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

Dominique Thabut[1,2], Vijay Shah[1,*]

[1]*Gastroenterology Research Unit, Advanced Liver Disease Study Group, Fiterman Center for Digestive Diseases, Mayo Clinic, Rochester, MN, USA;*
[2]*Université Pierre et Marie Curie, AP-HP, Service d'Hépato-Gastroentérologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France*

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-

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* Corresponding author.
E-mail address: shah.vijay@mayo.edu (V. Shah).
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.

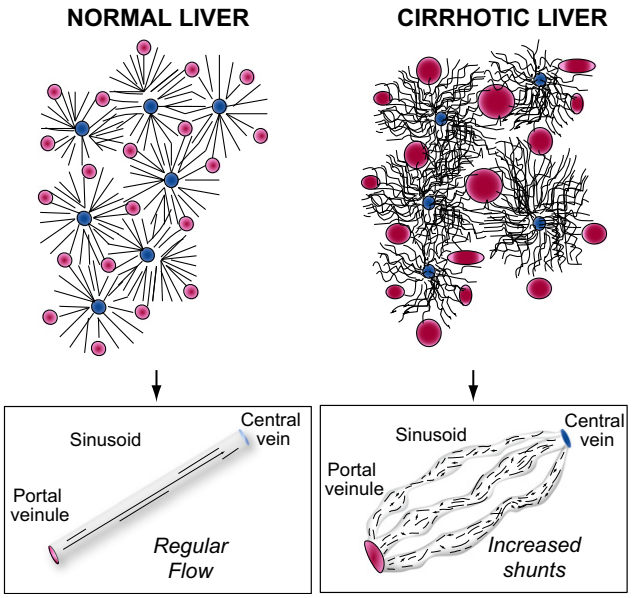

Fig. 1. Angiogenesis in cirrhosis and portal hypertension. Normal architecture of sinusoidal vessels is shown (left panel) with normal flow from portal venules, through sinusoids, into central veins (left box). The sinusoidal vascular network in the cirrhotic liver undergoes profound changes, with an 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-