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## ABOUT COVER

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MINIREVIEWS

# Research progress on signaling pathways in cirrhotic portal hypertension

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## Abstract

Portal hypertension (PHT) is an important consequence of liver cirrhosis, which can lead to complications that adversely affect a patient's quality of life and survival, such as upper gastrointestinal bleeding, ascites, and portosystemic encephalopathy. In recent years, advances in molecular biology have led to major discoveries in the pathological processes of PHT, including the signaling pathways that may be involved: PI3K-AKT-mTOR, RhoA/Rho-kinase, JAK2/STAT3, and farnesoid X receptor. However, the pathogenesis of PHT is complex and there are numerous pathways involved. Therefore, the targeting of signaling pathways for medical management is lagging. This article summarizes the progress that has been made in understanding the signaling pathways in PHT, and provides ideas for treatment of the disorder.

**Key words:** PI3K-AKT-mTOR; Portal hypertension; Rho-associated kinases; Liver cirrhosis; Signaling pathways; Farnesoid X-activated receptors; JAK2/STAT3



**Core tip:** Portal hypertension (PHT) is a syndrome of portal venous system hemodynamics in liver cirrhosis. Current therapeutic options are often insufficient to prevent progression of the disease. We therefore may find more effective clinical treatments by understanding the signal pathways involved in the disease. This paper is an up-to-date and thorough review of the signaling

pathways that may be involved in the pathogenesis of PHT in liver cirrhosis.

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## INTRODUCTION

Portal hypertension (PHT), the main consequence of cirrhosis, can lead to complications, such as variceal hemorrhage, ascites, and portosystemic encephalopathy. These complications may cause both diminished quality of life and mortality, and also may necessitate liver transplantation[1-3]. PHT is characterized by abnormally elevated intrahepatic venous pressure, which is due to various etiological factors. Increased intrahepatic vascular resistance (IHVR) and increased portal venous blood flow are the major pathological processes in the development of PHT[4]. IHVR is mainly determined by liver fibrosis, intrahepatic vasoconstriction, intrahepatic angiogenesis, and abnormal blood flow. Narrowing of intrahepatic microvessels, caused by fibrosis, can increase resistance and be responsible, in part, for increased responsiveness of these venules to vasoconstrictive substances[5]. Angiogenesis, the formation of new vessels from preexisting vasculature, is an important pathophysiological feature of PHT that enhances IHVR[4,6]. Another feature of PHT is the development of hyper-dynamic splanchnic circulation, with an increased blood flow in splanchnic organs that drain into the portal vein and a consequent increase in portal venous inflow[7]. The increased splanchnic and portal blood flow further elevates portal pressure. Although the pathophysiology of PHT has been studied extensively, its precise mechanisms are undefined.

An improved understanding of the molecular mechanisms of PHT is crucial to developing effective treatment strategies. Despite the incomplete knowledge of PHT pathophysiology, certain molecular pathways have been identified. The current review reveals that PI3K-AKT-mTOR, RhoA/Rho-kinase, JAK2/STAT3, farnesoid X receptor (FXR) and other signaling pathways might be targetable in the treatment of PHT. We believe that this summary of the roles of the signaling pathways in PTH may help investigators find relevant targets for PHT treatment.

## PI3K-AKT-MTOR SIGNALING

### *Overview of mTOR*

The kinase known as targets of rapamycin (TOR), belonging to the phosphatidylinositol kinase-related kinase, is an evolutionarily conserved protein kinase that was first found in yeast. The homologous substance of TOR in mammals is referred to collectively as mTOR[8]. mTOR is a ubiquitously expressed serine kinase that regulates cell growth and proliferation, and mTOR signaling plays a role in immunological processes, angiogenesis and fibrogenesis[9,10]. The mTOR signaling pathway is highly active in the evolution of PHT[11]. Mejias *et al*[9] found that rapamycin could reduce portal pressure by blocking mTOR and thus alleviate hyperdynamic visceral circulation, an effect that may be due to rapamycin's inhibition of lymphocyte proliferation, neovascularization, and fibrosis.

### *mTOR regulates fibrosis*

Mammals have two mTOR complexes: mTORC1 and mTORC2. mTORC1 is an important regulator of ribosome production and translation and has two downstream effectors, including the eukaryotic initiation factor 4E-binding protein-1 (4E-BP1) and ribosomal protein S6 kinase. mTORC1 integrates signaling from growth factor receptors, then activates the p70 ribosomal protein S6 kinase (p70S6K) by phosphorylation and inhibits the eukaryotic initiation factor 4E-BP1. Thus, mTORC1 forms two different signaling pathways to regulate mRNA translation and to control protein synthesis[12,13]. mTORC2 phosphorylates the serine/threonine protein kinase Akt/protein kinase B at serine residue Ser473[14] and participates in the regulation of phosphorylation and activation of cytoskeletal actin, protein kinase B (Akt/protein kinase B), protein kinase C, and glucocorticoid-induced protein kinase 1 in serum[8]. *In vivo*, growth factors, mitogen and other hormones lead to the activation of p70S6K by phosphorylation of mTOR through phosphatidylinositol 3-kinase-related kinase (PI3K)-Akt pathways, which upregulate the expression of cyclin D1, D3 and E to control cell-cycle progression[10]. One effect of this activity is increased proliferation of hepatic stellate cells (HSCs). Activation of HSCs increases the contractility of intrahepatic vessels, thereby increasing resistance to liver blood flow. p70S6K phosphorylation stimulates the production of the synthesis of collagen and other extracellular matrix components, predominately type Ⅰ collagen[15]. It is generally accepted that the activation of HSCs leads to fibrosis, which is one of the important steps in the development of PHT[16]. It has been proposed that activation of mTOR promotes both HSC proliferation as well as the synthesis of extracellular matrix, which accelerates liver fibrosis and the development of PTH[15,16].

### *PI3K-Akt regulates mTOR signaling involved in angiogenesis*

Akt, also called protein kinase B, is a threonine protein kinase akin to the PI3K protein family. One of the functions of Akt is direct phosphorylation of mTOR. Another is maintaining Rheb's GTP-binding state by inactivating tuberous sclerosis complex 2 to enhance

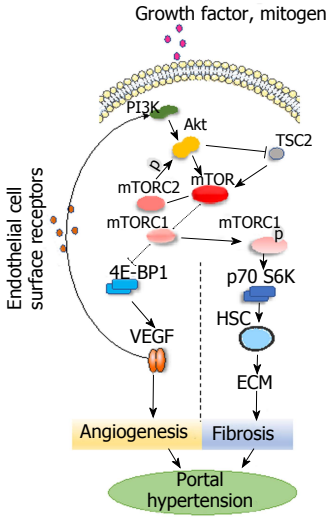


**Figure 1 PI3K-AKT-mTOR signaling pathways in the development of hepatic portal hypertension.** PI3K-AKT-mTOR: *In vivo*, growth factors, mitogens and hormones interact with PI3K, which activates Akt that then activates mTOR. Mammals have two mTOR complexes: mTORC1 and mTORC2. Akt can phosphorylate mTORC1 and then activate p70S6K via phosphorylation to inhibit 4E-BP1. Activated p70S6K promotes the proliferation of HSCs and stimulates both the production of ribosomes and the synthesis of collagen and other extracellular matrix constituents. mTORC1 can inhibit 4E-BP1, promote the splitting of VEGF, and regulate angiogenesis. Akt can inactivate tuberous sclerosis complex 2 and enhance mTOR activity. mTORC2 regulates Akt. Akt: Protein kinase B; ECM: Extracellular matrix; HSC: Hepatic stellate cell; mTOR: Mammalian targets of rapamycin; mTORC: Mammalian targets of rapamycin complex; p70S6K: p70 ribosomal protein S6 Kinase; TSC2: Tuberous sclerosis complex 2; VEGF: Vascular endothelial growth factor; 4E-BP1: 4E-binding protein-1.

mTOR activity[17,18]. Akt is an important upstream mediator of mTOR and is regulated by mTORC2[14]. In previous studies[15,19], the Akt/mTOR signaling pathway was activated in bile duct ligation-induced cirrhotic rats and was implicated in the activation of HSCs. The Akt/mTOR signaling pathway is the major downstream effector of PI3K and regulates cell growth, proliferation, motility and apoptosis[14,17]. While AKT directly affects mTOR, mTORC1 reciprocally regulates the growth factor responsiveness of PI3K and Akt through feedback inhibition[20,21]. The direct phosphorylation of 4E-BP1 by mTORC1 reportedly initiates translation of hypoxia inducible factor-1α (HIF-1α), which promotes the expression of vascular endothelial growth factor (VEGF), thereby regulating angiogenesis in physiological and pathological conditions[22,23]. Under certain conditions, VEGF and endothelial cell surface receptors bind to activate the PI3K-Akt signaling pathway and further activate mTOR kinase, thereby enhancing portal pressure (Figure 1). It may be effective for inhibiting the development of PHT by inhibiting Akt or mTOR directly. However, the specific effect needs further investigation.

## RHOA/RHO-KINASE SIGNALING

Activation of the RhoA/Rho-kinase signaling pathway, by participating in vasoconstriction and vasodilation responses[24-26], is one of the key mechanisms of PHT development.

### *Overview of RhoA*

The Ras homolog gene family member A (RhoA) is a member of the small molecular weight G proteins in the Ras superfamily. RhoA signaling participates in many cellular responses, including cell contraction, adhesion, proliferation and migration[27]. RhoA, a member of the GTP-binding protein Rho GTPase family, circulates between activated GTP-RhoA and stationary GDP-RhoA. RhoA-GDP and RhoA-GTP are interconverted by a dephosphorylation/phosphorylation process and then trigger or terminate a cellular cascade activation/reaction, acting as a "molecular switch". Only RhoA activates Rho-kinase in the membrane-bound activated state and has downstream effects[28,29].

### *RhoA/Rho-kinase signaling and portal pressure*

Geranylgeranyl pyrophosphate (GGPP), as a key substance in the transfer of RhoA to cell membranes, plays a role in the activation of the RhoA/Rho kinase signaling pathway. RhoA is linked to GGPP, a byproduct of cholesterol synthesis, to "lipidize" GGPP so it can be inserted into the cell membrane to form membrane-bound RhoA (a small GTPase protein on the cell surface) and activate the RhoA/Rho kinase pathway by binding to angiotensin[26,30,31]. Trebicka *et al*[32] found that statins, 3-hydroxy-3-methyl-glutaryl CoA reductase inhibitors, inhibited the expression of 3-hydroxy-3-methyl-glutaryl CoA reductase, which downregulated the expression of GGPP and then blocked the RhoA/Rho-kinase signaling pathway, leading to reduced activation of HSC. Liu *et al*[33] found that sodium ferulate can affect the activation of RhoA and the contraction of activated HSC by reducing the synthesis of GGPP in HSCs in liver cirrhosis. These actions reduce the intrahepatic resistance in cirrhotic rats. Zhang *et al*[34] found that a selective agonist of estrogen receptor β could reduce IHVR by reducing RhoA expression, thus inhibiting the myosin light chain activity and increasing the levels of endothelial nitric oxide synthase (eNOS), which leads to decreased portal vein pressure in cirrhotic ovariectomized rats.

Wei *et al*[35] demonstrated that sodium ferulate inhibits the hepatic RhoA/Rho-kinase signaling pathway and increases eNOS synthesis, eventually leading to reduced hepatic portal pressure in cirrhotic rats. This reaction indicates that the RhoA/Rho-kinase signaling pathway is involved in the formation of PHT. The activation of Rho kinase increases portal pressure in two ways: first, by inhibition of myosin light chain phosphatase, which produces a downstream effect that increases smooth muscle contractions[29,36]. Myosin phosphatase, myosin light chain, adducin, mono serine protein kinase, and protein kinase C-protein inhibitor protein (CPI-17) are substrates of Rho kinase. The

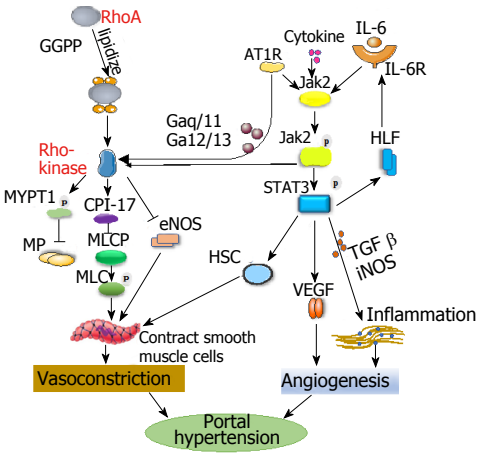


**Figure 2 Proposed signaling pathways in the development of hepatic portal hypertension.** RhoA/Rho-kinase: GGPP "lipidizes" RhoA to form membrane-bound RhoA and to activate Rho-kinase. AT1R stimulates JAK2 to phosphorylate and then activate Rho-kinase. Activated Rho-kinase phosphorylates the myosin targeting subunit 1, which inactivates myosin phosphatase. The inactivation of myosin phosphatase increases the phosphorylation of myosin light chain and promotes vasoconstriction. CPI-17 combines with myosin light chain phosphatase to inhibit the activation of the enzymes and promote the contraction of smooth muscle cells. The activation of Rho-kinase could downregulate the expression of eNOS and reduce its activity. The coupling of AT1R to Gaq/11 and Ga12/13 promotes Rho-kinase activation, which is involved in extracellular matrix production. JAK2/STAT3: Cytokines activate the JAK2/STAT3 pathway. Enhanced JAK2/STAT3 signaling upregulates TGF-β and iNOS expression and accelerates intestinal inflammation, which aggravates endothelial dysfunction and angiogenesis. IL-6 binds to its receptor, activates JAK2, phosphorylates it, and then causes the phosphorylation of STAT3 in cells, thereby activating HSC and promoting hypoxia inducible factor expression. These events can upregulate the activation of IL-6 and reactivate the STAT3 pathway, which forms a loop, constantly activating HSC, causing vessel contraction, and ultimately increasing portal pressure. AT1R: Angiotensin-type Ⅱ receptor 1; CPI-17: C-protein inhibitor protein; eNOS: Endothelial nitric oxide synthase; GGPP: Geranylgeranyl pyrophosphate; HIF: Hypoxia inducible factor; HSC: Hepatic stellate cell; IL-6: Interleukin-6; IL-6R: Interleukin-6 receptor; iNOS: Inducible nitric oxide synthase; JAK2: Janus kinase 2; MLCP: Myosin light chain phosphatase; MP: Myosin phosphatase; MYPT1: Myosin phosphatase target subunit 1; RhoA: Ras homolog gene family member A; STAT3: Signal transducers and activators of transcription; TGF-β: Transforming growth factor β; VEGF: Vascular endothelial growth factor.

most studied Rho kinase substrates involved in PHT formation are myosin phosphatase, myosin light chain and CPI-17. Activation of Rho kinase leads to the phosphorylation of myosin targeting subunit 1, which inactivates myosin phosphatase. Inactivation of myosin phosphatase did not lead to dephosphorylation of myosin light chain. This, in turn, leads to an increase in cytoplasmic myosin light chain phosphorylation and increased crosslinking of myosin, thereby promoting vasoconstriction. CPI-17 was combined with myosin light chain phosphatase to inhibit the activation of myosin light chain phosphatase and promote the contraction of smooth muscle cells[37]. The second way of increasing portal pressure is the downregulation of eNOS expression and reduction of its activity[38]. The activity of eNOS, which is another downstream target of the RhoA/Rho-kinase pathway[39] that is involved in regulating portal pressure, may be negatively-regulated by RhoA/Rho-eNOS activity; this effect causes the relaxation of vascular smooth muscle and plays a key role in maintaining the steady state of the vascular wall[40]. Rosado *et al*[41] found that terutroban, a thromboxane-A2/prostaglandin-endoperoxide receptor antagonist, reduced portal pressure by inhibiting Rho-kinase activity and enhancing eNOS-dependent vasodilatation in cirrhotic rats.

In addition, coupling of the angiotensin-type Ⅱ receptor 1 (AT1R) to heterotrimeric G proteins (Gaq/11 and Ga12/13) allows stimulation and activation of the RhoA/Rho kinase pathway, which is involved in extracellular matrix production; these reactions are crucial in the development of fibrosis and PHT[42,43] (Figure 2).

Thus, the RhoA/Rho kinase signaling pathway is important in regulating IHVR and increasing portal pressure. It may be effective for inhibiting vasoconstriction by inhibiting the key mechanisms in the RhoA/Rho-kinase signaling pathway, such as phosphorylation of myosin light chain directly. However, the specific effect needs further investigation.

## JAK2/STAT3 SIGNALING

### *Overview of JAK2/STAT3*

The janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway participates in numerous pathophysiological processes. Various cytokines produce corresponding tissue and cell-specific effects through combinations of four members of the JAK family and seven members of the STAT family. JAK2, the most conserved isoform of the JAK family, acts directly on downstream STAT3 in JAK/STAT signaling[44]. The JAK2/STAT3 pathway interacts with numerous cytokines that can be activated by angiotensin Ⅱ, interferon-γ, transforming growth factor β (TGF-β), etc. Upon activation, STAT3 is phosphorylated to become p-STAT3, which can form homodimers or heterodimers, translocate to the nucleus, and bind to specific regulatory sequences on DNA[45]; these products then regulate the expression of VEGF, TGF-β, eNOS, and inducible nitric oxide synthase (iNOS), a process that is important in cell proliferation, fibrosis and angiogenesis[46-48]. It has been found that JAK2/STAT3 signaling is overactive in PHT and involved in its development[44,49].

### *JAK2/STAT3 regulate angiogenesis and vasoconstriction*

Angiogenesis is considered one of the factors in the development of PHT. Pathological angiogenesis may lead to increased intrahepatic circulatory resistance, and subsequently cause PHT and its severe complications such as variceal bleeding. VEGF is one of the cytokines involved in the development of angiogenesis[50,51]. Wang *et al*[52] found that AG490, a specific antagonist of JAK2, decreased the formation

of new blood vessels in the liver by inhibiting the expression of JAK2/STAT3 signaling, which suppressed the activation of HSCs and reduced the expression of VEGF. JAK2/STAT3 signaling may stimulate vascular hyperplasia and decrease vascular tone by increasing the expression of VEGF, thus promoting the development of PHT. Interleukin-17 activates HSCs by STAT3 signaling, and activation of HSCs plays a key role in the formation of PHT[53]. IL-6 also activates the STAT3 pathway. IL-6 binds to its receptor, activates JAK2, phosphorylates it, and then causes the phosphorylation of STAT3 in cells; these reactions result in the activation of HSCs and promotion of HLF expression, which can upregulate the activation of IL-6 and reactivate the STAT3 pathway. Thus, a loop is formed that constantly activates HSCs, ultimately causing hepatic vessel contractions that lead to increased portal pressure[54].

Endogenous angiogenesis and increased eNOS-derived nitric oxide levels in PHT have been considered important in the maintenance of PHT, and JAK2/STAT3 has been reported to promote eNOS protein expression[52,55].

Visceral inflammation is usually present in patients with PHT, especially in those with advanced PHT, and the inflammation can accentuate endothelial dysfunction and angiogenesis[56]. Relevant studies[52] have shown that enhanced JAK2/STAT3 signaling accelerates intestinal inflammation in PHT rats by upregulating TGF-β and iNOS expression. These findings suggest that JAK2/STAT3 participates in the pathogenesis of PHT by regulating factors such as VEGF, eNOS, TGF-β and iNOS.

Recent studies[49,57] have found a relationship between the JAK2/STAT3 signaling pathway and RhoA/Rho-kinase signaling. JAK2 was shown to establish a link between AT1R and the RhoA/Rho-kinase pathway in smooth muscle cells. AT1R stimulates JAK2 to phosphorylate and then induce Arhgef1, the nucleotide exchange factor responsible for activating RhoA, which activates Rho-kinase, eventually leading to vasoconstriction (Figure 2).

## FXR PATHWAY

Activation of the above three signaling pathways mainly promotes the formation of PHT, while activation of the FXR pathway can reduce PHT.

### *Overview of FXR*

FXR is a bile acid-reactive transcription factor and member of the nuclear receptor superfamily (NR1H4)[58] that is highly expressed in the liver and small intestine. Like other nuclear receptor members, FXR has an N-terminal activation domain (AF1) that interacts with a cofactor, a conserved DNA-binding domain, and a unique ligand-binding domain, allowing receptor dimerization and the C-terminal activation domain (AF2) to regulate the interaction[59,60]. In recent years, it has been recognized that the FXR plays a key role in the metabolism of bile acids and intestinal flora, as bile acids and FXR closely interact[61,62]. In many liver diseases, FXR is involved in fibrosis, and in the gastrointestinal tract it has immunological activity and vascular function[63]. FXR is a major transcriptional regulator of genes involved in bile acid homeostasis and is a regulator of lipid and carbohydrate metabolism in the normal liver[64].

Studies have documented deficiency of the FXR system in rat cirrhosis models, and FXR agonists can improve PHT through various pathways by activating FXR, which is related to vascular regulation and PHT[64]. Small heterodimer partner, the direct target gene of FXR, is a downstream orphan nuclear receptor for FXR that inhibits many other nuclear receptors, including cholesterol 7 alpha-hydroxylase[65]; it is increased after stimulation of FXR agonist INT-747 in a cirrhosis model[64]. The beneficial effects of this process involve hemodynamic changes of intrahepatic endothelial dysfunction and the molecular repair of intrahepatic eNOS activity[64].

### *FXR regulates vasodilation*

In cirrhotic PHT, a decrease in intrahepatic eNOS activity is key to the pathogenesis of increased IHVR[6], which is mainly caused by impaired hepatic vascular dilatation through the combination of reduced eNOS activity and nitric oxide bioavailability[66,67]. FXR affects blood vessel nitric oxide signaling by increasing eNOS concentrations[68]. In animal models of cirrhosis, obeticholic acid, a steroid FXR agonist and chenodeoxycholic acid derivative, restored intrahepatic eNOS levels and enhanced the expression of dimethylarginine dimethylamidohydrolase-1 (DDAH-1). Increases in DDAH-1 reduce the level of systemic asymmetric dimethylarginine (ADMA), thus upregulating the expression of eNOS, and then modulating nitric oxide production, which eventually results in decreased portal vein pressure[64,69]. ADMA is a competitive inhibitor of the eNOS substrate L-arginine and decreases eNOS phosphorylation of vascular endothelial cells *in vitro* and *in vivo*[70]. DDAH-1 is a key enzyme that metabolizes liver ADMA[69]. In addition, studies have found that alanine-glyoxylate aminotransferase-2 (AGXT2), which is present in mitochondria, is involved in the metabolism of ADMA. Rodionov *et al*[71] found that ADMA levels were significantly reduced in the liver and plasma of AGXT2-overexpressing mice. Caplin *et al*[72] found that the ADMA levels were significantly increased in the plasma of AGXT2 knockout mice. The FXR agonist PX20606 upregulates GTP cyclohydrolase-1, a key enzyme in the synthesis of cofactor tetrahydrobiopterin (BH4), resulting in increased amounts of BH4; sufficient concentrations of BH4 are essential for eNOS to catalyze nitric oxide. The enhancement of eNOS activity and BH4 has improved nitric oxide-mediated sinus endothelial function[68]. FXR agonism also decreases inflammatory

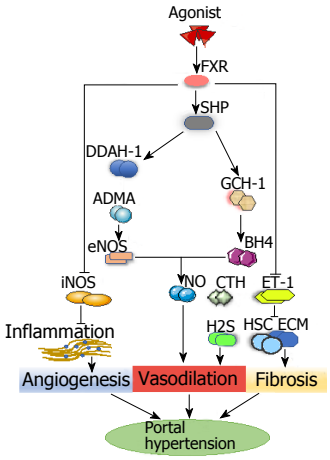


**Figure 3 FXR-mediated pathways in angiogenesis, vasodilation and fibrosis during portal hypertension.** FXR pathway: FXR agonist enhances the expression of FXR, which enhances the expression of DDAH-1 and GTP cyclohydrolase-1. DDAH-1 can reduce the levels of ADMA and upregulate the expression of eNOS. GTP cyclohydrolase-1 can increase the expression of BH4. This synergistic enhancement of eNOS and BH4 activity has improved nitric oxide-mediated sinus endothelial function. In addition, FXR agonism reduces the inflammatory response by reducing the expression of iNOS and cyclooxygenase 2 to improve PHT. FXR agonism decreases the expression of endothelin-1 and then inhibits HSC proliferation and extracellular matrix synthesis, which can ameliorate fibrosis. Repressed endothelin-1 can increase the production of cystathionase-mediated hydrogen sulfide, which can cause vasodilation. ADMA: Asymmetric dimethylarginine; BH4: Tetrahydrobiopterin; DDAH-1: Dimethylarginine dimethylamidohydrolase-1; ECM: Extracellular matrix; eNOS: Endothelial nitric oxide synthase; FXR: Farnesoid X receptor; GCH-1: GTP cyclohydrolase-1; $H_2S$: Hydrogen sulfide; HSC: Hepatic stellate cell; iNOS: Inducible nitric oxide synthase; NO: Nitric Oxide; SHR: Small heterodimer partner.

responses, and the associated development of PHT, by reducing the expression of iNOS and cycloogenase 2[73].

### *FXR regulates endothelial dysfunction*

The increase of internal vascular resistance caused by endothelial dysfunction is one of the factors in PHT formation. In some studies[68,74], endothelial dysfunction was mainly due to increased activity of vasoconstrictive factor (endothelin-1) and impaired nitric oxide signaling in sinusoidal endothelial cells. Endothelin-1 is a powerful vasoconstrictor in hepatic sinuses[75]. In liver damage, enhanced synthesis of endothelin-1 has activated HSCs, which promoted sine refactoring[6,68] and increased the amount of phosphorylated moesin, a marker of HSC contraction[75]. Endothelin-1 not only induces HSC proliferation and contraction, with consequent sinusoidal vasoconstriction, but also increases extracellular matrix synthesis[68]. FXR agonism ameliorated intrahepatic resistance[75] by decreasing the expression of endothelin-1[76], which inhibited endothelin-1-mediated contraction of hepatic stellate cell and increased the production of liver cystathionase-mediated hydrogen sulfide[68]. Cystathionase is a key enzyme for the local production of hydrogen sulfide, a potent nitric oxide-independent vasodilator[77] (Figure 3).

The above four signaling pathways have been extensively studied, however some novel signaling pathways need further study. Recent studies have shown that the increase in reactive oxygen leads to increased expression of Nuclear Factor-E2-related factor 2/Heme Oxygenase 1 (Nrf2/HO-1) in portal hypertensive rats. HO-1 is regulated by Nrf2 and can be used to induce hypovascular reactivity or as a vasodilator, which also results in increased expression of VEGF in the mesenteric artery of patients with PHT, which then forms the collateral portal vessels[78]. Therefore, reducing the portal pressure by inhibiting Nrf2/HO-1 signaling is effective. Zeng *et al*[79] found that Kruppel-like factor 2 inhibits the proliferation of sinusoidal endothelial cells and vascular formation by downregulating extracellular signal-regulated kinases 1/2 signaling, which inhibits the process of angiogenesis, and then ameliorates elevated portal pressure. Gao *et al*[80] found that combining celecoxib and octreotide not only significantly inhibited the expression of phospho-extracellular regulated kinase (p-ERK), HIF-1a, and VEGF, but also prevented HIF-1a from binding to VEGF by blocking the MAPK-ERK signaling pathway, which synergistically improves hepatic fibrosis and portal hypertonia in thioacetamide-induced cirrhotic rats by inhibiting both intrahepatic and extrahepatic angiogenesis. The mechanism responsible may be inactivation of the p-ERK-HIF-1$\alpha$-VEGF signaling pathway.

## CONCLUSION

In recent years, progress has been made in understanding how PHT develops and in the development of potential nonsurgical therapeutic approaches to PHT. The limitations of current PHT treatments are directed towards the outcomes of PHT, such as bleeding varices, and not towards the underlying causes. Several signaling pathways are involved in the pathogenesis of PHT, including PI3K-AKT-mTOR, RhoA/Rho kinase, JAK2/STAT3 and FXR. These pathways affect the development of PHT by regulating IHVR and portal vein blood flow. In addition, some newly discovered signaling pathways may be novel therapeutic targets, such as p-ERK-HIF-1$\alpha$-VEGF signaling. Efforts directed toward modifying the pathways should be explored for the effective prevention and treatment of PHT, however the pathways are incompletely understood and deserve further investigation.

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