

Transcription factors in liver fibrosis: Mechanistic insights and nanotechnology-driven therapeutic strategies (Review)

XIANFEI ZHOU¹, CHONGJUN YANG², ZHIYONG WENG³ and LIHUA LI⁴

¹Department of Hepatobiliary Surgery, Taizhou Municipal Hospital (Taizhou University Affiliated Municipal Hospital), School of Medicine, Taizhou University, Taizhou, Zhejiang 318001, P.R. China; ²Department of Pathophysiology, School of Basic Medicine, Shenyang Medical College, Shenyang, Liaoning 110000, P.R. China; ³School of Art and Design, Taizhou University, Taizhou, Zhejiang 318001, P.R. China; ⁴Department of Basic Medicine and Medical Laboratory Science, School of Medicine, Taizhou University, Taizhou, Zhejiang 318001, P.R. China

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Abstract. Liver fibrosis, a common pathological outcome of chronic liver diseases, is a dynamic process characterized by molecular and cell interactions. Transcription factors (TFs) are key in modulating gene expression programs that govern hepatocyte fate, metabolic homeostasis, inflammation and extracellular matrix remodeling. In hepatocytes, TFs such as hepatocyte nuclear factor 4 α and FOXA2 serve a key role in maintaining metabolic balance, with their dysfunction leading to lipid accumulation, oxidative stress and profibrotic signaling. In non-parenchymal cells, including hepatic stellate, Kupffer and liver sinusoidal and biliary epithelial cells, TFs such as YAP/TAZ, NF- κ B, STAT3 and GATA-binding factor 4 regulate activation, proliferation and intercellular communication, thereby influencing fibrosis progression or resolution. Advances in single-cell omics, spatial transcriptomics and epigenomics are elucidating the dynamic, cell type-specific TF networks involved in fibrosis and identifying therapeutic targets. Nanotechnology presents strategies for precise modulation of TFs and selective targeting of hepatic cell populations, facilitated by nanocarriers that enable the delivery of nucleic acids, pathway inhibitors and epigenetic modulators. Preclinical studies indicate promising antifibrotic effects of nanodelivery systems, however, challenges related to biocompatibility, targeting efficiency and clinical translation persist. This review aimed to summarize TF-mediated regulation in liver fibrosis and nanotechnology-based therapeutic approaches as well as future directions for precision antifibrotic therapy.

Contents

1. Introduction
2. Origin and functional activity of TFs
3. Transcriptional regulatory mechanisms in the liver
4. Transcriptional regulation of liver fibrosis progression
5. Nanomaterial-based targeting of TFs: Mechanisms and strategies for liver fibrosis therapy
6. Conclusion

1. Introduction

Liver fibrosis is a pathophysiological manifestation of chronic liver disease induced by viral infection, chemical insults, autoimmune disorders, alcohol abuse or complications from other disease. It results from persistent liver injury and is characterized by excessive extracellular matrix (ECM) accumulation. This condition represents a dynamic integrated process involving complex molecular, cell and tissue-level interactions. As a precursor to cirrhosis and hepatocellular carcinoma, liver fibrosis poses a threat to human health (1-3). Currently, chronic liver disease and cirrhosis account for >2 million deaths annually, constituting ~4% of all global deaths worldwide (4). To date, no pharmacological therapy has received approval specifically for an antifibrotic indication. Nonetheless, liver fibrosis is not necessarily irreversible. Growing clinical evidence, particularly from patients with chronic hepatitis B or hepatitis C virus infection, suggests that fibrosis can regress following effective control or elimination of the underlying cause, lifestyle modification and antiviral therapy (5,6). These findings have spurred extensive research into the molecular and cell mechanisms driving fibrosis resolution, with the aim of translating these insights into therapeutic strategies for restoring tissue integrity in human liver disease (5,6).

Recent advancements in single-cell RNA sequencing, high-dimensional multi-omics technologies (including proteogenomics and lipidomics) and spatial transcriptomics have enhanced the understanding of liver cellular heterogeneity in both health and disease (7,8). These methodologies provide key

Correspondence to: Professor Lihua Li, Department of Basic Medicine and Medical Laboratory Science, School of Medicine, Taizhou University, 1139 Shifu Road, Jiaojiang, Taizhou, Zhejiang 318001, P.R. China
E-mail: lilihua1018@sina.com

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insights into various processes associated with fibrosis regression, such as the removal or suppression of injurious stimuli (9), the elimination or inactivation of myofibroblasts (10), the resolution of inflammation alongside the restoration of anti-inflammatory signaling (11) and the apoptosis or deactivation of hepatic stellate cells (HSCs). Furthermore, they elucidate intercellular interactions and intracellular signaling events that dictate whether fibrosis progresses or regresses (5). Among these mechanisms, transcription factors (TFs) are key molecular mediators orchestrating fibrosis resolution. By binding to promoter or enhancer regions of target genes, TFs regulate gene expression of key molecular signals involved in liver fibrosis, thereby modulating downstream gene networks that govern the fibrotic process (12). During the development and regression of liver fibrosis, TFs exhibit pleiotropic roles across different cell compartments, influencing hepatocyte survival, inflammatory responses in Kupffer cells and phenotypic transition of HSCs (13). TFs regulate cellular proliferation and apoptosis to maintain dynamic cell equilibrium while critically modulating immune and inflammatory responses by controlling immune cell activation and the release of inflammatory mediators (12,14). TFs contribute to cellular stress responses, enabling cells to withstand damaging stimuli, thus influencing liver fibrogenesis through multiple interconnected pathways (12,15,16). Notably, the effects of TF activation or suppression exhibit high cell- and context-dependence. In non-parenchymal cells, activation of certain TFs may promote inflammatory and profibrotic responses, while alterations in TF activity in parenchymal cells may exacerbate or mitigate liver injury, contingent upon the specific TF, underlying etiology, disease stage and cellular state (17,18).

The present review aimed to summarize TF roles in liver fibrosis progression, particularly their compartment-specific functions and regulatory impact on chronic inflammation and fibrogenesis. By elucidating the precise molecular mechanisms by which TFs modulate fibrotic processes across hepatic cell populations, the present study aimed to identify potential targets for novel therapeutic strategies against liver fibrosis. A deeper understanding of these regulatory networks may facilitate the design of targeted interventions for halting or reversing liver fibrogenesis.

2. Origin and functional activity of TFs

TFs are genome-encoded proteins that regulate gene expression by binding specific DNA sequences in promoters, enhancers or other regulatory regions and recruiting transcriptional cofactors. Their activity is influenced by post-translational modification. In total, ~10% of human genes encode DNA-binding proteins, many of which function as TFs or transcriptional cofactors (19).

Gene expression is key to all living systems and is regulated by complex mechanisms that oversee every stage from RNA synthesis to protein degradation. Transcription initiation is the key control point within the gene expression cascade, modulated by two primary classes of DNA-interacting proteins: Gene-non-specific factors, such as RNA polymerase II, general TFs and enzymes involved in histone modifications and DNA methylation and gene-specific factors that confer regulatory precision at individual target loci (20). TFs initiate

gene regulatory programs by selectively binding specific DNA sequences, such as promoters and enhancers, thereby initiating transcriptional control. This dynamic capacity for decoding provides a molecular basis for establishing cell type specificity and developmental programs. Numerous genes serve as master regulators or selector genes, controlling the establishment of distinct cell identities of cell types and developmental patterns (21) while also modulating specific pathways such as immune responses (22).

Eukaryotic mRNA transcription progresses through three main steps (Fig. 1): Binding of transcriptional activators to cis-regulatory DNA sequences, recruitment of the preinitiation complex to the core promoter and elongation of the mRNA transcript (23). General TFs (TFIIA, TFIIF) drive basal transcription and form the preinitiation complex at the core promoter alongside RNA polymerase II. By contrast, specific TFs recognize distinct DNA motifs within cis-regulatory elements, including enhancers and silencers, which may be located proximally or distally from target promoters. By recruiting co-activator or -repressor complexes, these TFs contribute to the spatial and temporal regulation of gene expression (20). A key mechanism of transcriptional regulation relies on signal-dependent activation: TFs, such as NF- κ B and STAT family members, reside in the cytoplasm in an inactive state. Following exposure to specific stimuli, including inflammatory cytokines, growth signals or cellular stress, these factors undergo conformational changes driven by phosphorylation or chaperone dissociation, revealing their nuclear localization signal. This exposure enables their active translocation into the nucleus, allowing engagement with regulatory elements of target genes to initiate transcriptional programs (24).

The activity of TFs is primarily regulated through two mechanisms. First, their functional abundance is controlled at multiple levels, including transcriptional regulation that dictates the rate of mRNA synthesis, translational control that modulates ribosome binding efficiency to mRNA and post-translational modifications, such as phosphorylation or acetylation, that alter TF activity (25). Second, the accessibility of TF binding sites is modulated by epigenetic processes, including DNA methylation and histone modifications that influence promoter availability, as well as cell type-specific chromatin architecture (19,26). Variations in chromatin conformation and protein binding across cell types determine the accessibility of TFs to their DNA targets, thereby shaping TF activity (26). The primary function of TFs involves regulating gene expression by either activating or suppressing the transcriptional activity of RNA polymerase, thus controlling the expression of specific genes. Therefore, TFs are key for cell differentiation, tissue development, metabolic regulation and responses to environmental stimuli. Based on structural and functional characteristics, TFs are classified into families, including zinc finger, helix-loop-helix and leucine zipper proteins (27). These DNA-binding domains enable TFs to recognize specific DNA motifs, exerting control over gene expression (28,29).

TF activity is tightly regulated by intracellular signaling pathways, which modify TF function, stability and subcellular localization through post-translational modification, such as phosphorylation, ubiquitination and acetylation (30). TFs typically form complexes with other proteins to coordinate gene

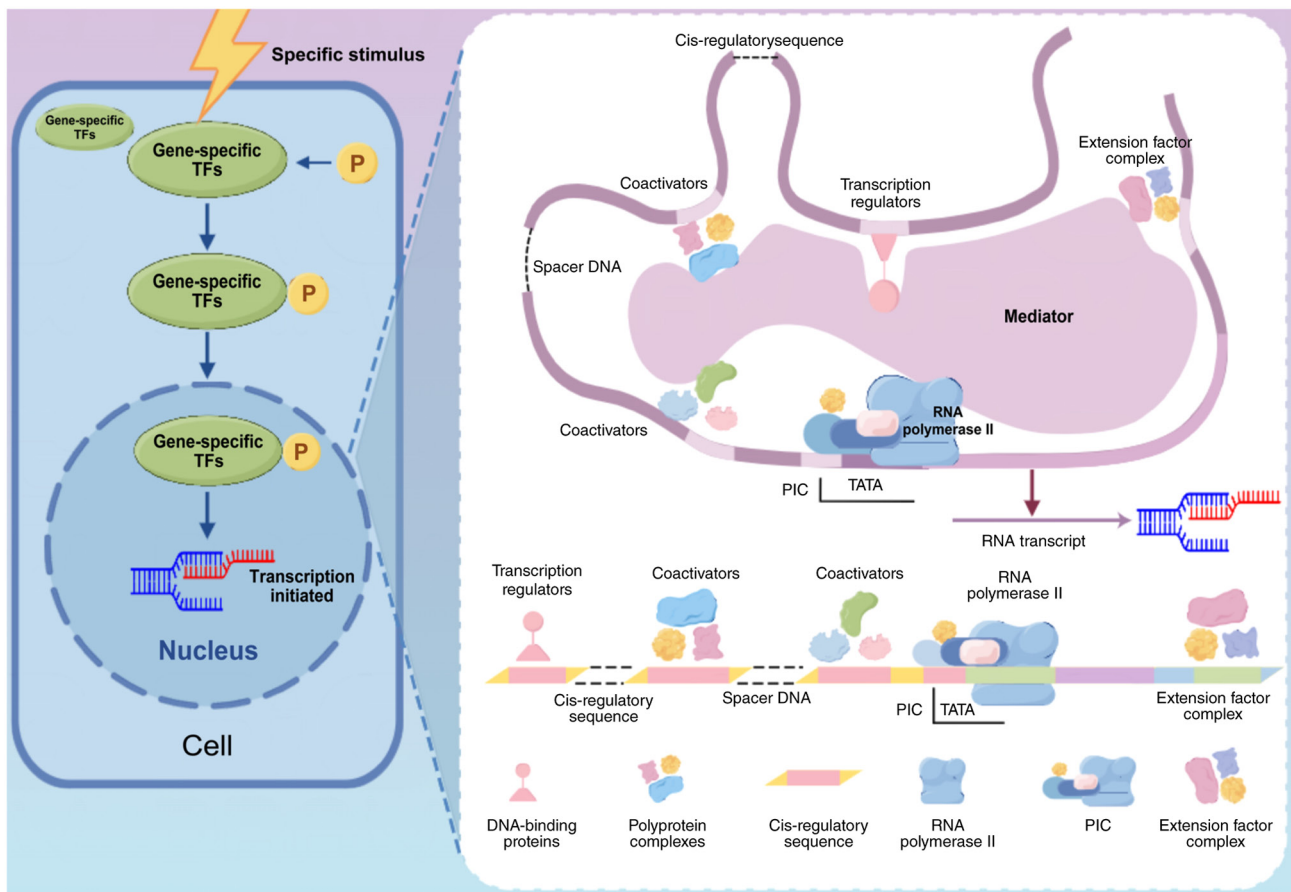


Figure 1. Schematic representation of the gene regulatory regions and the transcription initiation complex in eukaryotes. In stimulus-induced transcription initiation, activated TFs translocate into the nucleus and promote target-gene transcription. The process comprises three major stages. Gene-specific TFs bind to upstream cis-regulatory elements, such as enhancers, and recruit coactivators. At the core promoter, which contains elements such as the TATA box, the mediator complex and other regulatory factors facilitate the assembly of the PIC containing Pol II. With the assistance of elongation factors, Pol II initiates RNA synthesis and productive elongation. TF, transcription factor; PIC, preinitiation complex; Pol, polymerase.

expression regulation. While TFs are key for normal development and homeostasis, their aberrant expression or dysfunction is associated with organ-specific diseases. For example, TF abnormalities contribute to diabetes (pancreatic and duodenal homeobox 1 dysfunction in the pancreas) (31), cardiomyopathy and heart failure [GATA-binding factor (GATA)4 or NK2 homeobox 2-5 mutations] (32), neurodevelopmental defect and neurodegenerative disorders (PAX6 mutations leading to congenital eye malformation) (33) and immune dysregulation (STAT3 imbalance resulting in autoimmunity or immunodeficiency) (34). In the liver, TF dysregulation similarly serves a critical role; abnormal expression or malfunction of TFs disrupts hepatic metabolic homeostasis, activates pro-inflammatory and profibrotic cascades and drives hepatocarcinogenesis, contributing to conditions such as steatosis, hepatitis, cirrhosis and hepatocellular carcinoma (17,35,36).

3. Transcriptional regulatory mechanisms in the liver

Transcription factors (TFs) and their regulatory networks in hepatic parenchymal cells. Hepatic parenchymal cells sustain their key metabolic functions through a finely tuned, multilayered regulatory network composed of core TFs and dynamic signaling pathways. As a master regulator of liver development and metabolic homeostasis, hepatocyte nuclear factor

(HNF)4 α drives the transcriptional activation of target genes such as transmembrane 4 L six family member 5 by binding direct repeat 1 (DR1) motifs, thereby establishing a comprehensive regulatory framework that integrates lipid metabolism, glucose homeostasis and bile acid synthesis (37). The functional stability of HNF4 α is protected by dual mechanisms: The Wnt/ β -catenin pathway enhances its protein stability by inhibiting β -transducin repeat-containing protein-mediated ubiquitin-dependent degradation, while insulin signaling sustains HNF4 α activity by preventing phosphorylation via the PI3K/Akt/glycogen synthase kinase 3 β pathway. These complementary mechanisms ensure the persistent activity of HNF4 α during liver regeneration and metabolic adaptation (38,39). HNF4 α establishes hierarchical transcriptional cascades by activating forkhead box A2 (FOXA2), a critical switch for gluconeogenesis. The nucleocytoplasmic shuttling of FOXA2 is dynamically regulated by insulin/PI3K/Akt signaling; postprandial insulin elevation promotes inhibitory phosphorylation of FOXA2, leading to its nuclear export and suppression of gluconeogenic genes such as G6Pase, thus facilitating rapid blood glucose homeostasis (40). mTORC1 signaling suppresses FOXA2 transcriptional activity under nutrient excess by phosphorylating FOXA2 at Ser318, emphasizing the integration of cell energy-sensing systems with key metabolic programs (41).

At the intersection of stress response and metabolic remodeling, CCAAT/enhancer-binding protein (C/EBP) α exhibits a biphasic regulatory pattern. Acute inflammatory stimuli induce its expression via the IL-6/JAK/STAT3 pathway, promoting the synthesis of acute-phase proteins such as C-reactive protein, while simultaneously reprogramming fatty acid metabolic pathways through a PPAR γ -regulated module (42,43). Under energy stress, phosphorylation of C/EBP α at Thr222/Thr226 by AMPK impairs its DNA-binding capacity. This post-translational modification establishes a negative feedback loop with upstream signaling, balancing glycogen synthesis and lipid catabolism (44). The spatiotemporal control of lipid metabolism is exemplified by the ligand-dependent activation of liver receptor homolog-1 (LRH-1). This nuclear receptor is inhibited by fibroblast growth factor (FGF)19/FGF receptor (FGFR)4 signaling to limit excessive bile acid synthesis and downregulates the expression of its target gene 3-hydroxy-3-methylglutaryl-CoA reductase via the insulin/PI3K/Akt pathway. This interplay between membrane receptor signaling and metabolic nuclear receptors ensures precise coupling of peripheral hormonal cues with endogenous cholesterol biosynthesis (45,46).

In xenobiotic detoxification, the constitutive androstane receptor (CAR) and pregnane X receptor (PXR) system exhibits a distinctive ligand-activated regulatory mechanism. Upon exposure to exogenous compounds such as phenobarbital or pathological accumulation of endogenous bile acids, these orphan nuclear receptors undergo conformational changes that reveal coactivator-binding domains, initiating the cascade expression of drug-metabolizing enzymes such as cytochrome P450 family 3 subfamily A member 4 (CYP3A4) (47). Notably, the CAR/PXR heterodimer with retinoid X receptor (RXR) α demonstrates gene selectivity: By specifically binding the promoter region of CYP7A1, it regulates the rate of primary bile acid synthesis and participates in feedback mechanisms that maintain bile acid pool homeostasis, a key self-regulatory process in preventing cholestatic liver injury (48). These transcriptional regulatory modules integrate into dynamic networks through signal crosstalk. Within these networks, mTOR signaling suppresses FOXA2 activity to decrease gluconeogenesis while enhancing HNF4 α -driven lipid secretion (37,40). AMPK activation inhibits C/EBP α to limit glycogen accumulation and modulates cholesterol metabolism via LRH-1 phosphorylation (45,46). This multidimensional signal integration enables hepatocytes to adapt to changes in nutritional status, metabolic demand and xenobiotic exposure, maintaining systemic metabolic homeostasis while providing molecular targets to elucidate the pathogenesis of metabolic liver disease, such as non-alcoholic fatty liver disease and drug-induced liver injury (49). A concise overview of these interconnected regulatory mechanisms, including TFs and their regulatory networks in hepatic parenchymal cells, is summarized in Table I.

TFs and their regulatory mechanisms in hepatic non-parenchymal cells. Hepatic non-parenchymal cells maintain microenvironmental homeostasis through a complex network of transcriptional regulation, where intercellular signaling crosstalk and intrinsic regulatory mechanisms form a multilayered dynamic equilibrium. In the regulation of HSC

activation, the YAP/TAZ system exhibits dual responsiveness to biochemical and mechanical cues. The TGF- β /Smad3 pathway directly phosphorylates YAP/TAZ, promoting their nuclear accumulation and cooperative activation of profibrotic gene expression, including α -smooth muscle actin (α -SMA) and collagen type I (COL1A1) fibers via TEA domain (TEAD) TFs. Concurrently, changes in ECM stiffness activate the integrin β 1/focal adhesion kinase/Src signaling pathway, leading to F-actin cytoskeletal remodeling and inactivation of large tumor suppressor kinases, thereby releasing cytoplasmic YAP/TAZ. This mechano-chemical coupling mechanism is a core driver of fibrogenesis (50,51). Conversely, the LIM homeobox (LHX)2 regulatory network serves as an antifibrotic barrier through a tripartite mechanism: Its zinc finger domain directly binds the hepatocyte growth factor (HGF) promoter to drive regenerative signals, competitively binds Smad4 to suppress TGF- β signaling efficiency and activates the NRF2/KEAP1 pathway to enhance glutathione synthesis. The protein stability of LHX2 is regulated by the Akt/mTORC1 pathway activated under oxidative stress, forming a dynamic feedback loop that integrates stress adaptation and tissue repair (52,53).

Lipid metabolic reprogramming serves a central role in the phenotypic transition of HSCs. PPAR γ maintains the quiescent state by binding lipid-derived ligands such as 15-deoxy- Δ 12,14-prostaglandin J2 and suppressing pro-inflammatory gene expression through the recruitment of the SIRT1 deacetylase complex. Phosphorylation of AMPK α at Thr172 not only enhances the DNA-binding ability of PPAR γ but also decreases lipotoxic metabolite accumulation by inhibiting acetyl-CoA carboxylase phosphorylation, highlighting the interplay between metabolic sensing and epigenetic regulation in fibrotic remodeling (54,55).

The dynamic balance of the hepatic immune microenvironment relies on precise regulation of NF- κ B signaling in Kupffer cells. In the canonical pathway, lipopolysaccharide (LPS)-toll-like receptor (TLR)4 complexes activate a MyD88-dependent signaling cascade, leading to IKK β -mediated phosphorylation and degradation of I κ B α , which facilitates the nuclear translocation of the RelA/p65 dimer and initiates transcription of pro-inflammatory cytokines such as IL-6 and TNF- α . By contrast, the non-canonical pathway is driven by NF- κ B-inducing kinase-mediated phosphorylation of IKK α , regulating the p52/RelB heterodimer to sustain chronic inflammatory states (56,57). Liver sinusoidal endothelial cells (LSECs) adapt to hypoxia via the hypoxia-inducible factor (HIF)-1 α /Notch/VEGF pathway. Under hypoxic conditions, HIF-1 α evades von Hippel-Lindau-mediated ubiquitination and degradation, forming a complex with aryl hydrocarbon receptor nuclear translocator and binding hypoxia response elements in the VEGF promoter. Concurrently, Notch signaling activates the Delta-like canonical Notch ligand 4-Jagged1 ligand system through γ -secretase-mediated release of the Notch intracellular domain. This dual signaling amplification mechanism not only promotes angiogenesis but also enhances the antioxidant capacity of LSECs by inducing the NRF2/glutathione peroxidase 4 pathway (58,59). The polarization state of hepatic macrophages is governed by the NRF2/C/EBP β regulatory pathway. Under oxidative stress, NRF2 dissociates from Keap1, activating phase II detoxifying enzymes such as heme

Table I. Transcription factors in hepatic parenchymal cells.

Transcription factor	Function	Regulatory signaling pathways	Impact	(Refs.)
HNF4 α	Regulates lipid and glucose metabolism and bile acid synthesis; activates metabolic genes (TM4SF5, FOXA2)	Wnt/ β -catenin, insulin	Maintains hepatocyte proliferation and metabolic function; dysregulation leads to lipid metabolic disorder and promotes liver fibrosis	(34,35)
FOXA2	Regulates gluconeogenesis, lipid metabolism and bile acid synthesis; modulates N-glycosylation-associated genes involved in hepatic metabolic homeostasis	Insulin/PI3K/Akt, mTOR	Maintains glucose homeostasis; inhibition decrease gluconeogenesis; dysregulation leads to lipid accumulation and oxidative stress	(37)
PPAR α	Fatty acid β -oxidation, ketogenesis, anti-inflammatory effects	Fatty acids, AMPK	Activation by fatty acids or AMPK, promotes fatty acid catabolism	(40,69)
LRH-1	Regulates bile acid synthesis and cholesterol metabolism	FGF19/FGFR4, insulin/PI3K/Akt	Inhibits bile acid synthesis; dysfunction leads to abnormal cholesterol metabolism, promoting lipotoxicity and fibrosis	(42,43)
CAR	Xenobiotic detoxification (CYP2B/CYP3A), bilirubin metabolism	Exogenous ligands (phenobarbital)	Directly activated by xenobiotic ligands; induces drug-metabolizing enzymes	(44)
PXR	Regulates drug-metabolizing enzymes (CYP3A4), bile acid homeostasis	Xenotoxins (rifampin), endogenous bile acids	Ligand binding activates PXR, promoting detoxification and bile acid excretion	(45)
Nrf2 (NFE2L2)	Antioxidant defense (regulates glutathione synthetase) and detoxification enzyme expression	KEAP1/Nrf2/antioxidant response elements	Oxidative stress dissociates KEAP1-Nrf2, enabling Nrf2 nuclear translocation to activate antioxidant genes	(56,155)
C/EBP α	Controls hepatocyte differentiation, glycogen synthesis and acute-phase response	IL-6/JAK/STAT, AMPK	Promotes inflammatory response; phosphorylation inhibits activity, causing abnormal glycogen synthesis and lipid metabolism	(58)
C/EBP β	Liver regeneration, acute-phase response, lipid metabolism	IL-6/JAK/STAT, GH	IL-6 activates C/EBP β via STAT3; GH promotes C/EBP β expression via JAK2/STAT5	(58)
HNF1 α	Regulates bile acid synthesis, glucose metabolism and urea cycle gene expression	HNF4 α -dependent	HNF4 α activates HNF1 α expression	(61)
HNF6	Controls bile duct development, glucose metabolism and hepatocyte proliferation	Hedgehog, Notch	Hedgehog signaling promotes HNF6 expression; Notch inhibits HNF6 activity.	(64,168)
FXR	Regulates bile acid synthesis (inhibits CYP7A1) and lipid and glucose metabolism	Bile acid/FXR/RXR	Bile acids activate FXR, inhibiting bile acid synthesis and promoting excretion	(65)
SREBP-1c	Controls fatty acid synthesis (ACC, FAS) and cholesterol synthesis genes	Insulin/PI3K/Akt, sterol regulatory element	Insulin activates SREBP-1c; low sterol levels promote nuclear translocation of SREBP	(68)
CREB	Regulates gluconeogenesis (PEPCK, G6Pase), hepatocyte survival	cAMP/PKA, glucagon	cAMP activates PKA, phosphorylating CREB to promote gluconeogenesis	(167)

Table I. Continued.

Transcription factor	Function	Regulatory signaling pathways	Impact	(Refs.)
AhR	Regulates xenobiotic metabolism (CYP1A1/1A2), immune modulation	Polycyclic aromatic hydrocarbons (dioxins)	Binding of exogenous toxins to AhR induces detoxifying enzyme expression	(169)

ACC, acetyl-CoA carboxylase; AhR, aryl hydrocarbon receptor; AMPK, AMP-activated protein kinase; CAR, constitutive androstane receptor; CYP, cytochrome P450; FAS, fatty acid synthase; FOXA2, forkhead box A2; FXR, farnesoid X receptor; HNF 6 (ONECUT1), hepatocyte nuclear factor; LXR, liver X receptor; LXR, liver X receptor; PPAR, peroxisome proliferator-activated receptor; PXR (NR1I2), pregnane X receptor; RXR, retinoid X receptor; SREBP-1c, sterol regulatory element-binding protein 1c.

oxygenase (HO)-1 and NAD(P)H quinone dehydrogenase (NQO)1 while competitively inhibiting IKK β kinase activity to block NF- κ B signaling. C/EBP β undergoes phosphorylation-dependent conformational changes (phosphorylation at Thr235), enhancing cooperation with activator protein 1 (AP-1) to drive the expression of anti-inflammatory mediators such as IL-10 and arginase 1. This redox-sensitive transcriptional network serves a pivotal role in inflammation resolution and tissue repair (60,61,62).

Hepatic non-parenchymal cells establish a cross-cell regulatory network through paracrine signaling. Activated HSCs (aHSCs) secrete connective tissue growth factor (CTGF), which enhances the sensitivity of Kupffer cells to TLR4 signaling (63,64). Macrophage-derived TGF- β 1 induces endothelial-to-mesenchymal transition in LSECs via the Smad2/3 pathway (65). Endothelial cells release platelet-derived growth factor (PDGF)-BB, promoting stellate cell migration through activation of the PI3K/Akt/mTOR pathway (64,66). This multidirectional crosstalk drives a cycle contributing to pathological processes such as liver fibrosis and portal hypertension. TFs and their regulatory mechanisms in these cells are summarized in Table II.

4. Transcriptional regulation of liver fibrosis progression

Role of hepatocyte TF families in liver fibrosis development.

The initiation and progression of liver fibrosis are driven by the dynamic interplay between pathological processes, including metabolic dysregulation, inflammatory responses and cellular phenotypic transition (5,52). Abnormal regulation of TF networks serves as a central driving force. The HNF family, known as the molecular gatekeepers of hepatocyte differentiation and metabolic homeostasis, serves a critical role in maintaining hepatic physiological balance; its dysfunction directly disrupts this equilibrium. For example, HNF-1 α directly binds the promoter of CYP7A1 to regulate the rate-limiting step of bile acid synthesis. Downregulation of HNF-1 α reduces CYP7A1 transcriptional activity by >60% (67). This loss of precise regulation triggers compensatory hyperactivity of the bile acid synthetic pathway, leading to an abnormal increase in hydrophobic bile acids such as deoxycholic acid. This increase activates G protein-coupled bile acid

receptor 1 on the hepatocyte membrane, inducing calcium influx and mitochondrial membrane potential collapse (67,68). Toxic bile acids upregulate the TLR4/MyD88 signaling pathway in HSCs, resulting in a 3-5-fold increase in α -SMA expression and promoting COL1 secretion through Smad2/3 phosphorylation (69).

HNF-1 α regulates key urea cycle enzymes, including carbamoyl phosphate synthetase 1 and ornithine transcarbamylase, to maintain hepatocellular detoxification capacity. Loss of HNF-1 α function elevates blood ammonia levels to 2-3 times the normal concentration, directly inducing excessive mitochondrial reactive oxygen species (ROS) production in hepatocytes and activating the NLRP3 inflammasome in Kupffer cells. This activation promotes the maturation and release of IL-1 β and IL-18 (70).

HNF4 α is a key determinant of hepatocyte differentiation and metabolic homeostasis. During liver fibrosis, decreased HNF4 α expression diminishes PPAR α /carnitine palmitoyl-transferase 1 α -dependent fatty acid β -oxidation, resulting in lipid droplet accumulation and lipotoxic stress (41). HNF4 α downregulation disrupts the functional cooperation between HNF4 α and farnesoid X receptor (FXR), decreasing the expression of the bile salt export pump ATP-binding cassette subfamily B member 11 (ABCB11), impairing canalicular bile acid export and promoting intracellular bile acid accumulation (68,71). Lipid overload and bile acid stress activate inflammatory and stress-responsive pathways, including JNK/c-Jun and NLRP3 signaling, thus enhancing the secretion of hepatocyte-derived profibrotic mediators such as TGF- β 1 and PDGF, which facilitate HSC activation (72) (Fig. 2A). Additionally, loss of HNF4 α may shift hepatocyte metabolism toward glycolysis, leading to increased lactate export that acidifies the extracellular microenvironment, promoting lysyl oxidase (LOX)-dependent collagen cross-linking and matrix stabilization (73).

The functional balance of nuclear receptor families is key for maintaining hepatic metabolic and immune homeostasis. Under physiological conditions, FXR induces small heterodimer partner (SHP) expression, which suppresses CYP7A1 transcription and limits bile acid synthesis. Loss of FXR activity decreases SHP expression and releases CYP7A1 from this inhibitory control, leading to increased bile acid synthesis and

Table II. Transcription factors in hepatic non-parenchymal cells.

Transcription factor	Function	Regulatory signaling pathways	Impact	(Refs.)
GATA3	Drives Th2 differentiation and antiparasitic immunity	IL-4/STAT6	IL-4 via STAT6 promotes GATA3 expression to drive Th2 response	(1,121)
STAT4	Promotes Th1 differentiation and antiviral immune response	IL-12/JAK/STAT	IL-12 activates STAT4, enhancing IFN- γ secretion and cell immunity	(1,134)
T-bet	Drives Th1 differentiation and IFN- γ production	IFN- γ /STAT1	IFN- γ via STAT1 activates T-bet, forming a Th1 positive feedback loop	(1,134)
YAP/TAZ	Promotes HSC activation and fibrosis; responds to mechanical cues	Hippo, TGF- β /Smad	Upregulates collagen gene expression upon activation, directly driving fibrogenesis	(26,46)
STAT3	Regulates Th17 differentiation, inflammation and immune suppression	IL-6/JAK-STAT, IL-23	IL-6 activates STAT3 to promote pro-inflammatory Th17 differentiation	(39,75)
LHX2	Inhibits HSC activation; upregulates HGF and SMAD6	TGF- β /Smad, oxidative stress	Maintains HSC quiescence; overexpression suppresses fibrosis, downregulation promotes aberrant activation	(48)
NF- κ B	Regulates Kupffer cell inflammatory cytokine release (IL-6, TNF- α)	TLR4/MyD88, RIPK1	Excessive activation drives chronic inflammation, paracrine activation of HSCs and fibrosis progression	(52,57)
HIF-1 α	Regulates LSEC hypoxia adaptation and angiogenesis	VEGF/Notch, oxidative stress	Promotes angiogenesis under hypoxia; dysregulation disrupts the microenvironment and promotes fibrosis	(54)
NRF2	Regulates antioxidant gene expression (NQO1, HO-1); suppresses NF- κ B inflammation signaling	Oxidative stress	Mitigates oxidative damage and inflammation; deficiency exacerbates ROS accumulation and fibrosis	(56,155)
PPAR γ	Maintains HSC quiescence; regulates lipid metabolism and apoptosis	Fatty acid, AMPK	Suppresses HSCs activation upon activation; downregulation promotes myofibroblast transition and ECM deposition.	(71)
ETS-1	Regulates angiogenesis, cell migration and inflammation	Angiopoietin/Tie2	Angiopoietin-1 activates Tie2, driving ETS-1 nuclear translocation to enhance vascular stability	(107,110)
KLF2	Maintains endothelial anticoagulant phenotype, suppresses inflammation	Shear stress/Nrf2	Laminar shear stress via Nrf2 activates KLF2 to inhibit pro-inflammatory genes	(111)
HNF1 β	Regulates bile duct development, bile secretion and cell polarity	Notch, Hedgehog	Notch signaling activates HNF1 β to maintain bile duct structure; Hedgehog inhibits HNF1 β	(132,168)
Sox9	Regulates cholangiocyte differentiation, repair and proliferation	FGF/FGFR2, Wnt/ β -catenin	FGF signaling activates Sox9 to promote bile duct repair; Wnt signaling inhibits Sox9 activity	(145,146)
AhR	Regulates immune tolerance; suppresses excessive inflammation	Environmental toxins (dioxins)	Ligand binding to AhR inhibits NF- κ B, decreasing inflammation	(169)
Gli2	Hedgehog pathway effector; promotes HSCs activation and fibrosis	Hedgehog/SMO	Hedgehog ligand binding to SMO activates Gli2, inducing fibrotic gene expression	(170)

Table II. Continued.

Transcription factor	Function	Regulatory signaling pathways	Impact	(Refs.)
KLF6	Inhibits HSC activation; regulates cell cycle arrest	TGF- β /Smad	TGF- β via Smad3 suppresses KLF6, promoting HSC activation	(171)

AhR, aryl hydrocarbon receptor; BEC, biliary epithelial cell; DC, dendritic cell; ETS-1, E26 transformation-specific 1; GATA3, GATA-binding protein 3; HIF-1, hypoxia-inducible factor 1alpha; HNF1beta, hepatocyte nuclear factor 1beta; HSC, hepatic stellate cell; KLF, Kruppel-like factor; LHX2, LIM homeobox 2; LSEC, liver sinusoidal endothelial cell; MoM, monocyte-derived macrophage; NK, natural killer; SMO, Smoothened; Sox9, SRY-box transcription factor 9; STAT, signal transducer and activator of transcription; T-bet, T-box transcription factor 21 (gene symbol for T-bet); YAP, Yes-associated protein; ZEB2, zinc finger E-box-binding homeobox 2.

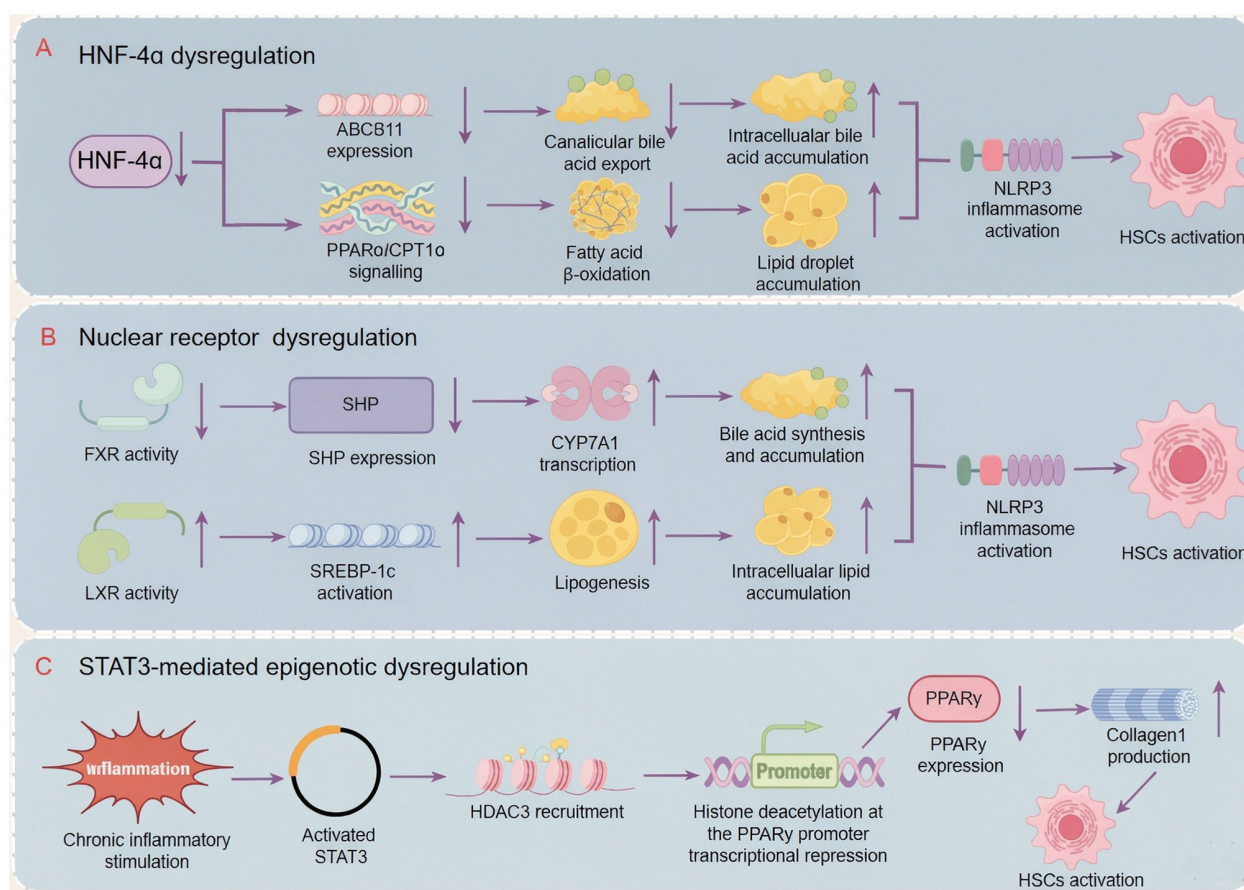


Figure 2. Transcription factor dysregulation in liver fibrosis. Dysregulated transcriptional networks disturb hepatic metabolic homeostasis and promote HSC activation. (A) Decreased HNF4 α expression attenuates PPAR α /CPT1 α -dependent fatty acid β -oxidation, resulting in lipid droplet accumulation and lipotoxic stress. HNF4 α downregulation compromises ABCB11-dependent canaliculi bile acid export, leading to intracellular bile acid accumulation. These metabolic disturbances activate inflammatory and stress-responsive pathways, including the NLRP3 inflammasome, and promote HSC activation. (B) Loss of FXR activity reduces SHP expression and relieves CYP7A1 from SHP-mediated transcriptional suppression, resulting in increased bile acid synthesis and accumulation. Aberrant LXR activation induces SREBP-1c-dependent lipogenesis and intracellular lipid accumulation. The resulting metabolic stress promotes NLRP3 inflammasome activation and promotes HSC activation through enhanced profibrotic signaling. (C) Chronic inflammatory stimulation promotes sustained STAT3 activation in HSCs. Activated STAT3 facilitates HDAC3 recruitment to the PPAR γ promoter, increasing local histone deacetylation and suppressing PPAR γ expression. Loss of PPAR γ -mediated transcriptional restraint enhances collagen I production and maintains HSC activation, thereby promoting extracellular matrix accumulation and liver fibrosis. HSC, hepatic stellate cell; HNF, hepatocyte nuclear factor; CPT, carnitine palmitoyltransferase; ABCB, ATP-binding cassette subfamily B; FXR, farnesoid X receptor; SHP, small heterodimer partner; CYP7A1, cytochrome P450 family 7 subfamily A member 1; LXR, liver X receptor; SREBP-1c, sterol regulatory element-binding protein-1c; HDAC, histone deacetylase.

contributing to bile acid overload (74). Concurrently, aberrant LXR activation induces SREBP-1c-dependent lipogenesis and intracellular lipid accumulation. This lipid overload promotes

NLRP3 inflammasome activation and promotes profibrotic signaling in HSCs (75) (Fig. 2B). The FXR agonist obeticholic acid may also attenuate TGF- β signaling in HSCs by

promoting Smurf2-mediated degradation of the TGF- β type I receptor (76).

The STAT family serves as a key signaling hub linking inflammation to fibrogenesis. PPAR γ , which is highly expressed in quiescent HSCs (qHSCs), maintains an antifibrotic transcriptional program that inhibits collagen production and HSC activation (77). During chronic inflammatory stimulation, activated STAT3 facilitates the recruitment of histone deacetylase (HDAC)3 to the PPAR γ promoter, increasing local histone deacetylation and suppressing PPAR γ transcription. The resulting loss of PPAR γ activity removes a key transcriptional restraint on collagen-related genes, promoting HSC activation (78,79) (Fig. 2C). Beyond this representative epigenetic pathway, persistent STAT3 signaling promotes fibrosis by maintaining tissue inhibitor of metalloproteinase-1 (TIMP-1) expression, upregulating glycolytic enzymes such as hexokinase 2 and lactate dehydrogenase A (LDHA) and enhancing microRNA (miR)-21-5p-mediated intercellular communication through hepatocyte-derived exosomes (80-82). Conversely, STAT1 may exert distinct stage-dependent effects, promoting inflammatory chemokine production during the early phase and contributing to sustained immune activation at later stages (83).

Crosstalk between multiple signaling pathways forms a cascade amplification network at the molecular, cell and tissue levels. At the TF interaction level, HNF4 α and FXR cooperate through shared recruitment of the coactivator PPAR γ coactivator-1 α (PGC-1 α) 1 α , forming a regulatory module. The dual loss of HNF4 α and FXR decreases the expression of mitochondrial biogenesis-associated genes, such as mitochondrial transcription factor A and ubiquinone oxidoreductase subunit B8, by 70-80%, resulting in >50% decrease in hepatocellular ATP production (68). This energy crisis compels hepatocytes to enhance autophagic flux via the Akt/mTORC1 pathway, however, excessive autophagic activity (30-50 autophagosomes/cell) leads to the lysosome-dependent release of cathepsin B, promoting fibrogenic signaling by activating protease-activated receptor 2 receptors in HSCs (84). At the epigenetic level, STAT3 forms a complex with DNA methyltransferase (DNMT)3b, selectively increasing CpG methylation of the PPAR γ promoter by 3-5-fold and simultaneously recruiting HDAC1 to remove H3K27 histone acetylation, establishing dual-layered epigenetic silencing (85). This cross-pathway epigenetic regulation confers an 'epigenetic memory' of the aHSC phenotype, sustaining fibrosis progression following the removal of the primary injurious stimulus.

At the metabolite signaling level, succinate accumulation (200-400 mM) resulting from HNF1 α deficiency inhibits prolyl hydroxylase, stabilizing HIF-1 α , which forms a transcriptional complex with STAT3 to cooperatively upregulate VEGF and CTGF expression. This promotes sinusoidal capillarization and ECM remodeling (86).

Transcriptional regulation in hepatocytes serves a key role in the development of non-alcoholic steatohepatitis (NASH) and liver fibrosis (14,87). During NASH progression, widespread changes in hepatocyte genomic and transcriptional landscapes lead to a loss of hepatocyte identity (87). This hepatocyte reprogramming is controlled by a fibrogenic TF network, including factors such as E74-like ETS transcription factor 3 and the zinc finger protein GLIS family zinc finger

(GLIS)2, which alter hepatocyte gene expression profiles, impair normal metabolic function and thereby contribute to fibrogenesis (14). Furthermore, these TFs modulate the secretion of hepatokines, mediators that influence communication between hepatocytes and HSCs, promoting HSC activation and proliferation, thus exacerbating fibrosis. Studies have also identified X-box binding protein 1 (XBP1) as an upregulated TF in the liver of patients with NASH (14,88). Conditional deletion of XBP1 in hepatocytes decreases lipid accumulation in mice, while Xbp1 deletion in macrophages ameliorates diet-induced steatohepatitis and fibrosis (88,89). Pharmacological inhibition of XBP1 prevent steatohepatitis and fibrosis in experimental models (88,89). These regulatory actions of TFs in NASH and liver fibrosis drive hepatocyte dysfunction and altered intercellular communication, promoting the transition from steatosis to more severe inflammation, fibrosis, and even cirrhosis. Consequently, TFs are not only central players in the molecular mechanisms of liver fibrosis but also promising therapeutic targets.

Transcriptional regulation of HSC state and liver fibrosis progression

Transcriptional control of HSC phenotype during fibrosis development and regression. The development and progression of liver fibrosis is associated with the phenotypic transition of HSCs. Under physiological conditions, qHSCs maintain hepatic metabolic homeostasis by storing vitamin A and expressing neural/adipogenic markers, including glial fibrillary acidic protein, PPAR γ , adipose differentiation-related protein and adiponectin receptor 1. This phenotype is governed by a network of TFs such as ETS, GATA, FOX, IFN-regulatory factor and PPAR γ (90). In chronic liver injury, qHSCs undergo phenotypic reprogramming marked by the depletion of vitamin A storage, downregulation of neural/adipogenic markers and transdifferentiation into aHSCs or myofibroblasts, which secrete profibrotic mediators. This transition is accompanied by the upregulation of fibrosis-associated markers, including α -SMA and platelet-derived growth factor receptor β , alongside the suppression of key adipogenic factors such as PPAR γ (91). Notably, shifts in the TF landscape play a pivotal role in HSC activation. The upregulation of profibrotic TFs, including AP-1, mesenchyme homeobox 2 (MET2), CCCTC-binding factor (CTCF), TEA domain transcription factor (TEAD), NF- κ B and regulatory factor X (RFX), promotes cell proliferation, increased contractility and excessive ECM synthesis, while impaired ECM degradation exacerbates fibrogenesis (12,74).

At the molecular level, HSC activation entails the coordinated interaction of multilayered transcriptional regulatory networks. The upregulation of c-Myb at the α -SMA promoter is a key step in transitioning to the myofibroblast phenotype, with SMAD and C/EBP families serving vital roles in regulating Col1 expression (92). The loss of C/EBP α expression and its antiproliferative function promotes fibrogenesis, whereas its overexpression inhibits both HSC proliferation and ECM synthesis (93). C/EBP β promotes collagen gene expression through its p35 splice isoform, while the p20 isoform serves as a negative regulator (62,93). Additionally, C/EBP δ contributes to antifibrotic regulation by directly suppressing COL1A1 gene expression (93). Runx2, another key transcriptional regulator,

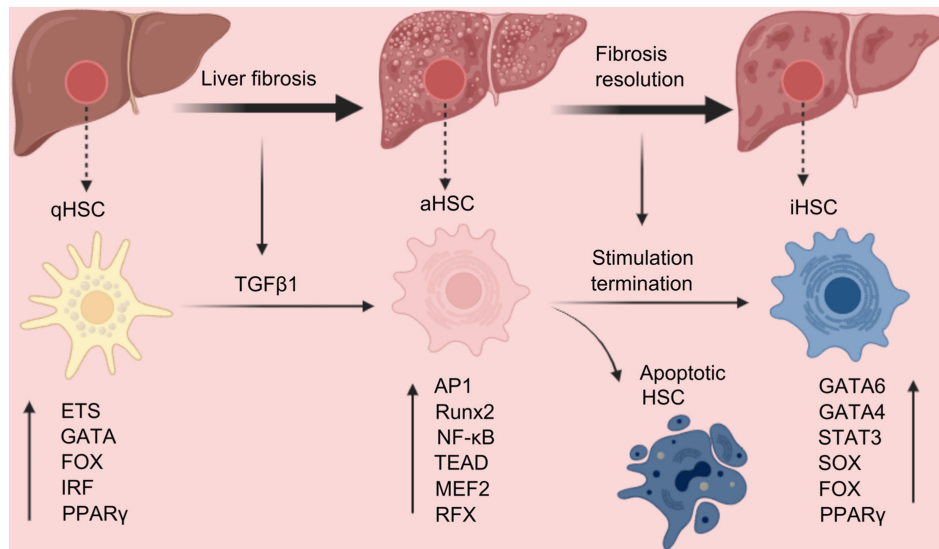


Figure 3. Schematic representation of the molecular regulatory network governing HSC state transition during liver fibrosis progression. qHSCs become activated into aHSCs under stimulation by factors such as TGF β 1, undergoing profibrotic epigenetic reprogramming mediated by transcription factors including AP1, Runx2, NF- κ B, TEAD, MEF2 and RFX. During fibrosis resolution, cessation of fibrogenic stimuli drives activated HSCs toward apoptosis or inactivation (iHSCs). This process is coordinated by transcription factors such as GATA6, GATA4, STAT3, SOX, FOX and PPAR γ , which reverse epigenetic modifications, restore the quiescent phenotype and terminate fibrogenic progression. qHSC, hepatic stellate cell; a, activated hepatic stellate cell; AP, activator protein; TEAD, TEA domain transcription factor; MEF, myocyte enhancer factor; RFX, regulatory factor X; iHSC, inactivated hepatic stellate cell; ETS, E26 transformation-specific; IRF, IFN-regulatory factor.

is markedly upregulated in aHSCs. Functional studies have shown that Runx2 knockdown inhibits HSC activation and liver fibrosis progression, while overexpression exacerbates the pathological process, highlighting its positive regulatory role in fibrogenic signaling (94,95). Dynamic balance between these TFs determines the extent of HSC activation and establishes a molecular basis for targeted antifibrotic intervention.

Studies on fibrosis regression have revealed dual pathways of HSC phenotypic plasticity: ~50% of aHSCs undergo apoptosis, while the remaining cells transition into inactivated HSCs, reverting to a quiescent-like state (5,6). This reversal involves the coordinated upregulation of TFs such as GATA6, PPAR γ , SOX, FOX, STAT and transcription factor 21 (TCF21) with GATA4 serving a key role. GATA4 facilitates HSC inactivation through a dual mechanism: It downregulates fibrogenic genes [actin α 2, smooth muscle (ACTA2) laminin subunit α 1 and COL1A1] and upregulates antifibrotic genes (STAT1, SMAD7, TCF21) (12,18). GATA4 directly binds to GATA motifs within the intronic regions of the endothelial PAS domain protein 1 gene, suppressing HIF2 α transcription and blocking hypoxia-mediated fibrogenic signaling (18). Preclinical studies indicate transplantation of human aHSCs into the livers of Rag2^{-/-} γ c^{-/-} mice, in the absence of fibrotic stimuli, leads to downregulation of Coll α 1 and α -SMA and upregulation of PPAR γ , confirming human HSCs exhibit similar plasticity features as those in murine models (6,12). This phenotypic reversibility provides a key theoretical basis for the development of antifibrotic therapeutic strategies.

The dynamic transcriptional regulatory network underlies all stages of liver fibrosis. During the quiescent phase, ETS, GATA, FOX and PPAR γ maintain the differentiated and homeostatic state of HSCs. In the activation phase, TFs such as AP-1, MET2, CTCF, TEAD, NF- κ B and RFX drive the fibrogenic phenotype. In the regression phase, GATA, PPAR γ ,

SOX, FOX, STAT and Tcf21 coordinate the reversion of aHSCs toward a quiescent-like state (Fig. 3). This multilayered and temporally orchestrated regulatory pattern suggests interventions targeting specific TFs or their interaction networks may offer effective strategies for fibrosis reversal. Elucidating the spatiotemporal mechanisms governing these TFs may provide a foundation for individualized antifibrotic therapy based on HSC phenotypic regulation.

Epigenetic regulation. The phenotypic plasticity of HSCs is governed not only by TF networks but also by precise epigenetic reprogramming that orchestrates dynamic transition. Under physiological conditions, qHSCs are maintained by an epigenomic landscape that regulates chromatin accessibility at key gene regulatory elements. This epigenetic blueprint defines the cell lineage-specific identity and response patterns to injury signals (96). During chronic liver injury, transdifferentiation of qHSCs into profibrotic myofibroblast-like cells necessitates global epigenetic remodeling: Adipogenic genes are silenced, profibrotic regulators are *de novo* expressed through epigenetic activation at open chromatin regions and cell cycle pathways support proliferation (97). This phenotypic switch involves dynamic changes in the expression profile of hundreds of genes, driven by the coordinated actions of DNA methylation, histone modification and chromatin remodeling complexes (98).

DNA methylation, a classical epigenetic regulatory mechanism, modulates gene activity through the addition of a methyl group at the 5' position of cytosine within CpG dinucleotides (99). Hypermethylation of promoter regions is typically associated with transcriptional silencing (97,98). During HSC activation, the genome exhibits an overall trend toward hypomethylation, with the transcriptional activation of profibrotic genes such as actin gamma 2, smooth muscle (ACTG2), LOXL1 and COL4A1/2 associated with decreased

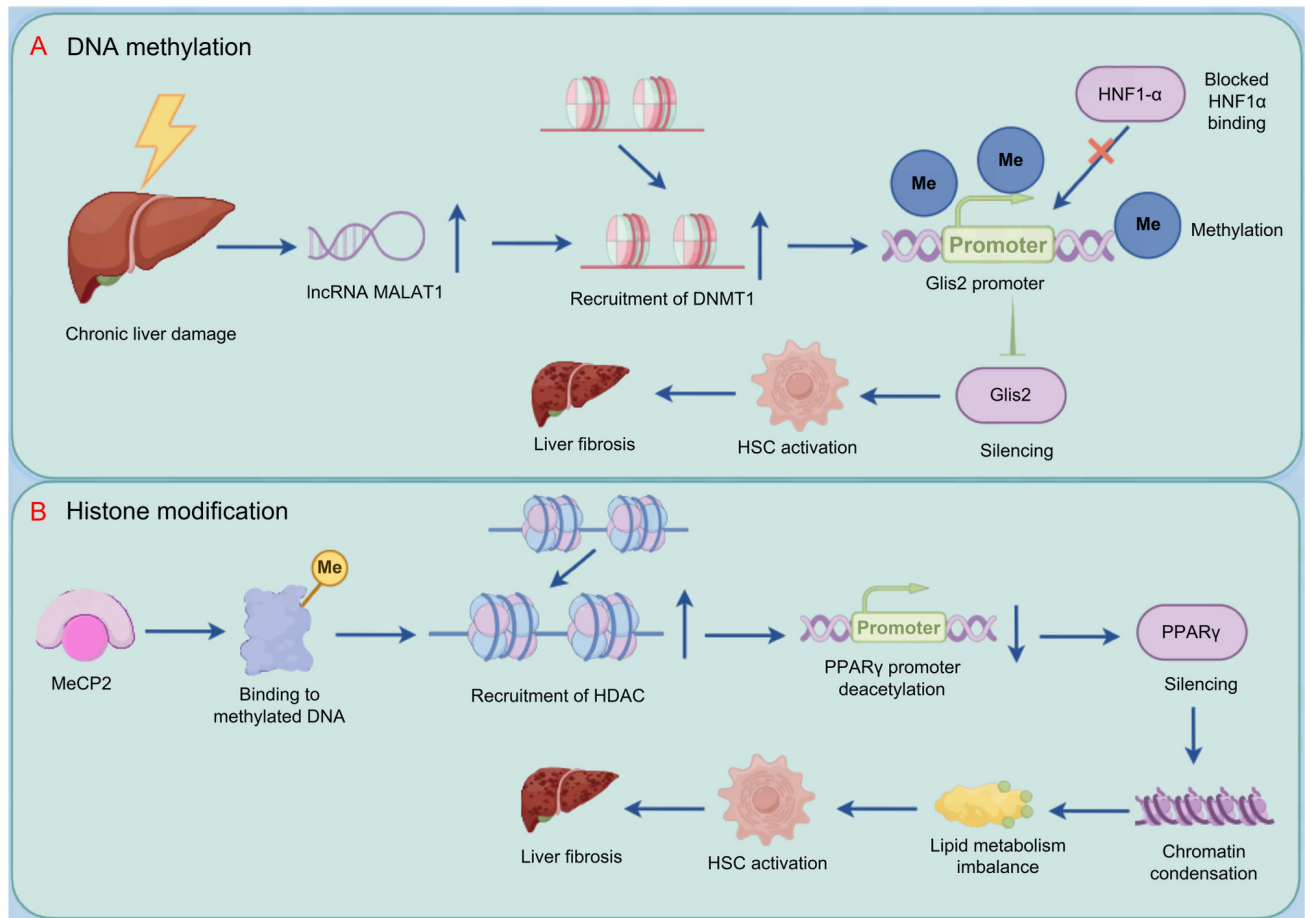


Figure 4. Epigenetic regulation in liver fibrosis. (A) Chronic liver injury upregulates lncRNA MALAT1, which further recruits DNMT1. DNMT1 mediates the methylation of the promoter region of the Glis2 gene, thereby inhibiting Glis2 expression. This activates HSCs and promotes the development of liver fibrosis. (B) MeCP2 binds to methylated DNA and recruits HDAC. HDAC induces deacetylation of the PPAR γ promoter, which results in lipid metabolism disorder and silencing of PPAR γ expression. This drives the activation of HSCs and the progression of liver fibrosis. DNMT, DNA methyltransferase; Glis, GLIS family zinc finger; HSC, hepatic stellate cell; MeCP2, methyl-CpG-binding protein 2; HDAC, histone deacetylase; lnc, long non-coding.

promoter methylation levels (100-102). The TF GLI-similar 2 (GLIS2) serves a critical role in maintaining HSC quiescence and its downregulation is associated with the progression of liver fibrosis. Under pathological conditions, the long non-coding RNA MALAT1 recruits DNMT1 to the GLIS2 promoter, inducing hypermethylation within CpG islands, which prevents binding of the liver-specific TF HNF1A and silences GLIS2 expression. This suggests that restoring GLIS2 expression by reversing aberrant DNA methylation may re-establish epigenetic homeostasis in HSCs and suppress fibrogenesis (103) (Fig. 4A).

Histone modifications, together with DNA methylation, underlie epigenetic regulation, modulating chromatin architecture and TF accessibility. Marks such as histone acetylation and methylation influence chromatin compaction and serve as 'molecular anchors' that recruit chromatin remodeling complexes and transcriptional coactivators or corepressors, forming a dynamic regulatory network (104). For example, methyl-CpG-binding protein 2 (MeCP2) has a dual role in HSC activation. MeCP2 binds methylated DNA while suppressing transcription of specific target genes. Additionally, MeCP2-mediated silencing of PPAR γ is key in HSC transdifferentiation; Suppression of PPAR γ , a master regulator of HSC quiescence, leads to lipid metabolic imbalance and

diminished inhibition of profibrotic pathways, accelerating fibrosis progression (105-107). The complexity of this epigenetic regulation is exemplified by MeCP2 functional versatility: It serves as a corepressor of antifibrotic genes such as PPAR γ and dynamically coordinates spatial and temporal coupling of DNA methylation and histone modifications through interaction with modifying enzymes, including HDACs (108) (Fig. 4B).

The cooperativity and reversibility of epigenetic events provide a unique perspective for liver fibrosis therapy. During HSC activation, DNA hypomethylation and chromatin opening at profibrotic gene promoters reinforce each other, establishing a positive feedback loop (109). Regulatory factors such as MeCP2 integrate DNA methylation and histone modification signals, thereby translating epigenetic information into specific gene expression programs (98,105). The dynamic balance of this multilayered regulatory network determines HSC fate decisions. In the fibrosis regression phase, targeted inhibition of DNMT1 or HDAC activity restores expression of key genes such as PPAR γ , thereby inducing reversion of aHSCs to a quiescent phenotype (103,107). Preclinical studies suggest that developing epigenetic therapy requires balancing mechanistic specificity and global regulatory impact; for example, selective inhibition of DNMT1 may relieve the silencing of antifibrotic

genes such as Glis2, while targeting the MeCP2-PPAR γ axis may simultaneously modulate DNA methylation and histone modification (103,105). Collectively, these findings demonstrate that precise interventions at dynamic nodes within the epigenetic regulatory network disrupt the self-reinforcing loop of profibrotic signaling and provide new avenues for reversing liver fibrosis.

Transcriptional regulation of LSEC state in liver fibrosis progression. LSECs are key components of the hepatic microvascular system and serve as critical regulators of liver fibrosis progression due to their structural and functional characteristics. LSECs form a discontinuous endothelial barrier in the sinusoidal wall and engage in the clearance of bloodborne components via scavenger receptors such as the mannose receptor, CD32b, lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1) and Stabilin-1/2. LSECs secrete vasoactive factors that coordinate the balance between hepatic immune regulation and regenerative repair (110-112). Under physiological conditions, LSECs maintain hepatocyte proliferative capacity and inhibit HSC activation by releasing regenerative signals, including HGF and nitric oxide (NO), thereby establishing an antifibrotic microenvironment (66,113). However, during acute or chronic liver injury, LSECs undergo a phenotypic switch characterized by capillarization, which includes basement membrane formation, loss of fenestrae and decreased regenerative function. This pathological remodeling disrupts vascular-derived signaling balance, promotes HSC activation and leads to excessive ECM deposition, driving fibrosis progression (114). Recent studies have identified TFs such as Kruppel-like factor (KLF)2, GATA4 and zinc finger E-box-binding homeobox (ZEB)2 as pivotal in maintaining endothelial homeostasis and suppressing fibrogenesis through the regulation of LSEC epigenetic programs and signaling networks (115,116).

KLF2, a mechanosensitive TF, upholds LSEC functional integrity through multiple mechanisms. At the molecular level, KLF2 activates the Nrf2 pathway, upregulating antioxidant genes such as HO-1 and NQO1, which reduces ROS levels and mitigates oxidative stress-induced damage. KLF2 suppresses TGF- β /Smad signaling to inhibit the production of profibrotic factors such as endothelin-1 and promotes endothelial NO synthase expression to enhance NO-mediated vasodilation (117,118). This dual regulation not only improves hepatic sinusoidal hemodynamics but also sustains LSEC fenestration through the paracrine secretion of growth factors such as VEGF, effectively preventing HSC transdifferentiation into myofibroblasts. KLF2 expression levels are inversely associated with the severity of liver fibrosis; loss of KLF2 functionality results in increased LSEC contractility and a proinflammatory phenotype, positioning KLF2 as a key nexus linking mechanical stress signals to antifibrotic responses (116,117) (Fig. 5A).

GATA4 preserves LSEC lineage-specific identity, thereby preventing pathological capillarization. Under homeostatic conditions, GATA4 directly regulates the expression of endothelial markers such as stabilin-2 and LYVE-1, maintaining LSEC fenestration and scavenger function while inhibiting aberrant activation of the proto-oncogene Myc (17,119). Loss of GATA4 expression leads to Myc-driven metabolic

reprogramming, promoting the transdifferentiation of LSECs toward a continuous endothelial phenotype, which is accompanied by increased secretion of profibrotic factors such as PDGF-BB. This activates HSCs and induces excessive ECM deposition. The resultant phenotypic switch fosters a cycle of sinusoidal microvascular disruption: Basement membrane thickening impairs nutrient exchange and exacerbates hepatocyte hypoxic injury and sustained PDGFR β signaling drives HSCs into an irreversibly activated state. Preclinical studies have demonstrated that restoring GATA4 expression via adenoviral delivery reverses LSEC capillarization and significantly decreases collagen deposition in carbon tetrachloride-induced liver fibrosis models, affirming the key role of GATA4 in maintaining endothelial identity (Fig. 5B) (17,115).

In addition to KLF2 and GATA4, TFs such as ZEB2 govern LSEC function through epigenetic remodeling. The loss of ZEB2 results in aberrant activation of the Notch signaling pathway, promoting transdifferentiation of LSECs into an arterial-like endothelial phenotype and increasing the secretion of proinflammatory cytokines, including IL-6 and TNF- α , thereby establishing a chronic inflammatory microenvironment (120). This epigenetically driven endothelial plasticity undermines hepatic immune tolerance and amplifies profibrotic signaling by recruiting bone marrow-derived fibroblasts via the CXCL12/CXCR4 pathway (65,120). Notably, crosstalk between TFs creates a complex regulatory network: KLF2 suppresses ZEB2 expression via inhibition of the NF- κ B pathway, while the antagonistic interaction between GATA4 and Myc modulates Notch pathway activity by altering the transcriptional regulation of Notch target genes (17,117). This multilayered regulatory architecture presents multiple potential nodes for targeted antifibrotic intervention.

Transcriptional regulation of LSECs exhibits spatiotemporal specificity and integrative signaling characteristics. In the early stage of liver injury, KLF2 rapidly responds to shear stress changes, maintaining endothelial barrier integrity. During chronic injury, progressive depletion of GATA4 leads to loss of lineage-specific identity and amplifies fibrogenic signaling cascades. Factors such as ZEB2 contribute to the maintenance of pathological endothelial phenotypes through epigenetic memory (115,116). This dynamic regulatory network indicates that stage-specific targeted intervention aimed at correcting TF imbalance may optimize antifibrotic efficacy. In-depth characterization of LSEC-specific transcriptional regulatory elements and their interaction networks may establish a theoretical foundation for developing endothelial phenotype-based antifibrotic therapeutic strategies.

Transcriptional regulation of hepatic macrophage populations in liver fibrosis progression. The dynamic regulation of hepatic macrophage populations is a central element in liver fibrosis progression. Their functional diversity arises from the spatiotemporal interplay between resident Kupffer cells and monocyte-derived macrophages (MoMs). As liver-resident 'sentinels', Kupffer cells exhibit self-renewal capacity and continually monitor the microenvironment to maintain homeostasis: Under physiological conditions, they enhance immune tolerance by clearing senescent red blood cells, pathogens and metabolic byproducts (121,122). Upon parenchymal injury, Kupffer cells detect damage-associated

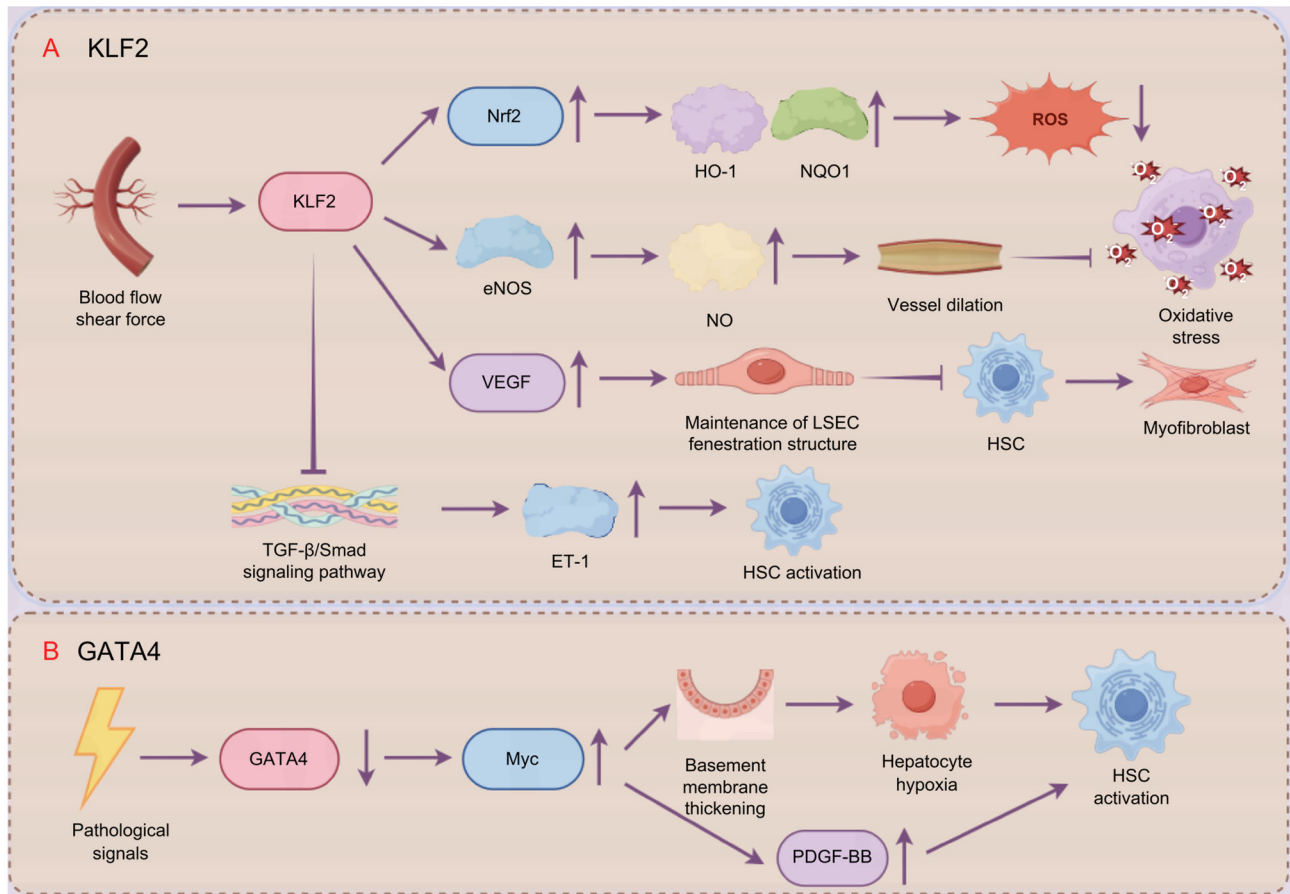


Figure 5. Pathways by which paracrine signals from LSECs mediate liver fibrosis. (A) Loss of KLF2 in LSECs leads to sustained NF- κ B activation, which promotes liver sinusoidal capillarization and fibrosis via VEGF secretion. (B) LSECs secrete PDGF, which cooperates with the GATA4/Myc signaling pathway to directly activate HSCs into a profibrotic phenotype, thereby exacerbating the progression of liver fibrosis. LSEC, liver sinusoidal endothelial cell; KLF, Kruppel-like factor; PDGF-BB, platelet-derived growth factor-BB; HSC, hepatic stellate cell; eNOS, endothelial nitric oxide synthase; ET, endothelin; HO, heme oxygenase; NQO, NAD(P)H quinone oxidoreductase; ROS, reactive oxygen species.

molecular patterns and secrete chemokines such as CCL2 and CCL5, facilitating the recruitment of circulating monocytes that differentiate into MoMs within the liver, forming a mixed macrophage pool (123). While early proinflammatory responses initiate tissue repair, persistent activation may perpetuate a cycle of inflammation and fibrosis. Notably, hepatic macrophages demonstrate epigenetic plasticity: Their phenotypes are dynamically reshaped by local microenvironmental cues, including fatty acid metabolites, apoptotic debris and cell-cell contact signals (123,124). These stimuli promote differentiation toward either proinflammatory M1 macrophages (secreting IL-1 β , TNF- α , IL-17) that activate HSCs, or anti-inflammatory M2 macrophages (secreting IL-10, TGF- β) that facilitate fibrosis resolution (124,125).

Paracrine crosstalk between macrophages and HSCs is a central hub in the fibrogenic signaling network. Kupffer cells directly induce HSC transdifferentiation into myofibroblasts via the IL-17/STAT3 pathway: IL-17 activates the NF- κ B pathway within HSCs, enhancing TGF- β 1 and COL1 expression, while STAT3 phosphorylation drives epigenetic reprogramming that amplifies α -SMA promoter activity, establishing a profibrotic phenotype memory (126,127). Simultaneously, a positive feedback loop is established between Kupffer cells and LSECs: VEGF released by LSECs during early injury stimulates Kupffer cells to produce IL-6, which, via JAK3/STAT3

signaling, promotes MoM polarization toward the M2 phenotype. M2 macrophages secrete PDGF, activating HSCs and inducing LSEC capillarization (128,129). This cascade of intercellular interactions demonstrates how macrophage phenotype imbalance accelerates fibrosis progression: M1 dominance leads to excessive TNF- α and IL-1 β production, inducing mitochondrial dysfunction in HSCs via ROS-dependent mechanisms and driving hyperproliferation, whereas excessive M2 activation fosters irreversible fibrotic scarring via TGF- β /Smad3-mediated ECM crosslinking (130,131).

Precise regulation of the JAK/STAT signaling pathway underpins macrophage phenotype switching at the molecular level. IFN- γ drives M1 polarization via the JAK1/STAT1 pathway, inducing inducible NO synthase expression to enhance bactericidal activity and recruiting T helper 1 cells through CXCL9/10 production, thereby exacerbating inflammatory injury (132). Conversely, IL-4 and IL-13 promote M2 differentiation through STAT6-mediated activation of arginase-1, while IL-6 and IL-10 signal via STAT3 phosphorylation to upregulate suppressor of cytokine signaling 3 (SOCS3), which inhibits STAT1 signaling through negative feedback, maintaining an anti-inflammatory macrophage phenotype (133,134). This balance is disrupted during fibrosis: Chronic injury leads to SOCS1 downregulation, relieving the inhibition of STAT1 and driving sustained M1 polarization,

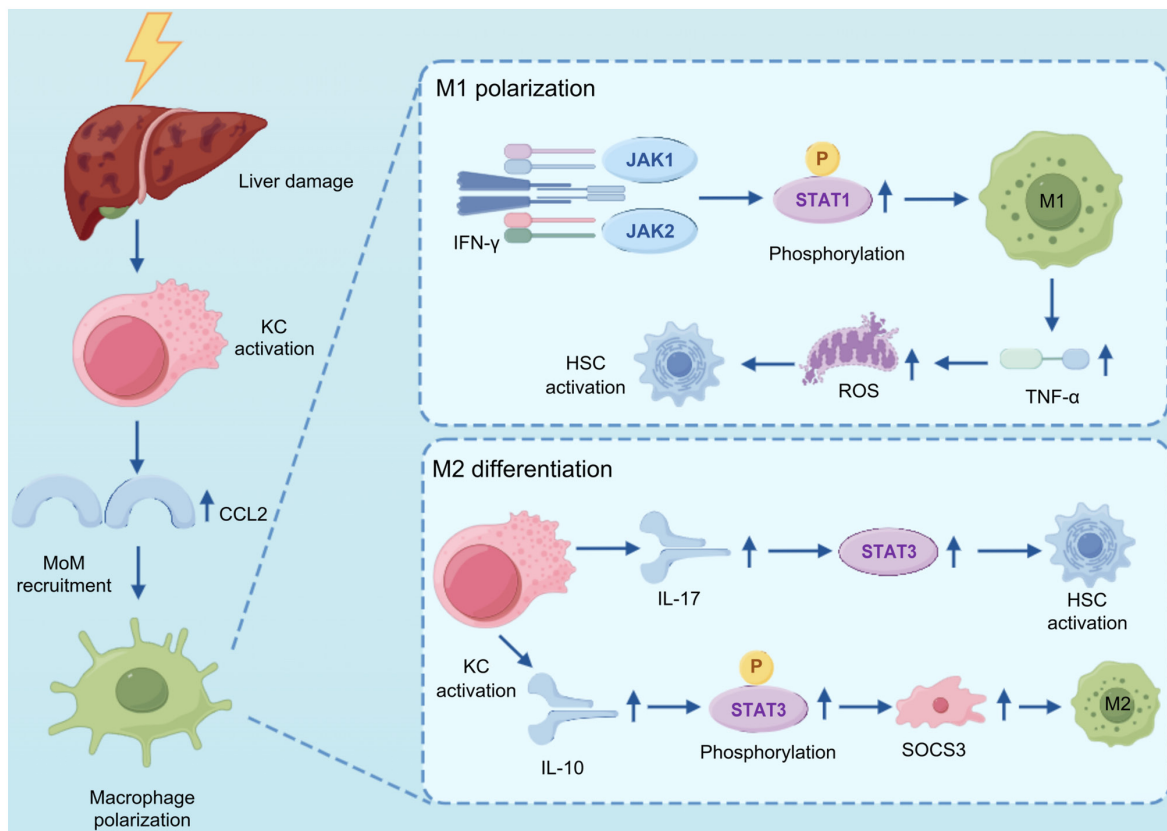


Figure 6. Dual-pathway mechanism by which macrophage polarization regulates HSC activation during liver injury. Liver damage activates KCs and recruits MoMs, driving their differentiation into M1 or M2 phenotypes. M1 polarization is mediated by the IFN- γ /JAK1/JAK2 pathway, leading to the production of TNF- α and ROS that promote HSC activation. M2 differentiation is driven by IL-10/STAT3 and IL-17/STAT1/SOCS3 signaling, which paradoxically sustain HSC activation and exacerbate fibrogenesis. HSC, hepatic stellate cell; KC, Kupffer cell; MoM, monocyte-derived macrophage; ROS, reactive oxygen species; SOCS, suppressor of cytokine signaling.

while hypoxia secondary to LSEC capillarization stabilizes HIF-1 α , enhancing STAT3 activity and promoting a profibrotic M2-dominant microenvironment (134,135) (Fig. 6). Preclinical studies have demonstrated that targeting STAT1/STAT3 signaling nodes (for example, using the JAK inhibitor tofacitinib) rebalances macrophage phenotypes and significantly decreases collagen deposition in carbon tetrachloride-induced fibrosis models (42,130,131). Furthermore, epigenetic interventions, including HDAC inhibitors that modulate SOCS expression, present promising strategies to overcome the M1/M2 polarization impasse.

Macrophage plasticity is dynamically regulated throughout liver fibrosis. During the early phase of injury, M1-dominant inflammatory responses facilitate debris clearance and create conditions conducive to tissue repair. In the progression phase, M2 macrophages drive ECM remodeling by secreting profibrotic mediators. In the regression phase, M2 macrophages transition toward a pro-resolution phenotype, enabling scar degradation via the regulation of the MMP9/TIMP1 balance (124,125). This dynamic shift is orchestrated by the interplay of TF networks, including NF- κ B, STAT, and PPAR γ , and metabolic reprogramming, exemplified by the transition from fatty acid oxidation to glycolysis. For example, PPAR γ activation in Kupffer cells enhances lipid scavenging and suppresses NLRP3 inflammasome assembly, while enhanced AMPK signaling in MoMs promotes mitochondrial biogenesis and sustains an anti-inflammatory phenotype (121,129).

Elucidating the crosstalk between metabolic and epigenetic programs across macrophage subpopulations may provide a foundation for developing spatiotemporally specific therapeutic intervention.

Transcriptional regulation of other non-parenchymal liver cells in fibrosis progression. The initiation and progression of liver fibrosis depend not only on the phenotypical transformation of HSCs but also on transcriptional regulatory networks and interactions between various non-parenchymal liver cells. In addition to HSCs, LSECs, and Kupffer cells, other cell types, including natural killer (NK) cells, dendritic cells (DCs) and biliary epithelial cells (BECs), contribute to shaping either a profibrotic or antifibrotic hepatic microenvironment through signaling pathways and TF-mediated mechanisms (136-138). NK cells, key components of the innate immune system, inhibit HSC activation via death receptor-mediated apoptosis. Upon activation by IL-18 or TLR3 ligands, the p38/PI3K/AKT signaling pathway enhances the expression of TNF-related apoptosis-inducing ligand and FasL, engaging death receptors on aHSCs to induce caspase cascades and eliminate fibrogenic cells (64,139,140). STAT1, a key mediator of interferon signaling, promotes NK cell cytotoxicity via phosphorylation while enhancing granzyme B release, directly targeting HSCs via mitochondrial pathways (Fig. 7A). This dual mechanism decreases collagen deposition in carbon tetrachloride-induced liver fibrosis models (140,141).

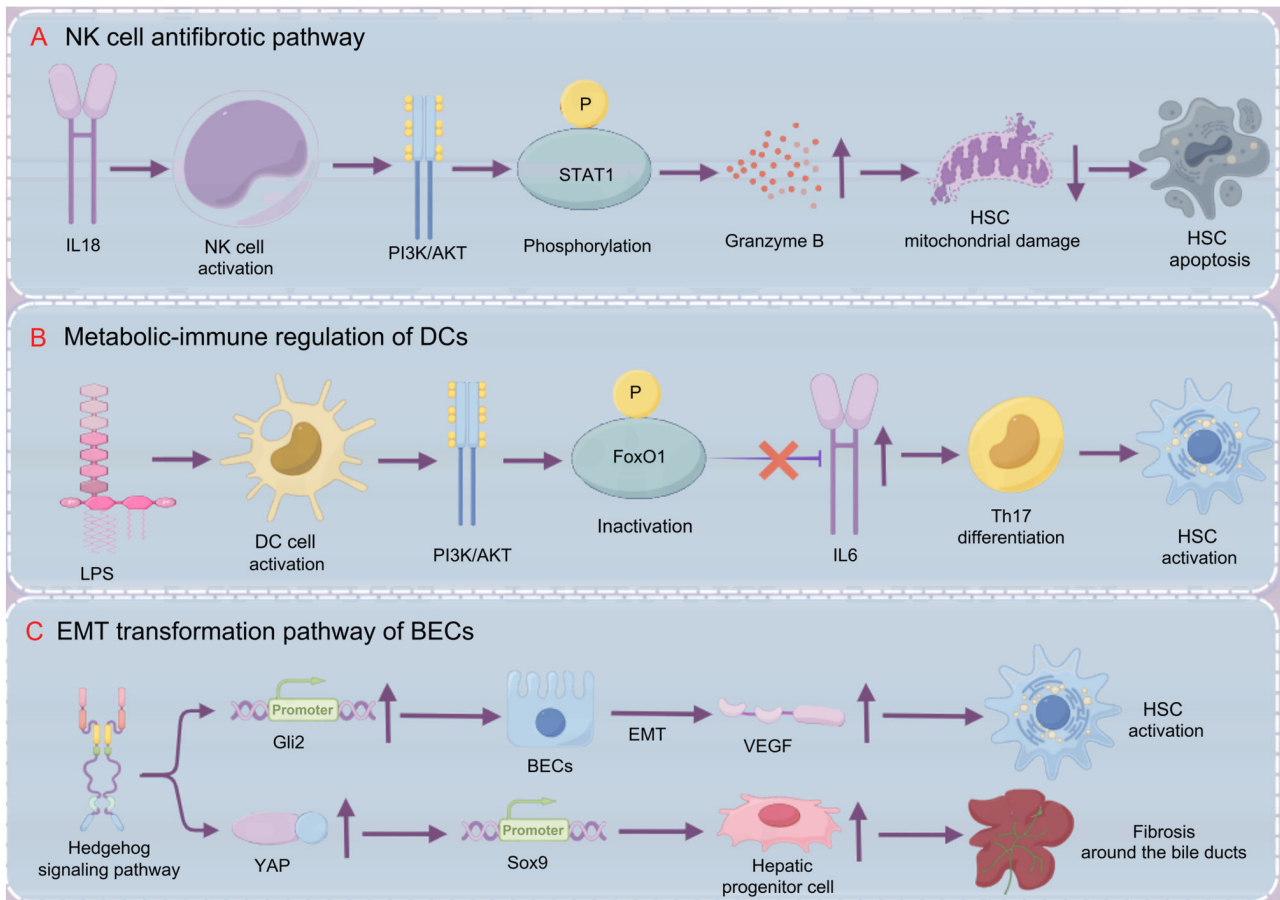


Figure 7. Integrated regulatory pathways of cell types involved in liver fibrosis progression. (A) NK cells are activated by IL-18 to trigger the PI3K/AKT/STAT1 signaling pathway, releasing granzyme B, which induces mitochondrial apoptosis in HSCs, thereby exerting antifibrotic effects. (B) LPS stimulation activates the PI3K/AKT pathway in DCs, leading to phosphorylation and inactivation of FoxO1, which relieves FoxO1-mediated suppression of pro-inflammatory genes transcription, increases IL-6-mediated Th17 differentiation and promotes HSC activation (C) BECs, via the YAP-Sox9 axis, induce aberrant proliferation of LPCs, contributing to peribiliary fibrosis lesions. Under Hedgehog signaling stimulation, transcription factors are upregulated to promote BEC EMT and VEGF secretion, which activates HSCs. NK, natural killer; HSC, hepatic stellate cell; LPS, lipopolysaccharide; DC, dendritic cell; Th, T helper; BEC, biliary epithelial cell; LPC, liver progenitor cell; EMT, epithelial-mesenchymal transition; YAP, Yes-associated protein; Gli, glioma-associated oncogene.

DCs regulate fibrosis progression through immuno-metabolic reprogramming. Stimulation with LPS activates the PI3K/AKT pathway in DCs, leading to phosphorylation and inactivation of forkhead box O1 (FoxO1). This relieves suppression of proinflammatory gene transcription, promoting DC maturation and secretion of cytokines such as IL-6 and IL-23, which drive Th17 cell differentiation and HSC activation (142-145) (Fig. 7B). This bidirectional regulation along the metabolism-immune axis is prominent in cholestatic liver diseases: Sustained FoxO1 activation upregulates PD-L1 expression, inducing DC tolerance and inhibiting CD8⁺ T cell-mediated HSC killing. The PI3K inhibitor LY294002 can reverse this effect, highlighting the potential of targeting the PI3K/AKT/oxO1 network to restore DC functional balance (146-148). Additionally, crosstalk between DCs and Kupffer cells establishes an inflammatory amplification loop: Kupffer cell-derived TGF- β suppresses DC antigen-presenting capacity via Smad3-dependent mechanisms, while DC-derived IL-12 activates the NLRP3 inflammasome in Kupffer cells. This positive feedback circuit serves a key role in fibrosis associated with NASH (129,143).

Transcriptional reprogramming of BECs provides a unique pathological perspective on liver fibrosis. Under

physiological conditions, BECs maintain bile duct integrity and contribute to liver regeneration through Sox9 activity (149,150). However, in chronic liver injury, aberrant activation of the Hedgehog (Hh) signaling pathway induces upregulation of TFs such as GLI family zinc finger 2 (GLI2), driving epithelial-mesenchymal transition (EMT) of BECs into mesenchymal-like cells with profibrotic properties (149-151). This phenotypic switch is accompanied by excessive secretion of growth factors, including VEGF and PDGF, which not only directly activate neighboring HSCs but also promote aberrant proliferation of liver progenitor cells (LPCs) via the YAP-Sox9 axis, contributing to periductular fibrotic lesions. In biliary atresia models, BEC-derived Hh ligands (Sonic Hh) bind Patched receptors on HSCs, triggering Gli-dependent upregulation of α -SMA and COL1A1 and enhancing CXCL12 secretion to recruit bone marrow-derived fibroblasts, thereby establishing a multicellular profibrotic interaction (152,153) (Fig. 7C). BEC plasticity exhibits bidirectional regulatory potential: EMT is reversed by inhibiting YAP nuclear translocation or blocking Hh signaling, while activation of the nuclear receptor FXR restores epithelial barrier function by suppressing Sox9 phosphorylation (149,150).

The transcriptional regulatory network between non-parenchymal liver cells is dynamic and spatially specific. For example, STAT1 activation in NK cells suppresses IL-17 production by Kupffer cells, thereby blocking STAT3 phosphorylation in HSCs (64,140). Conversely, IL-10 derived from DCs activates STAT6 signaling in BECs to promote biliary repair while inhibiting the TGF- β /Smad pathway in HSCs (141,148). This integration of intercellular signals underscores the multidimensional regulatory nature of liver fibrosis: In the early stage of injury, immune surveillance by NK cells and DCs limits fibrogenesis through the clearance of aHSCs; during progression, proinflammatory signals from Kupffer cells and BECs dominate, establishing a pathological microenvironment characterized by excessive ECM deposition; in the regression phase, DCs transition toward a tolerogenic phenotype, while BEC-LPC transdifferentiation facilitates tissue remodeling (140,141,148). Targeting specific TFs (STAT1, Gli2, FoxO1) or epigenetic modifiers (HDACs, DNMTs) allows precise modulation of functional states across these cell populations (154). Strategies such as clustered regularly interspaced short palindromic repeats/catalytically dead Cas9 (CRISPR/dCas9)-directed activation of STAT1 signaling in NK cells or pharmacological inhibition of BEC Hh signaling using smoothened (SMO) inhibitors have shown promise in preclinical models for reversing fibrosis (64,140,148). Deciphering the transcriptional dialogue between non-parenchymal liver cells may provide a theoretical framework for developing cell type-specific, multitargeted antifibrotic therapy.

5. Nanomaterial-based targeting of TFs: Mechanisms and strategies for liver fibrosis therapy

In the molecular pathogenesis of liver fibrosis, aberrant activation of TFs and disruption of epigenetic homeostasis are central regulatory hubs (109,147). Innovations in nanotechnology provide a multiscale intervention paradigm to address the limitations of conventional therapies. Nanomaterial-based targeted delivery systems, characterized by precise localization, stimuli-responsive release and efficacy, enable multilayered modulation of transcriptional regulatory networks within the fibrotic microenvironment (155). Surface functionalization strategies, such as conjugation with retinoic acid receptor ligands, COL-binding peptides or integrin $\alpha\beta 3$ antibodies, allow nanocarriers to penetrate the disordered sinusoidal endothelium, facilitating selective accumulation within aHSCs (156,157). Notably, vitamin A-A-functionalized liposomes demonstrate an 8-12-fold increase in targeting efficiency in fibrotic liver tissue compared with normal liver, attributed to marked upregulation of retinoic acid receptor- β during HSC activation (157). Microenvironment-responsive designs, such as ROS-sensitive linkers, MMP-cleavable peptides or pH-sensitive polymers, enable spatiotemporally specific drug release. For example, acid-labile poly(lactic-co-glycolic acid) (PLGA) nanoparticles delivering TGF- β small interfering (si) RNA rapidly disassemble in the acidic lysosomal environment of HSCs, decreasing Smad2/3 phosphorylation levels by >70% while minimizing off-target organ exposure (158). Moreover, multimodal therapeutic systems have demonstrated superior efficacy compared with single-agent delivery: Mesoporous silica nanoparticles co-encapsulating the STAT3 inhibitor

cucurbitacin B and miR-29b mimic simultaneously block the IL-6/STAT3 pathway and activate the TGF- β /Smad7 negative feedback loop, resulting in a 58% decrease in COL deposition area and a 64% decrease in α -SMA expression in a CCl₄-induced liver fibrosis model, confirming the advantage of cross-mechanism combination strategies (159). Existing research emphasizes four-dimensional intervention approaches: In gene silencing, gold nanoparticles loaded with TGF- β siRNA block COL1A1/CTGF transcription by inhibiting Smad4 nuclear translocation, achieving a 20-fold increase in hepatic delivery efficiency compared with free siRNA, while decreasing renal accumulation toxicity to physiological levels (160). In epigenetic regulation, chitosan nanoparticles delivering miR-146a target the 3' untranslated region of NF- κ B p65, suppressing IKK β phosphorylation (thereby downregulating TNF- α and other inflammatory mediators) and inhibiting DNMT activity to remodel the HSC epigenome, reversing 80% of hypermethylated loci in an alcoholic liver disease model (161). In gene editing, lipid nanoparticles encapsulating CRISPR/Cas9 enhance homologous recombination to activate the Nrf2 antioxidant pathway, restoring glutathione levels to 85% of normal and demonstrating a 3.7-fold increase in homologous recombination efficiency via nanocarrier delivery (162). For protein-protein interaction inhibition, PLGA nanoparticles loaded with the STAT3 inhibitor napabucasin mimic the SH2 domain to block STAT3 dimerization, increasing hepatic accumulation 12-fold compared with oral administration while decreasing cardiac tissue exposure and associated toxicity by 73%, highlighting the value of nanodelivery in expanding therapeutic windows (163). Biomimetic delivery strategies are engineered exosome-liposome hybrids that penetrate intracellular barriers via membrane fusion. For example, hybrid nanoparticles delivering recombinant Smad7 protein directly into the HSC cytoplasm competitively inhibit Smad2/3 phosphorylation and reverse myofibroblast transdifferentiation, achieving dose-dependent fibrosis reversal (half-maximal effective concentration=2.3 mg/kg) in preclinical studies, with efficacy 4.5-fold greater than conventional liposomes (156,164).

Despite the promise of nanotherapy, clinical translation faces three core challenges. First, the long-term accumulation toxicity associated with inorganic materials such as carbon nanotubes has prompted a shift toward biodegradable platforms, such as hyaluronic acid-polycaprolactone copolymers (156,165). Surface PEGylation and charge neutralization decrease immunogenicity to levels comparable with saline controls, however, achieving precise alignment between material degradation rates and drug release kinetics remains an obstacle (165). Second, downregulation of vitamin A receptors during fibrosis progression necessitates the development of multistage targeting systems. For example, matrix stiffness-responsive nanorobots equipped with piezoelectric sensors detect the mechanical properties of aHSCs (elastic modulus >8 kPa) and release CXCR4 antagonistic peptides to enhance lesion retention. Recent studies demonstrate that this strategy prolongs nanoparticle retention in advanced fibrotic livers for up to 72 h (156,166). Third, development of efficacy evaluation systems requires the integration of organoid-on-chip platforms with spatial multi-omics technologies. For example, 3D bioprinted fibrotic liver models allow high-resolution

(up to 5 μm) assessment of nanoparticle permeability, while single-cell assay for transposase-accessible chromatin using sequencing analysis of chromatin accessibility demonstrates that nanocarriers loaded with HDAC inhibitors increase PPAR γ promoter accessibility by 3.2-fold in HSCs, supporting the mechanistic basis for epigenetic reprogramming (167).

Future studies should focus on the development of intelligent, integrated diagnostic-therapeutic systems. In precision-controlled drug release, near-infrared light-responsive upconversion nanoparticles (inorganic luminescent nanomaterials with anti-Stokes luminescence properties) facilitate millimeter-scale spatially resolved drug delivery upon activation with 808 nm laser irradiation (167,168). A system loaded with the YAP inhibitor verteporfin decreases YAP nuclear localization by 82% within the irradiated zone without notable off-target effects in adjacent normal tissue, offering a novel paradigm for localized antifibrotic therapy (169). In personalized treatment strategies, machine learning algorithms integrating patient-specific TF profiles (covering 12 core nodes, including STAT3, NF- κ B and YAP) with nanoparticle physicochemical parameters (such as particle size, ζ potential and drug loading) have optimized STAT3/NF- κ B co-inhibition regimens (169,170). Phase II clinical trials demonstrate that this approach increases therapeutic response rates from 41% with conventional regimens to 67%, while decreasing the incidence of serious adverse events by 55% (156,171,172). At the frontier of immunometabolic modulation, nanoparticles co-delivering PD-1 antibodies and NRF2 activators block T cell exhaustion (restoring CD8 $^{+}$ T cell IFN- γ secretion to 2.3-fold above baseline) and enhance macrophage antioxidant capacity (reducing mitochondrial ROS levels by 68%). This dual-action strategy achieves both fibrosis reversal and tumor suppression in models of fibrosis with concurrent steatosis, providing a new path for combined antifibrotic and antitumor therapy (156,173). These breakthroughs have not only deepened the mechanistic understanding of TF-targeted nanoregulation but also propelled therapeutic strategies beyond single-target intervention toward multiscale network modulation, establishing a systems biology and bioengineering foundation for clinical translation.

6. Conclusion

Liver fibrosis is a common pathological response to chronic liver injury, presenting treatment challenges due to its association with metabolic dysfunction, persistent inflammation, phenotypic changes in hepatic cell population and excessive ECM deposition. TFs are key in these processes, translating extracellular and intracellular signals into cell-specific transcriptional programs. The present review summarizes the regulatory roles of TFs in liver fibrosis and their potential as therapeutic targets, with a particular focus on nanotechnology-based delivery strategies.

TF functions in liver fibrosis vary depending on cell type and biological context. In hepatocytes, TFs such as HNF4 α , FOXA2 and C/EBP α serve essential roles in metabolic homeostasis and adaptive responses, interacting with Wnt, insulin, IL-6 and nutrient-sensing pathways. Dysregulation of these TFs disrupts glucose, lipid and bile acid metabolism, aggravates hepatocyte injury and promotes the release of profibrotic mediators. In non-parenchymal cells, including

HSCs, Kupffer cells and LSECs, TFs such as YAP/TAZ, LHX2, PPAR γ , NF- κ B and HIF-1 α regulate cellular activation, inflammatory responses, angiogenesis and matrix remodeling. The activity of an individual TF is not uniform; it may vary with disease etiology, stage and cellular state. Moreover, TF programs in different hepatic cell populations are connected through paracrine signaling, where injured hepatocytes activate macrophages and HSCs, macrophage-derived cytokines regulate HSC activation and endothelial inflammatory responses and endothelial cells and aHSCs further modify the hepatic microenvironment. Such intercellular crosstalk sustains fibrosis even when the initial injury has been partially controlled.

TF activity is determined by multiple factors, including expression, subcellular localization, DNA binding, protein stability and interactions with transcriptional cofactors. These characteristics are dynamically regulated by extracellular stimuli, intracellular signaling pathways, post-translational modification and epigenetic mechanisms. This multilayered regulation partly explains why the same TF may exert opposing effects across cell types and stages of fibrosis. Advances in single-cell sequencing and spatial multi-omics approaches have enhanced the resolution of cell-specific TF networks and fibrosis-associated cell states. Nonetheless, numerous regulatory relationships inferred from these analyses do not prove causation, necessitating complementary loss/gain-of-function and rescue experiments, alongside validation in human tissue, organoids or precision-cut liver slices.

The cell-specific nature of TF regulation underscores the rationale for nanotechnology-based delivery. Nanocarriers improve the stability, cellular uptake and pharmacokinetic properties of small-molecule modulators, siRNAs, mRNAs, decoy oligonucleotides and gene editing components. Surface modification with cell-selective ligands may enhance delivery to aHSCs, hepatic macrophages, LSECs or hepatocytes while limiting systemic exposure. However, the therapeutic value of these systems should not be inferred solely from hepatic accumulation. Preferential sequestration by Kupffer cells may impede delivery to other target populations, while fibrosis-associated changes in vascular permeability, ECM density and receptor expression can alter nanoparticle distribution. Additional barriers to clinical translation include endosomal escape, immunogenicity, manufacturing reproducibility, long-term toxicity and differences between experimental models and human disease.

While treating underlying etiology can promote fibrosis regression in some patients, to the best of our knowledge, no therapies specifically targeting antifibrotic indications have been approved. Future studies should identify TFs with functions that are both cell- and stage-specific, establishing their causal roles in fibrosis progression or resolution, and determining whether they can be modulated within an acceptable therapeutic window. Nanotechnology may facilitate this by enabling more selective delivery, but its application necessitates evaluation of biodistribution, pharmacological activity and safety in clinically relevant models. Overall, TFs represent promising yet complex therapeutic targets. Integrating mechanistic studies with human-relevant experimental systems and rational delivery strategies is essential for translating TF-directed intervention into effective antifibrotic therapies.

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Authors' contributions

XFZ wrote and edited the manuscript and performed the literature review. CJY constructed figures and performed the literature review. ZYW contributed to conceiving and designing the study and constructed and revised the figures. LHL wrote and edited the manuscript and conceived the study. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent for participation

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Competing interests

The authors declare that they have no competing interests.

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