Beyond hepatic stellate cell heterogeneity: Resolving fibrosis, restoring regeneration (Review)

CHANG GAO[1,2*], GUIQING CHEN[1*], HONGYAN JIA[1*], HONG ZHU[3], YUN CAI[2], DAKAI YANG[1,2] and KAI ZHAO[2]

[1]Department of Laboratory Medicine, School of Medicine, Jiangsu University, Zhenjiang, Jiangsu 212013, P.R. China; [2]Department of Gastroenterology, Jintan Affiliated Hospital of Jiangsu University, Changzhou, Jiangsu 213200, P.R. China; [3]School of Life Sciences, Jiangsu University Jingjiang College, Zhenjiang, Jiangsu 212013, P.R. China

Received August 7, 2025; Accepted December 11, 2025

DOI: 10.3892/ijmm.2026.5733

Abstract. Hepatic stellate cells (HSCs), specialized liver-resident pericytes, play pivotal roles in both liver fibrogenesis and regeneration. Following hepatic injury, quiescent HSCs undergo activation and transdifferentiation into myofibroblasts, which drive tissue remodeling and scar formation. Recent advances have uncovered notable phenotypic and functional heterogeneity within HSC populations, with distinct subsets displaying context-dependent activation states and specialized functions across diverse liver pathologies. The present review synthesizes current insights into the dynamic spectrum of HSC phenotypes and the molecular mechanisms governing their plasticity, emphasizing the mechanisms through which niche-specific signaling, epigenetic regulation and metabolic reprogramming coordinate their functional diversity. The present review further discuss emerging therapeutic strategies that leverage this heterogeneity to selectively target pathogenic HSC subsets, while preserving their homeostatic roles, thereby opening new avenues for precision anti-fibrotic therapies and liver regeneration.

Correspondence to: Professor Dakai Yang, Department of Laboratory Medicine, School of Medicine, Jiangsu University, 301 Xuefu Road, Zhenjiang, Jiangsu 212013, P.R. China
E-mail: yangdakai@126.com

Dr Kai Zhao, Department of Gastroenterology, Jintan Affiliated Hospital of Jiangsu University, 500 Avenue, Jintan, Changzhou, Jiangsu 213200, P.R. China
E-mail: jtryzk@126.com

*Contributed equally

Abbreviations: HSCs, hepatic stellate cells; LSECs, liver sinusoidal endothelial cells; NPCs, non-parenchymal cells; KCs, Kupffer cells; ECM, extracellular matrix; LRAT, lecithin retinol acyltransferase; Col1a1, collagen type I alpha 1 chain; α-SMA/Acta2, α smooth muscle actin/actin alpha 2; CCl_4, carbon tetrachloride; MMPs, matrix metalloproteinases; NASH, non-alcoholic steatohepatitis; Ccl2, C-C motif chemokine ligand 2; TGF-β, transforming growth factor β; VitA, vitamin A; Tcf21, transcription factor 21; NAFLD, non-alcoholic fatty liver disease; Cdk1, cyclin-dependent kinase 1; Hgf, hepatocyte growth factor; IL, interleukin; TFs, transcription factors; ETS1/2, E26 transformation-specific transcription factor 1/2; GATA4/6, GATA binding protein 4/6; PDGF, platelet-derived growth factor; DNMTs, DNA methyltransferases; HDACIs, histone deacetylase inhibitors

Key words: hepatic stellate cells, heterogeneity, spatial-temporal regulation, precision targeting

Contents

1. Introduction

The liver orchestrates its vital functions through intricate cellular crosstalk among diverse cell populations (1). Hepatic stellate cells (HSCs), a specialized lineage of mesenchymal cells, are strategically positioned within the perisinusoidal space (space of Disse), forming critical anatomical interfaces between liver sinusoidal endothelial cells (LSECs) and hepatocyte cords (2-4). As key constituents of the non-parenchymal cell (NPC) compartment of the liver, comprising approximately one-third of NPCs in homeostasis (5,6), HSCs functionally interact with resident macrophages, LSECs, Kupffer cells (KCs), portal fibroblasts and recruited immune cells to regulate hepatic pathophysiology (1,7). This cellular interplay positions HSCs as central orchestrators of tissue responses during both liver injury and regeneration (8,9).

In a quiescent state, HSCs maintain hepatic homeostasis through vitamin A (VitA) storage and metabolism, immunomodulatory signaling, and the paracrine secretion of cytokines, growth factors and apolipoproteins (6,10,11). Following liver injury, mesenchymal cell activation drives pathogenic extracellular matrix (ECM) deposition, with transdifferentiated

myofibroblasts serving as the principal ECM producers (12,13). While multiple cellular sources, including portal fibroblasts and bone marrow-derived progenitors, contribute to the myofibroblast pool (14,15), lineage-tracing studies unequivocally identify HSCs as the dominant progenitors in the majority of liver fibrogenic contexts (16,17).

Conventional paradigms have portrayed HSCs as a functionally homogeneous population uniformly transitioning into profibrotic myofibroblasts (18,19). Acute injury triggers HSC activation through paracrine signals from neighboring cells, initiating transient myofibroblastic differentiation to support ECM-mediated tissue repair (6). By contrast, chronic injury leads to sustained HSC activation, resulting in pathological ECM accumulation and architectural distortion (20). Emerging evidence indicates that HSCs exhibit dynamic activation states beyond simple binary (quiescent vs. activated) classification. While activated HSCs (aHSCs) predominantly drive fibrogenesis, specific subpopulations demonstrate paradoxical anti-fibrotic or hepatoprotective functions (21). This functional diversity underscores the inherent heterogeneity and phenotypic plasticity of HSCs across disease phases.

The resolution of single-cell RNA sequencing (scRNA-seq) has revolutionized our understanding of mesenchymal cell diversity (22,23). High-dimensional analyses reveal spatially and temporally restricted HSC subpopulations in both healthy and diseased livers, each exhibiting unique transcriptional programs and functional specializations during fibrogenesis, immunomodulation and tissue regeneration (24). These discoveries not only redefine HSC biology, but also unveil novel therapeutic opportunities for the precision targeting of pathogenic HSC subsets, while preserving their reparative functions (25,26).

The present review synthesizes current insights into HSC heterogeneity, delineates context-dependent phenotypic switches driven by niche-specific cues and metabolic reprogramming, and discusses emerging strategies that can be used to therapeutically target HSC subpopulations in liver diseases.

2. Heterogeneity of HSCs

By integrating marker-based analyses, single-cell sequencing and spatial transcriptomic techniques, the multilayered heterogeneity of HSCs across transcriptional, functional and spatial dimensions has been revealed (27). Collectively, these perspectives converge to portray HSCs as context-dependent regulators whose identities vary with analytical scale and tissue niche (Table I). Single-cell transcriptomic profiling and lineage tracing have resolved a long-standing controversy, establishing quiescent HSCs (qHSCs) as progenitors of injury-induced myofibroblasts across liver diseases (28,29). Pseudotime analyses have revealed a dynamic continuum in which transitioning HSCs undergo transcriptional priming, fate bifurcation and context-dependent functional specialization during fibrogenesis (17). Crucially, this plasticity is spatially constrained by hepatic zonation, with periportal HSCs more responsive to inflammatory signals and pericentral HSCs more attuned to metabolic stress (17,30). Disease etiology further imprints epigenetic memory on aHSCs, reinforcing pathological feedback loops. Such multidimensional adaptability positions HSCs as biomechanical integrators that decode parenchymal damage patterns into spatially calibrated fibrotic responses, offering therapeutic entry points for precision anti-fibrotic strategies (Table II).

HSC heterogeneity in healthy livers. Previous studies have broadly categorized qHSCs as a single transcriptional cluster characterized by VitA storage and homeostatic functions (19,31-33). These cells are molecularly defined by the high expression of lecithin retinol acyltransferase (LRAT), a canonical marker of VitA metabolism, alongside quiescence-associated genes, such as peroxisome proliferator-activated receptor γ (PPARγ) and adipogenic genes, such as perilipin 2 and glial fibrillary acidic protein (GFAP), that enforce their dormant state (22,34). The maintenance of this inactive phenotype further involves stellate-specific markers, such as Reln and Ecm1, which regulate ECM interactions and signaling quiescence (35,36). Transcriptomically, qHSCs marked by nerve growth factor receptor (Ngfr), LRAT, and ADAMTS-like protein 2 (Adamtsl2) serve as the precursor pool for aHSCs, predominantly functioning as VitA reservoirs and homeostatic regulators in uninjured livers (17).

Under physiological conditions, the liver lobule is divided into three functional zones, namely the periportal (zone 1), midlobular (zone 2) and pericentral (zone 3). Each zone is characterized by distinct oxygen tension, metabolite concentrations and signaling molecules (37). Building on this spatial framework, recent scRNA-seq and spatial transcriptomic analyses have redefined zonally restricted qHSC subpopulations. qHSCs bifurcate into portal vein-associated HSC (PaHSC, $Ngfr^{high}$) and central vein-associated HSC (CaHSC, $Adamtsl2^{high}$) subpopulations (30,38,39). This zonation aligns with lobular gradients of oxygen, nutrients and signaling molecules, shaping HSC functional identities with PaHSCs primed for pro-fibrotic activation, while CaHSCs are more associated with detoxification (26).

Notably, a pre-specified qHSC subtype, termed 1-HSCs, has recently been identified in zone 1 of the healthy liver lobule (40). Although functionally quiescent under homeostatic conditions, 1-HSCs are spatially localized and poised for activation upon injury. Unlike conventional myofibroblast precursors, 1-HSCs primarily orchestrate sinusoidal capillarization in response to damage, revealing a reparative trajectory distinct from classical fibrogenesis (40). The identification of 1-HSCs further reinforces the notion that HSCs constitute a spatially organized ecosystem, wherein certain subpopulations are preconfigured for specialized responses despite appearing phenotypically dormant in steady-state conditions. These discoveries collectively illustrate that even in homeostasis, HSCs exist as a functionally partitioned ecosystem, their phenotypic diversity spatially encoded and primed for context-dependent responses.

Notably, the functional zonation of HSCs has identified VitA-enriched and VitA-deficient HSC subsets occupying distinct lobular niches, with VitA droplet size and distribution exhibiting zonation-dependent patterns (6,41). While PaHSCs display heightened VitA storage with desmin expression (42), VitA-poor HSCs near central veins may act as 'first responders' to injury, transitioning more rapidly into activated states (43).

Transcriptomic stratification in human livers further reveals a dichotomy within HSC subpopulations. Glypican

Table I. Overview of HSCs in different experimental settings.

Experimental setting	Phenotype	Representative subsets[a]	Core functions
Traditional marker-based identification	Quiescent phenotype	qHSC (43), AF-HSC (43)	VitA metabolism ECM homeostasis
	Quiescent-like HSC	Embryonic HSC (45),	Early activation response
	Activated phenotype	GFP-HSC (43)	
		aHSC (17,24,50-52)	ECM production and deposition Collagen synthesis
	Inactivated phenotype	iHSC (45)	Partial reversion to quiescence Fibrotic potential reduction
Single-cell transcriptomic classification	Quiescent phenotype	$Lrat^{high}$ HSC (48)	VitA metabolism
	Quiescent-like HSC	HSCcol-low (49)	Collagen production reduction
	Fibrogenic phenotype	HSCcol-high (49), $Col1a1^{+}$ HSC (48),	ECM formation and organization Collagen generation
		Scar-associated mesenchymal cells (21)	ECM deposition
	Inflammatory phenotype	$Rgs5^{+}$ aHSC (55), $Lrat^{+}Fbln2^{+}$ HSCs (61)	Immune response regulation
	Proliferative phenotype	Proliferating HSC (73), aHSC_prof (68)	Fibrosis regulating Liver zonation coordinating Cellular proliferation
	Activated phenotype	aHSC1-7 (55,62,68,69),	Cell migration and contraction
		$Acta2^{+}$ HSC(AAs) (48),	Wound healing
		Cycling HSC (48),	Proliferative capacity
		endothelial-chimeric stellate cell (35)	Microenvironment modulation(subgroup-specific)
		cyHSC (66)	Tumor-suppressing
		myHSC (66)	Tumor-promoting
		pro-regenerative HSC (47)	Hepatocyte proliferation stimulation
		Anti-regenerative HSC (47)	Hepatocyte proliferation cessation
	Mixed phenotype	$Clec3b^{+}$ HSC (22,55),	ECM construction
		Mixed HSC (47)	Cell scaffold establishment
	Inactivated phenotype	iHSC (30,75)	Fibrotic potential reduction Fibrotic stimulus sensitization
	Senescence phenotype	sHSC	Fibrosis limitation (75) Tumor-suppressing (81) Tumor microenvironment formation (77)
Single-cell and spatial transcriptomics-integrated classification	Quiescent phenotype	CaHSC (30,38,39)	Respond to pericentral injury signals
		PaHSC (30,38,39)	Respond to periportal injury signals
		HSC1 (portal-enriched) (44)	Metabolism of glycosaminoglycans
		HSC2 (central-enriched) (44)	Antigen presentation
		1-HSC (40)	Sinusoidal capillarization involvement
	Activated phenotype	HSC1, HSC2 (67)	Tumor-promoting Tumor stroma formation Tumor invasion and stroma remodeling
		aHSC (39)	Cell migration and Cell adhesion Wound healing
	Fibrogenic phenotype	Scar-associated mesenchymal cells (63)	Collagen generation ECM deposition

[a]In this column, the numbers in parentheses refer to reference citations. HSC, hepatic stellate cell; aHSC, activated HSC; CaHSC, central vein-associated HSC; PaHSC, portal vein-associated HSC; ECM, extracellular matrix; GFP, collagen-green fluorescent protein; AF, vitamin A auto-fluorescent; qHSC, quiescent HSC; HSCcol-low, Col1a1-low HSC cluster; HSCcol-high, Col1a1-high HSC cluster; iHSC, inactivated HSC; sHSC, senescent HSC; myHSC, myofibroblastic HSC; CyHSC, cytokine-producing HSC; Lrat, lecithin retinol acyltransferase; Acta2, actin alpha 2.

Table II. HSC subpopulations in liver homeostasis and diseases.

Model	HSC cluster	Gene labels	Phenotype/functions	(Refs.)
Healthy liver				
Human	HSC1	GPC3, NTRK2, EFEMP1, GEM, CCL2, THBS1	Quiescent phenotype ECM remodeling Metabolism of glycosaminoglycans	(44)
	HSC2	DBH, HHIP, VIPR1, PTH1R, RAMP1, EDNRB, AGTR1A	Quiescent phenotype Antigen presentation	(44)
	Embryonic HSC	Col1a1, GFAP, Desmin	Quiescent-like phenotype	(45)
Mouse	PaHSC	Ngfr, Igfbp3, Vipr1, Lrat, Rgs4, desmin	Precursors of aHSCs in periportal fibrosis	(30,38)
	CaHSC	Admtsl2, Spon2, RSPO3, Reln	Precursors of aHSCs in pericentral fibrosis Associated with detoxification	(30,38)
	AF-HSC	Ppara, Rxra	Retinol storage	(43)
	GFP-HSC	GFP, Acta2, Cyp2s1, Col1a1, Desmin	Early activation state Activation response	(43)
	1-HSC	Ngfr, SMMHC	Quiescent phenotype Sinusoidal capillarization involvement	(40)
Fibrotic liver				
CCl4 models	qHSC	Lrat, Adfp, Adipor1, Reln, Bmp5	Vitamin A metabolic process Regulation of lipid localization Vascular morphology support Vasodilation maintenance	(17,22,45)
	HSCcol-low	Fabp1, Bhmt, Adamtsl2, Col1a1	Quiescent-like state maintenance Collagen production reduction Injury signals response	(49)
	aHSC1	Cdc20, Ccnb2, Cenpf, Birc5, Cenpa, Stmn1, Cks2	Initial activation Proliferative capacity Mitosis regulation	(55)
	aHSC2	Acta2, Tnnt2, Casq2, Fgl2, Fhl2, Serpinf1, Meg3	Cell contraction Collagen organization Wound closure	(55)
	aHSC	Col1a1, Col1a2, Fn1, Mfap4, Dpt, Gas6, Lox	Cell adhesion involvement ECM production and deposition Collagen synthesis	(17,45)
	Immunomodulatory aHSC	Slpi, Saa3, Cxcl5, Clec2d, Ccl2, Ccl7, Cxcl1, Cxcl2	Inflammation and immune regulation ECM deposition	(17,22,55)
	aHSC	Acta2, Spp1, Tagln, Cxcl14, Vim, Tnc	Cell migration and contraction Collgen generation ECM deposition	(17,22)
	Clec3b^{+} HSC	Clec3b, Mmp2, Mmp3, Pi16, Fbln1, Mfap4, Mfap5, Tnxb, Dpt	Mixed phenotype Fibrosis involvement ECM construction Wound healing	(22,55)
	aHSC4	Bmp10, Rgs5, Mest, Ifitm1, Igfbp3, Angptl6	Tissue repair and Immune regulation Angiogenesis	(55)
	aHSC5/6	Pam, mt-Co3, mt-Atp, mt-Cytb	Special metabolic stress state Wound healing	(55)
	aHSC7	Lmod1, Actg2, Myh11, Myh9, Cnn1, Tnnt2	Cell migration and contraction	(55)
	HSCcol-high	Col1α1, Adamtsl2, Alcam, Acta2,	Fibrogenic phenotype	(49)

Table II. Continued.

Model	HSC cluster	Gene labels	Phenotype/functions	(Refs.)
		Fhl2, Itga8, Vim, Hspb1, Col1α2	Collgen generation ECM deposition	
	iHSC	Desmin, GFAP, Synemin	Fibrotic potential reduction Fibrotic stimulus sensitization	(45)
	sHSC	P53, p21, Mmp, Hmga1	Senescence phenotype Fibrosis limitation	(75)
Cirrhotic patients	Rgs5^{+} aHSC	Rgs5, POSTN	Immune response regulation	(55)
	HSC1	ACTA2, PDGFRB, MYH11, ADIRF	Collagen fiber assembly Cell contraction	(62)
	HSC3	RGS5, COX4I2, FABP4, NDUFA4L2	Activated phenotype	(62)
	HSC4	FBLN1, COL1A1, COL3A1, COL6A3	Fibrogenic phenotype	(62)
	Scar-associated mesenchymal cells	COL1A1, COL1A2, COL3A1, PDGFRA, TIMP1, CCL2	Fibrogenic phenotype Collgen generation	(21)
	Low-Tnnt2 aHSC	Fgl2, Tnnt2	Cell contraction Collagen organization	(55)
Metabolic liver disease				
NASH patients	qHSC	NRXN1	Vitamin A metabolic process	(64)
	aHSC	ACTA2, IGFBP7	Wound healing	(64)
	aHSC	RBP1, COL1A1, COL1A2, COL5A2, COL3A1, TIMP1, TIMP2, TIMP3	Fibrogenic phenotype ECM formation and organization	(64)
NASH mouse models	aHSC	Col1a1, Timp1, Acta2	ECM production and deposition Collagen synthesis	(30)
	aHSC	Cd36, Ly6c, Clec	Inflammation and immune regulation	(30)
	aHSC	IRF7, Adamtsl, Tpm1	Low activation level	(30)
	aHSC	Cdk1, Lox, Tpm2, Col1a1, Timp1, Acta2	Rapid proliferative capacity	(30)
	iHSC	Cxcl1, Gabra3, Bambi, Fbln7, Vipr, ApoE	Fibrotic potential reduction Fibrotic stimulus sensitization	(30)
NAFLD mouse models	Endothelial-chimeric stellate cell	Rgs5, Reln, Lum, Ecm1, ptprb, Clec4g	Angiogenesis Microenvironment modulation	(35)
AH mouse models	Lrat^{+}Fbln2^{+}H	Lrat, Fbln2, Cxcl2, Acta2,	Inflammation and immune regulation	(61)
	SC	Col1a1, Col1a2, Timp1, Mmp2, Aebp1	Proliferative capacity ECM deposition	
HCC				
Patients with HBV	HSC1	COL1A1, COL1A2, DCN	Tumor stroma formation Tumor-promoting	(67)
	HSC2	ACTA2, COL14A1	Tumor stroma remodeling Tumor invasion	(67)
DEN and CCl_4 induced mouse models	myHSC	Col1a1, Spp1, Mgp, Timp1, Serpine2, Ptn	ECM deposition Tumor-promoting	(66)

Table II. Continued.

Model	HSC cluster	Gene labels	Phenotype/functions	(Refs.)
	cyHSC	Hgf, Colec11, Cxcl9, Angptl6, Ecm1, Fcna, Colec10, Reln, Masp1	Cell growth factor production Tumor-suppressing	(66)
	aHSC_prof	αSMA, Blc, IL-3, IL-4, IL-5	Cytokine secretion Tumor-promoting	(81)
	sHSC	αSMA, P53, p16, p21, SA-β-gal, IFNγ	Immune cell regulation Tumor-suppressing	(81)
Obesity induced mouse models	sHSC	IL-6, IL1A, IL1B	Tumor microenvironment formation Pro-inflammatory factor secretion	(77)
Drug-induced liver injury				
Glyphosate	aHSC1	Col1a1, Col1a2, Sfrp1, Fbn2	Cell migration and contraction Collgen generation	(68)
	aHSC2	Col6a1, Col6a2, Rspo1, Megf6	ECM deposition and remodeling	(68)
	aHSC3	Ccl6, Ccl24, Cxcl9, C3ar1	Inflammation and immune regulation	(68)
	aHSC_prof	Mki67, Top2a, Ube2c, Ccnb1	Cellular proliferation Injury repair promotion	(68)
Triclosan	aHSC1	Timp1, Aebp1, Timp2, Ddr1, Bmpr1a, Fmod	Fibrogenic phenotype ECM deposition and remodeling	(69)
	aHSC2	Acta2, Col1a1, Col1a2, Col6a1, Col6a2, Igf1		(69)
	aHSC4	Ccr2, Ccl6, Cxcl10, Ccl24, Ccr12, Cxcl2, Cxcl13	Cell migration Inflammation regulation	(69)
	aHSC_prof	Mki67, Mcm6, Timp2	Cell proliferation involvement	(69)
Triptolide	aHSC1	Cxcl2, Ccl5, Fcer1g, Cd52, S100a4	Inflammation regulation Chemotactic involvement	(46)
	aHSC2	Acta2, Myh11, Igfbp5, Hspb1, Myl9, Saa3	Wound healing ECM organization	(46)
APAP/TAA	$Lrat^{high}$ HSC	Lrat, Rgs5, Rspo3	Quiescent phenotype Vitamin A metabolic process	(48)
	$Col1a1^{+}$ HSC	Col1a1, Col1a2, Col3a1, Col6a1, Col6a2, Col6a3	Fibrogenic phenotype Collgen generation ECM deposition and remodeling	(48)
	$Acta2^{+}$ HSC (AAs)	Acta2, Ccl2, Ccl7, Csf1, Il6, Il11, Tagln, Tagln2, p53, Timp1	ALF-activated phenotype Protein translation Immune regulation Injury repair	(48)
	Cycling HSC	Stmn1, Cdk1, lfit3, Col14a1, Mki67	Activated phenotype	(48)
Live regeneration				
PH rat models	Pro-regenerative HSC	Vegfa, Hgf, Igf1, Arg1, Stat3, Socs3, Tnfr1, Tgfb1	Pro-regenerative state Hepatocyte proliferation stimulation	(47)
	Anti-regenerative HSC	Col3a1, Col14a1, Ecm1, Spp1, Tgfbp2	Anti-regenerative state Hepatocyte proliferation cessation ECM production and remodeling	(47)

Table II. Continued.

Model	HSC cluster	Gene labels	Phenotype/functions	(Refs.)
			Cell migration	
	Mixed HSC	Rara, Rbp1, Tgfb1, Igf1, Arg1, Vegfa, Hgf, Col3a1, Col14a1, Ecm1, Tgfbp2	Adaptive HSCs Respond to external stimuli Hepatocyte proliferation promotion Cell scaffold establishment	(47)
PH mouse models	aHSC	Desmin, Lrat, GFAP, AdamTS13, Col1a1$^{\pm}$, Acta2$^{\pm}$	Intermediate activation state Matrix production Mild fibrotic response Balancing injury and repair	(73)
	Proliferating HSC	Cdk1, Fn1, Ecm1, Rspo3, Bmp1, Cenpf, Mki67, Top2a,	Wound healing Fibrosis regulating Liver zonation coordinating Liver regeneration and functional recovery	(73)
	sHSC	p16INK4a, SA-β-Gal, Desmin, IL-6, Cxcl2	Liver regeneration ECM remodeling Fibrosis limitation	(82)

CCl_4, carbon tetrachloride; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; AH, alcoholic hepatitis; HCC, hepatocellular carcinoma; PH, partial hepatectomy; DEN, diethylnitrosamine; myHSC, myofibroblastic HSC; cyHSC, cytokine-producing HSC; aHSC, activated HSC; sHSC, senescent HSC; APAP, acetaminophen; TAA, thioacetamide; HBV, hepatitis B.

3-expressing HSC1 localize to portal-central vascular regions and is enriched in elastic fiber-related genes, consistent with structural maintenance roles. By contrast, dopamine beta-hydroxylase -high HSC2 distribute diffusely along sinusoids, displaying antigen presentation pathways suggestive of immunomodulatory potential (44). Furthermore, developmental research has identified embryonic HSCs transiently express collagen type I alpha 1 chain (Col1a1) alongside GFAP and Desmin, but lack α smooth muscle actin [α-SMA; also known as actin alpha 2 (Acta2)], mirroring qHSC signatures, while retaining the plasticity required for later activation (45).

HSC heterogeneity during liver injury. The injury-activated transformation of HSCs reveals a dynamic spectrum of phenotypic states in which qHSC populations undergo significant changes that drive their differentiation and mobilization in response to tissue damage (17). However, despite this activation-driven depletion, a resilient subset of qHSCs persists across various disease models. These residual qHSC pools exhibit unique phenotypic and functional adaptations that enable their survival and potential contribution to tissue repair and regeneration (30,46-48). For instance, in carbon tetrachloride (CCl_4)-induced liver fibrosis, a distinct subset of stress-adapted qHSCs emerges, characterized by the expression of specific markers, such as betaine-homocysteine S-methyltransferase and fatty acid binding protein (Fabp)1 (49). This subset appears to represent a metabolically reprogrammed survival state by altering their metabolic pathways to adapt to the fibrotic environment, thereby preserving a reservoir capable of contributing to regeneration (17,49).

The myofibroblastic aHSCs conventionally characterized by Acta2, Col1a1 and tissue inhibitor of metalloproteinases 1 (Timp1) signatures (17,50-52), have been further delineated along the transitional activation gradients, revealing discrete clusters from quiescent reservoirs to fully differentiated matrix-producing myofibroblasts (53). For example, in early-stage non-alcoholic steatohepatitis (NASH), qHSCs undergo partial activation, contributing to low-grade fibrosis through controlled ECM deposition (30). As the disease progresses, a subset of HSCs acquires a highly profibrogenic phenotype, driven by pro-inflammatory signals from macrophages and damaged hepatocytes (30). Indeed, scRNA-seq indicates that HSC activation encompasses a spectrum of cell states rather than a uniform transition, with distinct subsets exhibiting transcriptional programs related to collagen synthesis, immune modulation, or matrix remodeling (27,54). Additionally, zonally restricted HSC activation patterns are observed, with PaHSCs exhibiting heightened responsiveness to cholestatic injury, whereas CaHSCs dominate in metabolic stress-induced fibrosis (55).

Notably, previous studies have uncovered a third 'inactive' HSC state (iHSCs) across various disease models in both human and mouse livers. These cells are transcriptionally distinct from classical qHSCs, exhibiting a low expression of fibrogenic genes and the upregulation of quiescence-associated genes, but not adipogenic genes (30,45). As an intermediate population, iHSCs are closer to qHSCs than to aHSCs, although they do not fully revert to qHSCs and remain poised for swift reactivation if fibrogenic stimuli recur (45). However, compared with terminally differentiated aHSCs, they retain partial quiescence features with reversible traits, making them a promising therapeutic target because restoring iHSCs to a quiescent state is easier than deactivating fully activated myofibroblasts. This concept has been functionally validated

using *in vivo* fate-mapping experiments in fibrotic regression models (45).

Activated phenotypic diversity. While α-SMA remains a canonical activation marker, its restricted expression to discrete HSC subsets in fibrotic niches underscores the existence of heterogeneous myofibroblast differentiation states (35,54). A breakthrough came with the identification of syndecan-4 as a pan-activation marker universally expressed in diverse injury contexts, mechanistically linked to HSC migration through integrin signaling and cytoskeletal remodeling (56).

Of note, HSC activation dynamics differ based on the underlying pathogenic stimulus. For example, NASH models induce lipid-associated activation signatures characterized by Fabp4 and perilipin 2 (Plin2) expression, while cholestatic injury promotes Twist1-driven ductular reaction phenotypes (32,57,58). Within similar pathologies, spatially restricted activation programs emerge in liver disease, with peri-injury HSCs becoming proliferative [platelet-derived growth factor (PDGF)Rβ^{high}], while periportal HSCs adopting inflammatory [C-C motif chemokine ligand 2 (Ccl2)-expressing] states (21). This phenotypic mosaicism reflects microenvironmental instructive signals ranging from transforming growth factor β (TGF-β) gradients to mechanical stiffness thresholds.

Heterogeneous activation of HSCs in liver fibrosis. The single-cell transcriptomic analyses of fibrotic liver models has revealed dynamic HSC activation states, ranging from quiescent VitA-storing cells to fully differentiated collagen-producing myofibroblasts. The activation cascade begins with early-responsive HSCs (Cdc20^{high}/Birc5^{high}) that proliferate rapidly upon injury, creating an expansion pool for downstream differentiation (38,55). These cells give rise to a matrix-remodeling HSC population [Acta2$^+$/regulator of G-protein signaling 5 (Rgs5)$^+$], which serves as central executors of fibrogenesis by secreting provisional ECM components, while simultaneously regulating neighboring HSC fate through paracrine signaling (55). A critical transitional Adamtsl2$^+$/Alcam$^+$ subpopulation emerges at this stage, exhibiting hybrid quiescent-activated features and functioning as a pivotal decision point (49). It is capable of either progressing toward terminal metabolically-committed HSCs or potentially reverting toward quiescence under appropriate signals such as PPARγ agonists (34,59).

Spatiotemporal analyses further demonstrate model-specific activation patterns, with CCl_4-induced injury favoring VitA$^+$ HSCs that retain metabolic capacity, while bile duct ligation models promote VitA-depleted progenitor-like populations (45,60,61). Functional specialization occurs through distinct phases, including inflammatory-phase [C-X-C motif chemokine ligand 5 (Cxcl5)$^+$/serum amyloid A3 (Saa3)$^+$], migratory-phase [Spp1$^+$/matrix metalloproteinase (Mmp)$^+$] and ECM-producing (C-type lectin domain family 3 member B-positive) hybrid cells, with vascular zonation dictating myofibroblast origins, as evidenced by transcription factor 21 (Tcf21)$^+$ CaHSCs driving CCl4-mediated fibrosis vs. portal Tcf21$^+$ populations dominating cholestatic injury (17,22,29).

Human cirrhosis exhibits an amplified, yet conserved differentiation trajectory progressing from RGS5$^+$/FABP4$^+$ transitional HSCs to fibulin (FBLN)1$^+$/COL1A1$^+$ terminal myofibroblasts, with spatial transcriptomics identifying periostin-positive aHSCs as primary fibrogenic effectors alongside rare RGS5$^+$ subsets potentially regulating inflammatory niches (55,62,63). The complexity of HSC heterogeneity is further compounded by aging through the emergence of distinct senescent subpopulations that perpetuate fibrotic microenvironments via senescence-associated secretory phenotype (SASP) mediated signaling, highlighting the multifaceted nature of HSC biology in liver fibrosis pathogenesis across different injury models and disease stages.

Heterogeneous activation of HSCs in metabolic liver disease and hepatocarcinogenesis. Recent advances in single-cell technologies have revealed both conserved and disease-specific patterns of HSC activation across various liver pathologies. A core transitional pathway (HSC1-HSC4), marked by sequential surface marker changes, emerges in both non-alcoholic fatty liver disease (NAFLD) and CCl_4-induced injury, demonstrating conserved mechanisms in the progression from quiescence to myofibroblastic states (35,54). Notably, this shared activation trajectory coexists with disease-specific adaptations. Particularly, in NAFLD, a unique endothelial-chimeric protein tyrosine phosphatase receptor type B (Ptprb)$^+$/lumican (Lum)$^+$ subset suggests vascular niche-dependent reprogramming (35), while alcoholic hepatitis features a multifunctional Lrat$^+$/Fbln2$^+$ population that simultaneously drives fibrosis through collagen deposition, modulates immunity and sustains proliferation through programmed death-ligand 1 (PD-L1) and autocrine PDGFRβ signaling (61).

The NASH microenvironment further diversifies HSC functionality, where different subpopulations cooperate to promote disease progression. While Timp1$^+$ cells initiate matrix remodeling, interferon regulatory factor (Irf)7$^+$ subsets recruit inflammatory macrophages, Cd36$^+$ populations perpetuate steatosis and cyclin-dependent kinase 1 (Cdk1)$^+$ clusters expand the myofibroblast pool (30). This functional specialization is evolutionarily conserved, as human NASH biopsies similarly exhibit ACTA2$^+$ subsets mediating reparative ductular reactions, while retinol binding protein 1-positive populations directly drive fibrogenesis (64). The transition to hepatocellular carcinoma (HCC) reveals an additional layer of complexity, with the balance between tumor-suppressive cytokine-producing Cxcl9$^+$ HSCs and pro-carcinogenic Col1a1$^+$ myofibroblastic subsets determining clinical outcomes (65,66). Spatial transcriptomics of HCC further reveal region-specific HSC subsets, with COL1A1-high HSC1 supporting tumor growth through matrix-rich desmoplasia, whereas ACTA2-high HSC2 adopts a contractile, pro-invasive phenotype (67). These findings collectively demonstrate how HSC heterogeneity creates distinct pathological niches, with disease progression depending on both conserved activation pathways and context-dependent adaptations that emerge in specific etiologies.

Heterogeneous activation of HSCs in drug-induced liver injury. Across diverse hepatotoxic agents, a core fibrogenic program emerges through the consistent appearance of collagen-producing myofibroblast subsets (Acta2$^+$/Col1a1$^+$), suggesting a fundamental response pathway to parenchymal

damage (29). However, the specific manifestation of HSC activation varies significantly with toxicant type, creating distinct pathological microenvironments.

Glyphosate exposure induces a characteristic four-subpopulation response that includes not only the expected fibrogenic clusters but also prominently features an inflammatory IL-6^{+}/Ccl6^{+} subset, indicating strong immunomodulatory effects (68). Similarly, triclosan triggers ECM-producing and proliferative populations, while uniquely generating migratory chemokine-expressing clusters (Cxcl2^{+}/Ccl2^{+}), potentially facilitating immune cell recruitment (69). The paradoxical effects of triptolide are particularly noteworthy, as it drives simultaneous pro-inflammatory [NOD-like receptor family pyrin domain containing 3 (NLRP3) activation] and reparative (Acta2^{+}/Myh11^{+}) HSC states, reflecting its complex therapeutic-toxic duality (46,70).

Acute liver failure models reveal another dimension of HSC plasticity, where fibrotic collagen-producing populations coexist with specialized Acta2^{+} repair-promoting subsets that orchestrate macrophage polarization through STAT6 signaling (71,72). This reparative population appears particularly prominent in acetaminophen and thioacetamide models, suggesting its potential role in acute injury resolution (48). The universal presence of cycling HSC populations, marked by Mki67/Cdk1 or Ccnb1 across all models, underscores the fundamental need for cellular expansion in injury response, while the varying proportions of fibrotic, inflammatory and reparative subpopulations reflect toxicant-specific microenvironmental programming (48).

Collectively, these findings demonstrate that while HSCs maintain core response modules to hepatic injury, their activation spectrum adjusts in a compound-specific manner, forming distinct cellular ecosystems that influence disease progression and recovery potential. The balance between these conserved and adaptive responses likely determines the ultimate pathological outcome, providing novel targets for tailored therapeutic interventions based on injury etiology.

Heterogeneous activation of HSCs in liver regeneration. The HSC response during liver regeneration following partial hepatectomy (PH) exhibits a distinct activation spectrum compared with pathological fibrosis, with specialized subpopulations orchestrating regenerative rather than fibrotic programs. The predominant weakly activated cluster (Acta2^{low}/Lrat^{+}) represents a novel adaptation to regenerative demands, maintaining quiescence markers while likely serving as a rapidly mobilizable reserve pool, a feature rarely observed in chronic injury settings where HSCs typically progress rapidly to full activation (73).

A PH-specific proliferative population emerges as a hallmark of regenerative HSC activation, co-expressing mitotic regulators (Cdk1/DNA topoisomerase II alpha) alongside regenerative cytokines (73). This dual functionality suggests an elegant coupling of self-renewal with paracrine support for hepatocyte proliferation that is conspicuously absent in the majority of injury models, where proliferating HSCs primarily contribute to fibrogenesis rather than regeneration (30,68,69).

Computational modeling reveals a sophisticated division of labor among regenerating HSCs, with pro-regenerative subsets [hepatocyte growth factor (Hgf)^{high}/Vegfa^{high}/Col1a1^{low}] actively suppressing fibrogenic programs to prioritize growth factor production, reflecting reprogramming that prevents the scarring typical of pathological responses (47). Notably, the discovery of a transitional 'mixed' state (Col1a1^{high}/Hgf^{high}) introduces a previously unrecognized layer of regulation, where these cells appear to function as biological rheostats that use Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) mechanosensing to dynamically adjust the fibro-reparative balance according to microenvironmental demands (47).

Heterogeneity of HSCs senescence and inactivation phenotypes. The progression from aHSCs to senescent phenotypes represents a critical adaptation in chronic liver disease, with cells exiting the cell cycle, yet remaining metabolically active and shaping disease outcomes context-dependently (74). In fibrotic environments, aHSCs transition into senescent HSCs (sHSCs) marked by TP53/CDKN1A-mediated cell cycle arrests yet paradoxically acquire pro-tumorigenic potential through SASP components, including inflammatory cytokines and matrix-remodeling proteases (18,75-77). Early metabolic dysfunction adds further complexity to this transition, generating Mrc1^{+}/Slc9a9^{+} sHSCs that evolve into inflammatory-senescent hybrids (Cxcl10^{+}/Ccl5^{+}), linking steatosis injury to progressive microenvironmental dysfunction (78).

The functional duality of sHSCs becomes particularly evident in HCC, where early TP53^{high} sHSCs suppress tumor growth via CXCL9-driven immune recruitment, while persistent NASH-derived sHSCs promote malignancy through TGFβ1/PDGFA-induced epithelial-mesenchymal transition (79-81). Contrastingly, in liver regeneration, transient sHSCs [interleukin (IL)-6^{+}/CXCL2^{+}] enhance hepatocyte proliferation, illustrating how senescence duration and niche signals determine beneficial vs. detrimental outcomes (82).

Parallel to senescence, aHSCs may also adopt inactivated states during injury resolution (34). These cells downregulate fibrogenic markers and partially regain quiescence-associated genes but retain epigenetic scars of activation, such as loss of lipid droplets (45). NASH regression models have identified a specialized CXCL1^{+}/GABRA3^{+} iHSC subset that balances reduced ECM production with heightened sensitivity to reactivation (30), while PH induces metabolically reprogrammed COL1A1^{low} iHSCs that persist in peri-sinusoidal niches (73).

3. Mechanisms regulating HSC heterogeneity

Microenvironment regulation of HSC plasticity. HSC heterogeneity largely arises from microenvironmental regulation, genetic or epigenetic modulation, and metabolic reprogramming (Fig. 1). Within the liver lobule, the spatial distribution of HSCs establishes functional diversity driven by zonation-specific gradients of oxygen, metabolites and signaling molecules (37,83). CaHSCs, residing in hypoxic and metabolite-rich zones, acquire pro-fibrogenic traits through hypoxia-inducible and CYP450-dependent pathways (37,84). By contrast, PaHSCs near the oxygen- and nutrient-rich portal triad serve as a proliferative reservoir during regeneration (85). Midlobular HSCs exhibit intermediate phenotypes balancing ECM remodeling and immune modulation (85).

Biomechanical heterogeneity further amplifies these zonal responses. Uneven ECM deposition generates stiffness

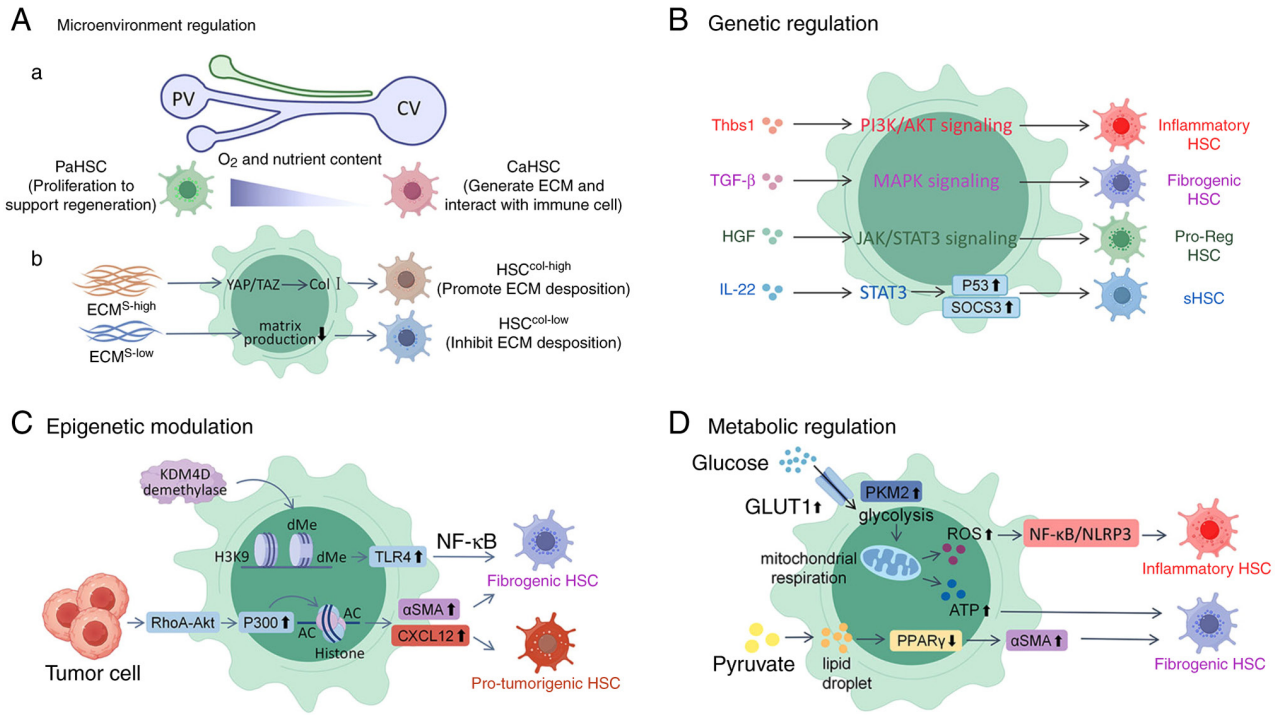

Figure 1. The molecular mechanisms regulating HSC heterogeneity. (A-a) HSC heterogeneity is spatially regulated by local microenvironmental cues. While CaHSCs residing in hypoxic, nutrient-poor pericentral regions rapidly produce ECM upon stimulation, PaHSCs in oxygen- and nutrient-rich periportal areas preferentially proliferate to support regeneration. (A-b) ECM stiffness regulates HSC phenotypic diversity. ECM-dense pericentral regions activate mechanosensitive YAP/TAZ pathways in HSCs, reinforcing ECM deposition and fibrosis, while softer periportal areas promote HSC migration and proliferation through suppressing matrix production. (B) HSC subsets are induced through distinct signaling pathways, driving their differentiation into inflammatory, fibrogenic, pro-regenerative, or senescent phenotypes. (C) The phenotypic plasticity of HSCs is governed by epigenetic reprogramming. While H3K9 demethylation induces TLR4/NF-κB signaling and activates fibrogenic HSC phenotypes, mechanical cues from the tumor microenvironment amplify histone acetylation at fibrotic loci, resulting in upregulation of α-SMA and CTGF, thus driving pro-fibrotic and pro-tumor HSC states. (D) The phenotypic diversity of HSCs stems from their remarkable metabolic plasticity. Following injury, enhanced GLUT1-mediated glucose uptake and PKM2-driven glycolytic flux fuels mitochondrial oxidative phosphorylation to support myofibroblast differentiation. Meanwhile, accumulated ROS production activates NF-κB/NLRP3 inflammasome pathways, driving HSC toward pro-inflammatory fate. Moreover, the metabolic reprogramming redirects pyruvate toward lipid synthesis, leading to lipid droplet reformation, which sustains fibrotic activity through PPARγ suppression and TGF-β activation. HSC, hepatic stellate cell; ECM, extracellular matrix; YAP, yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; TLR4, Toll-like receptor 4; α-SMA, α smooth muscle actin; CTGF, connective tissue growth factor; ROS, reactive oxygen species; NLRP3, NOD-like receptor family pyrin domain containing 3; PPARγ, peroxisome proliferator-activated receptor γ; PV, portal vein; CV, central vein; CaHSC, central vein-associated HSC; PaHSC, portal vein-associated HSC; pro-Reg HSC, pro-regeneration HSCs; sHSC, senescent HSC; KDM4D, lysine demethylase 4D; GLUT1, glucose transporter type 1; PKM2, pyruvate kinase M2.

gradients that differentially activate mechanotransduction pathways, YAP/TAZ signaling predominates in stiff pericentral regions to promote fibrosis, while softer periportal areas favor HSC migration and proliferation via integrin-dependent cues (49,86,87).

Spatial specialization is also shaped by paracrine and juxtacrine interactions with neighboring cells (88). Pericentral LSECs secrete Hedgehog ligands and pericentral KCs produce TGF-β to polarize HSCs toward a fibrogenic phenotype, whereas periportal LSECs release nitric oxide and periportal KCs secrete IL-10 to suppress excessive proliferation and support reparative functions (20,89-91). Hepatocytes also contribute to this zonation: Oxidative stress products from pericentral hepatocytes activate adjacent HSCs, while periportal hepatocytes provide pro-regenerative signals supporting proliferation (92,93).

HSCs further shape immune-metabolic niches through crosstalk with infiltrating immune cells. Pericentral subsets recruit monocytes via CCL2 and CXCL5 to exacerbate inflammation, whereas periportal HSCs modulate lipid antigen presentation and perpetuate steatoinflammation in NASH (22,30,55). These interactions integrate local damage-associated molecular patterns with systemic immune inputs, forming spatially organized regulatory networks that determine HSC behavior across disease contexts.

Emerging single-cell and spatial transcriptomic technologies have validated these mechanisms, revealing zonation-specific ligand-receptor interactions between HSCs and neighboring cell types and identifying spatially restricted activation markers. Collectively, these findings demonstrate that HSC heterogeneity represents an adaptive response to microenvironmental demands rather than random variation (37,85). Understanding such spatial organization provides therapeutic opportunities, selectively targeting pericentral HSCs to mitigate fibrosis or modulating periportal subsets to enhance regeneration. The future integration of spatial omics and functional mapping will further refine precision interventions for liver diseases.

Genetic regulation of HSCs plasticity. The activation of HSCs involves a tightly regulated transcriptional program that governs phenotypic transitions between quiescent, activated,

and inactivated/senescent states. In their quiescent state, HSCs maintain lipid droplets and express adipogenic transcription factors (TFs), such as C/EBPα and PPARγ, which suppress fibrogenic genes such as Col1a1 and α-SMA (34,55,94). Upon liver injury, lineage-determining TFs, including E26 transformation-specific transcription factor ½ (ETS1/2), GATA binding protein 4/6 (GATA4/6) and IRF1/2, which maintain quiescent phenotype in qHSCs, are repressed during activation, leading to the disruption of quiescence-associated genes such as PPARγ (34,59,95). During fibrosis resolution, PPARγ is re-expressed in iHSCs, collaborating with GATA6 to restore quiescence, highlighting the potential of GATA6 and PPARγ agonists as a promising target in anti-fibrotic therapy (34,59).

Similarly, in NASH models, ETS1 has been shown to preserve the quiescent identity of HSCs by suppressing pro-fibrogenic gene programs and maintaining lipid storage capacity, while IRF1 marks aHSCs and promotes inflammatory cytokine production and collagen deposition during the progression of NASH (30). Furthermore, the genetic ablation of GATA6 in HSCs disrupts their ability to revert to a quiescent state post-injury, as GATA6-deficient cells fail to upregulate lipid-droplet-associated proteins, such as PLIN2 and downregulate α-SMA expression, directly linking this TF to HSC deactivation and metabolic reprogramming (30). These findings underscore a TF-centric regulatory hierarchy governing HSC phenotypic plasticity.

The hierarchical integration of upstream signaling pathways dictates the fate of HSCs through metabolic and mechanical checkpoints. TGF-β and PDGF function as dominant fibrogenic drivers. TGF-β activates SMAD3 to enforce myofibroblast transdifferentiation (20,96), while PDGFRβ signaling licenses proliferative expansion via mechanistic target of rapamycin (mTOR)-dependent glycolytic reprogramming (97). Conversely, Wnt pathway modulators, such as Dickkopf-related protein 1 exert context-dependent control (98). While transient Wnt inhibition restores lipid storage by activating PPARγ-dependent lipogenic genes, chronic Wnt activation promotes senescence evasion via p21 suppression (99,100). Notably, telomerase-positive HSCs exemplify this regulatory plasticity, coupling TERT-mediated replicative longevity with retinol-responsive metabolic switching, as retinol uptake is reported to reactivate RXRα-driven lipid droplet biogenesis, enabling reversion to quiescence despite persistent activation cues (101,102).

Emerging evidence reveals that the induction of senescence in HSC operates through interconnected tumor suppressor networks, which integrate inflammatory, metabolic, and mechanical signals to enforce growth arrest and restrict ECM overproduction. For example, IL-22 signaling initiates a senescence cascade through the STAT3-mediated upregulation of suppressor of cytokine signaling 3 and TP53, driving HSC into growth arrest (103). This process is reinforced by the parallel activation of the p16/Rb pathway, which stabilizes the senescent phenotype by blocking cell cycle progression (75). sHSCs undergo dual transcriptional reprogramming. They suppress ECM-producing genes while enhancing immune surveillance molecules, such as major histocompatibility complex class II and PD-L1 (104,105). Notably, HSCs lacking both TP53 and INK4a/ARF evade senescence entirely, leading to hyperproliferation and aggravated fibrotic responses, highlighting the cooperative action of these tumor suppressor pathways in constraining pathological HSC activation (75). Concurrently, the loss of YAP-mediated mechanosensing disrupts cytoskeletal tension, inducing p21-dependent quiescence against aberrant activation (106). These overlapping pathways collectively indicate a 'senescence barrier' to suppress HSC-driven matrix deposition.

Of note, the integrity of this barrier determines pathological outcomes. Compromised TP53 or p16/Rb signaling dismantles senescence enforcement, releasing HSCs from growth constraints and permitting their transition into aggressive profibrotic effectors that functionally mirror tumorigenic stromal cells. Thus, this senescence-mediated barrier underscores the evolutionary conservation of tumor suppressor networks in fibrosis containment, where senescence acts not only as an anti-aging mechanism, but also as a spatial regulator ensuring fidelity of tissue repair.

Epigenetic regulation of HSC plasticity. The phenotypic plasticity of HSCs during fibrosis is also governed by coordinated epigenetic reprogramming involving DNA methylation, histone modifications, and non-coding RNA networks, which collectively translate microenvironmental stimuli into transcriptional outputs (107). Genome-wide methylation profiling reveals activation-state-specific 5-methylcytosine patterns, particularly at pericentromeric regions, with hypermethylation silencing anti-fibrotic loci, such as PPARγ and hypomethylation enabling pro-fibrotic drivers, such as spondin 2 via Wnt/β-catenin activation (108-110). The pharmacological inhibition of DNA methyltransferases (DNMTs) counteracts this shift, restoring quiescence by suppressing TGF-β receptor signaling (111).

Complementing these DNA-centric modifications, histone post-translational dynamics have been shown to reinforce fibrogenic commitment. For example, histone deacetylases (HDACs) remove H3K27 acetylation at ACTA2 promoters to sustain myofibroblast identity (112), while mechanical cues from fibrotic ECM stiffening trigger nuclear accumulation of p300, amplifying histone acetylation at fibrotic loci to lock HSCs into self-reinforcing activation (86,87,113). Concurrently, H3K9me3 deposition at senescence-associated genes and H3K9me2 demethylation at TLR4 enhancers link chromatin states to inflammatory fibrosis (114,115).

Non-coding RNAs further integrate metabolic and epigenetic regulation. The age-dependent decline of geromiRs derepresses IL-6/tumor necrosis factor α (TNF-α), fueling inflammation and pre-metastatic niches (116), while miR-23a and miR-195 coordinate lipid metabolism with DNA methylation patterns during phenotype switching (117). Moreover, the hypermethylation of SAD1/UNC84 domain protein 2 perturbs nuclear lamina dynamics, destabilizing the genome and driving chronic pathogenic activation (118).

This multilayered epigenetic plasticity positions HSCs as microenvironmental rheostats, dynamically calibrating fibrogenic responses. Targeting nodal regulators, such as DNMTs in early fibrosis or p300 in established scarring, could selectively disrupt pathological subsets, while preserving reparative functions.

Metabolic regulation of HSC plasticity. The phenotypic diversity of HSCs stems from their marked metabolic plasticity,

where dynamic shifts in glucose, lipid and mitochondrial metabolism govern their activation states. Following liver injury, HSCs undergo a metabolic reprogramming characterized by enhanced glucose transporter type 1-mediated glucose uptake and pyruvate kinase M2-driven glycolytic flux, fueling mitochondrial oxidative phosphorylation for myofibroblast differentiation (119). This transition is accompanied by reactive oxygen species accumulation that activates NF-κB/NLRP3 inflammasome pathways, driving pro-inflammatory polarization (120). Notably, although aHSCs were traditionally considered lipid-depleted, recent evidence indicates they maintain active lipid metabolism. Mechanistically, the metabolic reprogramming redirects pyruvate toward lipid synthesis, leading to lipid droplet reformation, a paradoxical feature that actually sustains fibrotic activity through PPARγ suppression and TGF-β activation (121).

Mitochondrial dynamics play a pivotal role in regulating the fate of HSCs. Studies have indicated that qHSCs maintain fusion-dominant states that support efficient β-oxidation, while aHSCs exhibit fission-prone mitochondria that generate oncometabolites such as succinate and 2-hydroxyglutarate (122-124). These metabolites stabilize hypoxia-inducible factor-1α and promote angiogenic secretomes (120).

In the tumor microenvironment, a metabolic cross-talk emerges between cancer cells and HSCs (125). Malignant cells export lactate through monocarboxylate transporter 4, creating an acidic microenvironment that reprograms neighboring HSCs (126,127). This acid adaptation triggers the release of MMP9 from HSCs, thereby fostering a permissive environment for metastatic spread (128,129).

The complex interplay between ammonia metabolism and HSC biology reveals an intriguing paradox. Disrupted ureagenesis in injured livers results in the accumulation of nitrogenous metabolites, which paradoxically elicit two opposing outcomes in HSCs (130). While promoting fibrogenic activation through mitochondrial stress, these metabolites simultaneously induce growth arrest through p53/p21-mediated senescence (131-133). This dual effect creates a biological checkpoint that limits uncontrolled HSC expansion while permitting controlled ECM deposition during tissue repair.

While notable progress has been made in understanding HSC metabolism, several fundamental questions persist about what drives their functional diversity. Currently available research has largely illuminated the metabolic changes occurring during initial activation; however, the exact mechanisms through which distinct HSC subpopulations, particularly those with immunomodulatory vs. pro-angiogenic properties, establish and maintain their unique metabolic identities, remain to be fully elucidated. Moreover, critical gaps remain in the knowledge of how nutrient-sensing mechanisms interface with epigenetic regulation to control HSC subset specification. The potential involvement of NAD^+-dependent metabolic sensors in coordinating mitochondrial function across different HSC activation states also warrants further investigation (134).

Resolving these unanswered questions could pave the way for more sophisticated therapeutic strategies. Such approaches would ideally target disease-promoting metabolic pathways in aHSCs, while sparing their beneficial roles in liver repair and regeneration. This precision targeting represents a crucial next step in developing effective anti-fibrotic treatments that maintain the innate regenerative capacity of the liver.

4. Targeting HSCs for liver disease intervention

Current approaches to modulate HSC activity focus on four primary mechanisms: i) The interruption of activation signaling cascades; ii) the selective induction of aHSC apoptosis; iii) targeting specific HSC subsets with defined pathogenic roles; and iv) reprogramming aHSCs toward quiescent or alternative functional phenotypes (Fig. 2). Single-cell transcriptomic studies have revolutionized the understanding of HSC heterogeneity, identifying distinct pro-fibrotic and pro-regenerative subpopulations that coexist in injured livers (135). These findings support the development of precision therapies capable of selectively targeting pathological subsets while sparing regenerative populations.

Inhibition of HSC activation. HSC inactivation has emerged as a cornerstone in the treatment of liver fibrosis and cirrhosis, aiming to halt or reverse the pathological accumulation of ECM in chronic liver diseases. HSC activation is orchestrated by an intricate signaling network integrating paracrine cues and metabolic reprogramming (136), including TGF-β/Smad3 (137,138), Wnt/β-catenin (139) and Akt/mTOR (22,140). Among these pathways, TGF-β signaling enhances glycolysis and de novo lipogenesis, both of which are indispensable for the activation of HSCs. This process can be disrupted by Acetyl-CoA carboxylase inhibitors, such as firsocostat, which has exhibited potential in reducing steatosis and fibrosis in preclinical models and in patients with NASH, although further investigations are warranted (NCT02856555) (119,141). The inhibition of stearoyl-CoA desaturase-1 by aramchol has been shown to attenuate HSC activation and fibrogenesis independently of steatosis reduction, highlighting the lipogenic contribution to HSC plasticity (142,143). Likewise, thyroid hormone receptor agonists exert direct anti-fibrotic effects by suppressing profibrogenic gene expression in HSCs and improving fibrosis through coordinated metabolic and stellate cell-mediated mechanisms (144,145). Glucagon-like peptide-1 receptor agonists, primarily known for alleviating steatosis and insulin resistance, further attenuate fibrosis when combined with the ATP-citrate lyase inhibitor, bempedoic acid, in mice with NASH, revealing a synergistic link between hormonal and metabolic signaling in HSC inactivation (146,147).

Beyond metabolic reprogramming, anti-fibrotic strategies also target canonical signaling pathways that drive HSC activation. Inhibitors such as galunisertib, a TGF-β receptor I kinase inhibitor, have been shown to exert anti-fibrotic effects in preclinical models, although clinical trials have revealed limited efficacy in advanced-stag cirrhosis, possibly due to the compensatory mechanisms or off-target effects (NCT01246986) (Table III) (148,149). Similarly, PDGF signaling, critical for HSC proliferation, can be blocked by tyrosine kinase inhibitors, such as imatinib or receptor antagonists; however, challenges in specificity persist (150,151). In addition, probiotics such as Mutaflor® inhibit HSC activation and fibrogenic signaling in NAFLD/NASH models via the Hedgehog and Hippo pathways, underscoring gut-liver cross-talk as a complementary anti-fibrotic target (152).

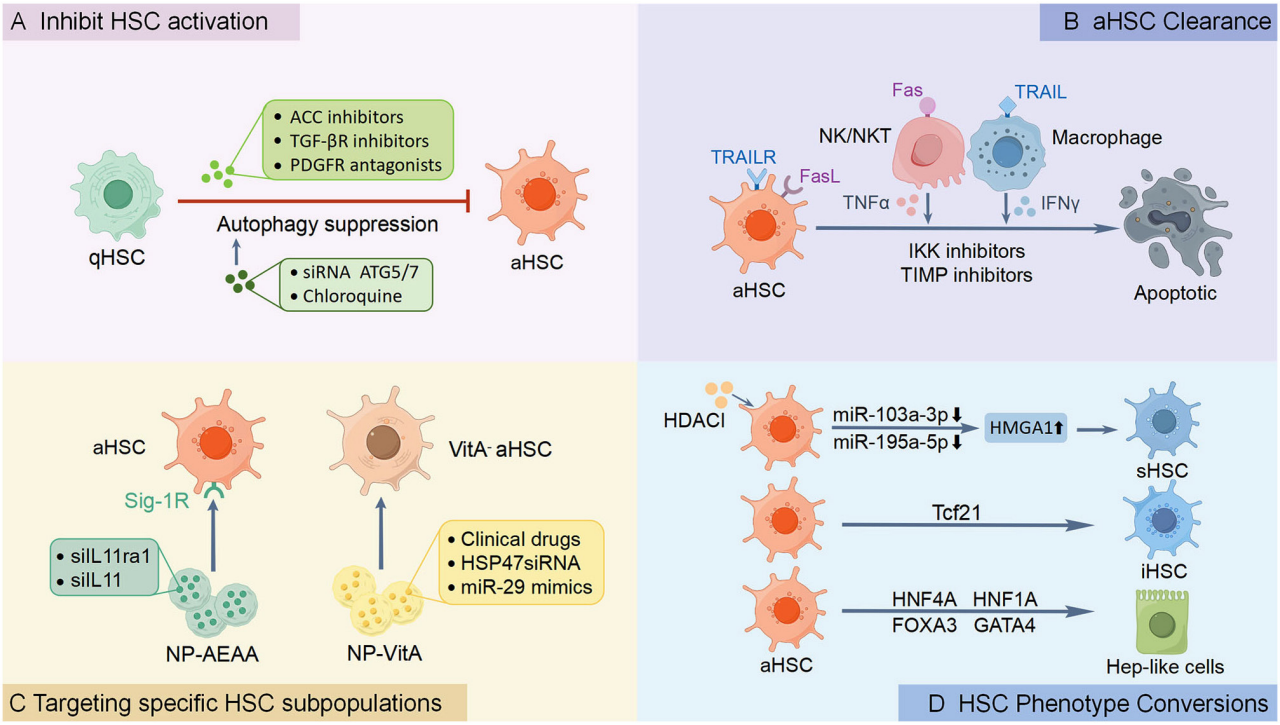

Figure 2. Therapeutic strategies targeting HSCs. (A) Inhibit HSC activation via targeting key signaling pathways using small-molecule inhibitors such as PDGF antagonists or TGF-β inhibitors. During the early stages of HSC activation, induction of autophagy by pharmacological inhibitors like chloroquine or genetic ablation of autophagy-related genes such as ATG5/7 attenuate collagen deposition and HSC activation. (B) Clearance of aHSC can be achieved by the crosstalk between immune cells and aHSC, or pharmacological interventions using small-molecule inhibitors such as IKK inhibitors, resulting in apoptosis of aHSC. (C) Targeting specific subsets of activated HSCs using NP-engineered vesicles carrying drugs or siRNA. For example, NP-AEAA, utilizes aminoethyl anisamide surface modifications to selectively target Sig-1R that are upregulated on activated HSCs in NASH progression. Another clinically validated targets include VitA-depleted aHSCs, which can be selectively addressed using VitA-coupled liposomal NPs. Furthermore, BMS-986263, a LNP encapsulating siRNA against HSP47 associated with collagen production, utilizes VitA to target aHSCs in fibrotic livers. (D) aHSCs can be reprogrammed into alternative phenotypes to reduce their profibrotic effects. The application of HDACIs induces aHSC transition into sHSC by upregulating HMGA1, while Tcf21 promotes reversion of aHSC to an inactivated state. Moreover, co-expression of TFs such as FOXA3, GATA4, HNF1A, and HNF4A enables HSC transdifferentiation into hepatocyte-like cells. HSC, hepatic stellate cell; PDGF, platelet-derived growth factor; qHSC, quiescent HSCs; aHSC, activated HSCs; NP, nanoparticle; AEAA, aminoethyl anisamide; Sig-1R, sigma-1 receptor; VitA, vitamin A; ACC, acetyl-CoA carboxylase; HSP47, heat shock protein 47; HDACIs, histone deacetylase inhibitors; HMGA1, high mobility group AT-hook 1; TF, transcription factor; Tcf21, transcription factor 21; iHSC, inactivated HSCs; Hep-like cells, hepatocyte-like cells; FOXA3, forkhead box A3; GATA4, GATA binding protein 4; HNF, hepatocyte nuclear factor.

Emerging evidence highlights the critical role of epigenetic dysregulation in maintaining HSC activation. DNMT inhibitors (DNMTIs, e.g., 5-azacytidine) and HDAC inhibitors (HDACIs, e.g., vorinostat) have demonstrated anti-fibrotic effects by remodeling chromatin architecture and suppressing collagen expression in aHSCs (153,154). The therapeutic potential of targeting non-coding RNAs is particularly promising, with microRNA (miRNA/miR)-29 family members showing efficacy in restoring epigenetic homeostasis and attenuating fibrogenesis in preclinical models (155).

Building upon the epigenetic mechanisms discussed earlier, autophagy emerges as another critical regulator of HSC behavior during liver fibrosis progression. In chronic liver injury, dysregulated autophagy plays a dual role in modulating HSC activation, survival and fibrogenic activity (156). During the early stages of HSC activation, autophagy serves as a crucial survival mechanism by providing energy substrates to sustain proliferation and collagen production under conditions of metabolic stress (156). This pro-fibrotic function is supported by preclinical evidence showing that pharmacological inhibitors such as chloroquine or genetic ablation of autophagy-related genes such as autophagy-related gene 5/7 significantly attenuate collagen deposition and HSC activation in rodent models (157,158).

However, the association between autophagy and fibrosis becomes more complex in advanced stages of disease. Paradoxically, excessive autophagic flux can trigger HSC senescence through p53/p21 pathway activation, leading to cell cycle arrest and reduced fibrogenic output (159,160). This dual nature has inspired innovative therapeutic strategies, including combination approaches that synergize autophagy inhibitors with pro-apoptotic agents to enhance HSC clearance.

Activated HSC clearance. The clearance of aHSCs is orchestrated through complex cellular crosstalk within the liver microenvironment, where multiple cell types collectively determine the fate of HSCs (161). LSECs play a dual regulatory role, maintaining HSC quiescence under physiological conditions through mediators including nitric oxide and hedgehog inhibitors (162); yet, transforming into pro-fibrotic stimulators upon injury-induced capillarization (162,163). This phenotypic switch highlights the therapeutic potential of vascular normalization strategies to restore LSEC function and mitigate fibrogenesis (163). The immune compartment further modulates HSC clearance through coordinated actions. Natural killer

Table III. The completed and ongoing clinical trials targeting HSCs.

Target/mechanism	Drug	Combination therapy	Phase	Disease type	Clinical trial outcome	Clinical trial no.
Completed clinical trails						
TGF-βR inhibitor	Galunisertib	Sorafenib (multikinase inhibitor) or Ramucirumab (VEGFR-2 mAb)	II	Advanced hepatocellular carcinoma	Prolonged OS, with acceptable safety.	NCT01246986
HSP47 siRNA	BMS-986263	N/A	II	Advanced liver fibrosis after HCV	Improved fibrosis, METAVIR and Ishak score, with acceptable safety.	NCT03420768
Probiotics	Align Probiotic Supplement Capsule	N/A	I/II	NASH/ NAFLD	Improved fibrosis, with acceptable safety.	NCT04175392
SCD1 inhibitor	Aramchol	N/A	IIb	NASH	Significantly reduced hepatic fat content, without worsening fibrosis. Showed safety and well tolerance.	NCT02279524
GLP-1R agonist	Semaglutide	N/A	II	NASH	Demonstrated reduction in hepatic fat content and improvement in NASH, but with limited effects on fibrosis.	NCT02970942
		N/A	II	NASH	Showed moderate therapeutic efficacy but limited clinical activity as monotherapy. Combination with therapy studies are ongoing.	NCT03987451
		Cilofexor (CILO) or Firsocostat (FIR)	II	NASH	Improved NASH and fibrosis, with acceptable safety.	NCT04971785
THR-β agonist	Resmetirom (MGL-3196)	N/A	II	NASH	Significantly reduced hepatic fat content and improved NASH and liver fibrosis.	NCT02912260
ACC inhibitor	GS-0976 (Firsocostat)	N/A	II	NASH	Significantly improved hepatic steatosis, with acceptable safety.	NCT02856555

Table III. Continued.

Target/mechanism	Drug	Combination therapy	Phase	Disease type	Clinical trial outcome	Clinical trial no.
Ongoing clinical trails						
HMG-CoA reductase inhibitors	Simvastatin	N/A	II/III	Advanced liver fibrosis	No results posted	NCT04971577
Kappa B kinase inhibitor	Sulfasalazine	N/A	II	Primary aclerosing cholangitis	No results posted	NCT03561584
THR-β agonist	Resmetirom (MGL-3196)	N/A	III	NASH cirrhosis	No results posted	NCT03900429

TGF-β, transforming growth factor-β receptor; OS, overall survival; HSP, heat shock protein; HCV, hepatitis C virus; METAVIR, a system for grading inflammation (A0-A3) and fibrosis (F0-F4) in HCV-related liver biopsy; Ishak A, 0-6 scale for grading portal-based liver fibrosis in viral hepatitis; NASH, Nonalcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; SCD1, stearoyl-CoA Desaturase-1; GLP-1R, glucagon-like peptide-1 receptor; THR-β, thyroid hormone receptor-β; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A.

(NK) cells induce activated HSC apoptosis via interferon γ secretion and death receptor engagement (20,164,165), while macrophage subsets differentially regulate fibrosis progression (166). For example, pro-inflammatory M1 macrophages promote HSC death through TNF-α signaling and potentiate NK cell cytotoxicity (167,168), whereas specialized restorative macrophages drive fibrosis resolution by secreting MMPs to degrade the ECM (169).

Pharmacological interventions targeting HSC clearance have emerged through multiple approaches, including IKK inhibitors and TIMP antagonists that rebalance NF-κB signaling and MMPs activity (170,171), as well as drug repurposing strategies exemplified by the antiviral agent tenofovir disoproxil fumarate which suppresses HSC survival through PI3K/Akt/mTOR pathway inhibition (172). While the selective depletion of aHSCs accelerates fibrosis resolution (106,173), excessive elimination risks compromising hepatic function through reduced liver mass and exacerbated inflammation (26,174). These observations underscore the need for precision therapeutics capable of discriminating between pathogenic and reparative HSC subpopulations (175).

Targeting specific HSC subpopulations. The advent of single-cell omics technologies has unmasked the functional diversity of HSC subpopulations, paving the way for precision interventions that selectively neutralize fibrosis-driving subsets, while preserving homeostatic or regenerative HSCs. Clinically validated targets include VitA-depleted aHSCs, which can be selectively addressed using VitA-coupled liposomal nanoparticles (NPs). For instance, BMS-986263, a lipid NP encapsulating siRNA against heat shock protein 47 associated with collagen production, utilizes VitA to target aHSCs in fibrotic livers (176). In a phase II trial (NCT03420768), BMS-986263 reduced collagen production in patients with advanced hepatic fibrosis, demonstrating proof-of-concept for HSC-specific delivery (177). Preclinically, VitA-coupled NPs loaded with miR-29 mimics restored miR-29, a key anti-fibrotic miRNA in aHSCs of CCl_4-treated mice, reversing fibrosis without hepatotoxicity (155,178). Another clinical-stage candidate, nanoparticle aminoethyl anisamide (NP-AEAA), utilizes aminoethyl anisamide surface modifications to selectively target sigma-1 receptors that are upregulated on aHSCs in NASH progression. In mice with diet-induced NASH, NP-AEAA delivering siRNA against IL-11 reduced liver inflammation and fibrosis by ~50%, with ongoing optimization for first-in-human trials (179).

Furthermore, receptor-specific NP systems have demonstrated significant potential for precision anti-fibrotic therapy. The IGF2 E12-C21 peptide-conjugated NP platform selectively binds IGF2R that are markedly upregulated during HSC transdifferentiation. In bile duct ligation models, this targeted delivery system enhanced fibrosis resolution through the preferential transport of anti-fibrotic compounds such as pentoxifylline to aHSC populations (180).

Complementary genetic approaches have further advanced the ability to precisely manipulate HSC activity. Preclinical studies utilizing GFAP-thymidine kinase transgenic models achieved the selective elimination of proliferating HSCs through ganciclovir administration, yielding a 70% reduction in fibrosis, while preserving qHSC pools and maintaining hepatic regenerative capacity (51,181). The parallel development of inducible genetic systems, such as PDGFRβ-CreERT2, has enabled temporal control over collagen-producing HSC ablation via tamoxifen induction, demonstrating the feasibility of promoter-specific interventions (182).

These approaches collectively represent significant advances in cell-type-specific therapeutic strategies, offering improved specificity compared to conventional broad-acting anti-fibrotics.

Nevertheless, the translation of HSC-targeted therapies from bench to bedside has encountered substantial challenges that underscore the complexity of liver fibrosis pathogenesis. The discouraging clinical performance of simtuzumab, a monoclonal antibody targeting lysyl oxidase like 2, in phase II

cirrhosis trials revealed critical limitations in therapeutic specificity and the adaptive capacity of the liver for compensatory ECM remodeling (183). Similarly, the TGF-β receptor inhibitor, galunisertib, despite exhibiting robust efficacy in preclinical models, demonstrated only modest clinical benefits in patients with advanced-stage fibrosis (184). These clinical experiences have catalyzed the development of more sophisticated therapeutic strategies designed to overcome these limitations.

Emerging solutions currently focus on dual-targeting approaches that combine VitA conjugates with PDGFRβ ligands to better address HSC heterogeneity, as well as microenvironment-responsive carriers that utilize fibrotic niche-specific enzymes like MMPs for spatially controlled drug release (185). Notably, recent breakthroughs in gene-editing platforms, particularly CRISPR-Cas9 targeting aHSC-specific phosphorylation sites of A-kinase anchoring protein 12, have demonstrated notable efficacy in preclinical fibrosis models through precise silencing of profibrotic pathways (186).

HSCs phenotype conversion. The notable plasticity of HSCs presents multiple therapeutic avenues for combating liver fibrosis, while promoting regeneration. Research has revealed that ~50% of aHSCs avoid apoptosis during fibrosis resolution, instead undergoing phenotypic reversion characterized by downregulation of fibrogenic markers and acquisition of a quiescent-like state resistant to reactivation (34,45). This plasticity has been conclusively demonstrated through transplantation studies where human aHSCs engrafted in immunodeficient mice regained lipid-storing capacity and other quiescent cell features (34). PPARγ activation plays a central role by restoring lipogenic programs that promote HSC inactivation (34,187). Equally critical is Tcf21, a TF that simultaneously suppresses profibrotic pathways, while activating quiescence-associated genes in both cellular and animal models (188). Complementary to these reversion pathways, the targeted induction of senescence through p53 activation has been shown to exert significant anti-fibrotic effects (189-191).

Emerging evidence demonstrates that targeted epigenetic modulation can effectively redirect aHSC fate toward beneficial phenotypes. The small molecule, CM272, a dual inhibitor of G9a histone methyltransferase and DNMT1, drives aHSC conversion into adipocyte-like cells by demethylating and reactivating the PPARγ promoter, resulting in the significant attenuation of fibrosis in preclinical NASH models (10,192). The therapeutic potential of this approach is further supported by the ability of CM272 to simultaneously suppress pro-fibrotic signaling pathways. while restoring metabolic functions characteristic of qHSCs (193).

HDACIs represent another class of epigenetic modifiers with significant anti-fibrotic effects. Valproic acid (VPA), a clinically approved HDACI, mediates aHSC senescence through miRNA-dependent mechanisms. By downregulating miR-103a-3p and miR-195-5p, VPA promotes the expression of high mobility group AT-hook 1, a critical driver of cellular senescence (194). This epigenetic-miRNA cascade not only induces growth arrest, but also shifts aHSCs toward an anti-fibrotic secretome phenotype characterized by enhanced MMP activity and reduced collagen production (22,195).

Notably, the complete lineage reprogramming of aHSCs has been achieved through TF overexpression. The combinatorial expression of forkhead box A3 (FOXA3), GATA4, hepatocyte nuclear factor (HNF)1A and HNF4A converts aHSCs into functional hepatocyte-like cells *in vitro*, which upon transplantation, can repopulate damaged liver parenchyma and ameliorate fibrosis (196,197). This direct reprogramming approach bypasses pluripotent intermediates, while maintaining the epigenetic memory of hepatic identity, providing potential advantages for regenerative applications. Mechanistically, FOXA3, a canonical pioneer factor, initiates this process by binding to compacted chromatin at hepatocyte-specific enhancers and displacing linker histone H1, thereby initiating local chromatin opening (198). GATA4 acts synergistically with FOXA3, and together they prime the epigenetic landscape for the core hepatocyte regulators (197). Subsequently, HNF4A binds to these accessible regulatory elements to activate a comprehensive suite of genes defining hepatocyte identity, including those governing metabolism and synthetic function (199). HNF1A reinforces this program by stabilizing the transcriptional network and activating HNF4A expression, creating a positive feedback loop that locks in the hepatocyte fate (197). Concurrently, the expression of the aHSC genetic program is effectively silenced, as evidenced by the downregulation of key markers including α-SMA and COL1A1. The reprogramming process also suppresses critical aHSC maintenance pathways, such as YAP/TAZ signaling, which is essential for maintaining the myofibroblastic phenotype (200,201). This combinatorial action of the four factors thereby orchestrates a complete phenotypic conversion, overriding the fibrogenic identity of aHSCs to re-establish functional hepatocyte properties *in vivo*.

5. Conclusions and future perspectives

The advent of single-cell and spatial transcriptomics has established HSC heterogeneity and plasticity as foundational to liver fibrogenesis and resolution. Given the recurrent failure of broad-spectrum anti-fibrotics, future therapeutic breakthroughs must leverage precision strategies capable of distinguishing pathogenic from reparative HSC subpopulations. Achieving this will require combinatorial approaches, such as cell-specific NP delivery or temporally controlled epigenetic reprogramming, to therapeutically guide HSC fate decisions, thereby selectively inhibiting fibrosis while actively promoting regeneration.

Acknowledgements

Not applicable.

Funding

The present study was supported by grants from the Key Laboratory Open Project Foundation of Jiangsu University (no. 8161280002), Science and Technology Plan (Apply Basic Research) of Changzhou City (no. CJ20230002), Science and Technology Plan (Apply Basic Research) of Changzhou City (no. CJ20241041), the Soft Science Research Program of Zhenjiang City (no. RK2025040), the Natural Science

Foundation of China (no. 82100666) and the Young Scientists Initiative Foundation of Jiangsu University.

Availability of data and materials

Not applicable.

Authors' contributions

DY conceived and supervised the study. DY and CG wrote the manuscript. GC and HJ contributed to the literature collection and the revision of the manuscript. HZ and YC assisted with the literature search, figure preparation and revision of the manuscript. KZ and DY finalized the manuscript and made the conceptual evaluation of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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