HEPATOLOGY FORUM

Volume 7, Issue 4, 2026 | 393–406 DOI: 10.14744/hf.2026.00221

REVIEW ARTICLE

Primary cilia orchestrate the multi-organ network in metabolic dysfunction-associated steatohepatitis

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Points to Note

- **Synthesis of Current Evidence:** Primary cilia may coordinate liver-gut-pancreas and brain-gut-liver axes in MASH by regulating metabolic, inflammatory, and fibrotic pathways.
- **Major Controversies:** Direct evidence in MASH remains limited, and whether ciliary dysfunction is a cause or consequence of disease is unclear.
- **Future Directions:** Studies should validate cilia-based biomarkers and test targeted therapies in MASH models and patient subgroups.

ABSTRACT

Metabolic dysfunction-associated steatohepatitis (MASH) is an increasingly prevalent cause of chronic liver disease and a major driver of cirrhosis and hepatocellular carcinoma worldwide. Although its pathogenesis involves complex interactions among metabolic, inflammatory, and neuroendocrine processes across multiple organs, current therapeutic strategies remain largely liver-centric and fail to address this systemic complexity. Primary cilia (PC) are evolutionarily conserved microtubule-based organelles that function as cellular sensory hubs, integrating extracellular signals and coordinating metabolic and inflammatory pathways. Emerging evidence from studies of ciliopathies, obesity, and neurodegeneration suggests that ciliary dysfunction may contribute to metabolic disorders affecting multiple organ systems. Here, we synthesize current evidence to propose a cilia-centered conceptual framework for MASH pathogenesis. We outline a dual-axis model in which PCs coordinate a horizontal metabolic axis linking the liver, gut, and pancreas to regulate glucose and lipid homeostasis, and a vertical neuro-metabolic axis connecting the brain, gut, and liver to integrate neural and endocrine signaling. Within these networks, cilia-associated pathways, including mammalian target of rapamycin, Hedgehog, Wnt/β-catenin, Notch, and transforming growth factor beta signaling, modulate key processes underlying steatosis, inflammation, and fibrogenesis. Dysfunction of PCs in hypothalamic neurons, pancreatic β-cells, intestinal stromal cells, and hepatic stellate cells may collectively amplify metabolic imbalance and inflammatory signaling, thereby promoting MASH progression. Understanding the systemic regulatory role of PC provides a unifying perspective on the multi-organ nature of MASH and highlights cilia-associated pathways as potential targets for therapeutic intervention.

Keywords: Liver-gut axis, metabolic dysfunction-associated steatohepatitis, microbiota-neuron-metabolism axis, primary cilia.

How to cite this article: Zhao Y, Tian Z, Dou D, Li R, Zhang Y, Chang Y, Bai C. Primary cilia orchestrate the multi-organ network in metabolic dysfunction-associated steatohepatitis. Hepatology Forum 2026; 7(4):393–406.

Received: October 22, 2025; **Revised:** March 06, 2026; **Accepted:** March 08, 2026; **Available Online:** October 30, 2026

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Introduction

Metabolic dysfunction-associated steatohepatitis (MASH) is rapidly reshaping the landscape of chronic liver disease worldwide. Globally, over one-third of adults are affected by metabolic dysfunction-associated steatotic liver disease (MASLD).[1] As a progressive stage of MASLD, MASH has become a significant driver of cirrhosis and hepatocellular carcinoma (HCC),[2] while also exacerbating the risk of cardiovascular events,[3] chronic kidney disease,[4] and neurodegenerative disorders.[5] This creates a cross-organ pathological network. Recent evidence suggests that single-target interventions are insufficient to address the complex, multi-axial pathology of MASH. However, primary cilia (PC) – organelles once regarded as "evolutionary relics" – mediate information transduction and cellular process regulation across multiple systems.[6] Consequently, the PC may serve as a critical hub for trans-systemic regulation.

Overview of PC

Cilia are microtubule-based structures, evolutionarily highly conserved, present on nearly all mammalian cells. They serve as crucial signaling hubs in energy metabolism and inflammation, participating in processes such as the cell cycle, signal transduction, and autophagy.[6] Cilia protrude from the cell surface as finger-like projections, consisting of a microtubule axoneme covered by a specialized plasma membrane anchored by a basal body or centriole. A dichotomous classification of cilia is based on motility differences arising from "9+2" to "9+0" microtubule configurations: motile cilia and non-motile cilia, the latter also termed PC.[7] The PC's capacity for sensing and modulating information has long been recognized.[6,8] Defects in ciliary structure or function can lead to ciliopathies, whose core manifestations or major complications include metabolic diseases such as obesity and diabetes.[9]

As a significant early warning sign of metabolic syndrome,[10] MASH is associated with abnormalities in PC structure and function: the loss of cilia on hepatic stellate cells (HSCs) exacerbates fibrosis progression through multiple pathways,[11,12] while ciliary dysfunction in the intestinal system not only worsens metabolic disturbances but also promotes brain functional decline.[13] As detailed in Section 4, PCs are present in HSCs, cholangiocytes, pancreatic islets, enteric neurons, and hypothalamic neurons. These nodes position the PC as an overlapping component of relevant networks, a common pathological nexus for the microbe-metabolism-neuron axis, and a potential therapeutic target for MASH.

Pathogenesis of MASH and Evidence for PC Abnormalities

The traditional exclusion-based term "non-alcoholic" has been superseded, with MASLD and MASH now adopted as standard nomenclature. MASLD requires the presence of hepatic steatosis plus at least one cardiometabolic risk factor, while MASH additionally involves inflammation and hepatocyte ballooning.[14,15] This review uses MASLD/MASH uniformly, retaining non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) when citing pre-2023 studies.[16]

MASH is a chronic liver disease driven and progressively aggravated by metabolic dysregulation. Its core pathogenesis involves a series of pathological processes including insulin resistance (IR), lipotoxicity, oxidative stress, organelle dysfunction, and apoptosis.[17] These processes can be exacerbated by metabolic abnormalities such as obesity, hypertension, and hypertriglyceridemia.[18,19] During disease progression, lipid accumulation in hepatocytes induces mitochondrial dysfunction and excessive reactive oxygen species generation, subsequently activating the JNK pathway and endoplasmic reticulum stress. This ultimately triggers hepatocyte apoptosis through pathways such as caspase-3, further activating HSCs and promoting fibrosis.[20–22]

Notably, the PC, as a ubiquitous organelle, mediates vital physiological and pathological signals in different organs. In the liver, PCs on cholangiocytes have been established as key mechano- and chemosensors. Through proteins like polycystin-2, they perceive changes in bile composition and flow, regulating intracellular Ca^{2+} and cAMP balance, thereby influencing cell proliferation and secretion.[23,24] Studies show that in genetic polycystic liver disease and experimental cholestasis models, PC functional defects (e.g., downregulation of polycystin-2) can lead to aberrant activation of vascular endothelial growth factor (VEGF) signaling, promoting angiogenesis and inflammatory-fibrotic responses.[25] Furthermore, in fibropolycystic liver disease models, defects in cilia-associated proteins can activate β-catenin signaling, driving the expression of chemokines such as CXCL10, recruiting macrophages, and exacerbating periportal fibrosis.[26]

In biliary atresia and most fibrocystic liver diseases, bending, shortening, loss, and genetic defects of PCs have been clearly associated with disease progression.[27–29] Notably, these diseases share a hypoxic microenvironment with MASH. Existing studies have observed an association between hypoxia-inducible factor 1-alpha (HIF-1α) activation and ciliary loss in cholangiocytes.[27,30] *In vitro* experiments exposing cholangiocyte epithelial cells to hypoxic conditions (0.5% O_2) directly reduced PC number and shortened their length. This suggests that hypoxia, a prevalent microenvironmental alteration in MASH and many chronic liver diseases,[31,32] likely causes similar physical disruption to PCs in intrahepatic cells. Therefore, hypoxia-induced PC dysfunction may be a potential mechanism for ductular reaction and fibrosis in MASH.

In a mouse model with cholangiocyte-specific knockout of the key PC gene Kif3a, PC-deficient cholangiocyte epithelial cells exhibited upregulation of senescence and DNA damage response pathway genes and downregulation of proliferation-related genes at the transcriptome level. These cells showed significantly reduced proliferative capacity and increased senescence markers (SA-β-Gal). When transplanted into injured livers, their engraftment and repair capacity were severely impaired. This indicates that PC dysfunction is sufficient to drive cells into senescence and deprive them of

regenerative potential. Notably, a self-reinforcing vicious cycle exists among hypoxia, PC damage, and cellular senescence.

Devarbhavi et al.,[33] showed that hypoxia can directly induce biliary epithelial cell (BEC) senescence; conversely, inducing cholangiocyte senescence significantly reduced the proportion of ciliated cells. Simultaneously, PC loss upregulated genes like HIF Hif1a. Therefore, in the pathological context of MASH, local hepatic hypoxia and metabolic stress may act as initial hits, damaging PC structure and function. Impaired PCs then push cholangiocytes or other liver cells into a senescent state. Inflammatory factors (senescence-associated secretory phenotype) secreted by senescent cells worsen the microenvironment, exacerbating hypoxia and metabolic abnormalities, and further inhibiting PC function, creating a negative feedback loop that impedes tissue repair.

Furthermore, the activated mammalian target of rapamycin (mTOR) pathway in MASH has been shown to bidirectionally regulate PC dynamics; mTOR inhibition enhances autophagy and promotes ciliary elongation, whereas its activation shortens cilia.[34] Thus, mTOR dysregulation in MASH may contribute to metabolic disturbances and disruption of cellular homeostasis by affecting PCs.

However, research on the role of PCs in MASH is still in its infancy. Although the aforementioned studies in related liver disease models have identified PC involvement in key pathways regulating inflammation and fibrosis, and MASH similarly features metabolism stress-induced inflammation and fibrosis, direct experimental evidence proving that PC structural or functional changes are a cause rather than a consequence of MASH onset remains very limited. Future studies need to systematically investigate PC morphological changes and their direct impact on hepatocyte lipid metabolism and inflammatory signaling pathways, specifically in MASH animal models or patient samples, to clarify their precise role in the MASH liver-gut-brain axis.

Multi-Axis Metabolic Imbalance in MASH Pathogenesis

A growing body of recent research recognizes the association between the "gut-liver axis" and MASH,[35] yet therapeutic breakthroughs remain scarce. We therefore summarize a more comprehensive framework of organ axes, including the "gut-liver-microbiota axis," the horizontal gut-liver-pancreas axis, and the vertical brain-gut-liver axis. This will serve as contextual background for subsequent discussion on leveraging PCs for MASH treatment.

Dysregulation of the Gut-Liver-Microbiota Axis

Microbial abundance, metabolites, and gut permeability play crucial roles in MASH development. Studies show that the gut microbiota of MASH patients has significantly higher abundances of Proteobacteria and Fusobacteria compared to healthy individuals.[36] Microbial metabolites also critically influence MASH. The gut microbiota converts primary bile acids (BAs, e.g., CA and CDCA) into secondary BAs, thereby activating the farnesoid X receptor (FXR) and the membrane receptor TGR5.[37] However, downregulated FXR expression in MASH patients leads to uncontrolled BA synthesis and exacerbates hepatic inflammation.[38] Furthermore, increased intestinal permeability allows harmful substances like endotoxins to reach the liver, activating immune responses and ultimately triggering hepatic inflammation.[39] These three factors interact and collectively contribute to MASH pathology, information vital for its treatment.

Dysfunction of the Liver-Gut-Pancreas Axis as a Metabolic Axis

Metabolic aspects of the liver-gut-pancreas axis relate to glucose and lipid homeostasis, reflected in increased risks of human comorbidities. MASH can induce IR, impairing insulin action (e.g., through reduced insulin receptor expression, ineffective receptor binding, or impaired insulin signaling).[40] Insulin regulates neuronal development and can induce neurodegeneration in the central nervous system (CNS) through signaling pathways such as the phosphatidylinositol-3-kinase (PI3K) and mitogen-activated protein kinase pathways, suggesting a bottom-up influence from MASH. Epidemiological studies indicate that MASH patients are at greater risk for type 2 diabetes (T2D).[41] The "twin-cycle" hypothesis proposes that fat accumulation in the liver and pancreas exacerbates IR, impairs pancreatic regulation of glucose homeostasis, and ultimately leads to T2D.[42] T2D significantly increases the risk of MASH in obese adults and accelerates progression from MASH to fibrosis, cirrhosis, and even HCC.[43] Related mechanisms primarily involve glucose and lipid metabolism (including glucotoxicity and lipotoxicity[44]), IR (increased lipolysis, FFA delivery to the liver, hepatic fatty acid β-oxidation causing oxidative stress[45]), and alterations in insulin secretion.

Dysfunction of the Brain-Gut-Liver Axis as a Neural Axis

The brain-gut-liver axis connects the CNS with gut microbiota, the enteric nervous system, and the neuroendocrine system, participating in the vertical systemic effects of MASH in the body. Direct evidence links MASH to brain function: Within the bidirectional regulatory mechanism of the vagus nerve, intrahepatic vagal afferent fibers sense lipid metabolism signals and provide feedback through the brainstem nucleus tractus solitarius to regulate hepatic very-low-density lipoprotein secretion; the CNS (e.g., hypothalamus) inhibits hepatic lipid synthesis through the leptin-vagal axis, a pathway often characterized by leptin resistance in MASH patients.[46] Chronic MASH leading to varying degrees of liver fibrosis can cause white matter lesions, thereby reducing cognitive function. Concurrently, in this chronic inflammatory state, reduced vagal tone further amplifies intrahepatic inflammatory responses.[47] In the gut, microbial metabolites such as short-chain fatty acids (SCFAs) directly regulate sympathetic nervous system activity through G protein-coupled receptor (GPCR)41,[48] which can promote microglial overactivation, leading to neuronal damage.[49]

Table 1. Impact of PC effect size in different organs on MASH progression

Object	PC effect size	Impact on MASH	Key processes	Evidence notes	Source
Hypothalamus	Inhibition of development/length shortening (depletion of IFT88/KIF3A)	Leads to adult-onset obesity and glucose dysregulation, presumed to increase MASH risk	Impairs degradation of lysosomal proteins, disrupts formation of embryonic POMC neuronal circuitry, causing lifelong adverse effects on food intake and energy metabolism	Indirect evidence; mouse model	[51]
Hepatocytes	Loss of function (KIF12 mutation/deletion)	Promotes hepatic steatosis, MASH, and early cirrhosis	Dysregulated degradation of KIF12-mediated lipogenic enzymes	Direct evidence; mouse model	[52]
HSCs	Structural disruption/ dysfunction (IFT88 knockout)	Drives liver fibrosis	IFT88 degradation destroys HSC cilia, stimulating HSC activation and fibrosis	Direct evidence; mouse model	[50]
Pancreatic β-cells	Structural loss/ disruption (TULP3 knockout)	Significantly impairs insulin secretion, potentially causing a severe diabetic phenotype, greatly increasing MASH risk	Mislocalizes G protein-coupled receptors (GPCRs) like free fatty acid receptor 4 (FFAR4) and prostaglandin E2 receptor, preventing response to downstream metabolic signals	Indirect evidence; mouse model	[53]
Intestinal cells (primarily lamina propria fibroblasts)	Structural loss/signaling abnormality (e.g., Wnt pathway dysregulation)	Increases risk of intestinal and systemic metabolic inflammation, promoting MASH fibrogenesis	PC disruption can dysregulate Wnt signaling, leading to gut barrier impairment and microbiota dysbiosis, key pathogenic factors in MASH	Indirect evidence; extrapolation from literature	[54–56]

PC: Primary cilia; MASH: Metabolic dysfunction-associated steatohepatitis; HSC: Hepatic stellate cell; POMC: Pro-opiomelanocortin.

PC: A Metabolic Hub for Cross-System Regulation in MASH

Within the liver, PCs prominently protrude from the apical surface of cholangiocytes, being present in BECs (BECs, also called cholangiocytes). PCs are also found on quiescent HSCs, where they disassemble during HSC activation and hepatic fibrogenesis.[50] Notably, a key mechanism in liver fibrosis is HSC activation. Although biopsy evidence for PCs on hepatocytes is currently lacking, this does not preclude the potential role of the PC as a metabolic hub regulating MASH pathological progression. Viewing MASH through the lens of the PC links it to metabolic syndrome, highlighting its therapeutic potential.

Before a detailed discussion, we first provide a succinct summary of how alterations in PC parameters (e.g., changes in length, functional gain or loss) within various organs discussed herein influence MASH progression, as detailed in Table 1.

PC and the Liver-Gut-Pancreas Axis: Regulation of the Energy Metabolism Axis

Within the gut-liver-pancreas axis, PC-mediated regulation of insulin secretion in β-cells (through GLP-1/FFAR4/GPCR signaling) and HSC activation are mechanisms most directly linked to MASH fibrosis.

In the pancreas, PCs exhibit motility,[57] enabling them to more effectively sense dynamic changes in microenvironmental metabolites like glucose. Axon-cilium synapses form between β-cell cilia and cholinergic islet innervation.[58] Internally, this allows real-time regulation of insulin secretion; externally, it facilitates signal transmission and linkage. This precise regulation depends, at least partly, on the enriched GPCR signaling platform on cilia, including the GLP-1 receptor sensing the gut hormone glucagon-like peptide-1 and FFAR4 sensing long-chain fatty acids.[59,60] PC function is also crucial for overall pancreatic development and homeostasis. Expression of the intraflagellar transport protein gene Ift88 in pancreatic ducts and islets, whose loss causes ciliary assembly defects, leads to exocrine tissue cyst formation, acinar cell apoptosis, and pancreatic atrophy.[61] Arrest or loss of PC formation is a hallmark across stages of pancreatic ductal adenocarcinoma, underscoring the necessity of PCs for normal pancreatic structure and function. Evidence indicates that PC structural abnormalities impair β-cell paracrine signaling and insulin secretion, ultimately correlating with diabetes development.[59,62] This review aims to explore and connect how PCs influence various stages of MASH; in this context, we posit this step as the initiating event in energy metabolism axis dysregulation.

We propose that dysregulation of PC signaling at the pancreatic end triggers a cascade of reactions throughout the liver-gut-pancreas axis, driving MASH progression. Impaired PC signaling in β-cells disrupts the timing and quantity of insulin secretion, inducing IR. PCs are key nodes integrating downstream PI3K/ protein kinase B (Akt)/ mTOR signaling from leptin and insulin; their absence or dysfunction disrupts this pathway, exacerbating both leptin and IR.[62] The resulting systemic metabolic disturbances – elevated free fatty acids and blood glucose – persistently burden the liver. Within the liver, metabolic stresses such as lipotoxicity and ER stress, along with the ensuing inflammatory state, impair PC function in hepatocytes and HSCs.[63] PC damage not only weakens cellular homeostasis maintenance (e.g., by affecting autophagic flux to exacerbate cellular stress[64–67]) but, more importantly, may release normal inhibition on pro-fibrogenic pathways such as Hedgehog (Hh) and Wnt.[68,69] Quiescent HSCs are

abnormally activated, transforming into myofibroblasts that produce excessive extracellular matrix (ECM), becoming central to fibrosis progression. At the intestinal end of the axis, the abundant PCs in lamina propria fibroblasts decrease in number and exhibit structural defects under inflammatory conditions,[70,71] potentially disrupting the balance of local tissue repair and immune regulation. Abnormal signals from these cells may further impact the liver through the portal system, collectively exacerbating MASH pathology.

Functional loss of PCs within the liver-gut-pancreas axis, as a systemic regulatory network, leads to glucose and lipid metabolism dysregulation. Combined with aberrant signals of intestinal origin, this creates a microenvironment that damages hepatic PC function and promotes HSC activation and fibrosis, thereby driving the irreversible progression from simple steatosis to MASH and fibrosis.

PC and the Liver-Gut-Brain Axis: Integrative Regulation of the Neuro-Metabolic Axis

PCs are present on neurons, where they control neurite growth and development[72] and process energy metabolism signals.[73] Hypothalamic PCs, in particular, regulate feeding behavior, acting as "central sensors" for energy homeostasis. PCs on pro-opiomelanocortin (POMC) and neuropeptide Y (NPY) neurons in the arcuate nucleus (ARC) are especially crucial. Evidence shows that disrupting these cilia (e.g., by knocking out IFT88 or KIF3A) impairs POMC neuron function, leading to adult-onset obesity,[51,74] establishing a causal link between ciliogenesis and body weight regulation. Moreover, central PCs modulate sensitivity to hormones including leptin and insulin.[75] The melanocortin 4 receptor (MC4R) pathway, localized to PCs, plays a central role.[76] POMC neurons release α-melanocyte-stimulating hormone, activating MC4R to suppress appetite;[77] similarly, defective MC4R gene expression can cause obesity.[78]

Thus, the hypothalamic-PC-MC4R axis can be viewed as a high-weight pathway in cilia-related appetite regulation, tightly coupled to leptin signaling. Leptin primarily acts on AgRP and POMC neurons in the ARC, suppressing appetite by activating POMC neurons. The leptin resistance common in obesity may form a vicious cycle with PC defects. For instance, the average length and surface area of hypothalamic cilia are significantly reduced (by over 40%) in obese mice,[79] a shortening phenotype likely both a consequence and an exacerbating factor of impaired signal transduction.

Extending this view to the liver-gut-brain axis, PCs constitute a systemic regulatory network. In the liver, PCs on HSCs and BECs regulate cell activation and proliferation through pathways like Hh, Wnt, and Notch, influencing fibrosis. Modulating Notch signaling can reduce fibrotic deposition.[80] Genetic (e.g., PKD2 mutation) or acquired (inflammatory cytokines, ER stress) damage can impair ciliary function, causing intracellular Ca^{2+}/cAMP signaling imbalance.[81] This triggers VEGF-driven angiogenesis and HSC activation[25] as well as β-catenin-mediated chemokine (e.g., CXCL10) secretion, recruiting macrophages and promoting inflammation and fibrosis.[26] These processes align with the ductular reaction and periportal fibrosis observed in MASH. We hypothesize that dysfunctional PC in intrahepatic cholangiocytes may integrate metabolic stress signals and translate them into VEGF-mediated angiogenesis and β-catenin/chemokine-mediated inflammatory-fibrotic responses, thereby driving progression from simple steatosis to MASH and fibrosis. In the CNS, PCs regulate hormonal activity. Impaired cilia may affect lipid metabolism, worsening MASH. Furthermore, PCs have been confirmed in some subtypes of glial cells and interstitial cells of Cajal within the enteric nervous system.[82] Studies also show that the gut microbiota regulates numerous host metabolic processes, including energy homeostasis, glucose metabolism, and lipid metabolism[83,84] and is even linked to brain regions processing sensory information.[85] This relationship is bidirectional: Brain-derived signals can top-down alter gut microbiota composition, and microbial metabolites can influence human brain structure.

We propose the following hypothesis: Hypothalamic PC dysfunction leading to feeding dysregulation and systemic metabolic disturbances will exacerbate hepatic lipid accumulation and inflammation through circulatory factors (e.g., bile acids, metabolites) or neural signals. Conversely, MASH-associated systemic inflammation and metabolic disturbances may also damage cilia in the hypothalamus and other brain regions, where microglial activation-mediated neuroinflammation is considered a key node linking peripheral metabolic disorder to central ciliopathy and cognitive decline.

Although the local functions of PCs in individual organs are being revealed, the integrated picture of how they synergistically drive MASH progression at the multi-organ axis level remains unclear. We propose an integrative hypothesis: Under genetic predisposition or high-fat diet induction, functional loss or shortening of the hypothalamic PC-MC4R signal is an early event in central regulatory failure, leading to hyperphagia and obesity. The ensuing hyperleptinemia, IR, and gut microbiota dysbiosis collectively create a microenvironment that damages PCs in hepatocytes and hepatic non-parenchymal cells, accelerating hepatic steatosis and inflammation. Simultaneously, peripheral inflammatory signals ascend to the brain, potentially damaging neuronal PC function by activating microglia, forming a vicious cycle that drives progression from simple steatosis to MASH and even extrahepatic complications. Future research should employ causal interventions at the axis level in MASH animal models and quantitatively assess the precise effect size of such interventions on core MASH phenotypes such as hepatic fat content, inflammation score, and fibrosis degree, to validate this hypothesis and elucidate core mechanisms.

Therapeutic Implications of PC-Associated Pathways in MASH

Based on the central role of PCs in MASH pathogenesis, interventions targeting their associated signaling pathways have emerged as a highly promising therapeutic strategy. Restoring or modulating PC function and the key pathways they mediate holds potential to intervene in disease progression across multiple layers, including lipid metabolism, inflammatory responses, fibrogenesis, and neuro-immune regulation.

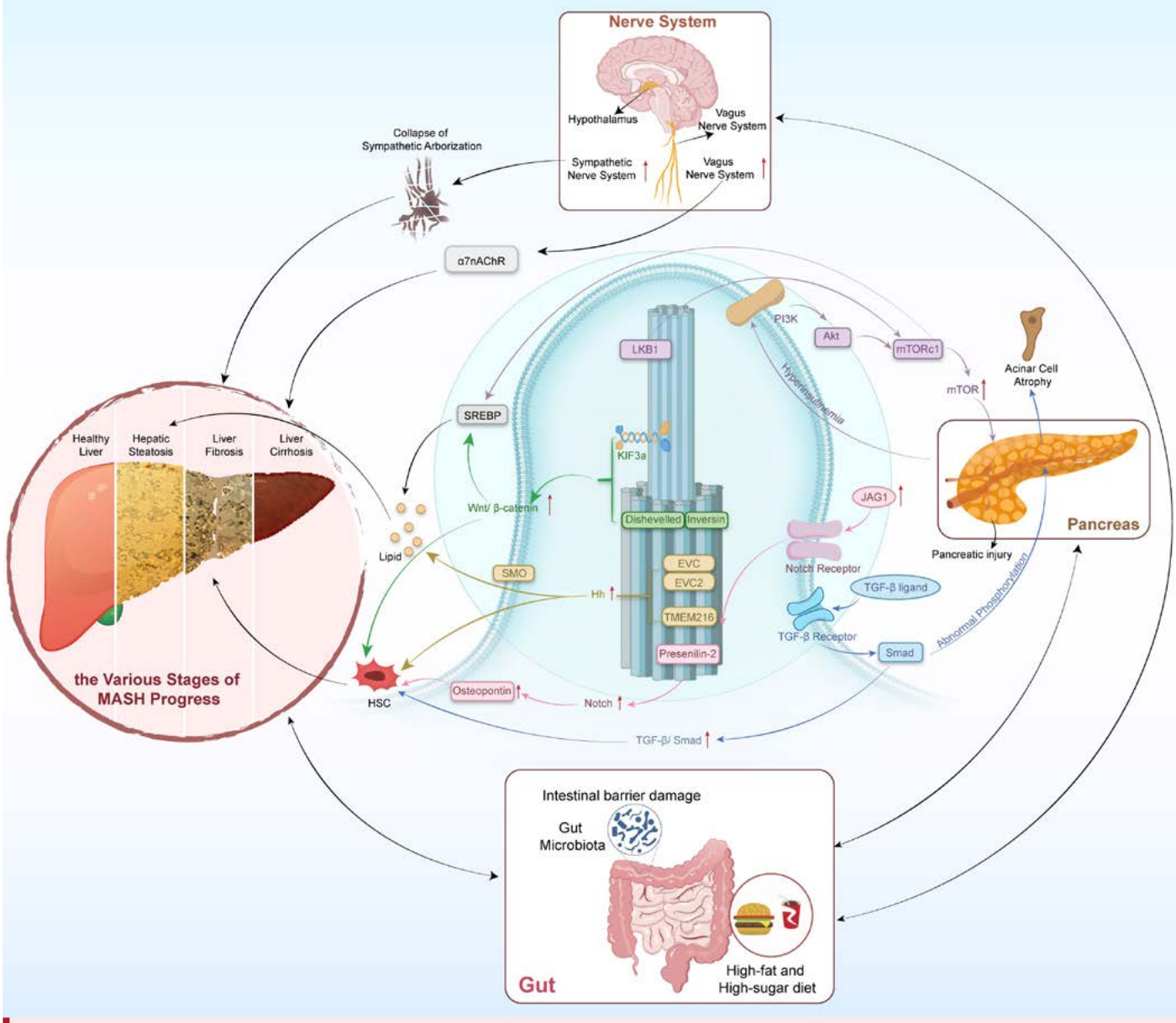


Figure 1. The regulatory pathway of the primary cilia in metabolic dysfunction-associated steatohepatitis. This schematic illustrates the pivotal role of PC as a signaling hub connecting the gut, pancreas, brain, and liver in MASH pathogenesis. PC dysfunction disrupts key pathways – including mTOR, Hh, Wnt/β-catenin, Notch, TGF-β/Smad, and neuro-metabolic axes – exacerbating lipid metabolism dysregulation, IR, inflammation, and fibrosis. This integrated view underscores the mechanistic basis for targeting ciliary function in MASH therapy.

The following sections elaborate on the therapeutic significance of PC-linked pathways – mTOR, Hh, Wnt/β-catenin, Notch, transforming growth factor beta (TGF-β)/Smad, and sympathetic/vagal nerve regulation – in MASH, exploring potential drug intervention directions based on these pathways (Fig. 1).

To further advance the clinical translation of this strategy, future efforts should focus on constructing a PC-based biomarker system (e.g., ciliary-associated proteins, specific imaging features) to enable precise identification and dynamic monitoring of disease status. Concurrently, identifying advantaged patient subgroups likely to benefit from cilia-targeted therapies is crucial. Such subgroups may include obese patients with T2D exhibiting advanced liver fibrosis and severe IR, or patients with metabolic-associated neurocognitive impairment. Implementing precision interventions for these key populations holds promise for breaking the current therapeutic bottleneck and achieving effective translation from mechanistic insight to clinical benefit.

mTOR Signaling Pathway

Liver kinase B1 protein, located within the PC, negatively regulates the mTOR complex 1 (mTORC1), serving as a key molecular link between PC mechanosensation and mTOR signaling.[86] mTORC1 activity correlates

with PC length, with enhanced activity increasing ciliary length.[87] Within the mTOR pathway, mTORC1 is a downstream effector of PI3K/AKT signaling. Following PI3K/AKT activation, phosphorylation and inhibition of the Tuberous Sclerosis Complex 2 (TSC2) relieves its suppression of Rheb, thereby activating mTORC1.[88] Activated mTORC1 promotes lipid synthesis through sterol regulatory element-binding protein (SREBP) transcription factors, fostering hepatic steatosis. Upstream, IR-associated hyperinsulinemia activates the PI3K/AKT/mTOR pathway, leading to lipid accumulation through the above process.[88,89] Concurrently, multiple pathological processes synergistically drive MASH initiation and progression, including oxidative stress[90] and chronic inflammation.[91] During oxidative stress, accumulated hepatic ROS can oxidatively modify the critical Cys124 residue of phosphatase and tensin homolog, inactivating it and thereby removing its negative regulation on PI3K/Akt. This further contributes to persistent aberrant activation of the PI3K/AKT/mTOR pathway. Chronic inflammation and hepatocyte injury activate HSCs, promoting fibrosis. Pro-fibrogenic factors like TGF-β secreted by HSCs continuously stimulate the PI3K/AKT pathway.[92] Collectively, these processes make the PI3K/AKT/mTOR pathway an engine driving progression from MASH to fibrosis and HCC.

Hh Signaling Pathway

Evc and Evc2 are transmembrane proteins that interact at the PC base; their knockout or defective expression attenuates Hh signaling.[93] TMEM216, a transmembrane protein at the ciliary base, also weakens Hh signaling when deficient.[94] Normally quiescent in the liver, the Hh pathway activates upon injury to facilitate regeneration. However, persistent liver damage leads to prolonged Hh signaling.[95] Hepatocytes continuously produce Hh ligands, causing aberrant pathway activation.[96] Overactivation upregulates the long non-coding RNA Hilnc through the downstream transcription factor Gli. Highly expressed Hilnc specifically binds the RNA-binding protein IGF2BP2 in the cytoplasm, stabilizing peroxisome proliferator-activated receptor γ (PPARγ), leading to elevated hepatic PPARγ protein levels and promoting lipogenesis.[96] Concurrently, Hh ligands released from damaged hepatocytes act in a paracrine manner on HSCs, activating their internal Hh pathway, evidenced by nuclear translocation of Gli proteins and target gene expression. Hh-Gli activation drives expression of pro-inflammatory factors (e.g., TNF-α, interleukin-6), exacerbating inflammation and injury, even promoting ballooning,[97] and fosters HSC activation and fibrogenic progression, thereby aggravating MASH.

Wnt/β-Catenin Signaling Pathway

The kinesin KIF3a participates in ciliary assembly, maintenance and regulates Wnt/β-catenin signaling.[98] Inversin acts as a molecular switch for Wnt signaling, forming a protein complex with Dishevelled.[99] A specific Inversin compartment exists within the PC; its absence does not affect PC structure but disrupts the establishment of polarized duct systems in the liver and pancreas.[100] Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection.[101] It can also activate the intestinal Wnt/β-catenin pathway. Moreover, restraint stress similarly disrupts intestinal homeostasis;[102] in this context, compensatory activation of the Wnt/β-catenin pathway can protect the gut-vascular barrier and delay NASH progression.[103] In the liver, liver-specific β-catenin knockout mice exhibit defects in bile acid and cholesterol homeostasis and increased susceptibility to metabolism-driven steatohepatitis.[104] Overactivation of the hepatic Wnt/β-catenin pathway upregulates lipogenic genes (e.g., SREBP-1c) and suppresses fatty acid oxidation genes (e.g., PPARα), collectively promoting hepatic lipogenesis.[105] Furthermore, excessive pathway activation suppresses PPARγ transcriptional activity through regulators such as necdin and DLK1. Decreased PPARγ expression promotes HSC proliferation, activation, and fibrosis.[106]

Notch Signaling Pathway

Notch receptors are located on the PC membrane, while Presenilin-2, the enzyme that cleaves and activates Notch, resides at the ciliary basal body. This spatial proximity provides a structural basis for localized Notch signal activation.[107] Aberrant Notch activation inhibits PC formation, shortening cilia and suppressing function.[108] Activated Notch signaling, through its intracellular domain (NICD), promotes expression of the transcription factor Sox9, which upregulates osteopontin.[109] Osteopontin, a key fibrogenic factor, directly drives HSC activation and promotes liver fibrogenesis.[109] This pathway's abnormal activation stems from increased expression of the upstream ligand Jagged1 (JAG1), a process driven by gut microbiota dysbiosis through the hepatocyte Toll-like receptor 4 (TLR4)-nuclear factor kappa (NF-κB) signaling axis.[110] Human liver biopsies and mouse NASH models show positive correlations between hepatic JAG1 expression and disease activity scores, fibrosis stage, and Notch target gene (HES1, HEYL) levels. Hepatocyte-specific Jag1 knockout protects mice from NASH-induced fibrosis.[111]

TGF-β/Smad Signaling Pathway

In the pancreas, PC deficiency (e.g., Kif3a, Ift88, or Cby1 knockout) leads to ciliary loss in pancreatic ductal cells, upregulates TGF-β1 expression, and activates downstream Smad3 signaling. This promotes pancreatic stellate cell activation and excessive ECM deposition, ultimately causing pancreatic inflammation, fibrosis, and acinar cell atrophy.[112] The PC membrane harbors TGF-β receptors. Upon ligand binding, activated receptors migrate from the ciliary membrane to the ciliary pocket and enter the cell through clathrin-mediated endocytosis. This process is crucial for activating downstream SMAD transcription factors (e.g., SMAD2/3), which then translocate to the nucleus to regulate target gene transcription.[113] In MASH, damaged hepatocytes and inflammatory cells release TGF-β1. Binding to receptors on HSCs activates downstream Smad2/3 phosphorylation. The resulting Smad complex translocates to the nucleus, promoting excessive ECM deposition.[114] In addition, TGF-β1 induces epithelial-mesenchymal transition in hepatic oval cells, converting them to HSCs and aggravating fibrosis.[115]

Table 2. Pharmacological modulators of primary cilia-associated metabolic signaling pathways relevant to MASH

Target pathway	Key preclinical/ clinical drug examples	Effects on MASH phenotype and considerations	PC-dependency for MASH effect?	PC-related notes	Current evidence level	Source
mTOR	Rapamycin	mTORC1 inhibitor; limits MASH progression across stages, induces autophagy, and insulin sensitivity.	Partially dependent	Promotes PC formation but shortens PC length.	Preclinical rodent studies; some clinical trials.	[132]
Hedgehog	GDC-0449; LED225	Blocks Smoothened (Smo) activity, inhibits Gli1 transcription, and alleviates MASH inflammation.	Partially dependent	SMO enriches at the PC membrane upon Hh pathway activation.	Preclinical rodent studies.	[133]
Wnt/β-catenin	Niclosamide	Inhibits Dvl2, reduces β-catenin stability, blocks Wnt signaling; applicable across MASH stages.	Partially dependent	Dvl2 protein localizes to the PC basal body region.	Preclinical rodent studies.	[134,135]
Notch	DAPT	Improves MASH pathology by inhibiting Notch1 activity, reducing lipid accumulation, and hepatocyte injury.	Partially dependent	Notch1 is a transmembrane receptor also located on the PC membrane.	Preclinical rodent studies.	[136]
	siJag1	Inhibits hepatic JAG1 expression, suppressing the Notch pathway and attenuating liver fibrosis.	Partially dependent	Receptor for JAG1 is present on the PC membrane.	Preclinical rodent studies.	[111]
TGF-β/Smad	SB431542-Loaded Liposomes	Inhibits TGF-β signaling, alleviates liver fibrosis; achieves high local concentration in the liver.	Possibly dependent	TGF-β receptors are located on the PC membrane.	Preclinical rodent studies.	[131]

PC: Primary cilia; MASH: Metabolic dysfunction-associated steatohepatitis; TGF-β: Transforming growth factor beta; mTOR: Mammalian target of rapamycin.

Sympathetic Nervous System Regulatory Pathway

In the nervous system, most neurons possess a single PC, which has been shown to be crucial for maintaining excitatory-inhibitory balance in neural circuits.[73] Animal studies indicate that PC loss or dysfunction in the ventromedial hypothalamus reduces sympathetic nerve tone and causes central leptin resistance, lowering energy expenditure and leading to obesity,[116] a high-risk factor for MASH. Investigations using three-dimensional (3D) immunoimaging to explore liver innervation integrity across NAFLD stages revealed degenerative features in sympathetic nerves, including collapsed dendritic arborization, with degeneration severity correlating with NAFLD pathology.[117] This results from chronic sympathetic over-excitation.[118] In this context, reducing aberrant hepatic sympathetic nerve activation can effectively counteract liver steatosis.[119] Therefore, both sympathetic suppression and chronic over-excitation are MASH risk factors, and intact PC structure likely exerts a positive influence on neuronal electrical activity.

Vagus Nerve System Regulatory Pathway

Muscarinic acetylcholine receptor 3 (mAChR M3) is present in the PCs of cerebrovascular cells,[120] a key target of the vagus nerve. Activating mAChR M3 enhances ciliary length[121] and delays MASH progression.[122] Hepatic macrophages, particularly Kupffer cells, are major immune players in MASH. Some studies indicate that reducing Kupffer cells by inhibiting inflammatory pathways (e.g., NF-κB) improves hepatic IR and alleviates MASH.[123] From a vagal perspective, research shows that vagus nerve stimulation activates the α7 nicotinic acetylcholine receptor (α7nAChR), which directly suppresses inflammation through cholinergic signaling and indirectly modulates the unfolded protein response (UPR) pathway in Kupffer cells to inhibit ER stress.[124] This suppresses three UPR arms: PERK/eIF2-α, ATF6, and IRE1/TRAF2/IKK,[125] thereby inhibiting inflammation. Activating α7nAChR inhibits hepatic necroptosis and alleviates acute liver injury,[126] suggesting a potential to delay MASH progression. Furthermore, the vagus nerve establishes streamlined direct connections between the brainstem and gut,[127] also influencing MASH progression.

Potential MASH Therapeutics Based on PC Pathways

At present, no MASH therapeutics explicitly developed based on PCs exist. However, potential links to PCs can be found among known preclinical or clinical drugs. For instance, Histone deacetylase 6 (HDAC6) mediates autophagy-dependent PC disassembly. HDAC6 overexpression in cholangiocarcinoma reduces PC expression and promotes tumor growth, while HDAC6 inhibition restores cilia, which may slow disease progression. The HDAC6 inhibitor ricolinostat inhibits cholangiocarcinoma cell proliferation, an effect enhanced when combined with ciliogenesis-promoting agents like the SCFAs

Table 3. Therapeutic modulation of primary cilia-related neuro-metabolic pathways in MASH

Target pathway	Key preclinical/ clinical drug examples	Effects on MASH phenotype and considerations	PC-dependency for MASH effect?	PC-related notes	Current evidence level	Source
Sympathetic Nervous System	Pegozatermin (PEGylated FGF21 analog); FGF21 and analogs (e.g., Efruxifermin)	Acts on CNS Vglut2+ glutamatergic neurons to increase hepatic sympathetic nerve activity, inhibiting de novo lipogenesis, reducing triglycerides, and fibrosis.	Not explicitly stated	Not explicitly stated.	Preclinical rodent studies; Clinical Phase IIb (HARMONY trial); Phase III.	[137–139]
Vagus Nerve System	Vagus nerve stimulators (e.g., 2-DG)	Vagal excitation releases ACh, acting on α7nAChR on Kupffer cells and HSCs, inhibiting NF-κB, etc., reducing hepatic inflammation/ fibrosis.	Not explicitly stated	Not explicitly stated.	Preclinical rodent studies.	[140,141]
	Cholinergic receptor agonists (e.g., M3 mAChR agonists; selective α7nAChR agonists)	Mimics the cholinergic anti-inflammatory pathway, inhibits hepatic innate immune cell activation, potentially blocking the inflammatory and fibrotic progression of MASH. Moreover, activation of cholinoceptors on hepatocytes may directly influence glucose and lipid metabolism.	Not explicitly stated	Not explicitly stated.	Preclinical rodent studies.	[141,142]

PC: Primary cilia; MASH: Metabolic dysfunction-associated steatohepatitis; CNS: Central nervous system; NF-κB: Nuclear factor kappa; HSCs: Hepatic stellate cells; α7nAChR: Alpha-7 nicotinic acetylcholine receptor.

butyrate.[128,129] Other studies show Ricolinostat can delay renal fibrosis through the TGF-β pathway.[130] This evidence suggests Ricolinostat might exert anti-fibrotic effects in MASH through PC-related mechanisms. Therefore, we posit that adding PC-restoring agents to conventional MASH treatment strategies could yield superior clinical efficacy, ideally through more precise selection based on specific PC pathways. It is also worth noting that lipid-based nanoparticles possess high liver-targeting efficiency, stability, and safety.[130] Their co-administration with relevant drugs (e.g., SB431542-Loaded Liposomes, as shown in the following tables)[131] may further improve therapeutic outcomes.

Tables 2 and 3 list drugs validated in clinical trials or animal studies to improve hepatic pathology and illustrate their relationship to PC pathways.

Limitations and Future Directions

While targeting PC offers a novel therapeutic avenue for MASH, significant limitations remain. The foremost bottleneck is the lack of longitudinal human data on PCs in the MASH context, primarily due to technical challenges in achieving high-resolution, high-throughput detection of PCs in clinical samples (especially paraffin-embedded tissues), making dynamic assessment of their signaling activity difficult. Furthermore, PC-associated signaling pathways exhibit considerable crosstalk, posing a risk of off-target effects during intervention. However, advances in detection technologies, such as novel elastography methods including ultrasound-based acoustic radiation force impulse imaging, can already assess liver fibrosis in ciliopathy patients. Future, more sensitive PC detection methods hold promise for revealing associations between different ciliary gene variants and fibrosis risk, and for identifying MASH subgroups more responsive to PC-targeted therapy.[143] Therefore, PCs may serve not only as therapeutic targets but also as biological indicators for disease monitoring and prognosis.

Conclusion

Regarding drug development, future efforts should focus on screening or designing compounds that can specifically modulate PC assembly, length, or signal transduction, based on known PC pathways, followed by systematic functional validation in MASH models. Studies should incorporate dynamic monitoring of PC-related biomarkers (e.g., ciliary structural proteins, signaling activity molecules) to clarify the correlation between drug efficacy and PC status. This would provide more compelling preclinical evidence for PC-targeted MASH therapy. Integrating cross-technology, cross-model research has the potential to gradually overcome current limitations and advance PC-targeted strategies from mechanistic exploration towards clinical translation.

Ethics Committee Approval: Ethics committee approval was not required, as this study is a review article and did not involve human participants, animal subjects, or identifiable personal data.

Conflict of Interest: There are no conflicts of interest.

Financial Disclosure: This work was supported by the Chinese Cardiovascular Association-Natural lipid-lowering drugs fund [Award Number: 2023-CCA-NLD-569 to Dou Dou].

Use of AI for Writing Assistance: No artificial intelligence (AI)-assisted technologies were used in the creation of this manuscript.

Author Contributions: Concept: YZ, ZT, DD, CB; Design: YZ, ZT, RL, YC; Supervision: DD, CB; Funding: DD; Analysis and/or Interpretation: YZ, ZT; Literature Search: YZ, ZT, RL, YC; Writing: ZT; Critical Review: YZ, ZT, RL, YC, DD, CB.

Peer-review: Externally peer-reviewed.

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