Review

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Liver sinusoidal endothelial cells: Physiology and role in liver diseases

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Summary

Liver sinusoidal endothelial cells (LSECs) are highly specialized endothelial cells representing the interface between blood cells on the one side and hepatocytes and hepatic stellate cells on the other side. LSECs represent a permeable barrier. Indeed, the association of 'fenestrae', absence of diaphragm and lack of basement membrane make them the most permeable endothelial cells of the mammalian body. They also have the highest endocytosis capacity of human cells. In physiological conditions, LSECs regulate hepatic vascular tone contributing to the maintenance of a low portal pressure despite the major changes in hepatic blood flow occurring during digestion. LSECs maintain hepatic stellate cell quiescence, thus inhibiting intrahepatic vasoconstriction and fibrosis development. In pathological conditions, LSECs play a key role in the initiation and progression of chronic liver diseases. Indeed, they become capillarized and lose their protective properties, and they promote angiogenesis and vasoconstriction. LSECs are implicated in liver regeneration following acute liver injury or partial hepatectomy since they renew from LSECs and/or LSEC progenitors, they sense changes in shear stress resulting from surgery, and they interact with platelets and inflammatory cells. LSECs also play a role in hepatocellular carcinoma development and progression, in ageing, and in liver lesions related to inflammation and infection. This review also presents a detailed analysis of the technical aspects relevant for LSEC analysis including the markers these cells express, the available cell lines and the transgenic mouse models. Finally, this review provides an overview of the strategies available for a specific targeting of LSECs.
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Introduction

The vascular endothelium, representing the interface between blood and other tissues, is not only a physical barrier, but contributes to different physiological and pathological processes, including hemostasis/thrombosis, metabolites transportation, inflammation, angiogenesis and vascular tone [1]. Liver sinusoidal endothelial cells (LSECs) form the wall of the liver sinusoids and represent approximately 15 to 20% of liver cells but only 3% of the total liver volume [2]. LSECs are highly specialized endothelial cells. They have a discontinuous architecture meaning that fusion of the luminal and abluminal plasma membrane occurs at other sites than cell junctions, in areas called 'fenestrae'. This review focuses on the role of LSECs in physiological conditions and their involvement in liver diseases.

LSECs in the normal liver

Formation of sinusoids during embryogenesis

As illustrated in Fig. 1, an early structural differentiation of hepatic sinusoids occurs between gestational weeks 5 and 12 in human embryos [3]. During that period, LSECs gradually loose cell markers of continuous endothelial cells including platelet endothelial adhesion molecule-1 (PECAM-1, also called cluster of differentiation (CD)31), CD34 and 1F10 antigen, and acquire markers of adult sinusoidal cells including CD4, CD32 and the intracellular adhesion molecule-1 (ICAM-1). This differentiation of LSECs is regulated by hepatoblasts, both via the vascular endothelial growth factor (VEGF) they release and via direct intercellular interactions [4,5].

The embryological origin of LSECs is still a matter of debate. Initial observational studies described capillaries progressively surrounded by growing cords of hepatoblasts in the septum transversum, suggesting that LSECs derive from the septum transversum mesenchyme, a part of the mesoderm [3,6,7]. However, recent cell lineage experiments performed in mice showed that the septum transversum gives rise to mesothelial cells, hepatic stellate cells, portal fibroblasts, and perivascular mesenchymal cells, but not to LSECs [8]. A part of LSECs rather derives from a common progenitor to endothelial and blood cells, called the "hemangioblast", as attested by overlapping expression of hematopoietic and endothelial cell markers by LSECs and by fate tracing experiments [9–14]. These progenitor cells form veins crossing the septum transversum, i.e., vitelin veins [15], umbilical veins or cardinal veins and then LSECs [16,17]. Another part of LSECs derives from the endocardium of the sinus venosus, a compartment of the primitive cardiac tube [18]. These two embryological origins might explain the heterogeneity of the markers expressed by LSECs in adults.

LSECs renewal

Although specific data are lacking, we can speculate that in a physiological state LSECs are quiescent, i.e., with a low proliferation rate and a long life span, similar to endothelial cells from large vessels [19]. LSECs renewal differs in physiological and in pathological conditions. Three cell types contribute to LSEC renewal, namely mature LSECs, intrahepatic or resident sinusoidal endothelial cell progenitors, and bone marrow derived sinusoidal endothelial cell progenitors [20]. Mature LSECs can self-proliferate in normal conditions, when stimulated with growth factors such as VEGF and FGF (fibroblast growth factor) [20,21]. Resident sinusoidal endothelial cell progenitors represent 1 to 7% of the LSECs of a normal rodent liver and probably contribute to LSECs regeneration [20]. Bone marrow derived sinusoidal endothelial cell progenitors do not participate in LSEC turnover in a normal liver [22]. By contrast, after liver injury, these cells are the main drivers of liver regeneration [20,22]. Indeed, a subtoxic dose of monocrotalin, a toxic agent for LSECs, elicits liver injury only when bone marrow is suppressed. In addition, infusion of bone marrow cells after a toxic dose of monocrotalin almost fully corrects liver lesions [23].

Hepatic blood flow regulation

Liver sinusoids have a dual blood supply, receiving blood flow from the portal vein (70%) and the hepatic artery (30%) [24]. Blood pressure equalizes in the sinusoid and blood is then drained into the hepatic veins and the inferior vena cava. Despite major circadian changes in hepatic blood flow due to digestion, hepatic venous pressure gradient remains at 4 mmHg or less in a normal individual, attesting a fine regulation of hepatic vascular tone [25]. Intrahepatic shear stress is recognized as a main driver of hepatic blood flow regulation [26]. Shear stress is a frictional force applied by blood flow on endothelial surface [26]. It is proportional to flow intensity and to blood viscosity and inversely proportional to the cubic radius of the vessel [26]. Intrahepatic shear stress has never been directly measured in human or animal. Its evaluation is indeed difficult since the radius of sinusoids is very small and varies within the liver. Moreover, viscosity is hard to estimate in this specific area and also varies with hemodilution. In normal conditions, in the liver like in other vascular beds, the endothelium is able to generate vasodilator agents in response to increased shear stress in order to attenuate the increase in blood pressure. The loss of this property is called endothelial dysfunction. An endothelial specific transcription factor induced by prolonged shear stress, called Kruppel-like factor 2 (KLF2) mediates this effect of shear stress [27]. KLF2 induces the endothelial upregulation of vasodilating agents including nitric oxide (NO) [28] (Fig. 2). Shah and colleagues previously demonstrated that LSECs are the main source of NO in the normal liver through endothelial nitric oxide synthase (eNOS) activation by shear stress [29]. KLF2 also induces the downregulation of vasoconstrictive molecules including endothelin-1 [28]. Other molecules released by LSECs regulating blood flow include the vasodilating agent carbon monoxide (CO) and the metabolites of the cyclooxygenase (COX) pathway (thromboxane A2, Prostacyclin) [30]. All these molecules act in a paracrine manner on hepatic stellate cells localized in the space of Disse [31]. Healthy LSECs maintain hepatic stellate cell quiescence, thus inhibiting their vasoconstrictive effect [34]. The concept that hepatic stellate cell activation induces sinusoid constriction is based on their expression of molecules found in smooth muscle cells including αSMA, on their position wrapped around the exterior of LSECs and on the *ex vivo* observation of their ability to contract [32,33]. Although still controversial, LSEC could also regulate blood flow by swelling, thus creating an inlet and an outlet sphincter [32]. Kupffer cells possess contractile proteins as well, but their role in the regulation of hepatic blood flow remains controversial [32]. In contrast to most vascular beds where blood flow is mostly regulated by smooth muscle cells, in the liver, smooth muscle cells play a limited role since, although present in hepatic arterioles, they are only found in limited numbers in portal venules [32].

Key point

In a normal liver, differentiated LSECs are gatekeepers of fibrogenesis by maintaining hepatic stellate cells in their inactivated state. LSECs regulate sinusoidal blood flow through their action on hepatic stellate cells and thus maintain a low portal pressure.

LSECs, a selective barrier

LSECs are positioned at an interface. On their sinusoidal side, they are exposed to the highly

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