



Review Article

Hepatic Stellate Cell Heterogeneity in Chronic Liver Fibrosis: Functional States and Translational Opportunities



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Abstract

Hepatic stellate cell (HSC) activation has traditionally been described as a binary transition from vitamin A-rich quiescent cells to alpha-smooth muscle actin-positive, collagen-producing myofibroblast-like cells. Advances in single-cell RNA sequencing, single-nucleus RNA sequencing, spatial transcriptomics, and chromatin-accessibility profiling now reveal a more complex and dynamic landscape. During chronic liver injury, HSCs can adopt five overlapping activation-associated states characterized by injury sensing, inflammatory signaling, proliferation, extracellular matrix production and contractility, together with a senescent state that represents a possible fate of activated HSCs. These states differ in their molecular markers, spatial distribution, regulatory pathways, and interactions with hepatocytes, liver sinusoidal endothelial cells, macrophages, natural killer cells, and cholangiocytes. Importantly, they are not fixed lineages and may coexist or interconvert during fibrosis progression and regression. This review revisits the classical quiescent-activated framework and proposes a state-based approach for interpreting HSC heterogeneity. We summarize the defining features and translational relevance of six major HSC functional states, discuss their multicellular niches, and highlight the opportunities and limitations of function-selective therapeutic targeting. A reproducible classification that integrates molecular identity, spatial context, and causal function may help refine antifibrotic treatment strategies.

Introduction

Liver fibrosis is a common pathological consequence of chronic liver diseases, including metabolic dysfunction-associated steatotic liver disease, viral hepatitis, alcohol-related liver disease, cholestatic liver disease, and autoimmune liver disease. It is characterized by excessive extracellular matrix (ECM) accumulation and progressive remodeling of hepatic architecture. As fibrous septa develop and lobular organization is distorted, intrahepatic vascular resistance increases, potentially leading to portal hypertension, hepatic decompensation, and hepatocellular carcinoma. Histological fibrosis regression has been documented after effective etiologic or pharmacological treatment in selected

settings.^{1–4} However, improvement in fibrosis stage should not be equated with complete reversal of established cirrhosis across all etiologies and disease stages. For example, paired-biopsy analyses in chronic hepatitis B virus infection showed that long-term tenofovir therapy was associated with fibrosis regression and reversal of cirrhosis in a proportion of patients.⁵ These observations establish fibrosis as a dynamic process rather than an invariably fixed end-stage lesion.

Persistent activation of hepatic stellate cells (HSCs) is a central event in fibrogenesis. Lineage-tracing studies have identified HSCs as the dominant collagen-producing population in several experimental models.^{4,6} Nevertheless, portal fibroblasts and mesothelial cells can also contribute to matrix deposition in specific injury contexts, and not all hepatic myofibroblasts therefore originate from HSCs.^{7,8} The classical binary model divides HSCs into quiescent HSCs (qHSCs) and activated HSCs (aHSCs). qHSCs reside in the space of Disse between hepatocytes and liver sinusoidal endothelial cells (LSECs), extend processes along the sinusoidal wall, and contain retinyl ester-rich lipid droplets that facilitate their identification and isolation.⁹ In addition to storing vitamin A, qHSCs maintain the sinusoidal microenvironment and support tissue homeostasis, with representative markers including LRAT, ECM1, and COLEC10.^{10–12} Recent work further demonstrated that qHSC-derived R-spondin 3 (RSPO3) reinforces local

Keywords: Hepatic stellate cells; Chronic liver fibrosis; Functional heterogeneity; Inter-cellular communication; Single-cell RNA sequencing; Therapeutic targeting.

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WNT signaling and contributes to hepatocyte zonation, metabolic function, liver size, and regeneration after injury.¹³ Thus, qHSCs are active organizers of the hepatic niche rather than passive precursors awaiting activation.

Following liver injury, HSCs lose retinoid-containing lipid droplets and become increasingly responsive to paracrine signals from damaged hepatocytes, Kupffer cells, LSECs, and other cell types. Platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF- β), together with increased platelet-derived growth factor receptor beta expression, promote the initiation and maintenance of HSC activation. Persistently activated HSCs acquire proliferative, ECM-synthetic, migratory, and contractile properties and express markers such as ACTA2, TAGLN, COL1A1, and COL1A2.^{12,14-16} When injury resolves, activated HSCs may undergo apoptosis or senescence, or transition into an inactivated state. Inactivated HSCs partially reacquire a quiescence-associated transcriptional program but remain distinct from original qHSCs, indicating that activation is reversible but leaves a molecular memory.¹⁷

The binary qHSC-aHSC framework also inadequately captures spatial heterogeneity. In healthy mouse liver, HSCs exhibit zonation along the portal-central axis: NGFR-high populations are enriched in periportal regions, whereas ADAMTSL2-high populations are more abundant around the central vein.¹⁸ RSPO3 likewise shows a pericentral bias, consistent with its role in maintaining the local WNT niche.¹³ Periportal and pericentral qHSC populations have also been identified in mouse models of steatohepatitis.¹⁷ Human HSC heterogeneity is evident but does not yet map directly onto the mouse system; GPC3-positive HSCs have been reported near portal and central veins, whereas DBH-expressing HSCs are distributed more broadly.¹⁹ Injury location further shapes the fibrogenic response. Centrilobular injury induced by carbon tetrachloride preferentially engages central vein-associated HSCs, whereas cholestatic injury begins in the portal compartment, where portal fibroblasts may contribute substantially to scar formation. Species- and model-specific spatial markers should therefore be interpreted cautiously.

High-resolution omics technologies have refined this classical model by resolving HSC states at single-cell and spatial levels. Single-cell RNA sequencing defines transcriptional programs in individual cells; single-nucleus RNA sequencing facilitates analysis of frozen human tissues; spatial transcriptomics links cell states to anatomic niches; and chromatin-accessibility profiling connects these states to regulatory programs. These approaches further demonstrate that HSC activation cannot be adequately represented as a uniform transition toward a single activated phenotype. Instead, individual HSCs may simultaneously engage partially overlapping functional programs involving injury sensing, inflammatory signaling, proliferation, matrix production, and contractility, and the relative dominance of these programs varies with anatomical location, injury context, and disease stage. Senescence is considered separately within this framework as a functional state that can arise when activated HSCs enter durable cell-cycle arrest. A recent review by Geng and Schwabe systematically summarized HSC heterogeneity from the perspectives of spatiotemporal zonation, intercellular interactions, and the multiple functions of HSCs in homeostasis, fibrosis, regeneration, aging, and cancer.²⁰ Building on these advances, the present review adopts a

more fibrosis-centered and function-oriented framework to integrate heterogeneous HSC populations across experimental models and human liver diseases.

In this framework, a functional state is defined by the predominant biological program and functional output of an HSC within a given spatial, temporal, and pathological context, rather than by a single marker, a fixed lineage, or a mutually exclusive transcriptomic cluster. The six states considered here, injury-responsive, inflammatory, proliferative, ECM-producing, contractile, and senescent HSCs, were selected because these programs recur across studies, have biologically interpretable functions, and are supported to varying degrees by transcriptomic, spatial, mechanistic, and functional evidence. The first five describe functional programs within the activated HSC compartment, whereas senescence is included because it has distinct functional outputs and also represents a possible fate of activated HSCs. Accordingly, [Figure 1](#) depicts senescence alongside apoptosis and inactivation to a qHSC-like state as alternative outcomes of activated HSCs. These categories do not imply six stable subtypes. A single HSC may engage multiple programs simultaneously and may change its predominant function during fibrosis progression or regression. The markers discussed in this review should therefore be interpreted as representative indicators of enriched functional programs rather than state-specific identifiers.

The objective of this review is to establish a function-oriented framework for interpreting HSC heterogeneity across chronic liver diseases and stages of fibrosis, to evaluate the molecular, spatial, and functional evidence supporting each major HSC state, and to determine whether these states reveal clinically meaningful windows for antifibrotic intervention ([Fig. 1](#) and [Table 1](#)).^{10-13,17,18,21-33} We further examine how multicellular niches shape HSC states, distinguish evidence from experimental models from evidence in human liver disease ([Fig. 2](#) and [Table 2](#)),^{21,31,34-43} and critically assess the cell-type specificity and translational potential of candidate therapeutic targets.

This narrative review was informed by a literature search of PubMed and Web of Science conducted through August 2026. Search terms included combinations of “hepatic stellate cell,” “liver fibrosis,” “heterogeneity,” “single-cell RNA sequencing,” “spatial transcriptomics,” “zonation,” “activation,” “inflammation,” “proliferation,” “extracellular matrix,” “contractility,” “senescence,” and “therapeutic targeting.” Additional relevant studies were identified from the reference lists of key original studies and recent reviews. Study selection was guided by the conceptual framework of this review rather than predefined inclusion criteria for a systematic review. Priority was given to original studies that supported HSC functional heterogeneity through single-cell or spatial omics, lineage studies, or direct functional assessment. Human liver studies were prioritized when evaluating clinical relevance and cross-disease reproducibility. Studies based only on transcriptional clustering and lacking spatial or functional validation were interpreted cautiously. Reviews were used mainly to provide background and trace relevant primary studies, whereas conclusions regarding individual HSC states and therapeutic targets were based primarily on original research.

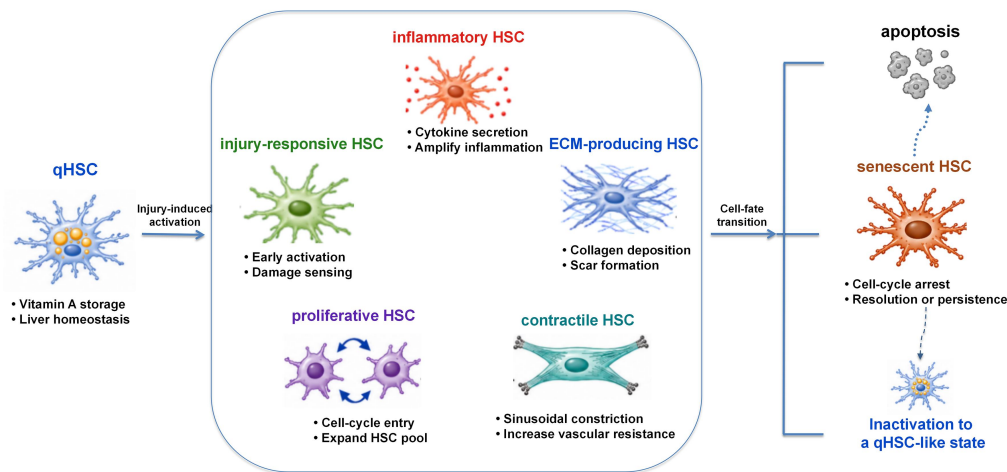


Fig. 1. Functional-state continuum and plasticity of hepatic stellate cells during chronic liver fibrosis. qHSCs maintain vitamin A storage and liver homeostasis. The six-state framework used in this review comprises five activation-associated functional states: injury-responsive, inflammatory, proliferative, ECM-producing, and contractile HSCs, together with a senescent state. After injury, qHSCs enter an injury-responsive state and may acquire overlapping inflammatory, proliferative, ECM-producing, and contractile programs. Senescence is both a functional state and a possible fate of activated HSCs, and is therefore depicted alongside apoptosis and inactivation to a qHSC-like state. Activated HSCs may subsequently undergo apoptosis, enter a persistent senescent state, or transition toward an inactivated qHSC-like state during fibrosis regression. Dashed arrows indicate potential subsequent fates of senescent HSCs: apoptosis or transition to an inactivated qHSC-like state. The schematic represents functional programs and potential transitions; it does not imply fixed morphology, mutually exclusive categories, or a universal sequence across etiologies. ECM, extracellular matrix; qHSC, quiescent hepatic stellate cell; HSC, hepatic stellate cell.

HSC functional states

The following sections organize HSC heterogeneity according to six major functional programs. These states should not be interpreted as mutually exclusive cell populations, nor do they represent fixed stages through which all HSCs must pass sequentially. They are recurrent biological programs that may coexist, and their relative dominance may vary with disease etiology, anatomical location, and fibrosis stage. Accordingly, discussion of each state distinguishes representative molecular features, direct functional evidence, reproducibility across studies, evidence in human disease, and the cell-type specificity of therapeutic targets.

Injury-responsive HSC

Injury-responsive HSCs denote a functional program characterized by enhanced sensing and integration of tissue-damage signals during the initiation or re-initiation of HSC activation. Although this program is often enriched early after injury, it should not be interpreted as an obligatory intermediate through which all HSCs must pass before acquiring other activated states. Their defining features include damage sensing, receptor remodeling, immediate-early transcriptional responses, and initial matrix reorganization. In a cross-etiology single-cell atlas, Merens *et al.* positioned THBS1-high HSCs between qHSCs and myofibroblasts and termed them initiatory HSCs.¹⁰ De Smet *et al.*²¹ further showed that activation-initiation programs are not confined to acute injury but may persist in chronic liver disease. THBS1, ANKRD1, and KLF6 are representative markers; however, each also participates

in broader stress responses and none is sufficiently specific to define this state alone.

Injury-responsive HSCs integrate signals from multiple cellular compartments. High-mobility group box 1 (HMGB1) released by damaged hepatocytes induces endoplasmic reticulum stress and promotes HSC activation.⁴⁴ Uptake of apoptotic bodies increases TGF- β 1 and type I collagen expression and activates oxidative stress-related pathways.^{45,46} During lipotoxic injury, hepatocyte-derived extracellular vesicles deliver microRNAs that suppress peroxisome proliferator-activated receptor gamma and facilitate the transition from quiescence to activation.⁴⁷ Free cholesterol accumulation in HSCs can also increase Toll-like receptor 4 abundance by inhibiting endosomal-lysosomal degradation, thereby sensitizing the cells to TGF- β signaling in experimental steatohepatitis.^{48,49} Through these mechanisms, injury-responsive HSCs convert information on hepatocyte death, metabolic dysfunction, immune activation, and vascular injury into a sustained profibrotic program.

Because this state lies near the entry point of pathological activation, it may provide an opportunity for early intervention. The purinergic P2Y₁₄ receptor is among the most directly supported targets. Hepatocyte-derived nucleotide sugars activate P2Y₁₄-dependent ERK and YAP signaling in HSCs, whereas HSC-specific deletion of P2Y₁₄ reduces activation and fibrosis in experimental models.^{22,50} Small-molecule P2Y₁₄ receptor inhibitors have also attenuated experimental fibrosis by suppressing the protein kinase A/Raf1/MEK/ERK cascade.⁵⁰ Nevertheless, the evidence remains predominantly preclinical, and pharmacological blockade of a pathway should not be equated

Table 1. Functional states, representative markers, principal functions, disease relevance and potential therapeutic targets or translational implications of hepatic stellate cells

Functional state	Representative markers	Principal functions	Disease contexts or stages	Potential therapeutic targets or translational implications	Key references
Quiescent HSCs	LRAT, ECM1, COLEC10	Store vitamin A; maintain hepatocyte zonation, metabolic function, sinusoidal homeostasis, and regeneration	Normal liver and fibrosis regression	Protect or restore homeostatic HSC function; maintain niche signals such as RSPO3	Merens <i>et al.</i> ¹⁰ ; Tsuchida and Friedman ¹¹ ; Friedman ¹² ; Sugimoto <i>et al.</i> ¹³
Injury-responsive HSCs	THBS1, ANKRD1, KLF6	Sense tissue injury, remodel receptors, initiate stress responses, and amplify early activation signals	Early and persistent activation across chronic liver diseases	P2Y14; block injury-derived activation signals	Merens <i>et al.</i> ¹⁰ ; De Smet <i>et al.</i> ²¹ ; Mederacke <i>et al.</i> ²²
Inflammatory HSCs	CCL2, CXCL1, CXCL10, CCL7, IL11, CD36	Receive immune signals, secrete cytokines and chemokines, and amplify inflammation-fibrosis feedback	MASH, chronic hepatitis B, alcohol-associated hepatitis, and carbon tetrachloride injury	CCL2/CCR2; PD-L1; MIF/CD74; cell-directed immunomodulation	Rosenthal <i>et al.</i> ¹⁷ ; Yang <i>et al.</i> ²³ ; Balog <i>et al.</i> ²⁴
Proliferative HSCs	MKI67, TOP2A, CENPF, CDK1, CDC20, STMN1	Expand the activated HSC pool and supply cells for subsequent inflammatory, ECM-producing, or contractile programs	MASH, carbon tetrachloride injury, and advanced fibrosis	PDGF/PDGFR; CD248; TM7SF3-TEAD1-related regulatory networks	Dobie <i>et al.</i> ¹⁸ ; Zhang <i>et al.</i> ²⁵ ; Wilhelm <i>et al.</i> ²⁶
ECM-producing HSCs	COL1A1, COL1A2, COL3A1, ACTA2, TAGLN, MMP2, TIMP1, LOX, LOXL1	Synthesize, crosslink, and stabilize collagen-rich matrix; increase tissue stiffness and sustain scar formation	Most fibrotic etiologies, advanced fibrosis, cirrhosis, and premalignant niches	HSP47/collagen processing; LOX/LOXL; α v β 6/ α v β 1 integrins	Dobie <i>et al.</i> ¹⁸ ; Ramachandran <i>et al.</i> ²⁷ ; Lawitz <i>et al.</i> ²⁸
Contractile HSCs	ACTA2, TAGLN, TPM1, VIM, TNC	Generate mechanical force, regulate sinusoidal caliber, and increase intrahepatic vascular resistance	Fibrosis stages associated with increased sinusoidal resistance and portal pressure	PCDH7; endothelin receptors; Rho kinase; integrin β 1-related pathways	Yang <i>et al.</i> ²³ ; Carter <i>et al.</i> ²⁹ ; Martin <i>et al.</i> ³⁰
Senescent HSCs	MRC1, SLC9A9, PTPRB, STAB2, SEMA6A	Undergo durable cell-cycle arrest; modify matrix turnover, immune surveillance, inflammation, and regeneration through context-dependent SASP programs	Chronic injury, fibrosis regression, liver regeneration, and hepatocarcinogenesis	Induce senescence during pathological expansion; clear senescent cells in persistent SASP phase; uPAR-directed senolytic strategies	Yashaswini <i>et al.</i> ³¹ ; Krizhanovsky <i>et al.</i> ³² ; Cheng <i>et al.</i> ³³

ECM, extracellular matrix; HSC, hepatic stellate cell; MASH, metabolic dysfunction-associated steatohepatitis; SASP, senescence-associated secretory phenotype. Functional states are not mutually exclusive, and the listed markers are representative rather than state-specific

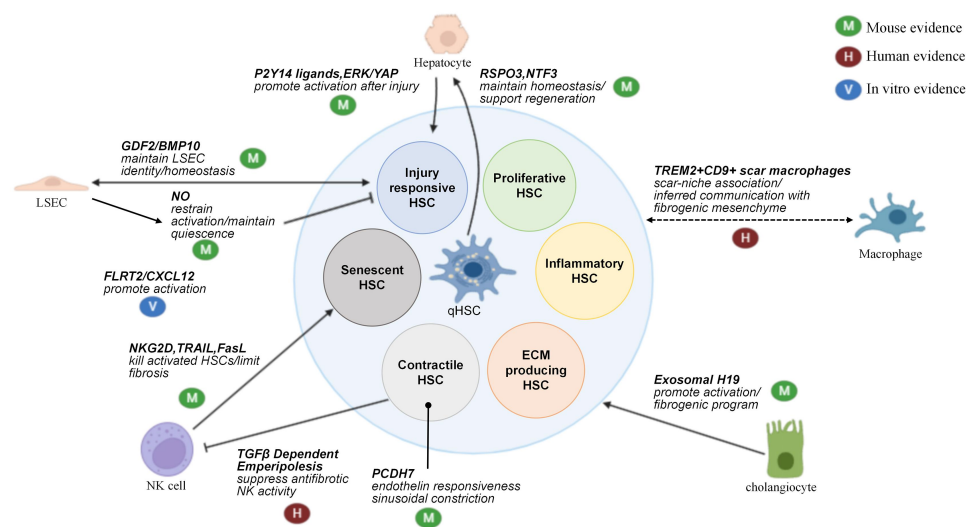


Fig. 2. Multicellular interactions that regulate hepatic stellate cell functional states. Hepatocytes, LSECs, macrophages, NK cells, and cholangiocytes provide signals that promote or restrain quiescent and activated HSC states. Representative pathways include hepatocyte-derived P2Y14 ligands and ERK/YAP signaling; qHSC-derived RSP03 and NTF3; HSC-derived GDF2 and BMP10; endothelial NO and FLRT2/CXCL12; TREM2-positive CD9-positive macrophage-associated signaling; NK-cell NKG2D/TRAIL/FasL-mediated cytotoxicity; TGF- β -dependent emperipolesis; PCDH7-dependent regulation of sinusoidal tone; and cholangiocyte-derived exosomal H19. Arrows indicate the direction of the interactions depicted. BMP10, bone morphogenetic protein 10; CXCL, C-X-C motif chemokine ligand; ERK, extracellular signal-regulated kinase; FasL, Fas ligand; FLRT2, fibronectin leucine-rich transmembrane protein 2; GDF2, growth differentiation factor 2; HSC, hepatic stellate cell; LSEC, liver sinusoidal endothelial cell; NK, natural killer; NKG2D, natural killer group 2D; NO, nitric oxide; NTF3, neurotrophin 3; P2Y14, purinergic receptor P2Y14; PCDH7, protocadherin 7; qHSC, quiescent hepatic stellate cell; RSP03, R-spondin 3; TGF- β , transforming growth factor beta; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TREM2, triggering receptor expressed on myeloid cells 2; YAP, Yes-associated protein; ECM, extracellular matrix.

with selective targeting of a stable HSC state. Therefore, injury-responsive HSCs have not yet been established as a stable, selectively targetable population in patients, and further human and spatial validation is required.

Inflammatory HSC

Inflammatory HSCs are defined by the predominance of immune-regulatory functions within the broader activation continuum. They may emerge early after injury and persist during ongoing disease. Single-cell studies of carbon tetrachloride injury, metabolic dysfunction-associated steatohepatitis (MASH), and alcohol-associated hepatitis have identified activated HSC populations with increased expression of cytokines and chemokines, including CCL2, CXCL1, CXCL10, CCL7, IL11, and CD36.^{17,23,51} In alcohol-associated hepatitis, an LRAT-positive FBLN2-positive HSC population displays both inflammatory and strongly profibrotic features, illustrating that inflammatory and ECM-producing programs are not mutually exclusive.^{24,52}

Inflammatory HSCs both receive immune signals and shape the immune microenvironment. Inflammatory mediators activate HSCs and cause excessive ECM deposition. Proinflammatory mediators secreted by activated HSCs further aggravate hepatic inflammation and promote scar formation. This process creates a cascade of amplification between inflammation and fibrosis and ultimately drives structural destruction and functional failure of the organ.⁵³ Tumor necrosis factor and interleukin 1 produced by

hepatic macrophages support the survival of activated HSCs through nuclear factor kappa B signaling.⁵⁴ Activated HSCs recruit CCR2-positive monocytes through the CCL2/CCR2 axis and promote the accumulation of CD163-positive macrophages.⁵⁵ Activated HSCs can also prolong neutrophil survival through granulocyte-macrophage colony-stimulating factor and interleukin 15, creating a positive feedback loop between inflammation and fibrogenesis.⁵⁶ Additional pathways include HSC-derived programmed death ligand 1, which modulates inflammatory output and TGF- β receptor-associated fibrogenic signaling, and the macrophage migration inhibitory factor/CD74 axis in hepatitis B virus-related fibrosis.^{57,58} These reciprocal interactions amplify inflammation, matrix deposition, and tissue injury.

From a translational perspective, inflammatory HSCs nominate CCL2/CCR2, programmed death ligand 1, and macrophage migration inhibitory factor/CD74 as potential intervention points, particularly in diseases characterized by persistent inflammation. However, these mediators are not HSC-specific and are also expressed by macrophages, cholangiocytes, LSECs, and other cells. CCL2 can be produced by activated HSCs, whereas the major CCR2-dependent responder populations include recruited monocytes and macrophages. Therefore, the antifibrotic effects of CCL2/CCR2 blockade cannot be attributed simply to direct targeting of inflammatory HSCs. For programmed death ligand 1, HSC-specific deletion alters HSC transcriptional programs and hepatic inflammation and attenuates carbon tetrachloride-induced

Table 2. Human single-cell, single-nucleus, and spatial evidence supporting hepatic stellate cell functional states across major chronic liver diseases

HSC functional state	MASLD/MASH	Viral hepatitis (HBV/HCV)	Alcohol-related liver disease (ALD)	Cholestatic liver disease (PBC/PSC)	Overall assessment
Injury-responsive HSC	& Activation trajectories and HSC-to-myofibroblast transition support initiation, without validating a distinct injury-responsive state ³⁵	# HSC activation trajectories exist, but no virus-specific injury-responsive HSC population has been resolved ^{21,39}	& Mesenchymal remodeling and alcohol-enriched HSC clusters support activation, not a distinct injury-responsive state ³⁷	& Activated stellate/mesenchymal populations occupy inflammatory fibrotic niches, without a validated injury-responsive program ^{40,41}	Mostly trajectory-based evidence; no reproducible disease-specific injury-responsive HSC state
Inflammatory HSC	* CD36+/CLEC+/CREM+ inflammatory HSCs show immune and cytokine programs, though not MASH-specific ³⁴	# No reproducible inflammatory HSC cluster has been resolved in current HBV datasets ³⁹	& Inflammatory mesenchymal programs are reported, but pure ALD lacks state-resolved inflammatory HSCs ³⁷	* PBC activated stellate cells express CCL21/CXCL14/TSLP; PSC evidence remains less state-resolved ^{40,41}	Direct evidence is strongest in MASH and PBC; viral hepatitis and pure ALD remain limited
Proliferative HSC	& Proliferation-related signaling is enriched, but reproducible MKI67/TOP2A/CDC20-positive HSC clusters remain unconfirmed ⁴³	# Dividing cells occur, but no HSC-specific proliferative state has been established ³⁹	# Mesenchymal expansion occurs, but HSC-specific cycling populations have not been demonstrated ³⁷	# Cycling populations lack confirmed HSC identity; no proliferative HSC state is established ^{40,41}	Human evidence remains weak and requires concurrent HSC identity and cell-cycle activity
ECM-producing HSC	* Activated HSCs express ECM genes and localize fibrogenic programs to MASH scar regions ³⁴⁻³⁶	* EMP1+ HSCs expand with fibrosis and enrich ECM-organization and collagen-matrix programs ³⁹	& Collagen-rich myofibroblasts and scar-associated mesenchyme support fibrogenesis, with incomplete HSC lineage resolution ^{37,38,42}	* Activated stellate cells show ECM/TGF-β programs; portal fibroblast contribution remains a caveat ^{40,42}	Best-supported human state, with strongest evidence in MASH and direct support in HBV/PBC
Contractile HSC	& Cytoskeletal and focal-adhesion programs are enriched, without direct human contractility measurements ^{34,43}	& HSCs enrich cytoskeletal, focal-adhesion, and cell-substrate adhesion programs without functional validation ³⁹	# Myofibroblast expansion occurs, but HSC-specific contractile output has not been demonstrated ³⁷	& ACTA2-positive stellate/mesenchymal populations occur, without HSC-specific human contraction assays ^{40,42}	Human evidence is program-level; causal contractility remains predominantly experimental
Senescent HSC	* Senescent HSCs are validated by human snRNA-seq and senescence assays; uPAR specificity declines late ³¹	# No state-resolved human HBV/HCV study establishes a senescent HSC population ³⁹	# A state-resolved senescent HSC population was not identified in the available ALD dataset ³⁷	# Senescent cholangiocytes are reported, but senescent HSCs remain unconfirmed in PBC/PSC ^{40,41}	Disease-specific human evidence is currently concentrated in MASH

Evidence grading: * direct human state-resolved support; & partial/indirect human support; # no convincing direct human state-resolved evidence. ALD, alcohol-related liver disease; ECM, extracellular matrix; HBV, hepatitis B virus; HCV, hepatitis C virus; HSC, hepatic stellate cell; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; snRNA-seq, single-nucleus RNA sequencing; TGF-β, transforming growth factor beta; uPAR, urokinase-type plasminogen activator

receptor. Standard gene and protein symbols are presented according to accepted nomenclature and are not separately expanded.

fibrosis, providing relatively direct genetic evidence for an HSC-intrinsic function. However, programmed death ligand 1 is broadly expressed across immune and nonimmune populations. HSC-intrinsic causal evidence therefore does not establish HSC-specific expression or HSC-selective therapeutic targeting. Systemic blockade may therefore have broad immunological consequences, and inhibition of a single inflammatory axis may be insufficient to disrupt the multicellular feedback network. Cell-selective delivery and combination strategies will be required to determine whether this state can be targeted safely and effectively.

Proliferative HSC

Proliferative HSCs are defined by active cell-cycle entry and expansion of the activated HSC pool. Their marker profiles vary across models. In experimental steatohepatitis, increased expression of MKI67, TOP2A, CENPF, CDK1, STMN1, and CDCA8 has been reported.¹⁷ Carbon tetrachloride models have identified related programs involving CDC20, CENPF, CCNB2, BIRC5, CENPA, STMN1, CKS2, HMGB2, and TUBB4B.²⁵ Other studies have quantified proliferation using composite scores based on MKI67, CCNA2, CCNB1, and CDCA8.¹⁸ These markers define cell-cycle activity rather than HSC lineage and should therefore be interpreted together with mesenchymal identity markers.

The platelet-derived growth factor (PDGF)-platelet-derived growth factor receptor (PDGFR) axis is a canonical driver of HSC proliferation and migration. CD248, also known as endosialin, is upregulated during chronic liver injury and promotes HSC expansion through a PDGF-regulated mechanism; systemic *Cd248* deficiency reduces HSC accumulation and fibrosis in mice.²⁶ More recent work showed that loss of TM7SF3 alters TEAD1 splicing and accelerates HSC activation and proliferation, whereas an antisense oligonucleotide that corrects TEAD1 splicing reduces these responses in an experimental MASH model.⁵⁹ In advanced MASH fibrosis, an extensive HSC autocrine network comprising multiple receptor-ligand interactions may further sustain cell expansion and activation independently of continued external injury signals.⁶⁰ These findings suggest that pathological HSC proliferation is more likely to be maintained by context-dependent upstream regulatory networks than by the cell-cycle machinery alone.

Proliferative HSCs can transition toward inflammatory, ECM-producing, or contractile states, and individual ECM-producing HSCs may remain proliferative. Accordingly, proliferation is better viewed as a relatively independent functional dimension of HSC activation rather than a temporal stage through which all HSCs must pass before acquiring other states. From a therapeutic perspective, direct inhibition of ubiquitous cell-cycle proteins such as MKI67, CDK1, or CDC20 would be unlikely to achieve HSC selectivity and could impair regeneration in other cell compartments. Current evidence therefore more strongly supports targeting upstream pathways that drive pathological HSC expansion. Although CD248 and PDGF-associated mechanisms are promising, available studies do not yet establish a selective pharmacological strategy for proliferative HSCs. Temporally restricted and cell-directed inhibition may be necessary to reduce pathological

expansion while preserving physiological repair.

ECM-producing HSC

ECM-producing HSCs are defined by a dominant matrix-synthetic program and represent a major effector state in chronic liver fibrosis.⁶¹ Activated HSCs and their myofibroblast-like descendants are important sources of fibrillar collagens and other matrix components.^{6,23} Single-cell studies in mouse fibrosis models show coordinated induction of COL1A1, COL1A2, COL3A1, ACTA2, TAGLN, MMP2, TIMP1, LOX, and LOXL1.¹⁸ In human cirrhosis, COL1A1-high mesenchymal cells coexist with TREM2-positive CD9-positive scar-associated macrophages and ACKR1-positive or PLVAP-positive endothelial cells within the fibrotic niche.²⁷ ECM production is therefore embedded in a multicellular scar microenvironment rather than being an isolated property of HSCs. Moreover, many matrix markers are shared with portal fibroblasts and mesothelial-derived cells in specific injury settings.^{8,62}

The formation and persistence of the ECM-producing state are controlled by interconnected biochemical and mechanical pathways. TGF- β -SMAD signaling drives myofibroblastic differentiation and collagen transcription.⁶³ The lysyl oxidase (LOX)/lysyl oxidase-like (LOXL) family mediates collagen crosslinking, stabilizes the fibrotic matrix, and limits spontaneous fibrosis reversal.^{64,65} Experimental inhibition of LOXL2 suppresses fibrosis progression and accelerates regression.⁶⁶ Matrix stiffness further reinforces the state: stiff substrates reduce matrix metalloproteinase 9 activity while increasing tissue inhibitor of metalloproteinases 1 secretion, thereby shifting matrix turnover toward continued accumulation.⁶⁷

ECM-producing HSCs also display spatial heterogeneity. In mouse liver, portal vein-associated HSCs and central vein-associated HSCs can be distinguished by zoned transcriptional programs. In carbon tetrachloride-induced centrilobular injury, central vein-associated HSCs are the dominant collagen-producing population and are enriched for lysophosphatidic acid receptor 1. Pharmacological antagonism of lysophosphatidic acid receptor 1 with BMS-986020 *in vitro* or AM095 *in vivo* reduces collagen deposition.¹⁸ The relative contribution of these spatial populations is expected to vary with the anatomical distribution and etiology of injury.¹⁸

ECM-producing HSCs are among the most extensively investigated targets in antifibrotic drug development. In a phase 2 randomized placebo-controlled trial in advanced hepatitis C virus-related fibrosis, the lipid nanoparticle BMS-986263 delivered small interfering RNA against heat shock protein 47, a collagen-specific molecular chaperone, and produced signals of histological improvement.²⁸ This study supported the feasibility of HSC-directed delivery but was not sufficiently large to establish definitive clinical efficacy. In contrast, simtuzumab, a monoclonal antibody against lysyl oxidase-like 2, failed to reduce hepatic collagen content or improve hepatic venous pressure gradient in phase 2b studies of bridging fibrosis and compensated cirrhosis caused by nonalcoholic steatohepatitis.⁶⁸ More recent strategies have moved upstream: bexotegrast, a dual $\alpha\beta6/\alpha\beta1$ integrin inhibitor, was safe and tolerable in the phase 2 INTEGRIS-PSC

trial, although histological fibrosis reversal has not yet been demonstrated.⁶⁹

Precise targeting of ECM-producing HSCs remains challenging. This state is a dynamic functional program rather than a stable lineage, and the same cell may concurrently exhibit inflammatory, proliferative, or contractile features. Many candidate markers are not conserved across species or are shared with other mesenchymal populations. In addition, reducing new collagen synthesis does not necessarily remove long-lived, crosslinked scar tissue. Broad suppression of HSCs or TGF- β signaling may also compromise wound repair and the homeostatic functions of qHSCs. Effective treatment may therefore require both prevention of new matrix deposition and promotion of controlled matrix degradation, delivered within an appropriate disease-stage window.

Contractile HSC

Contractile HSCs are characterized by actomyosin cytoskeletal remodeling and increased mechanical output. In carbon tetrachloride-induced mouse fibrosis, a contractile program enriched for ACTA2, TPM1, VIM, TAGLN, and tenascin C appears before the later induction of a strongly ECM-synthetic program, suggesting that enhanced contractility can precede maximal collagen production.²³ Contractile and ECM-producing states may subsequently coexist within the same cell. Importantly, ACTA2, TAGLN, VIM, and related cytoskeletal genes can also be expressed by other activated mesenchymal populations. They should therefore be regarded as representative components of a contractile program rather than specific markers of contractile HSCs.

Direct functional evidence supports an HSC role in sinusoidal mechanics. Using HSC-specific *Pcdh7* knockout mice and intravital multiphoton imaging, Carter *et al.*²⁹ showed that protocadherin 7 is enriched in HSCs and is required for full endothelin 1-induced sinusoidal contraction. PCDH7 deficiency also reduces collagen-gel contraction, Rho guanosine triphosphatase signaling, filamentous actin stress fibers, and focal adhesions *in vitro*.²⁹ Contractile capacity is not restricted to overtly activated HSCs: real-time measurements in individual non-activated mouse HSCs showed endothelin 1-induced contraction through calmodulin- and Rho kinase-related mechanisms.⁷⁰ The term contractile HSC should therefore denote a state with augmented contractile machinery and mechanical output, rather than simply any HSC capable of contraction.

Maintenance of the contractile HSC state is regulated by multiple mechanisms. Integrin beta 1 is a key regulator of the contractile and profibrotic phenotype. It sustains actomyosin organization through a p21-activated kinase-Yes-associated protein 1-myosin light chain 9 signaling axis.³⁰ Contractile HSCs may thus connect fibrotic remodeling to increased intrahepatic vascular resistance and portal hypertension. Potential targets include PCDH7, endothelin receptors, Rho kinase, and integrin beta 1-associated signaling. Because these pathways also regulate vascular tone and cytoskeletal function in other tissues, systemic inhibition may cause substantial hemodynamic or off-target effects. Human spatial validation and HSC-selective delivery strategies are therefore essential.

Senescent HSC

Senescent HSCs arise when a subset of activated HSCs enters durable cell-cycle arrest. This state cannot be defined by a single conventional marker such as p16, p53, senescence-associated β -galactosidase, or the senescence-associated secretory phenotype (SASP), because these features vary with trigger, timing, and tissue context. Single-cell analysis in metabolic dysfunction-associated steatohepatitis identified MRC1, SLC9A9, PTPRB, STAB2, and SEMA6A as markers associated with senescent HSC populations.³¹ A robust definition requires combined evidence of cell-cycle arrest, molecular identity, secretory function, and cellular origin.

Senescence can restrain fibrogenesis. In mouse liver fibrosis, senescent activated HSCs cease expanding, reduce ECM production, increase matrix-degrading and immune-surveillance programs, and become preferential targets for natural killer cell-mediated clearance.³² Interleukin 22 can induce HSC senescence and attenuate experimental fibrosis.⁷¹ A p53-dependent senescence program in HSCs also limits the development of a protumorigenic microenvironment by regulating macrophage behavior.⁷² Senescent HSCs may additionally support regeneration: pharmacological depletion with ABT263 after partial hepatectomy impairs hepatocyte proliferation, whereas retained senescent HSCs provide interleukin 6 and C-X-C chemokine receptor 2 ligands that promote regenerative responses.³³

Senescent HSCs are not uniformly protective. Persistent cells may continue to release SASP factors and thereby sustain inflammation, tissue injury, or tumor-promoting signals. In obesity-associated liver cancer models, deoxycholic acid-induced HSC senescence contributes to hepatocarcinogenesis, and the senescent HSC secretome can facilitate malignant progression in steatohepatitis-associated fibrosis.^{73,74} Therapeutic approaches must therefore distinguish beneficial transient senescence from harmful persistence. Urokinase-type plasminogen activator receptor (uPAR)-targeted chimeric antigen receptor T cells can clear senescent cells and reduce fibrosis in preclinical models.^{75,76} However, uPAR is not specific to senescent HSCs. Its cellular distribution changes markedly during MASH progression. In early experimental MASH, uPAR predominantly colocalizes with desmin-positive and α -SMA-positive HSCs, with limited overlap with F4/80-positive myeloid cells. As disease progresses, uPAR is expressed by HSCs, TREM2-positive macrophages, and polymorphonuclear myeloid-derived suppressor cells.³¹

Therefore, in advanced disease, the therapeutic effects of uPAR-directed approaches may reflect effects on both uPAR-positive HSCs and myeloid cells and cannot be attributed entirely to selective depletion of senescent HSCs. One strategy may be to induce highly proliferative HSCs to exit the cell cycle, whereas another may be to eliminate senescent HSCs that persist after the reparative phase. The optimal sequence and timing remain unresolved.

Interactions between HSC functional states and other liver cell types

The functional states described above are embedded within multicellular niches rather than operating in isolation. Bidirectional

communication with hepatocytes, LSECs, macrophages, natural killer cells, and cholangiocytes shapes HSC activation, persistence, regression, and homeostatic function. Importantly, the direction, functional consequence, and strength of evidence differ across individual interactions and may change with disease stage and tissue context. Multicellular communication should therefore be viewed as an integral component of HSC state identity and plasticity rather than as a set of ligand-receptor pathways with equivalent evidentiary weight (Fig. 2).

HSCs and hepatocytes

Under physiological conditions, qHSC-derived RSPO3 enhances WNT signaling and helps maintain hepatocyte zonation, metabolic gene expression, liver size, and regeneration.¹³ Neurotrophin 3 is another qHSC-derived paracrine factor; it signals through neurotrophic receptor tyrosine kinase 2 in midzonal hepatocytes, increases cyclin D1 expression, and supports midzonal hepatocyte proliferation.⁷⁷ These findings highlight the loss of homeostatic HSC functions as an underappreciated component of chronic liver disease.

After injury, hepatocytes directly promote the injury-responsive HSC state. Dying hepatocytes release nucleotide sugars, including uridine diphosphate-glucose, that activate P2Y14 receptor-ERK-YAP signaling in HSCs.²² Apoptotic bodies and extracellular vesicles provide additional profibrotic signals. HSCs reciprocally influence hepatocytes. Hepatocyte growth factor is enriched in qHSCs and cytokine-producing HSC populations, and HSC-specific *Hgf* deletion increases hepatocyte death, inflammation, and fibrosis. Conversely, type I collagen produced by ECM-rich HSC populations increases matrix stiffness and promotes accumulation of the transcriptional coactivator TAZ in hepatocytes, thereby facilitating proliferation and tumor formation in premalignant liver tissue.⁷⁸

HSCs and LSECs

Differentiated LSECs restrain HSC activation through nitric oxide signaling and can promote reversion of activated HSCs toward a low-activation state. Capillarized LSECs lose this protective function and instead promote fibrogenic HSC activation.^{79,80} LSEC-specific loss of c-Maf generates capillarized and secretory endothelial populations that upregulate FLRT2 and CXCL12 and activate HSCs *in vitro*.⁸¹ Endothelial state is therefore a major determinant of the transition between homeostatic and injury-responsive HSC programs.

HSCs also maintain endothelial identity. They are important hepatic sources of growth differentiation factor 2 and bone morphogenetic protein 10, which signal through activin receptor-like kinase 1 on LSECs and support sinusoidal differentiation.⁸² Contractile HSCs further regulate sinusoidal caliber through PCDH7-dependent mechanical output.²⁹ Thus, HSC-LSEC communication links vascular differentiation, sinusoidal tone, and fibrogenic remodeling.

HSCs and natural killer (NK) cells

NK cells recognize and eliminate activated HSCs. Early activated HSCs can be targeted through natural killer group 2D and killed through tumor necrosis factor-related apoptosis-inducing ligand-dependent mechanisms.⁸³ NK cells isolated from patients with hepatitis C virus infection also induce apoptosis of activated

primary human HSCs through tumor necrosis factor-related apoptosis-inducing ligand, Fas ligand, and natural killer group 2D.⁸⁴ NK cells additionally clear senescent HSCs, thereby limiting persistence of the fibrogenic cell pool.³²

This interaction is bidirectional. In hepatitis B virus-related cirrhosis, α -SMA-positive activated HSCs suppress the antifibrotic activity of NK cells through TGF- β -dependent emperipolesis.⁸⁵ Fibrosis progression therefore reflects not only increased resistance of HSCs to elimination but also active impairment of immune surveillance.

HSCs and macrophages

In human cirrhosis, TREM2-positive CD9-positive scar-associated macrophages are enriched within collagen-rich niches and communicate with activated mesenchymal populations, including proliferative and ECM-producing HSC states.²⁷ During regression of metabolic steatohepatitis, macrophages can instead promote matrix removal. TREM2-positive lipid-associated macrophages display enhanced collagen uptake and degradation, whereas *Trem2* deficiency impairs collagen clearance and HSC inactivation.⁸⁶ Macrophage function is therefore strongly stage dependent.

HSCs reciprocally support macrophage identity. HSC-derived growth differentiation factor 2 and bone morphogenetic protein 10 maintain activin receptor-like kinase 1-positive Kupffer cells. HSC-specific deletion of these factors shifts hepatic macrophages toward a monocyte-derived, HSC-activating phenotype.⁸² This homeostatic circuit provides another example in which fibrosis progression involves both the gain of pathogenic HSC states and the loss of protective qHSC-derived signals.

HSCs and cholangiocytes

Cholangiocytes are an important source of exosomal long noncoding RNA H19. H19-enriched exosomes are taken up by qHSCs and HSC-derived myofibroblasts, promote primary HSC activation, and support progression toward proliferative and ECM-producing programs. Loss of H19 attenuates fibrosis in bile duct ligation and *Mdr2*-deficient mouse models.⁸⁷

Cholangiocytes and HSCs also engage in contact-dependent, bidirectional interactions. In a three-dimensional coculture system, undifferentiated intrahepatic cholangiocyte organoids promoted activation of freshly isolated qHSCs, whereas HSCs enhanced cholangiocyte organoid proliferation.⁸⁸ Such reciprocal signaling may sustain ductular reaction and periductal fibrogenesis.

In cholestatic fibrosis, HSC-derived myofibroblasts must be distinguished from portal fibroblasts. In *Mdr2*-deficient mice, both activated HSCs and activated portal fibroblasts contribute to scar formation and can acquire ECM-producing features.⁸⁹ Collagen-positive cells around bile ducts should therefore not be assigned to an HSC state without lineage or molecular evidence.

Limitations

Several limitations should be considered when interpreting the functional-state framework proposed in this review. First, much of the mechanistic and causal evidence for HSC functional heterogeneity is derived from rodent models or cultured cells, whereas direct validation in human liver remains limited. Cross-species correspondence is further complicated by differences in disease etiology, fibrosis stage, anatomical context, and experimental plat-

forms. In addition, transcriptomic clusters should not be equated automatically with discrete biological states, because cluster definitions are influenced by analytical methods and many representative markers are shared across functional programs or hepatic cell populations. Robust classification will therefore require integration of transcriptomic signatures with protein-level, spatial, functional, and, where feasible, lineage-resolved evidence.

Second, evidence for individual HSC states remains uneven across etiologies and disease stages, and longitudinal human data are scarce, limiting distinction between stable states, transient responses, and points along continuous activation or regression trajectories. Therapeutic effects should also not be interpreted as evidence of HSC-state specificity, because many candidate pathways are active in multiple liver cell types. Finally, as a narrative rather than systematic review, study selection remains susceptible to publication and selection bias. Accordingly, the six-state framework should be viewed as an organizing model for integrating current evidence rather than a definitive taxonomy.

Conclusions

HSC activation is more accurately understood as a dynamic continuum than as a linear conversion from qHSCs to a single myofibroblast phenotype. The classical quiescent-activated model remains useful for describing the overall direction of change, but it does not capture the coexistence, overlap, and reversibility of functional programs within the same lesion. Injury-responsive HSCs sense tissue damage; inflammatory HSCs reshape immune signaling; proliferative HSCs expand the activated cell pool; ECM-producing HSCs generate and stabilize scar tissue; contractile HSCs increase mechanical output and vascular resistance; and senescent HSCs can either facilitate regression and repair or sustain chronic inflammation and tumor-promoting signals. These states are not mutually exclusive, and no single marker is sufficient for definitive classification.

Future studies should prioritize cross-etiology human validation and integrate molecular, spatial, and functional evidence to distinguish reproducible HSC states from dataset-specific transcriptional clusters. Therapeutic strategies should accordingly move from indiscriminate HSC elimination toward function-selective and stage-specific regulation. Early intervention may block injury sensing and pathological expansion; treatment during progression may reduce ECM production and abnormal contraction; and treatment during regression should preserve matrix degradation, immune clearance, and regeneration. Homeostatic qHSC signals should be protected whenever possible. The purpose of HSC classification is therefore not to generate an ever-expanding list of names, but to define clinically meaningful states that identify actionable therapeutic windows. Integrating functional identity, spatial context, and intercellular communication may provide a more precise framework for antifibrotic drug development.

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Conflict of interest

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Author contributions

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