



Antifibrotic therapy in MASLD: fibrosis reversal and HCC prevention

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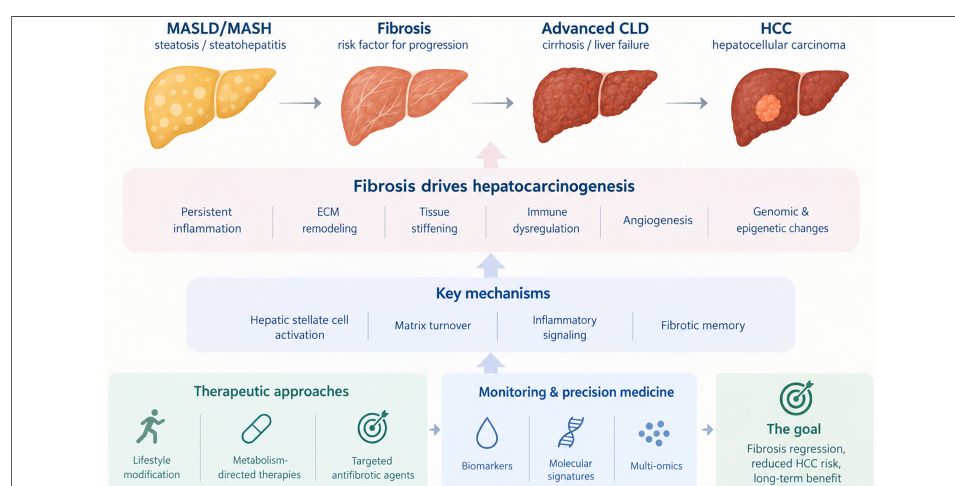
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Abstract

Metabolic dysfunction-associated steatotic liver disease/ metabolic dysfunction-associated steatohepatitis (MASLD/MASH) has become a leading cause of advanced chronic liver disease and hepatocellular carcinoma (HCC). Among all histological features, liver fibrosis is the strongest predictor of liver-related outcomes and is increasingly recognized not only as a marker of disease severity but also as an active driver of hepatocarcinogenesis. Fibrosis promotes malignant transformation through persistent inflammation, extracellular matrix (ECM) remodeling, tissue stiffening, immune dysregulation, angiogenesis, genomic instability, and epigenetic reprogramming. Although lifestyle modification and metabolism-directed therapies can improve steatosis and steatohepatitis, established fibrosis often persists, underscoring the need for targeted antifibrotic strategies. This review summarizes the cellular and molecular mechanisms underlying MASLD-associated fibrogenesis, with particular emphasis on hepatic stellate cell activation, matrix turnover, inflammatory signaling, and fibrotic memory. We discuss current and emerging therapeutic approaches, including lifestyle-based interventions, incretin-based therapies, thyroid hormone receptor- β agonists, peroxisome proliferator-activated receptor (PPAR) agonists, fibroblast growth factor 21 (FGF21) analogs, immunomodulatory agents, and direct antifibrotic strategies targeting transforming growth

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factor beta (TGF- β), platelet-derived growth factor (PDGF), ECM remodeling, mechanotransduction, and myofibroblast persistence. Recent clinical trials demonstrate encouraging histological improvements, particularly with metabolism-directed and pleiotropic agents; however, no randomized trial has yet shown that fibrosis regression reduces HCC incidence. Reliable non-invasive biomarkers, molecular risk signatures, liquid biopsy approaches, and multi-omics-based precision medicine will therefore be essential to monitor fibrosis regression, identify residual cancer risk, and guide individualized surveillance. We propose that antifibrotic therapy in MASLD/MASH warrants consideration not only as a strategy for fibrosis reversal but also as a potential disease-modifying approach to interrupt fibrosis-driven hepatocarcinogenesis and reduce the long-term burden of HCC.

INTRODUCTION

The therapeutic landscape of metabolic dysfunction-associated steatotic liver disease (MASLD) has changed fundamentally over the past few years. The introduction of disease-modifying pharmacological therapies, together with rapid advances in incretin-based treatments, thyroid hormone receptor- β agonists, and emerging direct antifibrotic agents, has transformed drug development from predominantly metabolic interventions towards mechanism-based combination strategies^[1]. Nevertheless, despite encouraging improvements in histological fibrosis observed in several phase II and III clinical trials, direct antifibrotic therapies remain limited, validated biomarkers of fibrosis regression are still evolving, and robust evidence demonstrating a reduction in hepatocellular carcinoma (HCC) incidence following fibrosis reversal is lacking^[2]. Consequently, whether fibrosis regression translates into durable cancer prevention remains one of the most important unanswered questions in contemporary hepatology^[3].

Emerging evidence suggests that persistent epigenetic alterations, aberrant extracellular matrix (ECM) architecture, immune dysregulation, and so-called *fibrotic memory* may sustain residual carcinogenic potential despite apparent histological improvement^[4]. Defining the extent to which these persistent molecular scars influence long-term HCC risk will be critical for developing rational surveillance strategies and identifying patients who may derive the greatest benefit from antifibrotic interventions^[5].

In this review, we critically examine the molecular mechanisms underlying fibrogenesis in MASLD, discuss the biological interplay between fibrosis and hepatocarcinogenesis, and provide a comprehensive overview of current and emerging antifibrotic therapeutic strategies. We further evaluate preclinical and clinical evidence supporting fibrosis regression as a potential strategy for HCC prevention, highlight the role of non-invasive and molecular biomarkers in monitoring therapeutic response and cancer risk, and discuss future directions towards precision medicine^[6]. We propose the central hypothesis that effective antifibrotic therapy in MASLD may be considered not only as a strategy to reverse liver fibrosis but also as a disease-modifying approach capable of interrupting the biological pathways that drive HCC development^[3].

The global burden of MASLD

MASLD has emerged as the most prevalent chronic liver disease worldwide and is now a major contributor to liver-related morbidity, mortality, and healthcare expenditure^[7]. Driven by the global epidemics of obesity, type 2 diabetes mellitus, and metabolic syndrome, MASLD encompasses a broad clinicopathological spectrum ranging from isolated hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH), progressive liver fibrosis, cirrhosis, and HCC^[8]. The recent transition from the NAFLD to the MASLD nomenclature reflects an evolving understanding of the disease as the hepatic manifestation of systemic metabolic dysfunction rather than an isolated liver disorder^[9,10]. Consequently, MASLD should be viewed within the broader context of cardiometabolic disease, requiring integrated therapeutic strategies that address both hepatic and extrahepatic complications^[11].

Liver fibrosis as the central determinant of clinical outcome

Among the histological features of MASLD, liver fibrosis has consistently emerged as the strongest predictor of liver-related events, hepatic decompensation, HCC, liver transplantation, and overall mortality^[12]. Although steatosis and hepatic inflammation initiate disease progression, it is the accumulation of ECM and the development of fibrosis that largely determine long-term clinical outcomes. Importantly, fibrosis is increasingly recognized as a dynamic biological process that reflects continuous interactions between metabolically stressed hepatocytes, activated hepatic stellate cells (HSCs), immune populations, and the hepatic microenvironment^[13-15]. This evolving understanding has shifted the therapeutic focus from reducing hepatic fat content alone towards preventing fibrosis progression and, ultimately, achieving fibrosis regression^[16].

Advanced liver fibrosis is a well-established marker of increased hepatocarcinogenic risk across several chronic liver diseases, including viral hepatitis, while in MASLD fibrosis severity is likewise closely associated with HCC risk^[17]. Progressive ECM remodeling alters tissue architecture and mechanical stiffness, promotes chronic inflammation, reshapes immune surveillance, stimulates angiogenesis, and establishes a tumor-permissive microenvironment that facilitates malignant transformation^[6,18]. These observations challenge the traditional view that cirrhosis alone represents the principal prerequisite for HCC development and instead suggest that the fibrotic process itself contributes directly to tumor initiation and progression. Moreover, although HCC may develop in non-cirrhotic MASLD, the risk rises substantially with increasing fibrosis stage, underscoring fibrosis as the central biological link between chronic metabolic liver injury and liver cancer^[19].

Why does antifibrotic therapy matter?

Hepatic fibrosis is the strongest predictor of liver-related morbidity, mortality, and HCC in MASLD, making it a central therapeutic target^[20]. Although current management strategies, including lifestyle modification and pharmacological interventions targeting obesity, insulin resistance, and metabolic dysfunction, can improve steatosis and hepatic inflammation, their effects on established fibrosis are often limited, particularly in advanced disease^[6,21]. Consequently, many patients remain at risk of disease progression despite improvements in metabolic parameters. Importantly, the therapeutic rationale extends beyond histological fibrosis regression. Fibrosis actively shapes the hepatic microenvironment by promoting chronic inflammation, ECM accumulation, tissue stiffness, and vascular remodeling, all of which contribute to hepatocarcinogenesis. Therefore, effective antifibrotic therapy may not only restore liver architecture but also reduce the risk of hepatic decompensation and HCC^[2,16].

Scope of this review

A central question in the management of MASLD is whether effective antifibrotic therapy can achieve benefits beyond histological fibrosis regression. Specifically, can targeted reversal of hepatic fibrosis not only restore liver architecture and function but also modify the pathogenic microenvironment that drives hepatocarcinogenesis, thereby reducing the long-term risk of HCC? Addressing this question is of considerable clinical importance, as fibrosis represents the strongest predictor of liver-related outcomes and HCC development in MASLD.

MECHANISMS DRIVING LIVER FIBROSIS IN MASLD

MASLD is initiated by chronic metabolic stress resulting from obesity, insulin resistance, type 2 diabetes mellitus, and other components of the metabolic syndrome^[20]. Rather than representing a simple consequence of excessive hepatic lipid accumulation, MASLD arises from a complex interplay between systemic metabolic dysregulation and hepatocellular stress responses that progressively transform a metabolically adaptive liver into a pro-inflammatory and profibrogenic organ^[22]. This concept has

superseded the historical "two-hit" hypothesis and is now encompassed within the "multiple-hit" model, in which genetic susceptibility, adipose tissue dysfunction, altered substrate flux, gut-derived factors, and intracellular stress pathways converge to drive disease progression.

Metabolic dysfunction

The earliest pathogenic event in MASLD is systemic metabolic dysfunction. Insulin resistance in adipose tissue increases lipolysis, leading to excessive delivery of free fatty acids to the liver, while hyperinsulinemia paradoxically maintains hepatic *de novo* lipogenesis through persistent activation of sterol regulatory element-binding protein-1c (SREBP-1c) and carbohydrate-responsive element-binding protein (ChREBP)^[23]. Simultaneously, impaired β -oxidation and reduced very-low-density lipoprotein export further exacerbate intracellular lipid accumulation. Consequently, hepatocytes become overwhelmed by an excessive lipid burden that exceeds their metabolic capacity, creating the foundation for cellular injury and fibrogenesis^[24]. Importantly, disease progression is determined less by the quantity of stored triglycerides than by the accumulation of toxic lipid intermediates that disrupt cellular homeostasis^[24].

Lipotoxicity represents the critical transition from benign steatosis to progressive liver injury. While triglyceride storage may initially serve as a protective mechanism by buffering excess fatty acids, saturation of this adaptive capacity results in the intracellular accumulation of lipotoxic metabolites, including saturated fatty acids, diacylglycerols, ceramides, lysophosphatidylcholines, and free cholesterol^[25]. These bioactive lipids activate stress-sensitive signaling pathways, including c-Jun N-terminal kinase (JNK), nuclear factor- κ B (NF- κ B), and the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, thereby promoting hepatocyte dysfunction, apoptosis, and inflammatory cytokine production. Injured hepatocytes subsequently release damage-associated molecular patterns (DAMPs), extracellular vesicles, and profibrogenic mediators that initiate crosstalk with Kupffer cells and HSCs, establishing the inflammatory milieu required for fibrosis development^[26].

Oxidative stress constitutes a major downstream consequence of lipotoxicity and is a central driver of hepatocellular injury. Increased mitochondrial fatty acid oxidation, peroxisomal oxidation, and cytochrome P450 2E1 activity generate excessive reactive oxygen species (ROS), which overwhelm endogenous antioxidant systems^[27]. ROS induce lipid peroxidation, oxidative DNA damage, and protein oxidation while amplifying inflammatory signaling through redox-sensitive transcription factors. Oxidative stress also enhances hepatocyte death and stimulates neighboring non-parenchymal cells through paracrine mechanisms, thereby perpetuating chronic inflammation and ECM production^[28]. Importantly, oxidative injury not only accelerates fibrogenesis but also contributes to genomic instability, providing a mechanistic link between advanced fibrosis and HCC^[29].

Mitochondria occupy a central position in MASLD pathogenesis owing to their essential role in hepatic energy metabolism. During the early stages of disease, mitochondrial β -oxidation is upregulated as a compensatory response to lipid overload^[27]. However, persistent substrate excess eventually impairs oxidative phosphorylation, disrupts mitochondrial dynamics, reduces ATP production, and promotes mitochondrial DNA damage. Defective mitophagy further facilitates the accumulation of dysfunctional mitochondria, resulting in sustained ROS generation and the release of mitochondrial DAMPs that activate innate immune pathways^[30]. This vicious cycle of metabolic overload, mitochondrial injury, and inflammation drives progressive hepatocyte damage and creates a microenvironment conducive to fibrogenesis^[31]. Recent studies further suggest that altered mitochondrial metabolism influences HSC activation, linking metabolic dysfunction directly to ECM deposition^[6].

Endoplasmic reticulum (ER) stress represents another pivotal consequence of chronic nutrient excess. Excessive lipid accumulation and increased demands for protein and lipid synthesis disrupt ER homeostasis, triggering activation of the unfolded protein response (UPR). Although transient UPR signaling is cytoprotective, persistent activation of the protein kinase R-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 alpha (IRE1 α), and activating transcription factor 6 (ATF6) pathways promotes apoptosis, inflammatory cytokine production, and metabolic dysregulation^[32]. Crosstalk between ER stress and mitochondrial dysfunction further amplifies oxidative stress, calcium dysregulation, and inflammasome activation, establishing a self-sustaining cycle of hepatocyte injury. Beyond its effects on parenchymal cells, ER stress also modulates macrophage activation and directly enhances HSC activation, thereby coupling metabolic stress to fibrosis^[26]. Recent evidence supports a role for gut-liver axis dysfunction in MASLD-associated fibrogenesis, whereby intestinal dysbiosis and impaired barrier integrity may increase exposure to bacterial products, including gut-derived lipopolysaccharide (LPS). LPS-mediated Toll-like receptor 4 (TLR4) signaling in hepatic immune cells and stellate cells can promote inflammatory and profibrogenic responses^[33].

Collectively, metabolic dysfunction, lipotoxicity, oxidative stress, mitochondrial injury, and chronic ER stress constitute an interconnected network of pathogenic events that transforms hepatic steatosis into progressive fibroinflammatory liver disease. Rather than acting independently, these mechanisms reinforce one another through multiple positive feedback loops, resulting in persistent hepatocyte injury and activation of the hepatic wound-healing response^[14]. This metabolic injury therefore represents the initiating event that precedes immune activation, HSC transdifferentiation, and pathological ECM deposition, providing the biological rationale for therapeutic strategies that target early metabolic stress as well as downstream fibrogenic pathways^[22,34].

A characteristic feature of fibrosis in MASLD is the persistent metabolic drive underlying hepatocellular injury and fibrogenic signaling. Unlike liver diseases initiated primarily by viral infection, alcohol toxicity, or biliary injury, MASLD develops in the context of systemic insulin resistance, adipose tissue dysfunction, increased hepatic fatty-acid delivery, enhanced *de novo* lipogenesis, and impaired mitochondrial lipid oxidation^[35]. The resulting accumulation of toxic lipid species induces mitochondrial dysfunction, oxidative and ER stress, and hepatocellular lipotoxicity. At the same time, dysfunctional adipose tissue and the gut-liver axis contribute to a chronic inflammatory state through altered adipokine signaling, increased endotoxin exposure, and activation of innate immune pathways such as TLR signaling^[35]. These metabolic and inflammatory signals promote hepatocyte injury and activate Kupffer cells and other immune populations, which in turn stimulate HSCs through profibrogenic mediators including transforming growth factor- β (TGF- β) and platelet-derived growth factor (PDGF)^[36]. Therefore, although oxidative stress, ER stress, inflammation, and HSC activation are shared mechanisms across chronic liver diseases, MASLD is distinguished by its sustained coupling to systemic metabolic dysfunction and hepatic lipid overload. This metabolic-immune interaction provides a major driver of progressive fibrosis in MASLD^[37].

Alcohol-driven effects on fibrosis in MASLD and MetALD

Alcohol consumption has traditionally been considered a distinct driver of alcohol-associated liver disease (ALD), whereas MASLD was defined by the absence of harmful alcohol consumption. This dichotomy is increasingly recognized as biologically artificial^[38]. Alcohol and cardiometabolic risk factors frequently coexist and interact, giving rise to MASLD with increased alcohol consumption (MetALD), a phenotype characterized by overlapping metabolic and alcohol-related mechanisms of liver injury^[39,40]. Emerging evidence indicates that alcohol and cardiometabolic risk factors act synergistically rather than simply additively, resulting in an accelerated risk of steatohepatitis, fibrosis, cirrhosis, and HCC^[40]. Alcohol can promote hepatic fibrogenesis through several interconnected mechanisms. Ethanol metabolism via alcohol

dehydrogenase and cytochrome P450 2E1 generates acetaldehyde and ROS, thereby inducing oxidative and ER stress, mitochondrial dysfunction and hepatocellular injury. Acetaldehyde can directly modify proteins and cellular signaling pathways, whereas ROS promote lipid peroxidation and amplify inflammatory responses^[40,41]. These processes increase the release of DAMPs from injured hepatocytes and thereby activate hepatic immune cells. Persistent hepatocyte injury establishes a feed-forward circuit in which inflammation and cell death continuously stimulate fibrogenic pathways^[41]. A major component of alcohol-induced fibrogenesis is the activation of hepatic macrophages. Chronic alcohol exposure alters Kupffer-cell function and promotes the recruitment and differentiation of monocyte-derived macrophages^[41]. These cells respond to gut-derived microbial products as well as hepatocyte-derived danger signals and produce inflammatory and profibrogenic mediators, including tumor necrosis factor (TNF), interleukin (IL)-1 β , IL-6 and TGF- β ^[42]. Importantly, current evidence indicates substantial heterogeneity among hepatic macrophages rather than a simple M1/M2 dichotomy. Distinct macrophage populations can either amplify fibrogenesis or participate in tissue repair and fibrosis resolution, depending on their spatial and temporal context^[30,41].

The interaction with metabolic dysfunction is particularly relevant in MetALD. Obesity, insulin resistance, adipose-tissue dysfunction and lipotoxicity create a pre-existing inflammatory and metabolic environment in which alcohol can exert disproportionately strong effects. Excessive hepatic lipid accumulation increases susceptibility to oxidative and mitochondrial stress, while dysfunctional adipose tissue enhances the delivery of free fatty acids and pro-inflammatory mediators to the liver. Alcohol may additionally exacerbate hepatic steatosis through altered NADH/NAD⁺ balance, impaired lipid oxidation and changes in lipid synthesis. Consequently, metabolic stress and ethanol exposure converge on common pathways of hepatocellular injury, immune activation and HSC stimulation^[38,39,43].

Overall, alcohol is therefore better understood not as an independent parallel pathway to metabolic liver disease. Rather, in MASLD and particularly in MetALD, alcohol converges with metabolic dysfunction at multiple levels - including hepatocellular stress, mitochondrial dysfunction, gut-liver signaling, macrophage activation and HSC-dependent fibrogenesis. This mechanistic convergence provides a rationale for assessing alcohol exposure as an integral component of fibrosis risk stratification and for considering alcohol reduction or abstinence as a central component of strategies aimed at preventing fibrosis progression^[39,40].

Chronic inflammation sustains fibrogenesis

Persistent hepatocellular injury in MASLD initiates a chronic inflammatory response that transforms an adaptive wound-healing program into progressive fibrogenesis. Lipotoxic hepatocytes release DAMPs, extracellular vesicles, mitochondrial DNA, and ROS, which activate resident and infiltrating immune cells through pattern recognition receptors. This sustained inflammatory milieu promotes HSC activation and ECM deposition, thereby linking metabolic injury to fibrosis progression^[44].

Among innate immune cells, Kupffer cells serve as the first responders to hepatocyte injury. Upon activation, they secrete pro-inflammatory and profibrogenic mediators, including tumor necrosis factor- α (TNF- α), IL-1 β , IL-6, TGF- β , and PDGF, thereby amplifying local inflammation and stimulating HSC activation^[45]. As disease progresses, resident macrophages are increasingly supplemented by monocyte-derived macrophages, which acquire distinct inflammatory and profibrotic phenotypes. These cells contribute to sustained cytokine production, matrix remodeling, and immune cell recruitment, while macrophage plasticity also makes them key regulators of fibrosis resolution^[16].

Neutrophils further exacerbate liver injury through the release of ROS, proteases, and neutrophil extracellular traps (NETs), which enhance inflammatory signaling and promote HSC activation^[46]. In parallel, adaptive immune cells, including T helper cell subsets, cytotoxic T cells, and B cells, reinforce

chronic inflammation through cytokine secretion and interactions with macrophages and HSCs. Conversely, impaired regulatory T-cell function may contribute to the loss of immune homeostasis observed in advanced MASLD^[30,47].

The inflammatory microenvironment is orchestrated by an extensive network of cytokines and chemokines, including CC chemokine ligand 2 (CCL2)-CC chemokine receptor 2 (CCR2), CC chemokine ligand 5 (CCL5), C-X-C motif chemokine ligand 10 (CXCL10), TNF- α , IL-1 β , IL-6, and TGF- β , which regulate immune cell recruitment, activation, and fibrogenic signaling^[48,49]. These pathways not only sustain chronic inflammation but also establish the molecular framework for persistent HSC activation and progressive ECM accumulation^[6]. Consequently, inflammatory signaling has emerged as an attractive therapeutic target, although clinical trials indicate that modulation of inflammation alone is unlikely to achieve meaningful fibrosis regression without directly addressing stellate cell activation and matrix remodeling^[12,44].

HSC activation: the final common pathway

HSC activation represents the final common pathway through which diverse metabolic, inflammatory, and toxic insults converge to drive hepatic fibrogenesis in MASLD. Recent advances in single-cell RNA sequencing and spatial transcriptomics have fundamentally revised the traditional concept of HSCs as a uniform population, revealing substantial cellular heterogeneity with distinct transcriptional states ranging from quiescent vitamin A-storing cells to inflammatory, proliferative, and highly fibrogenic subpopulations. These findings indicate that fibrosis progression is governed not only by the magnitude of HSC activation but also by the emergence and persistence of specific pathogenic HSC niches within the injured liver^[50-54].

In response to metabolic injury, lipotoxic hepatocyte-derived signals, including ROS, extracellular vesicles, apoptotic bodies, and DAMPs, initiate HSC activation. This process is further amplified by cytokines and growth factors released from macrophages, endothelial cells, and other non-parenchymal cells. Activated HSCs undergo myofibroblast differentiation, characterized by loss of quiescent features, acquisition of contractile properties, and enhanced synthesis of ECM components, particularly fibrillar collagens. Excessive ECM deposition disrupts hepatic architecture, promotes sinusoidal remodeling, and establishes a self-reinforcing profibrotic microenvironment^[55]. Loss of phosphoenolpyruvate carboxykinase 1 (PCK1) expression enhances HSC activation and facilitates the acquisition of a profibrogenic phenotype, while enforced PCK1 expression counteracts TGF- β 1-mediated activation, suggesting that PCK1 functions as an endogenous brake on stellate cell-driven fibrogenesis^[56].

TGF- β remains the central regulator of HSC-mediated fibrogenesis. Through small mothers against decapentaplegic (SMAD)-dependent signaling, TGF- β induces collagen production, suppresses matrix degradation, and stabilizes the myofibroblast phenotype^[57]. However, recent work has highlighted that TGF- β activity is not solely determined by cytokine abundance but critically depends on local activation mechanisms within the fibrotic niche. In particular, α v-containing integrins, including α v β 6 and α v β 1, facilitate the mechanical release of latent TGF- β from the ECM, thereby coupling matrix composition to persistent profibrogenic signaling^[58]. This integrin-TGF- β axis represents an attractive therapeutic target because it selectively interferes with fibrosis amplification while potentially preserving systemic TGF- β functions^[59].

Mechanical regulation has emerged as a fundamental driver of HSC activation. Progressive ECM accumulation increases hepatic stiffness, which is sensed by HSCs through integrin-mediated focal adhesion signaling, cytoskeletal remodeling, and mechanotransduction pathways involving focal adhesion kinase, Rho-associated kinase, and the Hippo pathway effectors Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ). Nuclear activation of YAP/TAZ promotes transcription of

profibrogenic genes and maintains the activated myofibroblast phenotype, creating a feed-forward loop in which fibrosis induces stiffness and stiffness further accelerates fibrosis. Targeting mechanotransduction pathways therefore represents a promising strategy to disrupt the self-sustaining nature of advanced fibrosis^[60,61].

The therapeutic targeting of HSCs has consequently become a major focus of antifibrotic drug development. Conventional systemic approaches have been limited by insufficient efficacy and off-target toxicity; therefore, recent strategies increasingly aim to achieve cell-specific delivery^[16]. Vitamin A-modified nanoparticles exploit the physiological retinol uptake pathways of HSCs to selectively transport antifibrotic cargos, including small interfering RNAs and small molecules^[20]. Similarly, ligand-functionalized lipid nanoparticles have demonstrated the ability to deliver RNA therapeutics directly to activated fibroblastic populations within the fibrotic liver. Although these approaches remain largely preclinical, they represent a major conceptual shift from broad pathway inhibition towards precision antifibrotic therapy^[16,62].

Collectively, emerging evidence positions HSCs not merely as passive collagen-producing cells but as dynamic regulators of metabolic adaptation, immune signaling, ECM remodeling, and mechanical sensing. Understanding HSC heterogeneity and the molecular circuits maintaining the activated state will be essential for developing therapies capable of inducing durable fibrosis regression and, ultimately, reducing the risk of HCC in MASLD^[12].

Fibrosis as a dynamic and potentially reversible process

For decades, hepatic fibrosis was regarded as an irreversible endpoint of chronic liver injury, reflecting the passive accumulation of ECM and progressive replacement of functional liver tissue by scar. However, extensive experimental and clinical evidence has fundamentally revised this concept, demonstrating that fibrosis is a dynamic and potentially reversible process governed by the continuous interplay between matrix synthesis, degradation, and remodeling. This paradigm shift has transformed fibrosis from a pathological consequence into a therapeutic target, providing the rationale for developing interventions aimed not only at halting disease progression but also at actively promoting fibrosis regression^[12,51].

The fibrotic liver is characterized by excessive deposition of ECM components, particularly fibrillar collagens type I and III, fibronectin, laminins, and proteoglycans. Although transient ECM accumulation represents a physiological response required for tissue repair, persistent activation of HSCs and myofibroblasts leads to uncontrolled matrix production, sinusoidal remodeling, increased tissue stiffness, and disruption of normal hepatic architecture. Importantly, the ECM is not merely a structural scaffold but functions as a biologically active signaling platform that regulates growth factor availability, inflammatory responses, cellular migration, and mechanotransduction. Consequently, fibrosis progression reflects not only enhanced collagen synthesis but also impaired matrix degradation and altered ECM composition^[14,50].

A central determinant of ECM turnover is the balance between matrix metalloproteinases (MMPs) and their endogenous inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). MMPs constitute a family of zinc-dependent proteases responsible for degradation of multiple ECM components, including interstitial collagens and basement membrane proteins. During fibrosis regression, restoration of MMP activity facilitates collagen breakdown, matrix remodeling, and recovery of hepatic architecture. Conversely, progressive fibrosis is associated with impaired ECM degradation due to increased TIMP expression and suppression of effective collagenolytic activity. This imbalance creates a permissive environment for persistent scar accumulation and maintenance of the activated myofibroblast phenotype^[13].

Among TIMPs, TIMP-1 has emerged as a critical regulator of fibrosis persistence. Beyond its classical role as an inhibitor of MMP activity, TIMP-1 promotes survival of activated HSCs and protects myofibroblasts from apoptosis, thereby contributing to the longevity of the fibrogenic cell population. Studies from Weiskirchen, Roeb, and colleagues have highlighted the importance of the MMP-TIMP axis as a key determinant of whether fibrosis remains progressive or enters a resolution phase. Diagnostically and therapeutically restoring ECM turnover therefore requires not only reducing collagen production but also reactivating endogenous mechanisms responsible for matrix clearance^[63-65].

Immune-mediated regulation represents another essential component of fibrosis resolution. Macrophages, in particular, exhibit remarkable functional plasticity during the transition from fibrosis progression to regression. Whereas inflammatory macrophage populations promote HSC activation and ECM deposition, restorative macrophage phenotypes contribute to matrix degradation through enhanced expression of collagenolytic enzymes, including specific MMPs, and facilitate the elimination or deactivation of myofibroblasts. Thus, fibrosis regression depends on coordinated interactions between immune cells, fibroblastic populations, and the ECM rather than on isolated modulation of a single pathway^[66].

Importantly, fibrosis regression has clinical implications extending beyond histological improvement. Advanced fibrosis creates a microenvironment characterized by chronic inflammation, altered immune surveillance, vascular remodeling, and increased cellular stress, all of which contribute to hepatocarcinogenesis^[6,32]. In MASLD, where metabolic injury frequently persists despite improvements in liver inflammation, targeting fibrosis may therefore represent a crucial strategy to reduce the long-term risk of HCC. Therapeutic success should consequently be evaluated not only by changes in fibrosis stage but also by the ability to restore hepatic homeostasis and prevent fibrosis-associated carcinogenesis^[67]. [Figure 1](#) illustrates the complex mechanisms initiating fibrosis and the interconnected cytokine networks underlying its progression.

LIVER FIBROSIS AS A DRIVER OF HEPATOCELLULAR CARCINOGENESIS

Fibrosis has traditionally been regarded as a histological indicator of advanced chronic liver disease and an important predictor of HCC risk. However, emerging evidence has fundamentally changed this perspective, demonstrating that fibrosis is not merely a passive consequence of persistent hepatic injury but an active biological driver of hepatocarcinogenesis. The fibrotic liver represents a complex, continuously evolving ecosystem in which chronic inflammation, ECM alterations, immune dysfunction, vascular remodeling, and cellular stress converge to create a tumor-permissive environment. In MASLD, this concept is particularly relevant, as fibrosis can persist despite partial metabolic improvement and continues to shape the hepatic microenvironment that supports malignant transformation^[6].

The transition from chronic liver injury to HCC is therefore not solely determined by the accumulation of genetic mutations within hepatocytes but by the progressive remodeling of the surrounding tissue ecosystem. Fibrosis induces profound changes in hepatocyte behavior, stromal signaling, immune surveillance, and vascular architecture, thereby facilitating tumor initiation, expansion, and therapeutic resistance^[68]. Understanding fibrosis as an active promoter of carcinogenesis provides the mechanistic rationale for antifibrotic strategies as potential cancer-preventive interventions^[69].

Chronic inflammation and persistent tissue injury

Persistent inflammation represents one of the earliest links between fibrosis and hepatocarcinogenesis^[6]. In MASLD, chronic metabolic stress caused by lipotoxicity, oxidative injury, and hepatocyte dysfunction results in continuous release of DAMPs, inflammatory mediators, and extracellular vesicles. These signals maintain activation of innate immune pathways and prevent complete resolution of tissue injury. Unlike acute

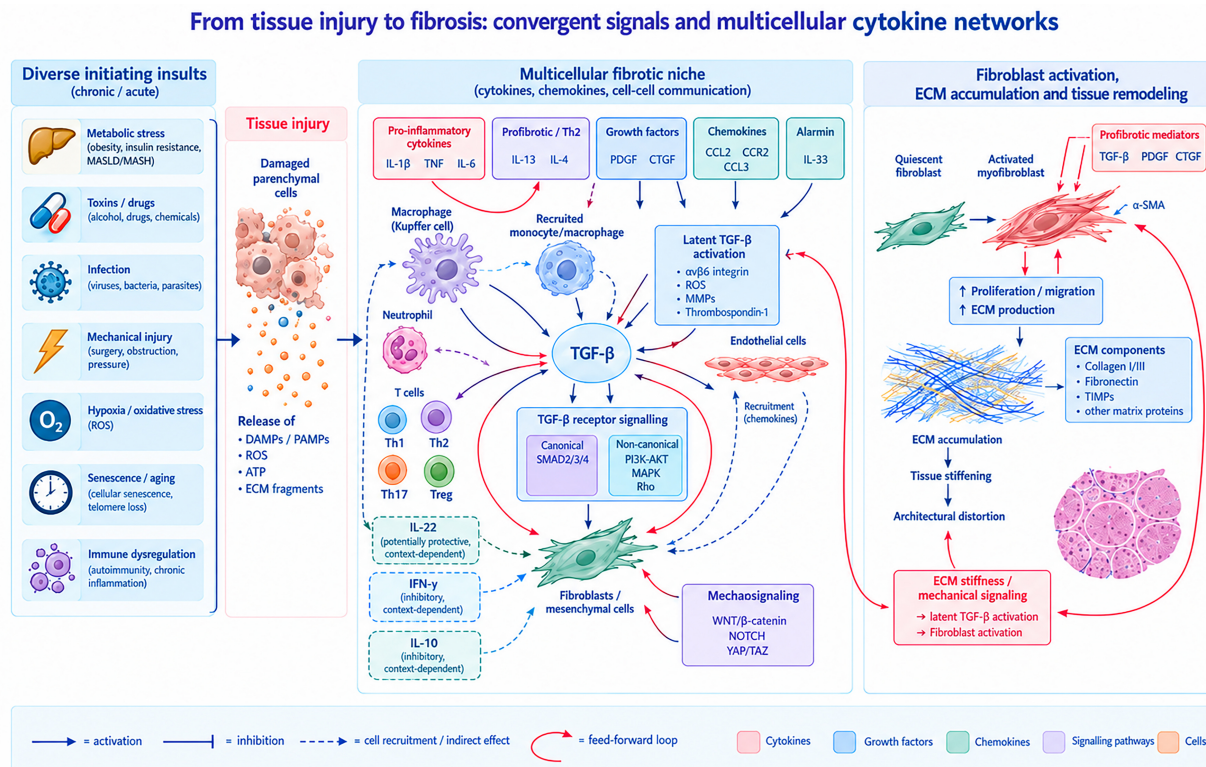


Figure 1. From tissue injury to fibrosis: convergent signals and multicellular cytokine networks. Fibrosis is a dynamic, multicellular process initiated by diverse acute or chronic tissue insults, including metabolic stress, toxins and drugs, infections, mechanical injury, hypoxia, oxidative stress, senescence, and immune dysregulation. Tissue injury induces the release of DAMPs, PAMPs, ROS, ATP, and ECM fragments, triggering inflammatory and fibrogenic responses. The fibrotic niche integrates signals from damaged parenchymal cells, macrophages, recruited monocytes, neutrophils, T-cell subsets, endothelial cells, and fibroblasts. Pro-inflammatory cytokines, including IL-1 β , TNF, and IL-6, together with profibrotic Th2 cytokines IL-13 and IL-4, growth factors such as PDGF and CTGF, chemokines, and alarmins, converge on fibroblasts and mesenchymal cells. TGF- β represents a central profibrotic mediator. Its activation from latent complexes involves, among other mechanisms, α v β 6 integrin, ROS, MMPs, and thrombospondin-1. TGF- β receptor signaling proceeds through canonical SMAD2/3/4-dependent and non-canonical PI3K-AKT, MAPK, and Rho pathways. Additional immune mediators, including IL-22, IFN- γ , and IL-10, exert context-dependent effects on fibrogenesis. Fibroblast activation is characterized by increased proliferation, migration, and ECM production, including collagen I/III, fibronectin, TIMPs, and other matrix proteins. Progressive ECM accumulation results in tissue stiffening and architectural distortion. Mechanosensitive pathways, including WNT/ β -catenin, NOTCH, and YAP/TAZ, further contribute to fibroblast activation and may promote latent TGF- β activation, thereby establishing self-reinforcing feed-forward loops. The figure illustrates the complex interplay between inflammatory, profibrotic, chemotactic, growth factor, and mechanical signals that drive tissue remodeling and fibrosis. The figure was conceptually designed by the authors and visually developed with assistance from ChatGPT (OpenAI). AKT: Protein kinase B; ATP: adenosine triphosphate; α -SMA: α -smooth muscle actin; CCL: CC chemokine ligand; CCR: CC chemokine receptor; CTGF: connective tissue growth factor; DAMPs: damage-associated molecular patterns; ECM: extracellular matrix; IFN- γ : interferon- γ ; IL: interleukin; MAPK: mitogen-activated protein kinase; MMPs: matrix metalloproteinases; PAMPs: pathogen-associated molecular patterns; PDGF: platelet-derived growth factor; PI3K: phosphoinositide 3-kinase; ROS: reactive oxygen species; SMAD: small mothers against decapentaplegic; TAZ: transcriptional coactivator with PDZ-binding motif; TGF- β : transforming growth factor- β ; Th: T helper; TIMPs: tissue inhibitors of metalloproteinases; TNF: tumor necrosis factor; Treg: regulatory T cell; YAP: Yes-associated protein.

inflammation, which promotes repair, chronic inflammation generates a maladaptive environment characterized by sustained cytokine production, oxidative stress, and repeated cycles of hepatocyte death and regeneration^[70].

Activated macrophages, including resident Kupffer cells and recruited monocyte-derived macrophages, contribute substantially to this inflammatory landscape by producing tumor-promoting mediators such as IL-6, TNF- α , IL-1 β , and TGF- β . These factors stimulate compensatory hepatocyte proliferation, enhance survival of damaged cells, and activate intracellular pathways including NF- κ B, signal transducer and

activator of transcription 3 (STAT3), and Wnt/ β -catenin signaling, which are frequently implicated in HCC development. Repeated regenerative pressure in an inflammatory environment increases the likelihood that hepatocytes carrying oncogenic alterations escape normal growth control mechanisms^[71]. Importantly, fibrosis reinforces chronic inflammation by preventing effective tissue restoration. The fibrotic niche promotes persistent activation of inflammatory cells and maintains abnormal communication between hepatocytes, stromal cells, and immune populations. Thus, fibrosis functions as an amplifier of injury-induced signaling, converting transient inflammatory responses into a self-sustaining tumor-promoting state^[6].

ECM remodeling and tissue stiffness

The fibrotic ECM represents a critical regulator of hepatocarcinogenesis. Beyond providing structural support, the ECM functions as a dynamic signaling platform that influences cellular differentiation, proliferation, migration, and survival. Progressive deposition of collagen-rich matrix alters the physical properties of the liver, resulting in increased tissue stiffness and profound changes in mechanotransduction pathways^[72]. Mechanical stress generated by a stiffened ECM is sensed by hepatocytes, HSCs, and tumor cells through integrins, focal adhesion complexes, and cytoskeletal networks. These signals activate mechanosensitive pathways involving focal adhesion kinase (FAK), Rho-associated kinase (ROCK), and the transcriptional regulators YAP and TAZ. Nuclear activation of YAP/TAZ promotes expression of genes involved in cell proliferation, stemness, epithelial-to-mesenchymal transition, and resistance to apoptosis, thereby creating conditions favorable for malignant transformation^[73].

Furthermore, abnormal ECM composition influences growth factor availability and receptor signaling. Matrix-bound cytokines and growth factors, including TGF- β , hepatocyte growth factor, and vascular endothelial growth factor (VEGF), can be released during ECM remodeling and promote tumor initiation and progression. Therefore, the fibrotic matrix acts not only as a physical barrier but also as an active regulator of oncogenic signaling^[74].

In MASLD-associated HCC, this mechanism may be particularly important because tumors frequently arise in a metabolically altered and fibrotic environment where matrix remodeling continues even in the absence of established cirrhosis. Consequently, targeting fibrosis-associated mechanical signaling represents an emerging strategy to interfere with the tumor-promoting properties of the hepatic microenvironment^[75].

Immune dysregulation and tumor immune escape

Fibrosis profoundly alters hepatic immune surveillance and contributes to the establishment of an immunosuppressive microenvironment. The healthy liver maintains a tightly regulated immune balance that allows tolerance to dietary and microbial antigens while preserving effective responses against pathogens and transformed cells. Fibrosis disrupts this equilibrium by altering immune cell composition, function, and spatial organization^[54].

Chronic activation of macrophages, regulatory T cells, myeloid-derived suppressor cells, and exhausted T-cell populations contributes to impaired anti-tumor immunity. Fibrotic livers demonstrate increased expression of immune checkpoint molecules, including programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) pathways, which suppress cytotoxic lymphocyte activity and facilitate immune escape. In parallel, dysfunctional antigen presentation and altered cytokine networks reduce immune-mediated elimination of premalignant hepatocytes^[76].

The fibrotic niche also promotes immune exclusion through structural and biochemical mechanisms. Dense ECM deposition alters immune cell trafficking and creates physical barriers that limit infiltration of effector lymphocytes. Moreover, activated stromal cells produce immunomodulatory mediators that suppress inflammatory responses and favor tumor tolerance^[6,77].

This relationship has important therapeutic implications, as fibrosis may influence responsiveness to immune-based cancer therapies^[78]. The persistence of a fibrotic microenvironment may therefore represent a major determinant of treatment resistance and highlights the potential value of combining antifibrotic strategies with immunotherapeutic approaches^[79].

Angiogenesis and vascular remodeling

Fibrosis is closely associated with profound alterations in hepatic vascular architecture. Progressive ECM deposition induces sinusoidal capillarization, characterized by loss of fenestrations in liver sinusoidal endothelial cells and impaired exchange between blood and hepatocytes^[80]. These vascular changes contribute to hypoxia, altered nutrient delivery, and activation of angiogenic pathways.

Hypoxia within fibrotic tissue stimulates stabilization of hypoxia-inducible factors (HIFs), which promote transcription of angiogenic mediators including VEGF and PDGF. Activated HSCs, endothelial cells, and macrophages further contribute to angiogenic signaling by releasing pro-angiogenic factors that support vascular remodeling^[74].

The resulting abnormal vasculature facilitates tumor initiation by providing survival signals to transformed cells and supports tumor expansion by supplying oxygen and nutrients. Moreover, dysfunctional tumor-associated vessels contribute to immune suppression by limiting immune cell trafficking and promoting endothelial expression of inhibitory molecules^[81,82].

Thus, fibrosis creates a vascular environment that favors malignant transformation and tumor progression. The intimate relationship between fibrogenesis, angiogenesis, and carcinogenesis explains why advanced fibrosis remains one of the strongest predictors of HCC development.

Genomic instability and the fibrotic tumor microenvironment

Although fibrosis does not directly induce genetic mutations, it creates the biological conditions that promote genomic instability and clonal selection. Chronic oxidative stress generated by inflammation, mitochondrial dysfunction, and metabolic injury causes DNA damage, impaired repair mechanisms, and accumulation of mutations within hepatocytes^[83]. Repeated cycles of hepatocyte death and regeneration further increase the probability that genetically altered cells expand within a selective environment. Recent spatial and single-cell analyses have demonstrated that HCC arises within highly organized cellular niches composed of malignant cells, fibroblasts, immune populations, and endothelial cells. These findings reinforce the concept that carcinogenesis is not solely a hepatocyte-autonomous process but emerges from interactions between transformed cells and their surrounding fibrotic ecosystem^[84].

Consequently, fibrosis should no longer be regarded merely as a marker of advanced liver disease but as an active driver of hepatocellular carcinogenesis. Through persistent inflammation, ECM remodeling, immune dysfunction, vascular alteration, and promotion of genomic instability, the fibrotic liver creates a tumor-permissive environment that facilitates malignant transformation and progression. Consequently, therapeutic strategies capable of preventing or reversing fibrosis may represent an important avenue not only for improving liver function but also for reducing the long-term burden of HCC in MASLD. Fibrosis is not merely a consequence of chronic liver disease but an active promoter of hepatocarcinogenesis.

THERAPEUTIC STRATEGIES FOR FIBROSIS REVERSAL IN MASLD

The therapeutic landscape of MASLD has evolved from targeting metabolic abnormalities alone towards a multidimensional approach addressing the interconnected processes of metabolic injury, inflammation, and fibrosis. Although lifestyle modification and metabolic therapies remain the foundation of disease management, their antifibrotic effects are frequently indirect and depend on successful modification of the underlying drivers of disease. In contrast, emerging direct antifibrotic strategies aim to interfere with the cellular and molecular mechanisms responsible for ECM accumulation and fibrogenic persistence. Given the complexity of MASLD pathogenesis, future therapeutic success will likely require rational combination approaches that simultaneously target metabolic dysfunction, inflammation, and fibrosis^[2,16].

Lifestyle-based interventions

Lifestyle modification remains the cornerstone of MASLD treatment and represents the most established strategy for improving hepatic steatosis, inflammation, and, in selected patients, fibrosis. Weight reduction is the most powerful determinant of histological improvement, with sustained loss of approximately 7-10% of body weight associated with meaningful reductions in steatohepatitis activity and potential fibrosis regression. Mechanistically, weight loss reduces adipose tissue inflammation, improves insulin sensitivity, decreases hepatic lipid influx, and attenuates lipotoxic stress, thereby indirectly reducing activation of inflammatory and fibrogenic pathways^[20,85,86].

Physical exercise provides additional metabolic and hepatic benefits independent of substantial weight loss. Aerobic and resistance training improve mitochondrial function, insulin sensitivity, and energy metabolism while reducing hepatic fat content. Exercise may also exert direct antifibrotic effects by decreasing oxidative stress, modulating inflammatory signaling, and improving the hepatic microenvironment^[87-89].

Bariatric surgery represents the most effective intervention for substantial and sustained weight reduction and has demonstrated marked improvements in steatosis, steatohepatitis, and fibrosis in patients with severe obesity. Beyond weight loss, bariatric procedures induce profound metabolic remodeling through changes in bile acid metabolism, gut hormone signaling, and microbiome composition. However, because only a subset of patients with MASLD are eligible for surgery, pharmacological strategies that reproduce these metabolic effects remain a major therapeutic priority^[24,48,90,91].

Metabolism-directed pharmacotherapy

Recent advances in metabolic pharmacology have significantly expanded therapeutic options for MASLD. Although these agents were not initially developed as antifibrotic therapies, several demonstrate indirect antifibrotic activity by reducing the metabolic stress that initiates and sustains fibrogenesis^[92,93].

Glucagon-like peptide-1 (GLP-1) receptor agonists such as semaglutide promote weight loss, improve insulin sensitivity, reduce hepatic steatosis, and suppress inflammatory pathways. Their beneficial effects on liver disease are primarily mediated through improved systemic metabolism and reduced lipotoxicity, although direct actions on hepatocytes, macrophages, and HSCs have also been suggested^[94,95].

Dual and triple incretin agonists, targeting combinations of GLP-1, glucose-dependent insulintropic polypeptide (GIP), and glucagon receptors, represent a next generation of metabolic therapies. These agents induce substantial weight reduction and improve glucose and lipid metabolism, potentially providing greater effects on liver inflammation and fibrosis. Their long-term impact on fibrosis outcomes remains under investigation^[96].

Peroxisome proliferator-activated receptor (PPAR) agonists target key regulators of lipid metabolism, inflammation, and insulin sensitivity. Activation of PPAR- γ promotes adipocyte differentiation and improves insulin sensitivity, whereas PPAR- α enhances fatty acid oxidation. Pan-PPAR agonists have demonstrated antifibrotic potential by simultaneously modulating metabolic and inflammatory pathways^[97,98].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, although primarily used for diabetes and cardiovascular protection, reduce hepatic steatosis, improve mitochondrial function, and attenuate oxidative stress. Their antifibrotic effects are likely indirect but may become clinically relevant through long-term reduction of metabolic and inflammatory stress^[99].

Although GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists have demonstrated beneficial effects on hepatic inflammation and fibrosis in clinical and preclinical studies, current evidence does not support a major direct antifibrotic action on human HSCs. Recent experimental data indicate that GLP-1 and GIP agonism does not directly alter fibrotic responses in human HSCs, suggesting that the antifibrotic effects observed clinically are predominantly mediated indirectly through weight loss, improved insulin sensitivity and glycemic control, reduced metabolic stress and attenuation of systemic and hepatic inflammation^[100]. Thus, the beneficial effects of GLP-1 receptor agonists are likely to manifest *in vivo* under the conditions of the study, but may not be recapitulated *in vitro* using established cell lines^[101].

Overall, metabolism-directed therapies primarily act through indirect antifibrotic mechanisms by removing upstream drivers of fibrosis. However, because established fibrosis can persist despite metabolic improvement, direct targeting of fibrogenic pathways remains necessary in patients with advanced disease^[102].

Direct antifibrotic therapies

To provide a conceptual framework for the therapeutic strategies discussed below, [Figure 2](#) illustrates the MASLD/MASH fibrosis-HCC axis and summarizes complementary intervention levels, including lifestyle-based interventions, metabolism-directed pharmacotherapies, immunomodulatory approaches, and direct antifibrotic therapies. Within this framework, direct antifibrotic therapies aim to inhibit the cellular processes responsible for ECM deposition, fibrosis maintenance, and scar persistence. HSCs represent a central therapeutic target because their transition into activated myofibroblasts drives collagen production and fibrotic matrix accumulation.

Targeting TGF- β signaling remains one of the most attractive approaches, given its central role in myofibroblast activation and collagen synthesis. However, systemic inhibition of TGF- β is limited by its essential functions in immune regulation and tissue homeostasis. More selective strategies targeting local activation mechanisms or downstream signaling pathways may therefore provide improved therapeutic safety^[103,104].

The PDGF pathway represents another important regulator of HSC proliferation, migration, and survival. Although broad PDGF inhibition has been challenging clinically, more selective approaches targeting fibrogenic signaling remain under investigation^[59,105].

Beyond cellular activation, antifibrotic therapies increasingly focus on ECM remodeling. Inhibition of lysyl oxidase-like protein 2 (LOXL2) aims to reduce collagen cross-linking and matrix stabilization, thereby enhancing scar reversibility. Cellular communication network factor 2 (CCN2), formerly known as connective tissue growth factor (CTGF) promotes fibroblast activation and ECM production and represents another potential therapeutic target. Galectin-3, a regulator of inflammation and fibrosis, contributes to

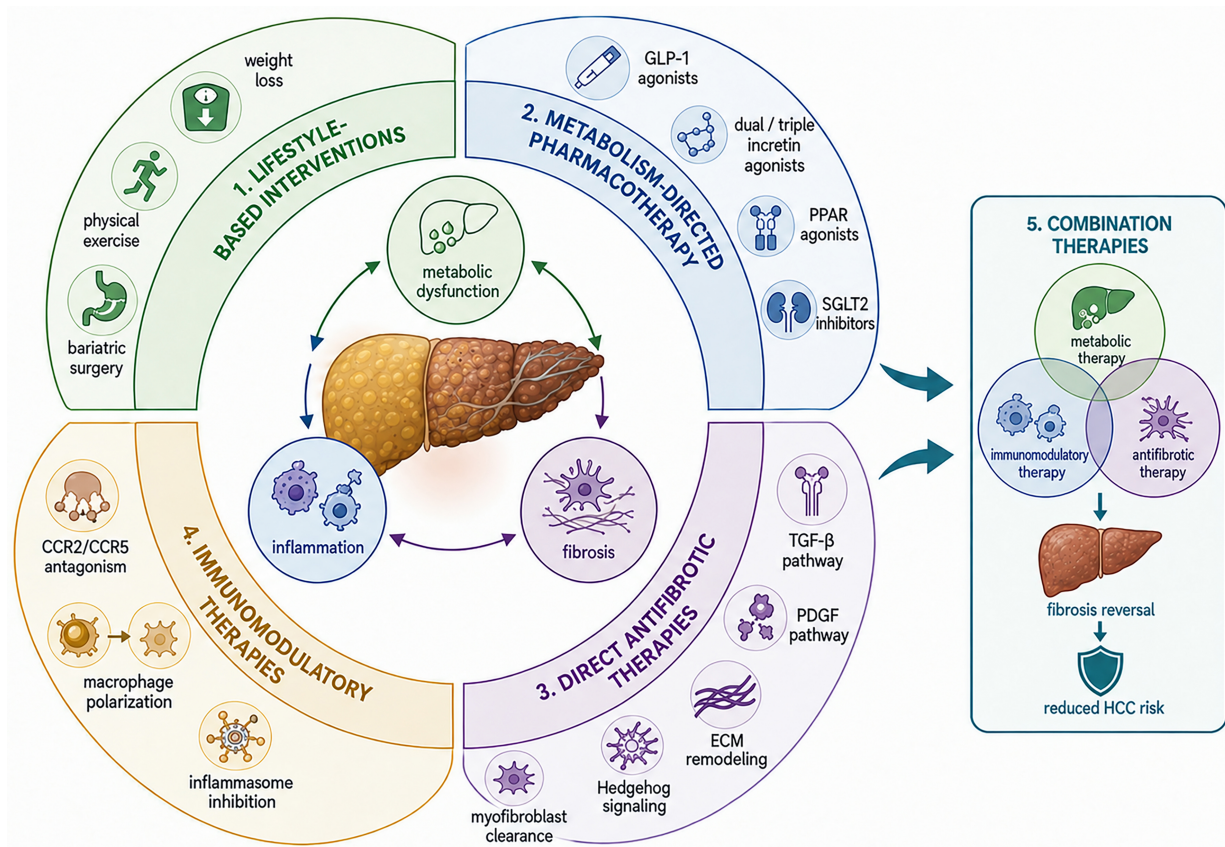


Figure 2. Therapeutic strategies targeting the MASLD/MASH fibrosis-HCC axis. Conceptual overview of interventions aimed at interrupting the pathogenic cycle linking metabolic dysfunction, hepatic inflammation, fibrosis, and hepatocarcinogenesis in MASLD/MASH. Lifestyle-based interventions, including weight loss, physical exercise, and bariatric surgery, target upstream metabolic drivers. Metabolism-directed pharmacotherapies, such as GLP-1 receptor agonists, dual or triple incretin agonists, PPAR agonists, and SGLT2 inhibitors, primarily improve systemic and hepatic metabolic dysfunction. Direct antifibrotic therapies target fibrogenic pathways, including TGF- β and PDGF signaling, Hedgehog signaling, ECM remodeling, and myofibroblast persistence or clearance. Immunomodulatory approaches, including CCR2/CCR5 antagonism, modulation of macrophage polarization, and inflammasome inhibition, aim to reduce inflammatory signaling that sustains fibrogenesis. Combination therapies integrating metabolic, immunomodulatory, and antifibrotic mechanisms may provide the greatest potential for fibrosis regression and, consequently, reduction of HCC risk. The figure was conceptually designed by the authors and visually developed with assistance from ChatGPT (OpenAI). CCR2/CCR5: C-C chemokine receptor 2/5; ECM: extracellular matrix; GLP-1: glucagon-like peptide-1; HCC: hepatocellular carcinoma; MASLD: metabolic dysfunction-associated steatotic liver disease; MASH: metabolic dysfunction-associated steatohepatitis; PDGF: platelet-derived growth factor; PPAR: peroxisome proliferator-activated receptor; SGLT2: sodium-glucose cotransporter 2; TGF- β : transforming growth factor- β .

macrophage activation and HSC stimulation, making it an attractive target for intervention. Furthermore, integrin inhibitors, particularly those targeting α v-containing integrins, may suppress fibrosis by preventing activation of latent TGF- β and disrupting mechanotransduction pathways^[106-109].

The Hedgehog signaling pathway has also emerged as an important regulator of HSC activation, myofibroblast persistence, and tissue repair responses. Modulating Hedgehog activity may therefore influence both fibrosis progression and regression^[110].

An additional therapeutic concept is the promotion of myofibroblast clearance. Rather than simply inhibiting activation, strategies inducing apoptosis, senescence, or reversion of activated HSCs may actively promote fibrosis resolution^[111]. Together, these approaches highlight the need to target not only individual profibrotic pathways but also the broader fibrotic microenvironment that sustains ECM remodeling, scar persistence, and potentially HCC-promoting tissue alterations, as summarized in Figure 2.

Immunomodulatory therapies

Because chronic inflammation sustains fibrosis, immune-directed therapies represent an important component of antifibrotic development. The chemokine pathways CCR2 and CC chemokine receptor 5 (CCR5) regulate recruitment of inflammatory monocytes and macrophages into the injured liver. Dual CCR2/CCR5 antagonism has demonstrated antifibrotic effects by reducing inflammatory cell recruitment and modulating macrophage activity, at least in mice^[112,113].

Beyond chemokine inhibition, therapeutic approaches increasingly aim to restore beneficial immune states. Modulating macrophage polarization from inflammatory towards restorative phenotypes may enhance ECM degradation and fibrosis resolution^[114]. Similarly, inhibition of inflammasome activation, particularly the NLRP3 inflammasome, may reduce inflammatory cytokine production and hepatocyte injury^[25]. However, immune modulation must be carefully balanced, as complete suppression of inflammatory pathways may impair tissue repair and immune surveillance.

Combination therapies: the future of fibrosis reversal

Given the multifactorial nature of MASLD, single-agent therapy is unlikely to achieve complete fibrosis reversal in advanced disease. MASLD simultaneously involves metabolic dysfunction, chronic inflammation, and persistent fibrogenic activation, each reinforcing the others through complex feedback mechanisms. Future therapeutic strategies will therefore likely require rational combinations of metabolic, anti-inflammatory, and direct antifibrotic agents. Metabolic therapies may reduce the initiating insult, immunomodulatory approaches may suppress chronic inflammatory amplification, and direct antifibrotic therapies may promote ECM degradation and restoration of tissue architecture^[115]. Such combination approaches resemble strategies successfully implemented in oncology and infectious diseases, where targeting multiple disease-driving pathways produces superior outcomes compared with single pathway inhibition. In MASLD, addressing the underlying metabolic dysfunction together with fibrosis-directed therapies may offer a complementary approach to promoting durable fibrosis regression and potentially reducing the long-term risk of HCC^[20,116-119]. Therefore, fibrosis reversal in MASLD will likely require a paradigm shift from targeting individual pathways towards precision combination therapies that simultaneously address metabolic dysfunction, inflammatory persistence, and fibrogenic remodeling^[35].

CAN ANTIFIBROTIC THERAPY PREVENT HEPATOCELLULAR CARCINOMA?

The prevention of HCC represents the ultimate clinical goal of antifibrotic therapy in MASLD^[3]. While fibrosis regression has traditionally been considered an indicator of improved liver prognosis, the emerging concept that fibrosis actively contributes to carcinogenesis raises a fundamental question: can reversing fibrosis modify the long-term risk of malignant transformation^[6,120,121]? If fibrosis is not merely a consequence but a driver of HCC development, then effective antifibrotic therapy may represent a form of cancer prevention^[3]. However, the relationship between fibrosis regression and HCC risk reduction is complex. Regression of scar tissue may substantially improve the hepatic microenvironment, but residual molecular alterations may persist, maintaining a degree of oncogenic potential even after apparent histological improvement.

Evidence from experimental models

Experimental models provide compelling evidence that fibrosis is not simply associated with carcinogenesis but actively promotes tumor initiation and progression. In mouse models of chronic liver injury, persistent activation of HSCs, ECM accumulation, and inflammatory signaling create a tumor-permissive environment characterized by increased hepatocyte proliferation, immune dysfunction, and altered stromal signaling^[122,123]. Genetic or pharmacological inhibition of fibrogenic pathways has been shown to reduce tumor burden in several models, supporting the concept that fibrosis itself represents a modifiable determinant of cancer

risk^[124,125]. Studies targeting key fibrogenic pathways demonstrate that suppression of HSC activation can influence carcinogenesis. Inhibition of TGF- β signaling, modulation of macrophage-driven inflammation, and interference with ECM-associated pathways reduce tumor-promoting signals within the liver microenvironment^[126]. Similarly, strategies promoting fibrosis regression, including depletion or reprogramming of activated myofibroblasts and restoration of matrix degradation, have been associated with reduced tumor development in experimental settings^[127]. Importantly, experimental studies have also revealed that the relationship between fibrosis and cancer is bidirectional. While fibrosis promotes carcinogenesis through inflammation, mechanical stress, and immune dysregulation, emerging tumors further remodel the fibrotic niche to support their own growth. Therefore, early intervention during the fibrogenic phase may provide the greatest opportunity to prevent malignant transformation^[6,128,129].

Clinical evidence linking fibrosis regression to reduced HCC risk

Clinical evidence supporting a direct cancer-preventive effect of antifibrotic therapy remains limited, largely because HCC development requires years or decades of follow-up and most antifibrotic trials have focused on histological improvement rather than cancer outcomes. Nevertheless, observational data strongly support fibrosis stage as the dominant determinant of HCC risk across chronic liver diseases, including MASLD^[130]. Patients achieving sustained suppression of the underlying liver injury, such as those successfully treated for chronic hepatitis C virus infection, demonstrate substantial reductions in HCC incidence^[131]. Importantly, the greatest reduction in cancer risk occurs in patients with significant fibrosis regression and elimination of ongoing inflammatory injury. These observations provide indirect evidence that modifying the fibrotic environment can influence carcinogenesis^[132]. Thus, substantial fibrosis regression may be associated with a reduced risk of hepatocellular carcinoma; however, this association does not establish a causal relationship, and its extrapolation to MASLD remains indirect and requires further validation.

In MASLD, the evidence is more challenging to interpret because metabolic dysfunction often persists despite improvement in steatosis or inflammation. Patients with advanced fibrosis remain at increased HCC risk even after metabolic improvement, highlighting that fibrosis represents both a marker of cumulative injury and an active determinant of future cancer development^[51]. Consequently, therapies capable of inducing true fibrosis regression may offer additional benefits beyond metabolic control by reducing the tumor-promoting properties of the fibrotic niche^[133]. However, whether pharmacological antifibrotic therapies directly reduce HCC incidence remains unproven. Current clinical trials are primarily designed around surrogate endpoints, including fibrosis stage, non-invasive biomarkers, and liver-related outcomes. Long-term prospective studies will be required to determine whether fibrosis regression achieved through targeted therapy translates into measurable reductions in cancer incidence.

Biomarkers predicting cancer prevention

Reliable biomarkers capable of identifying patients who achieve meaningful fibrosis reversal and reduced HCC risk are essential for evaluating antifibrotic strategies. Traditional fibrosis assessment by liver biopsy provides valuable histological information but is limited by sampling variability and cannot be repeatedly performed for long-term monitoring^[21,134].

Non-invasive biomarkers, including transient elastography, magnetic resonance elastography, and serum fibrosis scores such as the Enhanced Liver Fibrosis (ELF) test, provide complementary measures of fibrosis burden and ECM activity^[135,136]. Particularly, biomarkers reflecting active matrix remodeling may be more informative than static fibrosis measurements because they capture ongoing biological processes associated with cancer risk^[68]. Beyond conventional fibrosis markers, emerging molecular approaches may improve prediction of cancer prevention^[3]. Circulating extracellular vesicles, circulating tumor DNA, epigenetic signatures, transcriptomic profiles, and spatial genomics and molecular analyses may identify persistent

oncogenic activity despite apparent fibrosis regression. Integration of these biomarkers with clinical parameters may enable personalized surveillance strategies and identify patients who continue to require HCC monitoring despite therapeutic improvement^[137]. Importantly, reduction in fibrosis biomarkers should not automatically be interpreted as complete elimination of cancer risk. The biological consequences of chronic injury may persist beyond measurable changes in ECM deposition^[50,138].

Fibrotic memory and residual cancer risk

A major emerging concept in hepatocarcinogenesis is that fibrosis regression does not necessarily restore the liver to a completely normal state. Similar to other chronic tissue diseases, the liver may retain a form of fibrotic memory characterized by persistent molecular and cellular alterations that maintain susceptibility to malignant transformation^[4,139].

One component of fibrotic memory is the persistence of molecular scars within the hepatic microenvironment. Even after collagen degradation and reduction of fibrosis stage, residual changes in stromal architecture, altered cellular interactions, and persistent activation of inflammatory pathways may remain. Activated fibroblast populations can undergo incomplete reversion, maintaining transcriptional programs associated with tissue repair and tumor promotion^[4,139]. A second mechanism involves epigenetic memory. Chronic metabolic stress and inflammation induce stable alterations in DNA methylation, histone modification, and chromatin accessibility within hepatocytes and non-parenchymal cells. These changes can persist after removal of the initial stimulus and may maintain abnormal gene expression patterns associated with proliferation, oxidative stress resistance, and impaired tumor surveillance^[4,30].

Finally, fibrosis regression may not fully reverse all carcinogenic pathways activated during chronic liver injury. Long-standing inflammation can generate irreversible genomic alterations, including mutations affecting tumor suppressor genes, oncogenic pathways, and DNA repair mechanisms. Once genetically altered hepatocyte clones have emerged, removal of the fibrotic environment may reduce but not eliminate their malignant potential^[49,133]. These concepts have major implications for clinical management. Even patients with substantial fibrosis regression may require continued HCC surveillance if they have experienced prolonged periods of advanced fibrosis, metabolic injury, or cirrhosis. The goal of antifibrotic therapy should therefore be viewed as reducing cancer risk rather than completely abolishing it^[140].

Importantly, fibrotic memory may represent a persistent molecular state that remains even after the initial metabolic or inflammatory insult has been controlled. Epigenetic alterations, metabolic reprogramming, and persistent activation of HSCs may therefore constitute molecular scars that predispose the liver to renewed fibrogenesis^[141]. This concept raises the hypothesis that therapeutic reversal of such persistent cellular programs—through epigenetic modulation, metabolic reprogramming, or targeted inhibition of fibrogenic cell states—could promote more durable fibrosis regression. Future studies should therefore determine whether these molecular scars are reversible and whether their targeted elimination can prevent fibrosis recurrence or progression^[142].

In summary, fibrosis regression represents a promising strategy for reducing HCC risk by restoring hepatic architecture, decreasing inflammatory signaling, and disrupting tumor-promoting microenvironmental interactions. However, fibrosis reversal does not necessarily equate to complete elimination of HCC risk. Persistent molecular scars, epigenetic memory, and irreversible genetic alterations may maintain residual carcinogenic potential despite apparent improvement in fibrosis. Future antifibrotic therapies should therefore be evaluated not only by their ability to reverse fibrosis but also by their capacity to prevent malignant transformation and modify long-term cancer outcomes.

CLINICAL TRIALS AND EMERGING THERAPEUTIC LANDSCAPE

Recent clinical trials in MASH/MASLD-associated fibrosis highlight a rapidly evolving therapeutic landscape in which metabolism-directed and pleiotropic agents appear to show the most consistent histological signals [Table 1]. Resmetirom, a selective thyroid hormone receptor- β (THR- β) agonist evaluated in the Phase III MAESTRO-NASH trial, has demonstrated significant fibrosis improvement and represents a key milestone as the first therapy in this group to achieve regulatory approval on the basis of reproducible histological benefit^[143]. Incretin-based therapies, including semaglutide and tirzepatide, have shown clinically relevant effects, with semaglutide producing stronger effects on MASH resolution than fibrosis improvement and tirzepatide demonstrating significant fibrosis improvement in Phase II^[95,145]. Fibroblast growth factor 21 (FGF21) analogs such as efruxifermin and pegozafermin have also produced significant antifibrotic signals in Phase IIb studies, supporting the FGF21 pathway as a promising therapeutic target^[146,148]. By contrast, several agents targeting narrower inflammatory or fibrogenic pathways, including cenicriviroc and selonsertib, failed to confirm earlier signals in Phase III trials, underscoring the limitations of single-pathway inhibition in advanced disease. Obeticholic acid demonstrated histological benefit, but its development was discontinued because of an unfavorable benefit-risk profile, illustrating that antifibrotic efficacy alone may be insufficient for clinical success. Importantly, no completed randomized clinical trial has yet demonstrated a reduction in HCC incidence, largely because available studies were not designed or followed long enough to assess liver cancer prevention. Overall, current drug development increasingly favors combination approaches and pleiotropic metabolic therapies that target steatohepatitis, fibrosis, and the broader metabolic drivers of disease progression.

FUTURE PERSPECTIVES

The field of MASLD is undergoing a paradigm shift from a descriptive understanding of disease towards a precision medicine framework that integrates molecular profiling, risk prediction, and personalized therapeutic strategies. Rather than representing isolated technological advances, emerging developments collectively aim to improve patient stratification, optimize treatment allocation, and ultimately prevent disease progression and HCC^[4,54,152-154]. MASLD is a systemic metabolic disorder, and its clinical burden extends beyond liver-related complications, with cardiovascular disease and extrahepatic malignancies representing major contributors to morbidity and mortality. Accordingly, strategies aimed at reducing hepatic fibrosis and HCC risk should be integrated into a broader management approach addressing the cardiometabolic and extrahepatic consequences of MASLD^[155,156].

A central challenge is the identification of patients at greatest risk of progressive fibrosis, cirrhosis, and HCC, as only a subset of individuals with MASLD experience clinically significant disease progression^[20,21,24,120]. Until now, there have been no screening programs in place for early detection of liver fibrosis^[120]. Improved patient selection and timely therapeutic intervention therefore represent key priorities. The integration of clinical, biochemical, imaging, and molecular biomarkers is expected to facilitate earlier identification of high-risk individuals, enabling targeted surveillance and intervention before irreversible liver injury occurs^[157]. These advances underpin the transition towards precision medicine, whereby clinical decision-making is informed by an individual's genetic, metabolic, and molecular profile. Given the multifactorial pathogenesis of MASLD, involving interconnected metabolic, inflammatory, and fibrogenic pathways, combination therapies targeting complementary mechanisms are increasingly regarded as a rational strategy to achieve greater therapeutic efficacy than single-agent approaches^[98,115].

Concurrently, rapid advances in systems biology are transforming our understanding of disease mechanisms. Multi-omics approaches, integrating genomic, transcriptomic, proteomic, metabolomic, and lipidomic data, provide a comprehensive characterization of the molecular networks driving disease progression. These insights are further refined by single-cell sequencing, which resolves the cellular heterogeneity of the liver,

Table 1. Selected current and emerging therapies for MASH/MASLD-associated fibrosis and implications for HCC prevention¹

Therapy/Target	Trial/Phase/Key clinical evidence	Fibrosis improvement	HCC outcome data	Clinical interpretation
Resmetirom selective THR- β agonist	MAESTRO-NASH ^[143] NCT03900429 Phase III	Significant (24%-26% vs. 14% placebo)	No direct HCC data; long-term follow-up ongoing	First FDA-approved agent for MASH with moderate-to-advanced fibrosis
Semaglutide GLP-1 receptor agonist	ESSENCE ^[95] NCT04822181 Phase III	Significant but less pronounced than MASH resolution	No HCC data	Highlights potential dissociation between inflammatory resolution and structural reversal
Lanifibranor Pan-PPAR agonist	NATIVE extension ^[144] NCT04849728 Phase 2b program	Significant (48% vs. 29% placebo)	No HCC data	Multi-target metabolic modulation remains promising but awaits confirmatory Phase III evidence
Tirzepatide (Dual GIP/GLP-1 receptor agonist)	SYNERGY-NASH ^[145] NCT04166773 Phase II	Significant improvement (51%-55% responder rate vs. 30% placebo)	No HCC data	Marked metabolic efficacy supports multi-incretin strategies in progressive MASH
Efruxifermin (FGF21 analog)	HARMONY ^[146,147] NCT04767529 Phase IIb	Significant improvement (39%-41% vs. 20% placebo)	No HCC data	Demonstrates strong direct antifibrotic efficacy signals among investigational biologics
Pegozafermin FGF21 analog	ENLIVEN ^[148] NCT04929483 Phase IIb	Significant improvement (22%-27% vs. 7% placebo)	No HCC data	Confirms FGF21 pathway as a promising therapeutic target
Obeticholic acid (FXR agonist)	REGENERATE ^[149] Regulatory follow-up (2015-2018) NCT02548351 Phase III	Histological benefit, Significant improvement (23% vs. 12% placebo)	No HCC data	Development discontinued owing to an unfavorable benefit-risk profile despite antifibrotic efficacy
Cenicriviroc CCR2/CCR5 antagonist	AURORA ^[150] Termination (2022) NCT03028740 Phase III	No	No HCC data	Initial Phase II signal could not be replicated in Phase III
Selonsertib ASK1 inhibitor	STELLAR-3 and STELLAR-4 ^[151] Long-term analyses (2020) NCT03053050 NCT03053063 Phase III	No	No HCC data	Single-pathway inhibition proved insufficient in advanced fibrosis

¹Remarks: Metabolic-directed therapies, including THR- β agonists, FGF21 analogs, and incretin-based therapies, have shown more consistent histological signals than several single-pathway anti-inflammatory or antifibrotic approaches, although cross-trial comparisons remain indirect and should be interpreted cautiously. Several agents that showed encouraging Phase II efficacy failed during Phase III validation, emphasizing the necessity of confirmatory trials with robust histological endpoints. To date, no completed randomized clinical trial has demonstrated a reduction in HCC incidence; importantly, most trials were not designed or powered to assess HCC prevention, and follow-up durations remain insufficient for liver-related clinical outcomes. Current development increasingly favors combination or pleiotropic metabolic therapies over single-target approaches. ASK1: Apoptosis signal-regulating kinase 1; CCR2/CCR5: C-C chemokine receptor 2/5; ECM: extracellular matrix; FDA: Food and Drug Administration; FGF21: fibroblast growth factor 21; FXR: farnesoid X receptor; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide-1; HCC: hepatocellular carcinoma; MASLD: metabolic dysfunction-associated steatotic liver disease; MASH: metabolic dysfunction-associated steatohepatitis; NASH: non-alcoholic steatohepatitis; PDGF: platelet-derived growth factor; PPAR: peroxisome proliferator-activated receptor; THR- β : thyroid hormone receptor- β .

and spatial transcriptomics, which preserves tissue architecture while revealing cell-specific gene expression and intercellular interactions^[54]. Together, these technologies offer unprecedented insight into the mechanisms underlying fibrosis progression and hepatocarcinogenesis. Liquid biopsy represents another promising development. The analysis of circulating biomarkers, including cell-free DNA, RNA, extracellular vesicles, and proteins, offers a minimally invasive approach for longitudinal disease monitoring, early HCC detection, and assessment of treatment response, with the potential to reduce reliance on repeated liver biopsies^[66].

The increasing availability of high-dimensional clinical and molecular datasets has also accelerated the application of artificial intelligence (AI). Machine learning algorithms can integrate diverse data modalities

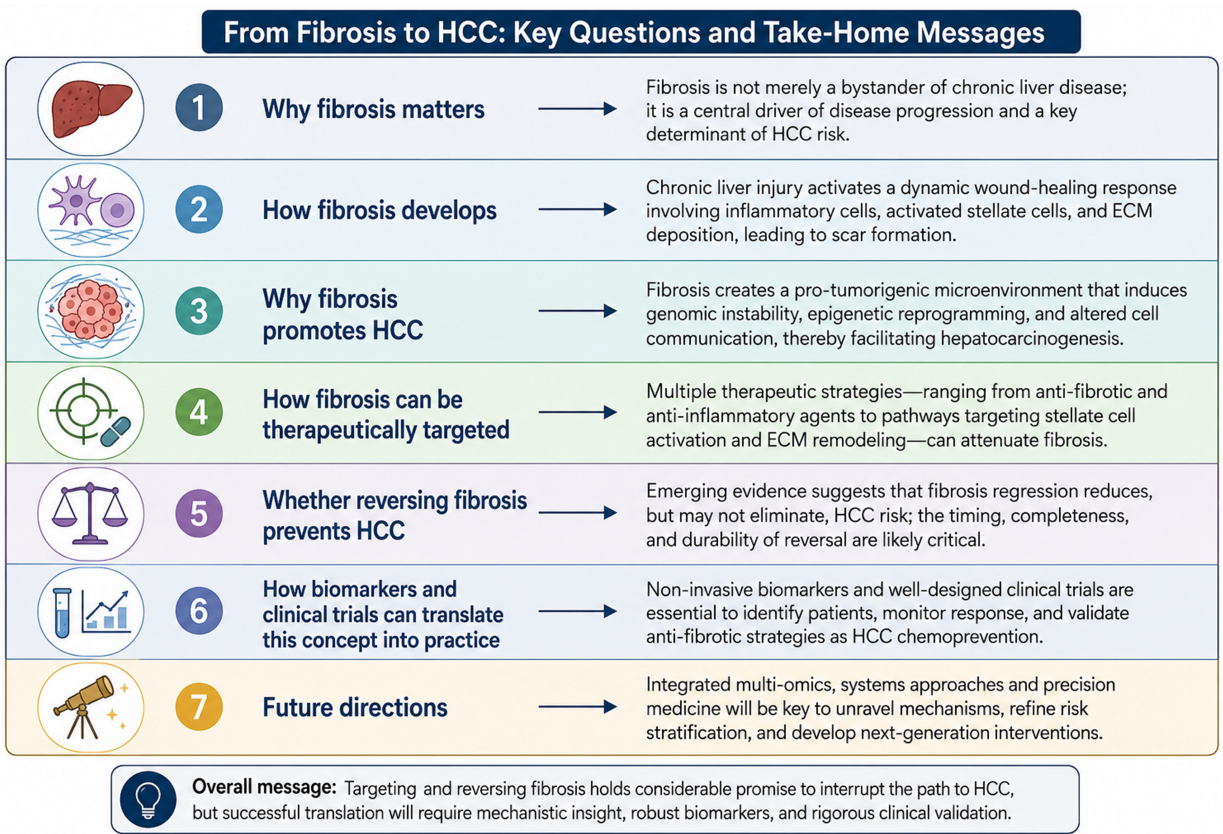


Figure 3. From fibrosis to HCC: key questions and take-home messages. Summary of the central concepts addressed in this review regarding fibrosis-driven hepatocarcinogenesis in MASLD and especially MASH. Fibrosis is not only a marker of chronic liver injury but also a major determinant of disease progression and HCC risk. Chronic hepatic injury activates wound-healing responses involving inflammatory cells, hepatic stellate cell activation, myofibroblast accumulation, and ECM deposition. The resulting fibrotic microenvironment promotes hepatocarcinogenesis through altered tissue architecture, genomic instability, epigenetic reprogramming, immune dysregulation, and disrupted intercellular communication. Therapeutic targeting of fibrosis may be achieved through antifibrotic, anti-inflammatory, metabolic, and stellate-cell-directed approaches. Although fibrosis regression is expected to reduce HCC risk, residual risk may persist depending on the timing, completeness, and durability of fibrosis reversal. Reliable non-invasive biomarkers, molecular risk signatures, and rigorously designed clinical trials are therefore essential to monitor therapeutic response, refine patient selection, and validate antifibrotic strategies as approaches to HCC chemoprevention. Integrated multi-omics, systems biology, and precision-medicine approaches will be critical for developing next-generation interventions. The figure was conceptually designed by the authors and visually developed with assistance from ChatGPT (OpenAI). ECM: Extracellular matrix; HCC: hepatocellular carcinoma; MASLD: metabolic dysfunction-associated steatotic liver disease; MASH: metabolic dysfunction-associated steatohepatitis.

to generate robust predictive models for fibrosis progression, HCC risk, and other clinically relevant outcomes. Such approaches are expected to enhance risk stratification and support personalized clinical decision-making^[12,121]. Finally, the identification of reliable surrogate endpoints for HCC prevention has become a major research priority^[3]. As HCC often develops only after many years of chronic liver disease, conventional clinical endpoints are impractical for therapeutic trials. Validated surrogate biomarkers that accurately reflect future cancer risk would substantially accelerate drug development and facilitate the evaluation of preventive interventions^[6]. Collectively, these developments illustrate the evolution of MASLD research towards a data-driven, molecularly informed, and patient-centered model of care. The integration of advanced biomarkers, multi-omics technologies, artificial intelligence, and rational combination therapies is expected to redefine disease management and improve the prevention of HCC^[3].

CONCLUSION

In conclusion, liver fibrosis is the principal determinant of prognosis in MASLD and may be regarded not merely as a histological marker of disease severity, but as a biologically active driver of hepatocarcinogenesis.

Effective therapeutic strategies may therefore move beyond isolated metabolic or anti-inflammatory approaches and integrate the targeting of metabolic dysfunction, inflammation, and fibrogenesis. In this context, antifibrotic therapy warrants consideration not only as a means to reverse fibrosis, but also as a potential strategy to reduce HCC risk. Future progress will depend on rational combination therapies, precision-medicine approaches, and validated biomarkers that identify patients most likely to benefit from early intervention. Future randomized screening trials should evaluate screening programs as integrated care pathways, assessing not only the diagnostic performance of screening tests but also the effectiveness of interventions aimed at preventing disease progression in individuals identified through screening. A summary of these findings is provided in [Figure 3](#).

DECLARATIONS

Authors' contributions

Conceptualised the study: Roeb E, Weiskirchen R

Contributed to the study design: Roeb E, Weiskirchen R

Performed the literature analysis and interpretation: Roeb E, Weiskirchen R

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool OpenAI GPT-5.5 (version 5.5, released 2026-04-23) was used solely for language editing and creating of the figures without unsupervised automatic generation. In addition, the AI tool ChatGPT-5.6 Luna (version 5.6, released 2026-07-09) was used solely to generate the Graphical Abstract. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

Weiskirchen R serves as the Guest Editor of the Special Topic: Fibrosis Driven Hepatocarcinogenesis in MASLD/MASH: Mechanisms, Biomarkers and Therapeutic Horizons. However, he was not involved in any stage of the editorial handling of this manuscript. Roeb E received honoraria for lectures and consultancy services, as well as reimbursement of travel and accommodation expenses, from the following companies: AbbVie, BMS, Boehringer Ingelheim, Falk Foundation, Gilead, Ipsen, Madrigal, Medac, MSD, Norgine, Pfizer, PM Results, Streamed up, Takeda, Thieme, Wiley Verlag.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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