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Pathophysiology of Portal Hypertension

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Abstract

Portal hypertension is a major complication of liver disease, which results from a variety of pathological conditions that increase the resistance to the portal blood flow into the liver. The primary cause of portal hypertension in cirrhosis is an increase in intrahepatic vascular resistance due to massive structural changes associated with fibrosis and increased vascular tone in the hepatic microcirculation. As portal hypertension develops, the formation of collateral vessels and arterial vasodilation progress, which results in increased blood flow to the portal circulation. Eventually the hyperdynamic circulatory syndrome develops, leading to esophageal varices or ascites. This review article will summarize the factors that increase 1) intrahepatic vascular resistance and 2) the blood flow in the splanchnic and systemic circulations in liver cirrhosis. Finally, the future directions of basic/clinical research in portal hypertension will be discussed.

Keywords

Hyperdynamic circulation; fibrosis; cirrhosis; nitric oxide; lymphatic system; splenomegaly

Introduction

Portal hypertension is a detrimental complication resulting from obstruction of portal blood flow, such as cirrhosis or portal vein thrombosis. [1, 2] In liver cirrhosis, increased intrahepatic vascular resistance to the portal flow elevates portal pressure and leads to portal hypertension (Figure 1). Once portal hypertension develops, it influences extrahepatic vascular beds in the splanchnic and systemic circulations, causing collateral vessel formation and arterial vasodilation. This helps to increase the blood flow into the portal vein, which exacerbates portal hypertension and eventually brings the hyperdynamic circulatory syndrome. [1, 2] Consequently, esophageal varices or ascites develops. This review article will discuss recent advances in understanding of factors that contribute to: 1) an increase in intrahepatic vascular resistance and 2) an increase in blood flow in the splanchnic and systemic circulations, and 3) the future directions of basic/clinical research in portal hypertension.

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I. Intrahepatic circulation

An overview—The primary cause of portal hypertension in cirrhosis is an increase in intrahepatic vascular resistance. In cirrhosis, increased intrahepatic vascular resistance is a result of massive structural changes associated with fibrosis/cirrhosis and intrahepatic vasoconstriction[2-4]. It is reported that intrahepatic vasoconstriction accounts for at least 25% of increased intrahepatic vascular resistance. [5] Phenotypic changes in hepatic cells, such as hepatic stellate cells (HSCs) and liver sinusoidal endothelial cells (LSECs), are known to play pivotal roles in increased intrahepatic vascular resistance and have been studied intensively. This section summarizes important factors that increase intrahepatic vascular resistance in liver fibrosis/cirrhosis.

1. Endothelial cell dysfunction—LSECs are the first line of defense protecting the liver from injury[2], and the cells exert diverse effects on liver functions including blood clearance, vascular tone, immunity, hepatocyte growth[6], and angiogenesis/sinusoidal remodeling.[7, 8] Therefore, LSEC dysfunction could lead to impaired vasomotor control (primarily vasoconstrictive), inflammation, fibrosis, and impaired liver regeneration[1, 9], all of which facilitate the development of liver cirrhosis and portal hypertension.

Decreased vasodilators: Nitric oxide (NO) is likely the most potent vasodilator molecule known today. In cirrhotic livers, NO production/bioavailability is significantly diminished, which contributes to increased intrahepatic vascular resistance.[2, 9-12] At least two mechanisms explain the decreased NO production. First, the NO synthesizing enzyme endothelial NO synthase (eNOS) is inhibited by negative regulators (such as caveolin-1), which are up-regulated during cirrhosis; as a result, NO production decreases.[11] Details regarding eNOS regulation in liver cirrhosis can be found elsewhere.[2, 12] Second, oxidative stress is increased in cirrhosis. LSECs receive oxidative stress in response to a wide variety of agents, such as bacterial endotoxins, viruses, drugs, and ethanol.[13-15] During cirrhosis, increased superoxide radicals spontaneously react with NO to form peroxynitrite (ONOO-), an endogenous toxicant[16], thereby decreasing NOs bioavailability as a vasodilator.[13] Antioxidant molecules such as vitamin C[14], vitamin E[17], superoxide dismutase (SOD)[15, 18], and N-acetylcysteine[19], have been shown to ameliorate intrahepatic vascular resistance and portal hypertension.

Increased vasoconstrictors: In cirrhosis, not only are vasodilators decreased, but vasoconstrictors, such as thromboxane A2 (TXA_2), are also increased. TXA_2 is produced by the action of COX-1 in LSECs.[20] The activity of COX-1 increases in cirrhotic livers, which results in greater quantities of TXA_2 and thereby increased intrahepatic vascular resistance. Inhibition of TXA_2 by the prostaglandin H_2/TXA_2 receptor blocker, SQ-29548, or blocking COX-1 activity by the COX-1 inhibitor, SC-560, attenuates the increased intrahepatic vascular resistance.[20, 21] ET-1 is another important vasoconstrictor when it binds to receptors on HSCs.[22-24]

2. Activated hepatic stellate cells—HSCs are perisinusoidal and pericyte-like cells, and reside in the space between LSECs and hepatocytes. In response to liver injury, HSCs are activated and transformed into myofibroblasts, which start to express several pro-inflammatory and fibrotic genes. Importantly, HSCs become contractile in an activated state. [22, 25-27] Increased recruitment of these activated HSCs around newly formed sinusoidal vessels increases intrahepatic vascular resistance in cirrhosis (Figure 2). [8, 28, 29] Therefore, activated HSCs play a crucial role in the development of portal hypertension due to their contractile phenotype.

Furthermore, activated HSCs display a decreased response to vasodilators, such as NO.[30] In addition, ET-1,which is increased in cirrhosis, enhances the contractions of HSCs.[25-27] Increased ET-1 production and decreased NO production in cirrhotic livers, therefore, augment intrahepatic resistance to the portal blood flow through activated HSCs, which facilitates the development of portal hypertension. However, the manipulation of ET receptors with ET receptor antagonists is complex due to their differential vasoactive effects based on their cellular locations.

3. Angiogenesis in the liver—In portal hypertension, angiogenesis plays a crucial role in intrahepatic circulation. An increased number of vessels in the fibrotic septa and the surrounding regenerative nodules has been observed in cirrhotic livers.[31] Activated HSCs and/or other myofibroblasts such as portal myofibroblasts are thought to promote angiogenesis in liver cirrhosis. In fact, activated HSCs activate LSECs by releasing angiogenic factors, such as angiopoietin[8, 32, 33] and vascular endothelial growth factor (VEGF).[34]

Irregular flow patterns, which are generated as a result of splitting (or intussusceptive) angiogenesis, may contribute to an increase in intrahepatic vascular resistance. In splitting angiogenesis, the two opposing walls of a capillary stretch and connect to each other, forming an intraluminal pillar. The junctions of the opposing endothelial cells are restructured, and the growth of the pillar is promoted. Finally, the capillary splits into two new vessels.[35] It has been reported that conditional Notch 1 knockout mice develop splitting angiogenesis, nodular regenerative hyperplasia, and portal hypertension. LSECs from these knockout mice exhibit reduced endothelial fenestrae. These observations indicate that Notch 1 is necessary for LSEC fenestration, and that the absence of Notch 1 leads to pathological angiogenesis, the development of nodular regenerative hyperplasia, and portal hypertension.[36]

II. Extrahepatic circulation

An overview

Once portal hypertension develops, porto-systemic collateral vessels form. Blood from the digestive organs diverts into these collateral vessels, but portal blood flowing from the splanchnic circulation increases to compensate for the blood escaping into the collateral vessels. Increased portal blood flow exacerbates portal hypertension. Furthermore, arterial vasodilation in the splanchnic and systemic circulations observed in cirrhosis helps to increase the blood flow to the portal vein. Therefore, reducing the collateral vessel formation alone would not ameliorate portal hypertension. Inhibiting arterial vasodilation in the splanchnic circulation to reduce blood flow to portal vein together is important in the treatment of portal hypertension.[2] This section discusses the mechanisms of collateral vessel formation and arterial vasodilation in the splanchnic and systemic circulations in cirrhosis with portal hypertension.

1. Collateral vessel formation

Porto-systemic collateral vessels develop in response to an increase in portal pressure. These collateral vessels form through the opening of pre-existing vessels or angiogenesis[37, 38], and are known to cause serious complications, including variceal bleeding and hepatic encephalopathy.[2, 39, 40] A change in portal pressure is thought to be detected first by the intestinal microcircular vascular bed, followed by arteries of the splanchnic circulation.[41] Subsequently, these vascular beds generate various angiogenic factors, such as VEGF[42-44] and placental growth factor (PlGF)[45], which promote the formation of porto-systemic collaterals.

Studies in experimental models of portal hypertension and cirrhosis have shown that porto-systemic collaterals are reduced by 18 to 78% with treatment by anti-VEGFR2[46], a combination of anti-VEGF (rapamycin)/anti-PDGF (Gleevec)[47], anti-PlGF[45], apelin antagonist[48], sorafenib[49, 50], and a cannabinoid receptor 2 agonist.[51] However, the reduction of these collaterals does not necessarily decrease portal pressure because it does not substantially change the blood flow to the portal vein. Therefore, the concomitant mitigation of arterial vasodilation is also needed to reduce portal pressure.

2. Arterial vasodilation in the splanchnic and systemic circulations

Vasodilation—NO is the most important vasodilator molecule that contributes to excessive vasodilation observed in the arterial splanchnic and systemic circulations in portal hypertension. Experimental models of portal hypertension with or without cirrhosis have shown that other vasodilator molecules, such as carbon monoxide (CO), prostacyclin (PGIs), endocannabinoids, and endothelium-derived hyperpolarizing factor (EDHF) are also induced.[2, 9, 12] The identity of EDHF is currently unknown, and the candidates include arachidonic acid metabolites [epoxyeicosatrienoic acid (EET)], potassium ions (K^+), components of gap junctions, or hydrogen peroxide.[2]

An increase in portal pressure triggers eNOS activation and subsequent NO overproduction. Changes in portal pressure are detected at different vascular beds depending on the severity of portal hypertension.[41] A small increase in portal pressure is sensed first by the intestinal microcirculation and increases VEGF production with a subsequent increase in eNOS levels in the intestinal microcirculation. When portal pressure further increases and reaches a certain level, vasodilation develops in the arterial splanchnic circulation (i.e., the mesenteric arteries). It is postulated that mechanical forces including cyclic strains and shear stress, which are caused by an increased blood flow associated with an increased portal pressure, activate eNOS and lead to NO production.[41, 46, 52-54] Subsequently, vasodilation develops in the arterial systemic circulation (i.e., the aorta).

Hypocontractility—Hypocontractility, decreased contractility to vasoconstrictors, is a characteristic of the arterial splanchnic and systemic circulations in portal hypertension. This phenomenon occurs largely due to the presence of excessive vasodilator molecules (i.e., NO) and the resulting excessive arterial vasodilation, but is to some degree attributable to various molecules produced in smooth muscle cells and neurons. Those molecules include endocannabinoids (vasodilators)[55, 56], neuropeptide Y[57], urotensin II[58, 59], angiotensin[60], and bradykinin[61, 62] (all vasoconstrictors), with the vasodilators increased and the vasoconstrictors decreased.

Neural factors—Neural factors are postulated to be involved in the development of the hyperdynamic circulatory syndrome, especially through the sympathetic system.[57, 63, 64] It is reported that sympathetic nerve atrophy/regression observed in the mesenteric arteries of portal hypertensive rats contributes to vasodilation and/or hypocontractility of those arteries.[65, 66] The role of neural factors in decreased contractile responses has not yet been fully understood and is an important area to be explored.

Structural changes of arteries—The thinning of arterial walls is observed in the splanchnic and systemic circulations of rats with cirrhotic livers.[67, 68] While this arterial thinning results from hemodynamic changes caused by portal hypertension, it may also sustain arterial vasodilation and worsen portal hypertension.[2, 24] While NO plays a role at least in part, the molecular mechanisms responsible for arterial thinning remain to be fully elucidated.

III. Future directions

An overview

Four important areas in the study of portal hypertension that have not been sufficiently explored are specified.

1. Microflora/bacterial translocation

In recent years, an accumulating body of evidence suggests the importance of gut microflora and bacterial translocation for the pathogenesis of a variety of diseases. Due to the anatomically-close location and the connection through the vascular system, the liver is continuously exposed to microbial products from the gut.[69] It has been known that bacterial translation is closely related to the development of ascites.[70] In addition, small changes in portal pressure are first sensed in the intestinal microcirculation. Increased portal pressure caused by portal hypertension may influence the gut–liver axis, further advance the pathology of liver fibrosis/cirrhosis, and exacerbate portal hypertension itself. Therefore, gut microflora may have an important role in a pathological loop that develops and maintains portal hypertension. Additionally, microflora may influence cytokine/chemokine production in the liver, which may also exacerbate portal hypertension.

2. Stem cell therapy

Stem cell therapy has received considerable attention as an alternative to liver transplantation. Indeed, studies have shown that stem cell transplantation improved liver functions in cirrhotic patients[71, 72] as well as experimental models of liver cirrhosis.[73, 74] While stem cell therapy has shown promising effects on the amelioration of liver fibrosis and portal hypertension, more studies are still needed.

3. The lymphatic system

The lymphatic system plays a central role in ascites and edema formation.[75] Further, an association between lymphangiogenesis and portal hypertension has been reported.[76] However, the detailed role and mechanisms of the lymphatic system in liver cirrhosis and portal hypertension are largely unknown, and these are important areas to be explored.[77, 78]

4. Splenomegaly

Spleen stiffness has recently received considerable attention as an indicator of portal hypertension[79] because it can be examined by non-invasive imaging systems such as transient elastrography[80] and acoustic radiation force impulse imaging.[79, 81] Some studies also suggest that spleen stiffness could predict the presence of varices[79-81] or ascites.[82] An experimental model of cirrhosis with portal hypertension has demonstrated that portal pressure positively correlated with the spleen size.[42]

In addition, a study using rats with partial portal vein ligation (PVL) showed that fibrosis and angiogenesis in the spleen was accompanied with splenomegaly induced by PVL, and that administration of rapamycin, an immunosuppressive agent, reduced splenomegaly as well as fibrosis and angiogenesis in the spleen.[83] Currently, the detailed mechanisms of how portal pressure induces splenomegaly remain to be fully elucidated.

Summary/Conclusion

With our knowledge of vascular biology, our understanding of the pathogenesis of portal hypertension has significantly advanced, revealing how vascular abnormalities both inside and outside the liver contribute to portal hypertension.[84] To ameliorate portal hypertension,

first and foremost, a decrease in intrahepatic vascular resistance in cirrhotic liver is needed. Therefore, an increased production of vasodilator molecules in LSECs and a decrease in HSC contraction are important. For example, induction of apoptosis of enhanced activated HSCs[85, 86], thereby decreasing contractile HSCs, could be a useful therapeutic strategy to decrease portal pressure.

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Key Points

- The primary cause of portal hypertension in liver cirrhosis is increased intrahepatic vascular resistance.
- A reduction of intrahepatic vascular resistance could ameliorate portal hypertension.
- Arterial vasodilation in the splanchnic and systemic circulations worsens portal hypertension.

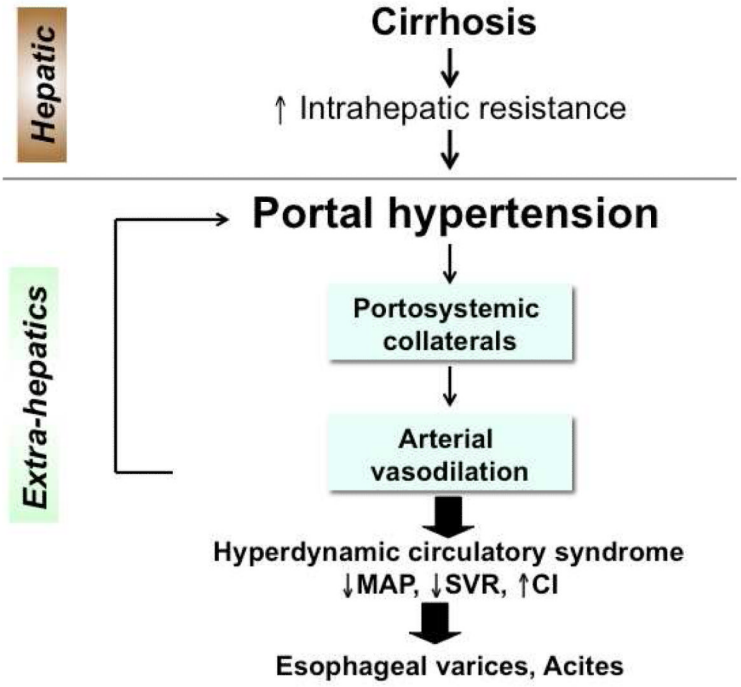

Figure 1.
Portal hypertension leads to the development of the hyperdynamic circulatory syndrome, characterized by decreased mean arterial pressure (MAP), decreased systemic vascular resistance (SVR) and increased cardiac index (CI).

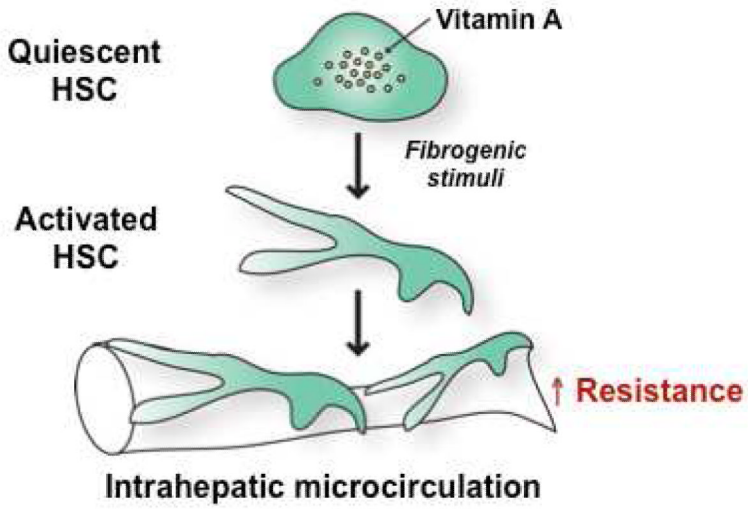

Figure 2. Activated hepatic stellate cells (HSCs) in liver cirrhosis increase intrahepatic vascular resistance

Quiescent HSCs are vitamin A storage cells and found in normal livers. In response to fibrogenic stimuli, such as transforming growth factor beta, HSCs are activated to become myofibroblasts, which exhibit a contractile and fibrogenic (collagen-producing) phenotype. These activated HSCs, located underneath liver sinusoidal endothelial cells, exert a contractile effect on the hepatic microcirculation, resulting in an increase in intrahepatic resistance.