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Journal of the Chinese Medical Association 78 (2015) 195–203

www.jcma-online.com

Review Article

Molecular mechanisms of circulatory dysfunction in cirrhotic portal hypertension

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Received August 1, 2014; accepted October 30, 2014

Abstract

Acute or chronic insults to the liver are usually followed by a tissue repairing process. Unfortunately, this action, in most cases, is not effective enough to restore the normal hepatic structure and function. Instead, fibrogenesis and regenerative nodules formation ensue, which are relatively nonfunctioning. The common final stage of the process is liver cirrhosis with increased intrahepatic resistance to portal venous blood flow. Throughout the entire course, the extrahepatic circulatory dysfunction, including increased splanchnic blood flow, elevated portal venous blood flow and pressure, decreased splanchnic and peripheral vascular resistance, tachycardia, and increased cardiac output, are noted and denoted as portal hypertension with hyperdynamic circulatory dysfunction. When such a condition is established, patients may suffer from fatal complications such as gastroesophageal variceal hemorrhage, hepatic encephalopathy, or hepatorenal syndrome. The cause of such a circulatory dysfunction is not fully elucidated. Nevertheless, clarification of the pathophysiology definitely contributes to the control of portal hypertension-related complications. Herein, the molecular mechanism of this intriguing disaster is reviewed and discussed.

Keywords: hyperdynamic circulation; liver cirrhosis; mechanism; portal hypertension

1. Introduction

Liver cirrhosis has been notorious for its fatal complications for hundreds of years. Although much effort had been made, the treatment efficacy was still suboptimal before subtle information began to be unveiled. In 1953, based on the observation that patients with cirrhosis were characterized by increased flow of blood to the periphery as "warm extremities, cutaneous vascular spiders, wide pulse pressure, and capillary pulsations in the nail beds", Kowalski and Abelmann[1] first noticed that cirrhosis was associated with a hyperdynamic circulatory condition. They also demonstrated an elevated cardiac output and decreased peripheral vascular resistance in these patients. Astonished by these findings, the investigators developed animal models to explore the mechanism. Scientists now agree that the most critical point is how and when the circulatory dysfunction is triggered and how it is maintained and aggravated. Although marvelous advances have been made in the past few decades, many more questions have been raised and need to be addressed.

2. Pathophysiology of hyperdynamic circulatory syndrome in cirrhosis

According to Ohm's law, the pressure in a vascular system is proportional to the resistance and flow in that system. In

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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http://dx.doi.org/10.1016/j.jcma.2014.10.004

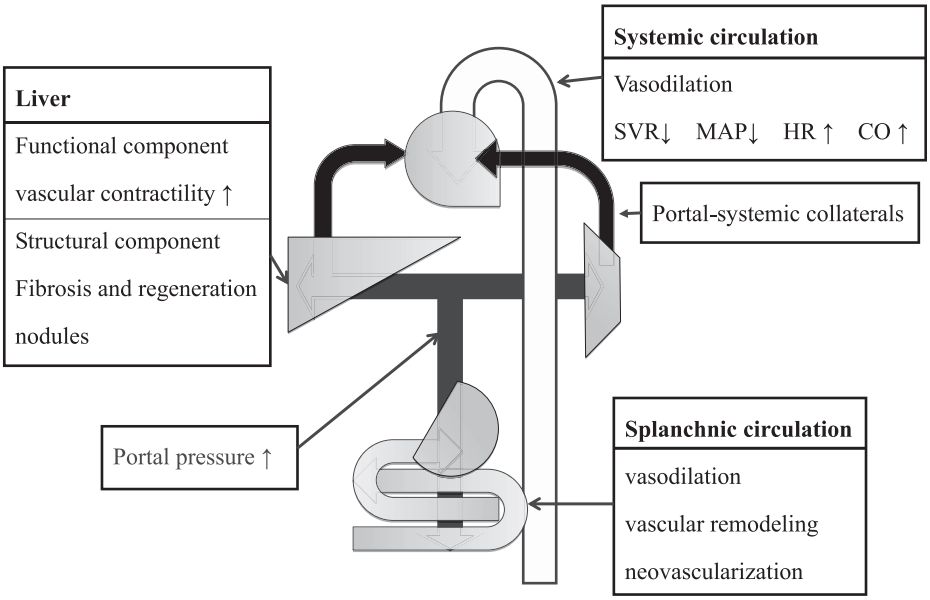

Fig. 1. Pathophysiological features of liver cirrhosis with hyperdynamic circulatory dysfunction. CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; SVR = systemic vascular resistance. *Note*: From "Caffeine ameliorates hemodynamic derangements and portosystemic collaterals in cirrhotic rat.," by S.J. Hsu, F.Y. Lee, S.S. Wang, I.F. Hsin, T.Y. Lin, H.C. Huang, et al, 2014, *Hepatology,* http://dx.doi.org/10.1002/hep.27679. Copyright © 2015 by the American Association for the Study of Liver Diseases. Adapted with permission.

cirrhosis, both increased hepatic resistance and splanchnic blood flow are believed to play key roles in elevated portal pressure (PP) (Fig. 1). Increased hepatic resistance is considered the primary event that triggers portal hypertension and splanchnic/peripheral vasodilatation in cirrhosis. To cope with the difficulty of sending portal tributary blood into the liver, the shunt between portal and systemic vascular beds, the so called portal-systemic collaterals, are established. Nevertheless, these are overwhelmed by the splanchnic vasodilation and markedly increased splanchnic/portal blood flow. Thereafter, PP elevates gradually. However, to compensate for the decreased splanchnic and systemic vascular resistance that lead to systemic hypotension, heart performance is compensatorily enhanced to elevate heart rate and cardiac output. However, these actions are usually insufficient to reverse the low blood pressure under the setting of marked peripheral vasodilatation. Such a condition leads to decreased effective intravascular volume, which stimulates vascular baroreceptors and volume receptors. Then, sympathetic nervous system, renin-angiotensin-aldosterone axis, and antidiuretic hormone are activated, followed by sodium/water retention and volume expansion. These are linked to complications such as edema, ascites, and hepatorenal syndrome.

3. Molecular mechanism

Although not fully elucidated, it is generally accepted that hyperdynamic circulatory dysfunction can be elicited by increased vasodilatory substance release, dysregulated response to vasoconstrictors, changes of vascular contractile signaling, vascular remodeling, and angiogenesis (Fig. 2).

3.1. Increased splanchnic vasodilatory substances release

In contrast to impaired vasodilatory response in hepatic microcirculation, in the splanchnic circulation, increased vasodilatory substance production contributes to enhanced endothelium-dependent relaxation, which precedes the development of hyperdynamic circulatory syndrome in cirrhotic portal hypertension.

3.1.1. Nitric oxide

Nitric oxide (NO) currently is the most recognized factor related to extrahepatic vasodilatation in cirrhosis.[2] It has been found that patients with cirrhosis have increased serum levels of NO metabolites.[3] More specifically, the concentration of NO metabolites in the portal venous plasma of patients with cirrhosis is significantly higher than that in systemic venous samples,[4] suggesting that NO release is enhanced in splanchnic vessels. A previous study also indicated that in patients with cirrhosis, infusion of an NO synthase (NOS) inhibitor increased forearm blood flow, supporting the role of NO in peripheral vasodilation.[5]

NO is an endothelium-derived vasodilator synthesized mainly by inducible (i)NOS and endothelial (e)NOS isoforms. Endothelial NOS is upregulated by vascular shear stress and acts via cofactors such as tetrahydrobiopterin (BH_4).[6] Which is the isoform that participates more in hyperdynamic circulation? Although Vallance and Moncada[7] proposed that iNOS led to NO overproduction and subsequent hyperdynamic circulation, substantial works have shown a lack of iNOS expression in vessels from portal hypertensive animals despite

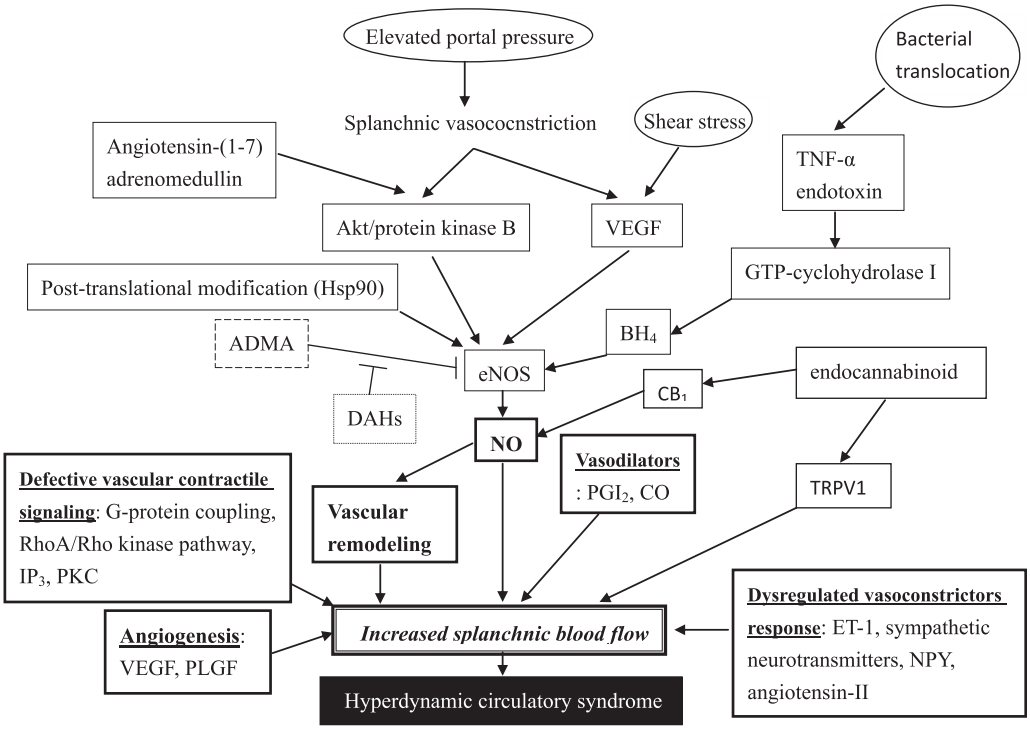

Fig. 2. Factors related to increased splanchnic blood flow and hyperdynamic circulatory syndrome. ADMA = asymmetric dimethylarginine; BH4 = tetrahydrobiopterin; CB_1 = cannabinoid receptor 1; CO = carbon monoxide; DAH = dimethylarginine dimethylaminohydrolase; eNOS = endothelial nitric oxide synthase; ET-1 = endothelin-1; GTP-cyclohydrolase I = guanosine triphosphate–cyclohydrolase I; Hsp90 = heat-shock protein 90; NO = nitric oxide; NPY = neuropeptide Y; PGI_2 = prostaglandin I_2; PLGF = placental growth factor; TNF-α= tumor necrosis factor-α; TRPV1 = transient receptor potential cation channel subfamily V member 1; VEGF = vascular endothelial growth factor.

enhanced NO production.[8] It is now accepted that eNOS rather than iNOS is the major contributor for NO overproduction and hemodynamic derangements in portal hypertension.[9] Indeed, the superior mesenteric vascular bed from portal hypertensive rats shows an enhanced NO production in response to shear stress.[10] On the molecular level, Tsai et al[11] demonstrated that eNOS activation occurs as early as 10 hours after the induction of portal hypertension. Theodorakis et al,[12] using iNOS- or eNOS-knockout mice, also identified that eNOS participates actively in the development of portal hypertension. Nevertheless, another study reported that eNOS knockout mice still developed hyperdynamic circulation after partial portal vein ligation (PVL), a surgical procedure to induce portal hypertension. Therefore, NO seems to be the principal but not the only mediator of portal hypertension, and compensatory upregulation of vasodilators facing NO deficiency might be implicated.[13]

Taking the upstream events into consideration, how is eNOS-derived NO overproduction triggered? It has been found that in rats with cirrhosis, bacterial translocation and increased circulating endotoxin activate guanosine triphosphate (GTP)–cyclohydrolase I, which generates BH_4 in mesenteric arteries. This is followed by enhanced eNOS activity and eNOS-derived NO overproduction.[14,15] Furthermore, eNOS is regulated by various protein–protein interactions and posttranslational modification.[6] For instance, Akt/protein kinase B activates eNOS in the splanchnic arterial bed in portal hypertensive rats.[16] Another finding is that PVL induced a sudden increase of PP. This is followed by a myogenic reflex and splanchnic vasoconstriction, which elicits phosphorylation and upregulation of eNOS through Akt/protein kinase B activation, leading to increased NO production and vasodilation.[11,16] Consistently, Abraldes et al[17] demonstrated that a mild increase in PP upregulated intestinal vascular endothelial growth factor (VEGF) and eNOS expressions, suggesting that PP itself triggers the cascade of vasodilatory substances synthesis. An increased interaction of eNOS with the molecular chaperone Hsp90[19] also contributes to the activation of eNOS at the posttranslational level. In addition, a survey revealed the increased mesenterial arterial messenger RNA expression of dimethylarginine dimethylami nohydrolase-1 and -2, enzymes that degrade asymmetric dimethylarginine, a NOS inhibitor, in portal hypertensive and rats with cirrhosis.[18]

3.1.2. Tumor necrosis factor-α

Tumor necrosis factor alpha (TNF-α), released by mononuclear cells in response to bacterial endotoxins, is a well-known mediator of NO release.[19] TNF-α inhibition blunts the development of hyperdynamic circulation in rats with portal hypertension[20] and cirrhosis.[21] Although it has been proved that endotoxemia and TNF-α enhance NO release, why does iNOS, the isoenzyme that is activated by inflammatory mediators, play a less significant role than eNOS in portal

hypertension? Tetrahydrobiopterin, an essential cofactor for NO synthesis, should be taken into consideration. In endothelial cells, TNF-α and lipopolysaccharides upregulate the key enzyme for BH_4 biosynthesis, GTP-cyclohydrolase I.[22,23] Tetrahydrobiopterin then directly enhances eNOS-derived NO bioavailability.[24] It has been demonstrated that TNF-α and lipopolysaccharide directly increased vascular NO synthesis in the absence of iNOS induction by increasing the BH_4 production.[22,25] In fact, BH_4 increased in mesenteric vasculature of rats with cirrhosis only under conditions of bacterial translocation.[15]

3.1.3. Prostacyclin (prostaglandin I_2, PGI_2)

Prostacyclin is an endothelium-derived vasodilator synthesized by cyclooxygenases. An increase in circulating PGI_2 has been observed in patients with cirrhosis.[26] Furthermore, PGI_2 participates in hyperdynamic circulation and PP elevation in portal hypertensive rats.[27] Indeed, the potential interaction between prostacyclin and NO should be addressed; in portal hypertensive rats with long-term prostacyclin inhibition, an enhanced release of NO was noted. Such a finding suggested that both vasodilatory systems interact to promote splanchnic hyperemia in portal hypertension.[28]

3.1.4. Carbon monoxide

Carbon monoxide (CO) is an endogenous molecule with vasodilatory properties.[29] CO binds hemoglobin to generate carboxyhemoglobin, an indicator of CO production. It has been observed that concentrations of blood carboxyhemoglobin are significantly increased in patients with cirrhosis.[30] CO is produced from the breakdown of heme to biliverdin via heme oxygenase (HO). Two isoforms of HO have been identified: HO-1 and HO-2. Increased HO-1 expression was found in aortas and mesenteric arteries of rats with cirrhosis. Zinc protoporphyrin, a selective HO inhibitor, ameliorates the hyperdynamic circulatory syndrome in rats with cirrhosis, suggesting the role of CO in arterial vasodilation.[31]

3.1.5. Angiotensin-(1–7)

A recent study has shown that systemic levels of the vasodilatory peptide angiotensin-(1-7) increase as liver fibrosis progresses.[32] In patients with cirrhosis at liver transplantation, the angiotensin-(1-7)/angiotensin II ratio is elevated in the splanchnic compared with the peripheral circulation, and splanchnic but not systemic angiotensin peptide levels negatively correlate with systemic vascular resistance.[32] Angiotensin II is cleaved by angiotensin-converting enzyme-2 to angiotensin-(1-7), which activates the G protein-coupled Mas receptor (MasR) and gives rise to vasodilation. The effects of angiotensin-(1-7)/MasR can be mediated by Gs protein and protein kinase A[33] or Akt-dependent pathways,[34] which stimulate eNOS phosphorylation and NO production.[35,36]

3.1.6. Adrenomedullin

Adrenomedullin is a potent vasodilatory peptide of which the circulating level is increased in patients with cirrhosis.[37] Adrenomedullin is implicated in increased NO release and plasma volume expansion, and its level is inversely correlated with peripheral resistance.[38] The implicated mechanisms include phosphorylation and activation of Akt and the increase of cGMP production.[39] Antiadrenomedullin antibody administration ameliorated the blunted contractile response to phenylephrine in aortas of rats with cirrhosis.[40]

3.1.7. Endocannabinoids

Endocannabinoids are a novel class of endogenous lipid ligands; anandamide is an example.[41] Endocannabinoids, through their binding to the CB_1 receptor, cause hypotension. Anandamide is increased in monocytes in cirrhosis, and CB_1 overactivation in mesenteric vasculature may contribute to splanchnic vasodilation and portal hypertension.[42] It has been hypothesized that in cirrhosis with bacterial translocation and endotoxemia, macrophages and monocytes release large amounts of endocannabinoids.[43] This leads to vasodilation via activating the CB1 receptors located in the vessels and perivascular nerves.[42] Domenicali et al[44] found that in rats with cirrhosis, anandamide dose-dependently relaxed mesenteric resistance arteries but not femoral arteries, providing evidence of a selective endocannabinoid action in the splanchnic circulation. Activation of endothelial CB_1 receptors increased NO production.[42] However, one study revealed that the hypotensive effect of anandamide was not influenced by NOS inhibitor or endothelial denudation, suggesting that NO does not play a major role in this response.[44] It is possible that CB_1 is not the only receptor implicated in endocannabinoid-mediated vasorelaxation. Indeed, anandamide can interact with the transient receptor potential cation channel subfamily V member 1 (TRPV1) receptor, which is expressed in perivascular nerves, as demonstrated by the finding that the concomitant use of CB_1 inhibitor and capsazepine, a TRPV1 blocker, almost fully abolished anandamide-induced vasodilatation, demonstrating that both CB_1 and TRPV1 receptors mediate the endocannabinoid-induced vascular effect in cirrhosis.[45] Furthermore, a previous study has shown that endocannabinoid-induced vasorelaxation also involved the activation of vascular K^+ channels in cirrhotic mesenteric arteries.[46]

3.2. Dysregulated response to vasoconstrictors

It is well known that NO overproduction participates in decreased vascular reactiveness to vasoconstrictors.[14,47] In addition to NO, recent evidence has indicated the roles of various vasoactive substances in such an abnormal vascular response.[48–69]

3.2.1. Endothelin-1

Endothelin-1 (ET-1), although known as a potent vasoconstrictor, also exerts various effects via different receptors: endothelin A (ET_AR) and B receptors (ET_BR1, ET_BR2).[48] ET-1 binds to ET_AR and ET_B2 to induce vasoconstriction, while its binding to ET_B1 leads to vasodilation.[49] A study of animals with bile duct ligation (BDL)-induced biliary cirrhosis

revealed that mesenteric ET-1 expression decreased after BDL. ET_BR expression increased in vascular smooth muscle cells and the microcirculation of mesenteric tissue, which was implicated in the attenuated vasoconstriction and enhanced vasodilation in splanchnic vasculature.[50] Furthermore, endothelin receptors can be desensitized by the phosphorylated G-protein-coupled receptor kinases (GRKs) and the binding of β-arrestin 2.[51] β-arrestin 2 and GRK2 desensitize ETRs thoroughly, ET_AR phosphorylation by GRK2 promotes the receptor binding to β-arrestin 2, which blocks the activation of G proteins and leads to rapid desensitization; in addition, independent of phosphorylation, GRK2 interacts with $G_{\alpha q}$ directly, which results in upcoupling of ETRs and their associated G proteins, thus impairing the ET-1 signaling.[52] A recent study revealed consistent finding that GRK2 expression was increased significantly in rats with cirrhosis, resulting in ET_AR desensitization and splanchnic vasodilatation.[50]

3.2.2. Sympathetic neurotransmitters

The sympathetic nervous system activates as a compensatory response to splanchnic and systemic vasodilation in cirrhosis and portal hypertension. Markedly increased norepinephrine concentrations in portal venous as compared to arterial and/or peripheral blood samples in humans[53] and animals with portal hypertension[54] have been noted. However, prolonged adrenergic stimulation leads to diminished responsiveness to subsequent exposure to catecholamines. This is the so-called ''desensitization''. Consequently, sustained sympathetic overactivation may lead to vascular desensitization, thereby aggravating splanchnic vasodilation in cirrhosis.[55,56]

3.2.3. Neuropeptide Y

Neuropeptide Y (NPY) is costored and coreleased with norepinephrine from sympathetic nerve terminals, inducing potentiation of α1-adrenergic vasoconstriction via G-protein-associated postsynaptic Y1 receptors.[57] NPY also sensitizes vascular smooth muscle response to norepinephrine.[58] The diminished capability of sympathetic nerves to release NPY in portal hypertensive splanchnic arteries and the regression of sympathetic innervation in the mesenteric arterial tree had been reported.[59] It is possible that the increased systemic norepinephrine level in cirrhosis[60] may enhance the α2-adrenergic presynaptic inhibition of NPY release.[61] Repeated stimulation of sympathetic nerves also leads to a depletion of NPY release.[62] Another linkage to decreased splanchnic NPY action is elevated dipeptidyl-peptidase IV (DPP-IV) activity in cirrhosis.[63] Dipeptidyl-peptidase IV proteolytically processes NPY[64] so that elevated DPP-IV activity may reduce NPY activity. Additionally, in the rat mesenteric bed, endothelins (ET-1, ET-3) inhibited NPY release.[65]

3.2.4. Angiotensin-II

The renin-angiotensin-aldosterone system (RAAS) is activated as a homeostatic response to counterbalance the vasodilatation in portal hypertension.[66] The vasoconstrictive effect of angiotensin-II is mediated via the type 1 receptor (AT_1R). However, increased expression of receptor desensitizing proteins, GRK2 and β-arrestin 2, has been implicated in vascular hyporeactivity to angiotensin-II in patients and rats with cirrhosis. The desensitization of AT_1R by GRK2 and β-arrestin 2 changed patterns of phosphorylated Ca^{2+}-sensitizing proteins and decreased Ca^{2+} sensitivity.[67] In addition, because receptor desensitization by GRKs and β-arrestins can be the result of strong receptor activation by their cognate ligands,[68,69] it is speculated that the elevated plasma concentrations of angiotensin-II in cirrhosis trigger the increased binding of β-arrestin-2 to AT_1 receptors in hypocontractile vessels.

3.3. Defective vascular contractile signaling

Although much evidence has addressed the roles of endothelium-derived vasoactive substances in splanchnic vasodilation, some studies found that endothelium denudation failed to improve vascular hyporeactivity to vasoconstrictors.[67,70] Other studies also found that despite an attenuated vascular reactivity to vasoconstrictors, the corresponding receptors were not downregulated or the receptor numbers and affinities were not altered.[71,72] Therefore, it is inferred that defects in vascular signal transduction may exist. Actually, *in vitro* and *in vivo* studies have indicated that vascular hyporeactivity can be attributed to changes downstream of the G-protein coupled receptors.[67,70]

It has been shown that mesenteric arteries from portal hypertensive rats had a reduced level of membrane-associated RhoA, probably reflecting a diminished activity of RhoA/Rho kinase pathway followed by increased activity of myosin light chain phosphatase and vasodilatation.[73] Another study provided evidence of defective Rho-kinase-mediated tone in mesenteric vessels of BDL rats.[74] In addition, Lin et al[75] reported that the formation of inositol trisphosphate after arginine vasopressin stimulation in rats with cirrhosis was substantially lower than that in sham-operated rats. The alteration of PKC also participates, at least partly, in the decreased vascular reactivity seen in rats with cirrhosis,[76] and NO plays a role in it.[77]

3.4. Vascular remodeling

Many diseases affecting the cardiovascular system are accompanied by structural modifications of the vascular wall, so-called vascular remodeling. This process, unfortunately, usually does not reverse, but rather exacerbates the original circulatory dysfunction.[78] A previous study indicated that the conductance vessels of rats with cirrhosis that underwent vascular remodeling. The most remarkable features are a decrease in the thickness and total area of the vascular wall and a reduction in the wall thickness/lumen diameter ratio, which is an estimation of the vascular contraction capability. Such an impairment was likely secondary to a decrease in the amount of vascular smooth muscle cells because a diminution in the number of nuclei in the medial layer of the vessels was noted.[79] Regarding the molecular mechanism, a reduction in ERK1/2 phosphorylation, matrix metalloproteinases

expression, and higher collagen IV and tissue inhibitor of metalloproteinase-2 abundance in cirrhotic vessels were noted, suggesting downregulation of cell growth, impaired ERK1/2 activation, and subsequent imbalance of extracellular matrix turnover.[78] These could be reversed by NO inhibition,[80] highlighting the pivotal role of NO in cirrhotic vascular remodeling. In another study, in mesenteric arteries from rats with cirrhosis, vessel strain was markedly elevated, indicating a reduction in vessel stiffness. The findings from strain-stress curve and elastic modulus in dependency on vessel stress also supported the involvement of structure-dependent factors. In addition, the cross-sectional area was significantly increased, indicating the hypertrophic outward remodeling.[81] These structural changes may maintain and aggravate the splanchnic vasodilation and increased flow in cirrhosis.

3.5. Angiogenesis

It is now recognized that the increase of portal inflow in portal hypertension is due not only to splanchnic vasodilation but also to enlargement of the splanchnic vasculature driven by angiogenesis.[82] In the splanchnic arteriolar territory, the newly formed vessels accommodate the increased blood flow to splanchnic organs associated with chronic portal hypertension. Unfortunately, the pathological angiogenesis further aggravates the splanchnic hyperdynamic circulation via increased blood flow and portal-systemic collaterals formation. The first *in vivo* evidence for an increased angiogenesis in the mesenteric microvasculature of rats with cirrhosis was shown by Geerts et al.[83] It has also been proved that growth factors are upregulated in portal hypertension, and contribute to the development and/or maintenance of increased splanchnic blood flow.[84]

3.5.1. Vascular endothelial growth factor

VEGF was purified and cloned in the 1980s based on its activities as a mitogen for endothelial cells.[85] Since then, it has become clear that VEGF plays a crucial role in angiogenesis. A previous study has indicated that the mesenteric VEGF and eNOS expressions increased in rats with cirrhosis and portal hypertension.[83] Actually, eNOS is a downstream mediator of VEGF.[86] Accumulating evidence further supports the beneficial effects of VEGF blockade in ameliorating splanchnic hyperdynamic circulation.[87] In the process of neovascularization, VEGF participates more in the initial stages via activating proliferation of endothelial cells and formation of endothelial tubules, whereas maturation of the newly formed vessels is mainly modulated by platelet-derived growth factor (PDGF), thereby stabilizing the vascular architecture of the new vessel.[88] Fernandez et al[84] have proved that combined inhibition of VEGF and PDGF signaling substantially reduced splanchnic neovascularization and pericyte coverage of neovessels, reflected by reductions in PP and superior mesenteric artery blood flow. Portosystemic collateralization was reduced as well.[84] The precise mechanism triggering VEGF-dependent angiogenesis in portal hypertension remains not fully elucidated. Indeed, several factors relevant to the pathogenesis of portal hypertension, including tissue hypoxia, cytokines, and mechanical stress, have been shown to upregulate VEGF expression,[89] and treatment strategies targeting at these upstream factors may be worth investigating.

3.5.2. Placental growth factor

Placental growth factor (PLGF) is a member of the VEGF family and a specific ligand for VEGF receptor 1. Unlike VEGF, PLGF plays a negligible role in physiological angiogenesis. Studies in transgenic mice revealed that the angiogenic activity of PLGF is restricted to pathologic conditions, without affecting healthy vessels.[90] A survey revealed that PLGF is upregulated in mesenteric tissues of mice with portal hypertension.[82] PLGF deficiency prevented portosystemic collateral formation and markedly ameliorated splanchnic hyperemia.[82] Furthermore, the PLGF knockout mice undergoing PVL did not develop mesenteric angiogenesis, and the mesenteric CD31 (an endothelial marker that is used as the index of angiogenesis) expression was significantly lower compared with that in wild-type PVL mice.[82]

3.5.3. Pigment epithelium-derived factor

The angiogenesis inducer VEGF and the endogenous negative regulator pigment epithelium-derived factor (PED) are unidirectionally upregulated and significantly correlated with pathological angiogenesis.[91] PEDF elevates as a compensatory response to avoid excessive pathological angiogenesis.[92] *In vivo* gene transfer of PEDF by adenoviral vectors (AdPEDF) in BDL rats during early stages of liver disease suppressed mesenteric pathological angiogenesis and lowered PP. Nevertheless, the antiangiogenic actions of AdPEDF were only modest when the adenovirus was given during the advanced stage.[93]

3.5.4. Vasohibin-1

An endogenous angioinhibitor, vasohibin-1 (VASH1), has been identified in a microarray analysis assessing genes upregulated by VEGF in endothelial cells.[94] Overexpressing VASH1 protein *in vivo* by gene therapy with an adenoviral vector (AdVASH1) substantially suppressed mesenteric pathological neovascularization and the severity of portosystemic collaterals in rats with cirrhosis. The inhibitory effect of AdVASH1 on angiogenesis could in part be explained by disruption of the VEGF-VASH1 negative-feedback loop with local downregulation of the excessive VEGF expression.[95]

4. Perspectives

Based on the encouraging investigations on molecular mechanisms of circulatory derangements in cirrhotic portal hypertension, it is anticipated that targeted treatment strategies may contribute to a significant advance for patients with cirrhosis also suffering from portal hypertension-related complications.

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