EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Intrahepatic angiogenesis and sinusoidal remodeling in chronic liver disease: New targets for the treatment of portal hypertension?

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Portal hypertension accounts for the majority of morbidity and mortality that is encountered in patients with cirrhosis. Portal hypertension is initiated in large part through increases in intrahepatic vascular resistance. Fibrosis, regenerative nodule formation, and intrahepatic vasoconstriction are classical mechanisms that account for increased intrahepatic vascular resistance in cirrhosis. Recent data suggest that intrahepatic angiogenesis and sinusoidal remodeling could also be involved in sinusoidal resistance, fibrosis, and portal hypertension. While angiogenesis is defined as the formation of new vessels deriving from existing ones, sinusoidal remodeling in its pathological form associated with cirrhosis is characterized by increased mural coverage of vessels by contractile HSC. Most attention on the mechanisms of these processes has focused on the liver sinusoidal endothelial cell (SEC), the hepatic stellate cell (HSC), and the paracrine signaling pathways between these two cell types. Interventions that target these vascular structural changes have beneficial effects on portal hypertension and fibrosis in some animal studies which has stimulated interest for pursuing parallel studies in humans with portal hypertension.

Mechanisms of portal hypertension

Portal hypertension is a major complication of cirrhosis, representing a leading cause of death or cause for liver transplantation. While portal hypertension affects multiple organs and vascular beds, its pathogenesis in large part originates from increases in intrahepatic vascular resistance and is further perpetuated by changes in the systemic circulation that culminate in an increased portal inflow; this has been reviewed in detail elsewhere [1]. In particular, mechanisms responsible for the increase in sinusoid resistance have been identified to include a mechanic factor which is a direct consequence of fibrosis deposition and a dynamic component related to endothelial dysfunction, deficient intrahepatic nitric oxide (NO) production, increased vasoconstrictor production, and other factors that promote increased contraction of hepatic stellate cells (HSCs) [2–7]. While vascular structural changes are well established pathological hallmarks of chronic cirrhosis [8,9] some recent data suggest that these structural changes could be reversible and could also be major determinants in resistance and pressure regulation. Vascular structural changes within the intrahepatic circulation that have received attention more recently include angiogenesis and sinusoidal remodeling. Angiogenesis is a dynamic process leading to the formation of new vessels from pre-existing blood vessels [10,11]. Angiogenesis occurs in almost all organs and is a critical step in a number of physiological and pathological conditions associated with tissue damage, wound healing, and remodeling. On the other hand, vascular remodeling occurs in a tissue in a disease context specific manner and is characterized broadly by changes in vessel structure [10]. In liver, vascular remodeling occurs within the hepatic sinusoids in cirrhosis as typified by increased density of contractile HSC wrapped around sinusoidal endothelial cells (SEC) that have lost a number of their specialized features (i.e., fenestrae, etc.) and has been referred to as pathological sinusoidal remodeling. This review will highlight recent findings on the relationship between angiogenesis, sinusoidal remodeling, and portal hypertension in terms of mechanistic links and the potential to intervene in these processes for therapeutic benefit in cirrhosis and portal hypertension.

Angiogenesis in the cirrhotic liver

The pathological role of SEC in cirrhosis and portal hypertension has been exemplified by studies showing impaired generation of vasoactive molecules such as eNOS-derived NO that contribute to endothelial dysfunction and an increased intrahepatic resistance as reviewed elsewhere [5]. However, evidence is now emerging for an important role of the SEC in liver angiogenesis. Angiogenesis is a dynamic process leading to the formation of new vessels from pre-existing blood vessels, by sprouting or intussusception, then lumen formation and eventually stabilization of nascent vessels [10]. In addition to this traditional angiogenic mechanism, new vessels may also develop through a process referred to as post-natal vasculogenesis whereby bone marrow derived endo-

Keywords: Portal hypertension; Cirrhosis; Angiogenesis; Vascular remodeling; Receptor tyrosine kinase.
Received 21 April 2010; received in revised form 7 July 2010; accepted 12 July 2010
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Abbreviations: NO, nitric oxide; HSCs, hepatic stellate cells; EC, endothelial cells; SEC, sinusoidal endothelial cells; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor; PDGFR-β, platelet-derived growth factor receptor beta; VEGFR2, VEGF receptor type 2.

thelial progenitor cells are recruited to sites of active vessel formation, integrate into the vascular wall, and promote vascular extension [11]. Angiogenesis can occur in physiological conditions, like liver regeneration, or in pathological settings like cirrhosis (Fig. 1) and tumor angiogenesis.

In cirrhosis, it is postulated that angiogenesis may be stimulated by tissue hypoxia. Hypoxia stimulates production of vascular endothelial growth factor (VEGF) which is one of the most important angiogenic growth factors, through a canonical pathway that involves the transcription factor HIF1α [12]. Although VEGF production is the most prominent from hepatocytes, HSC may also produce angiogenic molecules (discussed below), and recent studies have also identified an important autocrine VEGF signaling loop within endothelial cells themselves [13]. The mechanism of hypoxia in the cirrhotic liver has been studied extensively at the level of the hepatocytes with a focus on metabolic changes but could also occur in response to structural changes in the sinusoids including basement membrane deposition and loss of SEC fenestrae (also referred to as "capillarization"), which in turn could lead to impaired oxygen diffusion from the sinusoids to the parenchyma. It is likely that capillarization of sinusoids has different origins and spatial dynamics in different forms of chronic liver disease and is probably just one component of the broader sinusoidal changes that are occurring in chronic liver disease due to over-availability of angiogenic factors that accompany the chronic wound-healing process.

Although SEC are the most recognized cell type that participate in angiogenesis, recent advances suggest that pericytes such as HSC are also major contributors to angiogenesis. This may occur through direct and indirect mechanisms. Direct mechanisms include the ability of HSC to stabilize the new vessels and provide durability to the vessels that cannot be achieved by SEC alone in the absence of mural cells such as HSC [14]. On the other hand, indirect mechanisms are also likely to be important and include the ability of HSC to secrete angiogenic molecules that recruit and stimulate SEC thereby promoting a "pro-angiogenic sinusoidal matrix" [10]. For example, recent studies show that activated HSC secrete VEGF and angiopoietin-1, the molecules that promote angiogenesis [15–17]. In response, SEC synthesize PDGF and TGF-β, thereby stimulating HSC migration and recruitment to vessels [10]. Therefore, pericytes may contribute to angiogenesis through multiple mechanisms.

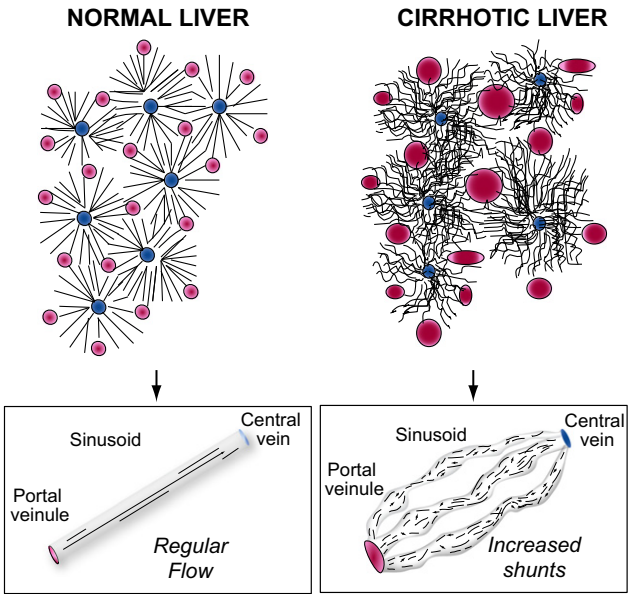

Fig. 1. Angiogenesis in cirrhosis and portal hypertension. Normal architecture of sinusoidal vessels is shown (left panel) with normal flow from portal venules, through sinusoids, into central veins (left box). The sinusoidal vascular network in the cirrhotic liver undergoes profound changes, with an increased number of sinusoidal vessels (angiogenesis) of varying diameter and flow pattern, organized into micronodules and macronodules (right panel). While angiogenesis has been proposed to increase fibrosis, these new vessels could also theoretically serve as portal pressure reducing intrahepatic shunts (right box).

What is the relationship between liver angiogenesis and portal hypertension? In the liver, angiogenesis is postulated to contribute to portal hypertension by promoting fibrogenesis. Indeed, angiogenesis and fibrosis develop in parallel in a number of organ beds including the kidney and the lung [10]. Angiogenesis appears to be a typical feature of liver fibrosis as well. For example, neovasculature and overexpression of pro-angiogenic molecules have been detected in liver biopsies of patients with chronic viral infection, primary biliary cirrhosis and auto-immune hepatitis [18,19]. Moreover, in human liver samples, angiogenesis directly correlates with the degree of hepatic fibrosis [15]. Similar findings were observed in animal studies using complementary models of liver fibrosis where fibrogenesis and angiogenesis develop in parallel during progression towards cirrhosis [15,20]. Furthermore, pharmacologic interventions that inhibit angiogenesis, especially use of receptor tyrosine kinase inhibitors such as Sorafenib or Sunitinib, decrease hepatic fibrosis [20–22]. Nevertheless, these specific agents may also inhibit PDGF receptor beta (PDGFR-β) which is an effector, not only for HSC angiogenesis but also a factor that influences other aspects of the HSC activation process. However, the drugs that specifically inhibit angiogenesis by targeting molecules not involved in HSCs fibrogenic pathway, like VEGF receptor type 2 (VEGFR2) or Tie2, also induce a decrease in hepatic fibrosis [15,23], providing further evidence for the importance of angiogenesis in the process of fibrogenesis.

What may be the rationale by which angiogenesis promotes fibrosis? Some have postulated parallels between fibrosis and liver tumors whereby metabolically active cells (tumor cells in the case of HCC and active HSC in the case of cirrhosis) require adequate blood flow and nutrition to maintain their metabolically active state and that local tissue hypoxia within the scar may be driving angiogenic factor release [22,24]. Another possibility, which is not mutually exclusive is that angiogenic SEC and activated HSC release growth factors that promote the function of one and the other. Furthermore, pro-angiogenic cytokines secreted by activated HSCs may have a pro-fibrogenic effect [16,17,23,25]. Lastly, inflammation may be a process that links angiogenesis and fibrosis since angiogenesis may provide access for inflammatory cell infiltrates that are thought to promote fibrogenesis over chronic timeframes [26]. However, a greater understanding is required pertaining to the relationship of these processes.

While these data suggest that angiogenesis may be a requisite step that promotes fibrogenesis, it is possible that vascular changes occur in a passive manner, secondary to fibrosis. Furthermore, there is some evidence that an inhibition of angiogenesis can even worsen fibrosis [27–29]. For example, in a recent study performed in two complementary models of cirrhosis, the administration of Cilengitide, an inhibitor of the vitronectin receptor integrin αβv3 that plays an important role in liver angiogenesis, promoted hepatic fibrosis and inflammation despite its anti-

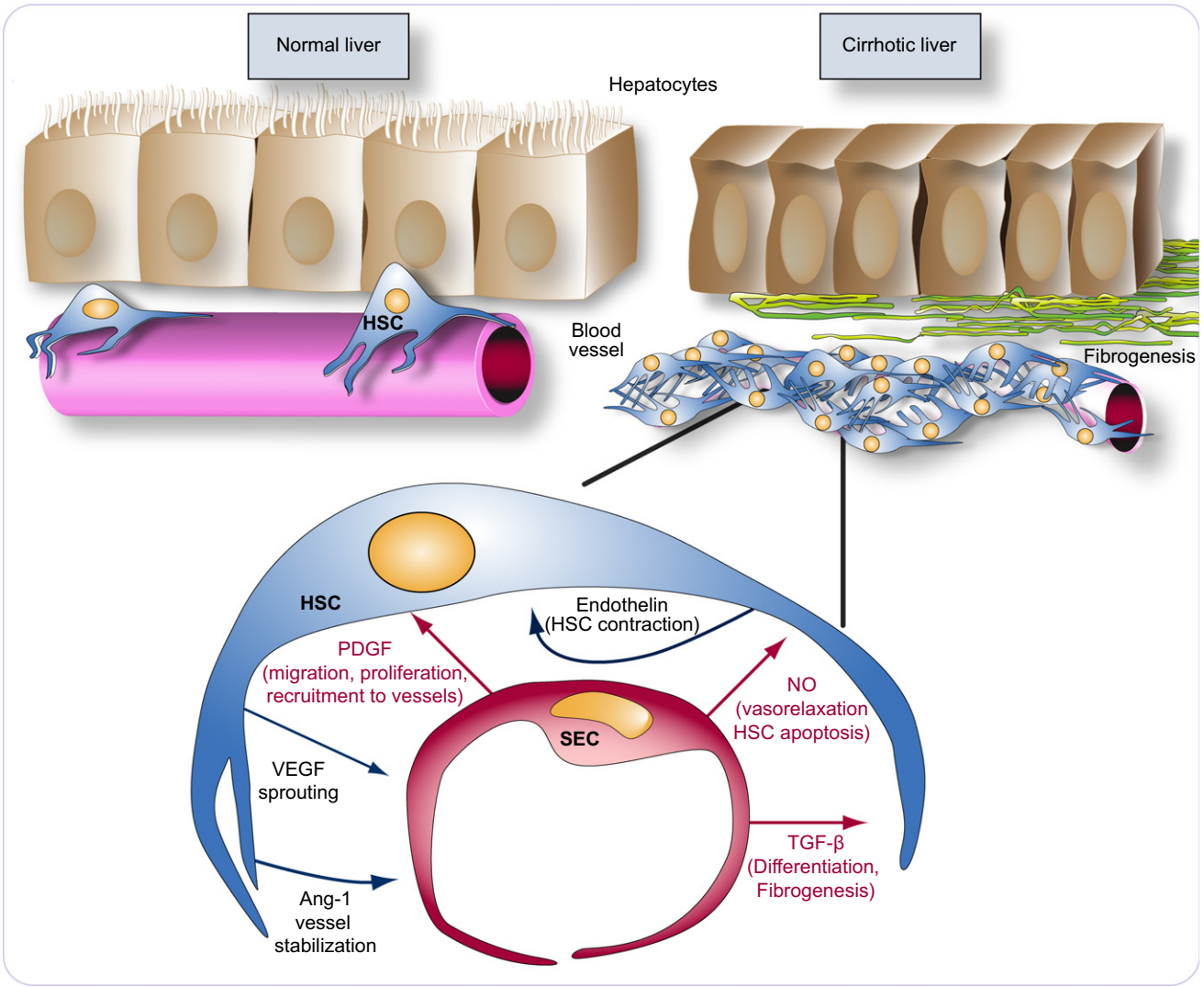

Fig. 2. Pathological sinusoidal remodeling in cirrhosis and portal hypertension. HSC align themselves around the sinusoidal lumen in order to induce contraction of the sinusoids. While in normal physiologic conditions, HSC contractility and coverage of sinusoids is sparse, in cirrhosis, increased numbers of HSC with increased cellular projections, wrap more effectively around sinusoids thereby contributing to a high-resistance, constricted sinusoidal vessel. At the cellular level, a number of growth factor molecules contribute to this process through autocrine and paracrine signaling between HSC and SEC. A number of these molecules are depicted along with their proposed role in paracrine function.

angiogenic effects [30]. It is possible that the disparate effects of anti-angiogenic drugs on fibrogenesis could be explained by their different targets. Nevertheless, this recent finding suggests a note of caution for the use of potent anti-angiogenic molecules in fibrosis and portal hypertension. This is particularly important since one could envision that angiogenesis induced blood flow could theoretically be important for the tissue repair that may be requisite in recovery from liver injury and cirrhosis or alternatively could provide a means for portal pressure decompressing shunt formation (Fig. 1).

Pathological sinusoidal remodeling in cirrhosis and portal hypertension

Activated HSC are probably the most pro-fibrogenic cells in the liver. However, in parallel to this important role, HSC also make an important contribution to the vascular structural changes in cirrhosis. For example, in addition to their supportive role in angiogenesis which was discussed above, HSC also play a dominant role in sinusoidal vessel structural changes in cirrhosis, a process referred to as pathological sinusoidal remodeling. Prior work has highlighted the role of sinusoidal vasoconstriction in the genesis of portal hypertension, where HSC operate as contractile machinery in response to vasoconstrictors such as endothelin and also relax in response to vasodilators such as NO [5,31]. Building on this concept, recent studies suggest that the mural coverage of sinusoidal vessels is enhanced by HSC in cirrhosis, and that because of the contractile nature of HSC, this process of "pathological sinusoidal remodeling" contributes further to a high-resistance, constricted sinusoidal vessel [14]. Indeed, HSC have the ability to align themselves in an effective way around the vessel lumen in order to achieve these structural changes [14]. This sinusoidal remodeling requires the recruitment of "angiogenic" stellate cells to the vascular wall or the activation of local HSC with extension of tentacle-like structures that encir-

cle the vessel lumen and adjacent SEC (Fig. 2). These long processes and their close juxtaposition with SEC ideally position them for paracrine signaling with SEC [10] that promotes vasoconstriction and continued sinusoidal structural changes.

A number of growth factors, signaling pathways mediate HSCs proliferation, migration, motility and recruitment to vessels in the process of sinusoidal remodeling, including platelet-derived growth factor (PDGF)/PDGF receptor and VEGF/VEGF receptor [10,17]. Although these ligands are technically growth factors, they maintain important chemotactic properties and highlight the important role that other chemotactic molecules and guidance/repulsion molecules play in the process of HSC recruitment and motility including ephrin family proteins and more traditional chemokine pathways [14,32]. Nonetheless, PDGF may be the most critical of these molecules based not only on work in the liver but also in broader studies examining the mechanisms of pericyte recruitment to vessels [14,33]. The activation of PDGFR triggers the downstream propagation of signals that include Raf-1, MEK, and extracellular-signal regulated kinase (ERK), which trigger a proliferative response while downstream phosphatidylinositol 3-kinase (PI 3-K) is thought to predominate for chemotaxis [34]. Recent studies show that a molecule more characterized for axonal guidance, termed, neuropilin-1 also contributes importantly to PDGFR chemotactic responses [35]. Interestingly, the inhibition of the PDGF signaling pathway by the receptor tyrosine-kinase inhibitor Imatinib reduced portal pressure in an animal model of cirrhosis through effects on sinusoidal remodeling and impaired HSC coverage of sinusoids with less consequential effects on fibrogenesis [14,36]. This is an important point because one may have predicted that HSC mass would correlate directly with the degree of fibrosis. However, it is becoming increasingly recognized that there are heterogeneous subpopulations of myofibroblasts in the liver, including those derived from HSC, periportal fibroblasts; bone marrow-derived cells and the epithelial-to-mesenchymal transition [37]. Thus, it is probable that all myofibroblasts do not have identical angiogenic capacities and indeed it has been suggested recently in a proteomic analysis that HSC may display more angiogenic features than portal myofibroblasts [38]. In total, these findings highlight the role of pathological sinusoidal remodeling in the process of increased intrahepatic vascular resistance and portal hypertension and in turn also highlight the possibility that targeting HSC motility and reversion of pathological remodeling could have therapeutic benefits.

In addition to the HSC driven sinusoidal remodeling that is described above, other forms of vascular remodeling are also occurring within the cirrhotic liver. Even within the sinusoids, not only HSC participate in sinusoidal remodeling since SEC which lose their fenestra, become associated with a basement membrane, and undergo a number of other phenotypic changes which seem to go hand-in-hand with "endothelial dysfunction" and probably contribute to enhanced HSC activation, proliferation, migration, and sinusoidal coverage as suggested in recent studies [39–41]. Thus, HSC activation is promoted not only by changes in extracellular matrix, inflammatory cytokines, and oxidative stress, but also secondary to changes in SEC phenotype. For example, recent studies in aggregate suggest that functional endothelium with an adequate NO generation (perhaps due to proper shear stress) could participate in maintaining HSC in a quiescent state but that deficient NO generation that is associated with cirrhosis allows unchecked HSC activation [39,41,42]. Vascular remodeling also occurs outside the sinusoids in cirrhosis. For example, in their pioneering studies, Rappaport and co-workers showed that the development of a scar in the cirrhotic liver was invariably accompanied by an intense vascular proliferation including the presence of "scar vessels" [9]. Indeed, it has been proposed that substantive vascular structural changes may limit potential efficiencies of anti-fibrotic therapies suggesting a clinical prognostic relevance to such vascular changes [43].

Are angiogenesis and sinusoidal remodeling therapeutic targets in humans?

As angiogenesis and sinusoidal remodeling may promote portal hypertension through multiple mechanisms discussed above, investigators have administered anti-angiogenic drugs in animal models of cirrhosis with the aim of decreasing portal hypertension. The previously discussed beneficial effects of Imatinib in portal hypertension is one example [14]. Moreover, Sorafenib, a multitarget receptor tyrosine kinase inhibitor approved in the treatment of unresectable hepatocellular carcinoma, has shown beneficial effects in a model of secondary bile duct ligation-induced cirrhosis [21,22] that is independent of its beneficial effects of decreasing splanchnic neovascularization and portosystemic collateral circulation, (another important site of angiogenesis with therapeutic implications but which is not explored in this review) [21,22]. Indeed, Sorafenib treatment induced a decrease of portal hypertension, as well as a reduction in intrahepatic fibrosis, intrahepatic inflammatory infiltrate, and intrahepatic neovascularization [22]. Moreover, the administration of another anti-angiogenic drug, i.e., Sunitinib, a multitarget receptor tyrosine kinase inhibitor, in a carbon tetrachloride rat model of cirrhosis, also resulted in a decrease in portal pressure, along with a decrease in inflammatory infiltrate, angiogenesis, and HSC activation/matrix deposition [20]. Therefore, small molecule inhibitors of receptor tyrosine kinases that target the growth factor pathways leading to angiogenesis and sinusoidal remodeling (i.e., VEGF, PDGF, Ang-1) are capable of lowering PHT, probably through a dual and converging anti-fibrogenic and anti-angiogenic role of action that affects both HSC and SEC.

However, the story could be more complex. If lowering angiogenesis in animal models of pre-hepatic portal hypertension decreases portal pressure by decreasing splanchnic neovascularization and venous collaterals, one might question whether decreasing intrahepatic collaterals may be detrimental, since these vessels could theoretically act as portal hypertension decompressing shunts. Furthermore, the beneficial role of angiogenesis in tissue regeneration and repair should not be underestimated. Lastly, as discussed earlier, some anti-angiogenic interventions provide evidence for the detrimental effects in preclinical models [27–30].

In conclusion, angiogenesis and sinusoidal remodeling in liver occur concurrently with fibrosis and portal hypertension and a number of experimental evidence support a causative role for these vascular changes in the genesis of fibrosis and portal hypertension in animal models. However, animal models do not always faithfully recapitulate the human state (as exemplified by the disparate results of TNFα inhibition in rodent as compared to human alcoholic liver disease [44–46]. Clearly we need to pursue human investigations with all proper safety measures in place. A good starting point may be a more in-depth analysis of the effects of Sorafenib on portal pressure and fibrosis in non-tumorous fibrotic tissues obtained in previously completed clinical studies [47].

Undoubtedly, new studies in angiogenesis, fibrosis, and portal hypertension will be forthcoming and will clarify our clinical options in humans with advanced liver disease.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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