VOLUME 30 NUMBER 4 October 2024
pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

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pISSN 2287-2728
eISSN 2287-285X

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Editorial

https://doi.org/10.3350/cmh.2024.0343
Clinical and Molecular Hepatology 2024;30:673-676

Unlocking the role of liver sinusoidal endothelial cells: Key players in liver fibrosis: Editorial on "Liver sinusoidal endothelial cell: An important yet often overlooked player in the liver fibrosis"

Yasuko Iwakiri

Department of Internal Medicine, Section of Digestive Diseases, Yale University School of Medicine, New Haven, CT, USA

Keywords: LSEC; Capillarization; Fenestrae; LSEC dysfunction

See Article on https://doi.org/10.3350/cmh.2024.0022

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 influence 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 are 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 for the maintenance of fenestrate remains to be fully understood. The loss of fenestrae diminishes LSECs' 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

Corresponding author : Yasuko Iwakiri
Department of Internal Medicine, Section of Digestive Diseases, Yale University School of Medicine, TAC S223B, 333 Cedar Street, New Haven, CT 06520, USA
Tel: +1-203-785-6204, Fax: +1-203-785-7273, E-mail: yasuko.iwakiri@yale.edu
https://orcid.org/0000-0001-8032-5654

Editor: Han Ah Lee, Chung-Ang University College of Medicine, Korea

Received : May 8, 2024 / **Accepted :** May 9, 2024

that cytochalasin D, an F-actin-depolymerizing agent, 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 that there was significant downregulation of both VEGF receptor Kdr (VEGFR2) and co-receptor Nrp1 in peri-central area (Zone 3 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 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 been 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 that 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 that there was 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 (Zone 3) 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 by increased adhesion molecule expression and secretion of cytokines and chemokines in liver pathophysiology. Notably, a recent study employing single-cell sequencing 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, there was 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 adeno-associated virus 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

Abbreviations:

LSECs, liver sinusoidal endothelial cells; HSCs, hepatic stellate cells; VEGF, vascular endothelial growth factor; NO, nitric oxide; eNOS, endothelial isoform of NO synthase; ECs, endothelial cells

https://doi.org/10.3350/cmh.2024.0343

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.

Acknowledgements

The author apologizes for any references that were not cited due to the limited reference requirement.

YI is funded by NIH grants (R01DK121511, 1R01DK117597, 5R01DK130362, and 1R21AA031400-01).

Conflicts of Interest

The authors have no conflicts to disclose.

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