Contribution of p38 MAPK in liver fibrosis: An overview of mechanisms, signaling pathways, and therapeutic targets (Review)

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Abstract. Liver fibrosis is a progressive pathological state characterized by aberrant accumulation of extracellular matrix (ECM), predominantly mediated by activation of hepatic stellate cells (HSCs). If left untreated, this condition can progress to cirrhosis, liver failure, and even hepatocellular carcinoma. As a pivotal constituent of the mitogen-activated protein kinase (MAPK) superfamily, p38 MAPK orchestrates critical cellular processes, including proliferation, differentiation, and stress responses. The p38 MAPK signaling cascade has been identified as a central orchestrator of the pathogenic mechanisms underlying liver fibrosis, mediating key processes such as HSC activation, ECM remodeling, inflammation, oxidative stress, and apoptosis. Developing novel antifibrotic therapies hinges on a comprehensive elucidation of the functional roles and regulatory mechanisms governing p38 MAPK. The present review aims to provide an exhaustive synthesis of the mechanisms and signaling networks by which p38 MAPK contributes to liver fibrogenesis. Its roles in HSC transformation, interactions with other critical pathways (including NF-κB, TGF-β/Smad, JAK/STAT, and PI3K/Akt), and involvement in inflammatory and oxidative responses are explored. Furthermore, the therapeutic potential of targeting p38 MAPK is highlighted by preclinical evidence from pharmacological inhibitors, natural compounds, and traditional medicines that modulate this pathway to attenuate fibrosis. In conclusion, while p38 MAPK represents a promising therapeutic target for liver fibrosis, future research should focus on developing isoform-specific inhibitors, understanding context-dependent signaling outcomes, and designing combination therapies to enhance efficacy and minimize off-target effects. This synthesis aims to bridge current molecular insights with clinical translation, offering a roadmap for future antifibrotic drug development.

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Abbreviations: AMPK, adenosine 5'-monophosphate-activated protein kinase; BMP-7, bone morphogenetic protein-7; CCl_4, carbon tetrachloride; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; ERK, extracellular signal-regulated kinase; HSCs, hepatic stellate cells; IL-, interleukin; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; MAFLD, metabolic dysfunction-associated fatty liver disease; MET, mesenchymal-to-epithelial transition; MKK3/6, MAPK kinase 3/6; MMPs, matrix metalloproteinases; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor-κB; p38 MAPK, p38 mitogen-activated protein kinase; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; ROS, reactive oxygen species; Smad, mothers against decapentaplegic homolog; α-SMA, α-smooth muscle actin; STAT, signal transducer and activator of transcription; TGF-β, transforming growth factor-β; TNF, tumor necrosis factor; YAP, yes-associated protein

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Key words: p38 MAPK, liver fibrosis, HSCs, ECM, signaling pathways, therapeutic targets, mechanisms

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1. Introduction

Liver fibrosis is a progressive pathological state characterized by the aberrant deposition of extracellular matrix (ECM) constituents, primarily collagen. This process causes structural damage and impairs liver function, ultimately progressing toward cirrhosis and subsequent liver failure, even hepatocellular carcinoma if left unchecked (1). Liver fibrosis

develops from prolonged liver damage, which can result from a range of causes, including viral hepatitis, excessive alcohol consumption, metabolic dysfunction-associated fatty liver disease (MAFLD), as well as other medical conditions. These chronic liver diseases account for ~2 million deaths annually, representing 4% of all deaths worldwide, and were the 12th leading cause of mortality globally in 2021, responsible for 2.3 million deaths (2,3). Liver fibrosis is a major clinical concern because it substantially contributes to global morbidity and mortality (4). There is a need to identify the molecular mechanisms and essential signaling pathways underlying liver fibrosis to develop more specific treatments that can halt and potentially even reverse it. Among the numerous signaling pathways governing this biological process, the p38 mitogen-activated protein kinase (MAPK) pathway has been identified as a pivotal component (5). The present review examines p38 MAPK functions in liver fibrosis by comprehensively evaluating its molecular mechanisms, pathway interactions, and therapeutic potential.

The p38 MAPK pathway is a critical signaling cascade that orchestrates a wide array of fundamental cellular events (6). The process begins when cells face various stressors, including elevated levels of growth factors and pro-inflammatory cytokines, as well as oxidative and mechanical stressors (7). Stimulation of p38 MAPK results in the phosphorylation of essential cellular effectors that control vital cellular processes, including inflammation, apoptosis, and fibrogenesis (8-10).

p38 MAPK is a multifunctional enzyme that contributes to the development of liver fibrosis by driving hepatic stellate cell (HSC) activation, inflammatory cytokine production, oxidative stress responses, apoptosis, and the regulation of fibrosis-related gene expression and profibrotic cytokine production, thereby leading to increased fibrotic damage (11-20). These mechanisms, along with its complex crosstalk with other signaling pathways, are detailed in a later section.

The therapeutic potential of modulation of p38 MAPK activity has become evident in the treatment of liver fibrosis. Studies have shown that p38 MAPK inhibitors hold promise for fibrosis treatment by inhibiting HSC activation and reducing fibrogenic cytokine production and collagen accumulation, resulting in improved liver function in animal models of liver fibrosis (12,14). Research using SB203580, a selective p38 MAPK inhibitor, showed encouraging preclinical results in liver fibrosis by decreasing HSC activation and collagen accumulation (21). Wu *et al* (22) showed that a traditional Chinese medicine worked as an antifibrotic agent through its ability to block the p38 MAPK signaling pathway. These findings highlight the role of the pathway in driving fibrogenesis and necessitate further exploration of p38 MAPK inhibitors and related compounds for clinical applications. A comprehensive overview of these pathological mechanisms, illustrating how diverse liver insults converge on p38 MAPK to drive HSC activation and ECM deposition, while also highlighting potential therapeutic intervention points, is provided in Fig. 1.

The development of specific treatments for liver fibrosis requires a complete grasp of p38 MAPK functions, including HSC activation, ECM remodeling, and its interactions with inflammatory and oxidative pathways. The present review provides an overview of p38 MAPK mechanisms that drive fibrogenesis, examines their relationships with essential signaling pathways, and assesses current treatment options using specific inhibitors and natural compounds.

2. Biological characteristics of p38 MAPK

p38 MAPK constitutes a pivotal component within the MAPK superfamily. The p38 MAPK signaling pathway exhibits notable responsiveness to a multitude of stressors, including growth factors, lineage specification to programmed cell death, environmental stressors, and pro-inflammatory cytokines, thereby establishing itself as a pivotal component of the cellular stress response. This pathway orchestrates the phosphorylation of downstream effectors, which in turn modulate gene expression and a range of cellular activities. The p38 MAPK signaling cascade holds substantial pathological relevance across a diverse spectrum of disease states, such as liver fibrosis, malignancies, cardiovascular disorders, and neurodegenerative diseases.

The biological functions attributed to p38 MAPK are multifaceted and largely context-dependent. A principal role of p38 MAPK involves the modulation of inflammatory reactions (23,24). Empirical research has demonstrated that p38 MAPK is activated in response to inflammatory signals, contributing to the upsurge in these cytokines and thereby amplifying the inflammatory cascade. Notably, inhibition of p38 MAPK signaling has been associated with reduced inflammation and improved outcomes in various experimental models of inflammatory diseases (25).

Beyond its role in inflammation, p38 MAPK also critically regulates cellular homeostasis through modulation of cell cycle progression, apoptosis, and the differentiation of diverse cell types, including myoblasts, chondrocytes, and stem cells (26). It is also pivotal in mediating cellular responses to diverse stressors, including oxidative damage, ultraviolet (UV) radiation, and hyperosmotic stress. Upon activation, p38 MAPK modulates the expression of antioxidant enzymes and finely balances survival vs. apoptotic signals, thereby facilitating cellular adaptation (27-29).

The involvement of p38 MAPK in apoptosis is particularly noteworthy. It can promote apoptosis through several mechanisms, including the activation of pro-apoptotic factors and the suppression of anti-apoptotic proteins. At the same time, in other contexts, it may promote cell survival by activating protective signaling pathways, highlighting its context-dependent functions (30).

The signaling dynamics of p38 MAPK are complex, with multiple feedback mechanisms and crosstalk with other signal transduction pathways, including the NF-κB and PI3K/Akt axes. This interplay can determine the ultimate cellular outcomes, such as survival vs. apoptosis, based on the specific cellular environment and the nature of the stimuli (23,31).

Beyond its essential roles in managing cellular stress and homeostasis, dysregulation of p38 MAPK has been increasingly implicated in various pathological conditions. Previous investigations have underscored the critical role of p38 MAPK in liver diseases, particularly fibrosis and inflammation. Furthermore, the therapeutic targeting of p38 MAPK has gained attention, particularly in diseases characterized by chronic inflammation and fibrosis, where inhibitors of this pathway may help mitigate disease progression and improve clinical outcomes (24,25,32). A diagram of the mechanisms

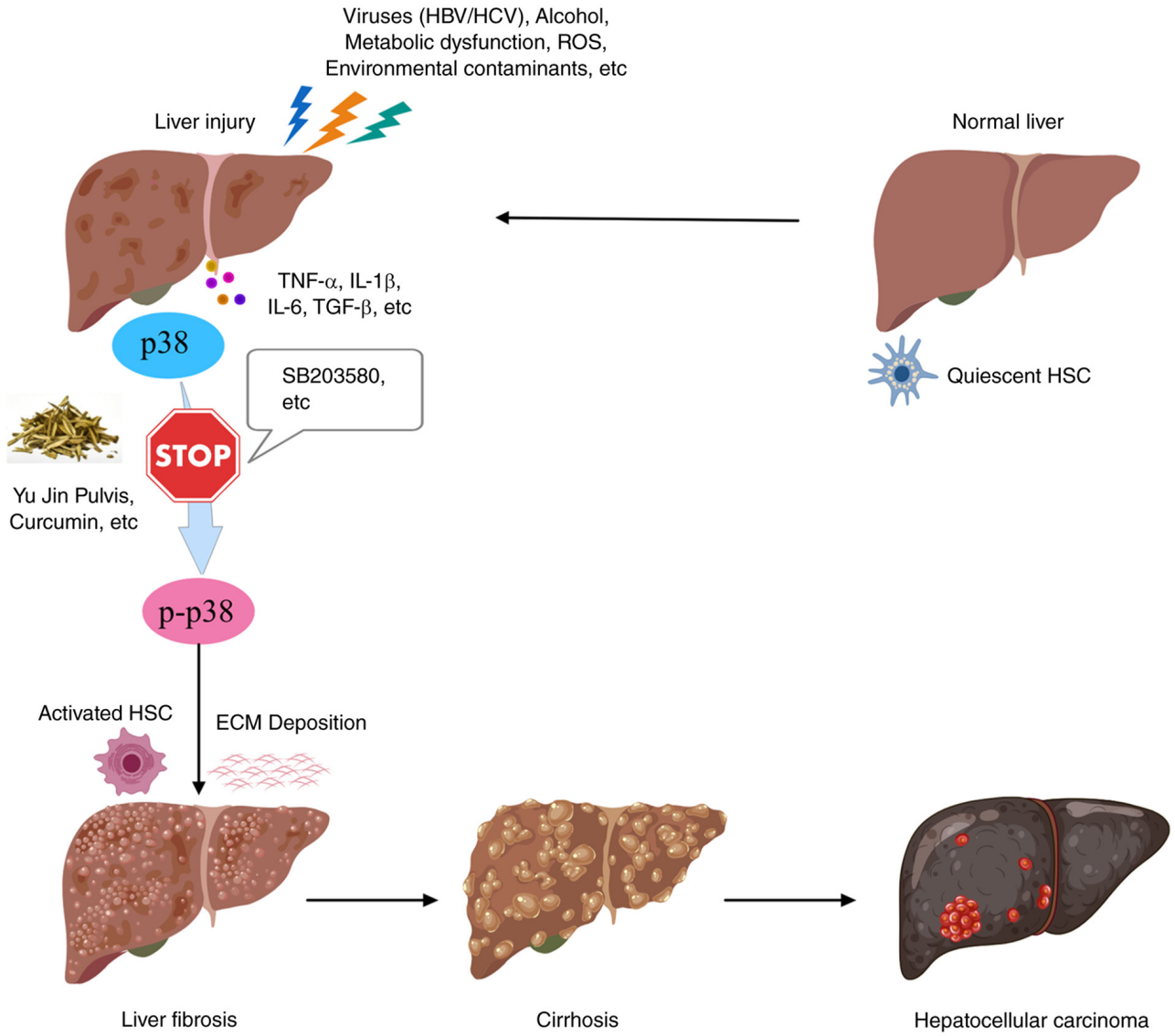

Figure 1. Schematic illustrating the pathological mechanisms underlying liver fibrosis, including the involvement of p38 MAPK, is presented. It also highlights potential points for therapeutic intervention (detailed in Fig. 4). This diagram illustrates the pivotal function of the p38 MAPK cascade in the progression of liver fibrosis. The liver becomes injured through various causes, including hepatitis viruses, alcohol consumption, metabolic problems, ROS, and environmental contaminants such as DBP and DEHP. The pro-inflammatory mediators IL-1β, IL-6, TGF-β and TNF-α function as primary upstream activators of p38 MAPK. Activation of p38 MAPK leads to the phosphorylation of multiple targets, thereby promoting HSC activation, myofibroblast differentiation, and cell proliferation. The process culminates in abnormal growth of ECM components, including collagen I and α-SMA. The liver develops fibrosis and cirrhosis through these pathological changes, which can also result in HCC. Research on p38 MAPK therapy shows promise through three approaches: Small-molecule inhibitors such as SB203580 and natural compounds, including curcumin and traditional Chinese medicines such as Yu Jin Pulvis, for treating liver fibrosis. p38 MAPK, p38 mitogen-activated protein kinase; ROS, reactive oxygen species; DBP, dibutyl phthalate; DEHP, di(2-ethylhexyl) phthalate; IL-1β, interleukin-1β; IL-6, interleukin-6; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; HSC, hepatic stellate cell; ECM, extracellular matrix; α-SMA, α-smooth muscle actin; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus.

that activate the p38 MAPK signaling pathway is shown in Fig. 2.

Structure and classification of p38 MAPK. p38 MAPK is a member of the MAPK family of kinases, which also includes ERKs and JNKs. It is a structurally conserved serine/threonine kinase characterized by a conserved kinase domain essential for enzymatic activity, along with regulatory regions that modulate its activation and substrate specificity (33). The kinase domain comprises a catalytic core that facilitates the transfer of phosphate moieties from adenosine triphosphate (ATP) to substrate proteins, a process known as phosphorylation.

The p38 MAPK family comprises four isoforms: p38α, p38β, p38γ, and p38δ, each encoded by a distinct gene and exhibiting unique tissue distribution, regulatory mechanisms, and functional roles (33). This classification helps understand how these isoforms contribute to the complexity of the p38 MAPK signaling pathway in health and disease (12,14). Among these, p38α is the most thoroughly characterized isoform and is ubiquitously expressed across almost all cell types, with predominant expression in the liver, heart, skeletal muscle, and brain, among others, where it is implicated in stress responses and apoptosis. By contrast, p38β is less understood but is hypothesized to have overlapping functions

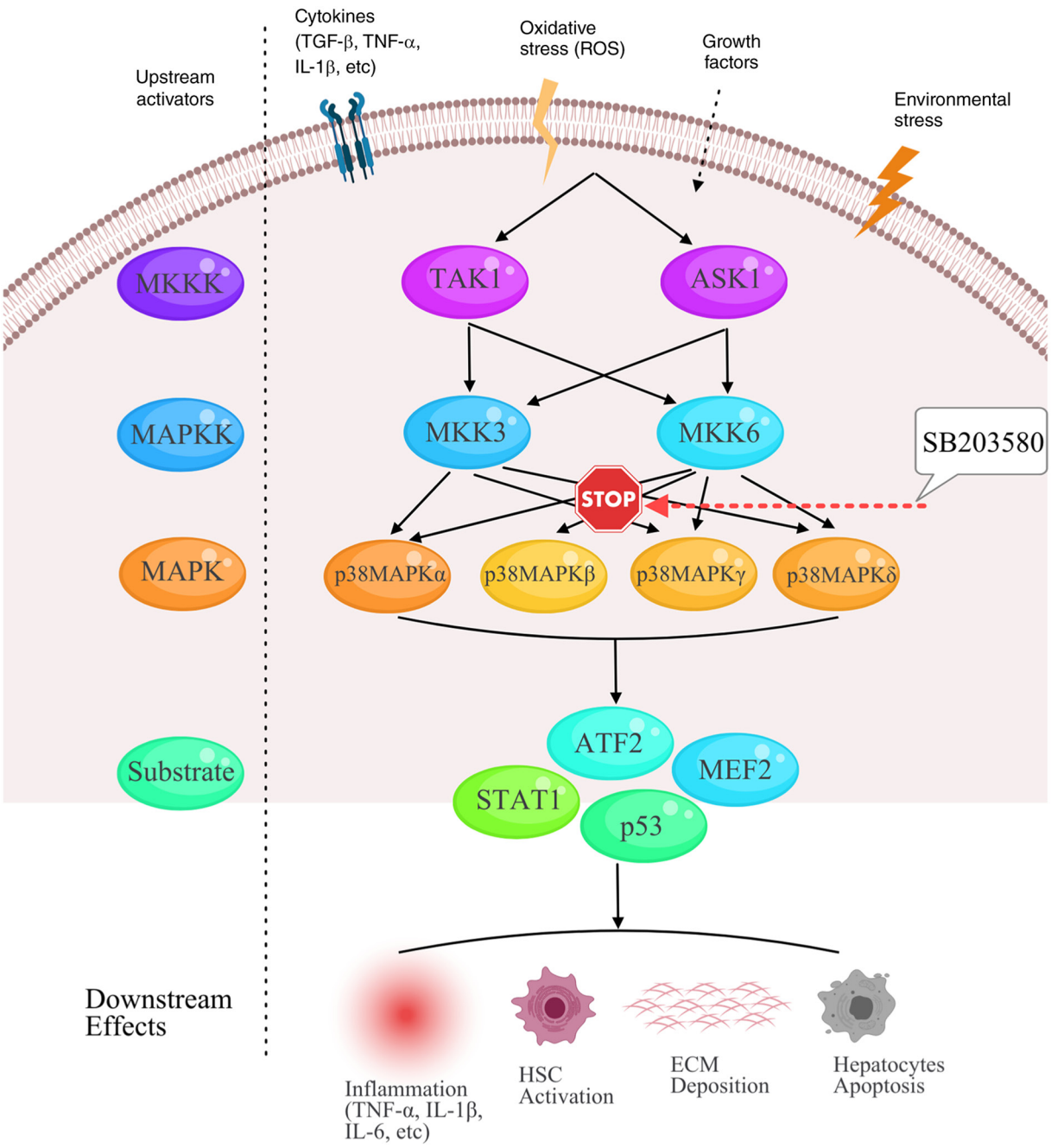

Figure 2. Mechanisms underlying the activation of the p38 MAPK signaling cascade. The schematic shows the molecular events that activate the p38 MAPK pathway in response to various external signals. The pathway is activated by stress signals, including TGF-β, IL-1β, and TNF-α, pro-inflammatory mediators, ROS, growth factors, and environmental stressors such as DBP and LPS. The activation process begins with a series of sequential kinase reactions, in which MKKKs activate specific MKKs, including MKK3 and MKK6. p38 MAPK becomes activated due to phosphorylation events which these signaling molecules trigger. p38 MAPK activation results in phosphorylation of multiple substrates, which include transcription factors such as ATF2, MEF2, and STAT1, and apoptotic regulators such as p53. Upon stimulation, p38 MAPK is activated, thereby triggering phosphorylation cascades involving ATF2, MEF2, STAT1, and p53 that control inflammation, HSC activation, ECM deposition, and hepatocyte apoptosis. The diagram shows the four p38 MAPK isoforms (p38α, p38β, p38γ, p38δ), which are differentially expressed and perform various cellular functions through this signaling pathway. TGF-β, transforming growth factor-β; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; ROS, reactive oxygen species; DBP, dibutyl phthalate; LPS, lipopolysaccharide; MKKK, mitogen-activated protein kinase kinase kinase; MKK, mitogen-activated protein kinase kinase; p38 MAPK, p38 mitogen-activated protein kinase; ATF2, activating transcription factor 2; MEF2, myocyte enhancer factor 2; STAT1, signal transducer and activator of transcription 1; p53, tumor protein p53; HSC, hepatic stellate cell; ECM, extracellular matrix.

with p38α in certain contexts. p38γ is predominantly found in skeletal muscle, where it is hypothesized to facilitate muscle differentiation, while p38δ is primarily expressed in the brain and associated with neuronal signaling. Consequently, the differential activation of these isoforms leads to varied biological outcomes depending on the cellular context and specific stimuli involved. A summary of the four p38 MAPK isoforms, their tissue distribution, and their reported roles in the liver is provided in Table I.

Beyond its structural diversity, p38 MAPK is functionally classified into two primary cascades: The inflammatory and stress response routes. In the context of inflammation, p38

MAPK is triggered by cytokines, including interleukin-1 (IL)-1 and tumor necrosis factor (TNF)-α, thereby stimulating the subsequent synthesis of pro-inflammatory mediators and contributing to chronic inflammatory diseases. Conversely, exposure to environmental stressors, such as oxidative stress or UV radiation, may activate p38 MAPK, leading to cell cycle arrest or programmed cell death, underscoring its essential role in regulating cell fate (34).

Mechanisms of activation of p38 MAPK. The activation of p38 MAPK includes multiple upstream signaling pathways and stimuli which work together to activate the enzyme. The activation process begins with phosphorylation reactions that start when pro-inflammatory cytokines IL-1 and TNF engage their respective cell-surface receptors. The receptor-ligand binding process activates multiple signaling pathways, which produce downstream responses. These pathways activate MAPK kinase kinases (MKKKs), which then phosphorylate and activate particular MAPK kinases (MKKs), notably MKK3 and MKK6. These MKKs subsequently activate p38 MAPK through phosphorylation at both threonine and tyrosine sites located in the activation loop (4). The phosphorylation event triggers a structural transformation which enables p38 MAPK to phosphorylate its target proteins, including transcription factors and other kinases, thereby eliciting multiple cellular responses (12,14).

The activation of p38 MAPK occurs through two primary mechanisms: Cytokine release and oxidative stress. The cellular oxidative stress response produces reactive oxygen species (ROS), which activate p38 MAPK through multiple different pathways. It is critically implicated in the pathogenesis of diverse disorders, including neurodegenerative diseases and cancer, by regulating cellular viability and apoptotic processes (14).

The activation of p38 MAPK is influenced by multiple signaling pathways, which include NF-κB. The activation level of p38 MAPK and its downstream effects depend on interactions among these signaling pathways (12).

The body activates p38 MAPK when it detects environmental pollutants. Environmental plasticizers cause liver collagen buildup and elevated fibrosis indicators by activating the p38 MAPK/NF-κB signaling pathways. These findings underscore the pivotal role of p38 MAPK in driving environmental toxin-induced hepatic injury (14,25).

The p38 MAPK activation pathway is present in both disease states and normal bodily functions. The activation of p38 MAPK during stem cell differentiation enables it to control gene expression, which determines cell fate. Research has shown that p38 MAPK signaling is indispensable for driving osteogenic differentiation, as it enables mesenchymal stem cells to differentiate into osteoblasts during normal development (25). This hierarchical kinase cascade, from upstream MKKKs to the dual phosphorylation of p38 MAPK is delineated in Fig. 2, and the diverse downstream effectors that mediate its pleiotropic cellular functions are subsequently illustrated.

Downstream effects of p38 MAPK. The p38 MAPK pathway elicits multiple effects that can result in protective or harmful responses, depending on the cell type and stimulus characteristics. The phosphorylation and subsequent activation of p38 MAPK trigger downstream effects that control inflammatory responses. In the context of liver fibrosis, p38 MAPK signaling increases the production of IL-6, TNF-α and IL-1β, thereby accelerating fibrosis progression (35).

The p38 MAPK signaling pathway is directly linked to apoptotic mechanisms. Phosphorylation of diverse downstream targets is triggered upon p38 MAPK activation. These substrates include pro-apoptotic factors such as BAD and caspases, which affect cell survival and apoptosis. Conversely, the p38 MAPK enzyme also protects cells from death by activating survival autophagy pathways during oxidative stress. The dual function of p38 MAPK yields a complex signaling molecule, as its output depends on both cellular conditions and the specific activation signals it receives (12).

In addition to its roles in inflammation and apoptosis, p38 MAPK participates in mechanisms that govern cellular differentiation. Research has shown that p38 MAPK signaling regulates the levels of essential transcription factors and osteogenic markers that guide osteogenic differentiation. Inhibition of p38 MAPK activity prevents mesenchymal stem cells from differentiating into osteoblasts, demonstrating that this pathway is essential for bone maintenance and repair (36). The regulatory function of p38 MAPK extends to multiple cell types, including immune cells, fibroblasts, and neurons, thereby affecting multiple biological processes and disease conditions (37,38).

The p38 MAPK pathway functions through numerous signaling pathways that activate NF-κB and ERK to control cellular responses. In inflammatory conditions, p38 MAPK can enhance NF-κB activation, leading to increased expression of inflammatory mediators. NF-κB controls p38 MAPK activity through a feedback loop that amplifies inflammatory responses. The p38 MAPK signaling pathway interacts with multiple pathways, demonstrating how cellular networks function as unified systems and creating opportunities for the development of specific medical interventions (14). The hierarchical activation of this pathway, from MKKKs to downstream effectors, is illustrated in Fig. 2.

3. Mechanistic insights into the contribution of p38 MAPK in hepatic fibrogenesis

This section explores the intricate mechanisms through which p38 MAPK influences the emergence and advancement of hepatic fibrosis. Research has indicated that p38 MAPK expression levels are markedly increased in fibrotic liver tissues and are associated with the extent of disease progression (21). The p38 MAPK pathway has been identified as a crucial component in the development of liver fibrosis, affecting a wide range of cellular processes, including inflammatory mechanisms, apoptosis, and fibroblast activation (39-42). The activation of this signaling cascade leads to the upregulation of fibrogenic markers and promotes HSC proliferation, contributing to fibrosis (43-48). Pro-inflammatory cytokines, oxidative stress, and other stimuli prevalent during liver injury often trigger the phosphorylation and subsequent activation of p38 MAPK (49-52).

The p38 MAPK signaling pathway is a pivotal mediator of the mechanisms underlying liver fibrosis (53). Its roles in HSC

Table I. p38 MAPK isoforms and their roles in the liver/liver fibrosis.

Isoform	Gene	Tissue distribution	Role in liver/liver fibrosis	Key mechanisms/context	(Refs.)
p38α	MAPK14	Ubiquitous; predominant expression in liver, heart, skeletal muscle, brain	Most extensively studied in liver fibrosis; mediates stress responses, inflammation, and apoptosis	Implicated in HSC activation, inflammatory cytokine production, and fibrogenic signaling. Central isoform in most preclinical studies using inhibitors such as SB203580 (which targets p38α/β).	(12,14,33)
p38β	MAPK11	Less understood; believed to have overlapping functions with p38α	Less studied in liver fibrosis; potential functional redundancy with p38α	May compensate for p38α in certain contexts, but specific role in liver fibrosis remains unclear.	(33)
p38γ	MAPK12	Predominantly in skeletal muscle	Not specifically reported in liver fibrosis	Mainly associated with muscle differentiation; liver expression low; likely minor role.	(33)
p38δ	MAPK13	Mainly expressed in brain, lso present in other tissues	Key role in MAFLD-associated fibrosis	Activated by free fatty acids in hepatocytes during MAFLD. Promotes YAP dephosphorylation and nuclear translocation, driving profibrogenic gene expression (CTGF, CYR61, ANKRD1, JUB). Inhibition of p38δ blocks YAP activation and downstream fibrotic effects.	(124,125)

MAPK, mitogen-activated protein kinase; HSC, hepatic stellate cell; MAFLD, metabolic-associated fatty liver disease; Yap, yes-associated protein; CTGF, connective tissue growth factor; CYR61, cysteine-rich angiogenic inducer 61; ANKRD1, ankyrin repeat domain-containing protein 1; JUB, ajuba LIM protein.

activation, inflammation, regulation of apoptosis, and interactions with other signaling pathways underscore the complexity of fibrogenesis (54,55).

Research has demonstrated that the p38 MAPK signaling cascade exhibits a profound and complex regulatory association with the transcriptional activation of diverse profibrotic mediators. Apart from TGF-β, a diverse array of profibrotic stimuli converges on p38 MAPK. These can be grouped into several functional categories, including growth factors and matricellular proteins [such as connective tissue growth factor (CTGF), and platelet-derived growth factor (PDGF)-D], metabolic and hormonal signals (such as leptin, angiotensin II, and 15-F2t-isoprostane), immune and inflammatory mediators [such as a polarized T helper type 2 (Th2) response], redox signaling [such as NADPH oxidase (NOX)5], components of certain pathogens [such as lipopolysaccharide (LPS), and human immunodeficiency virus protein gp120], additional intracellular mediators [such as β-arrestin 1, Ets domain transcription factor Elk-3 (Net/Sap-2/Erp), slit guidance ligand 2, and a disintegrin and metalloproteinase 8], the restructuring of the F-actin cytoskeleton, and even chemical insults (such as heroin derivatives and Iranian crack) (56-70). Mechanistically, these diverse activators all trigger the MKK3/6-p38 MAPK axis. For instance, leptin promotes HSC activation and fibrosis by inhibiting peroxisome proliferator-activated receptor (PPAR)γ via p38 MAPK, while LPS-induced p38 MAPK activation enhances Smad2 phosphorylation and collagen synthesis in HSCs (58,64). A comprehensive list of these stimuli is provided in Table II.

Moreover, the interplay between p38 MAPK and additional signaling pathways, including NF-κB, both of which participate in the inflammatory reaction and fibrogenesis, further complicates the understanding of its role in liver fibrosis (14). For example, p38 MAPK can modulate Smad protein activity, which is vital for mediating TGF-β signaling, thereby influencing the fibrotic response (71). In addition, hepatocyte growth factor (HGF) has been demonstrated to confer protective benefits against liver fibrosis by inhibiting p38 MAPK activation, thereby promoting HSC apoptosis and reducing collagen production (12). This highlights the prospect of combinatorial therapeutic strategies designed to simultaneously inhibit diverse signaling cascades involved in fibrosis, including p38 MAPK, to effectively manage liver fibrosis (14,20).

Additionally, previous investigations have identified how diverse environmental stimuli regulate the p38 MAPK signaling cascade in liver fibrosis. For example, exposure to environmental pollutants such as dibutyl phthalate (DBP), di(2-ethylhexyl) phthalate (DEHP) and microcystins has been linked to increased p38 MAPK activation and subsequent liver fibrosis, emphasizing the importance of understanding the impact of external factors on this signaling pathway (14,21,72). A diagram of the mechanisms underlying the activation of the p38 MAPK signaling cascade is shown in Fig. 2.

p38 MAPK in HSC activation and ECM remodeling. The functional activity of HSCs fundamentally drives the progression of hepatic fibrosis. Studying this process requires understanding how p38 MAPK activation leads to HSC activation. The liver contains HSCs, which function as fat-storing cells, and Ito cells, which play essential roles in liver health and disease development. The body maintains HSCs in a resting state, which enables them to store vitamin A and preserve liver ECM stability. These cells remain inactive until liver damage or inflammation occurs, which triggers their activation into proliferative cells that display myofibroblast-like features. The liver then develops fibrosis through two main changes: Increased α-smooth muscle actin (α-SMA) protein expression and excessive production of ECM components, especially collagen in HSCs. This fibrous tissue accumulation can eventually progress to hepatic fibrosis and cirrhosis (4,7,20).

Research has shown that p38 MAPK signaling interacts with HSC activation in response to various stimuli, including cytokines and growth factors, to induce fibrogenic responses in HSCs. The activation of p38 MAPK is a critical step, as it triggers multiple cellular responses, including inflammation, apoptosis, and fibrosis, then regulates fibrogenic genes, including collagen- and α-SMA-encoding genes, which are essential for activated HSCs (73). Inhibiting this pathway was shown to reduce fibrogenic marker expression, collagen deposition, and HSC activation in experimental models (4,12,14).

The TGF-β signaling pathway is the primary mechanism that activates HSCs during the fibrogenic response to liver injury (74). Research has shown that activation of the p38 MAPK pathway increases TGF-β1 production (20,75,76). Elevated TGF-β1 levels activate p38 MAPK in HSCs, creating a feedback loop. This loop activates HSCs via TGF-β1 while strengthening p38 MAPK signaling, thereby increasing fibrotic tissue formation (4,77,78). Additionally, research has indicated that the p38 MAPK signaling cascade is indispensable for mediating TGF-β-induced activation of HSCs and for the fibrogenic response (76,79).

In addition to TGF-β1, other factors, such as ROS and inflammatory cytokines, can activate p38 MAPK in HSCs, thereby promoting fibrosis (12). Research has shown that high glucose levels in diabetes induce oxidative stress, which activates p38 MAPK, initiating HSC activation and fibrosis (80). The study demonstrates that p38 MAPK functions as a key regulator controlling HSC responses to various activation factors (80).

The process of HSC activation and proliferation is complicated by the interactions of p38 MAPK with several signaling pathways. The survival or death of HSCs depends on their signaling pathway interactions, which determine the extent of fibrosis development (81-83). As shown in Fig. 2, both TGF-β and oxidative stress converge on the p38 MAPK activation cascade, ultimately leading to the phosphorylation of key transcription factors, including myocyte enhancer factor 2 (MEF2) and activating transcription factor 2 (ATF2), which drive HSC transdifferentiation and fibrogenic gene expression (84,85).

Beyond initiating activation, p38 MAPK is a master regulator of the ECM remodeling that characterizes fibrosis. Notably, the p38 MAPK signaling pathway also contributes to enhanced stability of α1(I) collagen messenger RNA (mRNA) in HSCs, which in turn promotes the production and build-up of type I collagen (86). Supporting the clinical relevance of this pathway, simultaneous profiling of serum proteome and hepatic phosphoproteome in patients with metabolic dysfunction-associated steatohepatitis (MASH) revealed that liver p38 MAPK activation is independently associated

Table II. Biochemical stimuli from multiple categories that converge on p38 MAPK to drive liver fibrogenesis.

Category	Stimulus/factor	Mechanism involving p38 MAPK	(Refs.)
Growth factors and matricellular proteins	CTGF	Promotes ECM deposition and inhibits degradation	(56)
	PDGF-D	Acts through p38 MAPK in HSC activation and ECM remodeling	(57)
Metabolic and hormonal signals	Leptin	Inhibits PPARγ2, SREBP-1c, and LXR-α via p38 MAPK to drive HSC activation and fibrosis	(58-60)
	Angiotensin II	Upregulates CTGF and ECM via AT1R/PKCα/p38 MAPK, engaging NF-κB and Smad2/3	(56)
	15-F_2t-isoprostane	Induces HSC proliferation and collagen synthesis via p38, ERK, and JNK	(61)
Immune and inflammatory signals	Th2 polarization	Requires active p38 MAPK to sustain profibrogenic response	(62)
Redox signaling	NOX5	Silencing reduces collagen by downregulating p38 MAPK	(63)
Components of certain pathogens	LPS	Promotes Smad2 phosphorylation and α-SMA/collagen I through p38 MAPK	(64)
	HIV gp120	Activates p38 MAPK and NF-κB to promote liver fibrosis	(65)
Additional intracellular mediators	β-arrestin 1	Upregulates MASP-1, activating HSCs via the p38/ATF2 axis	(35)
	Elk-3	Drives Egr-1-dependent EMT under p38 MAPK control	(66)
	Slit2	Promotes HSC proliferation through ERK and p38 MAPK	(67)
	ADAM8	Accelerates alcoholic liver fibrosis via p38 MAPK-mediated mechanisms	(68)
	F-actin remodeling	Correlates with HSC activation in a p38 MAPK-dependent manner	(69)
Chemical insults	Iranian crack	Induces liver damage and fibrosis partly via p38 MAPK stress kinases	(70)

CTGF, connective tissue growth factor; ECM, extracellular matrix; PDGF-D, platelet-derived growth factor D; HSC, hepatic stellate cell; PPARγ2, peroxisome proliferator-activated receptor γ2; SREBP-1c, sterol regulatory element-binding protein 1c; LXR-α, liver X receptor-α; AT1R, angiotensin II type 1 receptor; PKCα, protein kinase Cα; NF-κB, nuclear factor κB; Smad2/3, SMAD family member 2/3; 15-F_2t-isoprostane, 15-F_2t-isoprostane; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; Th2, T helper type 2; NOX5, NADPH oxidase 5; LPS, lipopolysaccharide; α-SMA, α-smooth muscle actin; HIV gp120, human immunodeficiency virus glycoprotein 120; MASP-1, mannan-binding lectin-associated serine protease 1; ATF2, activating transcription factor 2; Elk-3, ETS transcription factor ELK3; Egr-1, early growth response protein 1; EMT, epithelial-to-mesenchymal transition; ADAM8, a disintegrin and metalloproteinase domain-containing protein 8; F-actin, filamentous actin.

with hepatic collagen deposition (11). Moreover, p38 MAPK signaling has been linked to the induction of other profibrotic factors, creating a feed-forward loop that exacerbates ECM remodeling in fibrotic tissues. It also regulates the activity of matrix metalloproteinases (MMPs), enzymes that degrade ECM components. Several studies performed in fibroblasts indicated that p38 MAPK and NF-κB signaling cascades are pivotal in driving the expression of MMPs, specifically MMP-13, MMP-3, and MMP-1 (87-89). The suppression of the p38 MAPK signaling cascade can markedly attenuate MMP-13 gene expression in rat HSCs, thereby preventing MMP-13 from degrading the ECM components, especially collagen (90). This dual role of p38 MAPK in promoting ECM deposition while also facilitating its degradation underscores its importance in maintaining ECM homeostasis. For example, in a study investigating hepatic alveolar echinococcosis, increased expression levels of p38 MAPK were associated with elevated TGF-β1 and bone morphogenetic protein-7 (BMP-7) in liver specimens from patients, indicating a strong association between p38 MAPK activation and ECM remodeling in liver fibrosis (4). Similarly, in models of chronic liver injury induced by carbon tetrachloride (CCl_4), p38 MAPK was activated, promoting the expression of ECM components and contributing to the progression of liver fibrosis (21).

Furthermore, p38 MAPK activity is not confined to HSCs. p38 MAPK is also a key signaling molecule that mediates the defenestration process of liver sinusoidal endothelial cells (LSECs) in response to increased matrix rigidity, thereby accelerating the advancement of hepatic fibrosis by regulating cytoskeletal reorganization (91). The activation of the focal adhesion kinase (FAK)-p38 MAPK signaling pathway in LSECs occurs when liver matrix stiffness increases, leading to their pathological defenestration (loss of fenestrae) (91). Stiff substrates promote FAK phosphorylation, which subsequently activates p38 MAPK and its downstream effector p38-mitogen-activated protein kinase-activated protein kinase 2

(MK2) (91). p38-MK2 activation results in LIM kinase 1 phosphorylation, ultimately inducing cofilin inactivation through its role as an actin depolymerization protein. The process results in increased actin polymerization, leading to stress fiber formation and reorganization of the actin cytoskeleton (91). These changes cause the collapse of fenestrae-associated cytoskeletal rings and LSEC defenestration, which represents the first stages of capillarization and fibrosis (91). The process is reversed when p38-MK2 signaling is blocked with SB203580, which restores fenestrae structures and LSEC phenotypic markers in fibrotic liver samples across different disease stages (91). Additionally, p38 MAPK functions as a primary mechanotransducer, causing LSEC dysfunction when cells experience stiffness (86). As illustrated in Fig. 1, p38 MAPK serves as a central node that integrates a range of profibrotic signals and transduces them into the key pathological outcomes of HSC activation and excessive ECM deposition.

p38 MAPK-mediated inflammatory, oxidative stress and apoptotic signaling in fibrosis. The liver continues to sustain damage from ongoing inflammation and oxidative stress, which trigger hepatic fibrosis through multiple cellular and molecular mechanisms. The p38 MAPK pathway functions as a central signaling hub which combines inflammatory, oxidative, and apoptotic signals to control fibrotic disease progression.

p38 MAPK as a central amplifier of profibrotic inflammation. Chronic liver injury is marked by increased concentrations of pro-inflammatory cytokines, including TGF-β, IL-1β, TNF-α, and IL-17A (4,92). Rather than being a passive responder, p38 MAPK activation serves as a critical amplifier within this inflammatory milieu. Upon stimulation by these cytokines, p38 MAPK enhances the inflammatory response through multiple mechanisms: It upregulates the expression of inflammatory enzymes such as cyclo-oxygenase-2, modulates MMP activity, and potentiates NF-κB signaling (4,93). This leads to sustained production of key pro-inflammatory mediators, which not only cause direct tissue damage but also create a microenvironment that perpetuates HSC activation and survival.

The role of p38 MAPK extends beyond cytokine signaling to direct mediation of inflammation-related cell death and environmental responses. For example, in DBP-induced liver fibrosis, p38 MAPK activation links inflammatory stimuli to hepatocyte pyroptosis, followed by HSC activation, directly tying inflammatory signaling to fibrotic tissue remodeling (14). Furthermore, p38 MAPK is implicated in the inflammatory aspects of MAFLD, contributing to insulin resistance and subsequent fibrogenic signaling (94). Other factors, such as LPS, exacerbate inflammation by promoting p38 MAPK-mediated degradation of autophagy-related proteins, including autophagy-related gene 13 (Atg13), in HSCs, thereby disrupting cellular homeostasis and favoring a pro-fibrotic state (95). The aging liver also exhibits a p38 MAPK-mediated inflammatory and mildly fibrotic phenotype, which can be modulated by interventions such as caloric restriction, highlighting the role of the pathway in environment- and age-dependent fibrogenesis (96). Thus, p38 MAPK is not merely activated by inflammation; it orchestrates a feed-forward loop that sustains and intensifies the profibrotic inflammatory response.

Oxidative stress and p38 MAPK: A mutually reinforcing axis in fibrosis. Oxidative stress is a hallmark of chronic liver injury and a potent activator of p38 MAPK (97). This relationship forms a critical, self-reinforcing axis in fibrosis. Signals from damaged hepatocytes, such as ROS directly activate p38 MAPK, which in turn increases the expression of inflammatory genes and genes associated with apoptosis, such as Bcl-2-associated X protein (Bax), alongside a reduction in the levels of the anti-apoptotic protein Bcl-2 (98). Notably, p38 MAPK activation can further stimulate ROS generation, establishing a self-amplifying cycle that intensifies oxidative damage and tissue injury (99).

This cyclical interplay has profound implications for liver fibrosis. In hepatocytes, activation of p38 MAPK triggered by oxidative stress promotes cell death and the release of inflammatory cytokines, which subsequently activate HSCs and drive fibrosis (7,100). Simultaneously, ROS can activate NF-κB, which enhances p38 MAPK pathway activity, leading to increased inflammation and sustaining a pro-fibrotic environment, linking hepatocyte injury to fibrogenic responses (101,102). This suggests that targeting oxidative stress and p38 MAPK activation may offer therapeutic avenues for mitigating liver fibrosis.

The dual nature of p38 MAPK in oxidative stress is context-dependent: While it can mediate protective responses by regulating antioxidant defenses such as glutathione and inhibiting expression of inducible nitric oxide synthase under specific conditions, its chronic activation under persistent oxidative stress typically leads to detrimental outcomes, including cell cycle disruption and apoptosis (27). This functional duality underscores that p38 MAPK can act as both a stress sensor and a determinant of cell fate, with its outcomes finely balanced by the cellular context and cross-talk with other pathways (103). Pharmacological inhibition of p38 MAPK has shown protective effects by bolstering cellular antioxidant systems, underscoring its pivotal role as both a mediator and a potential therapeutic breakpoint in the oxidative stress-fibrosis cycle (28). How pro-inflammatory mediators, specifically IL-1β and TNF-α, alongside oxidative stress, serve as key upstream activators of the p38 MAPK signaling cascade, highlighting the molecular basis for its central role in amplifying inflammatory and oxidative responses during liver injury is illustrated in Fig. 2.

Apoptosis and p38 MAPK crosstalk in liver fibrosis. The equilibrium between cell survival and apoptosis is critical in liver injury, as excessive hepatocyte apoptosis can lead to further fibrogenesis. Research has indicated that the activation of p38 MAPK can either facilitate or suppress apoptosis, contingent on the specific cellular environment and stimuli. The p38 MAPK pathway has been associated with the modulation of apoptosis across a range of cell types, including hepatocytes (14). Prolonged oxidative stress in hepatocytes activates p38 MAPK, leading to apoptosis via mitochondrial damage and caspase activation, thereby exacerbating liver damage (12,104). Research findings show that MASH develops in response to oxidative stress, which activates the MAPK phosphatase-1-p38 MAPK-liver kinase B1 nuclear signaling pathway. This pathway suppresses the enzymatic activity of the α catalytic subunit of adenosine 5'-monophosphate-activated protein kinase (AMPK), thereby triggering caspase-6

activation and culminating in cellular demise. The resulting inflammation drives liver fibrosis and MASH progression (105). The p38 MAPK pathway functions differently in HSCs because it generates survival signals that enable these cells to survive and build the ECM (14). However, p38 MAPK has been recognized as a crucial mediator of the apoptotic effect of Ocoxin on HSCs (106). IL-18 works together with Toll-like receptor 3 ligand stimulation to activate natural killer (NK) cells, enhancing their cytotoxic functions through the p38 MAPK/PI3K/Akt signaling pathway. These activated NK cells eliminate HSCs through TNF-related apoptosis-inducing ligand-mediated degranulation, thereby preventing fibrosis progression (107).

The body regulates p38 MAPK activity in a cell-type-specific manner, creating challenges for developing therapeutic strategies targeting this enzyme. p38 MAPK inhibition, as shown in animal studies of CCl_4-induced fibrosis, decreases collagen accumulation but may impair hepatocyte restoration processes (12,14). The downstream effectors shown in Fig. 2, including p53 and other pro-apoptotic factors, mediate the cell death-promoting functions of p38 MAPK in hepatocytes, whereas alternative signaling outputs may support survival in activated HSCs.

p38 MAPK interplay with key signaling networks in liver fibrosis. The development of hepatic fibrosis depends on multiple signaling pathways that interact through crosstalk mechanisms to regulate fibrogenesis. A comprehensive network map of these interactions is provided in Fig. 3, illustrating how p38 MAPK serves as a central signaling hub that both receives inputs from and coordinates outputs to multiple pro-fibrotic pathways. Rather than viewing each pathway in isolation, these interactions can be grouped into functional classes: i) Core pro-fibrotic feed-forward loops that drive disease progression; ii) metabolic and mechanosensitive signaling axes that link cellular stress to fibrogenesis; iii) counter-regulatory and pro-resolution pathways that oppose fibrosis; and iv) parallel MAPK cascades that collectively determine cell fate. The signaling pathways that drive hepatic fibrosis progression become less active when patients undergo lifestyle interventions that reduce liver inflammation and improve metabolic health, providing clinical evidence for the reversibility of these network interactions (108,109).

Core pro-fibrotic feed-forward loops: TGF-β/Smad, NF-κB and JAK/signal transducer and activator of transcription (STAT) pathway. Among the pathways that intersect with p38 MAPK in liver fibrosis, TGF-β/Smad and NF-κB signaling form two interlocked feed-forward loops that are central to disease progression.

One of the most well-studied interactions involving p38 MAPK is its relationship with the TGF-β signaling cascade. The TGF-β1 signaling cascade is widely recognized as a principal mediator of hepatic fibrosis, promoting HSC activation and ECM deposition. Research has shown that TGF-β1 can initiate multiple downstream signaling cascades, including the Smad pathway, which is the main pathway of HSC activation and essential for mediating its fibrogenic effects (4,12). Additionally, TGF-β1 has been linked to the initiation of the p38 MAPK signaling cascade, which further amplifies the fibrogenic response by enhancing inflammation and apoptosis in hepatocytes (20). These findings indicate that the p38 MAPK pathway serves as an effector downstream of TGF-β signaling, mediating the fibrogenic effects of TGF-β1. For example, in a study investigating hepatic fibrosis, it was found that TGF-β1 induced the phosphorylation of p38 MAPK, which resulted in an upregulation of fibrogenic markers and an augmentation of collagen production, correlated with the severity of fibrosis in liver tissues (4). In another study, TGF-β was shown to stimulate CTGF expression, which in turn activated p38 MAPK, creating a feedback loop that exacerbated fibrosis (110). Upon receptor binding, TGF-β1 was demonstrated to activate Smad2 and Smad3, leading to their phosphorylation and nuclear translocation. This translocation was revealed to activate fibrogenic genes, including those encoding α-SMA and type I collagen (14,20). At the same time, TGF-β1 facilitated the production of sorting nexin protein-10 (SNX-10) through the p38 MAPK signaling cascade. In turn, SNX-10 modulated MMP9 release through direct protein-protein interactions, ultimately contributing to the progression of hepatic fibrosis (111). Furthermore, TGF-β1 stimulation triggered p38 MAPK activation, thereby enhancing MEF2C phosphorylation at the p38-specific residue, inducing activation of MEF2 and HSC (112). TGF-β1 also caused an increase in aerobic glycolysis in HSCs and stimulated the expression of glucose transporter 1 (GLUT1) in these cells via the stimulation of p38 MAPK, Smad, as well as PI3K/Akt signaling cascades. GLUT1 was shown to promote HSC glycolysis and activation (79). Research indicates that upregulation of integrin-β6 expression plays a pivotal role in the fibrogenic response associated with chronic cholestasis. p38 MAPK cascade facilitates TGF-β1-driven transcriptional upregulation of integrin-β6 mRNA within bile duct epithelial cells, specifically in MMNK-1 cell lines. This process is facilitated through the modulation of the activation of both activator protein 1 and Smad transcription factors (113). Notably, both p38 MAPK and Smad signaling pathways exert independent and additive effects on the transcriptional upregulation of the gene encoding type I collagen α1 chain. However, it is noteworthy that only p38 MAPK contributes to the enhancement of α1(I) collagen mRNA stability (71). Thus, feedback mechanisms characterize the relationship between p38 MAPK and TGF-β, as p38 MAPK activation can amplify TGF-β1 effects, thereby establishing a self-reinforcing cycle that intensifies fibrotic progression and leads to a vicious cycle of HSC activation and collagen deposition (114). Previous investigations have explored the potential of targeting the p38 MAPK pathway to mitigate TGF-β-induced fibrosis. Research involving liver fibrosis models has demonstrated that inhibiting p38 MAPK reduces TGF-β expression and its downstream effects, thereby ameliorating fibrosis (115-117).

The TGF-β/p38 MAPK loop is intimately coupled with NF-κB signaling. NF-κB functions as a transcription factor that regulates inflammatory responses and immune activation by controlling the expression of pro-inflammatory cytokine genes. The activation of p38 MAPK leads to the phosphorylation of inhibitor of κBα (IκBα), which removes its inhibitory function on NF-κB. The process enables NF-κB dimers to exit the cytoplasm and enter the nucleus, where they activate transcription of inflammatory cytokine genes, which in turn activate p38 MAPK (118). The two-way activation process between these

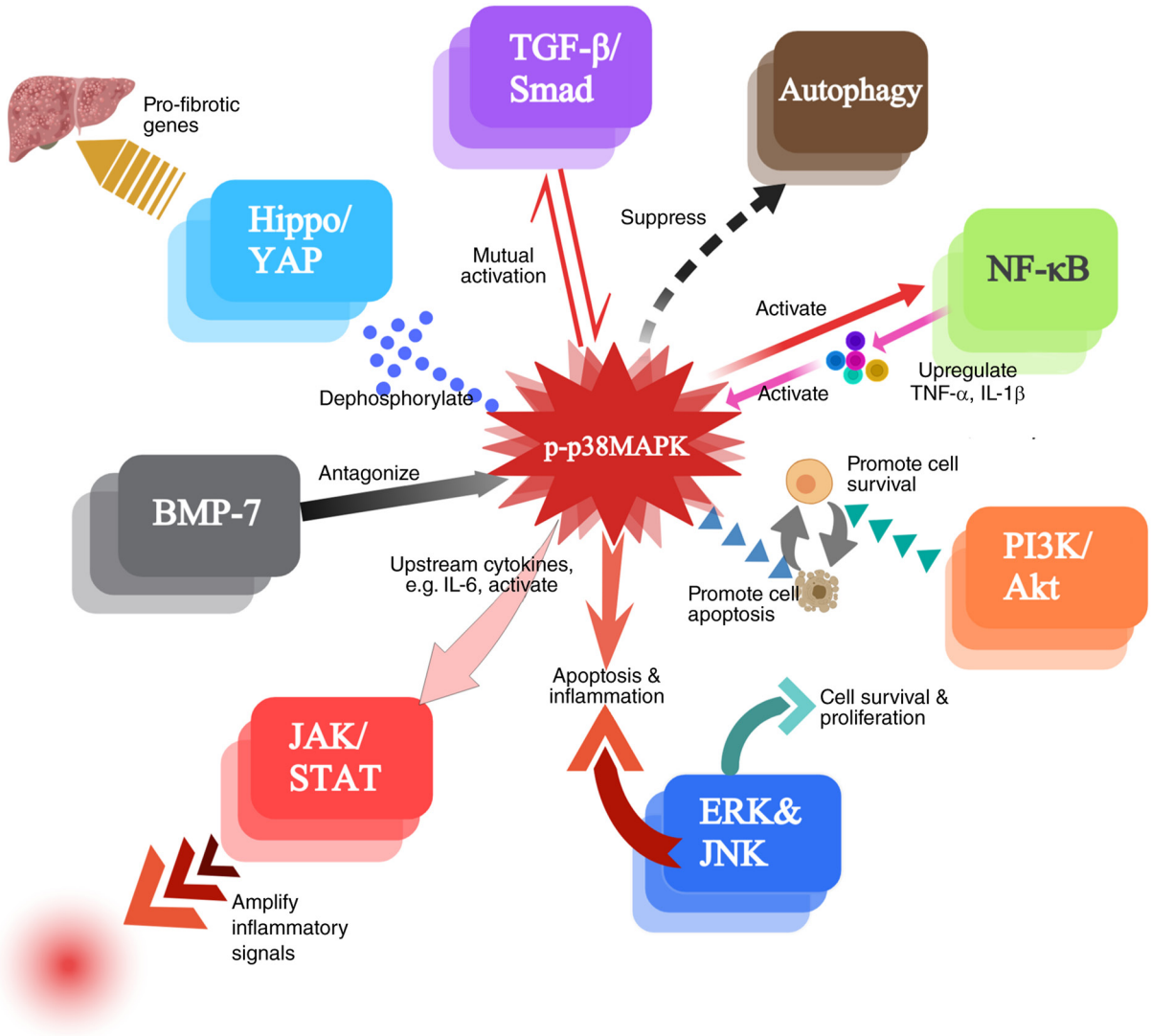

Figure 3. Network diagram of p38 MAPK interactions with other major signaling pathways. This diagram illustrates the extensive crosstalk between the p38 MAPK signaling pathway and other major signaling networks involved in cellular stress, inflammation, fibrosis, and apoptosis. p38 MAPK serves as a central hub that receives signals from various pathways and directs outputs to distinct signaling pathways to control three essential disease mechanisms, including HSC activation, ECM remodeling, and inflammatory reactions. The p38 MAPK pathway facilitates NF-κB activation. NF-κB activates p38 MAPK by increasing the production of the cytokines TNF-α and IL-1β. The PI3K/Akt signaling cascade is a pivotal mechanism that regulates survival, migration, apoptosis, and fibrogenesis in HSCs. The primary interactions occur between TGF-β/Smad and p38 MAPK, which serves a dual role, operating both downstream and upstream of the TGF-β cascade to boost Smad-dependent fibrogenic gene expression and create a self-reinforcing mechanism that accelerates fibrosis development. NF-κB: p38 MAPK facilitates the initiation of NF-κB signaling. In turn, NF-κB can further stimulate p38 MAPK activity via elevated levels of cytokines, including TNF-α and IL-1β. PI3K/Akt: Coordinated signaling influences various biological mechanisms, including survival, apoptosis, migration, and fibrogenesis in HSCs. JNK/ERK: The MAPK family members JNK and ERK work with p38 MAPK to activate stress responses that regulate apoptosis, cell proliferation, and inflammation. YAP: p38δ activation by free fatty acids results in YAP dephosphorylation and nuclear translocation, which produces profibrogenic gene expression during MAFLD. JAK/STAT: p38 MAPK-induced cytokines (such as IL-6) activate JAK/STAT signaling to maintain ongoing inflammatory and fibrotic responses. BMP-7 functions as a TGF-β blocking agent, which halts p38 MAPK activation to stop fibrosis development and trigger cell death in HSCs. The process of autophagy (AMPK/mTOR) depends on p38 MAPK to block autophagic flux through mTOR-mediated ULK1 suppression, which helps HSCs maintain their fibrogenic state. The network shows that p38 MAPK operates within a complex signaling network, making it an optimal target for combination therapies that block multiple profibrotic pathways. p38 MAPK, p38 mitogen-activated protein kinase; HSC, hepatic stellate cell; ECM, extracellular matrix; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; TGF-β, transforming growth factor-β; Smad, small mothers against decapentaplegic; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; YAP, yes-associated protein; MAFLD, metabolic-associated fatty liver disease; JAK, Janus kinase; STAT, signal transducer and activator of transcription; IL-6, interleukin-6; BMP-7, bone morphogenetic protein 7; AMPK, adenosine monophosphate-activated protein kinase; mTOR, mechanistic target of rapamycin; ULK1, unc-51-like autophagy activating kinase 1.

cells creates a self-reinforcing cycle which results in continuous tissue damage and inflammation. Research has shown that p38 MAPK activation during the development of liver fibrosis leads to increased NF-κB signaling, resulting in higher production of the pro-fibrotic factors TGF-β and CTGF (119). This interplay is exemplified by the fact that inflammatory cytokines, such as TNF-α and IL-1β, can trigger p38 MAPK activation, which subsequently enhances TGF-β expression, perpetuating a cycle of inflammation and fibrosis (21).

The tight coupling of these two feed-forward loops may explain why single-target interventions often fail. Dual inhibition of TGF-β and NF-κB signaling, or direct targeting of

their common downstream mediator p38 MAPK, has been proposed as a more effective strategy.

Moreover, the p38 MAPK and JAK/STAT signaling pathways also interact extensively during liver fibrosis. The activation of p38 MAPK leads to increased synthesis of TNF-α and IL-6, which not only feed back onto NF-κB but also activate the JAK/STAT pathway, thereby further enhancing inflammatory responses (120,121). The JAK/STAT signaling pathway is similarly activated after TGF-β1 cytokine binds to its receptor. The p38 MAPK and JAK/STAT pathways operate as a complex system that amplifies the inflammatory-fibrogenic network in the progression of liver fibrosis. This synergistic interaction creates a feed-forward loop that amplifies fibrogenic signaling, making co-targeting of these pathways an attractive therapeutic strategy (Fig. 3).

Metabolic and mechanosensitive signaling pathways: PI3K/Akt, yes-associated protein (YAP), autophagy, and bile acids. Beyond classical inflammatory and growth factor signals, metabolic and mechanical cues are integrated with p38 MAPK through the PI3K/Akt/mechanistic target of rapamycin (mTOR), YAP, and autophagy pathways and bile acids. The p38 MAPK and PI3K/Akt signaling cascades in liver fibrosis function together through coordinated activation, which strengthens their combined fibrotic effects. Research has indicated that the p38 MAPK signaling pathway interacts with the PI3K/Akt pathway, thereby protecting HSCs from apoptosis. It has been shown that blocking the PI3K/Akt signaling pathways renders p38 MAPK inhibitors more effective at inhibiting HSC activation driven by various p38 MAPK-dependent profibrotic mechanisms. Angiotensin II (AngII) increases the expression of essential proteins (PI3K, p-Akt, and p-P38 MAPK) in HSCs, thereby promoting fibrosis progression (12). The pathways show functional cross-talk because LY294002 treatment of PI3K and SB203580 treatment of p38 MAPK both block AngII-induced effects, including increased cell viability and migration, and elevated collagen I and α-SMA expression (12). HGF-overexpressed exosomes were shown to reduce both pathways, resulting in lower oxidative stress levels (NOX4 and malondialdehyde) and decreased p-p38 MAPK and PI3K/p-Akt activity *in vivo*, thereby treating CCl_4-induced liver fibrosis in mice (12). However, the context-dependent nature of this crosstalk is underscored by the finding that N-acetylglucosamine (GlcNAc)-carrying polymers, which mimic the multivalent GlcNAc moiety of O-linked β-GlcNAc-modified proteins, activate both p38 MAPK and PI3K/Akt signaling cascades in activated stellate cells. This activation produces anti-fibrotic effects by decreasing α-SMA expression and reducing collagen production (122). This seemingly paradoxical outcome underscores the context-dependent nature of p38 MAPK-PI3K/Akt crosstalk, where the net effect on fibrosis is dictated by factors such as activation kinetics, coincident signals, and downstream effector engagement. Moreover, it was demonstrated that PI3K-Akt-mTOR and p38 MAPK signaling cascades play a crucial role in the motility characteristics of HSCs. By contrast, the Smad-dependent TGF-β signaling cascade is primarily involved in their proliferation and contraction (123).

The metabolic stress connection is further strengthened by the p38 MAPK-YAP axis. Research has demonstrated that the activation of Hippo signaling transcriptional coactivator YAP1 in the context of MAFLD could be stimulated by the activation of p38 MAPK induced by free fatty acids (FFAs) (124). FFAs, which accumulate in hepatocytes during MAFLD, activate p38 MAPK (specifically the p38δ isoform MAPK13). This activation promotes the dephosphorylation/nuclear translocation of the transcriptional coactivator YAP. Once in the nucleus, the active form of YAP promotes transcription of profibrogenic target genes, including cysteine-rich protein 61, CTGF, ankyrin repeat domain 1, and ajuba homolog. The products of these genes stimulate HSC activation and subsequent ECM deposition, thereby driving the progression of liver fibrosis. Inhibition of p38 MAPK (via siRNA knockdown or chemical inhibitors such as SB203580) was shown to block FFA-induced YAP activation and its downstream fibrogenic effects. In addition, activation of HSCs by taurocholic acid was significantly associated with activation of the YAP signaling pathway, mediated by sphingosine 1-phosphate receptor 2 via the p38 MAPK pathway (125). The p38δ-YAP axis, shown in Fig. 3, represents a newly identified mechanism linking metabolic stress (FFAs) to fibrogenic gene expression, providing a rationale for targeting this specific isoform in MAFLD-associated fibrosis.

Autophagy adds another layer of metabolic regulation. The lysosomal degradation process of autophagy functions as a dual mechanism contributing to the progression of liver fibrosis. Basal autophagy plays a crucial role in maintaining cellular homeostasis. HSCs with impaired autophagic function may either survive longer and exacerbate fibrosis or undergo apoptosis, thereby mitigating fibrosis, depending on the specific context (126,127). The activation of p38 MAPK triggers the phosphorylation of the serine residue 757 within Unc-51-like autophagy activating kinase 1 (ULK1). This modification disrupts the ULK1-Atg13 complex, thereby blocking autophagic flux in activated HSCs via mTOR-dependent mechanisms, leading to increased collagen production and enhanced fibrogenesis (128). The p38 MAPK inhibitor SB203580 activates AMPK, thereby inducing autophagy, which strengthens the therapeutic effects of anti-fibrotic drugs (128). However, the natural compound harmine inhibits p38 MAPK and modulates AMPK/mTOR, relieving its suppression on the mTOR complex 1, reducing excessive autophagy in CCl_4-induced liver injury (129). This indicates that the outcome of p38 MAPK modulation of autophagy is highly dependent on the degree and context of pathway activation.

Bile acids further contribute to this metabolic signaling network. Research has focused on liver fibrogenesis by studying conjugated bile acids, specifically 12α-hydroxylated bile acids. Research has shown that liver tissue contains elevated bile acid levels of conjugated 12α-hydroxylated bile acids, which activate HSCs and promote liver fibrosis. Activation of the Takeda G-protein-coupled receptor, also known as G protein-coupled bile acid receptor 1, leads to phosphorylation-mediated upregulation of the p38 MAPK and ERK1/2 cascades (31). In a previous study, it was shown that metabolic factors, including bile acid buildup, affect fibrosis development by modulating essential signaling pathways. The study also demonstrated that modulation of bile acid signaling is a potential treatment approach (31). Collectively, the PI3K/Akt, YAP, autophagy, and bile acid pathways highlight the extensive integration of metabolic and mechanical signals at the p38 MAPK node,

although the context-dependent effects, which are sometimes pro-fibrotic, sometimes anti-fibrotic, call for careful evaluation of isoform-specific and cell-type-specific therapeutic strategies.

Counter-regulatory and pro-resolution pathways: BMP-7 and mesenchymal-to-epithelial transition (MET). In contrast to the pro-fibrotic circuits previously described, BMP-7 and the reversal of EMT represent endogenous counter-regulatory mechanisms that converge on p38 MAPK. BMP-7 functions as an essential factor that inhibits hepatic fibrosis. The compound blocks the fibrogenic effects of TGF-β1, induces HSC apoptosis, and reduces their collagen-producing capacity. The maintenance of liver homeostasis depends on the proper balance between TGF-β1 and BMP-7 signaling pathways. The body develops excessive fibrosis when its fibrosis regulation system becomes unbalanced. Research has shown that BMP-7 acts as a protective factor through its ability to stop TGF-β1 from activating the p38 MAPK pathway, which prevents fibrogenesis (4). HSC activation depends on EMT, and the MET of HSCs helps resolve fibrosis. A decrease in the TGF-β1:BMP-7 ratio was shown to lead to reduced levels of total and phosphorylated p38 MAPK, allowing cells to revert from EMT to MET. The transition became apparent through the loss of EMT markers, including α-SMA and desmin, while MET marker and E-cadherin reappeared (130). As shown in Fig. 3, BMP-7 counteracts TGF-β1 signaling by suppressing p38 MAPK activation, representing a natural counter-regulatory mechanism that could be harnessed therapeutically to promote fibrosis resolution. The development of pharmacological agents which activate BMP-7 signaling and block TGF-β1 and p38 MAPK activation pathways shows promise for treating and stopping fibrosis progression (7).

Parallel MAPK cascades: JNK and ERK. p38 MAPK also interacts with other MAPK signaling cascades, such as JNKs and ERKs. The p38 MAPK, JNK, and ERK pathways work together to regulate essential processes in liver fibrosis by modulating HSC activation, inflammation, apoptosis, and ECM deposition.

The JNK signaling pathway is essential for regulating both cell death and cell growth. The process is activated when cells face stress and inflammatory signals emerge, leading to liver fibrosis through hepatocyte apoptosis and an increased inflammatory response. JNK activation leads to c-Jun phosphorylation. c-Jun is a crucial transcription factor that regulates the expression of survival- and apoptosis-related genes (131). The activation of p38 MAPK and JNK pathways is of particular interest because they respond to identical triggers, producing a synchronized cellular response that determines cell survival or death based on activation timing and environment.

By contrast, the ERK signaling pathway primarily promotes cell proliferation and differentiation by being activated by growth factors and mitogens. The activity of p38 MAPK and JNK depends on ERK, which regulates their downstream effects. Research shows that the ERK and p38 MAPK pathways function together to regulate cell-cycle events and stress responses in polyploid, giant cancer cells, suggesting that HSCs employ similar mechanisms to develop fibrotic tissue (131).

The outcome of fibrosis results from the interaction between these two pathways. The activation of ERK promotes cell survival and proliferation, whereas persistent JNK/p38 MAPK signaling pathways lead to apoptosis and inflammation (132,133). In liver fibrosis, oxidative stress and cytokine release of TNF-α and IL-6 may activate all three MAPK signaling pathways, creating a sustained cycle of HSC activation and ECM deposition (134). The p38 MAPK and ERK pathways serve as targets for inhibition because this approach would break the self-sustaining cycle (135). The complex interplay among the p38 MAPK, JNK, and ERK pathways, which collectively determine cell-fate decisions ranging from proliferation to apoptosis in the context of liver fibrosis is shown in Fig. 3.

Signaling pathways related to inflammation. The inflammatory response is another critical component of hepatic fibrosis, and inflammatory signaling pathways often intersect with pathways involved in fibrogenesis. The p38 MAPK signaling cascade is activated through elevated levels of the pro-inflammatory mediators TNF-α and IL-6, resulting in a marked augmentation of fibrogenic response. HSC activation decreases when anti-inflammatory signals enter the system because these signals promote HSC death (136). The regulatory mechanisms of hepatic fibrosis become complex because pro-inflammatory and anti-inflammatory signals interact with each other and with p38 MAPK and other essential pathways. Collectively, the signaling network depicted in Fig. 3 establishes p38 MAPK as a central hub that integrates a range of fibrotic inputs and coordinates multi-pathway outputs. The most biologically significant mechanisms, the interlocked TGF-β/NF-κB/p38 feed-forward loops and the metabolic-mechanical axes converging on p38 MAPK, represent priority targets for therapeutic intervention. The complexity and context dependence of these interactions underscore the rationale for simultaneously targeting multiple nodes, or its downstream effectors within the network, in combination therapies for liver fibrosis. p38 MAPK interactions with key signaling pathways in liver fibrosis are summarized in Table III.

Epigenetic regulation of p38 MAPK: The role of microRNAs (miRNAs). Research has focused on studying how miRNAs interact with the p38 MAPK pathway to understand cellular processes that include inflammation, fibrosis, and cancer development. Non-coding RNAs, such as miRNAs, regulate gene expression post-transcriptionally as short molecules, influencing biological processes such as cell proliferation, differentiation, and apoptosis. The interaction between miRNAs and p38 MAPK depends on multiple factors, which include the cellular context and the specific miRNAs involved (137).

A previous study showed that specific miRNAs directly bind to components of the p38 MAPK pathway, thereby modulating their activity. It also demonstrated that miRNAs serve as vital regulators of the p38 MAPK pathway, which controls cellular responses to external stimuli. The study revealed that miR-146b-3p reduces p38 MAPK signaling in monocytes, thereby altering their inflammatory response (138). Notably, miRNAs can act as crucial upstream regulators of the pathway. For example, research in *Caenorhabditis elegans* has shown that elevated intestinal expression of miR-794 modulates the response to nanoplastic toxicity by affecting downstream transcription factors in both p38 MAPK- and insulin-mediated

Table III. Summary of p38 MAPK interactions with key signaling pathways in liver fibrosis.

Signaling pathway	Interaction with p38 MAPK	Mechanism/Key points	Functional role in liver fibrosis	(Refs.)
TGF-β/Smad	Bidirectional cross-talk, synergistic activation	p38 MAPK acts as both a downstream effector and an amplifier of TGF-β signaling. It collaborates with Smads to enhance transcription of fibrogenic genes (α-SMA, collagen I) and stabilizes collagen mRNA independently of Smads.	Promotes HSC activation, ECM deposition, and fibrosis progression. Creates a positive feedback loop sustaining fibrogenesis.	(4,14,71,79, 111-113,115, 116,216)
NF-κB	Reciprocal activation, positive feedback	p38 MAPK enhances NF-κB transcriptional activity;NF-κB promotes pro-inflammatory cytokine production (IL-6 and TNF-α) that further activates p38 MAPK	Amplifies inflammatory responses, sustains chronic inflammation, and promotes HSC activation and fibrosis.	(14,93,101)
PI3K/Akt	Coordinated regulation, functional cross-talk	Both pathways regulate HSC survival, migration, and fibrogenesis. p38 MAPK interacts with PI3K/Akt to balance pro-apoptotic and pro-survival signals.	Protects HSCs from apoptosis; promotes HSC activation, collagen production, and fibrosis progression. Combined inhibition yields synergistic anti-fibrotic effects.	(12,122,123)
YAP	Upstream activation (p38δ isoform)	FFAs activate p38δ, which promotes YAP dephosphorylation and nuclear translocation. Nuclear YAP drives transcription of pro-fibrotic genes (CTGF, CYR61, ANKRD1, and JUB).	Links metabolic stress (MAFLD) to HSC activation and ECM deposition. Represents a novel mechanism in obesity-associated fibrosis.	(124,125)
JAK/STAT	Indirect activation via cytokines	p38 MAPK induces IL-6 and TNF-α production, which subsequently activate JAK/STAT signaling.	Maintains ongoing inflammatory and fibrotic responses; contributes to HSC activation and disease progression.	(120,121)
BMP-7	Antagonistic	BMP-7 counteracts TGF-β1 signaling by inhibiting p38 MAPK activation, promoting HSC apoptosis, and reducing collagen production.	Serves as a protective, anti-fibrotic factor. Restores balance between EMT and MET, promoting fibrosis resolution.	(4,130)
JNK/ERK	Coordinated MAPK network	p38 MAPK, JNK, and ERK pathways interact to regulate cell proliferation, apoptosis, inflammation, and ECM deposition. ERK promotes survival/ proliferation; JNK/p38 promote stress responses.	Determines cell fate (survival vs. apoptosis) and net fibrotic outcome. Targeting multiple MAPKs may break the self-sustaining fibrotic cycle.	(106,131-135,214)
Autophagy (AMPK/ mTOR)	Inhibitory regulation	p38 MAPK phosphorylates ULK1 (Ser757), disrupting the ULK1-Atg13 complex and blocking autophagic flux via mTOR-dependent mechanisms.	Suppresses autophagy in activated HSCs, promoting collagen production and	(128,129)

Table III. Continued.

Signaling pathway	Interaction with p38 MAPK	Mechanism/Key points	Functional role in liver fibrosis	(Refs.)
			sustained fibrogenesis. p38 inhibition can restore autophagy and enhance anti-fibrotic effects.	
Bile acids (TGR5)	Activation	Conjugated 12α-hydroxylated bile acids activate TGR5, which in turn activates ERK1/2 and p38 MAPK signaling.	Links bile acid metabolism to HSC activation and fibrosis progression. Suggests bile acid signaling modulation as a potential therapeutic approach.	(31)

TGF-β, transforming growth factor-β; Smad, suppressor of mothers against decapentaplegic; p38 MAPK, p38 mitogen-activated protein kinase; α-SMA, α-smooth muscle actin; mRNA, messenger ribonucleic acid; HSC, hepatic stellate cell; ECM, extracellular matrix; NF-κB, nuclear factor κB; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; YAP, Yes-associated protein; FFA, free fatty acid; CTGF, connective tissue growth factor; CYR61, cysteine-rich angiogenic inducer 61; ANKRD1, ankyrin repeat domain-containing protein 1; JUB, ajuba LIM protein; MAFLD, metabolic dysfunction-associated fatty liver disease; JAK, Janus kinase; STAT, signal transducer and activator of transcription; BMP-7, bone morphogenetic protein-7; EMT, epithelial-to-mesenchymal transition; MET, mesenchymal-to-epithelial transition; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; AMPK, AMP-activated protein kinase; mTOR, mechanistic target of rapamycin; ULK1, unc-51-like autophagy activating kinase 1; Ser757, serine 757; Atg13, autophagy-related protein 13; TGR5, Takeda G protein-coupled receptor 5; ERK1/2, extracellular signal-regulated kinases 1 and 2.

signaling cascades (139). Furthermore, in human immune cells, treatment with inactivated probiotic strains can significantly downregulate p38 MAPK expression while concurrently altering the levels of immune-related miRNAs such as miR-146a and miR-155, providing direct evidence of miRNA-p38 MAPK interplay in immune regulation (137).

The p38 MAPK pathway interacts with miRNAs through multiple mechanisms which go beyond direct miRNA targeting. It is also mediated by various signaling cascades involving other pathways. Activation of the p38 MAPK pathway by miR-802 leads to oxidative stress and regulation of insulin resistance in liver fibrosis, according to research (140). Another study found that oxidative stress reduced miR-144 levels, leading to decreased expression of the SIN3 transcription regulator family member A (SIN3A). The study demonstrated that activation of the p38 MAPK signaling pathway was mediated by SIN3A downregulation, leading to HSC activation and worsening liver fibrosis (141). The study showed that miRNAs regulate p38 MAPK activity by modulating signaling networks that activate it. This regulation can be part of a complex network. For example, in lead-induced neurotoxicity, a regulatory network involving a long non-coding RNA (lncRpa), a circular RNA (circRar1), and miR-671 was shown to cooperatively promote the upregulation of apoptosis-associated genes, including p38, revealing a significant role for non-coding RNA networks in controlling p38 MAPK expression (142).

Research has shown that miRNA-p38 MAPK interactions hold therapeutic potential, as specific miRNA inhibitors and mimics can affect diseases resulting from p38 MAPK dysfunction. Such findings suggest that targeting miRNAs that regulate p38 MAPK could provide novel therapeutic avenues for treating conditions associated with chronic inflammation and fibrosis. Additionally, in the context of viral infections such as COVID-19, virus-induced immune-epigenetic reprogramming may affect MAPK signaling, suggesting that targeting the relevant miRNA-p38 MAPK axis could be a strategy to modulate dysregulated immune responses, such as macrophage activation syndrome (143). Furthermore, under other stress conditions, such as viral infection and cardiovascular dysfunction, the expression of transcription factors such as nuclear factor of activated T cells 5, which interacts with the p38 MAPK pathway, is also regulated by miRNAs and epigenetic modifications, expanding the significance of the miRNA-p38 MAPK regulatory network in disease (144).

4. Prospects of p38 MAPK as a therapeutic target for the management of liver fibrosis

The therapeutic potential of p38 MAPK as a target emerges from its role in regulating cellular functions, including apoptosis, proliferation, and differentiation, that are commonly disrupted in disease. The development of liver fibrosis depends on p38 MAPK, a vital mediator of cellular responses to stress and inflammation. The p38 MAPK signaling cascade shows promise as a potential intervention point for treating various medical conditions, including liver fibrosis and associated hepatic diseases. Research has shown that p38 MAPK inhibition reduces fibrosis symptoms across various experimental models, supporting its potential for human use (20). A

comprehensive overview of the therapeutic intervention points along the p38 MAPK signaling cascade, from upstream stimuli to fibrotic outcomes is provided in Fig. 4. Studies have shown that SB203580 and other pharmacological agents which block this pathway can lower the transcriptional levels of genes associated with fibrotic processes, such as heat shock protein 47, α-SMA, and procollagen type I α1. These preclinical studies demonstrate that the inhibitors reduce fibrotic changes while improving liver function (14,21,31,76,85,145,146). In a previous study, the first stage of HSC activation resulted in decreased α-SMA protein expression when p38 MAPK was blocked, but blocking this kinase in activated HSCs did not have a similar effect. The suppression of p38 activity led to increased HSC proliferation, independent of HSC activation status (85). This pathogenic cascade, schematically summarized in Fig. 1, highlights the multiple levels at which therapeutic intervention, ranging from synthetic inhibitors to natural compounds, can potentially disrupt p38 MAPK-driven fibrogenesis.

Notably, mechanistic studies reveal that p38 MAPK blockade reduces collagen deposition and suppresses inflammatory cytokine production (76,147). Exosomes from adipose-derived mesenchymal stem cells elevated HGF expression to reduce oxidative stress and fibrosis markers via PI3K/Akt/p38 MAPK pathway inhibition in CCL_4-induced liver fibrosis models (12).

The development of novel p38 MAPK inhibitors has also been a significant area of research. Research in preclinical models shows that PH-797804 and similar selective inhibitors have favorable pharmacological properties, leading to better treatment outcomes (148). The various classes of p38 MAPK-targeting agents, including synthetic inhibitors, natural compounds, traditional Chinese medicine (TCM)-based formulations, repurposed drugs, and miRNA-based therapies, are schematically summarized in Fig. 4, which illustrates their points of intervention along the fibrotic signaling pathway. The compounds block p38 MAPK kinase activity while exhibiting reduced binding to other targets, thereby improving their potential for medical use (149). The particular structure of these inhibitors helps patients avoid side effects, which can happen when kinase inhibitors interact with multiple targets.

Research into existing medications to modulate the p38 MAPK pathway has yielded promising results. For example, several natural compounds and traditional herbal medicines have been identified that can modulate the p38 MAPK pathway, providing additional avenues for therapeutic intervention (22).

TCMs include Yu Jin Pulvis as one of several effective treatments that show promise for managing hepatic fibrosis by modulating key signaling pathways. Research has shown that Jiawei Taohe Chengqi Decoction can reverse hepatic fibrosis in animal models by modulating the p38 MAPK pathway (7). Similarly, Dahuang Zhechong Pill was demonstrated to inhibit HSC fibrosis by downregulating the p38 MAPK/NF-κB/TGF-β1 signaling axis (150,151). Fuzheng Huayu Recipe has been shown to improve liver fibrosis by restoring the TGF-β1/BMP-7 balance, thereby suppressing p38 MAPK phosphorylation and promoting MET in HSCs (130). The core bioactive components of Yinchenhao Decoction, including benzyl acetate, vanillic acid, and polydatin, were found to work together to block the PI3K-Akt and p38 MAPK pathways in HSCs, resulting in anti-fibrotic effects (152).

There are also some plant extracts, such as both *Thunbergia laurifolia* (TL) and *Ginkgo biloba* extract (GBE), that demonstrate anti-fibrotic effects by targeting the p38 MAPK pathway. TL prevents fibrosis by inhibiting the Erk1/2 kinase and p38 MAPK activation pathways. The anti-fibrotic effects of GBE occur through inhibition of p38 MAPK, thereby preventing HSC activation and inflammation (54,153).

Natural compounds and their derivatives exhibit anti-fibrotic properties in liver tissue via p38 MAPK signaling inhibition in HSCs, except for harmine. They can be classified into three groups: i) Antioxidants that indirectly suppress p38 activation: Astragalus-derived astragaloside IV was shown to work with ferulic acid to block HSC activation through reduced p38 MAPK activity, which results from oxidative stress (102,154). ii) Direct p38 phosphorylation inhibitors: Short-term gossypetin treatment was demonstrated to block MKK3/6-p38 MAPK and p53 activation, thereby decreasing activation of HSCs and Kupffer cells (155). Likewise, compounds such as baicalin, quercetin, hydroxysafflor yellow A, oxymatrine, and a novel synthetic derivative of oleanolic acid (CPU-II2) were all reported to reduce liver fibrosis by directly inhibiting p38 MAPK phosphorylation (39,53,119,156,157). iii) Multi-target agents that simultaneously block p38 and other pro-fibrotic pathways: Compounds such as emodin, dioscin, curcumin, isorhamnetin, schisandrin B, spinosin, betulin, ankaflavin/monascin, salvianolic acid B, salvianolic acid A, butein, neferine, total C-21 steroidal glycosides, dilinoleoylphosphatidylcholine, γ-linolenic acid, and cannabidiol achieve broader pathway inhibition, targeting p38 MAPK alongside key partners such as TGF-β/Smad, sirtuin 1/nuclear erythroid factor 2-related factor 2 (Nrf2), methionine adenosyltransferase 2B, cannabinoid 2 receptor, NF-κB/IκBα, neuron-derived clone 77/apoptosis signal-regulating kinase 1 (ASK1), JNK, Akt/NF-κB, ERK, Nrf2/heme oxygenase-1, JAK1/STAT3, plasminogen activator inhibitor 1, NOX4, adenosine A2A receptor, and PPAR-α (40,76,77,117,158-171). Among these, schisandrin B and spinosin have shown promising *in vivo* efficacy with favorable safety profiles, whereas curcumin and quercetin suffer from poor bioavailability that limits clinical translation (39,117,159,161). A full list is provided in Table IV.

In addition, several drugs in clinical use have therapeutic potential against hepatic fibrosis by modulating the p38 MAPK signaling cascade. Abdelhamid *et al* (172) showed that empagliflozin enhances the anti-fibrotic effects of metformin by reducing p38 MAPKα and ERK1/2 activity, resulting in stronger AMPK-mediated NF-κB inactivation. Similarly, fluorofenidone was demonstrated to attenuate hepatic fibrosis by suppressing HSC activation through inhibition of phosphorylation of p38 MAPK, Smad3, ERK1/2 and JNK triggered by TGF-β1 stimulation (173). Similarly, pirfenidone was shown to function as an antifibrotic agent which prevents Th2 cell formation and decreases fibrosis caused by Th2 cells through its mechanism of blocking p38 MAPK signaling (62). Halofuginone was found to exert fibrolytic effects by activating p38 MAPK, leading to increased MMP-3 and MMP-13 expression in rat HSCs, indicating that this pathway may operate differently for fibrosis treatment (174). Research has shown that current medications can be repurposed to treat various medical conditions when p38 MAPK pathways are involved in disease development (175-177).

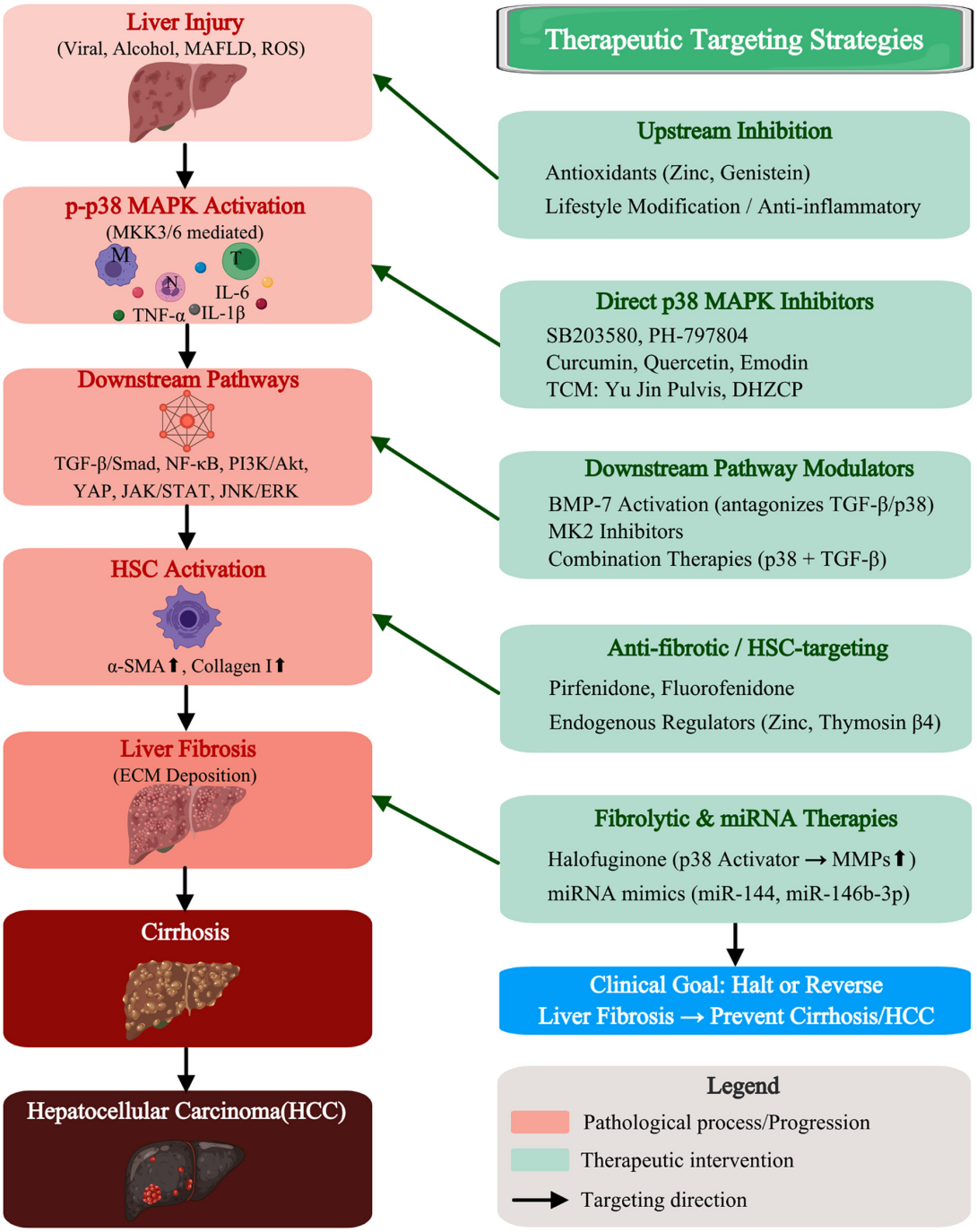

Figure 4. Therapeutic targeting of the p38 MAPK cascade in liver fibrosis. The schematic presents a comprehensive overview of the pathological progression (left column) and corresponding intervention strategies (right column) targeting different nodes of the p38 MAPK cascade. Left column, pathological progression: The cascade begins with liver injury (viral hepatitis, alcohol, MAFLD, ROS, environmental toxins), followed by p-p38 MAPK activation (via MKK3/6, with associated inflammatory cells and pro-inflammatory mediators, specifically IL-1β, IL-6 and TNF-α). Downstream signaling pathways (NF-κB, TGF-β/Smad, PI3K/Akt, YAP, JNK/ERK, JAK/STAT) then drive HSC activation (α-SMA↑, collagen I↑), resulting in hepatic fibrosis (ECM deposition), progression to cirrhosis, and ultimately HCC. Red boxes indicate pathological states; downward arrows denote disease progression. Right column, therapeutic targeting strategies: Intervention options are categorized by their point of action. Upstream inhibition (via antioxidants, lifestyle modifications) targets liver injury. Direct p38 MAPK inhibitors (SB203580, PH-797804; natural compounds such as curcumin, quercetin, emodin; TCM formulations such as Yu Jin Pulvis and Dahuang Zhechong Pill) block p-p38 activation. Downstream pathway modulators (BMP-7 activation, MK2 inhibitors, combination therapies) interfere with TGF-β/Smad and other signaling networks. Anti-fibrotic/HSC-targeting agents (pirfenidone, fluorofenidone, zinc, thymosin β4) inhibit HSC activation. Fibrolytic and miRNA-based therapies (halofuginone, a p38 activator that increases MMP-3/-13; miRNA mimics such as miR-144 and miR-146b-3p that indirectly suppress p38) promote ECM degradation or reduce p38 activity. Dashed green arrows indicate the therapeutic targeting direction toward the corresponding pathological step. Bottom right box, clinical goal: The ultimate objective is to halt or reverse liver fibrosis and prevent progression to cirrhosis or HCC. p38 MAPK, p38 mitogen-activated protein kinase; MAFLD, metabolic-associated fatty liver disease; ROS, reactive oxygen species; MKK, mitogen-activated protein kinase kinase; IL-1β, interleukin-1β; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor β-light-chain-enhancer of activated B cells; TGF-β, transforming growth factor-β; Smad, small mothers against decapentaplegic; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; YAP, yes-associated protein; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; JAK, Janus kinase; STAT, signal transducer and activator of transcription; HSC, hepatic stellate cell; α-SMA, α-smooth muscle actin; ECM, extracellular matrix; HCC, hepatocellular carcinoma; TCM, traditional Chinese medicine; BMP-7, bone morphogenetic protein 7; MK2, mitogen-activated protein kinase-activated protein kinase 2; MMP, matrix metalloproteinase; miR, microRNA.

Table IV. Summary of representative p38 MAPK inhibitors and activators with their antifibrotic profiles in liver fibrosis.

A, Inhibitors

Category	Representative Agent(s)	Mechanism of action (p38 MAPK-related)	Key efficacy in preclinical models	Research stage	Potential advantages	Limitations/ challenges	Model/evidence	(Refs.)
Synthetic small-molecule inhibitors	SB203580	Competitive ATP binding inhibitor selective for p38α/β; prevents phosphorylation of downstream substrates (ATF2 and MK2)	↓ HSC activation, ↓ α-SMA, ↓ Col I, ↓ inflammatory cytokines (TNF-α and IL-1β) in CCl_4 and DBP models	Preclinical (best-characterized tool compound)	Best-characterized tool compound; extensive *in vitro* and *in vivo* validation	Off-target effects (such as RIPK2 and CK1); lacks isoform absolute selectivity; limited clinical translation	CCl_4 and DBP-induced liver fibrosis models (rodent)	(14,84, 85,91)
	PH-797804	Potent, selective ATP-competitive p38α/β inhibitor with favorable pharmacokinetic profile	↓ fibrosis markers, ↓ collagen deposition in rodent fibrosis models	Advanced preclinical	Improved selectivity; favorable drug-like properties	Limited data specifically in liver fibrosis models; safety in chronic liver disease unknown	Rodent fibrosis models	(148)
Natural compounds (plant-derived)	Curcumin	Inhibits p38 MAPK phosphorylation; disrupts TGF-β1/p38 MAPK/ Smad crosstalk	↓ HSC activation, ↓ ECM deposition, ↓ oxidative stress	Preclinical	Multi-targeted (anti-inflammatory, antioxidant); oral bioavailability	Poor systemic bioavailability; requires high doses; limited clinical efficacy data	HSC *in vitro* models	(159)
	Quercetin	Suppresses p38 MAPK and NF-κB phosphorylation; modulates Bcl-2/ Bax balance	↓ HSC proliferation, ↓ collagen synthesis, ↓ apoptosis in hepatocytes	Preclinical	Broad bioactivity; well-tolerated; dietary source	Non-specific; pleiotropic effects complicate mechanistic interpretation	Liver fibrosis animal models	(39)
	Schisandrin B	Targets CB2 receptor in Kupffer cells; indirectly suppresses p38 MAPK/ NF-κB signaling	↓ hepatic inflammation, ↓ HSC activation, ↓ collagen deposition	Preclinical	Dual anti-inflam matory and anti-fibrotic; favorable safety profile	Mechanism indirect; p38 nhibition may tbe secondary to CB2 activation	CCl_4-induced liver fibrosis mouse model	(117)

Table IV. Continued.

A, Inhibitors

Category	Representative Agent(s)	Mechanism of action (p38 MAPK-related)	Key efficacy in preclinical models	Research stage	Potential advantages	Limitations/ challenges	Model/evidence	(Refs.)
	Emodin	Inhibits p38 MAPK and Smad signaling pathways	↓ α-SMA, ↓ Col I, ↓ HSC proliferation *in vitro*	Preclinical	Multi-pathway inhibition (p38 + Smad)	Limited *in vivo* pharmacokinetic data; potential hepatotoxicity at high doses	HSCs *in vitro*	(77)
	Dioscin	Activates Sirt1/Nrf2 axis; suppresses p38 MAPK phosphorylation	↓ oxidative stress, ↓ HSC activation, ↓ ECM accumulation	Preclinical	Combines antioxidant and anti-p38 effects	Insufficient large-animal validation	BDL and DMN-induced liver fibrosis models	(158)
	Astragaloside IV, gossypetin, baicalin, hydroxysafflor yellow A, oxymatrine, and oleanolic acid derivative (CPU-II2)	Directly inhibit p38 MAPK phosphorylation or block upstream activation	↓ HSC activation, ↓ fibrosis markers in various models	Preclinical	Diverse structural scaffolds; potential for optimization	Variable potency; mechanism details often incomplete	Various liver fibrosis models (CCl_4, HSCs)	(53, 102, 119, 154-157)
	Isorhamnetin, spinosin, betulin, ankaflavin/ monascin, salvianolic acid A/B, butein, neferine, Total C-21 steroidal glycosides, DLPC, γ-linolenic acid,	Achieve broader pathway inhibition targeting p38 MAPK alongside TGF-β/ Smad, NF-κB, Nrf2, JNK and ERK, PI3K/Akt	↓ HSC activation, ↓ ECM deposition, ↓ inflammation	Preclinical	Multi-target effects may enhance efficacy	Pleiotropic effects; primary target often unclear	Multiple liver fibrosis models (CCl_4, BDL, HSCs)	(40, 76, 160-171)

Table IV. Continued.

A, Inhibitors

Category	Representative Agent(s)	Mechanism of action (p38 MAPK-related)	Key efficacy in preclinical models	Research stage	Potential advantages	Limitations/ challenges	Model/evidence	(Refs.)
	cannabidiol, ursolic acids, and caffeine							
	Harmine	Inhibits p38 MAPK phosphorylation; modulates AMPK/mTOR signaling	↓ excessive autophagy, ↓ inflammation, ameliorates CCl_4-induced acute liver injury	Preclinical	Natural β-carboline alkaloid; unique autophagy-modulating mechanism	Context-dependent; opposite effect compared with SB203580 on autophagy; requires further validation in fibrosis models	CCl_4-induced acute liver injury model (mice)	(129)
TCM formulations	Yu Jin Pulvis	Blocks p38 MAPK and PI3K/Akt signaling pathways	↓ CCl_4-induced fibrosis, ↓ HSC activation, ↓ inflammatory infiltration	Preclinical	Multi-compound, multi-target synergy; historical clinical use	Complex composition; active components undefined; quality control challenges	CCl_4-induced liver fibrosis in rats	(22)
	Dahuang Zhechong pill	Downregulates the p38 MAPK/NF-κB/TGF-β1 pathway	↓ HSC activation, ↓ collagen deposition, ↓ pro-inflammatory cytokines	Preclinical	Classic TCM formula with demonstrated anti-fibrotic efficacy	Mechanism not fully deconvoluted; standardization issues	Rat models of hepatic fibrosis	(150, 151)
	Fuzheng Huayu Recipe	Restores TGF-β1/BMP-7 balance; suppresses p38 MAPK phosphorylation; promotes MET in HSCs	↓ HSC activation, ↓ EMT, □ MET, ↓ fibrosis stage	Clinically used in China for hepatitis fibrosis; multiple RCTs published	Clinically validated efficacy; restores EMT/ MET balance and promotes fibrosis resolution	Western validation limited; mechanistic complexity	Clinical trials (RCTs) in hepatitis fibrosis	(130)

Table IV. Continued.

A, Inhibitors

Category	Representative Agent(s)	Mechanism of action (p38 MAPK-related)	Key efficacy in preclinical models	Research stage	Potential advantages	Limitations/ challenges	Model/evidence	(Refs.)
	Jiawei Taohe Chengqi decoction, Yinchenhao decoction	Regulates p38 MAPK and PI3K/Akt pathways	Reverses hepatic fibrosis in animal models	Preclinical	Traditional use; multi-component synergy	Active components often undefined; quality control challenges	CCl_4-induced liver fibrosis animal models	(7, 152)
Drug repurposing candidates	Empagliflozin + Metformin	Reduces p38 MAPKα and ERK1/2 activity; enhances AMPK-mediated NF-κB inactivation	↓ CCl_4-induced fibrosis, ↓ oxidative stress, ↓ inflammation	Clinically approved for diabetes	Clinically approved; known safety profiles; synergistic potential	Not a direct p38 inhibitor; p38 modulation is indirect	CCl_4-induced liver fibrosis in mice	(172)
	Pirfenidone	Inhibits p38 MAPK signaling; restricts Th2 differentiation	↓ Th2 response, ↓ HSC activation, ↓ collagen deposition	Approved for IPF	Approved for IPF; repurposing opportunity	Moderate potency; multiple mechanisms beyond p38 inhibition	Experimental liver fibrosis (Th2-driven)	(62)
	Fluorofenidone (AKF-PD)	Inhibits TGF-β1-induced p38 MAPK, ERK1/2, JNK, and Smad3 phosphorylation	↓ HSC activation, ↓ ECM production, ↓ fibrotic markers	Preclinical/early clinical	Novel pyridone derivative; broad anti-fibrotic activity	Still in preclinical/ early clinical stages	Hepatic fibrosis models	(173)
Endogenous/ metal ion-based	Zinc supplementation	Antioxidant; directly inhibits p38 MAPK signaling in HSCs	↓ ethanol/ acetaldehyde-induced HSC activation, ↓ ROS, ↓ collagen	Physiologic nutrient	Physiologic nutrient; excellent safety profile; low cost	Indirect; p38 inhibition may be partial; efficacy in advanced fibrosis unclear	Ethanol/ acetaldehyde-induced HSCs	(115)
	Thymosin β4 (Tβ4)	Blocks NF-κB and JNK/ p38 MAPK signaling; inhibits NLRP3 inflammasome	↓ LPS/ATP-induced HSC activation, ↓ inflammation	Preclinical	Endogenous peptide; pleiotropic protective effects cost	Protein therapeutic; delivery challenges;	LPS/ATP-induced HSCs	(179)

ww IV. Continued.

B, Activators

Category	Representative Agent(s)	Mechanism of action (p38 MAPK-related)	Key efficacy in preclinical models	Research stage	Potential advantages	Limitations/ challenges	Model/evidence	(Refs.)
Drug repurposing candidate	Halofuginone	Activates p38 MAPK signaling (fibrolytic effect)	Increases MMP-3 and MMP-13 expression in rat HSCs	Preclinical	Distinct fibrolytic mechanism; promotes ECM degradation	Opposite to most p38 inhibitors; mechanism requires further validation; potential safety concerns	Rat HSCs *in vitro*	(174)

ATP, adenosine triphosphate; p38 MAPK, p38 mitogen-activated protein kinase; p38α, p38 mitogen-activated protein kinase α; p38β, p38 mitogen-activated protein kinase β; ATF2, activating transcription factor 2; MK2, MAPK-activated protein kinase 2; HSC, hepatic stellate cell; α-SMA, α-smooth muscle actin; Col I, collagen type I; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; CCl_4, carbon tetrachloride; DBP, dibutyl phthalate; TGF-β1, transforming growth factor-β1; Smad, suppressor of mothers against decapentaplegic; ECM, extracellular matrix; NF-κB, nuclear factor κB; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; CB2 receptor, cannabinoid receptor type 2; Sirt1, sirtuin 1; Nrf2, nuclear factor erythroid 2-related factor 2; BDL, bile duct ligation; DMN, dimethylnitrosamine; CPU-II2, oleanolic acid derivative CPU-II2; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; DLPC, dilauroyl phosphatidylcholine; AMPK, AMP-activated protein kinase; mTOR, mechanistic target of rapamycin; TCM, traditional Chinese medicine; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; BMP-7, bone morphogenetic protein-7; MET, mesenchymal-to-epithelial transition; EMT, epithelial-to-mesenchymal transition; RCT, randomized controlled trial; ERK1/2, extracellular signal-regulated kinases 1 and 2; Th2, T helper 2; IPF, idiopathic pulmonary fibrosis; AKF-PD, fluorofenidone; ROS, reactive oxygen species; Tβ4, thymosin beta 4; NLRP3, NOD-like receptor family pyrin domain-containing 3; LPS, lipopolysaccharide; MMP-3, matrix metalloproteinase-3; MMP-13, matrix metalloproteinase-13.

Furthermore, other endogenous compounds can also exert anti-liver fibrotic effects through p38 MAPK. Cyclin-dependent kinase inhibitor 2A/p16 deficiency was shown to lead to increased ROS production in HSCs via p38 MAPK activation, whereas thymosin β4 stopped HSC activation by blocking NF-κB and JNK/p38 MAPK signaling pathways, which are activated by NLRP3 after LPS exposure (178,179). The antioxidant enzyme glutathione S-transferase α3 was found to function as an HSC activation blocker, as it prevents activation of both glycogen synthase kinase 3β and p38 MAPK signaling pathways (180). Taurine was demonstrated to induce HSC apoptosis through increased TGF-β1 expression, which activates the p38 MAPK-JNK-caspase-9/8/3 signaling pathway (181).

Moreover, supplementation with metal ions, particularly zinc, has been observed to suppress ethanol- and acetaldehyde-induced HSC activation via various mechanisms. This effect is attributed to its role as an antioxidant and as an inhibitor of the p38 MAPK signaling pathway (115) (representative p38 MAPK inhibitors/activators and their anti-fibrotic effects in liver fibrosis are listed in Table IV).

Future studies should determine how different signaling pathways interact, informed by emerging research on liver fibrosis development. It has been shown that the TGF-β and p38 MAPK pathways work together to regulate fibrogenesis. The discovery shows that treatment of liver fibrosis requires a comprehensive approach that targets multiple disease mechanisms simultaneously to achieve improved treatment outcomes (31).

Despite promising data supporting p38 MAPK as a therapeutic target, challenges remain in the clinical translation of p38 MAPK inhibitors. The therapeutic efficacy and safety profiles of compounds in clinical trials remain under investigation. The specific characteristics of these inhibitors matter because p38 MAPK participates in various bodily processes so that broad inhibition would lead to unwanted side effects. The development of p38 MAPK therapies requires researchers to address two essential factors: Off-target effects and the need for specific inhibitors to reduce harmful side effects. The development of selective inhibitors targeting particular p38 MAPK isoforms or their downstream effectors may yield improved therapeutic outcomes with fewer side effects (182). The distinct expression patterns and functional characteristics of each p38 MAPK isoform, highlighting p38δ as a promising target in MAFLD-associated fibrosis are summarized in Table I.

The clinical development of p38 inhibitors has been marked by significant pharmacokinetic and therapeutic challenges, underscored by the dose-dependent exposure of agents such as the oral drug ralimetinib in patients with cancer, yet is plagued by off-target effects typical of conventional ATP-competitive inhibitors that disrupt physiological processes such as regulatory T-cell proliferation and cause serious adverse effects, discouraging clinical application (183-185). This challenge is further highlighted by research showing divergent therapeutic outcomes between the p38α-specific inhibitor VCP979 and the dual p38α/β inhibitor SB203580 in cancer-associated cachexia, emphasizing the need for improved selectivity (186). Lessons from failed trials in inflammatory diseases are instructive: In chronic obstructive pulmonary disease (COPD), losmapimod failed to improve physical capacity or pulmonary function notwithstanding favorable tolerability, and in atherosclerosis, BIRB 796 (doramapimod, an efficient and a specific inhibitor targeting p38 MAPK) and BMS-582949 (an orally active and potent inhibitor exhibiting high selectivity for p38α MAPK) did not reduce arterial inflammation when compared with the placebo, suggesting that p38 inhibition alone may be insufficient and may require combination strategies (187-189). In rheumatoid arthritis (RA), despite p38 MAPK being a central inflammatory mediator, numerous inhibitors have failed in advanced trials due to limited efficacy and tachyphylaxis, where initial anti-inflammatory effects wane over time (190,191). Selectivity and toxicity remain critical barriers, as non-selective inhibition of this master kinase disrupts fundamental physiological pathways, compromising the therapeutic window (190). Consequently, an emerging strategy is to target downstream effectors such as MAPK-MK2; early data show that MK2 inhibition can produce sustained anti-inflammatory effects in RA without the tachyphylaxis observed with direct p38 inhibitors (191). This approach represents a valuable lesson: Modulating the pathway at a more downstream node may preserve regulatory functions while improving efficacy and tolerability (190,191).

Future research should determine how p38 MAPK induces disease progression, develop targeted inhibitors, and test combination therapies that leverage the multiple signaling routes of p38 MAPK for medical applications. An integrated view of these therapeutic strategies, highlighting the hierarchical relationship between signaling nodes and intervention points, is presented in Fig. 4. Future research should determine how these inhibitors work and assess their potential medical benefits and safety. Advances in p38 MAPK signaling research will lead to improved treatment outcomes for patients with various chronic diseases through the development of specific, potent inhibitors. Given the extensive crosstalk illustrated in Fig. 3, combination therapies that simultaneously target p38 MAPK and its interacting pathways (such as TGF-β/Smad, NF-κB, or PI3K/Akt) may offer greater efficacy than a single-agent approach.

5. Current controversies and future directions

Despite the substantial evidence establishing p38 MAPK as a key driver of liver fibrosis, the literature reveals several apparent contradictions that warrant careful consideration. These discrepancies likely stem from the context-dependent nature of p38 MAPK signaling, in which outcomes vary by cell type, activation stage, upstream regulators, and the specific stimuli involved. Resolving these controversies will be essential for translating p38 MAPK-targeted therapies into clinical practice. Recent studies across different tissues and disease models have further illuminated these complexities and opened new avenues for therapeutic intervention (192-197).

Cell and context-specific functions. One of the most significant controversies concerns the dual role of p38 MAPK in cell survival and death. Research has shown that p38 MAPK activation can either promote or suppress apoptosis depending on the cellular context. For example, fibulin-1 was shown to promote HSC activation via the p38 MAPK

pathway, suggesting a pro-survival, pro-fibrogenic role in these cells (198). Conversely, in cardiomyocytes, upregulation of dual specificity protein phosphatase 4 was found to mitigate doxorubicin-induced cardiotoxicity by inhibiting the p38 MAPK/MK2 signaling axis, thereby underscoring the protective effect of p38 inhibition in parenchymal cells (199). In hepatocytes exposed to toxic agents, p38 MAPK activation under oxidative stress was demonstrated to lead to cell death, while in activated HSCs, it promoted survival and fibrogenic activity (14). The differential engagement of downstream substrates, such as p53 and Bax in hepatocytes vs. survival factors in HSCs, may explain these opposing outcomes (200-202). These opposing outcomes can be reconciled by conceptualizing p38 MAPK as a 'context-dependent rheostat': In mesenchymal cells such as HSCs and osteoblasts, its activation supports survival and differentiation, whereas in parenchymal cells such as hepatocytes and cardiomyocytes, it predominantly mediates stress-induced apoptosis (203,204). This cell-type-specific duality highlights that therapeutic targeting must consider not only the kinase itself but also the cell-type-specific downstream effector landscape. Given this duality, systemic p38 MAPK inhibitors are unlikely to succeed in liver fibrosis; instead, cell-type-specific delivery strategies (such as HSC-targeting nanoparticles) or isoform-selective inhibitors that spare hepatocyte p38α should be prioritized.

Stage-dependent effects and upstream regulation in HSC activation. Further complicating the picture, p38 MAPK appears to exert stage-dependent effects during HSC activation. Research has demonstrated that blocking p38 MAPK during the early stages of HSC activation reduces α-SMA expression, whereas inhibiting this kinase in already-activated HSCs fails to produce similar effects. Moreover, p38 suppression in activated HSCs paradoxically increased cell proliferation, suggesting that p38 MAPK may exert anti-proliferative functions once HSCs have fully transdifferentiated (85). These stage-dependent effects can be conceptualized through a 'temporal switch' model: In early HSC activation or acute inflammation, p38 MAPK drives a pro-fibrogenic and pro-inflammatory program, whereas in established disease, its sustained activation may shift toward growth-suppressive or tissue-remodeling functions. This implies that the therapeutic window for p38 MAPK inhibitors may be limited to early fibrotic stages, with potential risks if administered during established disease.

Emerging evidence suggests that targeting regulators upstream of p38 MAPK activation, rather than the kinase itself, may offer a more precise therapeutic window. In MASH, ubiquilin 1 (UBQLN1) was found to initiate the p38 MAPK pathway by mediating the degradation of its suppressor, suppressor of IKKε (SIKE). Inhibition of this UBQLN1-SIKE-p38 MAPK axis mitigated hepatic steatosis and fibrosis (196). This indicates that the pathological activation of p38 MAPK is tightly controlled by specific upstream modulators, and interventions at this level could be more effective and potentially stage-specific than direct kinase inhibition.

Dual roles in ECM remodeling and inflammation. p38 MAPK also displays opposing functions in ECM turnover. While it promotes ECM deposition by stabilizing collagen mRNA (86), it can also induce MMPs, including MMP-1, MMP-3, and MMP-13 (87-89). In intervertebral disc degeneration, baicalin exerted protective effects by suppressing the p38 MAPK signaling cascade, leading to downregulation of catabolic factors such as MMP-3 and MMP-13 (205). Conversely, its well-established role in driving the synthesis of pro-inflammatory cytokines, specifically IL-6, IL-1β, and TNF-α, has been confirmed in models of shoulder adhesive capsulitis and gastric ulcers, where p38 inhibition reduced inflammation and tissue fibrosis (197,206). Similarly, in the context of inflammation, p38 MAPK acts primarily as a pro-inflammatory mediator, yet it can also participate in protective antioxidant responses under certain conditions, such as genistein-mediated cardioprotection (27). This functional dichotomy can be understood through a 'temporal-spatial switch' model: In early acute responses, p38 MAPK drives pro-inflammatory cytokine synthesis and ECM remodeling, whereas in chronic settings, its sustained activation may shift toward catabolic MMP expression (such as MMP-3 and MMP-13) or tissue degradation. The net effect, pro-fibrotic or fibrolytic, is dictated by the balance between these outputs, which in turn depends on cell type, disease stage, and the duration of pathway engagement (103).

Autophagy and novel cell death mechanisms. The relationship between p38 MAPK and cellular degradation pathways extends beyond classical apoptosis to include autophagy and ferroptosis. Research indicates that inhibiting p38 MAPK with SB203580 restores the autophagic flux by blocking the inhibitory phosphorylation of p38 on ULK1 (128). Conversely, the natural compound harmine was shown to reduce excessive autophagy in CCl_4-induced liver injury by inhibiting p38 MAPK and modulating AMPK/mTOR signaling (129). In acute kidney injury induced by depleted uranium, downregulation of ethylmalonic encephalopathy 1 led to ROS-mediated activation of the p38 MAPK pathway, which subsequently promoted nuclear receptor coactivator 4-mediated ferritinophagy, ultimately triggering renal cell ferroptosis (207). In neutrophils, constitutive p38 MAPK phosphorylation was found to be involved in spontaneous apoptosis, as SB203580 and antisense oligonucleotides delayed apoptosis by ~24 h (208). These findings indicate that p38 MAPK serves as a 'stress-responsive hub' that integrates signals toward apoptosis, autophagy, or ferroptosis depending on the cellular context and upstream stimuli. For instance, in renal cells, p38 activation has been shown to lead to ferroptotic cell death, while in neutrophils, it has been found to promote spontaneous apoptosis as a physiological clearance mechanism (207,209). The final outcome is determined by the balance of ROS, AMPK/mTOR status, and the availability of iron-dependent pathways.

Challenges in clinical translation. The clinical translation of p38 MAPK inhibitors continues to face significant hurdles, primarily owing to adverse toxic effects and insufficient therapeutic benefit in complex diseases (210). While preclinical studies demonstrate promising anti-fibrotic efficacy, clinical trials in other inflammatory diseases have revealed issues with dose-dependent toxicity, off-target effects, and tachyphylaxis, where initial anti-inflammatory effects wane over time (190,191). For example, in COPD, losmapimod failed to

improve exercise tolerance despite good tolerability (187). In atherosclerosis, BIRB 796 (doramapimod) and BMS-582949 did not reduce arterial inflammation vs. placebo (188). These failures suggest that p38 MAPK inhibition alone may be insufficient and may require combination strategies (189). Moreover, the lack of isoform selectivity in early inhibitors likely contributed to adverse effects by disrupting physiological p38 MAPK functions in non-target tissues (184,185). These divergent therapeutic outcomes between p38α-specific inhibitors and dual p38α/β inhibitors in conditions such as cancer-associated cachexia further underscore the need for isoform-selective approaches (186).

Emerging strategies and future directions. To overcome current challenges, several strategies should be prioritized. Recognizing that direct p38 MAPK inhibition has faced clinical hurdles due to tachyphylaxis and toxicity, a shift toward more upstream or downstream nodes within the pathway is warranted. First, targeting downstream effectors such as MK2 may offer sustained anti-inflammatory effects without the tachyphylaxis observed with direct p38 MAPK inhibitors (191). Furthermore, exploiting upstream regulators, such as the UBQLN1-SIKE axis, or inducing inhibitory post-translational modifications, offers novel avenues for precise intervention that may avoid the toxicity associated with direct kinase inhibition. This upstream-downstream dichotomy can be framed as a 'hierarchical targeting strategy': Intervening at the level of a single, context-specific upstream regulator may yield more selective effects than blocking the pleiotropic p38 MAPK kinase itself, and targeting a downstream effector could circumvent compensatory feedback loops that cause tachyphylaxis.

Second, cell-type-specific targeting is being explored. For example, the myeloid-specific p38α inhibitor MPL-5821 was shown to potently augment the inflammatory and phagocytic responses of human macrophages against *Staphylococcus aureus* without causing systemic toxicity, thereby presenting a novel antibacterial approach (211). Hence isoform- and cell-type-selective inhibitors, such as MPL-5821, for specific cell populations (for example, myeloid cells) can minimize on-target, off-tissue effects (196,211,212). The distinct tissue distribution and functional roles of p38α, p38β, p38γ, and p38δ make isoform-selective inhibitors a promising avenue, particularly for p38δ, in MAFLD-associated fibrosis (33,124,125). This approach is supported by evidence that while p38α is ubiquitously expressed and drives canonical inflammatory responses, p38δ is enriched in myeloid and hepatic cells and is linked to steatohepatitis and fibrosis. Thus, isoform selectivity offers a 'cellular precision' strategy that could preserve the protective functions of other p38 isoforms in non-target tissues.

Third, the success of combination regimens in SMA models should be rigorously tested in fibrotic diseases, potentially pairing p38 pathway modulators with anti-fibrotic, anti-inflammatory, or metabolic agents (213). In spinal muscular atrophy (SMA), pharmacological inhibition of p38 MAPK synergized with survival motor neuron-upregulating drugs, enhancing motor neuron survival and synaptic rewiring, demonstrating a powerful combinatorial neuroprotective strategy (213). Given the extensive crosstalk illustrated in Fig. 3, co-targeting p38 MAPK with TGF-β/Smad, NF-κB, or PI3K/Akt may yield synergistic effects while allowing lower doses of individual agents, thereby minimizing toxicity (14,20). This combination approach is conceptually supported by the observation that p38 MAPK functions not in isolation but as a 'signaling hub' that integrates with the MAPK family (ERK and JNK) and the TGF-β1 pathway to drive HSC activation and ECM remodeling (106,214). A rational combination, for instance, pairing a p38 inhibitor with a TGF-β receptor kinase inhibitor, could disrupt both the initiation and the maintenance phases of fibrosis. Fourth, elucidating the precise molecular determinants that dictate the pro-fibrotic vs. the protective outcomes of p38 MAPK, whether they are post-translational modifications, interacting partners, or spatial signaling dynamics, will be essential for developing context-aware therapeutics. Emerging technologies, including single-cell transcriptomics and spatial proteomics, offer powerful tools to dissect p38 MAPK signaling heterogeneity across hepatic cell populations during fibrosis progression and regression.

Fifth, novel approaches to target the pathway are being discovered. A vitamin C-based nanostructure was found to inhibit hepatic stellate cell proliferation and fibrosis by covalently modifying p38 MAPK (vitcylation), blocking its nuclear translocation and inducing cell cycle arrest (212). This represents a move beyond traditional ATP-competitive inhibitors and potentially enabling context-specific modulation.

In summary, the contradictions in the p38 MAPK literature do not diminish its importance as a therapeutic target but rather underscore the need for more nuanced approaches. The apparent contradictions in cell survival, ECM turnover, and autophagy regulation can be reconciled by viewing p38 MAPK as a 'context-dependent signaling rheostat,' where its output is determined by a 'temporal-spatial switch' (pro-fibrotic early, anti-proliferative late) and a 'bidirectional modulator' of autophagy and cell death pathways (175,177,215). Previous studies reinforce p38 MAPK as a master regulator in fibrosis and related pathologies within a highly contextual signaling network (124,216-219). The apparent contradictions highlight its pleiotropic functions rather than invalidating it as a target. The future lies in developing sophisticated intervention strategies that account for cellular context, disease stage, and pathway crosstalk to harness their therapeutic potential safely. Moving forward, the field must prioritize isoform-specific targeting, stage-dependent interventions, and rational combination regimens to translate the promise of p38 MAPK modulation into effective clinical treatments for patients with progressive liver fibrosis.

6. Conclusions

The convergence of molecular, pharmacological, and clinical evidence positions p38 MAPK as a nodal signaling hub in the pathogenesis of liver fibrosis. Rather than acting as a linear mediator, p38 MAPK integrates diverse fibrotic inputs, including inflammatory cytokines, oxidative stress, and mechanical cues, and translates them into coordinated cellular outputs through extensive crosstalk with signaling cascades such as NF-κB, TGF-β/Smad, PI3K/Akt, and YAP. This central role, underscored by consistent preclinical efficacy of p38 MAPK inhibition across multiple injury models, establishes the pathway as a compelling therapeutic target.

However, several critical challenges must be addressed to translate these findings into clinical practice. First, the p38 MAPK pathway serves as a highly context-dependent signaling hub, with its often-opposing functions, such as promoting injury in some cell types, such as hepatocytes, while supporting survival in others, such as activated HSCs, demanding cell-type-specific or temporally controlled targeting strategies. The ultimate role of p38 is critically determined by the inherent function of the cell, divergent upstream activators and contexts, differential engagement of downstream substrates, and integration with other signaling networks. For example, the ASK1-p38 axis is a key driver of hepatocyte death in injury models. By contrast, its activity in the hepatic milieu also supports processes such as fibrosis that depend on the survival of activated HSCs (41,220). In hepatocytes, pro-inflammatory mediators, specifically IL-1β, TNF-α, oxidative stress, and DNA damage, typically activate p38 (especially p38α), signals often tightly coupled with death receptor pathways and endoplasmic reticulum stress, steering p38 toward pro-apoptotic outcomes. Conversely, in activated HSCs, p38 activation is frequently driven by pro-fibrotic growth factors, including PDGF and TGF-β, which primarily promote cell proliferation, migration, and ECM production within a signaling context that favors activation of survival-related downstream substrates. This cell-type-specific duality underscores the therapeutic challenge of targeting p38 in complex liver diseases, as systemic inhibition might simultaneously protect parenchymal cells while potentially mitigating fibrogenesis. Second, the four p38 MAPK isoforms exhibit distinct tissue distribution and functional roles; developing isoform-selective inhibitors (particularly p38α vs. p38δ) may improve efficacy and reduce off-target toxicity. Third, the complex crosstalk between p38 MAPK and other pro-fibrotic networks argues against single-agent approaches. Future therapeutic efforts should prioritize rational combination regimens that simultaneously disrupt multiple nodes, for example, co-targeting p38 MAPK and TGF-β signaling or integrating p38 inhibitors with antioxidants and senolytic agents.

Beyond pharmacology, key mechanistic questions remain unanswered. The precise molecular switches that dictate the pro-fibrotic vs. protective outcomes of p38 MAPK are poorly defined. Elucidating these determinants, whether post-translational modifications, interacting partners, or spatial signaling dynamics, will be essential for developing context-aware therapeutics. Emerging technologies, including single-cell transcriptomics and spatial proteomics, offer powerful tools to dissect p38 MAPK signaling heterogeneity across hepatic cell populations during fibrosis progression and regression.

In summary, p38 MAPK represents not merely a biomarker of liver injury but a functional linchpin of the fibrotic cascade. Advancing this target toward clinical application will require a paradigm shift from broad kinase inhibition to precision-oriented strategies that account for isoform specificity, cellular context, and pathway interdependence. By addressing these challenges, the field can transform mechanistic insights into durable therapies for patients with progressive liver fibrosis. Particularly, isoform-selective inhibitors targeting p38δ in MAFLD, or combination therapies co-targeting p38 MAPK and TGF-β receptors, represent the most promising near-term translational avenues.

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Competing interests

The authors declare that they have no competing interests.

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