essential for elucidating fibrogenesis and for the development of targeted therapeutic strategies.

4. Relationship between ECM and liver regeneration

Aberrant ECM remodeling orchestrates hepatic fibrogenesis, whereas subsequent matrix degradation and dynamic reorganization establish a regenerative niche that facilitates the transition from fibrosis to liver regeneration. Liver regeneration primarily proceeds through two mechanisms: The

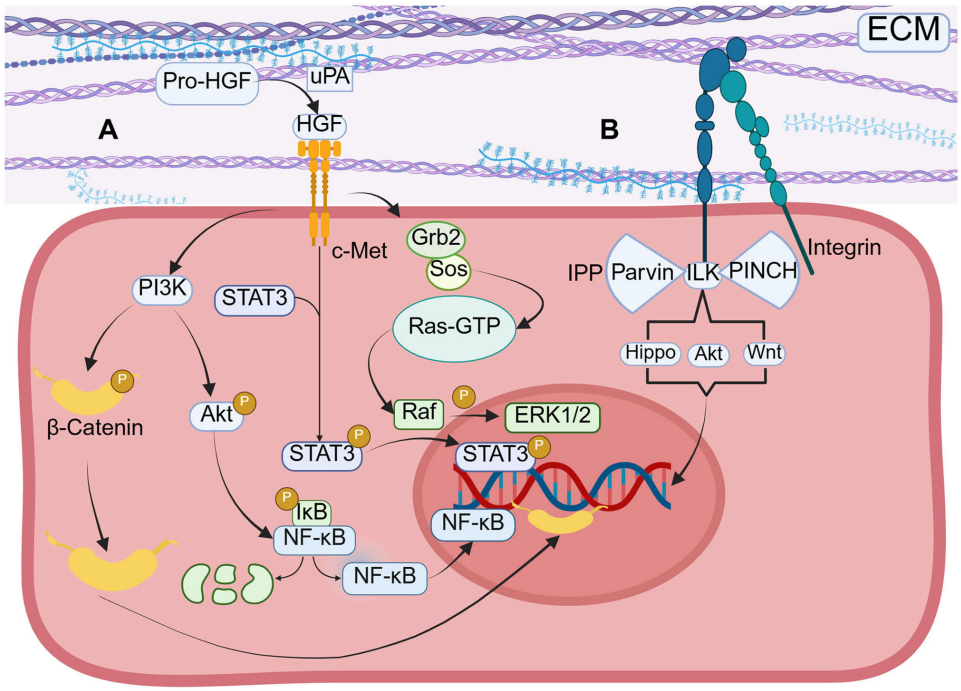

Figure 4. ECM-mediated signaling pathways driving hepatocyte proliferation during liver regeneration. Following liver injury, ECM components initiate proliferative signaling in hepatocytes through multiple cascades. (A) HGF/c-MET axis: Inactive pro-HGF is activated by uPA. Then HGF binding induces c-MET phosphorylation, triggering nuclear translocation of β-catenin (via PI3K); PI3K-dependent IκB kinase phosphorylation to cause NF-κB nuclear translocation; STAT3 phosphorylation, homodimerization and nuclear translocation; Ras/Raf/ERK activation via GRB2-SOS complex. (B) Integrin/ILK axis: Integrin engagement recruits ILK, forming the IPP complex. IPP modulates HIPPO pathway (LATS/YAP regulation), PI3K-Akt survival signaling, and Wnt/β-catenin pathway. These coordinated signals promote cell cycle re-entry and tissue regeneration. ECM, extracellular matrix; uPA, urokinase-type plasminogen activator; IPP, ILK-PINCH-Parvin; HGF, hepatocyte growth factor; ILK, integrin-linked kinase; NF-κB, nuclear factor kappa-B.

differentiation of bipotential oval cells into hepatic parenchymal cells or the re-entry of quiescent hepatocytes into the cell cycle through repeated rounds of proliferation (73). This process, often conceptualized as liver tissue engineering, depends on three essential components: Cellular elements, the ECM and signaling molecules (74). Notably, the contribution of the ECM to liver regeneration is highly context-dependent and is determined by its interactions with cytokines as well as its role in shaping spatial tissue architecture (Fig. 4).

HGF signaling. HGF is a multifunctional peptide cytokine secreted by mesenchymal cells, including HSCs, vascular endothelial cells and KCs (75). It regulates a wide range of cellular processes, including epithelial cell proliferation, motility, morphogenesis and tissue regeneration (76). Its receptor, c-Met, is a heterodimeric protein composed of ligand-binding, transmembrane tyrosine kinase and cytoplasmic domains (77). Following PHx, c-Met undergoes rapid tyrosine phosphorylation, reaching peak activation at ~60 min (78). Upon HGF binding, c-Met is activated and triggers downstream signaling events, including tyrosine phosphorylation and Wnt-independent nuclear translocation of β-catenin (79). This is followed by receptor internalization and subsequent ubiquitin-proteasomal degradation (80). During the early phase of liver regeneration, HGF/c-Met signaling activates multiple downstream pathways, including JAK/STAT3, PI3K/Akt/NF-κB and Ras/Raf cascades, which collectively promote hepatocyte proliferation and survival (81). ECM remodeling is closely regulated by TGF-β signaling (81). Although excessive TGF-β activity drives fibrogenesis, its physiological regulation is essential for normal regenerative processes. In the early regenerative phase, TGF-β-induced ECM deposition contributes to the activation of pro-HGF via integrin-dependent mechanisms (82). Subsequently, active HGF sustains hepatocyte regeneration while limiting excessive ECM accumulation, thereby preventing aberrant fibrotic responses (83,84). Collectively, these interactions highlight a tightly coordinated HGF-c-Met-ECM regulatory axis that balances liver regeneration and fibrosis.

Integrin and ILK. Integrins are heterodimeric transmembrane receptors that mediate bidirectional communication between the ECM and cells by transmitting both biochemical and mechanical signals. ILK, a serine/threonine kinase that binds to the cytoplasmic domain of β1 integrin (85), functions as a key mediator of ECM signal transduction. ILK assembles with PINCH and parvin to form the IPP complex, which acts as a central signaling hub regulating cellular proliferation, differentiation and survival through multiple pathways, including Hippo, PI3K/Akt and Wnt signaling cascades (86,87), via both adaptor and kinase-dependent functions. In hepatocytes, integrin αvβ3 is upregulated following PHx. Pharmacological antagonism using RGDfV impairs murine liver regeneration (88), highlighting the importance of integrin signaling in regulating cell cycle progression, particularly at the G1/S and G2/M transitions (89). By contrast, ILK plays a role in physiological liver regeneration. ILK-deficient mice exhibit a 58% increase in liver mass following PHx (90), prolonged regenerative duration, elevated HGF levels, increased total and phosphorylated protein kinase B (AKT) (91), and upregulated YAP expression. Notably,

the reduction in YAP phosphorylation observed in ILK-deficient mice, an event associated with enhanced proliferative activity, further underscores the complex regulatory role of ILK in coordinating ECM signaling, growth factor activity, and hepatocyte proliferation during liver regeneration.

Spatial geometry architecture. Beyond molecular signaling, hepatic spatial organization is increasingly recognized as a critical determinant of liver function and regeneration. At the macroscopic level, the portal triad (comprising the portal vein, hepatic artery and bile duct) and the central vein together establish a highly structured vascular network that is essential for delivering oxygen and nutrients required for effective liver regeneration (92-94). At the cellular level, the adult liver is composed primarily of hepatocytes (~60%), along with cholangiocytes (3-5%) and mesenchymal cell populations, including HSCs (~8%), KCs (~15%) and endothelial cells (15-20%) (95). Within this multicellular environment, the multipolar organization of hepatocytes is maintained through coordinated interactions with the ECM, cell adhesion systems and cytoskeletal architecture (96,97).

ECM remodeling following liver injury, including fibrotic deposition, exerts dual and context-dependent effects on hepatic regeneration (20). From a spatial perspective, the ECM provides a structural scaffold that facilitates the localization and presentation of signaling molecules. However, excessive fibrosis can isolate damaged regions, such as regenerative nodules, and may also create a permissive niche that shields malignant cells from immune surveillance (98,99). From a biomechanical perspective, increased ECM stiffness promotes the nuclear translocation of mechano-transducers, including YAP and transcriptional coactivator with PDZ-binding motif (TAZ) (100), both of which are essential for liver regeneration (101). In response to changes in matrix rigidity, cells reorganize cytoskeletal stress fibers and generate increased traction forces, which interface with growth factor signaling pathways to drive proliferative responses (102,103). These principles have been increasingly exploited in tissue engineering strategies. Biomimetic scaffolds incorporating growth factors and ECM components, such as three-dimensional collagen matrices, nanofibrous galactosylated chitosan, and decellularized liver scaffolds, have been developed to support hepatic regeneration (104-107).

Collectively, these perspectives, encompassing cytokine signaling, mechano-transduction and spatial tissue architecture, highlight the multifaceted role of the ECM in liver regeneration. Compared with the extensive body of research focused on ECM involvement in fibrosis, investigations into ECM-mediated regenerative processes remain relatively emergent, yet they are increasingly revealing novel mechanistic insights and therapeutic opportunities.

5. Relationship between ECM and regression of liver fibrosis

As previously discussed, it has long been widely accepted that liver fibrosis resulting from chronic liver injury or liver disease is largely irreversible (108). This view has posed significant challenges for the development of effective antifibrotic therapies. However, evidence from sequential liver biopsy studies

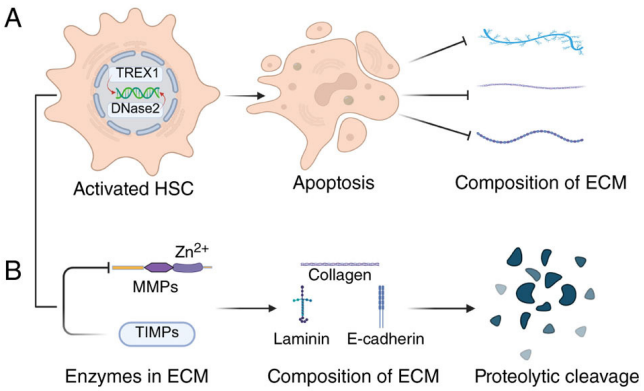

Figure 5. Dual therapeutic strategies for liver fibrosis regression. (A) HSCs clearance: Senescence and apoptosis of activated HSCs are induced through altered expression of DNA homeostasis regulators (DNase II, TREX1), reducing synthesis of key ECM components including collagens (I, III, IV), proteoglycans, glycoproteins, fibronectin and laminin. (B) Targeted ECM degradation: MMPs overcome inhibition by TIMPs to degrade structural ECM components (collagens, laminin, E-cadherin), facilitating matrix remodeling. HSCs, Hepatic stellate cells; ECM, extracellular matrix; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors of metalloproteinases; TREX1, three-prime repair exonuclease 1.

indicates that removal of the underlying etiological factors can lead to regression of hepatic fibrosis in patients with secondary biliary fibrosis, hepatitis C, hepatitis B, NASH and autoimmune hepatitis (109-113). These observations are of considerable clinical importance, as they provide a foundation for therapeutic strategies aimed at restoring normal liver structure and function. Both clinical and animal model studies (114-116) suggest that fibrosis regression is a dynamic and multifactorial process. Key mechanisms include reduced production of pro-inflammatory and profibrogenic cytokines, enhanced collagenolytic activity, clearance of activated HSCs, suppression of ECM synthesis and progressive dissolution of fibrotic scar tissue (58,117). With respect to ECM remodeling, two major therapeutic strategies have been extensively investigated: Targeting HSC clearance and enhancing MMP activity. These approaches represent complementary modes of ECM regulation, in which HSC clearance reduces the source of fibrogenic activity, while metalloproteinase activation promotes degradation and removal of accumulated fibrotic matrix. Accordingly, effective ECM-targeted therapy requires coordinated modulation of both cellular and matrix components to achieve fibrosis regression (Fig. 5).

HSCs. The preceding section highlighted the central role of HSCs in the pathogenesis of liver fibrosis. Early research primarily focused on HSC activation as the principal driver of fibrogenesis. However, more recent evidence suggests that fibrosis regression is closely associated with HSC senescence, as the senescence of activated HSCs contributes to fibrosis regression by eliminating a major source of ECM production (118). Notably, senescent activated HSCs accumulate in chronically injured livers. Although these cells remain metabolically active, they exhibit a stable cell-cycle arrest accompanied by a distinct gene expression profile. They also secrete a range of bioactive molecules and cytokines that regulate immune surveillance, inflammation, fibrogenesis and fibrosis regression (119,120). This senescence-associated phenotype is characterized in

part by the downregulation of DNase2 and three-prime repair exonuclease 1, both of which are involved in cytoplasmic DNA clearance (121). Functionally, senescent HSCs contribute to reduced ECM accumulation through multiple mechanisms, including suppression of B-cell lymphoma 2 expression, decreased synthesis of ECM components, and increased expression of ECM-degrading enzymes. In parallel, induction of HSC apoptosis represents an additional therapeutic strategy supported by experimental models. Selective depletion of activated HSCs has been shown to promote fibrosis regression. In murine systems, this can be achieved through several approaches, including genetic targeting via herpes simplex virus thymidine kinase expression under the glial fibrillary acidic protein promoter combined with ganciclovir administration, as well as pharmacological interventions such as gliotoxin, sulfasalazine, IκB kinase inhibition, and anti-tissue inhibitor of metalloproteinases (TIMP) antibodies (122,123). Collectively, these strategies have demonstrated significant efficacy in reducing fibrosis in experimental models.

MMPs. MMPs are a zinc-dependent endopeptidase superfamily that play an essential role in ECM degradation. Hepatic homeostasis is maintained through a dynamic balance between MMPs and their endogenous inhibitors, TIMPs. The MMP/TIMP ratio is a critical determinant of ECM composition and remodeling activity within the liver. Under physiological conditions, different MMP subtypes selectively degrade specific ECM components according to their distinct substrate specificities (124). Given the functional diversity of the MMP family, a detailed understanding of their individual roles in fibrosis regression and liver regeneration requires subtype-specific analysis (125). Accordingly, this section focuses on MMP subtypes that have been most strongly implicated in fibrosis regression and are supported by established experimental and clinical evidence.

MMP-1 is a collagenase that degrades collagen types I and III and plays a key role in the remodeling of cirrhotic scar tissue. In TAA-induced fibrotic rat models, transient overexpression of human MMP-1 has been shown to effectively reduce established liver fibrosis and promote hepatocyte regeneration by enhancing collagen degradation and stimulating hepatocyte proliferation (126). MMP-2 is expressed in human fibrotic livers and has been implicated in promoting HSC proliferation. However, its functional role remains complex and incompletely defined, although some studies suggest an association with attenuated fibrosis progression (127). MMP-3 (stromelysin-1) degrades multiple ECM components, including collagen types II, III and X, laminin, fibrillin and E-cadherin. In addition, it activates pro-collagenases such as MMP-1, MMP-8 and MMP-13, thereby indirectly amplifying collagen degradation (128). MMP-9 (gelatinase B), primarily secreted by KCs, is upregulated during KC activation and is activated by plasmin and stromelysins (129). Notably, overexpression of a catalytically inactive MMP-9 mutant (E402Q) in CCl_4-treated rats significantly reduced liver fibrosis and decreased HSC trans-differentiation. This effect is attributed to the mutant's ability to competitively displace endogenous MMP-9 from TIMP-1, thereby enhancing overall ECM degradation. MMP-10 (stromelysin-2) is upregulated in macrophages following liver injury and promotes M2 macrophage polarization (130). During PHx or BDL, MMP-10 expression increases, whereas its deficiency impairs resolution of necrotic tissue and exacerbates liver injury, suggesting an important role in liver repair and regeneration (131). In addition, other MMP family members, including MMP-12, MMP-13 and MMP-14, have also been implicated in the regulation of fibrosis progression (132-134); however, further evidence is required to fully elucidate their specific roles.

Other matrix proteins. In addition to MMPs, other ECM-associated proteins also play critical roles in liver fibrosis regression, including members of the CCN protein family described previously. The CCN family comprises six multifunctional matricellular proteins, each characterized by conserved structural domains, including an IGF-binding domain, a vWF domain, a TSP1 domain, and a CT cysteine knot motif. Notably, all members except CCN5 contain this complete set of four domains. Through these conserved structural modules, CCN proteins regulate extracellular signaling and modulate cell-matrix and cell-cell interactions across a wide range of biological processes (65). However, CCN-mediated regulation is highly context-dependent and exhibits dual functional effects in liver fibrosis. Specifically, CCN2 and CCN4 are generally associated with profibrotic activity, whereas other family members exert predominantly antifibrotic effects. For example, CCN1 (Cyr61) mediates antifibrotic effects by binding integrin α6β1 and inducing ROS accumulation via the RAC1-NADPH oxidase 1 complex, ultimately promoting cellular senescence in activated HSCs and PFs (69). In addition, CCN3 overexpression has been shown to suppress fibrosis-associated signaling by downregulating CCN2 and CCN4 expression in fibroblasts. CCN5, which lacks the CT heparin-binding domain present in other CCN proteins, functions as a dominant-negative regulator that inhibits CCN2-mediated fibrogenic activity (135,136).

In summary, liver fibrosis regression is primarily driven by coordinated ECM degradation and the modulation of HSC activity, with matrix-associated proteins playing central and multifaceted regulatory roles in this process.

6. Drug therapy for liver fibrosis based on ECM

The treatment of liver fibrosis remains in the early stages of development and is currently dominated by pharmacological intervention strategies. In the present study, relevant therapeutic agents were identified through a systematic review of drug-related clinical trials available in public databases [ClinicalTrials.gov (https://clinicaltrials.gov/)]. The selection criteria included: i) Completed or ongoing trial status, ii) a clearly defined pharmacological classification or mechanistic description of the drug, and iii) detailed information regarding its application in the treatment of liver fibrosis (Table I). Based on these criteria, a subset of drugs targeting the ECM was further analyzed in depth. These agents were evaluated with respect to their mechanisms of action, therapeutic advantages and limitations, clinical applicability, and potential future development prospects.

HSCs targeted therapy. As previously discussed, targeting the proliferation and activation of HSCs represents a promising

Table I. Drug research related to the treatment of liver fibrosis (Status is based on the latest update in ClinicalTrials.gov as of the retrieval date).

NCT Number	Study	Study status	Interventions	Phase	Mechanism
NCT05542615	Prolonged release pirfenidone for advanced residual liver Fibrosis (MINERVA).	Recruiting	Prolonged-release pirfenidone	Phase 2	Anti-fibrotic and anti-inflammatory molecule that suppresses TGF-β, TNF-α, IL-1, IL-6 and NF-κB activation, thereby reducing TNF-α and IFN-γ levels.
NCT05224128	Effect of Imatinib in patients with advanced liver fibrosis	Unknown	Imatinib	Phase 1/ Phase 2	A PDGF tyrosine kinase inhibitor that upregulates miR-124 and interferes with the IL-6/STAT3 signaling cascade, suppressing HSC activation.
NCT04727320	The clinical application of Tauroursodeoxycholic Acid in patients with liver fibrosis	Unknown	Tauroursodeoxycholic acid	Early Phase 1	A conjugated bile acid (UDCA + taurine) exerting anti-inflammatory, hepatoprotective, litholytic and lipid-lowering effects.
NCT03957629	Optimized Treatment of Peginterferon Alfa 2a in treatment experienced patients With HBV Related liver fibrosis	Unknown	Tenofovir + PEG-Interferon alfa 2a	NA	PEG-IFN α-2a promotes HBsAg and HBeAg seroconversion, exhibits anti-tumor benefits, and may reduce hepatocarcinogenesis (drug essence not specified).
NCT03770936	Effect of some drugs on liver fibrosis	Recruiting	Candesartan/Ramipril	Phase 3	Angiotensin receptor blockers (ARBs) and ACE inhibitors that target the renin-angiotensin system, block AT1 receptor-induced HSC proliferation and Kupffer cell activation and suppress downstream effectors such as TGF-β1.
NCT03486899	A study of experimental medication BMS-986036 in adults with NASH and Stage 3 Liver Fibrosis	Completed	BMS-986036 (Pegbelfermin)	Phase 2	A PEGylated recombinant human FGF21 analogue with extended half-life enabling weekly dosing for NASH-related liver fibrosis.
NCT03420768	A study of experimental medication BMS-986263 in adults with advanced hepatic fibrosis after cure of Hepatitis C	Completed	BMS-986263	Phase 2	Retinol-conjugated lipid nanoparticles containing HSP47 siRNA; bind to retinol-binding protein for HSC-specific delivery, silence HSP47, disrupt collagen deposition, and promote HSC apoptosis.
NCT03059446	Rollover study of Cenicriviroc for the treatment of liver fibrosis in participants with NASH	Terminated	Cenicriviroc	Phase 2	A dual CCR2/CCR5 antagonist that blocks CCR2+ macrophage-driven inflammation, angiogenesis and HSC activation, as well as CCR5-mediated direct fibrogenic effects.
NCT02499562	A Phase II clinical trial of Hydronidone Capsules (F351) in patients with liver fibrosis induced by HBV chronic hepatitis	Completed	Hydronidone (F351)	Phase 2	Reduces TGF-β1 expression and hydroxyproline production, attenuating liver fibrosis progression after chronic injury (drug essence not specified).
NCT02241616	Traditional Chinese Medicine combined with entecavir to treat refractory liver fibrosis in liver cirrhosis due to HBV	Unknown	Entecavir + Fuzheng Huayu (FZHY) + TCM granules	Phase 4	FZHY (composed of 6 herbs) reshapes the liver matrix, inhibits HSC activation, and reduces hepatocyte damage.
NCT02230670	A study of IDN-6556 in subjects with liver cirrhosis	Completed	IDN-6556	Phase 2	A pan-caspase inhibitor that blocks the cysteine protease family, thereby inhibiting apoptosis and inflammatory/ immune responses triggered by cell death.

Table I. Continued.

NCT Number	Study	Study status	Interventions	Phase	Mechanism
NCT02030977	The effects of resveratrol supplement on biochemical factors and hepatic fibrosis in patients with NASH	Completed	Resveratrol	Phase 2/ Phase 3	A polyphenol dietary supplement that activates Sirt1, inactivates NF-κB, and inhibits TNF-α, protecting the liver from steatosis and fibrosis.
NCT01707849	The impact of everolimus-based immunosuppression in the evolution of hepatitis C fibrosis after liver transplantation	Completed	Everolimus	Phase 3	An mTOR inhibitor that blocks mTOR signaling, which plays a pivotal role in HSC activation, thereby affecting hepatitis C fibrosis progression after liver transplantation.
NCT01051219	Anti-fibrotic effects of Losartan in NASH evaluation study	Completed	Losartan	Phase 3	An angiotensin II receptor antagonist (AIIA) that targets AT1 receptor signaling, reduces activated HSC deposition, and inhibits inflammation and fibrosis.

NASH, non-alcoholic steatohepatitis; HSC, hepatic stellate cell.

therapeutic strategy for liver fibrosis. Representative agents include candesartan and ramipril, which function as angiotensin II type 1 (AT1) receptor blockers and angiotensin-converting enzyme inhibitors, respectively (137). In the healthy human liver, HSCs do not express the AT1 receptor. However, during chronic liver injury, HSCs transdifferentiate into MF-like cells that acquire AT1 receptor expression. Angiotensin II subsequently upregulates TGF-β1 mRNA expression in KCs, thereby establishing a positive feedback loop within the hepatic microenvironment. In this context, TGF-β1 further activates HSCs, which in turn amplify TGF-β1 production, reinforcing fibrogenic signaling through AT1 receptor-dependent mechanisms. The aforementioned pharmacological inhibitors disrupt this pathway, thereby suppressing HSC activation and proliferation, reducing ECM deposition, and ultimately contributing to fibrosis attenuation (138). Notably, related clinical studies have not consistently stratified patients according to fibrosis stage, instead evaluating the effects of these inhibitors across a broad spectrum of liver fibrosis severity. Although a substantial number of such studies exist (139-141), numerous are limited by small sample sizes and incomplete clinical trial phases. In addition, potential adverse effects associated with these agents must also be carefully considered. Another emerging therapeutic approach is BMS-986263, a retinol-conjugated lipid nanoparticle delivering small interfering RNA (siRNA) targeting heat shock protein 47 (HSP47) (142). HSP47 is a molecular chaperone that binds to triple-helical procollagen within the endoplasmic reticulum, preventing improper folding or aggregation of collagen molecules. In preclinical models, HSP47 expression is markedly upregulated in fibrotic tissues, suggesting its involvement in pathological collagen accumulation and fibrogenesis. Silencing HSP47 via siRNA is therefore proposed to attenuate fibrosis by reducing excessive collagen deposition following liver injury, potentially through effects on activated HSCs. This strategy has also been evaluated in patients with advanced liver fibrosis; however, its clinical application is limited by notable infusion-related adverse reactions, which may hinder broader therapeutic adoption.

Imatinib, which interferes with the IL-6/STAT3 signaling axis, has also been shown to suppress HSC activation and proliferation through distinct molecular mechanisms. Additional pharmacological strategies targeting HSCs include cenicriviroc, a dual antagonist of chemokine receptors CCR2 and CCR5, as well as the mammalian target of rapamycin inhibitors rapamycin and everolimus (143). However, the current evidence base for these agents remains limited. In most cases, investigations are largely confined to preclinical animal studies, with relatively superficial mechanistic characterization and a lack of robust clinical validation.

ECM targeted therapy. At present, there remains a lack of substantial clinical evidence regarding the efficacy of pharmacological agents that directly target the ECM in the treatment of liver fibrosis. Although several compounds have been proposed and supported by preliminary mechanistic studies, detailed investigations specifically addressing ECM-targeted therapeutic effects remain limited (142). More recently, research attention has shifted toward immunomodulatory strategies, particularly immune cell-based therapies. For instance, reparative macrophages exhibit high expression of MMP12 and

MMP13, promote HSC apoptosis, facilitate ECM degradation, and enhance the clearance of apoptotic cells (144). However, despite these promising preclinical findings, immunotherapy faces significant translational challenges, including patient heterogeneity and difficulties in defining an optimal therapeutic window, both of which limit its clinical applicability.

The aforementioned therapeutic strategies primarily target the ECM and its cellular source, HSCs. However, it is well recognized that the ECM plays a critical role not only in the normal liver but also during the regenerative process following liver injury. As previously discussed, the ECM contributes to the construction of the hepatocyte-associated microenvironment in the healthy liver, and during liver regeneration, it serves as a temporary scaffold to support HGF/c-Met signaling and hepatocyte proliferation. Consequently, these therapies, while addressing liver fibrosis, may also affect normal physiological responses or the regenerative capacity of the injured liver. Therefore, careful consideration of the timing and dosage of these agents is essential, and further clinical trials are needed to provide evidence-based guidance. In addition, monitoring of liver fibrosis is of great importance, as it is useful for determining the optimal time for drug withdrawal or for initiating the use of relevant inhibitors (for example, those that enhance TIMP responses).

Other approaches. Besides the aforementioned mechanisms, two additional important aspects of pharmacological research in liver fibrosis include the use of hepatoprotective agents and the treatment of underlying etiologies to reduce cause-specific fibrogenesis. Hepatoprotective agents primarily function by suppressing hepatic inflammation, protecting hepatocytes, and exerting antioxidant effects. Commonly used drugs in this category include glycyrrhetinic acid preparations (for example, magnesium glycyrrhizinate injection and diammonium glycyrrhizinate enteric-coated capsules), silymarin (145), and polyene phosphatidylcholine (146). Ursodeoxycholic acid exhibits similar hepatoprotective properties, including promotion of bile flow, protection of liver function, dissolution of gallstones, reduction of serum lipid levels, and anti-inflammatory effects. In addition, several traditional Chinese medicine formulations also demonstrate hepatoprotective activity, such as Fuzhenghuayu Capsules, Anluo Huaxian Pills, and Compound Biejia Ruangan Tablets. Among these, Fuzhenghuayu Capsules have been extensively studied and consist of six herbal components processed under standardized quality control and manufacturing procedures. Experimental and clinical evidence suggests that Fuzhenghuayu Capsules can remodel the hepatic ECM, inhibit HSC activation, and reduce hepatocyte injury (147). Another important therapeutic category includes antiviral agents, such as tenofovir alafenamide and tenofovir disoproxil fumarate (148), which act by targeting the underlying viral etiologies of liver disease and thereby preventing progression to fibrosis.

Overall, current research on the treatment of liver fibrosis remains at a relatively early stage, with most evidence derived primarily from animal studies, which poses significant challenges for clinical translation. Among the more extensively investigated strategies, such as AT1 receptor inhibitors and HSP47 mRNA silencing approaches, human trials have been conducted in both early- and late-stage liver fibrosis, demonstrating measurable but variable efficacy. Nevertheless, it should be emphasized that these studies are generally limited by extremely small sample sizes, and expanding well-powered clinical cohorts represents a critical direction for future research. Within the context of ECM-targeted therapies, immunotherapy has emerged as a relatively novel approach. It promotes HSC apoptosis through macrophage-mediated phagocytosis and related signaling pathways, partially overlapping with mechanisms described for several pharmacological agents discussed previously. However, immunotherapeutic strategies face inherent limitations, including pronounced interindividual variability in immune responses and the potential risk of off-target or excessive cytotoxic effects. In advanced liver fibrosis, where disease burden is severe, conventional pharmacological interventions often fail to achieve satisfactory therapeutic outcomes. Although the aforementioned agents may confer certain benefits, their efficacy is markedly reduced compared with that observed in early-stage fibrosis. Therefore, effective management of liver fibrosis requires a comprehensive etiological approach, including antiviral therapy, anti-inflammatory treatment and hepatoprotective agents, aimed at eliminating the underlying causative factors and improving hepatic function. In combination with adjunctive strategies targeting HSC activation and ECM degradation, this integrated therapeutic framework may offer a more effective approach for the management of liver fibrosis.

7. Conclusion

Based on the aforementioned discussion, the ECM plays a central role in liver regeneration, liver fibrosis and fibrosis regression. These processes are fundamentally governed by a dynamic equilibrium within ECM remodeling and turnover. Among them, liver fibrosis represents the most extensively studied area, reflecting its long-established association with ECM dysregulation and chronic liver injury. By contrast, research on fibrosis regression remains relatively limited, largely due to the scarcity of effective ECM-targeted therapeutic strategies. Current interventions primarily focus on either reducing ECM production by targeting its cellular sources, such as HSCs, or enhancing ECM degradation through MMP-mediated pathways. However, investigations in these directions are still ongoing and remain incompletely defined. Liver regeneration, by comparison, is the least explored aspect of ECM biology. In this context, the ECM functions predominantly as a structural and regulatory mediator of signal transduction rather than as a direct effector, resulting in relatively fewer mechanistic studies and therapeutic targets. Nevertheless, these three biological processes, occurring within and in interaction with the ECM, exhibit a high degree of interconnected signaling complexity in the regulation of liver repair and regeneration. Importantly, signaling events within these pathways are closely coupled to the physical architecture and dynamic remodeling properties of the ECM. Therefore, elucidating the intrinsic biophysical and biochemical properties of the ECM, and clarifying how these properties regulate key signaling networks in liver regeneration, represents a promising and important direction for future research.

Furthermore, future research should extend beyond the ECM itself. While elucidating the fundamental properties of the

ECM remains essential, a comprehensive understanding also requires investigation of its interactions with surrounding hepatic parenchymal and non-parenchymal cells. This includes its roles in shaping the microenvironment, providing structural support, regulating cytokine sequestration and availability, and mediating mechano-transductive signaling. In summary, examining the ECM within the integrated context of the liver as a whole organ is likely to yield more accurate and physiologically relevant insights into liver pathology than studying the ECM in isolation.

Returning to the core research areas, liver fibrosis, fibrosis regression and liver regeneration, their close association with the ECM underscores ECM targeting as a rational therapeutic strategy, as already reflected in current clinical and experimental practice. Pharmacological agents such as candesartan, imatinib, and losartan exemplify this approach by modulating HSC activity, the principal source of pathological ECM deposition, thereby contributing to antifibrotic effects. Nevertheless, drug development in this field remains at a relatively early stage. As noted previously, most studies are characterized by a narrow investigative scope, with numerous candidate agents remaining confined to preclinical or early experimental phases, which presents substantial challenges for clinical translation. In addition, a considerable proportion of investigated compounds primarily target upstream disease etiologies rather than ECM-specific fibrogenic mechanisms, thereby offering limited direct insight into ECM-centered fibrosis regulation. Accordingly, broadening research perspectives and integrating multi-level mechanistic approaches will be essential for advancing more effective therapeutic strategies for liver fibrosis.

A review of the available literature and clinical research findings highlights several important limitations in current drug development for liver fibrosis. First, the scope of pharmacological investigation remains relatively narrow, with most studies focusing on a limited set of agents or poorly characterized compounds, which often exhibit low translational efficiency to clinical practice. Second, although numerous pharmacological studies have been conducted, a substantial proportion have either failed to demonstrate meaningful long-term outcomes or have been discontinued, resulting in limited cumulative progress in the field. Third, the selection of therapeutic agents frequently prioritizes the underlying etiologies of liver disease rather than fibrosis-specific mechanisms. For example, antiviral therapies remain the cornerstone of treatment for hepatitis B and hepatitis C, which, while clinically essential, complicates detailed mechanistic investigation into their direct effects on hepatic fibrogenesis. As a result, the specific contributions of numerous agents to ECM remodeling and fibrosis regression remain insufficiently characterized. Nevertheless, ongoing clinical and preclinical studies continue to investigate a range of pharmacological interventions targeting liver fibrosis, numerous of which are closely associated with ECM dynamics and remodeling processes.

Finally, with regard to liver cancer, particularly HCC, liver fibrosis represents a major and clinically significant risk factor. The majority of HCC cases develop in the context of underlying fibrosis or cirrhosis, indicating that fibrotic remodeling plays a central role in establishing a premalignant hepatic microenvironment. This association is likely driven by pathological ECM remodeling during both fibrogenesis and fibrosis regression, which can facilitate the release and activation of growth factor signaling cascades, thereby promoting hepatocellular proliferation and increasing oncogenic potential. Numerous studies have investigated the prognosis and progression of HCC (149-151).

Collectively, these findings underscore the importance of intensified research into liver fibrosis, as improving fibrosis prevention and treatment strategies is fundamentally linked to reducing the risk of subsequent HCC development.

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Authors' contributions

YZ and ZQ wrote the manuscript. YD collected data. HW and JH were responsible for providing guidance. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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