Review Article

Role of Hydrogen Sulfide and Hypoxia in Hepatic Angiogenesis of Portal Hypertension

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Abstract

The pathogenesis of portal hypertension remains unclear, and is believed to involve dysfunction of liver sinusoidal endothelial cells (LSEC), activation of hepatic stellate cells (HSC), dysregulation of endogenous hydrogen sulfide (H_2S) synthesis, and hypoxia-induced angiogenic responses. H_2S, a novel gas transmitter, plays an important role in various pathophysiological processes, especially in hepatic angiogenesis. Inhibition of endogenous H_2S synthase by pharmaceutical agents or gene silencing may enhance the angiogenic response of endothelial cells. Hypoxia-inducible factor-1 (HIF-1) is the main transcription factor of hypoxia, which induces hepatic angiogenesis through up-regulation of vascular endothelial growth factor (VEGF) in HSC and LSEC. H_2S has also been shown to be involved in the regulation of VEGF-mediated angiogenesis. Therefore, H_2S and HIF-1 may be potential therapeutic targets for portal hypertension. The effects of H_2S donors or prodrugs on the hemodynamics of portal hypertension and the mechanism of H_2S-induced angiogenesis are promising areas for future research.

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Introduction

Portal hypertension is defined as a portal pressure gradient

(PPG) >6 mmHg or hepatic venous pressure gradient (HVPG) >5 mmHg.[1,2] The condition is often accompanied by gastroesophageal varices, ascites, and splenomegaly. The pathogenesis of portal hypertension involves multifaceted cellular and molecular mechanisms, including dysfunction of liver sinusoidal endothelial cells (LSEC), activation of hepatic stellate cells (HSC), dysregulation of endogenous hydrogen sulfide (H_2S) synthesis, and hypoxia-induced angiogenic responses.[3,4] In portal hypertension, hepatic sinusoidal vascular remodeling leads to impaired oxygen supply to liver parenchymal cells, resulting in the formation of hepatic hypoxic microenvironment (HHME). The HHME in turn leads to pathological angiogenesis as well as other adaptive changes in the liver.[5] Hypoxia-inducible factor-1 (HIF-1) is the main transcription factor of hypoxia response and the main regulator of oxygen homeostasis.[6] The interaction between HIF-1 and proangiogenic factors is an essential pathophysiological event in the process of angiogenesis induced by hypoxic conditions.[7,8]

H_2S is a new member of the gas transmitter family.[9] Recent studies have demonstrated the involvement of endogenous H_2S in regulating angiogenic responses.[9,10] Importantly, H_2S upregulates the expression of vascular endothelial growth factor (VEGF) and participates in the regulation of VEGF-mediated angiogenic signaling pathway.[11] HIF-1 and H_2S are both potential mediators of the angiogenic response in HHME, coregulating the development of portal hypertension. Therefore, this review focuses on the pathophysiological roles as well as mechanisms of H_2S and HIF-1 in regulating hepatic angiogenesis, providing potential therapeutic targets for the treatment of portal hypertension.

Adaptive changes in HHME

Tissue oxygen tension is a key factor in maintaining cell viability. The physiological gradient of oxygen tension in the hepatic lobules has a profound effect on the function of hepatic parenchymal cells. The unique dual blood supply system of the liver produces an oxygen partial pressure (pO2) in different liver zones, with a pO2 of 60–65 mmHg in the periportal region and 30–35 mmHg in the perivenous region.[12] Thus, periportal hepatocytes and perivenous hepatocytes differ in the expression of many enzymes involved in glucose metabolism, including insulin receptors, glucagon receptors, phosphoglycerate kinase, and pyruvate kinase.[13] Periportal hepatocytes are primarily responsible for oxidative metabolism, gluconeogenesis, and synthesis of urea and bile, while perivenous hepatocytes are the primary sites of glucose up-
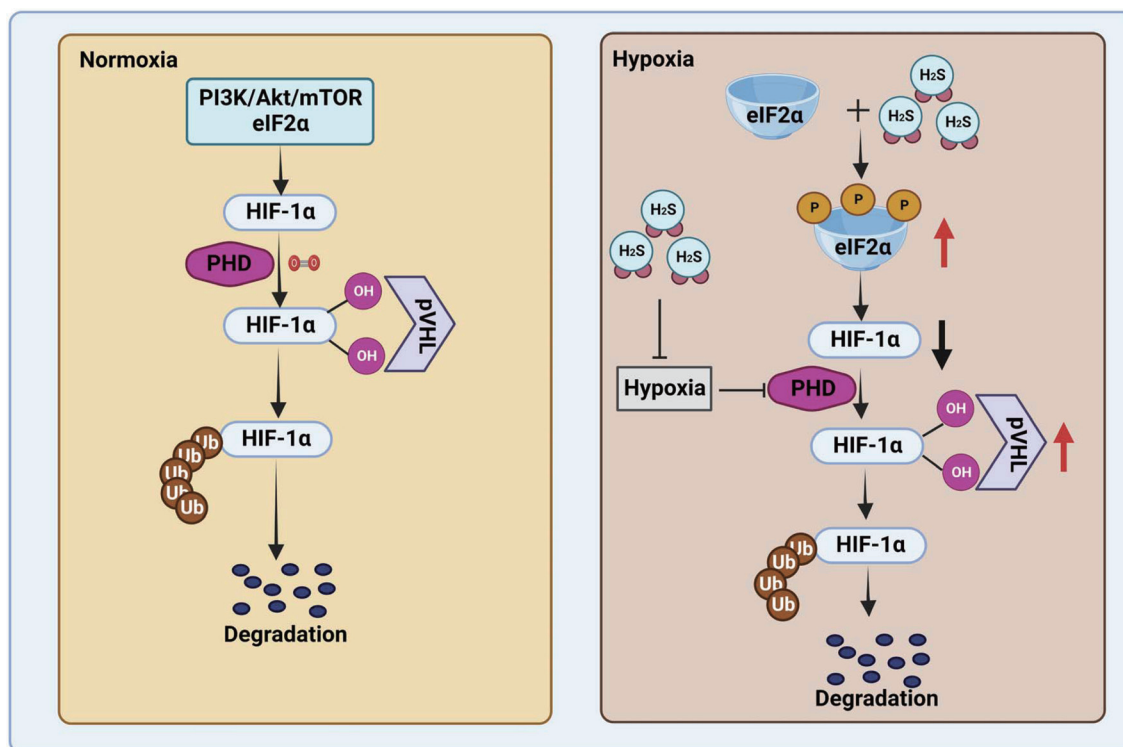
Fig. 1. Pathways of HIF-1α synthesis/degradation under normoxic and hypoxic conditions. Translation of HIF-1α protein under normoxic conditions is mainly dependent on the activation of PI3K/Akt/mTOR signaling pathway. HIF-1α is hydroxylated by PHD under normoxic conditions and subsequently binds to VHL protein to form a complex. The complex in turn recruits ubiquitin ligases to target HIF-1α for proteasomal degradation. Under hypoxic conditions, H_2S induces phosphorylation of eIF2α, thereby inhibiting HIF-1α translation. In addition, H_2S reverses hypoxia-induced inhibition of PHD activity and thus promotes the degradation of HIF-1α. HIF-1α, hypoxia-inducible factor 1α; PHD, prolyl hydroxylase; VHL, von Hippel-Lindau; H_2S, hydrogen sulfide; eIF2α, eukaryotic translation initiation factor 2α.

take, glutamine formation and metabolism.[14] Exposure of hepatocytes to different levels of oxygen tension affects their ability to respond to hypoxic microenvironments. Primary rat hepatocytes cultured under conditions approximating periportal oxygen tension (pO_2 of 60–65 mmHg) were able to survive briefly in a hypoxic environment, whereas hepatocytes cultured under conditions approximating perivenous oxygen tension (pO_2 of 30–35 mmHg) were intolerant to hypoxic stimulation and underwent rapid apoptosis.[12,15] This suggests that under hypoxic conditions such as increased hepatic metabolic demand, or tissue ischemia, perivenous hepatocytes may suffer greater injury when oxygen tension drops below a threshold level.

HIF-1, an oxygen-sensitive transcription factor, is the core factor mediating the hypoxic response.[16] HIF-1 is a heterodimer consisting of the hypoxia-inducible and oxygen-sensitive HIF-1α subunits and the constitutively expressed HIF-1β subunits.[17] HIF-1 heterodimers bind to hypoxia responsive elements in target genes, thereby enhancing transcription of target genes. Under normoxic conditions, it is difficult to detect HIF-1α protein in normal cells because of its rapid degradation. The two specific proline residues within the oxygen-dependent degradation domain in HIF-1α are hydroxylated by prolyl hydroxylase (PHD) under normoxic conditions.[18] Hydroxylated HIF-1α then binds to von Hippel-Lindau protein (VHL). This complex in turn recruits ubiquitin ligases to target HIF-1α for proteasomal degradation.[18] Translation of HIF-1α protein under normoxic conditions is dependent on activation of the PI3K-Akt-mTOR pathway and mitogen-activated protein kinase pathway.[19] Phosphorylation of eukaryotic translation initiation factor 2α (eIF2α) and inhibition

of mTOR activity under hypoxic conditions are believed to be responsible for the inhibition of HIF-1α protein expression (Fig. 1).[19,20]

Interaction between hypoxia and H_2S

H_2S is believed to be the third gaseous signaling molecule which is widely expressed in mammalian cells and tissues.[21] Three enzymes are known to be involved in the production of endogenous H_2S, namely cystathionine beta synthase (CBS), cystathionine gamma lyase (CSE), and 3-Mercapto-pyruvate sulfotransferase (3-MST).[9] An increasing body of evidence has revealed the cross-talk between HIF-1 and H_2S. In a study, knockdown of *CSE* was shown to affect H_2S production, which impaired the stability of HIF-1α, suggesting that endogenous H_2S is important for the regulation of HIF-1 signaling pathway.[22] However, another study found no effect of H_2S on HIF-1 level in EB8 cells under hypoxic conditions.[23] Moreover, treatment of cells with 1 mM NaHS, an exogenous H_2S donor, inhibited mitochondrial oxygen consumption, thereby enhancing oxygen levels in hypoxic cells. Under hypoxic conditions, H_2S inhibited the stability of HIF-1α protein.[23] The authors concluded that H_2S promoted the degradation of HIF-1α under hypoxic conditions due to NaHS-induced inhibition of mitochondrial oxygen consumption. Notably, the study used 1 mM NaHS, a high concentration of H_2S that is clearly outside the physiological range of endogenous H_2S (10–100 μM) and was potentially toxic to cells.

In a study using 10–100 μM NaHS, H_2S significantly reduced HIF-1α protein levels under hypoxic conditions.[24] Fur-

ther, addition of the translation inhibitor actidione blocked the effect of NaHS on HIF-1α protein levels, indicating that H$_2$S mediated inhibition of HIF-1α. The findings demonstrated that the key mechanism of H$_2$S-induced HIF-1α down-regulation was inhibition of HIF-1α translation rather than through the ubiquitin-proteasome degradation pathway.[24] eIF2α was shown to be a key regulatory molecule for initiation of translation in eukaryotic cells. Phosphorylation of eIF2α was shown to prevent the formation of translational initiation complex and thus inhibit protein translation.[25] H$_2$S-induced downregulation of HIF-1α was partially reversed in *eIF2α* knockdown cells under hypoxic conditions.[24] The findings suggest that inhibition of HIF-1α translation under hypoxic conditions may be related to H$_2$S-induced eIF2α phosphorylation (Fig. 1).

Although the accumulation of HIF-1α in cells is largely dependent on VHL, new evidence suggests that VHL-independent degradation pathways may play an equally important role in regulating HIF-1α.[26,27] Cysteine synthase-1 was homologous to CBS, which had a negative regulatory effect on EGL-9 family hypoxia-inducible factor-1, thereby enhancing the stability of HIF-1.[27] Thus, H$_2$S may lead to the accumulation of HIF-1 under hypoxic conditions by promoting the interaction between EGL-9 family hypoxia-inducible factor (HIF) and cysteine synthase-1.[27] Although this pathway appears to be less dependent on intracellular oxygen levels, further studies are required to elucidate the potential involvement of this pathway in the regulation of HIF-1 levels by H$_2$S under hypoxic conditions.

Molecular mechanisms of angiogenesis in HHME

Studies have demonstrated the occurrence of pathological angiogenesis throughout the progression of portal hypertension.[28] Furthermore, hepatic angiogenesis and the concomitant vascular remodeling play a significant role in the development of portal hypertension and its associated complications.[29]

Role of hypoxia/HIF in hepatic angiogenesis

Hypoxia is one of the most potent stimuli known to drive angiogenesis.[30] The HIF-mediated hypoxic response results in enhanced transcriptional activity of a range of cell surface receptors and target genes, which enhances the sensitivity of endothelial cells to angiogenic factors and accelerates the process of liver cirrhosis.[31] The process of liver cirrhosis was shown to be accompanied by liver parenchymal hypoxia, which induced hepatic angiogenesis through up-regulation of VEGF in HSC and LSEC via HIF-1α.[32] VEGF expression induced sustained capillarization in LSEC, leading to the disappearance of fenestrations on the surface of the hepatic sinusoids. This undermined oxygen exchange between LSEC and hepatic parenchymal cells, resulting in a local hypoxic microenvironment.[33] Remodeling of the hepatic vascular architecture may increase intrahepatic vascular resistance, which leads to cirrhotic portal hypertension. Studies have shown that inhibition of HIF-1α expression reduces the synthesis and secretion of VEGF, thereby suppressing hepatic angiogenesis.[6] Apparently, HIF-1α plays an essential role in hypoxia-induced pathological angiogenesis in the liver by regulating VEGF expression. In addition, under hypoxic conditions, HIF-1α was shown to induce overexpression of angiopoietin-1, a critical factor in the regulation of angiogenesis.[34] Angiopoietin-1 then bound to its receptor Tie-2 and recruited mural cells to wrap around LSEC, thereby promoting the progression of liver fibrosis. That was confirmed by another study in which angiopoietin-1 and its specific re-

ceptor Tie-2 were significantly upregulated in liver tissue of rats with CCl$_4$-induced liver fibrosis.[35] In addition to HIF-1α, HIF-2α also plays a role in hypoxia-induced angiogenesis. Knockdown of *HIF-2α* gene was shown to up-regulate the expression of VEGFR1, which prevented VEGF from interacting with VEGFR2 and thus negatively regulated hepatic angiogenesis.[36] The above findings indicate that hypoxia and pathological angiogenesis may play a synergistic role in the progression of liver cirrhosis.[31]

H$_2$S-related signaling pathways in angiogenesis

Recent studies have confirmed the role of endogenous H$_2$S in the activation of mitogen-activated protein kinase cascade.[37] Elevated levels of ERK1/2 and p38 phosphorylation were observed after stimulation of endothelial cells with VEGF, which may be blocked by *CSE* silencing. The ATP-sensitive potassium channel is the main mediator of the H$_2$S effect and is located upstream of p38.[37] Direct inhibition of endogenous synthesis of H$_2$S with pharmacological agents or *CSE* gene silencing resulted in reduced intracellular cyclic guanosine monophosphate (cGMP) levels, whereas overexpression of *CSE* upregulated cGMP by direct inhibition of phosphodiesterase activity by H$_2$S.[38] In addition, H$_2$S production activated the PI3K/Akt signaling pathway, leading to endothelial nitric oxide synthase (eNOS) phosphorylation and eNOS activation.[39] Activation of the PI3K/Akt pathway may result from inhibition of lipid phosphatase and tensin homologue expression by H$_2$S.[40] Vasodilator stimulated phosphoprotein phosphorylation at Ser239 was upregulated in endothelial cells treated with L-cysteine, demonstrating that endogenous H$_2$S activated the cGMP/PKG pathway.[38] The accumulation of cGMP in turn activated PKG, which stimulated the angiogenic effect of endothelial cells.[38] In addition, the pro-angiogenic effect of the 3-MP/3-MST/H$_2$S pathway was shown to be significantly associated with the activation of Akt. In a study, knockdown of *3-MST* resulted in reduced levels of Akt and vasodilator-stimulated phosphoprotein phosphorylation.[41] Based on the above evidence, H$_2$S is considered as an essential gaseous signal molecule involved in the regulation of angiogenesis.

Interaction between H$_2$S and angiogenic factors

As previously described, CSE inhibitors or *CSE* gene silencing inhibited VEGF-mediated angiogenic effects.[38] This finding further suggests that treatment of endothelial cells with VEGF promotes the synthesis of H$_2$S. Although the underlying mechanism of this effect has not been fully elucidated, it is believed to be mediated through calcium-dependent activation of CSE.[38] However, in another study, adenovirus-mediated triple gene transfection of *CBS*, *CSE*, and *3-MST* upregulated VEGF expression and downregulated the expression of anti-angiogenic factors.[42] The above evidence indicates that H$_2$S is a downstream effector molecule of VEGF signaling, but may also be present upstream of VEGF signaling. Further studies are required for an in-depth characterization of the regulatory relationship between H$_2$S and VEGF.

The binding of VEGF to VEGFR2 causes its homodimerization, leading to phosphorylation of a series of tyrosine residues. In a recent study, a disulfide bond existing between Cys1045 and Cys1024 of VEGFR2 was found to alter the active conformation of VEGFR2 and inhibit its activity.[43] Nucleophilic attack on disulfide bonds by H$_2$S led to reduction of the disulfide bond and enhanced VEGFR2 tyrosine kinase activity.[43] In another study, knockdown of *CBS* in endothelial cells inhibited VEGF signaling by reducing the transcription of VEGFR2 and NRP-1.[44] That study further revealed that the
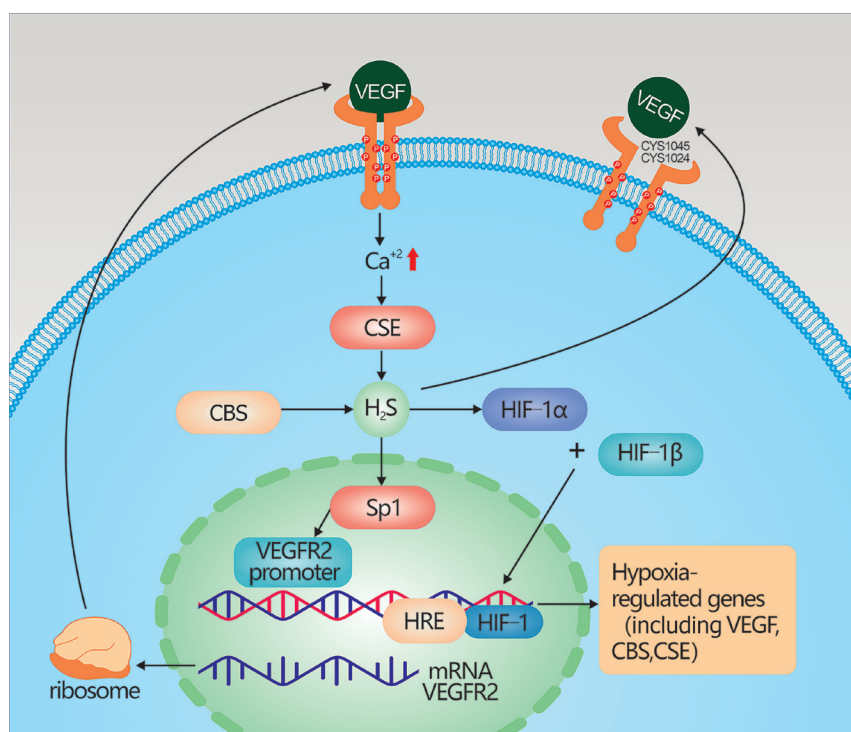
Fig. 2. Proposed interactions among H$_2$S, VEGF, and HIF-1. The binding of VEGF to VEGFR2 may activate CSE through a calcium-dependent pathway, which in turn promotes endogenous H$_2$S production. Nucleophilic attack by H$_2$S on the disulfide bond between Cys 1045-1024 leads to reduction of the disulfide bond and enhances VEGFR2 tyrosine kinase activity. CBS-derived and CSE-derived H$_2$S enhances the stability and transcriptional activity of Sp1, which further promotes the transcription of VEGFR2. H$_2$S results in increased HIF-1α levels, DNA binding, and transcriptional activity. VEGFR2, vascular endothelial growth factor receptor 2; VEGF, vascular endothelial growth factor; CSE, cystathionine-γ lyase; CBS, cystathionine-β synthase; HIF, hypoxia-inducible factor; HRE, hypoxia response element; Sp1, specificity protein 1; H$_2$S, hydrogen sulfide.

downregulation of VEGFR2 transcriptional activity was mediated by reduced stability of transcription factor specific protein 1 (Sp1).[44] Exogenous supplementation of H$_2$S donors in *CBS*-knockdown endothelial cells restored Sp1 levels and its binding to the VEGFR2 promoter, thereby reactivating the VEGF signaling pathway. A schematic illustration of the hypothetical interactions among H$_2$S, VEGF, and HIF-1 is shown in Figure 2.

Similar to VEGF, fibroblast growth factor 2 (FGF-2) is a pro-angiogenic and pro-fibrotic factor that inhibits endothelial cell apoptosis.[45] However, in contrast to VEGF, FGF-2 is insensitive to hypoxia.[45] HIF and VEGF expression occurred simultaneously and were co-localized to the same region; however, FGF-2 expression was observed much later and did not coincide with the distribution of hypoxic regions, which suggested that angiogenesis was mainly mediated by VEGF in response to hypoxia, while FGF-2 may contribute to maintain advanced angiogenesis.[46] Furthermore, H$_2$S inhibitors did not attenuate the FGF-mediated angiogenic response, suggesting that the pro-angiogenic effect of FGF was independent of H$_2$S.[47] Although H$_2$S may not be required for FGF signaling, H$_2$S can up-regulate FGF levels *in vivo*. In a recent study, both FGF and VEGF expression levels were elevated following hindlimb ischemia in wild-type mice, whereas this response was reduced in *CSE*-knockout mice.[48] Further studies are required to elucidate the potential role of H$_2$S in angiogenic signaling of other growth factors.

Vasodilatory effects of H$_2$S in portal hypertension

Studies have shown that the exogenous H$_2$S donor NaHS

has vasodilatory effects similar to nitric oxide (NO).[49] Perfusion with NaHS attenuated norepinephrine-induced hepatic vasoconstriction in normal and cirrhotic liver.[49] Notably, although in normal liver the vasodilatory effects were reproduced by cysteine supplementation, the effects of cysteine in cirrhotic liver gradually diminished with the progressive loss of hepatic parenchymal cells.[50] H$_2$S acts as a vasodilator in the portal circulation, and perfusion of cirrhotic livers with exogenous H$_2$S donors was shown to compensate for defective NO production in a rat model of portal hypertension.[49]

In addition to causing endothelial dysfunction, homocysteine has been shown to cause contraction of HSC. This homocysteine-induced contraction of HSC is reversed by H$_2$S.[21] HSC contraction is associated with regulation of liver sinusoidal blood flow and intrahepatic resistance, and it is hypothesized that H$_2$S may be involved in regulating HSC contraction together with LSEC-derived paracrine cytokines.[21] Briefly, reduced levels of H$_2$S in the portal microcirculation cause an increase in intrahepatic resistance, not only because it is part of endothelial dysfunction, but also because it facilitates the activation and contraction of HSC. Another postulated mechanism of the vasodilatory effect of H$_2$S in liver involves its interaction with NO. However, perfusion of rat livers with nonselective eNOS and inducible nitric oxide synthase (iNOS) inhibitors failed to reverse the vasodilatory effects of H$_2$S on norepinephrine-induced vasoconstriction.[49] Inhibition of CSE with propargylglycin did not induce further constriction of liver sinusoidal microvessels using high flow rate liver perfusion. Interestingly, in patients with cirrhosis exhibiting splanchnic hyperdynamic circulation, NO levels

Table 1. Anti-angiogenesis therapeutic drugs in portal hypertension

Drugs	Experimental model	Site of angiogenesis	Target	Ref
Sorafenib	NASH; PBC; CCl4-induced cirrhosis	Intrahepatic angiogenesis	Raf/MEK/ERK signaling pathway; VEGFR; PDGFR	63–66
Sunitinib	CCl4-induced cirrhosis; human HSC; primary human LSEC	Intrahepatic angiogenesis	VEGFR-1/2/3; PDGFR-α/β; FGFR	67,68
Brivanib	NASH; PBC	Intrahepatic angiogenesis	VEGFR; FGFR	69,70
Simvastatin	CCl4-induced cirrhosis; human HSC	Intrahepatic angiogenesis	KLF2	71,72
Largazole	CCl4-induced cirrhosis; human HSC	Intrahepatic angiogenesis	VEGFR2; TGF-β	73
Rapamycin and imatinib	Partial portal vein ligation	Extrahepatic angiogenesis	VEGF; VEGFR2; PDGF; PDGFR-β	74
Bosentan	PBC	Extrahepatic angiogenesis	Endothelin receptors; iNOS; COX-2	75
Pioglitazone	PBC	Extrahepatic angiogenesis	NF-κB; VEGF; PDGF	76
Thalidomide	PBC	Extrahepatic angiogenesis	TNF-α-VEGF-NOS-NO pathway	77
Curcumin	PBC	Extrahepatic angiogenesis	VEGF; COX-2	78

NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; CCl4, carbon tetrachloride; HSC, hepatic stellate cells; LSEC, liver sinusoidal endothelial cells; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor; KLF2, Krüppel-like factor 2; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; SSTR2, somatostatin subtype receptor 2; TNF-α, tumor necrosis factor alpha; Ang1, angiopoietin 1; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; NO, nitric oxide; COX-2, cyclooxygenase-2; NF-κB, factor kappa-light-chain-enhancer of activated B cells.

were elevated by dysregulated eNOS production compared to healthy controls, while circulating H_2S levels appeared to be reduced.[51]

Hypoxia-induced angiogenesis in portal hypertension

HHME in patients with cirrhotic portal hypertension leads to liver sinusoidal capillarization, increased intrahepatic vascular resistance, and formation of intrahepatic shunts.[52,53] In addition, vasoconstrictors (e.g., endothelin-1) were upregulated in response to hypoxia, thereby increasing microcirculatory resistance in the liver and exacerbating hepatocyte hypoxia.[53] In hypoxic cirrhotic tissue, regenerative nodules were surrounded by a dense vascular plexus consisting of many microvessels that originated from pre-existing intrahepatic vascular branches. That progressed with the fibrous repair process, bypassing the liver parenchyma, and eventually leading to intrahepatic shunts.[29] Hyperdynamic splanchnic circulation is an important feature of portal hypertension.[54] Increased blood flow to the visceral organs flowing into the portal vein leads to increased portal blood flow, which causes portal hypertension. Previously, this phenomenon was believed to be associated with vasoconstriction and diastolic dysfunction, and the formation of collateral circulation was considered to be a mechanical consequence of elevated blood pressure.[55] However, recent studies have shown that angiogenesis may contribute to the maintenance of hyperdynamic splanchnic circulation and the development of collateral circulation, which is closely associated with VEGF- and PDGF-induced neovascularization and remodeling.[56]

Non-cirrhotic portal hypertension is a group of heterogeneous hepatic vascular diseases characterized by portal hypertension in the absence of cirrhosis.[57] Damage to the liver sinusoidal endothelium facilitates the entry of erythrocytes into the space of Dissé and the formation of perisinusoidal fibrosis. This hypoxic state induces excessive release of pro-angiogenic factors such as VEGF.[48] In addition, chronic hypoxia in the centrilobular areas induced nodular regenerative hyperplasia.[58] More evidence is required to fully elucidate the role of hypoxia and H_2S in regulating angiogenesis of non-cirrhotic portal hypertension.

Therapeutic implications of anti-angiogenesis agents for portal hypertension

Currently, the pharmacological effects of most anti-angiogenesis drugs have been investigated in experiments involving animal models as shown in Table 1. However, clinical evidence that supports the use of anti-angiogenesis drugs to treat portal hypertension is limited. Coriat *et al*.[59] first evaluated the effects of sorafenib on portal vein and systemic hemodynamics in seven patients with hepatocellular carcinoma and cirrhosis. Five of the patients were assessed as Child-Pugh class A, and two as Child-Pugh class B. Sorafenib (400 mg) was administered twice daily for 1 month. The results showed that the blood flow of portal vein decreased by 36%, but there was no significant change in the blood flow in the azygos vein and abdominal aorta. Another study explored the effects of sorafenib on HVPG and systemic hemodynamics in 13 patients with liver cirrhosis and hepatocellular carcinoma. Ten were Child-Pugh class A and three were Child-Pugh class B. The study also assessed the expression of genes related to liver fibrosis, angiogenesis, and inflammation. All patients received sorafenib (400 mg) twice a day for two weeks. In four of the 11 patients with clinically significant portal hypertension, HVPG was decreased by more than 20% from baseline. The levels of VEGF, PDGF, placental growth factor, and TNF-α were also downregulated.[60]

The main disadvantage of tyrosine kinase inhibitors is hepatotoxicity.[61] Poor liver function limits their application in patients with hepatocellular carcinoma complicated with cirrhotic portal hypertension. Selective delivery of drugs to target cells (especially HSC) by targeted drug delivery systems may be a promising direction to solve this problem.[62] Additional preclinical and clinical evidence on targeting HIF or H_2S agents in portal hypertension is required to support the clinical use of these drugs.

Summary and perspective

Angiogenesis is an essential pathophysiological event in the formation of the portal collateral circulation and the development of portal hypertension. The pathogenesis of portal hypertension is believed to involve H_2S- and hypoxia-induced hepatic angiogenesis. Endogenous H_2S plays a critical role in the regulation of vascular endothelial homeostasis, which may promote angiogenesis and induce vasodilation. H_2S upregulates the expression of VEGF in the HHME and participates in the regulation of VEGF-mediated angiogenesis. Therefore, H_2S and HIF are potential therapeutic targets for portal hypertension. The effects of H_2S donors or prodrugs on the hemodynamics of portal hypertension and the mechanism of H_2S-induced angiogenesis are promising areas for future research.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (HY, HD), acquisition of data (MT, ZG), analysis and interpretation of data (HY, MT, ZG), drafting of the manuscript (HY), critical revision of the manuscript for important intellectual content (SW, HD), administrative, technical, or material support (HD), and study supervision (SW, LL, HD). All authors have made a significant contribution to this study and have approved the final manuscript.

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