Letters in Applied NanoBioScience
Open-Access Journal (ISSN: 2284-6808)

Review
Volume 15, Issue 2, 2026, 83
https://doi.org/10.33263/LIANBS152.083

Mechanotransduction Pathways in Liver Fibrosis: a Comprehensive Narrative Review

Muhammad Jehangir [1,*], Kashif Kashmiri [2], Muhammad Tayyab [3], Rakhmatullokh Kakhramonov [4], Ali Danish Alvi [5,*]

[1] Jiangsu Provincial University Key Laboratory of Intelligent Medical Sensing Materials and Devices, Institute of Chemical Biology and Functional Molecules, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China
[2] School of Pharmacy, Medical Campus of Shihezi University No. 59, North 2nd Road, Shihezi City, Xinjiang, China.
[3] School of Pharmaceutical Sciences, Nanjing Tech University, Nanjing, China
[4] China Pharmaceutical University, Nanjing 211198, Jiangsu, China
[5] School of Pharmaceutical Sciences, Nanjing Tech University, Nanjing, China
* Correspondence: jehangirm62@gmail.com; l20236110518@njtech.edu.cn;

Received: 10.08.2025; Accepted: 28.02.2026; Published: 30.06.2026

Abstract: Liver fibrosis involves progressive extracellular matrix (ECM) remodeling that creates a stiff microenvironment, driving hepatic stellate cell (HSC) activation. This narrative review summarizes current advances in the understanding of mechanotransduction pathways—including integrin signaling, *Hippo–YAP/TAZ*, *TGF-β*, and mechanosensitive ion channels—that convert mechanical cues into profibrotic responses. We highlight how ECM stiffness and cytoskeletal tension regulate HSC activation, inflammation, and fibrogenesis. Recent therapeutic approaches aim to modulate tissue mechanics or inhibit key mechanotransduction targets such as *Rho/ROCK* and *YAP/TAZ*, showing promising antifibrotic potential in preclinical studies. By integrating emerging mechanistic insights and progress in drug development, this review provides future research directions toward clinically viable mechanotransduction-based therapies.

Keywords: liver fibrosis; hepatic stellate cells; extracellular matrix; anti-fibrotic therapies; Signaling pathways; hippo pathway; Rho/ROCK; notch signaling.

1. Background

The mechanisms of cell interactions with the extracellular matrix (ECM), adjacent cells, and surrounding fluids determine its capacity to detect physical stress. A set of intracellular molecular mechanisms collectively termed mechanotransduction converts mechanical stimuli into biochemical responses in living systems, thereby influencing various cellular characteristics [1-3]. The hepatic microstructure possesses unique mechanical properties, and an optimal microenvironment is vital for its specialized roles in synthesis, metabolism, detoxification, and immune protection [4]. Mechanotransduction pathways are deeply involved in both liver repair and injury. When the liver experiences mechanical stress, these pathways convert physical forces into biochemical signals that guide cellular behavior and drive tissue remodeling [5]. Recent studies on liver cells have revealed new evidence that mechanical signals play a crucial role in the onset and progression of liver diseases. Structural and

functional abnormalities within the liver can both arise from and contribute to abnormal mechanical stress [6]. Mechanotransduction pathways are particularly significant among the multiple cellular mechanisms contributing to liver injury [7,8]. Two well-characterized mechanotransduction pathways, *RhoA/ROCK* and *YAP/TAZ*, regulate cellular behavior and phenotype across multiple liver cell types. Integrin-mediated focal adhesions serve as the primary structures that sense mechanical cues from the hepatic extracellular matrix (ECM), while downstream signaling routes such as *SRF* and *YAP/TAZ* respond dynamically to changes in liver tissue stiffness during chronic fibrosis [9,10].

Identifying potential therapeutic targets within these cellular signaling cascades is critical for advancing the treatment of liver diseases. In recent years, substantial progress in understanding the molecular and cellular mechanisms underlying liver injury and cirrhosis has paved the way for the development of novel antifibrotic agents. Several of these compounds have already reached phase II or III clinical trials, while others are moving closer to regulatory approval [11]. Although substantial progress has been achieved, mechanotransduction in liver fibrosis remains a dynamic and evolving field of study. Key pathways such as *YAP/TAZ* and *TGF-β* have been extensively characterized, whereas others—including *Notch signaling* and *Rho GTPase* networks—have received comparatively less attention. This review aims to summarize the major mechanotransduction pathways and their pharmacological targets, emphasizing their roles in hepatic stellate cell (HSC) activation and the early stages of hepatic fibrogenesis. By examining these critical signaling mechanisms, this work seeks to provide a deeper understanding of their functions and potential as therapeutic intervention points.

2. Search Strategy

A systematic literature search was conducted for this narrative review to ensure that the most comprehensive and up-to-date developments were covered. Relevant research articles, reviews, and short communications published over the last five years (2020–2025) were retrieved from online databases including Xmol, Google Scholar, ScienceDirect, PubMed, SciSpace, Elicit, and Research Rabbit. The main search keywords included "liver fibrosis," "mechanotransduction," "hepatic stellate cells," "*YAP/TAZ*," "*RhoA/ROCK*," "*Notch signaling*," and "*TGF-β*."Studies that explore the role of mechanotransduction pathways in liver fibrosis and liver diseases, or hepatic stellate cell activation, were added. Experimental data, both *In vitro* and *in vivo*, and all kinds of review papers were taken into consideration. However, articles that were not in English or lacked information on mechanotransduction or liver fibrosis and mechanotransduction pathways were not included. Recent findings, molecular understanding, and feasible therapeutic implications of key signaling pathways were highlighted throughout the selection process. To identify new research gaps and potential fields for future study, the collected literature was reviewed, arranged by routine, and summarized.

3. Types of Mechanical Stimuli in Liver Injury

An increase in matrix stiffness, shear stress, compression, and mechanical stretch significantly impacts liver injury and regeneration. To regulate gene transcription and biological responses, mechanoreceptors collect data on mechanical forces and transmit it to the cell. Mechanotransduction is the name given to the process that occurs in response to mechanical stimuli [12]. Mechanotransduction is mediated by the cytoskeleton, the extracellular matrix, and focal adhesions, which are linked to integrins [13-15]. Because they

activate portal fibroblasts and hepatic stellate cells, chronic liver diseases, such as cancer and fibrosis, contribute to the development of a stiff liver, as noted by Joung *et al*. Drug-induced liver damage (which may be exacerbated by mechanical changes in the liver environment), Pu Delves further explains the function of mitochondrial and endoplasmic reticulum stress [16-18]. Research has demonstrated that long-term mental stress can worsen liver damage and fibrosis [19-22]. Altering the composition of gut microbiota causes inflammation in liver tissue. This occurs because ingested lipopolysaccharides (LPS) trigger inflammation by activating the Toll-like receptor 4 (TLR4) pathway in the liver [23].

4. The Molecular Mechanism Involved in Mechanotransduction

Molecular genetics has taken over the medical sector, putting molecular biology on the back burner. This is noteworthy given that numerous diseases arise from mechanical or structural abnormalities in tissues. This process might be affected by alterations in the extracellular matrix, cellular mechanics, or dysregulation of molecular pathways that enable cells to detect mechanical signals and respond chemically or electrically. The molecular processes underlying the initial phase of mechanosensing, which involves tensioned protein complexes translating changes in physical force into cellular signaling, remain a mystery [24]. Protein phosphorylation, allostery control of enzyme activity, and binding sites are the same principles of signal transmission for both biochemical and mechanically driven signaling, although there are notable distinctions. In their Commentary, Huveneers *et al*. aim to understand the molecular mechanisms by focusing on mechanotransduction at cell-cell junctions [25]. In their analyses of the responses of blood vessels and chondrocytes to mechanical stimuli, Yamashiro and Zhao both highlight the roles of several receptors and downstream pathways [26,27]. The sensory nerve terminals are the first sites of mechanotransduction in mammals, where mechanical stresses are rapidly transformed into electrical impulses. Kassianidou further explores the role of nucleocytoplasmic transport in the selective translocation of mechanosensitive transcription factors. New studies have elucidated the molecular identities and basic properties of mechanotransducer channels. Mechanical stimulation may activate cation channels (Piezo1, TRPV4, and ENaC), which, *in turn, activate several* mechanotransducer channels.

5. Major Signaling Pathways in Liver Fibrosis and HCC

Wang *et al*. offer a thorough review of the signaling pathways involved in liver regeneration and repair. These results, *taken together, show the critical role of signaling pathways in liver injury and regeneration, which may inform* the development of specific therapies. Mechanical stresses and alterations in the extracellular matrix environment after damage greatly affect liver regeneration [30]. Notch signaling, YAP/TAZ, and RHO/ROCK are among the crucial signaling pathways engaged in numerous cellular activities, including metabolism, cancer, and stem cell biology. The interconnection and regular cooperation of these pathways in regulating cell fate and behavior increase the complexity of cellular signaling networks [31]. Emphasizing the importance of the Rho/ROCK pathway in several diseases, Han focused primarily on its relevance in liver damage [32]. Moreover, Jaeschke underlined the critical role of reactive oxygen species in inflammatory liver injury, under the control of the Rho/ROCK signaling pathway [33].

5.1. Hippo Yap/Taz signaling pathway and its therapeutic inhibition in liver fibrosis and HCC.

According to Sino Dupont *et al*., YAP and TAZ are central components of the Hippo signaling pathway and play critical roles in mechanotransduction. The Hippo pathway is a fundamental mechanism by which cells respond to various mechanical signals, including stress, extracellular matrix (ECM) stiffness, adhesion, and cell shape [34,35]. While YAP/TAZ act as key effectors of these signals, the molecular mechanisms linking mechanical input to Hippo signaling remain unclear [36]. Initially identified in Drosophila, the Hippo pathway regulates tissue growth [37]. MST1/2, LATS1/2, SAV1, MOB1A/B, and the transcriptional coactivators YAP and TAZ constitute its essential elements in mammals. These are regulated through a series of SAV1 and MOB1A/B phosphorylation events [38-41]. When activated, the Hippo pathway inhibits YAP/TAZ nuclear translocation, thereby suppressing their interaction with TEAD transcription factors [42].

Persistent YAP activation—observed in fibrotic human livers and CCl_4-treated animal models—is associated with increased ECM stiffness and tissue damage [43-45]. Various types of liver injury, such as non-alcoholic steatosis and bile acid accumulation, can also promote YAP/TAZ activation. In alcoholic hepatitis (AH) and non-alcoholic steatohepatitis (NASH), altered Hippo signaling results in elevated YAP/TAZ expression [46]. Notably, hepatocyte-specific expression of S127A-YAP increases macrophage recruitment and fibrosis [47]. While inhibiting YAP/TAZ could impair liver regeneration in healthy tissue, such inhibition shows therapeutic potential for liver diseases like cirrhosis and hepatocellular carcinoma (HCC) by suppressing fibrotic and oncogenic programs [48-50]. Targeting the YAP/TEAD interaction may offer therapeutic value, with compounds such as verteporfin showing efficacy in preclinical models despite certain limitations [51,52]. Other agents, such as ivermectin [53], sirtuin 6 [54,55], the He Yiqi Huxue formulation [56], resveratrol, and morin [57], have been shown to exert inhibitory effects through various mechanisms. YAP/TAZ has been shown to exert inhibitory effects through various mechanisms. However, complete inhibition may have adverse consequences, as shown in models with liver-specific deletion of both YAP and TAZ, which displayed diminished regenerative capacity [58,59]. These findings highlight the dual roles of YAP/TAZ in liver repair and pathology, underscoring the need for further research to balance therapeutic inhibition without compromising liver function [60]. The major regulators and downstream effects of the Hippo signaling pathway in liver pathology are summarized in Table 1.

Table 1. Summary of the Hippo signaling pathway.

Name	Hippo signaling pathway	References
Mechanism	A tumor suppressor pathway that regulates organ size, cell proliferation, apoptosis, and differentiation. *MST1/2* kinases activate *LATS1/2*, which phosphorylate *YAP/TAZ*, sequestering them in the cytoplasm or marking them for degradation. When Hippo is inactive (OFF), *YAP/TAZ* Signaling to the nucleus and binds TEAD transcription factors, driving the expression of growth-promoting genes like *CTGF* and *CYR61*.	[61]
Receptor	*YAP/TAZ, MST1/2, LATS1/2, TEAD*	[62]
Location	Liver tissue, like (Biliary epithelial cells [BECs], hepatocytes, hepatic stellate cells [HSCs]) and other mammalian tissues.	[63]
Function	**Homeostasis**: Maintains liver size and organ integrity **Regeneration**: Enhances hepatocyte proliferation, BEC differentiation, and ECM synthesis. **Repair**: Mediates interactions with Hedgehog and *Notch pathways* for liver regeneration. **Immunity**: Modulates Kupffer cell activation and cytokine release for inflammation control.	[64-66]
Pathway role	**Fibrosis and Cirrhosis:** *YAP/TAZ* overactivation causes HSC activation and excessive ECM production. **Cancer:** Persistent *YAP/TAZ* activation promotes hepatocellular carcinoma (HCC).	[68-70]

Name	Hippo signaling pathway	References
	Impaired Regeneration: Chronic liver diseases disrupt normal Hippo signaling, leading to ineffective liver repair.	
Therapeutic Target	*YAP/TAZ* Modulation: Target Hedgehog-YAP interaction to prevent HSC activation. Cytokine Pathways: Inhibit *IL-6* or *TGF-β* to reduce inflammation. Metabolic Targets: Block glutaminolysis to reduce HSC proliferation. *PPARγ* Agonists: Reverse HSC fibrogenic phenotype. *Cyr61* Inhibition: Decreases macrophage recruitment to suppress fibrosis.	[71-72]

5.2. Role of the Rho/ROCK pathway in liver fibrosis and NAFLD: therapeutic importance of its inhibition.

Rho GTPases, first identified in 1981, are small monomeric GTP-binding proteins with around 20 family members weighing 20–40 kDa [73]. A key downstream effector is Rho-associated coiled-coil-containing protein kinase (ROCK), a serine/threonine kinase [74]. The Rho/ROCK pathway regulates smooth muscle contraction, stress fiber formation, and cell motility, contributing to cell adhesion and migration [75]. Dysregulation of this pathway is implicated in inflammation, fibrosis, and metabolic disorders [76]. The two mammalian ROCK isoforms—ROCK1 (ROKβ) and ROCK2 (ROKα)—are activated by Rho GTPases in response to pro-fibrotic stimuli such as ECM stiffness, *TGF-β*, and lysophosphatidic acid [77,78]. Figure 1 presents the various upstream receptors and downstream effects of this pathway. Among Rho GTPases, RhoA, RhoC, RhoG, Rac1, and Cdc42 are most studied for their roles in cell proliferation, differentiation, apoptosis, gene transcription, and cytoskeletal regulation [79,80]. Alan Hall's research linked RhoA, Rac1, and Cdc42 to stress fibers, lamellipodia, and filopodia, respectively, underscoring their role in actin cytoskeleton remodeling and cell-matrix adhesion [81]. The *Rho–ROCK* pathway plays a vital role in hepatic stellate cell (HSC) activation—a key process in liver fibrosis [82,83]. ROCK2, in particular, drives fibrogenic immune cell functions and ECM remodeling, further advancing fibrosis [84,85]. Yee Jr. showed that Rho controls cytoskeletal changes in stellate cells, and its inhibition with C3 transferase reverses HSC activation features [86]. Inhibiting the *Rho/ROCK* pathway, especially *ROCK2*, has demonstrated potential to reverse liver fibrosis and improve hepatic function in various models, including thioacetamide-induced and CCl4-induced fibrosis [87]. *ROCK2* inhibition modulates immune, fibrotic, and metabolic pathways, making it a promising target [88,89]. Selective inhibitors like GV101 and ANG4201 have shown antifibrotic effects in NASH mouse models, improving fibrosis and reducing ALT/AST levels [13,90]. Similarly, RXC007 and KDO25 suppress *ROCK2* and reduce macrophage activity, preventing or reversing fibrosis [91,92]. *ROCK* inhibitors such as RKI-1447 and fasudil mitigate NAFLD and diabetes-induced fibrosis by reducing ECM accumulation and inflammatory factors [93,94]. Y-27632, a *Rho-p160ROCK* pathway blocker, prevents HSC activation in CCl4 models, supporting its potential as a therapeutic candidate. The major regulators, functions, and therapeutic inhibitors of the ROCK pathway involved in liver fibrosis are presented in Table 2.

Despite encouraging results, targeting the *Rho/ROCK* pathway presents challenges due to its roles in various physiological processes. Off-target effects and the complex nature of liver fibrosis necessitate thorough preclinical and clinical evaluation to ensure treatment safety and specificity.

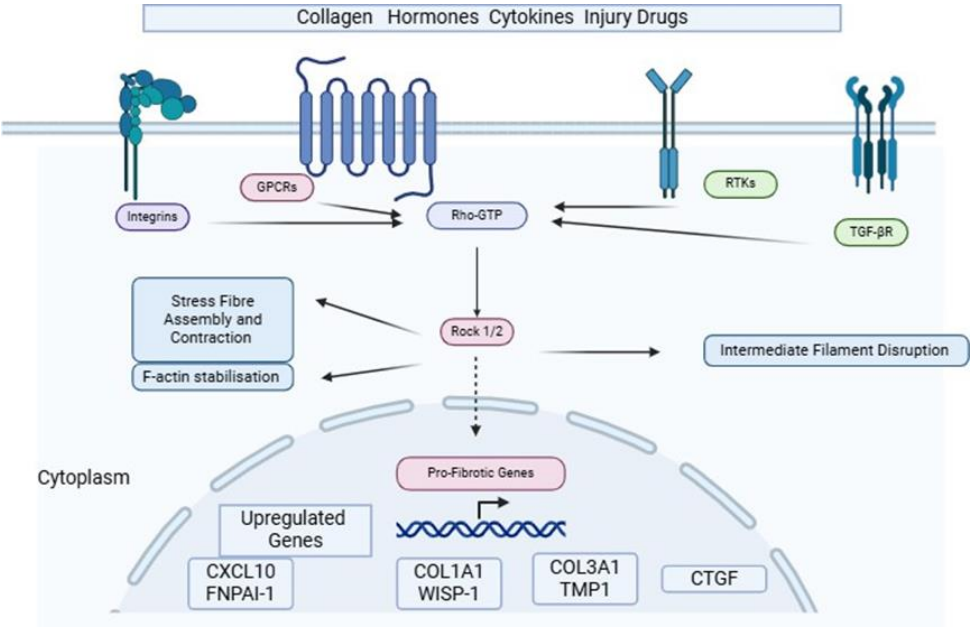

Figure 1. Schematic representation of the Rho/ROCK pathway in liver fibrosis progression. The figure was created using www.biorender.com.

Table 2. The key aspects of the Rho/ROCK pathway.

Name	Rock signaling pathway	References
Mechanism	ROCK is activated downstream of *Rho GTPases* (e.g., *RhoA*, *RhoB*, *RhoC*) via the *Rho*-binding domain (RBD). Activation promotes cytoskeletal dynamics, migration, and stress fiber formation.	[95]
Receptor	*RhoA*, *RhoB*, and *RhoC* serve as upstream activators. ROCK itself interacts with substrates like MYPT1 and LIM kinase to regulate actomyosin contractility and adhesion	[96]
Location	*ROCK1*: Found in non-neuronal tissues (e.g., liver, spleen, and kidney) *ROCK2*: Abundant in brain, muscle, and heart tissues.	[97]
Function	Cytoskeletal regulation: Controls stress fiber and focal adhesion formation. Cell migration: Facilitates motility. Fibrosis: Drives liver fibrosis by activating myofibroblasts and ECM production.	[98]
Pathway role	In liver diseases, excessive *ROCK* activity leads to fibrosis by promoting hepatic stellate cell activation, inflammatory cytokine expression, and tissue scarring.	[99]
Therapeutic Target	Non-Selective Inhibitors: Fasudil and Y-27632 Selective *ROCK2* inhibitors: SLx-2119 targets fibrosis with reduced side effects.	[100]

5.3. Notch signaling pathway in liver fibrosis and its therapeutic inhibition.

The *Notch signaling* pathway is a juxtacrine signaling system that facilitates direct communication between adjacent cells [101]. In mammals, four *Notch receptors* (*NOTCH1–4*) have been identified, each possessing both shared and unique biological functions [102]. These genes are located on human chromosomes 9 (*NOTCH1*), *1 (NOTCH2)*, *19 (NOTCH3)*, and *6 (NOTCH4)*, respectively [103,104]. Each of the four Notch receptors is expressed within the mesenchymal and epithelial cell populations of the adult liver [105]. Specifically, *Notch1* and *Notch2* are primarily localized in epithelial liver cells, whereas *Notch3* and *Notch4* are expressed in mesenchymal and endothelial cells [106]. Five major Notch ligands—*DLL1*, *DLL3*, *DLL4*, *JAG1*, and *JAG2*—are known in mammals, each fulfilling distinct yet complementary functions [107]. *DLL1* facilitates cell differentiation and intercellular communication, whereas *DLL3* promotes apoptosis, thereby restricting excessive cell proliferation [108]. *DLL4* activates the *NF-κB* signaling pathway, thereby enhancing VEGF secretion and promoting tumor metastasis, while *JAG1* facilitates angiogenesis and *JAG2* supports cell survival and proliferation [109]. Canonical Notch signaling is initiated when the extracellular domain of a *Notch receptor* binds to its ligand located on a neighboring cell [110]. A step-by-step description of this process is shown in Figure 2, which shows the various

proteolytic activities that result in both canonical and non-canonical signaling. Ligand binding induces two proteolytic cleavages: first by *ADAM* metalloproteases, which release the extracellular domain, and second by the γ-secretase complex, which liberates the Notch intracellular domain *(NICD*). The *NICD* then translocates to the nucleus, forming a transactivation complex that regulates transcription of target genes such as *HES1* and *SOX9* [111].

Recent studies have demonstrated that *Notch signaling* regulates diverse aspects of liver metabolism, regeneration, repair, inflammation, and vascular homeostasis, and plays a crucial role in the development of fibrosis and hepatocellular carcinoma [112]. *In vitro* studies have shown that rat hepatic stellate cells (*HSCs*) express Notch receptors, and upon activation and transdifferentiation into myofibroblast-like cells, they begin to produce the ligand *JAG1* [113]. In fibrotic liver tissue, the expression levels of Notch3 and Jagged1 are markedly elevated [114], with Jag1 being upregulated in bile ductules, hepatocytes, and activated *HSCs* [115]. Sawitza *et al*. demonstrated that *Jag1* acts as a cell-surface ligand that stimulates collagen and α-smooth muscle actin (*α-SMA*) synthesis in *HSCs* [116]. Similar signaling mechanisms have been observed in pulmonary fibrosis, indicating that Notch-mediated fibroblast activation may extend beyond hepatic tissue [117]. In healthy adults, Notch signaling activity in hepatocytes is minimal; however, its expression correlates positively with disease severity. Elevated levels of *NOTCH1*, *NOTCH2*, and the downstream effector *HES1* have been observed in *NASH* patients and in high-fat-diet-induced *NASH* mouse models, where they promote de novo adipogenesis and hepatic steatosis [118]. In quiescent *HSCs*, *Notch1* and *Notch3* are expressed at low levels but are significantly upregulated upon activation and transdifferentiation [119]. Aberrant Notch activation is likely mediated by *TLR4–JAG1/Notch* signaling interactions [120]. Downstream, *SOX9-dependent* activation of *SPP1* enhances osteopontin (*OPN*) secretion, which in turn activates *HSCs* and drives extracellular matrix (*ECM*) accumulation, promoting fibrosis [121].

Beyond its direct effects on hepatic stellate cells (*HSCs*), Notch signaling indirectly regulates fibrogenesis through interactions with hepatocytes and liver sinusoidal endothelial cells *(LSECs*). Under physiological conditions, *LSECs* produce nitric oxide (*NO*), which helps maintain *HSC* quiescence. Following liver injury, however, *LSECs* undergo capillarization, deposit extracellular matrix (*ECM)* components, develop a basement membrane, and exhibit reduced NO synthesis—processes that collectively drive *HSC* activation and fibrotic matrix deposition [122,123]. Therapeutically, inhibition of Notch signaling using γ-secretase inhibitors (*GSIs*) blocks the release of the Notch intracellular domain (*NICD*) and prevents subsequent transcriptional activation. In mouse models of cholestatic liver injury, *GSI* treatment effectively suppressed Notch signaling and attenuated fibrosis following CCl_4 administration [124]. However, the simultaneous inhibition of *Notch1* and *Notch2* disrupted intestinal stem cell homeostasis, resulting in gastrointestinal side effects such as impaired gut function, as reported in clinical trials [125]. Additionally, the natural polyphenol curcumin has been reported to suppress Notch1 activation, downregulate Jagged1 and *Hes1* expression, and consequently inhibit downstream *Notch signaling* [126]. Given the above explanation, further research is required to determine Based on the above findings, further research is needed to determine whether selective inhibition of the Notch signaling pathway could be employed to treat liver diseases while minimizing undesirable side effects. The key components, mechanisms, and therapeutic modulators of the Notch signaling pathway, which regulates biliary development, liver regeneration, metabolism, and fibrosis, are summarized in Table 3.

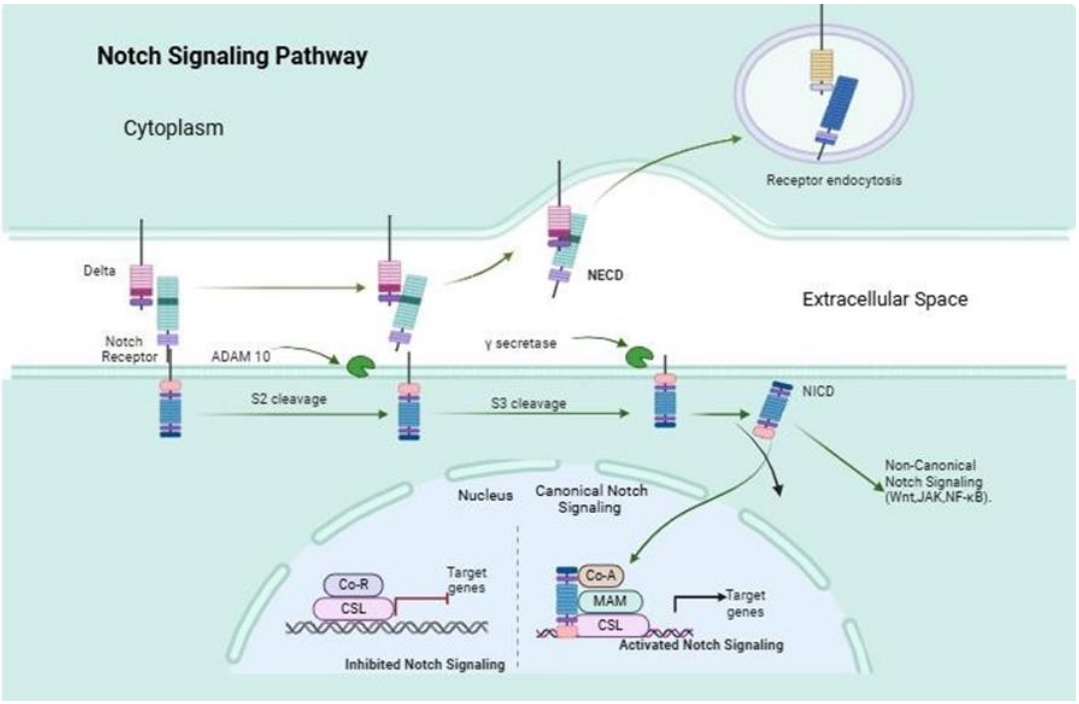

Figure 2. Canonical and non-canonical activation of the Notch signaling pathway. The figure was created using www.biorender.com.

Table 3. Highlighted the key components, roles, and therapeutic targeting of the Notch signaling pathway in the liver.

Name	Notch signaling pathway	References
Mechanism	A juxtracrine signaling mechanism where ligands (e.g., *JAG1*, *DLL1*, *DLL4*) bind to receptors (*NOTCH1–4*). Binding triggers cleavage by γ-secretase (S3 cleavage), ADAM10 releases the Notch intracellular signaling that translocates to the nucleus to activate *the* target genes like HES1, SOX9, and others that regulate cell fate and tissue repair.	[127]
Receptor	*NOTCH1–4*, *JAG1*, *DLL1*, *DLL4.*	
Location	Liver tissues like Hepatic stellate cells, Hepatic cells, portal mesenchymal cells, and Biliary cells Epithelial cells.	
Function	Biliary Development: Critical for bile duct formation and morphogenesis. Liver Regeneration: Regulates hepatocyte proliferation and biliary repair after damage. Liver Metabolism: Influences glucose and lipid metabolism through interactions with FOXO1 and mTOR pathways.	[128]
Pathway role	Alagille Syndrome: Mutations in *JAG1* or *NOTCH2* lead to bile duct paucity and cholestasis. Liver Fibrosis: Overactivation promotes HSC activation and ECM deposition. NASH/Metabolic Disorders: Dysregulation contributes to insulin resistance, steatosis, and fibrosis.	[129]
Therapeutic Target	Fibrosis Therapy: γ-secretase inhibitors (e.g., DAPT). Hedgehog inhibitors (e.g., GDC-0449) and TGFβ modulation to prevent HSC activation. Metabolic Therapy: Modulating *Notch-FOXO1-mTOR* pathways to improve glucose metabolism and reduce steatosis. Biliary Development: Targeting SOX9 or downstream *Notch* effectors for bile duct repair	[130]

Table 4. The mechanical cues among different liver diseases.

Liver disease	Mechanical cues	Source of mechanical change	Pathways involved	Cellular response	References
NAFLD	Matrix stiffness, lipid accumulation.	ECM expansion and hepatocyte ballooning under steatosis	Integrin-FAK, *YAP/TAZ*,	HSCs activation, inflammation, and endothelial dysfunction	[13]
Fibrosis	Increased ECM stiffness and interstitial tension	Collagen I/III deposition.	Integrin/FAK-*Src*, *RhoA/ROCK*, *YAP/TAZ*, *TGF-β* signaling	Activation of HSCs *α-SMA expression*	[131]

Liver disease	Mechanical cues	Source of mechanical change	Pathways involved	Cellular response	References
Cirrhosis	High stiffness and portal pressure.	Scar tissue formation, nodular architecture, and vascular remodeling.	*Hippo/YAP*, mechanosensitive ion channels (ENaC, TRPV)	Chronic HSC activation, angiogenesis, and portal hypertension	[132]
Hepatocellular Carcinoma (HCC)	ECM stiffness and altered shear stress	Tumor matrix stiffness and aberrant perfusion.	Integrin-FAK, *YAP/TAZ*, *RhoA/ROCK*.	cytoskeletal remodeling, increased invasion, tumor progression, and therapy resistance.	[133]
Cholestatic Disease	Bile canaliculi stretch, and pressure overload	Obstructed bile flow.	*Piezo1* (calcium signaling).	Cholangiocyte proliferation, inflammation, periportal fibrosis	[134]

6. Future Research Direction and Perspective

Despite significant advances in understanding the functions of the Hippo/YAP/TAZ, Rho/ROCK, and Notch signaling pathways in liver fibrosis, HCC, and NAFLD, translating these discoveries into targeted therapies remains a major challenge. Future research must unscramble pathway-specific modulation to minimize off-target effects—such as the development of isoform-selective *ROCK2* inhibitors, ligand- or receptor-specific Notch antagonists (e.g., *JAG1 or NOTCH3*), and context-sensitive *YAP/TAZ* modulators that maintain liver regeneration while inhibiting fibrosis. Integrating high-throughput omics techniques with mechanobiological insights may reveal new treatment targets and crosstalk mechanisms. Furthermore, successful clinical translation will necessitate the identification of accurate biomarkers to enable early detection and effective therapy monitoring. Moving these strategies forward through rigorous preclinical studies and well-structured clinical trials could completely change the way that liver fibrosis and NAFLD are treated.

7. Conclusion

Mechanotransduction significantly influences liver injury pathogenesis and progression by integrating various mechanical stimuli and cellular responses. A nuanced comprehension of these mechanotransduction pathways offers a foundation for identifying effective therapeutic targets to manage liver diseases. Liver injury involves a multifaceted interaction among mechanical cues, such as shear stress, stretch, and stiffness, that triggers intricate mechanotransduction cascades. These responses, orchestrated through signaling pathways, cytoskeletal alterations, and integrin-mediated cell adhesion, intricately contribute to the development and progression of liver disease. Strategically targeting pivotal mechanotransduction pathways presents promising avenues for therapeutic intervention. Strategies such as modulation of the Hippo/YAP/TAZ pathway and interference with Notch signaling have the potential to ameliorate liver injury and fibrosis. Moreover, emerging therapeutic targets, such as the Rho GTPase and Notch signaling pathways, offer novel avenues to impede disease progression. Continuing research on the cellular and molecular processes that connect mechanical forces in liver sinusoids to their biological functions, and using this knowledge to understand the specific mechanisms of liver fibrosis, could lead to the discovery of new therapeutic targets and the development of disease management strategies based on mechanical principles. Thus, more detailed and targeted studies are needed to evaluate the

clinical safety of these inhibitors and to investigate novel drugs targeting these pathways with minimal off-target side effects. This will be a revolution in the treatment of liver fibrosis.

Author Contributions

Author Contributions: Conceptualization, M.J. and A.D.A.; methodology, M.J.; software, A.D.A.; formal analysis, K.K.; investigation, K.K.; literature search, M.J. and K.K.; data curation, K.K.; writing—original draft preparation, M.J. and K.K.; writing review and editing, M.J., K.K., M.T., R.K., and A.D.A.; supervision, A.D.A. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

No new data were created or analyzed in this study. Data sharing does not apply to this article.

Funding

This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgments

We would like to express our special thanks to Professor Ye Zhao at the School of Pharmaceutical Sciences at Nanjing Tech University for guiding and supporting us and for providing insights that truly made this work possible.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Jain, N.; Olatunji Waidi, Y.; Debnath, S.; Vannaladsaysy, V.; Datta, S. Mechanotransduction alterations in tissue-engineered tumor models for new drug interventions. *Pharm. Pharmacol. Int. J.* **2024**, *12*, 148-165, https://doi.org/10.15406/ppij.2024.12.00446.
2. Goykadosh, B.M.; Chandar, V.; Parameswaran, H. Mechanotransduction at a distance: How cells can sense matrix properties using calcium. *Biophys. J.* **2024**, *123*, 242a, https://doi.org/10.1016/j.bpj.2023.11.1534.
3. Ferrai, C.; Schulte, C. Mechanotransduction in stem cells. *Eur. J. Cell Biol.* **2024**, *103*, 151417, https://doi.org/10.1016/j.ejcb.2024.151417.
4. Hu, Y.; Wang, R.; An, N.; Li, C.; Wang, Q.; Cao, Y.; Li, C.; Liu, J.; Wang, Y. Unveiling the power of microenvironment in liver regeneration: an in-depth overview. *Front. Genet.* **2023**, *14*, 1332190, https://doi.org/10.3389/fgene.2023.1332190.
5. Ye, J.; Li, F.; Hua, T.; Ma, K.; Wang, J.; Zhao, Z.; Yang, Z.; Luo, C.; Jia, R.; Li, Y. Liver mechanosignaling as a natural anti-hepatitis B virus mechanism. *Nat. Commun.* **2024**, *15*, 8375, https://doi.org/10.1038/s41467-024-52718-3.

6. Shen, J.; Chen, Y.; Zhang, Y.; Zhang, C.; Liu, H. Multifaceted roles of IL-17 in bone and tendon health. *Int. J. Biol. Macromol.* **2025**, *294*, 139498, https://doi.org/10.1016/j.ijbiomac.2025.139498.
7. Jehangir, M.; Chorliyeva, M.; Muhammad, T.; Ali, W.; Alvi, A.D.; Zafar, A.A. Unravelling TGF-β Signaling and Integrin-Mediated Mechanotransduction: Key Drivers of Liver Fibrosis. Cognizance *J. Multidiscip. Stud.* **2025**, *5*, 44-72, https://doi.org/10.47760/cognizance.2025.v05i05.005.
8. Wang, Z.; Wang, W.; Luo, Q.; Song, G. High matrix stiffness accelerates migration of hepatocellular carcinoma cells through the integrin β1-Plectin-F-actin axis. *BMC Biol.* **2025**, *23*, 8, https://doi.org/10.1186/s12915-025-02113-1.
9. Zhang, X.; Al-Danakh, A.; Zhu, X.; Feng, D.; Yang, L.; Wu, H.; Li, Y.; Wang, S.; Chen, Q.; Yang, D. Insights into the mechanisms, regulation, and therapeutic implications of extracellular matrix stiffness in cancer. *Bioeng. Transl. Med.* **2024**, *10*, e10698, https://doi.org/10.1002/btm2.10698.
10. Luo, X.; Yang, J.; Zhao, Y.; Nagayasu, T.; Chen, J.; Hu, P.; He, Z.; Li, Z.; Wu, J.; Zhao, Z. Engineering spatially-confined conduits to tune nerve self-organization and allodynic responses via YAP-mediated mechanotransduction. *Nat. Commun.* **2025**, *16*, 66. *Nat. Commun.* **2025**, *16*, https://doi.org/10.1038/s41467-024-55118-9.
11. Durazzo, M.; Ferro, A.; Navarro-Tableros, V.M.; Gaido, A.; Fornengo, P.; Altruda, F.; Romagnoli, R.; Moestrup, S.K.; Calvo, P.L.; Fagoonee, S. Current Treatment Regimens and Promising Molecular Therapies for Chronic Hepatobiliary Diseases. *Biomolecules* **2025**, *15*, 121, https://doi.org/10.3390/biom15010121.
12. Kang, N. Mechanotransduction in Liver Diseases. *Semin. Liver Dis.* **2019**, *40*, 084-090, https://doi.org/10.1055/s-0039-3399502.
13. Zhao, Y.-Q.; Deng, X.-W.; Xu, G.-Q.; Lin, J.; Lu, H.-Z.; Chen, J. Mechanical homeostasis imbalance in hepatic stellate cells activation and hepatic fibrosis. *Front. Mol. Biosci.* **2023**, *10*, https://doi.org/10.3389/fmolb.2023.1183808.
14. Mierke, C.T. Extracellular Matrix Cues Regulate Mechanosensing and Mechanotransduction of Cancer Cells. *Cells* **2024**, *13*, 96, https://doi.org/10.3390/cells13010096.
15. Casarella, S.; Ferla, F.; Di Francesco, D.; Canciani, E.; Rizzi, M.; Boccafoschi, F. Focal Adhesion's Role in Cardiomyocytes Function: From Cardiomyogenesis to Mechanotransduction. *Cells* **2024**, *13*, 664, https://doi.org/10.3390/cells13080664.
16. Joung, J.Y.; Cho, J.H.; Kim, Y.H.; Choi, S.H.; Son, C.G. A literature review for the mechanisms of stress-induced liver injury. *Brain Behav.* **2019**, *9*, e01235, https://doi.org/10.1002/brb3.1235.
17. Min, K.; Karuppannan, S.K.; Tae, G. The impact of matrix stiffness on hepatic cell function, liver fibrosis, and hepatocellular carcinoma—Based on quantitative data. *Biophys. Rev.* **2024**, *5*, 021306, https://doi.org/10.1063/5.0197875.
18. Pu, S.; Pan, Y.; Zhang, Q.; You, T.; Yue, T.; Zhang, Y.; Wang, M. Endoplasmic Reticulum Stress and Mitochondrial Stress in Drug-Induced Liver Injury. *Molecules* **2023**, *28*, 3160, https://doi.org/10.3390/molecules28073160.
19. Brennan, P.N.; MacMillan, M.; Manship, T.; Moroni, F.; Glover, A.; Troland, D.; MacPherson, I.; Graham, C.; Aird, R.; Semple, S.I. Autologous macrophage therapy for liver cirrhosis: a phase 2 open-label randomized controlled trial. *Nat. Med.* **2025**, *31*, 979-987, https://doi.org/10.1038/s41591-024-03406-8.
20. de Sousa Rodrigues, M.E.; Bekhbat, M.; Houser, M.C.; Chang, J.; Walker, D.I.; Jones, D.P.; Oller do Nascimento, C.M.P.; Barnum, C.J.; Tansey, M.G. Chronic psychological stress and high-fat high-fructose diet disrupt metabolic and inflammatory gene networks in the brain, liver, and gut and promote behavioral deficits in mice. *Brain Behav. Immun.* **2017**, *59*, 158-172, https://doi.org/10.1016/j.bbi.2016.08.021.
21. Gries, J.J.; Lazarus, J.V.; Brennan, P.N.; Siddiqui, M.S.; Targher, G.; Lang, C.C.; Virani, S.S.; Lavie, C.J.; Isaacs, S.; Arab, J.P. Interdisciplinary perspectives on the co-management of metabolic dysfunction-associated steatotic liver disease and coronary artery disease. *Lancet Gastroenterol. Hepatol.* **2025**, *10*, 82-94, https://doi.org/10.1016/s2468-1253(24)00310-8.
22. Younossi, Z.M.; Stepanova, M.; Racila, A.; Henry, L.; Labriola, D.; Taub, R.; Nader, F. Health-related quality of life (HRQL) assessments in a 52-week, double-blind, randomized, placebo-controlled phase III study of resmetirom (MGL-3196) in patients with metabolic dysfunction–associated steatohepatitis (MASH) and fibrosis. *Hepatology* **2025**, *81*, 1318-1327, https://doi.org/10.1097/hep.0000000000001084.
23. Zhang, S.; Liu, B.; Huang, L.; Zhang, R.; An, L.; Liu, Z. Metabolomics reveals that chronic restraint stress alleviates carbon tetrachloride-induced hepatic fibrosis through the INSR/PI3K/AKT/AMPK pathway. *J. Mol. Med.* **2023**, *102*, 113-128, https://doi.org/10.1007/s00109-023-02395-4.

24. Xu, M.-Y.; Guo, C.-C.; Li, M.-Y.; Lou, Y.-H.; Chen, Z.-R.; Liu, B.-W.; Lan, L. Brain-gut-liver axis: Chronic psychological stress promotes liver injury and fibrosis via gut in rats. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 1040749, https://doi.org/10.3389/fcimb.2022.1040749.
25. Yamashiro, Y.; Yanagisawa, H. The molecular mechanism of mechanotransduction in vascular homeostasis and disease. *Clin. Sci.* **2020**, *134*, 2399-2418, https://doi.org/10.1042/cs20190488.
26. Zhao, Z.; Li, Y.; Wang, M.; Zhao, S.; Zhao, Z.; Fang, J. Mechanotransduction pathways in the regulation of cartilage chondrocyte homoeostasis. *J. Cell. Mol. Med.* **2020**, *24*, 5408-5419, https://doi.org/10.1111/jcmm.15204.
27. Kassianidou, E.; Kalita, J.; Lim, R.Y.H. The role of nucleocytoplasmic transport in mechanotransduction. *Experim. Cell Res.* **2019**, *377*, 86-93, https://doi.org/10.1016/j.yexcr.2019.02.009.
28. Valizadeh, A.; Majidinia, M.; Samadi-Kafil, H.; Yousefi, M.; Yousefi, B. The roles of signaling pathways in liver repair and regeneration. *J. Cell. Physiol.* **2019**, *234*, 14966-14974, https://doi.org/10.1002/jcp.28336.
29. Xiao, B. Mechanisms of mechanotransduction and physiological roles of PIEZO channels. *Nat. Rev. Mol. Cell Biol.* **2024**, *25*, 886-903, https://doi.org/10.1038/s41580-024-00773-5.
30. Wang, N. IL-6-Mediated Liver Regeneration: Exploring Key Signaling Pathways and Cellular Mechanisms. *Highl. Sci. Eng. Technol.* **2024**, *123*, 417-422, https://doi.org/10.54097/00e5gf15.
31. Shi, Q.; Xue, C.; Zeng, Y.; Yuan, X.; Chu, Q.; Jiang, S.; Wang, J.; Zhang, Y.; Zhu, D.; Li, L. Notch signaling pathway in cancer: from mechanistic insights to targeted therapies. *Signal Transduct. Target. Ther.* **2024**, *9*, 128, https://doi.org/10.1038/s41392-024-01828-x.
32. Elkattawy, H.; Mahmoud Abdelmonem Elsherbini, D.; Ali Ebrahim, H.; Abdullah, D.; Al-Zahaby, S.; Nosery, Y.; El-Sayed Hassan, A. Rho-Kinase Inhibition Ameliorates Non-Alcoholic Fatty Liver Disease in Type 2 Diabetic Rats. *Physiol. Res.* **2022**, *71*, 615-630, https://doi.org/10.33549/physiolres.934869.
33. Nakhaei-Rad, S.; Pudewell, S.; Mirzaiebadizi, A.; Nouri, K.; Reichert, D.; Kordes, C.; Häussinger, D.; Ahmadian, M.R. From Quiescence to Activation: The Reciprocal Regulation of Ras and Rho Signaling in Hepatic Stellate Cells. *Cells* **2025**, *14*, 674, https://doi.org/10.3390/cells14090674.
34. Zhang, H.; Yang, M.; Kim, S.H.; Li, I.T.S. Integrin force loading rate in mechanobiology: From model to molecular measurement. *QRB Discov.* **2025**, *6*, https://doi.org/10.1017/qrd.2024.28.
35. Monaghan-Benson, E.; Aureille, J.; Guilluy, C. ECM stiffness regulates lung fibroblast survival through RasGRF1-dependent signaling. *J. Biol. Chem.* **2025**, *301*, 108161, https://doi.org/10.1016/j.jbc.2025.108161.
36. Islam, R.; Hong, Z. YAP/TAZ as mechanobiological signaling pathway in cardiovascular physiological regulation and pathogenesis. *Mechanobiol. Med.* **2024**, *2*, 100085, https://doi.org/10.1016/j.mbm.2024.100085.
37. Xu, Q.; Diekwisch, T.G.H. Tissue pressure and YAP during organogenesis. *Nat. Cell Biol.* **2024**, *26*, 510-511, https://doi.org/10.1038/s41556-024-01392-0.
38. Dasgupta, I.; McCollum, D. Control of cellular responses to mechanical cues through YAP/TAZ regulation. *J. Biol. Chem.* **2019**, *294*, 17693-17706, https://doi.org/10.1074/jbc.REV119.007963.
39. Dupont, S. Regulation of YAP/TAZ Activity by Mechanical Cues: An Experimental Overview. In The Hippo Pathway: Methods and Protocols, Hergovich, A., Ed.; Springer New York: New York, NY, **2019**; pp. 183-202, https://doi.org/10.1007/978-1-4939-8910-2_15.
40. Russell, J.O.; Camargo, F.D. Hippo signalling in the liver: role in development, regeneration and disease. *Nat. Rev. Gastroenterol. Hepatol.* **2022**, *19*, 297-312, https://doi.org/10.1038/s41575-021-00571-w.
41. Fu, M.; Hu, Y.; Lan, T.; Guan, K.-L.; Luo, T.; Luo, M. The Hippo signalling pathway and its implications in human health and diseases. *Signal Transduct. Target. Ther.* **2022**, *7*, 376, https://doi.org/10.1038/s41392-022-01191-9.
42. McCrea, E.M.; Makrides, N.; Tabata, T.; Vogel, H.; Howitt, B.; Reineking, W.; Vilches-Moure, J.G.; Wang, M.; Zhang, X.; Attardi, L.D. Ptpn14 Knockout Mice Reveal Critical Female-Specific Roles for the Hippo Pathway. *bioRxiv* **2025**, 2025.2001. 2013.632464, https://doi.org/10.1101/2025.01.13.632464.
43. Lou, L.; Peng, K.; Ouyang, S.; Ding, W.; Mo, J.; Yan, J.; Gong, X.; Liu, G.; Lu, J.; Yue, P. Periostin-mediated NOTCH1 activation between tumor cells and HSCs crosstalk promotes liver metastasis of small cell lung cancer. *J. Exp. Clin. Cancer Res.* **2025**, *44*, 6, https://doi.org/10.1186/s13046-024-03266-7.
44. Bangru, S.; Chen, J.; Baker, N.; Das, D.; Chembazhi, U.V.; Derham, J.M.; Chorghade, S.; Arif, W.; Alencastro, F.; Duncan, A.W. ESRP2–microRNA-122 axis promotes the postnatal onset of liver polyploidization and maturation. *Genes Dev.* **2025**, *39*, 325-347, https://doi.org/10.1101/gad.352129.124.

45. Schiavoni, G.; Messina, B.; Scalera, S.; Memeo, L.; Colarossi, C.; Mare, M.; Blandino, G.; Ciliberto, G.; Bon, G.; Maugeri-Saccà, M. Role of Hippo pathway dysregulation from gastrointestinal premalignant lesions to cancer. *J. Transl. Med.* **2024**, *22*, 213, https://doi.org/10.1186/s12967-024-05027-8.
46. Tu, C.-E.; Liu, Y.-F.; Liu, H.-W.; Jiao, C.-M.; Liu, Q.; Hung, M.-C.; Li, P.; Wan, X.-B.; Fan, X.-J.; Wang, Y.-L. D-ribose-5-phosphate inactivates YAP and functions as a metabolic checkpoint. *J. Hematol. Oncol.* **2025**, *18*, 2, https://doi.org/10.1186/s13045-024-01655-1.
47. Liu, K.; Wehling, L.; Wan, S.; Weiler, S.M.; Tóth, M.; Ibberson, D.; Marhenke, S.; Ali, A.; Lam, M.; Guo, T. Dynamic YAP expression in the non-parenchymal liver cell compartment controls heterologous cell communication. *Cell. Mol. Life Sci.* **2024**, *81*, 115, https://doi.org/10.1007/s00018-024-05126-1.
48. Yu, Z.; Zhang, H.; Li, L.; Li, Z.; Chen, D.; Pang, X.; Ji, Y.; Wang, Y. Microglia-mediated pericytes migration and fibroblast transition via S1P/S1P3/YAP signaling pathway after spinal cord injury. *Exp. Neurol.* **2024**, *379*, 114864, https://doi.org/10.1016/j.expneurol.2024.114864.
49. Lee, S.H.; Kim, S.A.; Park, S.J.; Lee, M.Y.; Seo, H.W.; Issabayeva, G.; Hyun, J.Y.; Park, S.J.; Lim, H.J.; Jang, W.D. NUAK2 inhibitors, KHKI-01128 and KHKI-01215, exhibit potent anticancer activity against SW480 colorectal cancer cells. *Anticancer Res.* **2024**, *44*, 2909-2919, https://doi.org/10.21873/anticanres.17103.
50. Leng, J.; Wang, C.; Liang, Z.; Qiu, F.; Zhang, S.; Yang, Y. An updated review of YAP: A promising therapeutic target against cardiac aging? *Int. J. Biol. Macromol.* **2024**, *254*, https://doi.org/10.1016/j.ijbiomac.2023.127670.
51. Merlin, J.P.J.; Crous, A.; Abrahamse, H. Combining Photodynamic Therapy and Targeted Drug Delivery Systems: Enhancing Mitochondrial Toxicity for Improved Cancer Outcomes. *Int. J. Mol. Sci.* **2024**, *25*, 10796, https://doi.org/10.3390/ijms251910796.
52. Wei, Y.; Hui, V.L.Z.; Chen, Y.; Han, R.; Han, X.; Guo, Y. YAP/TAZ: Molecular pathway and disease therapy. *MedComm* **2023**, *4*, e340, https://doi.org/10.1002/mco2.340.
53. Darvishi, M.; Nouri, M.; Rahimi, R.; Heidari-Soureshjani, S.; Hashemi Rafsanjani, S.M.R. A Systematic Review of the Impact of Resveratrol on Viral Hepatitis and Chronic Viral Hepatitis-related Hepatocellular Carcinoma. *Curr. Mol. Med.* **2025**, *25*, 589-604, https://doi.org/10.2174/0115665240284347240125072555.
54. Zhang, R.; Zhan, Y.; Lang, Z.; Li, Y.; Zhang, W.; Zheng, J. LncRNA-SNHG5 mediates activation of hepatic stellate cells by regulating NF2 and Hippo pathway. *Commun. Biol.* **2024**, *7*, 266, https://doi.org/10.1038/s42003-024-05971-7.
55. Chène, P. Direct Inhibition of the YAP : TEAD Interaction: An Unprecedented Drug Discovery Challenge. *ChemMedChem* **2024**, *19*, https://doi.org/10.1002/cmdc.202400361.
56. Kwon, A.; Lee, N.Y.; Yu, J.-H.; Choi, M.G.; Park, J.; Koo, J.H. Mitochondrial stress activates YAP/TAZ through RhoA oxidation to promote liver injury. *Cell Death Dis.* **2024**, *15*, 51, https://doi.org/10.1038/s41419-024-06448-5.
57. Papavassiliou, K.A.; Sofianidi, A.A.; Papavassiliou, A.G. YAP/TAZ-TEAD signalling axis: A new therapeutic target in malignant pleural mesothelioma. *J. Cell. Mol. Med.* **2024**, *28*, e18330, https://doi.org/10.1111/jcmm.18330.
58. Xiong, X.; Kuang, H.; Liu, T.; Lin, J.D. A Single-Cell Perspective of the Mammalian Liver in Health and Disease. *Hepatology* **2020**, *71*, 1467-1473, https://doi.org/10.1002/hep.31149.
59. Krenkel, O.; Tacke, F. Liver macrophages in tissue homeostasis and disease. *Nat. Rev. Immunol.* **2017**, *17*, 306-321, https://doi.org/10.1038/nri.2017.11.
60. Shu, W.; Yang, M.; Yang, J.; Lin, S.; Wei, X.; Xu, X. Cellular crosstalk during liver regeneration: unity in diversity. *Cell Commun. Signal.* **2022**, *20*, 117, https://doi.org/10.1186/s12964-022-00918-z.
61. Gao, J.; Fan, L.; Zhao, L.; Su, Y. The interaction of Notch and Wnt signaling pathways in vertebrate regeneration. *Cell Regen.* **2021**, *10*, 11, https://doi.org/10.1186/s13619-020-00072-2.
62. Xiang, D.; Zou, J.; Zhu, X.; Chen, X.; Luo, J.; Kong, L.; Zhang, H. Physalin D attenuates hepatic stellate cell activation and liver fibrosis by blocking TGF-β/Smad and YAP signaling. *Phytomedicine* **2020**, *78*, 153294, https://doi.org/10.1016/j.phymed.2020.153294.
63. Moon, H.; Cho, K.; Shin, S.; Kim, D.Y.; Han, K.-H.; Ro, S.W. High Risk of Hepatocellular Carcinoma Development in Fibrotic Liver: Role of the Hippo-YAP/TAZ Signaling Pathway. *Int. J. Mol. Sci.* **2019**, *20*, 581, https://doi.org/10.3390/ijms20030581.
64. Pibiri, M.; Simbula, G. Role of the Hippo pathway in liver regeneration and repair: recent advances. *Inflamm. Regen.* **2022**, *42*, 59, https://doi.org/10.1186/s41232-022-00235-5.

65. Zhao, Y.; Wang, H.; He, T.; Ma, B.; Chen, G.; Tzeng, C. Knockdown of Yap attenuates TAA-induced hepatic fibrosis by interaction with hedgehog signals. *J. Cell Commun. Signal.* **2023**, *17*, 1335-1354, https://doi.org/10.1007/s12079-023-00775-6.
66. Dutta, R.K.; Jun, J.; Du, K.; Diehl, A.M. Hedgehog Signaling: Implications in Liver Pathophysiology. *Semin. Liver Dis.* **2023**, *43*, 418-428, https://doi.org/10.1055/a-2187-3382.
67. Unver, N.; McAllister, F. IL-6 family cytokines: Key inflammatory mediators as biomarkers and potential therapeutic targets. *Cytokine Growth Factor Rev.* **2018**, *41*, 10-17, https://doi.org/10.1016/j.cytogfr.2018.04.004.
68. Shihan, M.H.; Sharma, S.; Cable, C.; Prathigudupu, V.; Chen, A.; Mattis, A.N.; Chen, J.Y. AMPK stimulation inhibits YAP/TAZ signaling to ameliorate hepatic fibrosis. *Sci. Rep.* **2024**, *14*, 5205, https://doi.org/10.1038/s41598-024-55764-5.
69. Maden, C.H.; Fairman, D.; Chalker, M.; Costa, M.J.; Fahy, W.A.; Garman, N.; Lukey, P.T.; Mant, T.; Parry, S.; Simpson, J.K. Safety, tolerability and pharmacokinetics of GSK3008348, a novel integrin αvβ6 inhibitor, in healthy participants. *Eur. J. Clin. Pharmacol.* **2018**, *74*, 701-709, https://doi.org/10.1007/s00228-018-2435-3.
70. Slack, R.J.; Macdonald, S.J.F.; Roper, J.A.; Jenkins, R.G.; Hatley, R.J.D. Emerging therapeutic opportunities for integrin inhibitors. *Nat. Rev. Drug Discov.* **2021**, *21*, 60-78, https://doi.org/10.1038/s41573-021-00284-4.
71. Raven, A.; Lu, W.-Y.; Man, T.Y.; Ferreira-Gonzalez, S.; O'Duibhir, E.; Dwyer, B.J.; Thomson, J.P.; Meehan, R.R.; Bogorad, R.; Koteliansky, V. Cholangiocytes act as facultative liver stem cells during impaired hepatocyte regeneration. *Nature* **2017**, *547*, 350-354, https://doi.org/10.1038/nature23015.
72. Desai, S.S.; Tung, J.C.; Zhou, V.X.; Grenert, J.P.; Malato, Y.; Rezvani, M.; Español-Suñer, R.; Willenbring, H.; Weaver, V.M.; Chang, T.T. Physiological ranges of matrix rigidity modulate primary mouse hepatocyte function in part through hepatocyte nuclear factor 4 alpha. *Hepatology* **2016**, *64*, 261-275, https://doi.org/10.1002/hep.28450.
73. Wheaton, A.K.; Agarwal, M.; Jia, S.; Kim, K.K. Lung epithelial cell focal adhesion kinase signaling inhibits lung injury and fibrosis. *Am. J. Physiol. - Lung Cell. Mol. Physiol.* **2017**, *312*, L722-L730, https://doi.org/10.1152/ajplung.00478.2016.
74. Jain, S.; Paliwal, A. Exploring the Role of Rho Kinase Enzyme in the Management of Metabolic Syndrome. *Curr. Enzyme Inhib.* **2025**, *21*, 2-20, https://doi.org/10.2174/0115734080332355241007060211.
75. Zanin-Zhorov, A.; Chen, W.; Moretti, J.; Nyuydzefe, M.S.; Zhorov, I.; Munshi, R.; Ghosh, M.; Serdjebi, C.; MacDonald, K.; Blazar, B.R. Selectivity matters: selective ROCK2 inhibitor ameliorates established liver fibrosis via targeting inflammation, fibrosis, and metabolism. *Commun. Biol.* **2023**, *6*, 1176, https://doi.org/10.1038/s42003-023-05552-0.
76. Matoba, K.; Takeda, Y.; Nagai, Y.; Sekiguchi, K.; Yokota, T.; Utsunomiya, K.; Nishimura, R. The Physiology, Pathology, and Therapeutic Interventions for ROCK Isoforms in Diabetic Kidney Disease. *Fronti. Pharmacol.* **2020**, *11*, https://doi.org/10.3389/fphar.2020.585633.
77. Choudhary, M.I. Frontiers in cardiovascular drug discovery, Volume 5; Bentham Science Publishers: Oak Park, IL, USA, **2022**.
78. Al-Koussa, H.; Atat, O.E.; Jaafar, L.; Tashjian, H.; El-Sibai, M. The Role of Rho GTPases in Motility and Invasion of Glioblastoma Cells. *Anal. Cell. Pathol.* **2020**, *2020*, 9274016, https://doi.org/10.1155/2020/9274016.
79. Bobkov, D.E.; Lukacheva, A.V.; Gorb, A.I.; Poljanskaya, G.G. The role of the Rho family small GTPases in regulation of normal and pathological processes. *Cell Tissue Biol.* **2024**, *66*, 3-19, https://doi.org/10.31857/s0041377124010012.
80. de Castro Sampaio, S.S.; Ramalho, M.C.C.; de Souza, C.S.; de Almeida Rodrigues, B.; de Mendonça, G.R.S.; Lazarini, M. RHO subfamily of small GTPases in the development and function of hematopoietic cells. *J. Cell. Physiol.* **2024**, *240*, e31469, https://doi.org/10.1002/jcp.31469.
81. De Belly, H.; Gallen, A.F.; Strickland, E.; Estrada, D.C.; Zager, P.J.; Nagy, T.L.; Burkhardt, J.K.; Turlier, H.; Weiner, O.D. Long range mutual activation establishes Rho and Rac polarity during cell migration. *bioRxiv* **2025**, *2024*, 616161, https://doi.org/10.1101/2024.10.01.616161.
82. Sousa-Lima, I.; Kim, H.J.; Jones, J.; Kim, Y.-B. Rho-Kinase as a Therapeutic Target for Nonalcoholic Fatty Liver Diseases. *Diabetes Metab. J.* **2021**, *45*, 655-674, https://doi.org/10.4093/dmj.2021.0197.
83. Zhang, Y.; Ren, L.; Tian, Y.; Guo, X.; Wei, F.; Zhang, Y. Signaling pathways that activate hepatic stellate cells during liver fibrosis. *Front. Med.* **2024**, *11*, https://doi.org/10.3389/fmed.2024.1454980.

84. Zhou, Y.; Ling, T.; Shi, W. Current state of signaling pathways associated with the pathogenesis of idiopathic pulmonary fibrosis. *Respir. Res.* **2024**, *25*, 245, https://doi.org/10.1186/s12931-024-02878-z.
85. Ji, P.; Li, Y.; Wang, Z.; Jia, S.; Jiang, X.; Chen, H.; Wang, Q. Advances in precision gene editing for liver fibrosis: From technology to therapeutic applications. *Biomed. Pharmacother.* **2024**, *177*, 117003, https://doi.org/10.1016/j.biopha.2024.117003.
86. Park, S.; Kim, J.; Yang, S.; Kang, S.H.; Kang, W.; Paik, Y.-H. Exogenous S1P via S1P receptor 2 induces CTGF expression through Src-RhoA-ROCK-YAP pathway in hepatic stellate cells. *Mol. Biol. Rep.* **2024**, *51*, 950, https://doi.org/10.1007/s11033-024-09868-w.
87. Nalkurthi, C.; Schroder, W.A.; Melino, M.; Irvine, K.M.; Nyuydzefe, M.; Chen, W.; Liu, J.; Teng, M.W.; Hill, G.R.; Bertolino, P. ROCK2 inhibition attenuates profibrogenic immune cell function to reverse thioacetamide-induced liver fibrosis. *JHEP Rep.* **2022**, *4*, 100386, https://doi.org/10.1016/j.jhepr.2021.100386.
88. Ye, Q.; Li, X.; Gao, W.; Gao, J.; Zheng, L.; Zhang, M.; Yang, F.; Li, H. Role of Rho-associated kinases and their inhibitor fasudil in neurodegenerative diseases. *Front. Neurosci.* **2024**, *18*, https://doi.org/10.3389/fnins.2024.1481983.
89. Zhao, C.; Wu, Z.; Yao, Z.; Zhang, F.; Zhao, R.; Cao, X.; Ling, S.; Jiang, X. The tumorigenic effect of the high expression of ABRACL in glioma and its potential as a therapeutic target. *Heliyon* **2024**, *10*, e36597, https://doi.org/10.1016/j.heliyon.2024.e36597.
90. Seccia, T.M.; Rigato, M.; Ravarotto, V.; Calò, L.A. ROCK (RhoA/Rho Kinase) in Cardiovascular–Renal Pathophysiology: A Review of New Advancements. *J. Clin. Med.* **2020**, *9*, 1328, https://doi.org/10.3390/jcm9051328.
91. Dawson, J.E.; Bryant, A.; Walton, B.; Bhikot, S.; Macon, S.; Ajamu-Johnson, A.; Jordan, T.; Langridge, P.D.; Malmi-Kakkada, A.N. Contact area and tissue growth dynamics shape synthetic juxtacrine signaling patterns. *Biophys. J.* **2025**, *124*, 93-106, https://doi.org/10.1016/j.bpj.2024.11.007.
92. Watabe, Y.; Kobayashi, S.; Nakayama, T.; Takahashi, S.; Yoshihara, M. Expression status transition of NOTCH1 accompanies chromatin remodeling in human early retinal progenitor cells. *F1000Research* **2025**, *14*, https://doi.org/10.12688/f1000research.159630.1.
93. Shi, Q.; Jiang, S.; Zeng, Y.; Yuan, X.; Zhang, Y.; Chu, Q.; Xue, C.; Li, L. A Notch signaling pathway-related gene signature: Characterizing the immune microenvironment and predicting prognosis in hepatocellular carcinoma. *J. Transl. Intern. Med.* **2025**, *12*, 553-568, https://doi.org/10.1515/jtim-2024-0020.
94. Wang, J.; Jiang, W. The Effects of RKI-1447 in a Mouse Model of Nonalcoholic Fatty Liver Disease Induced by a High-Fat Diet and in HepG2 Human Hepatocellular Carcinoma Cells Treated with Oleic Acid. *Med. Sci. Monit.* **2020**, *26*, https://doi.org/10.12659/msm.919220.
95. Xu, H.; Wang, L. The Role of Notch Signaling Pathway in Non-Alcoholic Fatty Liver Disease. *Front. Mol. Biosci.* **2021**, *8*, https://doi.org/10.3389/fmolb.2021.792667.
96. Zhang, X.; Wang, Y.; Zhao, W.; Yang, S.; Moussian, B.; Zhao, Z.; Zhang, J.; Dong, W. Excess Dally-like Induces Malformation of Drosophila Legs. *Cells* **2024**, *13*, 1199, https://doi.org/10.3390/cells13141199.
97. Zack, S.R.; Alzoubi, O.; Satoeya, N.; Singh, K.P.; Deen, S.; Nijim, W.; Lewis, M.J.; Pitzalis, C.; Sweiss, N.; Ivashkiv, L.B. Another notch in the belt of rheumatoid arthritis. *Arthritis Rheumatol.* **2024**, *76*, 1475-1487, https://doi.org/10.1002/art.42937.
98. Gou, L.; Liu, H.; Pan, Z.; Wu, X.; Gong, C.; Hu, J. Jagged 2 inhibition attenuates hypoxia-induced mitochondrial damage and pulmonary hypertension through Sirtuin 1 signaling. *Plos One* **2024**, *19*, https://doi.org/10.1371/journal.pone.0297525.
99. Sachan, N.; Sharma, V.; Mutsuddi, M.; Mukherjee, A. Notch signalling: multifaceted role in development and disease. *FEBS J.* **2023**, *291*, 3030-3059, https://doi.org/10.1111/febs.16815.
100. Owen, D.H.; Giffin, M.J.; Bailis, J.M.; Smit, M.-A.D.; Carbone, D.P.; He, K. DLL3: an emerging target in small cell lung cancer. *J. Hematol. Oncol.* **2019**, *12*, 61, https://doi.org/10.1186/s13045-019-0745-2.
101. Pitulescu, M.E.; Schmidt, I.; Giaimo, B.D.; Antoine, T.; Berkenfeld, F.; Ferrante, F.; Park, H.; Ehling, M.; Biljes, D.; Rocha, S.F. Dll4 and Notch signalling couples sprouting angiogenesis and artery formation. *Nat. Cell Biol.* **2017**, *19*, 915-927, https://doi.org/10.1038/ncb3555.
102. Bakalenko, N.; Kuznetsova, E.; Malashicheva, A. The Complex Interplay of TGF-β and Notch Signaling in the Pathogenesis of Fibrosis. *Int. J. Mol. Sci.* **2024**, *25*, 10803, https://doi.org/10.3390/ijms251910803.
103. Gallenstein, N.; Tichy, L.; Weigand, M.A.; Schenz, J. Notch Signaling in Acute Inflammation and Sepsis. *Int. J. Mol. Sci.* **2023**, *24*, 3458, https://doi.org/10.3390/ijms24043458.

104. Zhang, N.; Yang, A.; Zhang, W.; Li, H.; Xu, A.; Yan, X.; Han, Q.; Wang, B.; You, H.; Chen, W. Crosstalk of lysyl oxidase-like 1 and lysyl oxidase prolongs their half-lives and regulates liver fibrosis through Notch signal. *Hepatol. Commun.* **2024**, *8*, e0391, https://doi.org/10.1097/hc9.0000000000000391.
105. Garg, C.; Khan, H.; Kaur, A.; Singh, T.G.; Sharma, V.K.; Singh, S.K. Therapeutic implications of sonic hedgehog pathway in metabolic disorders: Novel target for effective treatment. *Pharmacol. Res.* **2022**, *179*, 106194, https://doi.org/10.1016/j.phrs.2022.106194.
106. Stojanovic, M.; Kalanj-Bognar, S. Toll-like receptors as a missing link in Notch signaling cascade during neurodevelopment. *Front. Mol. Neurosci.* **2024**, *17*, https://doi.org/10.3389/fnmol.2024.1465023.
107. Romeo, S.; Phimister, E.G. Notch and Nonalcoholic Fatty Liver and Fibrosis. *N. Engl. J. Med.* **2019**, *380*, 681-683, https://doi.org/10.1056/NEJMcibr1815636.
108. Yu, J.; Zhu, C.; Wang, X.; Kim, K.; Bartolome, A.; Dongiovanni, P.; Yates, K.P.; Valenti, L.; Carrer, M.; Sadowski, T. Hepatocyte TLR4 triggers inter-hepatocyte Jagged1/Notch signaling to determine NASH-induced fibrosis. *Sci. Transl. Med* **2021**, *13*, eabe1692, https://doi.org/10.1126/scitranslmed.abe1692.
109. Zhu, C.; Kim, K.; Wang, X.; Bartolome, A.; Salomao, M.; Dongiovanni, P.; Meroni, M.; Graham, M.J.; Yates, K.P.; Diehl, A.M. Hepatocyte Notch activation induces liver fibrosis in nonalcoholic steatohepatitis. *Sci. Transl. Med.* **2018**, *10*, eaat0344, https://doi.org/10.1126/scitranslmed.aat0344.
110. Kim, B.-S.; Hwang, I.; Ko, H.R.; Kim, Y.K.; Kim, H.J.; Seo, S.W.; Choi, Y.; Lim, S.; Kim, Y.K.; Nie, S. EBP1 potentiates amyloid β pathology by regulating γ-secretase. *Nat. Aging* **2025**, *5*, 486-503, https://doi.org/10.1038/s43587-024-00790-1.
111. Das, S.; Albalushi, H. Altered Notch Pathway and Cancer Stem Cells. In Cancer Stem Cells and Cancer Therapy, Kalkan, R., Ed.; Springer Nature Switzerland: Cham, **2024**; pp. 159-181, https://doi.org/10.1007/978-3-031-74842-4_6.
112. Jeong, P.-S.; Kang, H.-G.; Cha, D.; Jeon, S.-B.; Kim, M.J.; Song, B.-S.; Sim, B.-W.; Lee, S. Role of the Notch signaling pathway in porcine oocyte maturation. *Cell Commun. Signal.* **2025**, *23*, 1, https://doi.org/10.1186/s12964-024-01996-x.
113. Isotani, R.; Igarashi, M.; Miura, M.; Naruse, K.; Kuranami, S.; Katoh, M.; Nomura, S.; Yamauchi, T. Nicotine enhances the stemness and tumorigenicity in intestinal stem cells via Hippo-YAP/TAZ and Notch signal pathway. *eLife* **2025**, *13*, https://doi.org/10.7554/eLife.95267.4.
114. Kuintzle, R.; Santat, L.A.; Elowitz, M.B. Diversity in Notch ligand-receptor signaling interactions. *eLife* **2025**, *12*, https://doi.org/10.7554/eLife.91422.3.
115. Lam, W.-L.M.; Gabernet, G.; Poth, T.; Sator-Schmitt, M.; Oquendo, M.B.; Kast, B.; Lohr, S.; de Ponti, A.; Weiß, L.; Schneider, M. RAGE is a key regulator of ductular reaction-mediated fibrosis during cholestasis. *EMBO Rep.* **2025**, *26*, 880, https://doi.org/10.1038/s44319-024-00356-7.
116. Ang, C.H.; Arandjelovic, P.; Cheng, J.; Yang, J.; Guo, F.; Yu, Y.; Nelameham, S.; Whitehead, L.; Li, J.; Silver, D.L. Self-maintenance of zonal hepatocytes during adult homeostasis and their complex plasticity upon distinct liver injuries. *Cell Rep.* **2025**, *44*, 115093, https://doi.org/10.1016/j.celrep.2024.115093.
117. Yang, J.; Li, L.; An, Z.; Lv, Y.; Li, R.; Li, J.; Guo, M.; Sun, H.; Yang, H.; Wang, L. Role of hepatocyte-specific FOXO1 in hepatic glucolipid metabolic disorders induced by perfluorooctane sulfonate. *Environ. Pollut.* **2025**, *367*, 125632, https://doi.org/10.1016/j.envpol.2025.125632.
118. Almalki, W.H.; Almujri, S.S. Aging, ROS, and cellular senescence: a trilogy in the progression of liver fibrosis. *Biogerontology* **2024**, *26*, https://doi.org/10.1007/s10522-024-10153-3.
119. Gallagher, J.; Sheflin-Findling, S. Chapter 17 - Congenital cholestatic liver disease⊛. In Hepatology, Satapathy, S.K., Mamun Al, M., Singh, S.P., Eds.; Academic Press: **2025**; pp. 467-481, https://doi.org/10.1016/B978-0-443-26710-9.00017-1.
120. Cai, H.; Zhang, J.; Chen, C.; Shen, J.; Zhang, X.; Peng, W.; Li, C.; Lv, H.; Wen, T. Prognostic assessment of early-stage liver cirrhosis induced by HCV using an integrated model of CX3CR1-associated immune infiltration genes. *Sci. Rep.* **2025**, *15*, 1771, https://doi.org/10.1038/s41598-024-80422-1.
121. Wilkerson-Vidal, Q.C.; Wimalarathne, M.M.; Hunt, E.C.; Mercado, L.; David, M.A.; Apperson, C.R.; Smiley, A.; Love-Rutledge, S.T.; Vogler, B.W.G. Male LEW.1WR1 Rats Develop Metabolic Dysfunction, Steatohepatitis, and Liver Damage. *Endocrines* **2024**, *5*, 166-185, https://doi.org/10.3390/endocrines5020012.
122. Condorelli, A.G.; Nobili, R.; Muglia, A.; Scarpelli, G.; Marzuolo, E.; De Stefanis, C.; Rota, R.; Diociaiuti, A.; Alaggio, R.; Castiglia, D. Gamma-secretase inhibitors downregulate the profibrotic NOTCH signaling pathway in recessive dystrophic epidermolysis bullosa. *J. Investig. Dermatol.* **2024**, *144*, 1522-1533.e10, https://doi.org/10.1016/j.jid.2023.10.045.

123. Ding, J.; Yang, Y.-Y.; Li, P.-T.; Ma, Y.; Zhang, L.; Zhou, Y.; Jin, C.; Li, H.-Y.; Zhu, Y.-F.; Liu, X.-P.; Liu, Z.-J.; Jia, H.-L.; Liu, P.-G.; Wu, J. TGF-β1/SMAD3-driven GLI2 isoform expression contributes to aggressive phenotypes of hepatocellular carcinoma. *Cancer Lett.* **2024**, *588*, 216768, https://doi.org/10.1016/j.canlet.2024.216768.
124. Adams, J.; Jafar-Nejad, H. The Roles of Notch Signaling in Liver Development and Disease. *Biomolecules* **2019**, *9*, 608, https://doi.org/10.3390/biom9100608.
125. Zhang, N.; Guo, F.; Song, Y. HOXC8/TGF-β1 positive feedback loop promotes liver fibrosis and hepatic stellate cell activation via activating Smad2/Smad3 signaling. *Biochem. Biophys. Res. Commun.* **2023**, *662*, 39-46, https://doi.org/10.1016/j.bbrc.2023.04.011.
126. Ramos-Tovar, E.; Muriel, P. Molecular Mechanisms That Link Oxidative Stress, Inflammation, and Fibrosis in the Liver. *Antioxidants* **2020**, *9*, 1279, https://doi.org/10.3390/antiox9121279.
127. Tang, S.-p.; Mao, X.-l.; Chen, Y.-h.; Yan, L.-l.; Ye, L.-p.; Li, S.-w. Reactive Oxygen Species Induce Fatty Liver and Ischemia-Reperfusion Injury by Promoting Inflammation and Cell Death. *Front. Immunol.* **2022**, *13*, https://doi.org/10.3389/fimmu.2022.870239.
128. Govorova, I.A.; Nikitochkina, S.Y.; Vorotelyak, E.A. Influence of intersignaling crosstalk on the intracellular localization of YAP/TAZ in lung cells. *Cell Commun. Signal.* **2024**, *22*, 289, https://doi.org/10.1186/s12964-024-01662-2.
129. Color-Aparicio, V.M.; Tecalco-Cruz, A.C.; Delgado-Coello, B.; Sosa-Garrocho, M.; Mas-Oliva, J.; Vázquez-Victorio, G.; Macías-Silva, M. TGF-β and HIPPO Signaling Pathways Interplay in Distinct Hepatic Contexts. *Gene Expr.* **2024**, *23*, 223-231, https://doi.org/10.14218/ge.2023.00192.
130. Nicoletti, M.; Chiodo, L.; Loppini, A. Biophysics and Modeling of Mechanotransduction in Neurons: A Review. *Mathematics* **2021**, *9*, 323, https://doi.org/10.3390/math9040323.
131. Sharip, A.; Kunz, J. Mechanosignaling via Integrins: Pivotal Players in Liver Fibrosis Progression and Therapy. *Cells* **2025**, *14*, 266, https://doi.org/10.3390/cells14040266.
132. Mitten, E.K.; Baffy, G. Mechanotransduction in the pathogenesis of non-alcoholic fatty liver disease. *J. Hepatol.* **2022**, *77*, 1642-1656, https://doi.org/10.1016/j.jhep.2022.08.028.
133. Wang, J.; Zhang, B.; Chen, X.; Xin, Y.; Li, K.; Zhang, C.; Tang, K.; Tan, Y. Cell mechanics regulate the migration and invasion of hepatocellular carcinoma cells via JNK signaling. *Acta Biomater.* **2024**, *176*, 321-333, https://doi.org/10.1016/j.actbio.2024.01.024.
134. Guo, J.; Li, L.; Chen, F.; Fu, M.; Cheng, C.; Wang, M.; Hu, J.; Pei, L.; Sun, J. Forces Bless You: Mechanosensitive Piezo Channels in Gastrointestinal Physiology and Pathology. *Biomolecules* **2024**, *14*, 804, https://doi.org/10.3390/biom14070804.

Publisher's Note & Disclaimer