Decoding fibroblast activation: Transcriptional networks in hepatic stellate cells and across fibrotic organs (Review)

DENITA CHAROENTHANAKITKUL[1,2] and CHAIYABOOT ARIYACHET[1,2]

[1]Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand;
[2]Center of Excellence in Hepatitis and Liver Cancer, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

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Abstract. Fibrosis is a progressive pathological process characterized by excessive extracellular matrix (ECM) deposition and structural remodeling that ultimately leads to organ dysfunction. In organs such as the liver, lung, heart and kidney, sustained activation of fibroblasts and their differentiation into myofibroblasts are key drivers of fibrotic progression. Growing evidence suggests that these cellular transitions are regulated by intricate transcriptional networks that integrate inflammatory, metabolic and mechanical signals. Liver fibrosis provides a well-established framework for studying the transcriptional regulation of fibroblast activation, largely driven by the differentiation of hepatic stellate cells (HSCs) into collagen-secreting myofibroblasts. Various transcription factors coordinate major signaling pathways to regulate fibroblast proliferation, ECM production and cell survival. These transcriptional programs not only sustain fibrogenesis but also influence whether fibrotic responses resolve or progress to chronic tissue scarring. In the present review, current advances in understanding transcriptional regulatory networks governing fibroblast activation were summarized, with a primary focus on HSCs while highlighting shared mechanisms across multiple fibrotic organs. Emerging therapeutic strategies targeting transcription factors and their upstream regulatory pathways were further discussed. A deeper understanding of these transcriptional circuits may facilitate the development of novel antifibrotic therapies and enhance strategies for resolving fibrosis in various organs.

Correspondence to: Dr Chaiyaboot Ariyachet, Department of Biochemistry, Faculty of Medicine, Chulalongkorn University, 1873 Paettayaphat Building, Rama IV Road, Phatumwan, Bangkok 10330, Thailand
E-mail: chaiyaboot.a@chula.ac.th

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Contents

1. Introduction

Fibrosis is a pathological condition characterized by excessive accumulation of extracellular matrix (ECM) components and progressive tissue scarring across multiple organs, including the liver, lung, skin, kidney and heart (1). Persistent fibrosis disrupts normal tissue architecture and function, ultimately leading to organ dysfunction and life-threatening complications (1,2). At the cellular level, fibrosis is primarily driven by the sustained activation of fibroblasts or fibroblast-like cells, which acquire a myofibroblast phenotype characterized by enhanced proliferation, contractility, and secretion of collagen and other ECM proteins (3). Increasing evidence indicates that these fibrotic processes are tightly regulated by complex transcriptional regulatory networks that integrate signals from inflammatory, metabolic and mechanical pathways.

Among fibrotic diseases, liver fibrosis represents one of the most prevalent and well-characterized forms of tissue fibrosis (4). It arises primarily from the activation of hepatic stellate cells (HSCs), specialized liver-resident mesenchymal cells that differentiate into myofibroblast-like cells in response to chronic liver injury. During this process, diverse transcription factors coordinate signaling pathways that regulate HSC activation, proliferation, ECM production and inflammatory responses (5).

Understanding the transcriptional mechanisms that govern these processes is critical for elucidating the molecular basis of liver fibrosis and identifying potential therapeutic targets. Moreover, numerous transcriptional regulators involved in HSC activation are conserved across different organs, suggesting that insights gained from liver fibrosis may provide

a broader understanding of fibrotic mechanisms in other tissues.

Therefore, the present review summarizes the current knowledge on transcription factors that regulate fibrogenic signaling pathways, with a primary focus on HSC activation and liver fibrosis. Fibrotic mechanisms across multiple organs, fibrosis resolution, and emerging antifibrotic therapies targeting transcription factors and key signaling pathways were further examined. By integrating recent advances in transcriptional regulation, the present review provides a conceptual framework to enhance understanding of fibrotic disease mechanisms and guide future therapeutic development.

2. HSC activation: A model of fibroblast reprogramming

HSCs are a population of liver cells localized in the subendothelial space of Disse, which lies between liver sinusoidal endothelial cells (LSECs) and hepatocytes (6). The primary functions of HSCs are to store retinyl esters and vitamin A and to maintain ECM homeostasis in the liver (7,8). Under normal physiological conditions, HSCs remain in the quiescent state, which is characterized by the expression of retinol-binding proteins, glial fibrillary acidic protein (GFAP), and peroxisome proliferator-activated receptor gamma (PPARγ) (6,8).

There are several factors that maintain the quiescent phenotype of HSCs. For instance, LSECs in the normal liver inhibit hepatic fibrogenesis and promote the reversion of activated HSCs to a quiescent state through vascular endothelial growth factor (VEGF)-stimulated nitric oxide production. PPARγ also positively regulates hepatocyte growth factor, which may reduce HSC activation and collagen secretion. Moreover, the retinoic acid receptors, retinoid X receptors, the pregnane X receptor, and the *LHX2* gene contribute to maintaining the quiescent phenotype of HSCs (6,9).

Activation of HSCs is driven by coordinated transcriptional and epigenetic programs that govern the transition from a quiescent state to a myofibroblast phenotype. This transition is characterized by the loss of cytoplasmic lipid droplets and the acquisition of a spindle-shaped, contractile morphology, accompanied by increased cell proliferation, adhesion, ECM production, and secretion of inflammatory cytokines. At the molecular level, activated HSCs upregulate myofibroblast markers such as α-smooth muscle actin (α-SMA) and ECM-related genes encoding type I and III collagens and fibronectin (6-8). Consistent with these observations, HSCs have been identified as the principal source of myofibroblasts in liver fibrosis (10). These phenotypic changes promote the migration of activated HSCs to sites of injury, where they contribute to fibrous scar formation (8). The process of HSC activation is classically divided into two phases: Initiation and perpetuation. Initiation involves the priming of quiescent HSCs, rendering them responsive to cytokines and other extracellular signals that drive inflammatory cell infiltration and early ECM remodeling. Perpetuation represents a sustained activated state in which HSCs fully differentiate into myofibroblasts and exhibit persistent ECM gene expression, proliferation, contractility and chemotactic activity (7,11). HSC activation is regulated by multiple factors that promote acquisition and maintenance of the activated phenotype. Transcriptional and epigenetic regulators, including Kruppel-like factor 6 (KLF6), Gα-interacting vesicle-associated protein, and methyl-CpG-binding protein 2 (MeCP2), contribute to the transformation of quiescent HSCs into myofibroblasts (12-14). In parallel, reactive oxygen species (ROS) are generated in response to profibrogenic mediators, including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β) and angiotensin II, and contribute to the amplification of profibrotic signaling and gene expression (15,16). Beyond their fibrogenic role, activated HSCs also acquire angiogenic properties. PDGF-stimulated HSCs regulate vascular tubule formation, increase sinusoidal caliber, and enhance hepatic blood flow. Through these mechanisms, HSCs, together with PDGF signaling, contribute to the remodeling and dynamic regulation of the hepatic microvascular architecture (9,17). Moreover, the resolution phase of HSC activation occurs following the removal of the injurious stimulus and is characterized by apoptosis, senescence, or phenotypic reversion of activated HSCs toward a quiescence-like state (11).

Collectively, HSCs exhibit remarkable phenotypic plasticity, enabling transitions between quiescent, activated, and resolving states during liver injury and repair (Fig. 1). The molecular regulators and transcriptional programs governing these phenotypic transitions are discussed in detail in the following sections.

3. Transcriptional regulation of HSC activation

The transition of HSCs from a quiescent to an activated state is controlled by multilayered transcriptional and epigenetic networks that translate injury-associated signals into sustained fibrogenic gene expression. Perturbation of these regulatory programs disrupts cellular homeostasis, promotes excessive ECM deposition, and drives progressive liver fibrosis. This section examines how transcriptional circuits and chromatin-based mechanisms coordinate HSC responses to liver injury, encompassing identity-defining transcription factors, inflammation- and stress-responsive signaling networks, and epigenetic processes that stabilize the activated state (Fig. 2).

Core transcriptional drivers of HSC activation. Lineage- and context-specific transcription factors form an interconnected regulatory hierarchy that governs the transition of HSCs from quiescence to persistent activation. Early injury signals, including TGF-β and inflammatory mediators, initiate fibrogenic transcriptional programs, whereas downstream pathways involving Wnt/β-catenin, YAP/TAZ-mediated mechanotransduction, and stress-responsive transcription factors reinforce and stabilize the activated phenotype through the cooperative regulation of shared target genes.

SMAD3 is the principal downstream transcriptional mediator of TGF-β signaling that drives HSC activation and fibrogenic gene expression. Following TGF-β stimulation, SMAD3 translocates to the nucleus, where it induces myofibroblastic differentiation and ECM production. TGF-β also engages JAK1-STAT3 signaling, with early SMAD-independent STAT3 activation followed by sustained SMAD3-dependent transcription. Coordinated SMAD3 and STAT3 activity ultimately establishes and maintains the fibrogenic transcriptional program in activated HSCs (18).

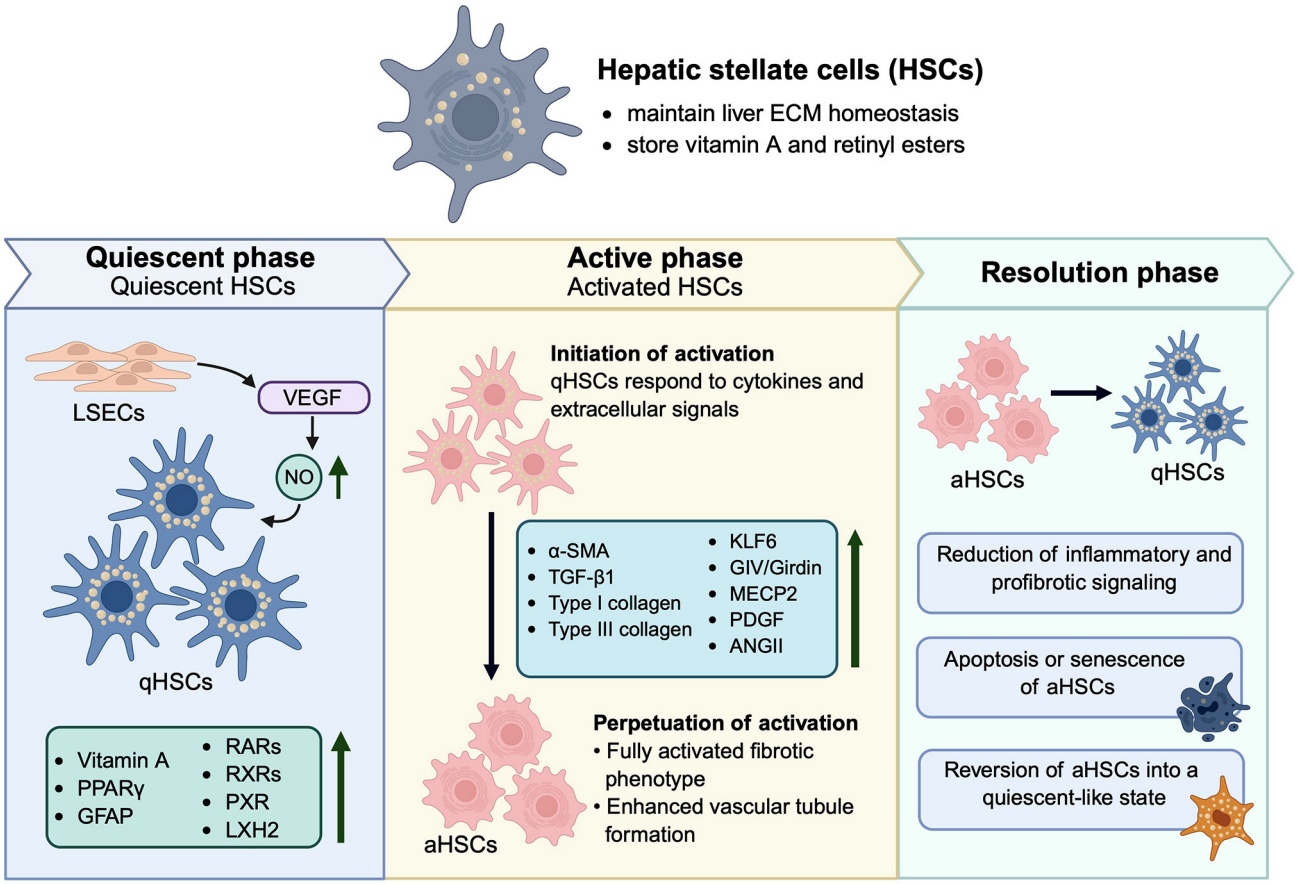

Figure 1. Phases of hepatic stellate cell activation and resolution. HSCs maintain ECM homeostasis and store vitamin A in the quiescent state. Upon injury, HSCs undergo activation, characterized by the induction of fibrogenic markers and transition to a fully activated myofibroblast-like phenotype with enhanced ECM production and vascular tubule formation. After removal of the injurious stimulus, fibrosis may resolve through reduced inflammatory signaling, apoptosis or senescence of activated HSCs, and partial reversion to a quiescent-like state. HSCs, hepatic stellate cells; aHSCs, activated HSCs; qHSCs, quiescent HSCs; ECM, extracellular matrix; LSECs, liver sinusoidal endothelial cells; PPARγ, peroxisome proliferator-activated receptor gamma; NO, nitric oxide; GFAP, glial fibrillary acidic protein; α-SMA, α-smooth muscle actin; PDGF, platelet-derived growth factor; MeCP2, methyl-CpG-binding protein 2; TGF-β1, transforming growth factor β1.

Acting downstream of TGF-β/SMAD3 signaling, zinc finger protein 469 (ZNF469) amplifies fibrogenic transcription by directly binding to collagen gene loci following TGF-β1 induction. This promotes ECM gene expression, collagen synthesis and matrix accumulation, thereby stabilizing the activated HSC phenotype (19).

In addition to promoting ECM synthesis through ZNF469, TGF-β/SMAD3 signaling reinforces early HSC activation through dermatopontin (DPT). DPT suppresses PPARγ-, PPARα- and Dectin-1-mediated protective pathways, thereby promoting profibrotic transcriptional reprogramming, whereas its depletion restores these antifibrotic programs and limits fibrogenic progression (20).

Parallel to canonical TGF-β/SMAD3 signaling, sustained SMAD1 signaling also contributes to HSC activation. RUNX1 transcriptionally induces the deubiquitinase USP9X, preventing SMAD1 degradation and prolonging SMAD1-dependent profibrotic transcription, thereby promoting HSC proliferation, migration and fibrogenic expansion (21).

MEK-ERK signaling further reinforces early HSC activation through E26 transformation-specific protein 1 (ETS1). Preferentially expressed in quiescent and early activated HSCs, ETS1 couples MEK-ERK signaling to the repression of the PPARγ axis and cooperates with RUNX1 to establish activation-associated transcriptional programs before declining as HSCs transition to a fully activated state (22,23).

Mechanosensitive transcriptional coactivators Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) integrate matrix stiffness with fibrogenic transcription during HSC activation through the Hippo pathway, a key regulator of liver homeostasis and regenerative responses. In response to increased matrix stiffness and mechanical stress, YAP/TAZ translocate to the nucleus, where they cooperate with TEAD transcription factors to activate genes involved in HSC proliferation, survival and ECM production, thereby reinforcing tissue remodeling and fibrosis. Beyond directly regulating fibrogenic genes, YAP/TAZ function as signaling integrators by cooperating with stress-responsive transcriptional programs, including activator protein 1 (AP-1), to amplify mechanotransduction-driven HSC activation (24-26).

While TGF-β/SMAD3 establishes the initial fibrogenic transcriptional response, mechanical and developmental pathways further determine the persistence and magnitude of this program. The Wnt/β-catenin pathway reinforces HSC activation by promoting profibrotic transcription. Upon Wnt

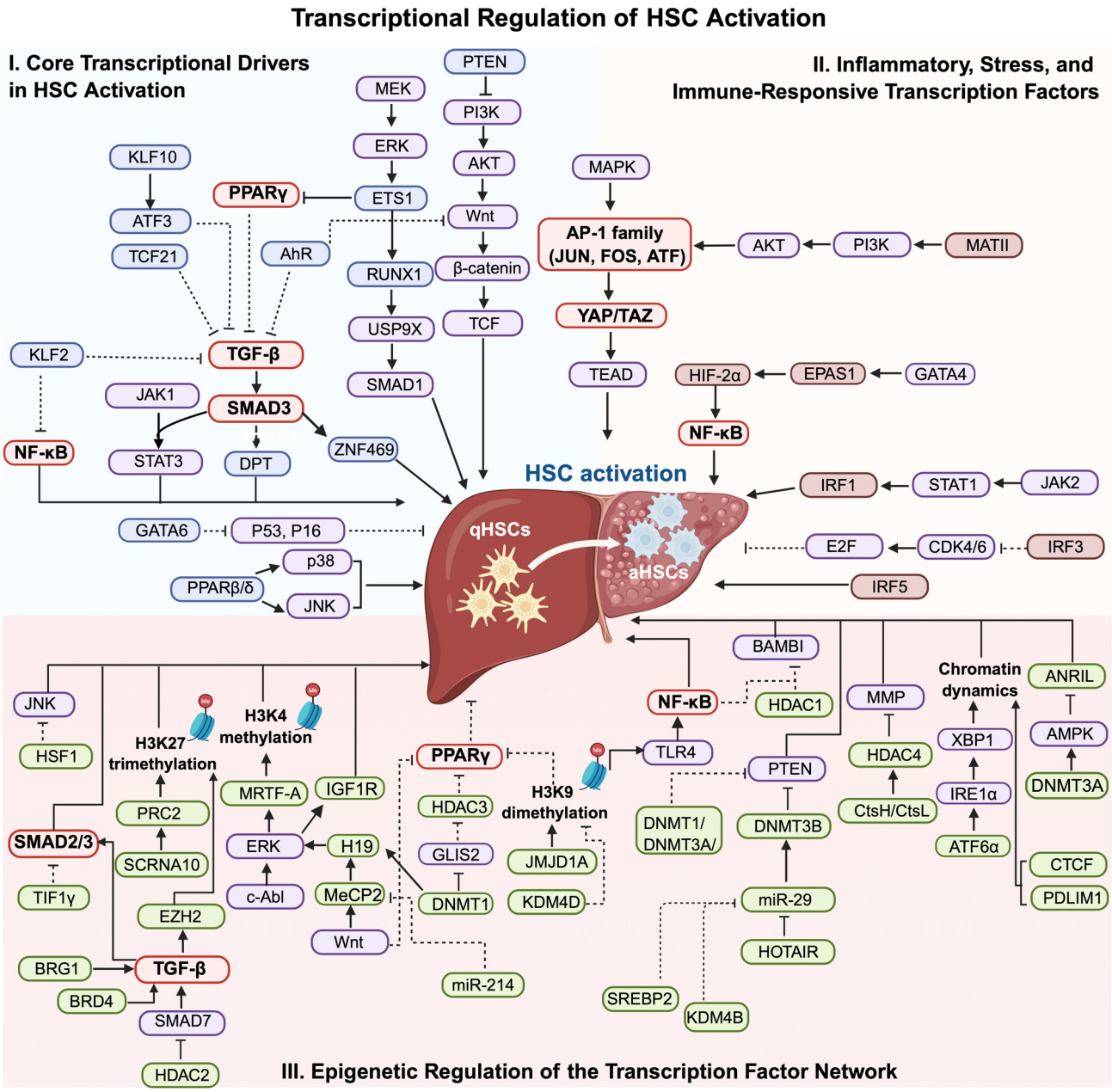

Figure 2. Transcriptional and epigenetic regulation of HSC activation. Schematic overview of the interconnected signaling, transcriptional, and chromatin-regulatory networks governing HSC activation. Canonical fibrogenic signaling pathways (purple) converge on core transcriptional hubs (red outline), including TGF-β, SMAD3, YAP/TAZ, AP-1, NF-κB and PPARγ, which integrate multiple profibrotic signaling pathways to orchestrate HSC activation. Additional transcription factors (blue) further modulate specific aspects of the fibrogenic transcriptional program. Inflammatory, stress-responsive, and immune-responsive transcription factors (brown) integrate environmental and metabolic cues to amplify fibrogenic responses. Epigenetic regulators and chromatin-associated factors (green) reinforce transcriptional reprogramming and stabilize the activated HSC state. Together, these multilayered regulatory modules establish and maintain persistent fibrogenic gene expression during liver fibrosis. HSCs, hepatic stellate cells; qHSCs, quiescent HSCs; TGF-β, transforming growth factor β; PPARγ, peroxisome proliferator-activated receptor gamma; miR, microRNA.

activation, β-catenin accumulates in the nucleus and cooperates with T-cell factor (TCF) transcription factors to induce genes that drive HSC activation and ECM production. Consistent with this role, genetic disruption of β-catenin impairs HSC activation and collagen deposition, highlighting Wnt/β-catenin signaling as a key regulator of fibrogenic transcription during liver injury (27).

Counterbalancing profibrotic signaling, several endogenous transcriptional regulators act as molecular brakes that constrain HSC activation by suppressing TGF-β signaling, inflammatory responses, oxidative stress and metabolic reprogramming. Through these regulatory networks, they maintain a transcriptional state that limits the acquisition and persistence of the activated fibrogenic phenotype. PPARγ functions as a master transcriptional brake on HSC activation by antagonizing TGF-β/SMAD3-dependent fibrogenic transcription. In quiescent HSCs, PPARγ directly suppresses SMAD3 activity, limiting the expression of profibrotic genes such as α-SMA, connective tissue growth factor (CTGF) and collagen (28,29). During chronic liver injury, epigenetic silencing and downregulation of PPARγ release this restraint, enabling HSC activation, proliferation and ECM deposition.

Beyond inhibiting TGF-β signaling, PPARγ integrates metabolic regulation through CCAAT/enhancer-binding proteins, liver X receptor α, sterol regulatory element-binding protein-1c, and the adiponectin axis to maintain HSC homeostasis and suppress fibrogenic programs (30,31). By contrast, PPARβ/δ is enriched in activated HSCs and promotes proliferation through p38 and JNK-MAPK signaling, highlighting the opposing roles of PPAR family members in fibrosis (30).

Additional transcriptional regulators modulate TGF-β-driven HSC activation by promoting a less fibrogenic transcriptional state. Krüppel-like factor 10 (KLF10) attenuates TGF-β signaling through the KLF10-ATF3 regulatory axis, thereby suppressing downstream fibrogenic programs and limiting excessive HSC activation. Similarly, transcription factor 21 (TCF21) suppresses TGF-β signaling and reprograms activated HSCs from an ECM-producing phenotype toward a quiescence-associated transcriptional profile. Together, these regulators counteract persistent TGF-β-driven transcriptional reprogramming and restrain the acquisition of the activated fibrogenic state (32,33).

Endogenous anti-activation regulators further maintain HSC identity by integrating inflammatory, metabolic and stress-responsive pathways. Krüppel-like factor 2 (KLF2) coordinates anti-inflammatory and antioxidant signaling by suppressing the TGF-β and NF-κB pathways while activating Nrf2. By simultaneously inhibiting NF-κB-mediated inflammatory transcription and TGF-β-dependent fibrogenic gene expression, KLF2 limits the convergence of inflammatory and profibrotic signaling programs that sustain HSC activation, thereby promoting the apoptosis of activated HSCs and reducing fibrogenic gene expression (34). Similarly, the aryl hydrocarbon receptor (AhR) links environmental and metabolic sensing to HSC fate by restraining Wnt and TGF-β/SMAD3 signaling, whereas loss of AhR promotes profibrotic transcriptional reprogramming and HSC activation (35). Beyond restraining these signaling pathways, GATA6 provides an additional layer of fate control by preserving quiescent HSC identity under homeostatic conditions and inducing autophagy-dependent p53/p16-mediated senescence following injury, thereby limiting persistent fibrogenic activity (36).

Additional regulatory checkpoints modulate the magnitude and persistence of HSC activation. Phosphatase and tensin homolog deleted on chromosome 10 (PTEN) restrains fibrogenic signaling by inhibiting phosphoinositide 3-kinase (PI3K)/AKT activity, whereas its loss enhances AKT activation and permissive Wnt signaling, promoting HSC survival, activation and ECM accumulation (37). Similarly, Forkhead box F1 (FOXF1) acts as a context-dependent regulator of HSC activation dynamics. Although FOXF1 loss permits HSC activation without markedly increasing proliferation, it reduces matrix metalloproteinase-9 (MMP9) activity, a mediator of HSC-to-myofibroblast transition, suggesting that FOXF1 limits the intensity and duration of fibrogenic responses rather than enforcing a fixed quiescent state (38,39).

Collectively, these regulators form an interconnected transcriptional network that integrates cytokine, mechanical, metabolic and stress signals to determine HSC fate. The balance between fibrogenic drivers and anti-activation pathways controls the magnitude, duration and stability of HSC activation, thereby shaping the transition to or from a persistent myofibroblastic phenotype.

Inflammatory, stress and immune-responsive networks. Inflammatory and stress-responsive transcriptional networks integrate immune-derived cytokines, innate sensing pathways, mechanical stress, and metabolic perturbations to establish persistent fibrogenic programs in HSCs. Rather than acting as isolated regulators, these pathways converge on shared transcriptional hubs that regulate inflammatory activation, cellular stress adaptation and phenotypic stability during fibrosis progression.

The interferon regulatory factor (IRF) family exemplifies this integration by linking immune sensing to distinct HSC responses through context-dependent signaling pathways. In inflammatory environments, JAK2/STAT1 activation induces IRF1 nuclear translocation, promoting cytokine and chemokine expression that amplifies immune signaling within HSCs without directly affecting cell survival (40,41). Conversely, innate immune sensing through the STING-IRF3 axis can restrain fibrogenic expansion by inducing RB-dependent cell cycle arrest, reducing cyclin-dependent kinase (CDK)4/6-mediated RB phosphorylation, suppressing E2F activity, and promoting HSC senescence. However, IRF3 activity is highly context-dependent, as alternative signaling inputs can shift its function toward HSC activation. By contrast, IRF5 contributes primarily through immune microenvironment remodeling, whereby its activation in hepatic macrophages promotes M1 polarization, inflammatory cytokine production and hepatocyte injury, thereby indirectly enhancing HSC activation and fibrosis progression (42,43).

These immune-derived signals converge with stress-activated pathways through AP-1, a MAPK-responsive transcriptional hub that integrates inflammatory, metabolic, oxidative and mechanical stimuli into fibrogenic gene programs. AP-1 complexes composed of JUN, FOS and ATF family members regulate chromatin accessibility and cooperate with mechanosensitive YAP/TAZ-TEAD signaling to amplify shared profibrotic targets, linking extracellular stress signals to persistent HSC activation (44,45). As fibrosis progresses, inflammatory cytokines and matrix stiffening become increasingly interconnected, with MAPK-dependent AP-1 signaling and nuclear YAP/TAZ converging on shared profibrotic transcriptional programs that reinforce HSC activation. The composition and activity of AP-1 dimers are dynamically regulated by cytokines, growth factors and cellular stress, enabling context-dependent transcriptional responses during fibrosis (44,45). Among AP-1 family members, JUN acts as a dominant effector in activated HSCs, with phosphorylated JUN enriched at activation-associated chromatin regions following mechanical stimulation and fibrotic injury. Mechanistically, c-JUN activation downstream of MATII-mediated PI3K/AKT signaling integrates metabolic and inflammatory inputs to sustain fibrogenic transcription and HSC activation (45,46). Collectively, these findings highlight AP-1 as a central transcriptional hub linking inflammatory signaling with YAP/TAZ-mediated mechanotransduction, thereby coordinating integrated profibrotic transcriptional networks during HSC activation.

In addition to inflammatory and mechanical stress responses, hypoxic signaling provides another layer of transcriptional adaptation that sustains HSC activation. Hypoxia-inducible factor-2α (HIF-2α), encoded by EPAS1, links metabolic stress with inflammatory signaling in the fibrotic liver. Under homeostatic conditions, GATA4 restrains HIF-2α expression, whereas its derepression during liver injury promotes NF-κB-dependent inflammatory responses and lipid accumulation in HSCs, particularly in non-alcoholic steatohepatitis (NASH)-associated fibrosis. Through these metabolic and inflammatory adaptations, HIF-2α reinforces the activated fibrogenic state under hypoxic conditions (47,48).

Together, these inflammatory, stress-responsive and metabolic pathways converge on interconnected transcriptional hubs that integrate immune signals, mechanical cues and cellular stress to establish persistent fibrogenic programs in HSCs. This coordinated network enables adaptive responses to injury while promoting the stabilization of the activated phenotype during chronic fibrosis.

Epigenetic mechanisms. Beyond transcription factor-driven signaling networks, HSC activation and fibrogenic persistence are tightly regulated by epigenetic mechanisms that control chromatin accessibility, transcriptional memory and the reversibility of cell-state transitions. These regulatory layers shape how HSCs interpret and retain injury signals through the modulation of enhancer activity, DNA methylation, histone modifications and higher-order chromatin organization. Through the coordinated actions of chromatin readers and remodelers, DNA methylation machinery, histone-modifying enzymes and chromatin-associated transcription factors, these epigenetic programs reinforce the activated state or enable reversion to quiescence.

Enhancer occupancy represents a key epigenetic mechanism that enables sustained fibrogenic transcription in activated HSCs. Bromodomain-containing protein 4 (BRD4), a BET family epigenetic reader, links injury-associated signaling pathways to enhancer-driven fibrogenic transcription in activated HSCs. BRD4 occupancy at the COL1A1 enhancer promotes collagen expression, whereas BET inhibition with JQ1 reduces enhancer engagement and attenuates fibrogenic activation (49). In response to TGF-β signaling, BRD4 reinforces HSC proliferation and persistence by promoting p300-dependent H3K27 acetylation at the PLK1 promoter, thereby sustaining cell-cycle progression and myofibroblastic conversion (50). BRD4 also integrates inflammatory signaling through the CXCL6-SMAD2-BRD4-c-MYC-enhancer of zeste homolog 2 (EZH2) axis, which reinforces the repression of antifibrotic programs and stabilization of the activated phenotype (51). Beyond fibrogenic regulation, BRD4 exhibits context-dependent interactions with metabolic pathways, including FXR signaling, highlighting its role as an epigenetic coordinator that links inflammatory, metabolic and profibrotic cues during liver injury (52).

Beyond enhancer recognition by epigenetic readers, chromatin accessibility is further regulated by ATP-dependent remodeling complexes that determine the transcriptional permissiveness of fibrogenic loci. ATP-dependent SWI/SNF chromatin remodeling complexes regulate fibrogenic permissiveness by reshaping chromatin accessibility in activated HSCs. Through their core components, including BAF250a (ARID1A) and BRG1, SWI/SNF complexes integrate metabolic and profibrotic signals to establish transcriptional states that either promote or restrain HSC activation. While BAF250a contributes to the maintenance of metabolic and inflammatory homeostasis, BRG1 facilitates TGF-β/SMAD3-dependent chromatin remodeling and ECM gene expression. Dysregulation of SWI/SNF activity therefore promotes a permissive chromatin landscape that sustains fibrogenic transcription and HSC activation (53).

Higher-order genome organization represents an additional layer of epigenetic regulation that stabilizes HSC fate by controlling spatial interactions between regulatory elements. CCCTC-binding factor (CTCF), a master regulator of chromatin topology, is upregulated during HSC activation and may contribute to the formation of activation-associated chromatin landscapes. Although depletion of PDZ and LIM domain protein 1 (PDLIM1) reduces CTCF expression and impairs HSC activation, CUT&Tag analysis indicates that global CTCF chromatin occupancy remains relatively stable, suggesting that CTCF function depends on context-specific chromatin interactions rather than widespread changes in genome-wide binding (54).

DNA methylation establishes a persistent fibrogenic memory in HSCs by silencing regulatory networks that normally restrain activation. DNMT1, DNMT3A and DNMT3B promote this transition through the hypermethylation of antifibrotic regulators, including PTEN and microRNA (miR)-29 family members, thereby enhancing Wnt-associated MeCP2/EZH2 activity and suppressing the quiescence-maintaining PPARγ axis (6). This methylation landscape is further reinforced by long non-coding RNAs (lncRNAs) that function as epigenetic modulators. HOTAIR promotes DNMT3B-dependent PTEN repression through miR-29b sequestration, whereas H19 enhances ERK1/2-IGF1R signaling through the regulation of the DNMT1/MeCP2 pathway. In parallel, ANRIL methylation and SCARNA10-mediated PRC2 recruitment promote repressive chromatin states, including increased H3K27me3 deposition at TGF-β pathway genes, further stabilizing the activated fibrogenic phenotype (55-58).

Epigenetic repression is further reinforced by MeCP2, which links DNA methylation signals to the transcriptional control of HSC fate. Phosphorylated MeCP2 binds to the PPARγ promoter and suppresses its transcription, thereby promoting HSC proliferation and fibrogenic activation (59). Canonical Wnt signaling increases MeCP2 abundance, further enhancing PPARγ repression, whereas Wnt inhibition restores PPARγ expression through miR-132/miR-212-mediated reduction of MeCP2 occupancy. Conversely, miR-214 directly targets MeCP2 to attenuate HSC activation, highlighting the Wnt-MeCP2-PPARγ axis as a key regulator of fibrogenic transcriptional stability (60,61).

Histone modifications further shape HSC fate by dynamically regulating the balance between permissive and repressive chromatin states during the fibrogenic transition. In response to TGF-β signaling, EZH2, the catalytic subunit of PRC2, is induced and promotes H3K27me3 deposition at target loci, resulting in the repression of antifibrotic gene programs and enhanced fibronectin expression during HSC activation (62). Conversely, histone demethylases regulate the

removal of repressive marks to maintain chromatin plasticity and govern the transition between quiescent and activated states. JMJD1A preserves HSC quiescence by removing H3K9me2 marks at the PPARγ promoter, whereas the loss of JMJD1A disrupts this quiescence-associated chromatin state and facilitates fibrogenic activation (63). Similarly, the KDM4 family exhibits context-dependent effects on HSC fate, with KDM4B supporting a quiescence-associated phenotype through SREBP2-mediated activation of miR-29 transcription, while KDM4D promotes activation by removing H3K9me2/3 marks at inflammatory loci and enhancing Toll-like receptor 4 (TLR4)-NF-κB signaling (64,65).

Histone deacetylases (HDACs) further stabilize fibrogenic chromatin states by integrating profibrotic signaling with the transcriptional repression of antifibrotic programs and impaired matrix turnover. HDAC2 promotes HSC activation by suppressing the inhibitory SMAD7 pathway, thereby enhancing TGF-β signaling, whereas HDAC1 cooperates with NF-κB to repress BAMBI, a negative regulator of TGF-β signaling, linking inflammatory stimuli to sustained fibrogenic transcription (66,67). In parallel, the class IIa histone deacetylase HDAC4 contributes to fibrosis persistence by limiting ECM degradation. During HSC activation, downregulation of the cysteine cathepsins CtsH and CtsL stabilizes HDAC4, resulting in reduced MMP expression and enhanced ECM accumulation (68).

Importantly, epigenetic regulation does not operate independently of transcription factor networks but instead serves as an interface that converts extracellular signals into durable chromatin states. MRTF-A promotes fibrogenic transcription by recruiting histone methyltransferases to fibrotic promoters, increasing H3K4 methylation and sustaining nuclear activity through c-Abl-ERK feedback (6,69). By contrast, GLIS2 maintains a quiescence-associated chromatin state through PPARγ-HDAC3 interactions but is silenced by DNMT1-mediated promoter methylation during HSC activation. Stress-responsive pathways also engage chromatin remodeling mechanisms, as ATF6α links endoplasmic reticulum stress signaling to IRE1α-XBP1-dependent transcriptional regulation, while ATF3 modulates fibrogenic chromatin states through the context-dependent recruitment of HDAC1 to target loci (70-74).

Importantly, these pathways do not function as independent signaling modules but instead form a hierarchical, cooperative network during HSC activation. TGF-β/SMAD3 signaling serves as the initiating driver that establishes the early fibrogenic transcriptional program by inducing myofibroblast differentiation and ECM production. As activation progresses, Wnt/β-catenin signaling reinforces this program by promoting HSC proliferation, survival, and sustained ECM synthesis while simultaneously opposing quiescence-associated pathways. At later stages, matrix accumulation and increased tissue stiffness activate YAP/TAZ, which cooperate with SMAD3, AP-1 and TEAD transcriptional complexes to maintain the expression of ECM-associated genes and establish transcriptional persistence. Thus, TGF-β/SMAD3, Wnt/β-catenin and Hippo/YAP signaling collectively function as interconnected transcriptional regulators that drive the transition from initial HSC activation to stable fibrotic remodeling.

Together, these mechanisms demonstrate that epigenetic regulators function as molecular memory systems that integrate extracellular signals with chromatin remodeling to stabilize either fibrogenic activation or HSC quiescence.

4. Organ-specific transcription factor dynamics

The transcriptional networks described in HSC activation provide a framework for understanding fibrogenic regulation across tissues. Extending beyond liver fibrosis, this section examines how conserved regulatory principles and organ-specific transcription factors collectively shape fibroblast activation in diverse fibrotic diseases, including those affecting the lung, kidney, heart and skin.

Lung fibrosis. Pulmonary fibrosis, particularly idiopathic pulmonary fibrosis (IPF), is a relentlessly progressive interstitial lung disease characterized by aberrant alveolar regeneration, sustained fibroblast activation, excessive ECM accumulation and irreversible distortion of pulmonary architecture. Characteristic histological findings include the usual interstitial pneumonia pattern with fibroblast foci, temporal heterogeneity and honeycombing. Repetitive epithelial injury, coupled with dysregulated epithelial-mesenchymal signaling, macrophage reprogramming, fibroblast plasticity, cellular senescence and persistent TGF-β pathway activation, collectively contributes to disease progression (75,76).

The central transcriptional network driving pulmonary fibrosis is organized around TGF-β/SMAD signaling, which integrates mechanical cues and lineage-specific transcriptional regulators to sustain fibroblast activation. Canonical SMAD2/3 signaling promotes fibroblast-to-myofibroblast differentiation and ECM production, while increasing matrix stiffness reinforces this response through YAP nuclear translocation and TEAD-dependent activation of TWIST-driven mesenchymal programs, thereby establishing a feed-forward loop between tissue mechanics and persistent fibroblast activation (77,78). Recent evidence further implicates ZNF469 in the TGF-β/SMAD3 signaling axis. ZNF469 is upregulated in response to TGF-β stimulation and cooperates with SMAD3 at fibrogenic target loci, as demonstrated by CUT&RUN analysis, thereby promoting the transcriptional programs that drive lung fibrogenesis (79). Within this signaling framework, RUNX1 is induced following bleomycin injury and TGF-β stimulation, promoting myofibroblast differentiation and ECM production. This effect is further amplified by the Hoxaas3-miR-450b-5p axis downstream of TGF-β/SMAD4 signaling (80,81). PRRX1 similarly cooperates with SMAD2/3 signaling to enhance fibroblast proliferation and differentiation, whereas RUNX2 expression is largely confined to epithelial compartments and is associated with epithelial remodeling rather than direct fibroblast activation (82-84).

Beyond fibroblast differentiation, epithelial lineage programs and mechano-transductive signaling cooperate to amplify TGF-β-dependent fibrogenesis. SOX9 promotes fibroblast migration, myofibroblast differentiation and ECM deposition, while IL-4-induced SOX9 expression in epithelial cells drives aberrant airway lineage reprogramming, linking epithelial plasticity to progressive fibrosis (85-87). Multiple upstream pathways further enhance TGF-β activity, including

WNT5A-mediated JNK/ROCK signaling, which promotes latent TGF-β activation and fibroblast differentiation, and osteoglycin-dependent stabilization of integrin αv, which strengthens TGF-β signaling (88,89). Consistent with this integrated network, FOXM1 promotes TGF-β-dependent epithelial-mesenchymal transition (EMT) and reinforces progressive fibrotic remodeling (90).

Mechanical and cytoskeletal signaling further stabilize these transcriptional programs independently of canonical SMAD activation. Matrix stiffness activates NFATC4 to regulate CTHRC1 and collagen expression (91), whereas the Arp2/3 complex promotes fibroblast differentiation through Akt/GSK3β/β-catenin signaling independently of SMAD2 phosphorylation (92). In parallel, ROCK1/2 signaling contributes to epithelial apoptosis and fibrotic remodeling while reinforcing TGF-β activity, and its inhibition reduces α-SMA expression and fibrosis progression (92,93).

Epigenetic and stress-responsive pathways further stabilize profibrotic transcriptional programs downstream of TGF-β signaling. TGF-β1-TβRI-SMAD3 signaling induces the DNA methylation reader MBD2, which promotes fibroblast-to-myofibroblast differentiation through the repression of antifibrotic genes such as Erdr1 (94). In parallel, oxidative stress reinforces these transcriptional circuits through MEOX1, which links NOX4-derived ROS to SMAD2/3 activation, CTGF expression, cellular senescence and collagen synthesis (95).

Cardiac fibrosis. Cardiac fibrosis represents a major component of myocardial remodeling and contributes to arrhythmia, heart failure, and sudden cardiac death. It occurs either as replacement fibrosis following cardiomyocyte apoptosis or as diffuse interstitial fibrosis driven by persistent pathological signaling. Activated fibroblasts arise primarily from resident cardiac fibroblast populations, which originate from diverse developmental sources such as the proepicardium, endothelial cells, and the neural crest and occupy multiple cardiac niches (96,97).

Following cardiac injury, fibroblast activation is initiated by convergent injury-associated signals that establish a profibrotic transcriptional state. TGF-β/SMAD signaling represents the central transcriptional axis governing this transition, with TGF-β1 promoting fibroblast-to-myofibroblast conversion, proliferation, adhesion, invasion and collagen secretion primarily through SMAD3 activation. By contrast, Notch signaling functions as a regulatory checkpoint that limits excessive fibrogenic responses, as N1ICD overexpression suppresses TGF-β-driven activation, an effect reversed by SMAD3 reactivation (98). SMAD2 and SMAD3 further coordinate post-infarction myofibroblast expansion and spatial organization by regulating integrin expression and planar cell polarity signaling, thereby linking transcriptional activation to tissue remodeling (99).

Beyond the initial activation phase, the TGF-β-driven fibrogenic program is reinforced by lineage-associated transcriptional regulators that stabilize fibroblast identity and ECM production. RUNX1 is strongly induced after myocardial injury and cooperates with the transcriptional coactivator p300 to activate ECM gene expression and promote fibroblast differentiation (100). Beyond its role in fibroblasts, RUNX1 also contributes to myocardial remodeling by promoting mitochondrial dysfunction in border-zone cardiomyocytes, while RUNX1 inhibition reduces α-SMA expression, improves connexin-43-mediated cardiomyocyte-fibroblast communication, and limits scar formation (29,101,102). Consistently, miR-101 attenuates cardiac fibrosis through RUNX1 suppression and inhibition of TGF-β1/SMAD2 signaling, highlighting regulatory feedback mechanisms that constrain persistent activation (103).

As fibrosis progresses, additional transcriptional programs integrate growth factor-, mechanical-, and matrix-derived signals with the core TGF-β pathway. TFAP4 promotes fibroblast proliferation, migration, contractility and ECM organization through ITGA11-dependent AKT signaling, whereas IRX2 enhances angiotensin II-induced remodeling by facilitating EGR1-dependent SMAD3 phosphorylation (104,105). SOX9 further links developmental transcriptional programs with fibrogenic signaling by promoting EMT-derived fibroblast formation and ECM deposition downstream of the PDGF and TGF-β/SMAD3 pathways (106-108). These cytokine-driven programs are reinforced by mechanical feedback, whereby AngII-RhoA-mediated YAP activation promotes MRTF-A-dependent profibrotic transcription, and Wnt/β-catenin signaling in TCF21-lineage fibroblasts enhances ECM production and hypertrophic remodeling (109,110). Finally, collagen sensing through DDR2-ERK1/2-SRF signaling provides an additional layer of matrix-dependent regulation, linking extracellular remodeling to fibroblast survival and sustained activation (111).

Counterbalancing these profibrotic networks, endogenous inhibitory pathways and epigenetic regulators modulate the stability of the activated fibroblast state. HSF1 suppresses pressure overload-induced fibrosis through interaction with SMAD3, whereas cardiomyocyte-restricted KLF6 limits fibrosis by repressing TSP4 transcription (112,113). Epigenetic regulation further reinforces fibroblast activation, as DNMT3A-mediated repression of RASSF1A enhances Ras-ERK signaling and fibroblast proliferation, while DNMT3A inhibition restores RASSF1A expression and suppresses collagen and α-SMA production (114). In addition, non-coding RNAs fine-tune TGF-β signaling, with miR-21, miR-216a and lnc-Ang362 amplifying SMAD signaling through the repression of SMAD7, whereas miR-19b promotes fibroblast proliferation through PTEN targeting independently of collagen synthesis (115-118). ATF4 further exacerbates diabetic cardiomyopathy by inducing oxidative stress and promoting Smurf2-mediated HIPK2 degradation (119).

Renal fibrosis. Renal fibrosis is a central pathological feature of chronic kidney disease (CKD) and a major driver of irreversible renal failure. At the center of this process, TGF-β orchestrates fibrogenic responses through canonical and non-canonical signaling pathways that coordinate epithelial plasticity, fibroblast activation, inflammatory remodeling and ECM deposition. Progressive matrix accumulation disrupts normal kidney architecture and impairs tissue perfusion, ultimately leading to irreversible nephron loss. Pathologically, renal fibrosis is characterized by the replacement of functional nephrons with activated fibroblasts and myofibroblasts, accompanied by excessive ECM accumulation, resulting in tubular

atrophy, chronic interstitial inflammation, glomerulosclerosis and vascular rarefaction (120,121).

Fibrotic progression in the kidney is governed by interconnected transcriptional and mechanical signaling networks downstream of TGF-β that regulate epithelial dedifferentiation, fibroblast activation and ECM remodeling. RUNX1 promotes renal tubular EMT by enhancing TGF-β-induced PI3K-AKT signaling (122). Likewise, SOX4 directly cooperates with SMAD3 within the TGF-β1/SMAD3 pathway to promote tubular epithelial dedifferentiation and fibroblast activation (123).

As injury persists, these initial TGF-β-driven responses are reinforced by transcriptional programs that connect epithelial plasticity with mechanical remodeling. The SOX9-NAV3-YAP1 axis provides an example of this transition, in which renal injury-induced NAV3 promotes actin polymerization and cell migration, leading to sustained activation of the mechanosensitive transcription factor YAP1. Through this mechanism, epithelial responses become coupled to mechanotransduction pathways that stabilize the fibrogenic state (124). Additional transcriptional regulators further amplify this program. Twist1 cooperates with Prrx1 to induce tenascin-C expression, promoting fibroblast activation while disrupting tubular integrity and enhancing inflammatory cytokine production during renal fibrosis (125). Similarly, EGR1 reinforces TGF-β signaling by transcriptionally inducing PAR1, thereby increasing the expression of fibrosis-associated genes (126).

Renal fibrosis is not driven solely by intrinsic fibroblast programs but is sustained by reciprocal interactions between inflammatory and fibrogenic signaling pathways. In this context, inflammatory signaling cooperates with TGF-β to reinforce fibrogenesis. IRF-1 promotes renal fibrosis by suppressing the antifibrotic protein Klotho through the inactivation of C/EBP-β, thereby linking inflammatory signaling to persistent fibroblast activation (127). In parallel, SMAD3-dependent induction of Pou4f1 promotes macrophage-to-myofibroblast transition, providing a direct mechanistic link between chronic inflammation and progressive renal fibrosis (128).

As fibrosis advances, mechanical signals generated by ECM accumulation further reinforce these transcriptional programs. TGF-β1 and TNF-α induce the expression of the RhoA guanine nucleotide exchange factor GEF-H1, which forms a positive feedback loop with RhoA-MRTF-SRF signaling to sustain cytoskeletal remodeling (129). Downstream activation of the MRTF-SRF pathway promotes focal adhesion formation and remodeling of the extracellular microenvironment surrounding fibroblasts, thereby reinforcing persistent fibrogenic activation (130).

Despite these profibrotic pathways, several endogenous transcriptional regulators limit fibrosis through the inhibition of TGF-β signaling and inflammatory responses. KLF4 attenuates TGF-β1-induced inflammation by suppressing the expression of MIF and MCP-1 (131). KLF13 acts as a negative feedback regulator by suppressing collagen synthesis through SIN3A- and HDAC1-dependent epigenetic regulation downstream of TGF-β1 (132). Likewise, NR4A1 suppresses TGF-β signaling together with inflammatory activation, oxidative stress and mitochondrial dysfunction, thereby limiting renal fibrogenesis (133).

Ultimately, persistent renal fibrosis is stabilized through epigenetic mechanisms that establish transcriptional memory. ATF3 enhances SMAD3-dependent fibrogenic responses by maintaining H3K27 acetylation at fibrosis-associated loci while repressing SMAD7 through HDAC6-mediated loss of H3K14 acetylation (134,135). In parallel, MRTF-A promotes collagen transcription through the recruitment of p300 and histone-modifying enzymes, including H3K18/H3K27 acetyltransferases and H3K4 methyltransferases, thereby generating a permissive chromatin environment that sustains ECM production (136). Together, these mechanisms illustrate how TGF-β signaling, inflammatory inputs, mechanotransduction and epigenetic regulation converge to establish persistent transcriptional networks that drive renal fibrosis.

Skin fibrosis. Skin fibrosis primarily arises from the persistent activation of dermal fibroblasts driven by sustained TGF-β signaling, which is reinforced by coordinated inflammatory, mechanical and transcriptional networks. In systemic sclerosis (SSc) and pathological scarring, STAT3 serves as a central signaling hub that integrates TGF-β and inflammatory cytokine pathways. Increased STAT3 activation in dermal fibroblasts and immune cells promotes myofibroblast differentiation, ECM production and fibrotic gene expression, whereas pharmacological inhibition of STAT3 markedly attenuates dermal fibrosis (137,138).

Following cutaneous injury, TGF-β signaling acts as a central initiating pathway that drives fibroblast activation and establishes a persistent fibrogenic transcriptional state. Downstream of this signaling axis, multiple transcriptional regulators cooperate to amplify SMAD-dependent fibrogenic programs rather than acting independently. ATF3 enhances SMAD3 transcriptional activity through c-JUN-dependent mechanisms, while SOX11-induced periostin establishes a positive feedback loop that sustains TGF-β signaling. Additional regulators, including FOXM1, CRIF1, IRF3, miR-152-5p and AP-1 family members such as FOSL2, further reinforce collagen synthesis and fibroblast activation by converging on this fibrogenic transcriptional network (139-145).

As fibrotic remodeling progresses, mechanical and ECM-derived signals further stabilize these transcriptional programs. Matrix stiffening promotes MRTF-A nuclear translocation, inducing collagen and CTGF expression, while the expansion of injury-responsive PRRX1-positive fibroblast populations contributes to persistent wound-associated fibrotic remodeling (146,147). In parallel, ECM-associated regulators establish reinforcing interactions between matrix deposition and fibroblast activation. ZNF469 promotes collagen production and fibroblast activation in hypertrophic scars and keloids, whereas SFRP2, SPARC and RUNX2 enhance matrix synthesis through Wnt and PI3K/AKT signaling, further maintaining the activated fibroblast phenotype (148-151). Although these pathways promote fibrosis persistence, endogenous regulatory mechanisms can counteract excessive activation. KLF4 functions as an antifibrotic regulator by activating BMP4 transcription, suppressing fibroblast-to-myofibroblast transition, and limiting pathological ECM accumulation (152).

Beyond intrinsic fibroblast regulation, inflammatory signals from the surrounding tissue microenvironment further reinforce fibrogenic transcriptional networks. STAT1

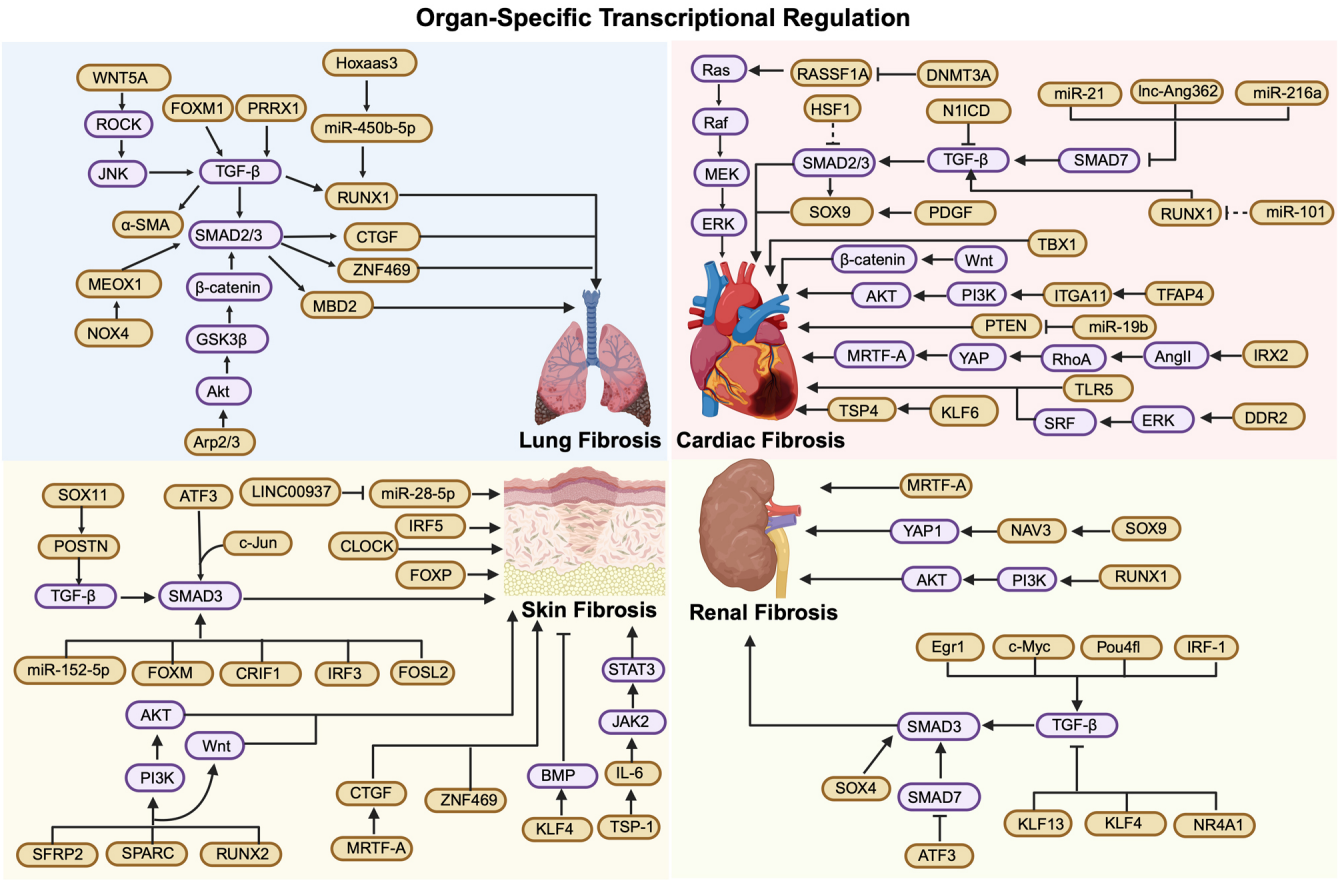

Figure 3. Organ-specific transcriptional regulation of fibrosis. This diagram summarizes the transcriptional and signaling networks regulating fibroblast activation and ECM remodeling across major fibrotic organs, including the lung, heart, skin, and kidney. Although fibrosis in these tissues is primarily centered on the TGF-β/SMAD signaling axis, additional pathways such as Wnt/β-catenin, PI3K/AKT, ERK, and mechanotransduction signaling (purple) interact with diverse transcription factors and noncoding RNAs (yellow) to modulate fibroblast proliferation, differentiation, and matrix production. Organ-specific regulators further integrate inflammatory signaling, developmental programs, and ECM sensing to shape tissue-specific fibrotic responses. Collectively, these interconnected networks illustrate how conserved profibrotic signaling frameworks are adapted by distinct transcriptional modules to drive fibrosis across different organs. ECM, extracellular matrix; miR, microRNA; TGF-β, transforming growth factor β; α-SMA, α-smooth muscle actin.

activation downstream of keratinocyte-derived EGFR ligands regulates fibrotic gene expression independently of interferon signaling, whereas IRF5 promotes immune-fibroblast communication and EMT. In keloids, thrombospondin-1 activates the IL-6/JAK2/STAT3 signaling pathway to amplify profibrotic transcription, while super-enhancer-associated regulators such as FOXP1 and CLOCK maintain proliferative and anti-senescent fibroblast states. Non-coding RNA-mediated regulation further contributes to this regulatory landscape, with LINC00937 limiting ECM accumulation through the sequestration of miR-28-5p (153-158).

Collectively, these studies demonstrate that fibrotic remodeling across organs is governed by a conserved hierarchical regulatory architecture centered on TGF-β/SMAD signaling, within which transcription factors cooperate with mechano-transductive pathways, inflammatory mediators, and epigenetic regulators to stabilize fibroblast activation and ECM accumulation, while tissue-specific developmental programs shape the unique transcriptional responses of individual organs. Rather than acting independently, numerous transcription factors converge on this common TGF-β/SMAD-centered regulatory axis, integrating inflammatory signaling, mechanotransduction and chromatin remodeling to coordinate myofibroblast differentiation, ECM synthesis and cellular plasticity (Fig. 3). Among these, SMAD3 emerges as the principal transcriptional hub, functioning cooperatively with conserved regulators, including RUNX1, SOX family members, ATF3, MRTF-A and YAP/TAZ-dependent transcriptional complexes. The recurrent involvement of ZNF469, RUNX1, SOX9, ATF3 and MRTF-A across multiple organs suggests that these factors constitute a core fibrogenic transcriptional network rather than organ-restricted regulators. Nevertheless, the biological output of these shared transcription factors remains highly context dependent, as their downstream target genes and interacting cofactors are determined by the tissue-specific chromatin landscape, cellular origin and local microenvironment. Consequently, the same transcription factors may govern distinct processes, including epithelial plasticity in the lung and kidney, cardiomyocyte-fibroblast communication in the heart, and dermal fibroblast activation in the skin. This context-dependent transcriptional organization likely explains why therapeutic modulation of broadly expressed transcription factors often produces heterogeneous outcomes across organs despite targeting common upstream signaling pathways. These findings highlight the importance of developing therapeutic strategies that target conserved transcriptional networks while accounting for the tissue-specific regulatory circuits that govern cell-type specificity and therapeutic response.

5. Transcriptional control of fibrosis resolution

The previous section discussed how transcriptional circuits and chromatin-based mechanisms mediated by transcriptional regulators drive fibrogenesis across the liver and other organs. By contrast, fibrosis resolution is now recognized as an active, highly regulated process involving coordinated cellular and molecular reprogramming. Although liver fibrosis was long considered an irreversible pathological process, substantial evidence now indicates that it can resolve following removal of the underlying etiological insult. Importantly, fibrosis resolution reflects a transition to a partially reversible transcriptional state rather than the full restoration of quiescence, suggesting that fibrogenic gene networks remain epigenetically primed for reactivation (40). Fibrosis resolution involves the coordinated suppression of inflammatory and profibrotic signaling pathways, leading to a reduction in activated HSCs and enhanced degradation of the ECM. This process is associated with increased production of MMPs by multiple hepatic cell types, including Kupffer cells, dendritic cells, HSCs and hepatocytes, which promote the degradation and remodeling of type I and type IV collagen, thereby facilitating tissue repair (8,159,160). Apoptosis of activated HSCs also represents a central mechanism driving fibrosis resolution. Activated HSCs express multiple death receptors, including FAS (CD95), tumor necrosis factor receptor 1, p75 neurotrophin receptor and TRAIL receptors, whose activation induces apoptotic signaling. By contrast, increased expression of anti-apoptotic mediators such as tissue inhibitor of metalloproteinase-1 (TIMP-1) and TGF-β promotes HSC survival and limits fibrosis resolution (6). TIMP-1 promotes activation of the NF-κB signaling pathway, leading to increased expression of anti-apoptotic genes, including BCL2, while suppressing pro-apoptotic mediators such as BAX, PUMA and p53. Consequently, activated HSCs become resistant to apoptosis, thereby sustaining fibrogenesis. Consistent with this mechanism, pharmacological inhibition of IκB kinase, a key upstream kinase in the NF-κB signaling cascade, together with inhibition of TIMPs, promotes apoptosis of activated HSCs and accelerates liver fibrosis resolution in mice (8). While TGF-β is widely recognized as a profibrotic cytokine, it has also been reported to induce MMP-9 and MMP-12 expression under specific conditions, thereby promoting ECM remodeling and potentially contributing to fibrosis resolution in a context-dependent manner (161).

During liver fibrosis resolution, fibroblast deactivation is orchestrated by a restricted set of lineage-defining transcription factors. PPARγ is a master regulator of HSC quiescence that is markedly suppressed during fibrogenic activation and partially re-expressed during fibrosis resolution, thereby contributing to the repression of ECM-associated genes and restoration of the quiescent HSC phenotype (162,163). Beyond its role in maintaining HSC quiescence, PPARγ exerts broad antifibrotic effects through multiple transcriptional mechanisms. PPARγ transcriptionally activates NRF2, a master regulator of antioxidant defense, together with its downstream target GPX4, thereby enhancing protection against lipid peroxidation and ferroptosis (164). Emerging evidence further indicates that PPARγ activation inhibits autophagy in activated HSCs through the suppression of transcription factor EB (TFEB), a master regulator of lysosomal biogenesis and autophagy. Treatment with the PPARγ agonist rosiglitazone suppresses TFEB activation, reduces autophagic activity, and attenuates liver fibrosis (165). Similarly, GATA6 has been implicated in regulating cellular plasticity during fibrosis resolution (162,163). In the liver, GATA6 directly binds to the NOS3 (eNOS) promoter to maintain LSEC differentiation and fenestration. During liver injury, activation of YAP suppresses GATA6 expression, resulting in reduced eNOS signaling, LSEC capillarization and progression of hepatic fibrosis. Conversely, restoration of GATA6 expression in endothelial cells attenuates LSEC capillarization and ameliorates liver fibrosis, highlighting the critical role of the YAP/GATA6/eNOS signaling axis in maintaining hepatic vascular homeostasis (166). VEGF further contributes to fibrosis resolution by restoring sinusoidal permeability through the NO/sGC/cGMP signaling pathway, thereby promoting LSEC de-capillarization. During fibrosis resolution, VEGF inhibition impairs sinusoidal permeability and reduces monocyte migration, adhesion and infiltration into the fibrotic liver. Consequently, VEGF neutralization and macrophage depletion decrease CXCL9 and MMP13 production by scar-associated macrophages, thereby limiting ECM remodeling and delaying fibrosis resolution (167). Incomplete resolution of liver fibrosis is characterized by downregulation of fibrogenic genes without re-expression of classical quiescent markers, including ADFP, ADIPOR1 and GFAP. As a result, reverted HSCs remain transcriptionally primed and retain the capacity for rapid reactivation upon subsequent fibrotic stimuli, thereby contributing to fibrosis recurrence (6).

In cardiac fibrosis, resolution predominantly occurs through apoptosis of activated cardiac fibroblasts. However, a subset of cardiac fibroblasts exhibits resistance to apoptosis and persists within the fibrotic scar (168). Transcription factors such as p53 also play an important role in regulating mesenchymal-to-endothelial transition (MEndT) during cardiac fibrosis resolution by directly binding to the promoter regions of endothelial-specific genes, including the endothelial transcription factors HOXA9 and HOXD3, which are essential for endothelial differentiation (169). Through promoting MEndT, p53 facilitates neovascularization while reducing the number of activated cardiac fibroblasts, thereby contributing to cardiac repair. However, p53 functions appear to be context dependent, as global p53 deletion attenuates pressure overload-induced cardiac fibrosis through increased HIF-1α and VEGF signaling, highlighting its cell type-specific roles in cardiac injury and repair (170).

Resolution of pulmonary fibrosis requires coordinated regulation of fibroblast plasticity and ECM turnover to facilitate the restoration of normal lung architecture following injury. The skeletal muscle differentiation regulator MyoD has been implicated in regulating fibroblast phenotype transitions during fibrosis. MyoD expression is increased during fibrotic progression, where it contributes to maintenance of the differentiated myofibroblast state, whereas its downregulation during fibrosis resolution promotes reversal of the myofibroblast phenotype (171). Mitogen-induced activation of ERK1/2 MAPK and CDK signaling pathways suppresses MyoD expression, facilitating reversal of the myofibroblast phenotype (171). In parallel, KLF4 promotes fibrosis resolution by suppressing fibroblast activation and restoring myofibroblast plasticity.

KLF4 enhances the antifibrotic effects of prostaglandin E2/cAMP signaling, leading to reduced fibroblast proliferation, ECM production, and differentiation while promoting apoptosis. Furthermore, KLF4 induces myofibroblast dedifferentiation and restores sensitivity to apoptotic signals such as Fas (172,173). KLF4 overexpression also suppresses HIF-1α signaling, inducing ER stress-mediated apoptosis and reducing pulmonary fibrosis (174). Additionally, KLF4 overexpression inhibits TGF-β1-induced EMT, thereby contributing to the attenuation of pulmonary fibrosis (175).

Similar to liver fibrosis resolution, the reversibility of renal fibrosis has been demonstrated in experimental models and is closely associated with the attenuation of TGF-β1-mediated profibrotic signaling. Restoration of signaling balance through antagonistic pathways, including bone morphogenetic protein-7 (BMP7), promotes fibrosis resolution by counteracting TGF-β-driven fibroblast activation. Modulation of BMP7 activity by the kidney-specific antagonist USAG-1 further highlights a potential organ-selective therapeutic strategy capable of improving renal function while minimizing systemic adverse effects (176). Despite these advances, the molecular and cellular mechanisms underlying renal fibrosis resolution remain to be fully elucidated.

By contrast, the mechanisms governing fibroblast deactivation during skin fibrosis remain incompletely elucidated. The transcriptional and microenvironmental signals driving the transition from persistent fibroblast activation to tissue restoration are still poorly defined, highlighting an important area for future investigation.

Collectively, studies of HSC inactivation provide a conceptual framework for understanding fibroblast plasticity across tissues. Apoptosis, phenotypic reversion, cellular senescence, and transcriptional reprogramming emerge as conserved mechanisms underlying fibrosis resolution. These findings suggest that therapeutic strategies aimed at reinforcing fibroblast deactivation programs, rather than exclusively inducing cell death, may offer more durable antifibrotic outcomes across multiple organs. Nevertheless, further investigation into fibroblast fate determination and transcriptional remodeling during fibrosis resolution in different tissues remains essential for advancing regenerative antifibrotic therapies.

6. Therapeutic targeting of transcription factors and their pathways

The findings discussed in the previous sections establish transcriptional regulation as a key determinant of both fibrogenesis and fibrosis resolution. Consequently, persistent activation of injury-responsive transcription factors stabilizes fibroblasts in a pathogenic myofibroblast state, underscoring that fibrosis is a fundamentally transcription-driven disorder. This section reviews emerging antifibrotic strategies that target the transcriptional networks sustaining pathogenic fibroblast activation across multiple organ systems (Table I).

Liver fibrosis. Therapeutic strategies for liver fibrosis increasingly reflect a multidimensional approach to suppress HSC activation, dampen inflammatory signaling, and correct metabolic dysfunction, particularly in the context of NASH-associated disease. Structural refinement of antifibrotic agents has led to the development of pirfenidone derivatives such as hydronidone, which reduce hepatotoxicity while preserving inhibition of TGF-β signaling. Hydronidone suppresses hydroxyproline production and promotes HSC apoptosis (177,178). Clinical studies in patients with chronic hepatitis B-related fibrosis have progressed to phase II trials, with phase III studies in preparation (179,180).

Targeting developmental and transcriptional pathways has also shown therapeutic promise. Modulation of the WNT/β-catenin signaling pathway with PRI-724 attenuates ECM deposition and hepatic inflammation in experimental models of acute liver injury. PRI-724 disrupts the interaction between β-catenin and CREB-binding protein (CBP), thereby shifting signaling away from CBP-dependent transcription associated with cellular proliferation and fibrogenesis and promoting fibrosis resolution (177,181). PRI-724 has also advanced to early clinical evaluation, with studies reported in Phase I/IIa trials (182). Similarly, inhibition of the Notch signaling pathway using γ-secretase inhibitors such as DAPT and avagacestat reduces HSC activation and TGF-β1 expression, further supporting the therapeutic potential of pathway-specific interventions (177,183).

Metabolic dysregulation represents a central driver of NASH-related fibrosis, and several therapeutic classes aim to restore metabolic homeostasis. Fibroblast growth factor (FGF) analogs, including pegozafermin, have demonstrated substantial metabolic and histological improvements in NASH, supporting the therapeutic potential of FGF21-based analogs for the treatment of metabolic liver disease and hepatic fibrosis in phase IIb clinical trials (184). Similarly, efruxifermin (Fc-FGF21) has demonstrated significant metabolic, anti-steatotic and antifibrotic benefits in individuals with NASH and is also being evaluated in phase IIb clinical trials (185-187). Aldafermin, an FGF19 analog, has demonstrated antifibrotic and metabolic benefits in patients with NASH in phase IIb clinical trials, highlighting the therapeutic potential of FGF19-based metabolic modulation for liver fibrosis and metabolic liver disease (188,189). In addition to FGF-based therapies, other metabolism-targeting approaches are under investigation. Tirzepatide, a dual GIP/GLP-1 receptor agonist, has been shown to promote fibrosis resolution without worsening fibrosis in phase II clinical trials and improves metabolic parameters such as body weight, glycemic control, and lipid profiles while reducing circulating biomarkers associated with liver injury, inflammation and fibrosis in patients with type 2 diabetes, suggesting that dual incretin receptor activation may alleviate NASH-related pathophysiology by improving metabolic regulation and reducing hepatic stress (190).

Complementing these strategies, PPAR agonists such as elafibranor, targeting PPARα and PPARδ; saroglitazar, targeting PPARα and PPARγ; and lanifibranor, targeting PPARα, PPARγ and PPARδ, have demonstrated beneficial effects by improving steatosis, reducing inflammation, and alleviating fibrosis-associated biomarkers (178). Among these agents, lanifibranor has been evaluated in phase IIb clinical trials in patients with NASH and has demonstrated improvements in cardiometabolic parameters together with histological improvement of fibrosis (191,192). Elafibranor improves key metabolic pathways implicated in NASH, including lipid metabolism, insulin sensitivity and inflammatory signaling.

Table I. Therapeutic strategies targeting transcription factor-associated signaling networks in organ fibrosis. The table summarizes key agents, their molecular targets, effects on transcriptional and signaling pathways regulating fibroblast activation and ECM deposition, and their stages of clinical development.

Authors, year	Organ	Drug/agent	Target	Transcriptional/signaling effect	Clinical trial status	(Refs.)
Di *et al*, 2025; Zhao *et al*, 2022; Cai *et al*, 2023; Cai *et al*, 2025	Liver	Hydronidone	TGF-β	Inhibits SMAD-driven collagen transcription	Phase II (phase III in preparation)	(177-180)
Di *et al*, 2025; Osawa *et al*, 2015; Kimura *et al*, 2022		PRI-724	WNT/β-catenin/CBP	Inhibits β-catenin-CBP interaction and profibrotic transcription	Phase I, Phase IIa	(177,181,182)
Di *et al*, 2025; Bansal *et al*, 2015		DAPT/ Avagacestat	γ-secretase	Inhibits TGF-β and NOTCH signaling pathways	Preclinical	(177,183)
Harrison *et al*, 2022; Harrison *et al*, 2021		Aldafermin	FGF19	Suppresses bile acid synthesis and maintains metabolic homeostasis	Phase IIb	(188,189)
Hartman *et al*, 2020		Tirzepatide	GIP/GLP-1	Improves metabolic regulation and reduces hepatic injury and stress	Phase II	(190)
Ratziu *et al*, 2016		Elafibranor	PPARα/δ	Activates PPARα/δ and regulates metabolic and inflammatory pathways	Phase II	(193)
Gawrieh *et al*, 2021		Saroglitazar	PPARα/γ	Improves lipid metabolism and reduces lipotoxicity	Phase II	(194)
Francque *et al*, 2021; Cooreman *et al*, 2024		Lanifibranor	PPARα/γ/δ	Activates pan-PPAR and improves metabolic, cardiometabolic, and antifibrotic signaling	Phase IIb	(191,192)
Richeldi *et al*, 2022; Kato *et al*, 2021	Lung	Nintedanib	FGFRs, VEGFRs, and PDGFRs	Reduces collagen deposition and inflammatory chemokines	Phase III	(195,196)
King Talmadge *et al*, 2014; Ruwanpura *et al*, 2020; Torre *et al*, 2024		Pirfenidone	TGF-β, PDGF, matrix metallo-proteinases	Inhibits fibroblast proliferation, collagen synthesis, and inflammatory cytokine production	Phase III	(197-199)
Raghu *et al*, 2022		BG00011	$\alpha_v\beta_6$	Blocks mechano-transductive release of latent TGF-β	Phase IIa	(202)
Maden *et al*, 2018		GSK3008348	$\alpha_v\beta_6$	Blocks mechano-transductive release of latent TGF-β	Phase I	(203)
Wuyts *et al*, 2026		Bexotegrast	$\alpha_v\beta_6/\alpha_v\beta_1$	Blocks mechano-transductive release of latent TGF-β	Phase IIb/III	(204)
Mercer *et al*, 2016; Lukey *et al*, 2019		Omipalisib (GSK2126458)	PI3K/mTOR	Suppresses fibroblast proliferation and TGF-β-induced collagen synthesis	Phase I	(205,206)
Herrmann *et al*, 2022; Richeldi *et al*, 2022		BI 1015550	PDE4B	Enhances cAMP signaling with anti-inflammatory and antifibrotic effects	Phase II	(207,208)

Table I. Continued.

Authors, year	Organ	Drug/agent	Target	Transcriptional/signaling effect	Clinical trial status	(Refs.)
Di *et al*, 2025		SRN-001	Amphiregulin	Reduces fibroblast proliferation and myofibroblast differentiation	Phase I	(177)
Chioccioli *et al*, 2022		MRG-229	microRNA-29	Downregulates profibrotic gene expression	Preclinical	(209)
Zhang *et al*, 2023		AAV9-Tspyl2	CDA1	Suppresses TGF-β1/Smad3 signaling and collagen deposition	Preclinical	(210)
Yi *et al*, 2021; Sun *et al*, 2022; El-Damanawi *et al*, 2024	Kidney	Metformin	TGF-β, AMPK	Decreases ECM deposition and myofibroblast activation	Preclinical + clinical	(211-213)
Zhou *et al*, 2018		XL-001	CB2R	Abolishes TGF-β1-triggered fibrogenic response and reduces collagen I expression and cytokine production	Preclinical	(214)
Biju *et al*, 2025; Galal *et al*, 2025		Pentoxifylline	TNF-α, NF-κB	Suppresses proinflammatory cytokines and NF-κB signaling	Phase III	(217,218)
Park *et al*, 2022; Vincenti *et al*, 2017		Fresolimumab	TGF-β1, TGF-β2, TGF-β3	Neutralizes TGF-β signaling, reduces collagen deposition, and reduces tubular apoptosis	Phase II	(215,216)
Chen *et al*, 2024; Amrute *et al*, 2025	Heart	Ro5-3335	RUNX1	Reduces collagen deposition and inflammatory gene expression	Preclinical	(223,224)
Mu *et al*, 2025; Zhou *et al*, 2026		Berberine	TGF-β, Smad2, Smad3	Reduces vascular inflammation and cardiomyocyte stiffness while enhancing antioxidant capacity	Preclinical	(225,226)
Liu *et al*, 2017; Li *et al*, 2023		Naringenin	CDK4/6, CDK2, AMPK, NOX2, MAPK	Inhibits collagen synthesis, induces cell cycle arrest, and reduces oxidative stress	Preclinical	(227,228)
Xu *et al*, 2025; McMurray *et al*, 2019		Dapagliflozin	Sodium-glucose cotransporter 2	Inhibits Wnt/β-catenin-driven fibrosis and ECM production	Phase III	(229,230)
Abraham *et al*, 2024; Baird *et al*, 2015	Skin	Imatinib	PDGFR, c-Abl	Reduces fibroblast activation and collagen production	Phase II	(233,234)
Rodríguez-Castellanos *et al*, 2014		Pirfenidone	TGF-β, PDGFs	Suppresses profibrotic signaling, inflammation, and ECM accumulation	Phase II	(237)
Huang *et al*, 2016; Distler *et al*, 2019		Nintedanib	TGF-β, FGFRs, VEGFRs, PDGFRs	Inhibits fibroblast activation and prevents skin fibrosis	Phase III	(235,238)

Table I. Continued.

Aauthors, year	Organ	Drug/agent	Target	Transcriptional/signaling effect	Clinical trial status	(Refs.)
Hou *et al*, 2022		Baricitinib	JAK1/2	Alleviates skin thickening and digital ulcers	Phase I/II	(241)
Khanna *et al*, 2022		Tofacitinib	JAK1/2, IFNs	Suppresses interferon-related gene expression	Phase I/II	(242)
Wang *et al*, 2025		Lapatinib	EGFR/ human epidermal growth factor receptor 2	Inhibits TGF-β signaling and fibroblast activation	Preclinical	(243)

PPAR, peroxisome proliferator-activated receptor; ECM, extracellular matrix; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; TGF-β, transforming growth factor-β; FGF, fibroblast growth factor; FGFR, FGF receptor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

In phase II clinical trials, elafibranor treatment led to the resolution of NASH without worsening fibrosis, particularly at higher doses, while also reducing markers of liver injury and systemic inflammation (193). Saroglitazar also improved lipoprotein particle composition and size, reduced lipotoxic lipid species, and decreased liver fat content in a Phase II clinical trial (194).

Collectively, these therapeutic advances reflect a paradigm shift from single-pathway inhibition to the integrated modulation of signaling, metabolic and transcriptional networks that sustain hepatic fibrogenesis.

Lung fibrosis. Therapeutic strategies for lung fibrosis increasingly reflect a multidimensional approach to suppress fibroblast activation, attenuate inflammation, and restore tissue homeostasis. Recently, antifibrotic therapies such as nintedanib and pirfenidone have been approved and have been shown to slow disease progression. Nintedanib is a tyrosine kinase inhibitor (TKI) that targets FGF receptors, VEGF receptors and PDGF receptors (PDGFRs). It suppresses growth factor-driven profibrotic signaling, which leads to reduced collagen deposition, inflammatory chemokine production and fibrosis progression (178). Phase III clinical trials demonstrated that nintedanib effectively slows disease progression in IPF, leading to its clinical approval for the treatment of IPF (195). Open-label extension studies further confirmed that nintedanib continues to reduce the rate of disease progression and the incidence of acute exacerbations in patients with IPF (196). Pirfenidone has been approved for the treatment of IPF since 2014 after the completion of a phase III clinical trial (197). Pirfenidone exerts antifibrotic effects primarily by inhibiting the TGF-β and PDGF signaling pathways, promoting MMP2 and MMP9 activity, suppressing fibroblast proliferation, and reducing type I and type III collagen synthesis (198). In addition, pirfenidone has anti-inflammatory effects by decreasing the secretion of proinflammatory cytokines, including TNF-a and IL-6 (199). Moreover, studies investigating the combined use of nintedanib and pirfenidone have demonstrated therapeutic potential in IPF without increasing the risk of serious adverse events compared with monotherapy (200,201).

Building upon these foundations, emerging therapeutic strategies increasingly target upstream drivers of fibroblast activation and matrix remodeling. Inhibition of TGF-β activation through integrin $\alpha_v\beta_6$ blockade, using agents such as BG00011, GSK3008348 and bexotegrast, aims to disrupt the mechano-transductive release of latent TGF-β and is currently being evaluated in clinical trials (202-204). Parallel therapeutic strategies also target additional profibrotic pathways. Omipalisib (GSK2126458), a PI3K/mTOR inhibitor, suppresses fibroblast proliferation and TGF-β-induced collagen synthesis in primary human lung fibroblasts and IPF-derived lung tissue. In early-phase clinical studies, omipalisib demonstrated dose-dependent inhibition of PI3K/mTOR signaling in both the systemic circulation and the lungs of patients, along with reduced aberrant glucose signaling in fibrotic regions of the lungs in IPF (205,206). BI 1015550 is a selective PDE4B inhibitor that exerts anti-inflammatory and antifibrotic effects by enhancing cAMP signaling. *In vivo*, orally administered BI 1015550 demonstrated efficacy in established mouse models of lung fibrosis, including bleomycin- and silica-induced models,

by modulating model-specific fibrotic parameters. *In vitro* studies using human fibroblasts from patients with IPF showed that BI 1015550 inhibited TGF-β-induced myofibroblast differentiation and suppressed fibroblast proliferation (207). In clinical trials, treatment with BI 1015550, either as monotherapy or in combination with background antifibrotic therapy, prevented the decline in lung function in patients with IPF (208).

Finally, RNA-based strategies provide precise approaches to modulate fibrotic signaling networks. SRN-001 is a novel small interfering RNA (siRNA) therapeutic that targets amphiregulin, a growth factor involved in fibroblast proliferation and myofibroblast differentiation. It uses Self-Assembled Micelle inhibitory RNA technology and is currently under investigation in phase I clinical trials (177). MRG-229 is a next-generation miR-29 mimic with enhanced stability and delivery potential that suppresses TGF-β-induced fibrosis by downregulating profibrotic targets. It has demonstrated antifibrotic efficacy in both *in vitro* and bleomycin-induced *in vivo* models, along with a favorable safety profile across multiple species. Notably, reduced circulating miR-29 levels are associated with poorer survival in patients with IPF, highlighting its potential as both a therapeutic target and a biomarker (209).

Although gene therapy approaches show considerable promise for the treatment of lung fibrosis, further investigation is required to support their clinical translation. For example, AAV9-Tspyl2 gene therapy targets cell division autoantigen-1 (CDA1), a key regulator of TGF-β signaling, DNA damage repair, cell proliferation and gene expression. *In vivo*, AAV9-Tspyl2-mediated CDA1 overexpression significantly attenuated weight loss following bleomycin-induced injury, reduced collagen deposition, and decreased TGF-β1 and phosphorylated Smad3 levels (210).

Renal fibrosis. In renal fibrosis, therapeutic strategies increasingly converge on suppressing TGF-β-driven signaling, inflammatory cascades, and fibroblast activation while also incorporating emerging regenerative approaches.

Metabolic and renin-angiotensin-aldosterone system-related therapies further contribute to antifibrotic control. Metformin suppresses TGF-β signaling through activation of AMP-activated protein kinase (AMPK), thereby reducing ECM synthesis and myofibroblast activation. Consistent with this mechanism, metformin attenuates adenine-induced renal fibrosis in preclinical models (211). Advances in drug delivery have further enhanced its therapeutic potential. Metformin-grafted chitosan improves renal accumulation and prolongs drug retention in unilateral ureteral obstruction (UUO) models, leading to reduced apoptosis and inflammation with minimal toxicity (212). Clinically, metformin use has been associated with a lower risk of kidney failure, reduced all-cause mortality, and fewer cardiovascular events, although its long-term effects on kidney function remain to be fully defined (213).

In parallel, targeting the endocannabinoid system offers an additional antifibrotic strategy. The CB2R inverse agonist XL-001 mitigates renal inflammation and fibrosis by reducing macrophage infiltration and cytokine production while suppressing TGF-β1-driven fibrogenic responses. In UUO models, XL-001 reduces fibrotic lesions, type I collagen and fibronectin expression, α-SMA expression and tubular injury (214).

Although several therapies indirectly suppress TGF-β signaling, direct neutralization of TGF-β has also emerged as a promising antifibrotic strategy. Fresolimumab, a human monoclonal antibody that neutralizes TGF-β1, TGF-β2 and TGF-β3, reduces TGF-β activity and type III collagen deposition while alleviating tubular apoptosis (215). In a phase II clinical study of primary focal segmental glomerulosclerosis, fresolimumab-treated patients demonstrated a trend toward improved preservation of renal function compared with those receiving placebo (216).

Anti-inflammatory approaches also play an important role. Pentoxifylline inhibits proinflammatory mediators such as TNF-α and interleukins, and suppresses NF-κB signaling (217). In randomized controlled trials involving patients with CKD, pentoxifylline improved renal function and reduced fatigue, a common clinical symptom (218).

Finally, regenerative and cell-based therapies, particularly those utilizing mesenchymal stem cells (MSCs) and extracellular vesicles (EVs), have emerged as promising strategies for limiting renal fibrosis by simultaneously targeting multiple profibrotic signaling pathways. One of the principal mechanisms involves suppression of TGF-β/SMAD signaling. Bone marrow-derived MSCs (BMSCs) delayed the progression of diabetic nephropathy-associated renal fibrosis *in vivo* by reducing TGF-β/SMAD3 signaling, accompanied by decreased expression of the ECM regulator plasminogen activator inhibitor-1, thereby attenuating glomerular and tubular matrix accumulation (219). Similarly, MSCs have been engineered as delivery vehicles for antifibrotic miRs. In a UUO mouse model, MSCs overexpressing miR-let-7c delivered the miR through exosomes, resulting in suppression of TGF-β1-mediated signaling and attenuation of renal injury (220). Beyond direct inhibition of TGF-β signaling, MSC-derived therapies also alleviate renal fibrosis by suppressing inflammatory pathways. In a UUO-induced CKD rat model, conditioned medium from human umbilical cord MSCs inhibited TLR4-mediated activation of the NF-κB pathway, thereby reducing inflammation, EMT and renal fibrosis (221). Likewise, BMSC-derived EVs enriched with miR-181d, which is abundantly expressed in healthy kidneys, attenuated renal fibrosis in UUO rats by directly targeting KLF6, leading to inhibition of the NF-κB signaling pathway and a subsequent reduction of fibrosis (222).

Cardiac fibrosis. In cardiac fibrosis, therapeutic strategies encompass neurohormonal blockade, transcriptional modulation, metabolic regulation, inflammasome inhibition and vesicle-based interventions. Inhibition of RUNX1 by Ro5-3335 has been shown to improve cardiac contractile function following myocardial infarction, potentially by reducing cathepsin levels associated with cell death pathways in a rat model (223). Ro5-3335 also reduced dense collagen scar formation and infarct size in ischemia-reperfusion models of heart failure while decreasing inflammatory gene expression in macrophages (224).

Natural compounds further contribute to antifibrotic regulation. Berberine, a bioactive isoquinoline alkaloid derived from *Coptis chinensis*, alleviates myocardial fibrosis by disrupting TGF-β, Smad2 and Smad3 signaling while reducing

myocardial and microvascular inflammation and cardiomyocyte stiffness in a high-fat, high-sucrose rat model (225). In angiotensin II-induced cardiac fibrosis models, berberine also inhibited atrial structural remodeling and cardiac dysfunction, enhanced antioxidant capacity, and reduced NLRP3 inflammasome activation (226). Naringenin, a flavonoid abundant in citrus plants, inhibits fibroblast proliferation and collagen synthesis, induces cell cycle arrest at the G0/G1 phase, and limits progression into the S phase through modulation of cyclin D1-CDK4/6 and cyclin E2-CDK2 complexes in preclinical studies (227). In addition, naringenin attenuated isoproterenol-induced cardiomyocyte hypertrophy by reducing oxidative stress through modulation of AMPK, NOX2 and MAPK signaling (228).

Metabolic therapies also play an important role. Sodium-glucose cotransporter 2 inhibitors such as dapagliflozin exert antifibrotic effects by reducing type I and III collagen secretion and downregulating α-SMA expression through inhibition of Wnt β-catenin signaling. In cardiomyocytes, dapagliflozin reduces oxidative stress and apoptosis while mitigating inflammation by decreasing proinflammatory cytokines, including IL-6, IL-1β and TNF-α, and increasing IL-10 levels in preclinical models (229). In a phase III clinical trial involving patients with heart failure following myocardial infarction, dapagliflozin reduced the risk of worsening heart failure (230).

Complementing these approaches, EV-based strategies represent a promising regenerative frontier. EVs derived from induced pluripotent stem cells (iPSCs) reduce aging-related arterial stiffness and hypertension while improving endothelium-dependent vascular relaxation and arterial compliance in aged mouse models. These effects are accompanied by attenuation of elastin degradation and type I collagen deposition, leading to improved vascular remodeling (231). EVs secreted from human iPSC-derived cardiovascular progenitor cells also exert cardioprotective effects on the infarcted heart through lncRNA-related mechanisms. Injection of human iPSC-derived cardiovascular progenitor cell-derived EVs into acutely infarcted murine myocardium significantly improved cardiac function and reduced fibrosis at 28 days after myocardial infarction, accompanied by improved vascularization and enhanced cardiomyocyte survival at border regions (232). Further development of these transcriptionally targeted strategies requires continued evaluation of their safety and efficacy in clinical settings.

Skin fibrosis. In keloid and SSc, therapeutic innovation has progressively shifted toward molecularly targeted strategies aimed at disrupting the interconnected signaling networks that sustain fibroblast activation and pathological ECM deposition. Rather than relying solely on broad immunosuppression, current approaches seek to precisely interfere with the molecular drivers of fibrosis.

Among these strategies, TKIs have demonstrated significant antifibrotic potential. Imatinib inhibits tyrosine kinases such as PDGFR and c-Abl, thereby suppressing fibroblast activation and collagen production (233). In an open-label pilot phase II clinical trial involving patients with sclerotic-type chronic graft vs. host disease with dermal fibrosis manifestations, imatinib treatment improved skin softening and reduced hyperpigmentation (234).

Broader-spectrum agents such as pirfenidone and nintedanib target multiple profibrotic pathways, including TGF-β and PDGFs, thereby contributing to reductions in skin thickening and matrix accumulation (235,236). Topical pirfenidone gel, evaluated in a phase II clinical study involving patients with scleroderma, demonstrated improvements in histological and clinical features of dermal infiltration and fibrosis (237). In preclinical models of SSc, nintedanib inhibited fibroblast activation and prevented skin fibrosis in both bleomycin-induced and chronic graft-vs.-host disease models (235). Furthermore, in a phase III clinical trial in patients with SSc, nintedanib treatment improved the modified Rodnan skin score, a measure of skin sclerosis (238).

Emerging immunomodulatory therapies further expand this therapeutic landscape. The JAK1/2 inhibitors baricitinib and tofacitinib attenuate proinflammatory and profibrotic cytokine signaling in murine models of SSc (239,240). In a single-center, open-label clinical study, baricitinib alleviated skin thickening and promoted healing of digital ulcers in patients with SSc (241). In a phase I/II clinical study involving patients with diffuse cutaneous SSc, tofacitinib improved skin scores and modulated gene expression associated with fibroblast activation while suppressing interferon-regulated genes implicated in disease progression (242).

Receptor-level interventions have also shown promise. Lapatinib, a dual EGFR and human epidermal growth factor receptor 2 inhibitor, attenuates skin fibrosis by disrupting TGF-β signaling in bleomycin-induced mouse models and reduces the proliferation and activation of keloid xenografts in humanized animal models (243).

Across different fibrotic organs, therapeutic interventions largely converge on disrupting the signaling pathways and transcription factors that drive fibroblast activation and ECM accumulation. Among these, the TGF-β signaling pathway remains the most frequently targeted, reflecting its central role as a conserved mediator of fibrosis across multiple organs. Accordingly, numerous antifibrotic agents have been developed to inhibit TGF-β signaling either directly or indirectly. Notably, some approved antifibrotic drugs demonstrate efficacy in more than one fibrotic disease. For example, pirfenidone and nintedanib, which were initially developed for pulmonary fibrosis, have also shown antifibrotic potential in skin fibrosis. These findings suggest that targeting shared fibrotic mechanisms across organs may facilitate drug repurposing and broaden the therapeutic applications of existing antifibrotic agents. Further investigation into the cross-organ efficacy of current antifibrotic therapies may expand treatment options and improve clinical outcomes for patients with diverse fibrotic diseases.

Finally, advances in localized molecular delivery systems represent a promising frontier for targeting intracellular regulators of fibrosis, particularly transcription factors, which have been considered challenging therapeutic targets because of their intracellular localization and the lack of well-defined drug-binding pockets (244). Precision nano-delivery platforms, including liposomes, lipid nanoparticles, engineered exosomes and other EV-based carriers, offer opportunities to selectively deliver therapeutic cargos such as small molecules, mRNAs, miRs, siRNAs and gene-editing components directly to fibrotic tissues. Although these platforms have demonstrated encouraging preclinical efficacy, further optimization

is required to improve tissue specificity, cellular uptake, therapeutic stability and biosafety. Future delivery systems should therefore be designed to accommodate the unique cellular composition and microenvironment of each fibrotic organ, thereby maximizing therapeutic efficacy while minimizing off-target effects (245). In parallel, emerging drug discovery platforms are expected to accelerate the development of next-generation antifibrotic therapies. Patient-derived iPSCs differentiated into disease-relevant cell types provide valuable models for investigating disease mechanisms, evaluating drug responses, and enabling personalized drug screening. Complementing these experimental platforms, advances in artificial intelligence (AI)-driven drug discovery, including virtual screening, *de novo* molecular design, and predictive modeling, are transforming the identification and optimization of novel therapeutic compounds (246). The convergence of targeted molecular delivery platforms, patient-specific disease models, and AI-assisted drug discovery is expected to facilitate the precise modulation of fibrosis-associated transcriptional networks, accelerating the development of next-generation antifibrotic therapies with improved efficacy, safety, and translational potential across multiple fibrotic diseases.

7. Future directions

Direct targeting of transcription factors in fibrosis represents a promising therapeutic strategy, as it may more effectively suppress fibrotic programs than approaches targeting upstream signaling pathways. However, this strategy remains constrained by limited druggability, compensatory signaling networks, and challenges in achieving precise, tissue-specific delivery, particularly for RNA- and gene-editing-based approaches. These limitations highlight the need to move beyond single-factor inhibition toward coordinated, network-level modulation of pathogenic transcriptional programs and underscore the importance of developing next-generation drug design strategies that improve the specificity and tractability of transcription factor-targeted therapies.

Future progress will depend on a deeper understanding of fibroblast plasticity, pathway crosstalk and microenvironmental influences, alongside a clearer delineation of the transcriptional networks that drive fibrosis. Continued advances in single-cell and spatial transcriptomics will further refine the understanding of fibroblast heterogeneity and regulatory circuitry, enabling precise identification of cell populations responsible for fibrotic progression. Coupled with improved experimental models that more faithfully recapitulate human disease, these insights will be essential for translating mechanistic understanding into effective therapies. Ultimately, these efforts will support the development of more precise, durable, and potentially reversible antifibrotic strategies centered on transcriptional identity and fibroblast fate.

8. Conclusion

Fibrosis is a complex and multifactorial process characterized by sustained fibroblast activation, excessive ECM accumulation, and progressive tissue remodeling. Transcription factors have emerged as central regulatory hubs that integrate signaling pathways, epigenetic regulation and microenvironmental cues to control fibroblast activation and phenotypic plasticity. Accordingly, coordinated transcriptional networks play a critical role in maintaining profibrotic programs across different tissues and disease stages.

The present review summarizes the current understanding of transcription factor-driven regulation of fibroblast activation and matrix remodeling across liver and other fibrotic organs while highlighting emerging therapeutic strategies targeting transcriptional regulators in fibrotic diseases. Nevertheless, the complexity of transcriptional regulation in fibrosis underscores the need for continued investigation and integrative approaches that bridge mechanistic insights with translational applications. A deeper understanding of transcription factor dynamics and regulatory networks will be essential for advancing precision antifibrotic therapies and improving clinical outcomes across fibrotic diseases.

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Authors' contributions

CA and DC contributed to the conception and design of the review. DC drafted the manuscript. CA and DC revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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