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REVIEW

PIEZO1 channel mechanosensing in hepatobiliary physiology and disease

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Abstract

The hepatobiliary system is constantly exposed to dynamic mechanical forces, including fluid shear stress, bile canaliculi pressure, and extracellular matrix stiffness. Although traditionally studied for its metabolic and detoxifying functions, it is now increasingly recognized as a mechanosensitive organ. This review focuses on PIEZO1 mechanically gated ion channels that transduce physical cues into calcium-dependent signaling events. PIEZO2, the only other PIEZO isoform, is not known to be relevant in the hepatobiliary system. We examine the current knowledge on PIEZO1 in liver physiology, highlighting its roles in liver sinusoidal endothelial cells, hepatocytes, and macrophages. In health, PIEZO1 regulates key processes such as bile acid synthesis (through nitric oxide-mediated suppression of *CYP7A1*), bile flow, antioxidant defense, and iron homeostasis. In disease, PIEZO1 activity is linked to pathological processes such as inflammation, fibrosis, and angiogenesis in the context of cirrhosis and hepatocellular carcinoma. We discuss the idea that the liver alternates between two functional states depending on portal vein flow: a high-flow state favoring detoxification and metabolism, and a low-flow state that prioritizes bile acid production. Understanding how PIEZO1 contributes to these transitions offers new insights into liver's ability to adapt its function and metabolism. Further research on hepatobiliary PIEZO1 will advance the understanding of how physical exercise promotes health and opens new opportunities for enhancing liver regeneration after surgical resection and liver function in chronic diseases such as fibrosis and cirrhosis.

blood flow; liver; mechanosensing; PIEZO1; regeneration

INTRODUCTION

Liver disease poses a significant global health challenge with its prevalence expected to rise exponentially in the coming years. Currently, liver disease accounts for up to 4% of all deaths worldwide, mainly in the form of liver cirrhosis, liver cancer, and acute hepatitis (1). Moreover, many cancers, particularly those originating from the gastrointestinal tract, metastasize to the liver, necessitating liver surgery. Many liver diseases are associated with alterations in the liver blood flow and tissue stiffness. A prime example is the progression to liver cirrhosis, which typically begins with parenchymal damage due to fatty infiltration, infection, or exposure to toxins, such as alcohol (2). This damage sets off a cascade of mechanical changes linked to altered extracellular matrix (ECM) deposition and turnover: the liver stiffens, the portal vein pressure increases, and elevated vascular resistance impairs blood flow. These changes trigger a vicious cycle of inflammation, fibrosis, and eventually liver failure.

Thus, how cells sense, interact with, and adapt to physical forces in the liver, a process described by the discipline of mechanobiology, represents a rapidly evolving area of hepatobiliary disease research. There is increasing interest in the potential implications of PIEZO1, a mechanosensitive cell membrane channel, in various aspects such as liver regeneration (3) and therapeutic targeting (4, 5). Mechanical force sensing (mechanosensing) is used in almost every tissue in the human body. Although this is most evident in tissues such as the skin or mucosae that come in direct contact with physical stimuli, it also occurs in other tissues, such as liver

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parenchymal cells sensing the stiffness of the surrounding supportive matrix or liver endothelial cells sensing the force of blood flow. In the last decade, there has been a surge of discoveries in this area of research, particularly due to the discovery of the cell membrane proteins PIEZO1 and PIEZO2. Evidence is currently lacking for a role of PIEZO2 in hepatobiliary biology, therefore in this narrative review we focus on PIEZO1 (6, 7).

PIEZO1 forms a transmembrane channel that generate nonselective cation permeability across the cell membrane, promoting calcium ion (Ca^{2+}) and sodium ion (Na^{+}) influx. It was discovered in 2010 by Coste et al. (8) through a small RNA interference screen aimed at identifying genes involved in mechanically activated ionic currents in a neuroblastoma cell line. This large transmembrane protein forms an ion channel as a trimer of PIEZO1 proteins. It is activated by various mechanical forces, such as membrane tension, stiff extracellular environment, and fluid shear stress (9), and pharmacological modulators such as the selective PIEZO1 activator Yoda1 (10, 11). PIEZO1 has been found to play crucial roles in various physiological processes such as vascular development (12, 13), red blood cell (RBC) volume regulation (14), and epithelial cell homeostasis (15). It links mechanical stimuli to intracellular signaling cascades, importantly elevating the cytosolic and intracellular store Ca^{2+} concentrations to activate multiple downstream signaling systems (13) including Ca^{2+}-dependent proteases (e.g., calpain, ADAM10, and ADAM17) and other pathways such as the YAP/TAZ (yes-associated protein/transcriptional coactivator with PDZ-binding motif) pathway (16–18). Other proteins such as integrins and G protein-coupled receptors contribute to the mechanobiology of the hepatobiliary system (19, 20), but here we focus on PIEZO1, the discovery of which was so significant, it was recognized by the Nobel Prize in Physiology or Medicine in 2021.

Despite the wealth of research on mechanotransduction, the links between the molecular mechanisms of PIEZO1, interactions with other mechanosensitive pathways, and liver disease progression remain relatively poorly understood. We first review relevant liver anatomy and cell function due to their importance in mechanical properties and responses. We then summarize recent discoveries concerning the role of PIEZO1 in liver biology, with a focus on its implications in health and disease, and its relevance to surgical intervention. By highlighting the intersection of mechanotransduction and liver pathophysiology, we aim to shed light on a promising avenue for future research and therapeutic strategies, potentially helping to advance the management of liver diseases, including liver cancer.

LIVER ANATOMY AND PHYSIOLOGY RELATED TO MECHANOSENSING

The liver, the largest solid organ in humans, is responsible for multiple functions essential to body homeostasis. These include triaging of all substances that have been absorbed from the intestines, neutralization of toxins, and transformation of nutrients for either storage or release into the blood stream for utilization in other organs and tissues. To enable this function, the venous blood from the entire alimentary tract first arrives to the liver, through the portal vein, before entering the systemic circulation. Further blood supply from the hepatic arteries, branching off the celiac axis, ensures blood rich in oxygen reaches the liver functional unit, the liver lobule. Blood arriving from the portal venules and hepatic arterioles combine to enter the liver sinusoids, where key functions take place (Fig. 1). The processed blood passes through the lobule, into the hepatic veins before returning to the systemic circulation through the inferior vena cava for drainage into the right atrium of the heart.

The liver lobule comprises four types of cells: *1*) the liver sinusoidal endothelial cells (LSECs), *2*) the hepatocytes, *3*) the hepatic stellate cells (HSCs), and *4*) the Kupffer cells (resident macrophages). Each of these cell types has specific functions, but all work in close collaboration while interacting through endocrine, paracrine, and autocrine mechanisms. They use various mechanosensitive mechanisms (2). In brief, after the blood from the portal vein and hepatic arteries enters the sinusoids, it flows through canals lined by LSECs. LSECs derive from common endothelial cell precursors or are recruited directly from the bone marrow in the context of injury (21). When healthy, they lack a significant basal membrane and morphologically have fenestrations organized into sieve plates, which allow macromolecules, but not blood cells, to travel from the sinusoidal space to the space of Disse (22). The LSECs, which express PIEZO1 (12), are exposed to the shear stress of the sinusoidal blood flow on one side and the stiffness of the extracellular matrix (ECM) and underlying cells at the space of Disse on the other (Fig. 1). Physiological liver sinusoidal shear stress is ~0.05 Pa (23), and tissue stiffness is ~5 kPa (24). The LSECs and matrix protect the hepatocytes lying on the opposite side of the space of Disse from direct exposure to blood, while allowing access to the molecules that require processing. The hepatocytes excrete the unwanted catabolites in the bile canaliculi for extraction toward the biliary tree. The hepatocytes are exposed to both the stiffness of the ECM and the pressure within the bile canaliculi as they slowly expand through receiving the bile (Fig. 1).

Understanding of liver anatomy and physiology is essential in appreciating how the ability of the cells to sense mechanical stimulation impacts liver function in health and disease. Such mechanosensitive mechanisms are involved in a multitude of functions as discussed further in this review.

MECHANOSENSING IN THE PORTAL VEIN

The blood flow to the liver dynamically adjusts in response to the physiological conditions experienced by the body. Portal vein blood supply to the liver decreases during physical exercise and increases after food consumption. This phenomenon has been proven using Doppler ultrasonography, which combines measurements of portal vein surface area and velocity to calculate portal vein flow (25–27). In addition, four-dimensional magnetic resonance imaging (4-D MRI) has been used to achieve similar insights (28).

Thijssen et al. (29) examined the impact of exercise on portal vein flow in individuals with spinal cord injuries. In their study, subjects with lower spinal cord injuries and able-bodied participants exhibited reduced portal vein flow during arm crank exercises. However, no change in portal vein flow

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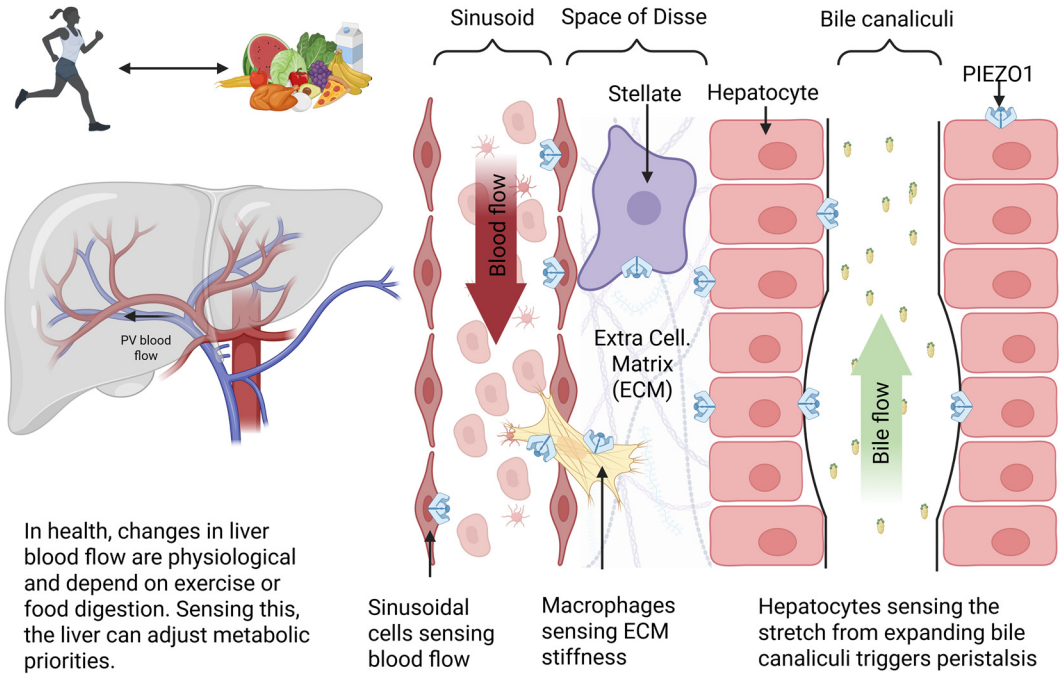

Figure 1. Anatomy of mechanohepatobiliary biology. *Left*: schematic representation of the liver dual blood supply and the physiological changes in blood flow depending on physical activity and consumption of food. *Middle*: blood flow in the liver sinusoids, which are composed of liver sinusoidal endothelial cells (LSECs). PIEZO1 channels are located on the LSEC membranes and can sense the changes blood flow and shear stress applied to the wall of the sinusoids. Adjacent is the space of Disse, which is filled with extracellular matrix (ECM). Molecules pass through the LSECs into the space of Disse and enter in contact with the hepatocytes that can metabolize/store/excrete depending on the body's needs. Stellate cells connect LSECs with hepatocytes and play a major role in the ECM stiffness by producing collagen. Macrophages are free to move between the spaces helping to remove cellular debris. All the above cells express PIEZO1, therefore having ability to sense the changes in the ECM stiffness. *Right*: representation of the bile canaliculi comprised of hepatocytes, where the canaliculi stretch because of production of bile the PIEZO1 channels are activated, resulting in contraction and peristalsis. Figure created with a licensed version of BioRender.com.

was observed in individuals with higher spinal cord injuries involving sympathetic denervation of the splanchnic organs. These findings indicate that sympathetic innervation likely plays a key role in regulating portal vein flow during exercise, suggesting that the changes in liver blood flow may involve more complex mechanisms than simple redistribution of blood to exercising muscles (30–32).

All studies consistently conclude that physical exercise reduces portal vein flow, with the degree of reduction being dependent on exercise intensity. In extreme cases, portal vein flow may decrease to unrecordable levels (33). Teichgräber et al. (34) observed that the hepatic vein flow (indicating drainage of the liver) remains largely unchanged despite reductions in portal vein flow, suggesting compensatory mechanisms. It was hypothesized that the hepatic artery flow increases to offset the reduction in portal vein flow, although arterial flow could not be directly measured using Doppler ultrasonography (34). The idea was supported by Jakab et al. (35), who momentarily occluded the portal vein in anaesthetized patients having pancreatic operations to demonstrate a sharp increase of the hepatic artery flow immediately after portal vein occlusion.

The metabolic capacity of the liver is also influenced by portal vein blood flow. During exercise, participants exhibited reduced clearance of indocyanine green (ICG), a compound used as a marker of liver function, compared with nonexercising participants. Conversely, maximum ICG clearance was observed in individuals who consumed a meal following ICG injection (36). This suggested that the liver adjusts its metabolic capacity based on portal vein flow independent of the total blood supply to the liver tissue, which largely remains unchanged. This prioritization of certain functions, such as detoxification, during the high portal vein flow (postprandial state) suggests further specialization during the low portal vein flow state.

Endesh et al. (37) studied PIEZO1 in the portal vein contractile tone. By experimenting on the portal vein of wild-type mice and mice with selective deletion of endothelial PIEZO1, they showed that PIEZO1 activation induces relaxation of the portal vein via nitric oxide (NO) production through the activation of (endothelial) NO synthase 3 (NOS3) (37). Following this, Lichtenstein et al. (38) demonstrated that reduced portal vein flow in mice increased bile production and excretion, a process mediated by endothelial PIEZO1. They cannulated murine portal vein and perfused with two different flow rates. Upregulated expression of *Cyp7a1*, a pivotal gene in classical bile synthesis, was observed when the flow rate was lowered, suggesting that high flow inhibits *Cyp7a1* expression. This regulation by flow was absent in mice lacking endothelial PIEZO1. Further experiments demonstrated increased bile production in PIEZO1-deleted mice as well as reduced hepatic cholesterol, plasma lipids, and hepatic and visceral fat deposition. This was likely the result of utilization of cholesterol and lipids to form bile acids. The study proposed that increased portal vein flow activates PIEZO1 in the liver endothelium leading

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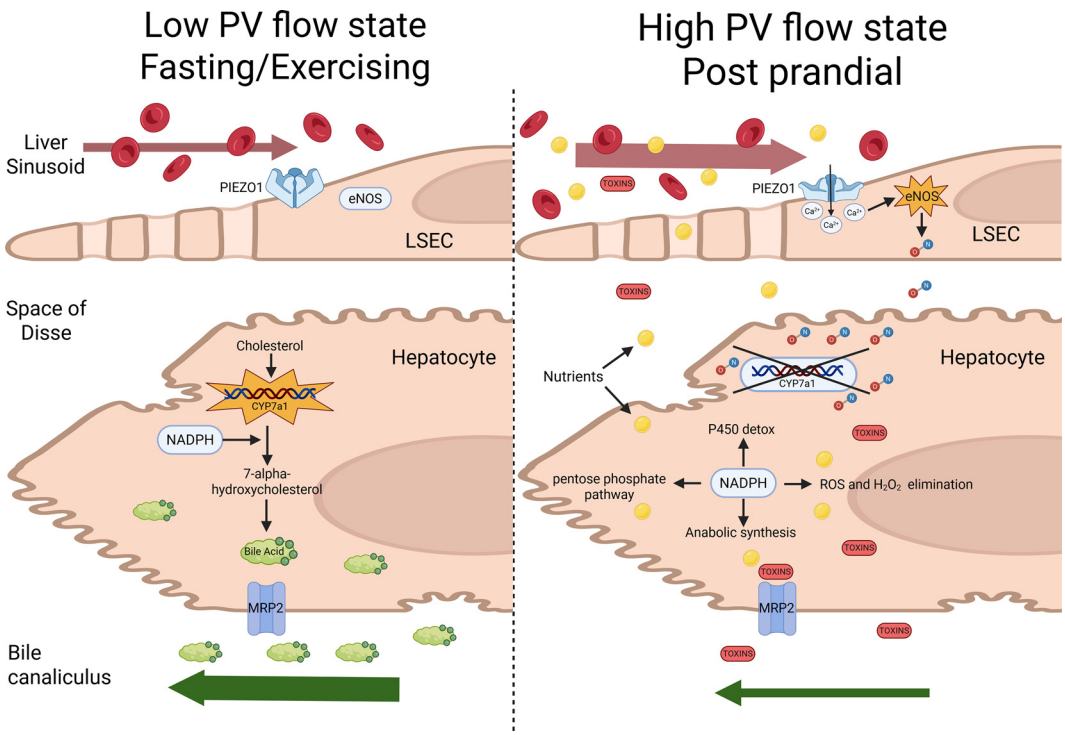

Figure 2. Hepatocyte function in low (fasting/exercise) and high (postprandial) portal flow. In the low-flow state, PIEZO1 channels on liver sinusoidal endothelial cells (LSECs) remain closed, resulting in no inhibition of *CYP7A1* in adjacent hepatocytes. This promotes bile acid synthesis, with nicotinamide adenine dinucleotide phosphate (NADPH) and other metabolic resources directed toward the hydroxylation of cholesterol and bile acid production. In contrast, high portal vein flow activates PIEZO1, triggering Ca^{2+} influx and subsequent activation of eNOS (NOS3), leading to the production of nitric oxide (NO). NO diffuses across the space of Disse and suppresses *CYP7A1* expression in hepatocytes. During this postprandial state, bile acid synthesis is downregulated, and NADPH is redirected toward anabolic and detoxification pathways, including cytochrome P450 activity and antioxidant defense. MRP2, multidrug resistance-associated protein 2; ROS, reactive oxygen species. Figure created with a licensed version of BioRender.com.

to phosphorylation of NOS3. NO is readily diffusible and results in the inhibition of *Cyp7a1* in the hepatocytes (Fig. 2) (38). An additional link between PIEZO1 and portal vein mechanosensing is suggested by recent experiments in mice investigating the role of PIEZO1 in ascites formation in the context of cirrhosis-induced portal hypertension. Wei et al. (39) compared mice with endothelial-specific PIEZO1 deletion with controls for conditional knockout following a combination of induced liver cirrhosis (thioacetamide or carbon tetrachloride treatment) plus partial portal vein ligation. They demonstrated an overall reduction in ascitic volume in the PIEZO1 deletion group, whereas the portal vein pressures remained elevated and comparable to those in the control group (39).

Therefore, during fasting or exercise, the liver appears to prioritize bile production and storage. Conversely, postprandial conditions prompt a shift in liver function toward facilitating digestion and detoxification, as demonstrated by the increased ICG clearance. There is indirect evidence for the necessity of this functional switch in liver states. Bile acid synthesis is energy demanding, requiring large amounts of metabolic resources such as nicotinamide adenine dinucleotide phosphate (NADPH) for the cytochrome P450-mediated hydroxylation steps, particularly through *CYP7A1* (40). This same pool of NADPH is also essential for detoxification pathways and intermediary metabolism (41–43), processes that become increasingly critical in the postprandial phase. Furthermore, elevated concentrations of intracellular bile acids, especially hydrophobic species, have been shown to induce endoplasmic reticulum stress, activate the unfolded protein response, and trigger hepatocellular injury (44, 45). This is particularly evident in conditions like cholestasis, where impaired bile acid clearance leads to hepatocyte dysfunction. Suppressing bile acid synthesis during periods of high nutrient load may thus serve as a protective mechanism to conserve metabolic resources, prioritize detoxification, and prevent intracellular bile acid accumulation (Fig. 2). This aligns with the utilization of the gallbladder to store the bile produced during the low-flow state for usage during the high-demand high-flow state.

Modern lifestyle patterns, characterized by frequent snacking and low physical activity, likely disrupt this natural rhythm, contributing to the onset of metabolic syndrome, diabetes, and hepatic steatosis. Prolonged postprandial state of elevated portal vein flow paired with reduced exercise induced low-flow state, may impair bile synthesis and lipid metabolism. These insights underscore the potential for lifestyle interventions such as intermittent fasting and structured exercise regimens to mitigate hepatocyte stress. PIEZO1 deletion led to a perceived low portal vein flow state in mice, which appeared beneficial (38). Research already supports that even brief periods of exercise can significantly improve liver outcomes in steatotic liver disease independent of energy restriction (46, 47), and even have a positive impact in the control of diabetes (48, 49). As our understanding of the liver's mechanosensory functions expands, targeted lifestyle modifications

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and pharmacological interventions may emerge as effective strategies for addressing liver diseases. Progress with pharmacological modulators of PIEZO1 is discussed in MODULATION AND PROSPECTS FOR THERAPEUTICS.

Endothelial PIEZO1 has also been suggested to play a role in the development of the liver through the NOTCH (Notch homolog) pathway, an extensively researched cell signaling system that affects cell differentiation and vascular formation. The NOTCH pathway's importance in the initial development and maintenance of the liver vasculature health is well established (50, 51). PIEZO1 plays a pivotal role in the function of this pathway through the activation of ADAM10, a metalloproteinase that regulates the activation of NOTCH1 (17). Conditional deletion of endothelial PIEZO1 suppressed the expression of multiple NOTCH1 target genes in the hepatic vasculature of mice. Experiments using human microvascular endothelial cells indicated that the NOTCH1 activation through cleavage at the S3 site is PIEZO1 dependent. This work suggested an important link between blood flow changes acting through shear stress-mediated endothelial PIEZO1 and NOTCH1 target gene activation.

BILE FLOW

Hepatocytes within the liver lobules secrete bile into bile canaliculi (BC), which are specialized structures formed at the junctions between adjacent hepatocytes (Fig. 1). The contraction of the BC facilitates the movement of bile, directing it into the bile tubules and major bile ducts for excretion. The mechanisms underlying BC contraction were advanced by the work of Gupta et al. (52). This team developed a BC model from isolated rat hepatocytes seeded onto a collagen sandwich. Once the formation of visible BC was achieved, they observed that Ca^{2+} influx was responsible for triggering contractions through actomyosin activation. This process was mediated by PIEZO1, demonstrated by using the PIEZO1 activator Yoda1, which increased the frequency of peristaltic contractions. Conversely, nonspecific PIEZO1 inhibitor *grammostola spatulata* mechanotoxin-4 (GsMTx4) reduced this activity. PIEZO1 chemical modulators are discussed in more detail later in this review. The mechanism appears to have been autonomous, functioning independently of external signaling pathways involving hormones or other transmitters. When bile pressure stretches the canalicular membrane beyond a specific threshold, PIEZO1 channels are activated, initiating the contraction and peristalsis of the BC (Fig. 1). These findings provide a deeper understanding of the mechanotransduction processes governing bile flow, indicating the critical role of PIEZO1 in maintaining hepatic function and bile secretion dynamics.

Similarly, PIEZO1 involvement is also key to the function of cholangiocytes, which line the bile ducts. Desplat et al. (53) performed experiments on murine primary cholangiocytes, recovering cells positive for cytokeratin 19 (CK19), a typical cholangiocyte marker but negative for albumin, a hepatocyte marker. Exposure of these cells to a hypoosmotic environment triggered Ca^{2+} influx through activation of PIEZO1. Hypoosmotic stress was proposed to lead to swelling of the cells and stretch of the membrane, activating PIEZO1, which leads to Ca^{2+} influx to balance the osmolality, coupled with ATP release. PIEZO1-mediated endothelium-dependent relaxation predominates in portal vein when there is combined mechanical and osmotic stress (37). The involvement of PIEZO1 was suggested by the effects of Yoda1 (a selective PIEZO1 activator) and genetic disruption of PIEZO1 in the endothelium.

IRON METABOLISM

PIEZO1 variants such as Met2225Arg in the outer cap structure of the channel have been identified as an underlying cause of dehydrated hereditary stomatocytosis (DHS), also known as xerocytosis, which is a rare form of hemolytic anemia leading to hepatic iron overload (54–56). The pathogenesis of DHS is characterized by increased Ca^{2+} influx into RBCs due to overactivation of PIEZO1 in their cell membranes. This influx triggers the efflux of potassium ions (K^+) through Ca^{2+}-activated K^+ channels and water that follows, rendering the cells dehydrated and susceptible to lysis. Andolfo et al. (57) established a link between PIEZO1 gain-of-function (GOF) variants and hepatic iron metabolism. They observed that iron overload in patients with DHS did not correlate with the degree of hemolysis or their requirements for blood transfusions, raising the suspicion of an undiscovered mechanism responsible for the iron metabolism deficiency. They used HuH7, HepaRG cells, and HepG2 (hepatocyte cell lines) for their experiments and transfected them with PIEZO1 mutant constructs. Using PIEZO1 activators and inhibitors (Yoda1 and GsMTx4), they suggested that PIEZO1 activation downregulates the hepcidin antimicrobial peptide (*HAMP*) gene, which encodes hepcidin, a key regulator of iron homeostasis. Hepcidin governs iron entry into the circulation, and its dysregulation due to PIEZO1 mutations is responsible for hepatic siderosis.

Building on these findings, Ma et al. (58) investigated whether other cell types also contribute to iron metabolism through PIEZO1 activity, specifically RBCs and macrophages. Their experiments, based on engineered PIEZO1 gain-of-function (GOF) mice, found that mice expressing GOF PIEZO1 only in RBCs did not show evidence of iron deposition in the liver. Then after engineering mice expressing GOF PIEZO1 in macrophages, they found age-onset iron overload with hepatic siderosis and reduced hepcidin levels, even in the absence of RBC mutations. Their experiments demonstrated that PIEZO1 impacts macrophage-mediated phagocytosis, as suggested also in other studies of phagocytosis (59), and the clearance of damaged RBCs from the circulation. They also discovered a PIEZO1 mutation prevalent in African Americans leading to age-dependent, often subclinical, siderosis. The mutation was heterozygous in 30.3% of the self-reported healthy population.

These findings suggest a complex interplay of PIEZO1-related mechanisms involving various cell types in the regulation of iron metabolism. This evidence underscores the significance of PIEZO1 in cellular and systemic iron metabolism and highlights its potential as a therapeutic target in conditions involving iron dysregulation (Fig. 3). In liver injury, additional mechanisms such as cell swelling could influence iron metabolism.

DRUG METABOLISM AND REPAIR

Although the role of PIEZO1 in drug metabolism and liver repair has not been extensively investigated, Wang et al. (60)

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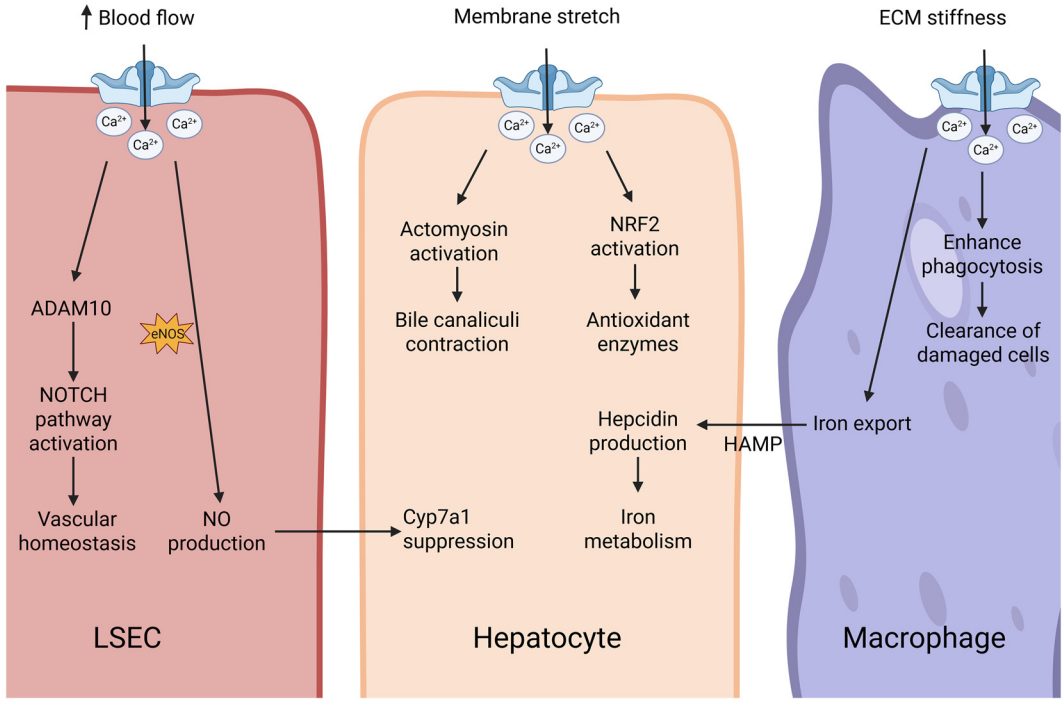

Figure 3. PIEZO1-dependent signaling in liver function. Roles of PIEZO1 in three liver cell types: *1*) liver sinusoidal endothelial cells (LSECs), *2*) hepatocytes, and *3*) liver macrophages. In LSECs (*left*), PIEZO1 is activated by shear stress from portal vein blood flow, leading to calcium ion (Ca^{2+}) influx and activation of ADAM10, which promotes NOTCH1 signaling and maintains endothelial identity and vascular homeostasis. Concurrently, PIEZO1 triggers eNOS (NOS3) activation and nitric oxide (NO) production, which diffuses to hepatocytes and suppresses *CYP7A1* expression, thereby reducing bile acid synthesis. In hepatocytes (*middle*), PIEZO1 responds to local membrane tension (e.g., bile canaliculi stretch), promoting actomyosin contraction and bile flow. It may also activate nuclear factor erythroid 2-related factor 2 (*NRF2*), enhancing antioxidant defenses. In macrophages (*right*), PIEZO1 promotes iron export, indirectly suppressing hepcidin (HAMP) expression in hepatocytes. In addition, PIEZO1 enhances phagocytic clearance of damaged cells, supporting tissue homeostasis. HAMP, hepcidin antimicrobial peptide. Figure created with a licensed version of BioRender.com.

used mice and cell lines to investigate if PIEZO1 is associated with acetaminophen (paracetamol) overdose liver necrosis. They found that PIEZO1 activates nuclear factor erythroid 2-related factor 2 (*NRF2*), a gene responsible for the expression of antioxidant genes such as encoding glutathione-*S*-transferase (*GST*) and encoding quinone oxidoreductase 1 (*NQO1*). In their experiments, the authors demonstrated that PIEZO1 was activated in the early stages of acetaminophen overdose, likely secondary to cell swelling and distention of the membrane. Subsequent treatment with PIEZO1 activator Yoda1 alleviated the adverse poisoning consequences such as cell death. However, there is also a duality of function in acute liver failure. As an example, Zhao et al. (61) demonstrated that PIEZO1 expression on macrophages is linked to proinflammatory cytokine release and cell damage in acute liver failure. Thus, in this context, reduction of macrophage PIEZO1 was beneficial and Yoda1 amplified the damage (Fig. 3).

LIVER CIRRHOSIS AND REGENERATION

Liver cirrhosis is a serious and poorly understood condition with limited treatment options beyond liver transplantation (62, 63). Comprehensive extracellular matrix deposition and crosslinking leads to increased resistance and stiffness of liver tissue. At early stages of cirrhosis, there is dysfunction of LSECs, which lose their characteristic fenestrations and transform into a capillary endothelial cell phenotype. Concurrently, the transition of HSCs from a quiescent to an activated state leads to increased collagen deposition in the extracellular matrix (64–66). Although the impact of increased tissue stiffness has been known for decades, the role of mechanosensing has gained attention only in the past few years.

Wang et al. (67) investigated the changes caused by increased ECM stiffness in the liver. Their experiments, based on engineered mice with deletion of PIEZO1 from the bone marrow-derived monocytes (BMDMs), revealed that PIEZO1 is crucial in BMDM ability to repair early fibrotic damage in the liver tissue. More specifically, when macrophages were exposed to stiffer environment, they showed improved efferocytotic function (i.e., ability to phagocytose dead and damaged cells). Pharmacological activation of PIEZO1 increased the efferocytotic capability and accelerated the resolution of inflammation and fibrosis. In contrast, when BMDMs with selective deletion of PIEZO1 were tested, they showed impaired function. These findings suggest that BMDMs sense the stiffness of the matrix through PIEZO1 and thereby adjust their activity to overcome the fibrotic damage.

On the contrary, Luo et al. (68) showed that in human and murine fibrotic liver, there was an overexpression of PIEZO1. Focusing on BMDMs, they suggested that PIEZO1 activation of this subcategory of macrophages might be associated with advancement of liver fibrosis. By experimenting in mice with PIEZO1-deleted BMDMs, they demonstrated that

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PIEZO1 activation was associated with increased inflammatory response through interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) production. Furthermore, BMDMs activated HSCs, resulting in deposition of collagen in the ECM and increased tissue stiffness. A further study using similar techniques demonstrated that lithospermic acid can attenuate liver fibrosis through PIEZO1 deactivation (69). The conflicting results of these studies highlight the complexity of the underlying mechanisms of fibrogenesis and fibroresolution and the need for further investigation of the role of PIEZO1 in this context.

Hilscher et al. (70) investigated the effect of blood flow and pressure changes on the liver. They experimented with mouse LSECs and performed a partial ligation of the inferior vena cava. They found that increased mechanical forces were applied to LSECs, leading to PIEZO1 activation, upregulation of the NOTCH1 pathway, and production of C-X-C motif chemokine ligand 1 (CXCL1) and other neutrophil chemotactic agents. The activated neutrophils interacted with platelets to promote formation of neutrophil extracellular traps (NETs), which are composed of extracellular DNA fibers bound to histones and granular proteins such as neutrophil elastase. They propagate microthrombus formation in the sinusoids and aggravate portal hypertension. PIEZO1-expressing neutrophils promote NET formation in influenza virus infection (71) and the relevance of this to the liver would be interesting to investigate. Thus, PIEZO1 activation, either on the LSECs or directly on neutrophils, contributed toward inflammatory damage and NET release in the context of impaired outflow.

The importance of NETs is also evident in liver damage after transplantation. Yu et al. (72) investigated rats subjected to liver transplantation. The rats were divided into two groups receiving either liver subjected to increased warm ischemia time or not (72). As expected, the increased warm ischemia time grafts had lower hepatic artery blood flow and overexpression of proteins related with formation of NETs. Immunohistochemistry confirmed the increased presence of NETs around injured bile ducts, and this was associated with upregulation of PIEZO1 and NOTCH1 pathway proteins. It was previously reported that mechanical stress and integrin β-2-intercellular adhesion molecule-1 (ICAM-1) clustering synergistically activate PIEZO1 and its downstream proto-oncogene tyrosine kinase Src (SRC)/proline-rich tyrosine kinase 2 (PYK2) signaling to promote cellular extravasation (73). Thus, the researchers performed a proteomic quantification of warm ischemic liver transplant samples and showed increases in PIEZO1, SRC, and protein-tyrosine kinase 2-β (Ptk2b) (72). They concluded that activation of PIEZO1 secondary to the warm ischemic injury and reduced hepatic artery flow results in bile duct damage through extravasated NETs.

Increased portal vein flow promotes liver regeneration after resection (74, 75) and recently was found to activate PIEZO1 in the endothelial cells (30, 38). A potential pathway involves one of the best-characterized downstream effects of PIEZO1 activation, the production of NO through NOS3 (30, 37, 38). Notably, NO has been shown to promote hepatocyte proliferation and liver regrowth in multiple models mainly through epidermal growth factor (EGF) activation (76, 77). This hypothesis is further supported by earlier work demonstrating impaired regeneration in NOS3-deficient mice (78). Supporting this theory, Hu et al. (79) investigated the role of PIEZO1 in liver regeneration using a partial portal vein ligation model in rats, and observed increased portal blood flow to the nonligated lobes that stimulated liver regeneration. Microscopic ultrasound imaging confirmed hyperperfusion of the remnant lobes, which demonstrated enhanced hepatocyte proliferation, particularly in zones 1 and 2 of the lobule as shown by K_i-67 (proliferation marker antigen K_i-67) staining. In vitro, human umbilical vein endothelial cells (HUVECs) and hepatocyte-like SK-Hep1 cells were treated with the PIEZO1 agonist Yoda1, which triggered upregulation of EGF receptor ligands, including heparin-binding EGF-like growth factor (HBEGF), amphiregulin (AREG), and epiregulin (EREG). These secreted factors promoted proliferation and partial epithelial-mesenchymal transition in mouse primary hepatocytes, demonstrated by K_i-67 expression and changes in epithelial markers. To further investigate the role of portal vein flow in regeneration through PIEZO1, fasting was used to reduce total portal flow during the regeneration phase. A reduction of regeneration was indeed observed while administration of Yoda1 (PIEZO1 agonist) partially restored the hepatocyte proliferation. The findings support a model in which PIEZO1 acts as a critical mechanosensor in endothelial cells, linking portal flow dynamics to regenerative paracrine signaling in the liver.

The above findings collectively suggest that PIEZO1 plays a dual role in liver disease and regeneration, with effects that depend on the cellular context and mechanical environment. When PIEZO1 is optimally stimulated (e.g., by increased laminar flow in portal vein), it is associated with positive feedback mechanisms, whereas abnormal stimulation (venous obstruction/tissue swelling) has the opposite effects. Dual roles of this type may be explained by a mechanical set point (80).

PIEZO1 activation has been suggested in livers with reduced arterial pressure and venous outflow obstruction (70, 72), which contradicts the canonical view of PIEZO1 as a flow-activated sensor. One possible explanation is that hepatocyte membrane swelling (commonly observed in outflow obstruction) could directly activate PIEZO1. Alternatively, PIEZO1 might be activated by increased pressures in the sinusoidal space, resulting in increased mechanical stress on LSECs. Future studies are warranted to define these mechanical contexts in vivo. Exploration of the effects of increased portal vein flow in human liver regeneration under physiological conditions would aid in delineating the specific pathways and mechanical set points involved in the process.

LIVER CANCER

Given that PIEZO1 is associated with regenerative and angiogenetic pathways (12), it is expected that various tumor types will use PIEZO1 as they progress and become more malignant. PIEZO1 can be activated by both the increased blood flow and the increased stiffness of ECM that often takes place in the background of cancer (81). Examples of cancers involving PIEZO1 activity in their development include pancreatic, gastric, ovarian, squamous cell cancers, and melanoma (82–86). PIEZO1 activation is associated with well-known pathways promoting cancer development including transforming growth factor-beta (TGF-β) (85),

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Table 1. *PIEZO1-dependent signaling pathways in HCC*

Proposed PIEZO1-Dependent Pathway	Associated Effect in HCC	References
PIEZO1 → YAP/TAZ activation	Increased proliferation and tumor growth	Zhang et al. 2024 (91); Liu et al. 2021 (93)
PIEZO1 → MAPK pathway (JNK, ERK, p38)	Enhanced mitotic activity and cell survival	Liu et al. 2021 (93)
PIEZO1 → TGF-β signaling through Rab5c recruitment	Promotion of EMT and metastasis	Li et al. 2022 (90)
PIEZO1 → HIF-1α and VEGF induction	Angiogenesis, vascular remodeling	Li et al. 2022 (89); Ye et al. 2022 (95)
PIEZO1 → Invadopodia formation under matrix stiffness	Increased invasive and metastatic potential	Zhang et al. 2024 (91)
PIEZO1 overexpression in tumor tissue (clinical correlation)	Associated with collagen deposition and poor prognosis	Li et al. 2022 (89); Zhang et al. 2024 (91); Ye et al. 2022 (95)

Summary of proposed molecular pathways downstream of PIEZO1 that contribute to HCC progression, based on in vitro studies, animal models, and clinical correlations. These include activation of proliferative, angiogenic, and invasive mechanisms, as well as associations with poor patient outcomes. EMT, endothelial-to-mesenchymal transition; ERK, extracellular signal-regulated kinase; HCC, hepatocellular carcinoma; HIF-1α, hypoxia-inducible factor 1-alpha; JNK, Jun *N*-terminal kinase; MAPK, mitogen-activated protein kinase; TAZ, transcriptional coactivator with PDZ-binding motif; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor; YAP, yes-associated protein.

phosphoinositide 3-kinase-Akt signaling pathway (PI3K-Akt) (84), and Hippo/YAP (87, 88).

Research on hepatocellular carcinoma (HCC) has found correlations between increased ECM stiffness, activation of PIEZO1, and enhanced cancer progression. In four studies, researchers investigated the expression of PIEZO1 in HCC samples acquired from cohorts of 372, 372, 374, and 280 patients (89–92). They all suggested a correlation between expression of PIEZO1 and poor outcomes, including reduced overall survival and disease-free survival after surgical resection. In two of the studies, the upregulation of PIEZO1 was correlated positively with increased deposition of collagen and increased stiffness (89, 91). Furthermore, research on HCC cell lines and orthotopic development of HCC in mice showed a strong correlation between PIEZO1 activation and upregulation of several mitotic and regenerative pathways that play roles in cancer advancement. Those include activation of TGF-β, hypoxia-inducible factor 1-alpha (HIF-1α), and eventually VEGF (a target of anticancer treatment) as well as activation of mitogen-activated protein kinase (MAPK) through c-Jun *N*-terminal kinase (JNK), p38, and extracellular signal-regulated kinase (ERK) activation of YAP (89–91, 93, 94). Similar findings were acquired by experiments on hepatoblastoma tissue and by using hepatoblastoma cell lines (HepG2 and Huh6) (95). In addition, PIEZO1 was positively related to the development of invadopodia, a characteristic of higher malignant potential, and cancer cell migration (91) (Table 1). Improved outcomes were achieved at the cellular level by negating the PIEZO1 activity, either using a chemical inhibitor or by genetically modifying the cells to silence PIEZO1 (94). A study by Huo et al. (92) both supported previous findings and identified a link between PIEZO1 activation and resistance to sorafenib, a multikinase inhibitor used as first-line treatment in advanced HCC. As a result of these findings, PIEZO1 is proposed as an oncogene, and there are ongoing efforts to identify ways to use the new knowledge into developing medication to manipulate function in vivo.

MODULATION AND PROSPECTS FOR THERAPEUTICS

From a translational perspective, both pharmacological and mechanical modulation of PIEZO1 offers promising therapeutic avenues. The most widely used agonist experimentally is Yoda1, a synthetic small molecule that activates PIEZO1 by stabilizing its open conformation (96). Yoda2, a more potent and water-soluble analog, has since been developed to enhance the agonist pharmacological capability (97). Specific PIEZO1 antagonists are not yet properly established although Dooku1, a chemical related to the PIEZO1-specific agonists Yoda1 and Yoda2 (98), has PIEZO1 antagonist properties in some conditions and may be suitable as a specific antagonist or partial agonist. The spider venom peptide GsMTx4 is not only an inhibitor of PIEZO1 channels but also PIEZO2 and other ion channels (10, 99). Benzbromarone (100) and other broader cation channel blockers, such as ruthenium red, gadolinium, and escin (8, 101), inhibit

Table 2. *PIEZO1 modulators and their mechanism of action*

Compound	Effect on PIEZO1	Mechanism of Action
Yoda1	Agonist	Stabilizes the open conformation of PIEZO1
Yoda2	Agonist	More potent and water-soluble analogue of Yoda1
Dooku1	Antagonist (Yoda1-specific)	Competitively inhibits Yoda1-induced activation without affecting mechanosensitivity
Benzbromarone	Inhibitor	Blocks PIEZO1-dependent Ca^{2+} influx
GsMTx4	Inhibitor (nonselective)	Alters membrane tension, inhibiting mechanosensitive ion channels including PIEZO1
Escin	Inhibitor	Reduces PIEZO1-mediated calcium influx in endothelial cells
Ruthenium Red	Inhibitor (nonspecific)	Blocks a range of cation channels, including PIEZO1
Gadolinium	Inhibitor (nonspecific)	Blocks stretch-activated channels by obstructing ion conduction

GsMTx4, *grammostola spatulata* mechanotoxin-4.

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PIEZO1 but lack specificity (Table 2). Recent reviews summarize the pharmacological landscape of PIEZO modulators (10, 11). In addition to chemical tools, PIEZO1 can be activated mechanically by low-intensity focused ultrasound, which induces membrane stress and has been shown to trigger PIEZO1-dependent Ca^{2+} influx in various cell types (102, 103). Whether ultrasound can be applied to liver tissue to elicit PIEZO1-specific effects remains to be investigated.

Although PIEZO1 modulators have been widely used in vitro, only a few studies have evaluated their systemic application in vivo (10, 100, 104). In the context of the liver, Hu et al. (79) administered Yoda1 intraperitoneally and observed enhanced hepatocyte proliferation under fasting conditions, supporting a role for PIEZO1 in promoting liver regeneration. In vitro, several studies have demonstrated that Yoda1, GsMTx4, and other compounds modulate PIEZO1 function in liver-specific cells, including hepatocytes, LSECs, and liver-derived cancer cell lines. These findings are summarized in Table 3, which outlines the cell types, species, modulators used, and functional outcomes. Together, these studies support the feasibility of targeting PIEZO1 pharmacologically in liver models and suggest that both agonists and antagonists may be beneficial depending on the context.

CONCLUSIONS

Advancements in our understanding of liver mechanosensing through the discovery of PIEZO1 have transformed our knowledge of liver physiology and disease. PIEZO1 has emerged as a central theme in liver functionality, with broad implications across bile secretion, fibrosis, oncogenesis, and regeneration. It seems to importantly integrate the diverse physical forces acting upon the hepatobiliary system and translates them into coordinated cellular responses. Across liver sinusoidal endothelial cells, hepatocytes,

Table 3. *PIEZO1 modulators used in liver derived cells and their actions*

Paper Title	Cell Type/Species	Modulator	Action
Shear stress activates ADAM10 sheddase to regulate Notch1 through the Piezo1 force sensor in endothelial cells (17)	Primary LSECs/human	Yoda1	PIEZO1 activation promoted Notch1 cleavage; no inhibitor used
Bile canaliculi contract autonomously by releasing calcium into hepatocytes through mechanosensitive calcium channels (52)	Primary hepatocytes/rat	Yoda1, GsMTx-4	PIEZO1 activation induced calcium signaling; GsMTx-4 blocked canalicular contraction
Piezo1-Pannexin1 complex couples force detection to ATP secretion in cholangiocytes (53)	Cholangiocytes/mouse	Yoda1	PIEZO1 activation induced ATP release; no inhibitor used
Endothelial force sensing signals to parenchymal cells to regulate bile and plasma lipids (38)	Primary LSECs/mouse	Yoda1	PIEZO1 activation promoted NOS3 phosphorylation and suppressed Cyp7a1 expression; no inhibitor used
Gain-of-function mutations in PIEZO1 directly impair hepatic iron metabolism through the inhibition of the BMP/SMADs pathway (57)	HepG2, HuH7 (HCC cell lines)/human	Yoda1, GsMTx-4	PIEZO1 activation altered iron metabolism; GsMTx-4 blocked the effect
EGFR-mediated crosstalk between vascular endothelial cells and hepatocytes promotes Piezo1-dependent liver regeneration (79)	Systemic mouse treatment, SK-Hep1, primary mouse hepatocytes/human-mouse	Yoda1	PIEZO1 activation promoted EGFR ligand secretion and hepatocyte proliferation in cells; no inhibitor used
Piezo1 alleviates acetaminophen-induced acute liver injury by activating *Nrf2* and reducing mitochondrial ROS (60)	AML12 cells, primary mouse hepatocytes/mouse	Yoda1	PIEZO1 activation protected hepatocytes through *Nrf2* activation; no inhibitor used
Activation of Piezo1 contributes to matrix stiffness-induced angiogenesis in hepatocellular carcinoma (89)	MHCC97H and Hep3B (HCC cell lines)/human	Yoda1, GsMTx-4	PIEZO1 activation enhanced angiogenesis through HIF-1α stabilization; GsMTx-4 inhibited effect
The function of Piezo1 in hepatoblastoma metastasis and its potential transduction mechanism (95)	HepG2, Huh6 (HB cell lines)/human	Yoda1	PIEZO1 activation enhanced HIF-1α/VEGF-mediated metastasis; no inhibitor used
Piezo1 promoted hepatocellular carcinoma progression and EMT through activating TGF-β signaling by recruiting Rab5c (90)	HCCLM3, Hep3B (HCC cell lines)/human	Yoda1, GsMTx-4	PIEZO1 activation promoted TGF-β/Smad2/3 signaling; GsMTx-4 partially blocked Ca^{2+} influx
A synergistic regulation works in matrix stiffness-driven invadopodia formation in HCC (91)	MHCC97H and Hep3B (HCC cell lines)/human	Yoda1, GsMTx-4	PIEZO1 activation promoted migration and invadopodia formation; GsMTx-4 blocked the effect
Escin ameliorates inflammation through inhibiting mechanical stretch and chemically induced Piezo1 activation in vascular endothelial cells (101)	Primary liver endothelial cells (MLECs)/mouse	Yoda1, Escin	Yoda1 activated PIEZO1; Escin inhibited Ca^{2+} influx and inflammatory signaling

ATP, adenosine triphosphate; EMT, endothelial-to-mesenchymal transition; HCC, hepatocellular carcinoma; HIF-1α, hypoxia-inducible factor 1-alpha; LSECs, liver sinusoidal endothelial cells; MAPK, mitogen-activated protein kinase; NO, nitric oxide; NOS3, nitric oxide synthase 3; *NRF2*, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor.

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cholangiocytes, and macrophages, PIEZO1 contributes to the regulation of bile acid synthesis, bile flow, antioxidant defense, iron metabolism, inflammation, and vascular behavior. Its sensitivity to portal vein flow provides a framework for understanding how the liver shifts between functional states that prioritize either metabolism and detoxification or bile acid production. In pathological settings, PIEZO1 is increasingly associated with the mechanical alterations that characterize fibrosis, portal hypertension, drug-induced injury, and liver cancer.

FUTURE RESEARCH DIRECTIONS

PIEZO1's associations with harmful outcomes do not necessarily imply its causal role in pathology. Further work is needed to determine whether PIEZO1 initiates or simply participates in hepatobiliary disease processes. An area for future research is PIEZO1 contributions to liver regeneration under physiological and pathological conditions. Understanding how endothelial and parenchymal cells sense increases in portal flow and other changes in mechanical forces after liver injury or surgical resection will potentially clarify the early events that trigger hepatocyte proliferation. Defining how PIEZO1 activation interacts with NO signaling and participates in endothelial to hepatocyte communication and zone-specific regenerative responses could help explain how the liver mounts an effective regenerative program. A future area for research is the altered mechanobiological context of hyperperfusion, as occurs in remnant liver and is implicated in small-for-size syndrome (105). Such work has the potential to identify whether modulation of PIEZO1 could support regeneration or protect vulnerable remnant tissue after major hepatectomy or living donor transplantation.

Beyond regeneration, a broader research agenda is needed to define how PIEZO1 signaling shapes hepatic physiology and disease across multiple contexts. Clarifying the mechanical thresholds that separate adaptive from pathological activation will be vital for interpreting the diverse PIEZO1 findings across fibrosis, iron metabolism, cholangiocyte biology, and cancer progression. Progress may depend on mapping cell-specific downstream signaling networks, including interactions with ADAM proteases, NO pathways, inflammatory circuits, and oncogenic programs. Advances in biophysical stimulation methods including ultrasound-based mechanomodulation offer opportunities to study PIEZO1 function in more controlled settings. Integration of these approaches with human models such as primary cells, explants, organoids, and high-resolution flow imaging could be crucial for translating mechanobiology into interventions that enhance regeneration, reduce fibrosis progression, and improve outcomes in chronic liver disease and liver surgery.

There have been important pharmacological discoveries for PIEZO1, but further progress is needed and pharmacological results need to be considered with caution. PIEZO1 contributions have, in some instances, been suggested only based on the results with activators such as Yoda1 or Yoda2 and nonspecific inhibitors such as GsMTx4. Activator effects may be unphysiological, not accurately resembling the actions of mechanical forces. As with most pharmacology, the concentration of each agent needs to be carefully chosen, with the lowest effective dose used where possible. Research for the discovery of new, more potent, activators with favorable pharmacological profiles is under way. There are efforts to find PIEZO1-specific inhibitors, and here progress with biologically active antibodies and nanobodies can be hoped for. Organ-targeted delivery systems may enable localized pharmacological modulation of PIEZO1 while minimizing effects on other systems that often also express PIEZO1. The liver presents an opportunity for targeted delivery since selective catheterization of segmental arteries for delivery of therapeutic agents and embolization of the portal vein for regeneration purposes are already routine in surgical practice.

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The views expressed are those of D.J.B. and the other authors, not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

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D.J.B. is a partner of CalTIC GmbH, a pharmaceutical start-up company with a mission to develop TRPC antagonists as a new class of medicines for the treatment of metabolic disease/obesity and pathological cardiac remodeling. P.L. is part of the National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre. None of the other authors has any conflicts of interest, financial or otherwise, to disclose.

AUTHOR CONTRIBUTIONS

C.K. prepared figures; C.K. drafted manuscript; C.K., S.K.P., P.L., J.B.M., L.D.R., N.E., T.M.W., A.S., A.R.H., K.R.P., D.J.B., and L.L. edited and revised manuscript; C.K., S.K.P., P.L., J.B.M., L.D.R., N.E., T.M.W., A.S., A.R.H., K.R.P., D.J.B., and L.L. approved final version of manuscript.

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