Editorial article for Qu et al., “Liver Sinusoidal Endothelia cell: An Important Yet Often Overlooked Player in the Liver Fibrosis”.

Title:
Unlocking the Role of Liver Sinusoidal Endothelial Cells: Key Players in Liver Fibrosis

Yasuko Iwakiri, PhD
Department of Internal Medicine, Section of Digestive Diseases, Yale University School of Medicine, New Haven, CT 06519, USA

# Correspondence
Yasuko Iwakiri, PhD
Section of Digestive Diseases, Department of Internal Medicine, Yale School of Medicine
TAC S223B, 333 Cedar Street, New Haven, CT 06520, USA
Tel: +1-203-785-6204
Fax: +1-203-785-7273
Email: yasuko.iwakiri@yale.edu
ORCiD: 0000-0001-8032-5654
Twitter handler: @Yasukolwakiri

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Liver sinusoidal endothelial cells (LSECs) are a critical component of the liver's microenvironment, constituting approximately 90% of the liver endothelial cell population[1, 2]. They play a vital role in liver homeostasis by regulating vascular tone, blood filtration, nutrient exchange, and immune modulation. However, in the context of liver fibrosis, which can progress to cirrhosis and cause serious complications such as portal hypertension, the function of LSECs becomes compromised. This dysfunction contributes significantly to the pathogenesis of liver fibrosis.

The review article by Qu et al.[3] comprehensively discussed how LSECs contribute to liver fibrosis development and highlighted the molecular mechanisms underlying LSEC dysfunction. The authors also discussed how LSECs influences functions of hepatic stellate cells (HSCs), hepatocytes and immune cells, leading to inflammation and fibrosis. While previous research has focused heavily on HSCs and hepatocytes as major players of fibrogenesis, the role of LSECs has been overlooked. LSEC dysfunction disrupts normal liver microcirculation, impairs liver regeneration, and promotes inflammation and fibrogenesis through dysregulated signaling pathways involving cytokines, chemokines, and angiogenic factors. Given the fact that there is no FDA approved anti-fibrotic drugs for liver fibrosis, understanding LSEC biology holds significant promise for a potentially novel therapeutic target for liver fibrosis.

LSEC dysfunction is associated with structural changes such as loss of fenestrae and capillarization (i.e., development of basement membrane of LSECs). The mechanism of the maintenance of fenestrate remains to be fully understood. The loss of fenestrae diminishes LSEC's antigen-presenting capability, consequently impairing immune response regulation. This review article by Qu et al.[3] succinctly summarizes various studies elucidating potential factors regulating fenestrae, such as cytoskeletal proteins. The contraction and dilatation of fenestrae in LSECs are regulated by actin cytoskeleton[4]. It has been demonstrated that cytochalasin D (Cyto D), an F-actin-depolymerizing agent, which predominantly dispelled the formation of large stress fibers in dedifferentiated LSECs, leading to the reformation of fenestrate and consequently mitigating liver fibrosis[5]. Thus, the strategies targeting LSECs' dynamic remodeling processes, such as cytoskeletal regulation and maintenance of fenestrae, show promise in mitigating fibrosis[5].

The mechanism underlying LSEC capillarization remains incompletely understood. Capillarization is often characterized by an upregulation of CD34 expression in LSECs, which in
normal state do not express. It is reported that vascular endothelial growth factor (VEGF), produced by hepatocytes and HSCs, maintains the phenotype of LSECs[6]. However, in cirrhotic livers, VEGF secretion is increased[7], suggesting that LSEC capillarization may result from disruption in downstream VEGF signaling rather than lack of VEGF itself. In fact, it was shown significant downregulation of both VEGF receptor Kdr (VEGFR2) and co-receptor Nrp1 in peri-central area (Zone3 LSECs) of cirrhotic mouse liver[1], potentially contributing to LSEC capillarization.

 Decreased nitric oxide (NO) production by endothelial isoform of NO synthase (eNOS) is also considered as a key marker of endothelial dysfunction[8]. This dysfunction precedes noticeable liver injury and affects not only hepatocytes but also HSCs, contributing to fibrogenesis. Restoring eNOS-derived NO production has shown to inhibit HSC activation and maintain them in a quiescent state, thereby inhibiting fibrogenesis[6]. The review article[3] also touches upon the reduced scavenging capacity of LSECs in cirrhotic livers. LSECs are one of the most powerful scavengers in the body, playing an important role in clearance of wastes and pathogens in blood originated from the gut and the systemic circulation[9-11]. This activity is related to their expression of various endocytosis receptor genes including scavenger receptors (Scarb1, Scarb2, Stab1 and Stab2) and mannose receptor (Mrc1) as well as genes of related activities such as Fc gamma-receptor IIb2 (Fcgr2b/CD32b). It was found downregulation of all these genes in cirrhotic livers, suggesting decreased endocytic and clearance capacities of LSECs[1]. This may make cirrhotic patients more susceptible to infection and systemic inflammation. Interestingly, all these endocytosis-related genes were also most downregulated in pericentral (Zone3) LSECs in cirrhotic mice. The decreased endocytic capacity of LSECs may be associated with their capillarization as well, because decreased CD32b was also used as an indicator of LSEC capillarization in some studies[12].

The heterogeneity of LSECs, a crucial aspect not addressed in this review article by Qu et al.[3], plays a pivotal role in liver pathology. LSECs exhibit zonal-specific alterations within the liver, contributing to the progression of liver fibrosis and cirrhosis. These cells form a distinct subset of endothelial cells (ECs) unique to the liver, and recent advancements, particularly in single-cell analysis techniques, have unveiled their complex molecular heterogeneity. This deeper understanding has shed light on the molecular mechanisms underlying liver fibrosis and portal hypertension, emphasizing the significance of LSEC dysfunction accompanied with increased
adhesion molecule expression, and secretion of cytokines and chemokines in liver pathophysiology. Notably, a recent study, employing single cell-sequencing (scRNA-seq) in human-derived liver nonparenchymal cells from normal and cirrhotic patients, identified two disease-specific EC populations, characterized by CD34+PLVAP+VWA1+ and CD34+PLVAP+ACKR1+ [13]. The authors named them “scar-associated ECs”. In cirrhotic mouse livers, a significant upregulation of CD34, PLVAP and ACKR1 in LSECs of all zones in cirrhotic livers[1]. These findings suggest a potential avenue for targeted therapy by focusing on LSECs expressing these specific genes, offering a more disease-specific approach to managing cirrhosis.

In conclusion, while various therapeutic approaches have demonstrated efficacy in preclinical studies, the translation of these findings into effective clinical treatments for cirrhosis remains challenging. Targeting LSECs specifically, possibly through the AAV system or nanoparticle-based delivery systems, holds potential as a novel therapeutic avenue. It’s also crucial to differentiate between capillarization and angiogenesis when targeting LSECs effectively for anti-fibrotic strategies[14]. To date no perfect markers have been identified that distinguish LSECs from other vascular ECs[7, 15], leading to the absence of established LSEC-specific Cre mouse models [7, 16]. Well-recognized LSEC markers in healthy livers include the surface receptor CD32b [17], C-Type Lectin Domain Family 4 Member G (CLEC4G) [18], Lyve1 [19], and Stab2 [20]. Electron microscopy remains the gold standard for identifying LSECs based on their fenestrae. Furthermore, examining specific molecular markers of dysregulated LSECs in acute or chronic experimental liver disease models presents some challenges. Future research aimed at comprehensively understanding the intricate biology of LSECs in both healthy and diseased states will play a pivotal role in the development of targeted therapies tailored to LSECs and in elucidating their intricate interplay within the liver microenvironment. Such endeavors are indispensable for the advancement of effective treatments for liver fibrosis and its associated complications.
References


