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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Lymphatic Dysfunction as a Novel Therapeutic Target in Nonalcoholic Steatohepatitis

The primary function of the lymphatic system in the liver is to collect interstitial fluid (lymph) and drain it to lymph nodes through lymphatic capillaries, ultimately returning it to the systemic circulation. Lymphatic capillaries consist of one layer of lymphatic endothelial cells (LECs) with unique button-like junctions allowing proteins, lipoproteins, and immune cells in interstitial fluid to be taken in. Alterations in these functionally specialized LEC junctions may impair LEC permeability and drainage functions, contributing to disease pathogenesis. In liver diseases, the number of hepatic lymphatic vessels generally increases. However, questions remain as to how increased lymphatic vessels are related to liver pathology and whether the function of LECs is altered in liver diseases. Despite its apparent importance, the hepatic lymphatic system has not been adequately studied.

In a study published in the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Burchill et al[1] demonstrated that alterations of LEC identity and function could lead to the development of nonalcoholic steatohepatitis (NASH). They first evaluated lymphatic vessel numbers in the livers of NASH patients with different pathologic stages and showed a positive correlation between lymphatic vessel numbers and NASH staging. Consistently, an increase in lymphatic vessels was also observed in mice with NASH. Second, with single-cell RNA sequencing (scRNA-seq) analysis of LECs isolated from control and NASH mice, they showed that transcripts important for the identify of LECs, such as Prox-1, Lyve-1, podoplanin, and Vegfr3, were significantly decreased in NASH despite an increase in lymphatic vessels, pointing to a change in the identity and function of LECs. Third, they showed a reduction in the hepatic lymphatic drainage function in NASH mice, which was restored by recombinant vascular endothelial growth factor C (rVEGF-C), the best-known lymphangiogenic factor, with a concomitant reduction in hepatic inflammation.

Regarding the mechanism underlying impaired hepatic lymphatic drainage, the same authors previously reported that oxidized low-density lipoprotein (oxLDL), highly elevated in serum of both patients[2] and mice[3] with NASH, was capable of suppressing Prox-1 and its related gene,Vegfr3, in LECs in vitro.[4] On the basis of this observation and the finding from scRNA-seq analysis in the current study, they postulated that oxLDL might alter LEC function through transforming LECs to vascular EC-like cells, leading to decreased permeability and lymphatic drainage in mice with NASH. The authors showed that wild-type mice treated with oxLDL exhibited a significant reduction in lymphatic drainage, recapitulating the situation observed in NASH mice. Furthermore, in an in vitro setting, oxLDL treatment decreased permeability of single-layer LECs, increased expression of vascular endothelial cadherin, a junction protein, and increased the ratio of Vegfr2/Vegfr3 in these cells. These changes are indicative of LEC transformation toward a vascular EC phenotype, resulting in a tighter junction than normal LECs. Of note, oxLDL (which is generated in inflammatory conditions), but not native LDL, impaired LEC identify and function, linking the inflammatory condition of NASH to the impairment of LEC permeability and lymphatic drainage.

This study provides new insight into the impairment of the hepatic lymphatic system as a pathologic mechanism leading to the development of NASH and the role of oxLDL in this impairment. Importantly, amelioration of impaired hepatic lymphatic drainage by rVEGF-C suggests that it may have therapeutic potential for NASH. This promise would be further confirmed with solid evidence showing improvement of NASH, such as decreased steatosis and fibrosis, by rVEGF-C. Furthermore, it is also possible that dysfunction of liver sinusoidal endothelial cells (LSECs), which engage upstream of lymph flow, may contribute to impaired lymphatic drainage in NASH. Because LSECs also express VEGFR3, a receptor for VEGF-C, rVEGF-C treatment could ameliorate LSEC dysfunction, resulting in improvement of lymphatic drainage. There are also some caveats to the role of oxLDL in impaired LEC permeability in vivo because of its possible multiple effects on other hepatic cells that could affect LEC permeability and lymphatic drainage. Oxidized LDL is a potent chemoattractant for circulating monocytes and directly activates macrophages in disease conditions. With regard to the possible involvement of LSECs in impaired lymphatic drainage mentioned above, oxLDL is also reported to induce liver injury through defenestration of LSECs.[5] Further investigations into these questions and others will significantly advance our understanding of the hepatic lymphatic system in health and disease. Because the therapeutic efficacy of ectopic administration of VEGF-C and resulting increased lymphatic drainage has been shown in mice with hepatic ischemia-reperfusion injury[6] and other diseases in different organs such as the brain,[7] lymphatic vessels and lymphatic drainage could be novel therapeutic targets for various liver diseases including NASH. The current study by Burchill et al[1] has vividly displayed this potential.

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References

1. Burchill MA, Finlon JM, Goldberg AR, et al. Oxidized low-density lipoprotein drives dysfunction of the liver lymphatic system. Cell Mol Gastroenterol Hepatol 2021:11:573–595.
2. Ampuero J, Ranchal I, Gallego-Duran R, et al. Oxidized low-density lipoprotein antibodies/high-density lipoprotein cholesterol ratio is linked to advanced non-alcoholic fatty liver disease lean patients. J Gastroenterol Hepatol 2016;31:1611–1618.
3. Zucker S, Hymowitz M, Rollo EE, et al. Tumorigenic potential of extracellular matrix metalloproteinase inducer. Am J Pathol 2001;158:1921–1928.
4. Tamburini BAJ, Finlon JM, Gillen AE, et al. Chronic liver disease in humans causes expansion and differentiation of liver lymphatic endothelial cells. Front Immunol 2019;10:1036.
5. Zhang Q, Liu J, Liu J, et al. oxLDL induces injury and defenestration of human liver sinusoidal endothelial cells via LOX1. J Mol Endocrinol 2014;53:281–293.
6. Nakamoto S, Ito Y, Nishizawa N, et al. Lymphangiogenesis and accumulation of reparative macrophages contribute to liver repair after hepatic ischemia-reperfusion injury. Angiogenesis 2020;23:395–410.
7. Hsu S-J, Zhang C, Jeong J, Lee S-I, McConnell M, Utsumi T, Iwakiri Y. Enhanced meningeal lymphatic drainage ameliorates neuroinflammation and hepatic encephalopathy in cirrhotic rats. Gastroenterology 2020. https://doi.org/10.1053/j.gastro.2020.11.036 (In press).

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