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PORTAL HYPERTENSION (K BROWN, SECTION EDITOR)

Pathogenesis of Portal Hypertension: Extrahepatic Mechanisms

Mercedes Fernandez[1] · Marc Mejias[1] · Ester Garcia-Pras[1] · Javier Gallego[1] · Nuria Pell[1] · Marta Ramirez[1] · Salvador Naranjo-Suarez[1] · Alba Barrachina-Catala[1] · Angiogenesis in Liver Disease Research Group

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Abstract Chronic liver diseases, including hepatic cirrhosis, chronic hepatitis, alcoholic liver disease, and hepatocellular carcinoma, are one of the commonest causes of death and liver transplantation in adults worldwide. They are accompanied by profound disturbances that are not limited to the intrahepatic circulation, but involve also the splanchnic and systemic vascular beds. These hemodynamic disturbances are responsible for the development of portal hypertension, the most frequent and severe of cirrhosis. This syndrome is characterized by a pathological increase of blood pressure in the portal vein and concomitant increases in splanchnic blood flow and portosystemic collateral vessel formation. Increased blood flow in splanchnic organs draining into the portal vein augments in turn the portal venous inflow. Such increased portal venous inflow perpetuates and exacerbates portal pressure elevation and determines the formation of ascites during chronic liver disease. In addition, portosystemic collateral vessels include the gastroesophageal varices, which are particularly prone to rupture causing massive gastroesophageal bleeding. Collateral vessels are also responsible for other major consequences of chronic liver disease, including portosystemic encephalopathy and sepsis. Extrahepatic mechanisms are clearly of major importance for disease progression and aggravation of the portal hypertensive syndrome. Accordingly, most of the therapies currently used in portal hypertension do not act inside the liver but they actually target the increased splanchnic blood flow. This paper reviews the consequences of the splanchnic circulatory abnormalities in portal hypertension and the complex signals capable of increasing vasodilatation, hyporesponsiveness to vasoconstrictors and angiogenesis in the splanchnic vascular bed and the portosystemic collateral circulation in this pathological setting.

Keywords Vasodilatation · Hypocontractility · Gastroesophageal varices · Angiogenesis · Mesenteric vascular bed · Portosystemic collateral circulation · Cirrhosis

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✉ Mercedes Fernandez
mercefernandez@ub.edu

Angiogenesis in Liver Disease Research Group

[1] IDIBAPS Biomedical Research Institute, CIBERehd, University of Barcelona, Rossello 153, 08036 Barcelona, Spain

Introduction

Portal hypertension is one of the most significant complications of chronic liver diseases, which are leading causes of death and liver transplantation worldwide [1–3]. It is characterized by a pathological increase in blood pressure in the portal vein and concomitant increases in splanchnic blood flow and formation of portosystemic collateral vessels, which are responsible for life-threatening consequences like gastroesophageal variceal bleeding, portosystemic encephalopathy, and sepsis [1–4]. The portal hypertensive syndrome is initiated by an increase in vascular resistance to portal blood flow at a presinusoidal (portal vein thrombosis), sinusoidal (cirrhosis of the liver, chronic hepatitis, alcoholic liver disease, and hepatic schistosomiasis), or postsinusoidal level (Budd-Chiari syndrome). The dominant cause of portal hypertension relates to liver cirrhosis, which increases resistance through the hepatic sinusoids due to distortion of the liver vascular architecture caused by fibrosis, scarring, and nodule formation, as well as by hepatic sinusoidal cellular alterations, with imbalance between vasodilators and vasoconstrictors, promoting sinusoidal constriction [5–7]. Another major driver of portal hypertension locates extrahepatically and is an increased

splanchnic blood flow. The combination of both factors, increased resistance and increased flow, determines the final increase in portal pressure [1]. This article reviews current concepts of the pathogenic role and mechanisms leading to the increased splanchnic blood flow in portal hypertension in order to provide a rational basis for the establishment of new and more effective therapeutic and prophylactic strategies. This is of particular significance since the management of patients with chronic liver disease and advanced portal hypertension continues to be a critical and prevalent clinical problem, for which few therapeutic options are available. New and effective therapeutic strategies to improve the prognosis of cirrhotic patients are therefore urgently needed.

Why Is Increased Splanchnic Blood Flow Important?

Maintenance and Aggravation of Portal Hypertension

Changes in the splanchnic circulation are critical components of the portal hypertensive syndrome. Thus, blood flow in splanchnic organs draining into the portal vein tends to increase in cirrhosis, particularly in advanced stages of portal hypertension [8, 9]. Consequently, portal venous inflow is enhanced, further perpetuating and exacerbating the portal pressure elevation [10, 11]. This is explained by the Ohm's law, according to which the portal pressure gradient (i.e., the difference between portal pressure and the inferior vena cava pressure) augments as a result of the interrelationship of portal blood flow and the vascular resistance that opposes that flow ($\Delta P = Q \times R$).

Formation of Portosystemic Collaterals

The development of portosystemic collateral vessels, which derive portal blood to the systemic circulation bypassing the liver, is one of the most clinically threatening complications of portal hypertension and cirrhosis. The most common collateral vessels are the gastroesophageal varices, which are fragile and particularly prone to leak blood and even rupture, causing upper gastrointestinal tract bleeding [12]. This hemorrhage is often torrential and difficult to staunch, and, despite many advances made in this field, it continues to be the most dramatic and lethal complication of portal hypertension [4, 13, 14]. Furthermore, because portosystemic venous shunts bypass the liver, noxious substances (drugs, toxins, hormones, bacterial products, nitrogen containing compounds, including ammonia) that are normally metabolized by the liver can escape from collaterals to the central venous system, leading to other potentially lethal consequences, such as portosystemic encephalopathy, spontaneous bacterial peritonitis, or systemic infections. Additionally, portosystemic shunting could be in part responsible for the raised systemic levels of vasodilators, such as glucagon [15]. We now know that collateral vessels and varices are active structures since their development and progression depends on the dynamic interplay of distinct pathophysiological events, including vasodilation, vascular remodeling, angiogenesis, hemodynamic pressure stress, various factors released from all involved cells plus still unknown variables to be included.

Systemic Hyperdynamic Circulation

Splanchnic hyperdynamic circulation in portal hypertension and cirrhosis is characteristically associated with systemic hyperdynamic circulation, with reduced arterial pressure and peripheral resistance and increased cardiac output. Peripheral vasodilation is thought to play a major role in the activation of endogenous neurohumoral systems leading to sodium retention, expansion of plasma volume, and accumulation of ascites, spontaneous bacterial peritonitis, and systemic infections, eventually leading to multiorgan syndrome failure in patients with cirrhosis [1–3].

How Is Splanchnic Blood Flow Increased?

The current understanding is that the increase in splanchnic blood flow is a highly complex multifactorial process that involves different but complementary mechanisms: mesenteric arteriolar vasodilation, decreased vascular responsiveness to endogenous vasoconstrictors, and also the de novo formation and maturation of new blood vessels, through active neoangiogenesis [10, 11]. These mechanisms may be driven by similar environmental variables and work in a coordinated manner with the final common goal of increasing blood flow in splanchnic organs. This feature also highlights the potential clinical relevance of applying combination therapies acting both on prevention/regression of new splanchnic vessels by antiangiogenic agents and on modulation of vasomotor dynamics by vasoactive substances.

Vasodilation

Glucagon

Many studies have shown that an increased amount of humoral vasodilators of splanchnic origin, mainly glucagon, contributes to the systemic and splanchnic vasodilation and the vascular hyporesponsiveness to vasoconstrictors observed in portal hypertension. Glucagon undergoes hepatic metabolism and may accumulate in the systemic circulation because of reduced hepatic uptake due to liver disease and/or portosystemic shunting [15]. Hyperglucagonism in portal hypertension may also be due to hypersecretion from pancreatic α-cells [16].

Nitric Oxide

The endothelium-derived vasodilator nitric oxide (NO) plays a key role regulating splanchnic and systemic hemodynamics in portal hypertension. Unlike liver microcirculation where NO production is deficient, in the splanchnic vasculature, there is an increased synthesis of NO due to increased expression and activity of endothelial NO synthase (eNOS) [17–20], highlighting the paradox of portal hypertension with common pathways affected by different tissue-dependent alterations, which poses significant challenges for providing adequate treatment because what can be beneficial for one territory could be detrimental for the other and vice versa [21]. NO causes vasodilation through stimulation of soluble guanylyl cyclase to generate cGMP in vascular smooth muscle cells. Major stimuli for eNOS in portal hypertension include vascular endothelial growth factor (VEGF), shear stress, and inflammatory cytokines [22–24]. The enzymatic activity of eNOS is regulated by tetrahydrobiopterin, which is a known cofactor and enhancer of eNOS activity that increases during bacterial translocation [24]. Binding of eNOS to the molecular chaperone heat shock protein-90 [25], and the eNOS phosphorylation by Akt [19] are additional mechanisms of the upregulation of eNOS in portal hypertension. Neuronal NOS [26, 27] and the inducible NOS [28] could also contribute to splanchnic vasodilation in portal hypertension [28]. Interestingly, NO is also implicated in the vascular hyporeactivity to vasoconstrictors in portal hypertension and could also facilitate vascular angiogenesis [22, 29–35]. Therefore, selective modulation of NO production may be a promising strategy for preventing the development of splanchnic hyperdynamic circulation in portal hypertension.

Carbon Monoxide

Carbon monoxide (CO) is a product of the heme oxygenase (HO) reaction, which catalyzes the enzymatic conversion of heme into CO, biliverdin, and ferrous iron. CO shares many structural and biological properties with NO and has been shown to have important cellular functions. CO production is increased in splanchnic organs during portal hypertension due to HO-1 induction [36, 37] and contributes to the circulatory abnormalities of this syndrome, including splanchnic vasodilatation and hyporeactivity to vasoconstrictors [37, 38]. It also plays a role facilitating pathological angiogenesis [39]. But, HO-1 is also a stress-inducible enzyme, which can be expressed and upregulated by virtually all cells facing contact with noxious stimuli. Hence, HO-1 induction can be regarded as a general response to oxidant stress. First, HO enzymatically breaks down heme, thereby mitigating the hazardous cellular effects of this prooxidant [39]. Second, biliverdin and its reduced product bilirubin are both potent free radical scavengers with antioxidant and anti-inflammatory properties [39]. Third, iron released from heme enhances the synthesis of ferritin, which additionally has antioxidant capabilities. The precise mechanisms whereby HO-1 gene expression is upregulated in portal hypertension are still unknown. HO-1 is transcriptionally activated by numerous physical or chemical factors, some of which may be increased during portal hypertension, including cytokines, endotoxin, oxidative stress, and shear stress.

Prostacyclin

Prostacyclin is an endogenous cyclooxygenase (COX)-derived vasodilator prostanoid produced by vascular endothelial cells that causes vascular smooth muscle relaxation by activating adenylate cyclase and augmenting the intracellular level of cyclic AMP. Experimental studies clearly show that prostacyclin contributes to splanchnic vasodilatation and vascular hypocontractility in portal hypertension [40, 41]. The production of prostacyclin can be stimulated by factors similar to those that stimulate the constitutive isoform of NO synthase (eNOS), including shear stress and proinflammatory substances. Interestingly, prostacyclin synthesis may also be stimulated in endothelial cells by microparticles [42]. These microparticles are small vesicles that originate from plasma membranes of endothelial cells, platelets, leukocytes, and erythrocytes and circulate in the peripheral blood. Circulating microparticles can transfer antigens and receptors to cell types that are different from their cell of origin, being an important mechanism of intercellular communication. They can play a significant role in vascular function and inflammation by modulating NO and prostacyclin production in endothelial cells, and stimulating cytokine release and tissue factor induction in endothelial cells, as well as monocyte chemotaxis and adherence to the endothelium. Increased levels of microparticles have been found in portal hypertension. From a practical point of view, microparticles could be considered to be potential candidates for targeted therapies.

Endocannabinoids

Previous studies have highlighted the importance of endogenous cannabinoids in the pathogenesis of hyperdynamic circulation in cirrhosis and portal hypertension. They can promote vasodilatation acting on cannabinoid CB1 receptors [43, 44] and CB2 receptors [45], through mechanisms that can be NO-dependent [43, 45] or -independent [44].

Hypocontractility

Vascular hypocontractility, decreased contractility to vasoconstrictors, is a characteristic of the splanchnic and systemic circulations in portal hypertension and cirrhosis [46]. This phenomenon occurs largely because of the presence of

excessive vasodilator molecules (ie, NO) and the resulting excessive arterial vasodilation. But it is also to some degree attributable to specific alterations in the normal pathways that lead to contraction of vascular smooth muscle cells in splanchnic vessels. These disturbances include defective Rho-kinase signaling, and desensitization of the vasoconstrictor receptors by phosphorylation and binding to beta-arrestin [46, 47]. In addition, it has been recently shown that the activity of the angiotensin-converting-enzyme-2 is increased in splanchnic vessels during portal hypertension leading to increased local production of the vasodilator Ang-(1–7), activation of the Mas receptor and thereby smooth muscle cell relaxation, which further contributes to vascular hypocontractility [48]. The reactivity to the adrenergic vasoconstrictor neurotransmitter noradrenaline could also be altered due to atrophy of mesenteric sympathetic innervation [49], and subsequent neurotransmission inhibition and vasoconstriction impairment [50, 51].

Angiogenesis

Angiogenesis refers to new microvessel formation via sprouting or splitting from preexisting vessels. Upon exposure to proangiogenic signals like vascular endothelial growth factor (VEGF), endothelial cells activate, become mobile and protrude filopodia, forming tip cells, which initiate new sprouts [52, 53]. Stalk cells follow tip cells, proliferate to support sprout elongation, and establish a vessel lumen [54]. Microvessel loops are then formed when tip cells anastomose with neighboring sprouts. After the microvessel forms a lumen, endothelial cells secrete growth factors, such as platelet-derived growth factor (PDGF), to attract pericytes and smooth muscle cells that stabilize the nascent vessel. Endothelial cells and pericytes become sensitized to the chemotactic and proliferative effects of the various growth factors by upregulating their receptors, predominantly VEGF receptor-2 and PDGF receptor-β [55].

In the context of portal hypertension and chronic liver disease, angiogenic phenomena represent a critical and clinically important pathological hallmark, participating to the development of increased splanchnic blood flow and portosystemic collateralization [10, 56]. Neovascularization and splanchnic vasodilatation work in a cooperative fashion to maintain and perpetuate the syndrome of portal hypertension. Angiogenesis also play a pivotal feature in the liver, contributing to the establishment and maintenance of an abnormal architecture distinctive of the cirrhotic liver, which in turn is intimately linked to fibrogenesis and inflammation [57, 58]. Accordingly, inhibition of neovessel formation using different strategies translates into multifold beneficial effects in portal hypertension and chronic liver disease, attenuating portal pressure elevation, splanchnic hyperemia, portosystemic collateralization, and liver fibrogenesis, as it has been seen in animal models [59–61, 62••, 63].

Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) is the main factor implicated in angiogenesis associated with cirrhosis and portal hypertension. Thereby, the VEGF signaling pathway promotes neovascularization in cirrhotic liver and mesentery in a portal hypertensive context, increasing the splanchnic blood flow and contributing to the development of portosystemic collateral vessels, intrahepatic fibrosis, and inflammation [10, 56, 61, 63, 64]. In addition to promoting pathologic angiogenesis and remodeling in splanchnic, portocollateral, and intrahepatic circulations [10, 56], excessive VEGF production also contributes to the splanchnic vasodilation and hypocontractility that characterizes portal hypertension through augmentation of NO production [22]. These pathogenic processes synergistically contribute to increase splanchnic blood flow and portosystemic collateralization, sustaining and aggravating portal hypertension. In fact, some studies showed that the blockade of VEGF or its receptor (VEGFR2) was effective in decreasing portal pressure and mesenteric neoangiogenesis, and therefore, reducing splanchnic blood flow and portosystemic collateralization [61, 62••, 63] accompanied by attenuation of liver fibrosis [60, 65, 66••, 67]. Although these studies demonstrated that VEGF signaling could be a good target for clinical application in portal hypertension and cirrhosis, clinical trials have been disappointing because undesirable effects like endothelial injury, vascular leakage, and enhanced bleeding risk in patients with hepatocellular carcinoma [68]. It must be taken into account that these anti-VEGF approaches inhibit also the physiological VEGF [69], which is essential in maintenance of vascular homeostasis of healthy vessels and other physiological processes that usually occur in the adult, as wound healing or tissue repair [70]. Accordingly, it is critical achieve a specific inhibition against pathological angiogenesis and pathological levels of VEGF without affecting physiological levels to maintaining homeostasis of preexisting vasculature.

Platelet-Derived Growth Factor

During portal hypertension, other growth factors, besides VEGF, are upregulated in the mesentery and cirrhotic liver. Among them, platelet-derived growth factor (PDGF) and its receptor, PDGFR- β, have been shown to play an important role in the excessive neovascularization of these vascular beds [71–73]. Thus, PDGF is secreted by endothelial cells during angiogenesis and acts paracrinically inducing the recruitment of PDGFR-β-positive pericytes that will increase neovessel stabilization and maturation by acting as supportive vascular smooth muscle cells. The importance of PDGF is highlighted by the synergistic benefit in reducing circulatory abnormalities in portal hypertension observed in a combined antiangiogenic treatment using VEGF and PDGF inhibitors

simultaneously [63]. This is due to an increased exposition of endothelial tubes mediated by the removal of pericyte coverage by anti-PDGF molecules, which makes endothelial cells more susceptible to anti-VEGF treatment. Thus, the use of low doses of the multikinase inhibitor sorafenib, used for the treatment of hepatocellular carcinoma [68], which targets simultaneously VEGFR-2, PDGFR-β, and Raf kinase, significantly reduces portosystemic collateralization, hyperdynamic splanchnic circulation, intrahepatic fibrosis, and portal pressure in experiments in rats with intra- and extrahepatic portal hypertension [59, 60, 62••], with potential beneficial effects also in humans [74].

Placental Growth Factor

Experimental studies have highlighted the potential benefits of antagonization of placental growth factor (PlGF). PlGF belongs to the VEGF family and is upregulated in portal hypertension, but it is not required either for physiologic angiogenesis or vascular homeostasis, but amplifies VEGF activity in pathologic conditions. Accordingly, targeting PlGF has shown promise in improving the disturbances of portal hypertension and cirrhosis in animal models [66••, 67].

Vasohibin-1

Endogenous inhibitors of angiogenesis may also play an important role in portal hypertension antiangiogenic therapies. Vasohibin-1 is a novel endogenous inhibitor selectively induced by VEGF as a consequence of a specific negative-feedback mechanism. An ectopic and non VEGF- regulated overexpression of vasohibin-1 by adenoviral-mediated gene transfer disrupted the VEGF-vasohibin-1 negative-feedback loop, reducing VEGF production to steady-state levels enough to guarantee vascular homeostasis or physiological angiogenesis associated with wound healing. This experimental approach resulted on an efficient suppression of pathological neovascularization, which translated into reduction of portal pressure and portosystemic collateral vessel formation and attenuation of intrahepatic fibrogenesis in cirrhotic rats [75]. These results suggest that supplementing with VASH1 might signify a novel and promising therapeutic strategy in chronic liver disease dealing [75, 76].

PEDF

Pigment epithelium derived factor (PEDF) was first described in the 1980s as a neurotrophic factor, but its further characterization has revealed that it also possesses strong antiangiogenic activity. This latter feature has turned PEDF into a very interesting factor due of its possible use in therapeutic strategies to treat pathologies with a neovascular component. Recent studies in experimental models of cirrhosis have shown that PEDF is upregulated in the liver and the mesentery, in parallel with VEGF, and both coinciding with mesenteric neovascularization and liver fibrogenesis in time and space [77], suggesting that PEDF overexpression might respond to a compensatory mechanism aimed at counteracting the proangiogenic effects of VEGF. In the aforementioned study, PEDF overexpression by adenovirus-mediated gene transfer upsets the balance between VEGF and PEDF in favor of inhibition and angiogenesis, resulting in a reduction of pathologic neovascularization and a decrease in portal pressure. These results suggest that exogenous PEDF supplementation during the early phase of cirrhosis could be a promising therapeutic tool for the prevention of disease progression and hence decreasing the risk of developing overt liver cirrhosis in patients [77, 78]. Of note, a prominent advantage of using endogenous inhibitors of angiogenesis, such as PEDF, is that these molecules would be less likely to activate drug resistance genes and, therefore, may become a promising breakthrough for effective antiangiogenic therapy.

CPEB Proteins

Our research group has recently identified a new mechanism of regulation of pathologic VEGF expression and angiogenesis through sequential and non-redundant functions of two members of the family of cytoplasmic polyadenylation element binding proteins, CPEB1 and CPEB4 [79••]. Cytoplasmic polyadenylation element binding (CPEB) proteins are RNA-binding proteins that bind to and regulate the expression of a specific group of messenger RNA (mRNAs), which have, on their non-coding 3′-untranslated regions (3′UTR), some sequences named cytoplasmic polyadenylation elements (CPEs) [80–82]. We have found that one of these CPEB-regulated mRNAs is VEGF mRNA. Upon portal hypertension and cirrhosis induction, there is a rapid upregulation and activation by autophosphorylation of the serine/threonine kinase Aurora kinase-A in the mesentery and the liver, which could be triggered by hemodynamic forces, shear and mechanical stress, increased blood flow, cytokines, and vascular growth factors, which may increase within the precise neovascularization microenvironment. Activated Aurora kinase-A, in turn, phosphorylates and activates CPEB1 [83–85]. Activation of CPEB1 then promotes alternative nuclear processing within 3′ UTRs of VEGF and CPEB4 mRNAs, resulting in deletion of translation repressor elements from mature transcripts. The subsequent overexpression of CPEB4 promotes cytoplasmic polyadenylation of VEGF mRNA, increasing its translation and generating high levels of VEGF [79••]. Importantly, this CPEB-mediated regulatory mechanism

operates only in pathologic conditions, when CPEB1 and CPEB4 are overexpressed as we have seen in portal hypertension and cirrhosis, being essential for pathologic angiogenesis but dispensable for physiologic neovascularization [79••]. Thus, targeting CPEBs could lead to safer treatment outcomes by specifically reducing excessive pathologic VEGF production instead of indiscriminately perturbing both pathologic and physiologic VEGF synthesis, minimizing potential adverse side-effects. Consistent with this notion, CPEB depletion reduces portosystemic collateralization and mesenteric neovascularization and attenuates the progression of the portal hypertensive syndrome in mice, without affecting the normal vasculature or physiological angiogenesis [79••]. Therefore, these studies underscore CPEBs as attractive targets for portal hypertension and chronic liver disease therapy. These findings may also have broader implications in other pathological conditions involving dysregulated angiogenesis including cancer.

Vascular Stem/Progenitor Cells

Most research in the neovascularization field has focused on angiogenesis, the formation of neovessels from activation and proliferation of mature endothelial cells in existing vasculature. However, it is now evident that alternative vascularization mechanisms may occur postnatally, including vasculogenesis, the de novo formation of vessels out of vascular stem/progenitor cells, which historically was thought to occur exclusively during embryological development. Indeed, recent studies from our group have identified vascular stem/progenitor cells residing dormant in the vascular wall of postnatal mesenteric vessels under normal conditions, but possessing sphere-forming ability and proliferative potential, producing large numbers of daughter cells (i.e., proliferative progenitors or transit-amplifying cells) that differentiate toward either endothelial cells or smooth muscle cells when activated by injury stimuli, such as upon portal hypertension and cirrhosis induction [86••]. Importantly, these cells structurally and functionally contribute to abnormal neovessel formation indicating that abnormal neovascularization in this pathological setting might conceivably be a heterogeneous process, arising through a combination of both angiogenesis and vasculogenesis. Mechanistically, we also found that the RNA-binding protein CPEB4 is an important factor responsible for the proliferative activity of stem/progenitor cell progeny [86••], adding therefore another facet to the "proangiogenic" activity of CPEB4, namely regulation of cell proliferation in vascular stem/progenitor cell descendants, which could coordinately act with the recently demonstrated VEGF-dependent function [79••]. These findings may also have direct translational implications. Thus, therapeutic targeting of both vascular stem cell-derived neovascularization (vasculogenesis) and new vessel growth mechanisms that utilize non-stem cell constituents (angiogenesis) may effectively block abnormal neovessel formation and improve antiangiogenic therapeutics.

Conclusions

Chronic liver diseases, including liver cirrhosis, are major causes of death worldwide, but their therapeutic options still remain severely limited. The only cure for advanced liver disease is hepatic transplant; however, donor livers are a scarce resource, and only few patients on the transplant waiting list receive one, but many people die before they can get a new liver. Deciphering of the molecular and cellular mechanisms underlying the pathophysiology of portal hypertension will certainly translate into development of novel treatment strategies to improve the therapeutic outcome in patients suffering from chronic liver disease.

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Compliance with Ethical Standards

Conflicts of Interest MF, MM, EGP, JG, NP, MR, SNS, and ABC declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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