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REVIEW

The Hepatic Lymphatic Vascular System: Structure, Function, Markers, and Lymphangiogenesis

Masatake Tanaka and Yasuko Iwakiri

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

SUMMARY

Research on the lymphatic vascular system has advanced rapidly during the last decade, and lymphatic dysfunction is now implicated in the pathogenesis of multiple diseases. This review provides an overview of the lymphatic vascular system in the liver.

The lymphatic vascular system has been minimally explored in the liver despite its essential functions including maintenance of tissue fluid homeostasis. The discovery of specific markers for lymphatic endothelial cells has advanced the study of lymphatics by methods including imaging, cell isolation, and transgenic animal models and has resulted in rapid progress in lymphatic vascular research during the last decade. These studies have yielded concrete evidence that lymphatic vessel dysfunction plays an important role in the pathogenesis of many diseases. This article reviews the current knowledge of the structure, function, and markers of the hepatic lymphatic vascular system as well as factors associated with hepatic lymphangiogenesis and compares liver lymphatics with those in other tissues. *(Cell Mol Gastroenterol Hepatol 2016;2:733–749; http://dx.doi.org/10.1016/j.jcmgh.2016.09.002)*

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The lymphatic and blood vascular systems together constitute the circulatory system, and both have essential physiological activities. The lymphatic vascular system maintains tissue fluid homeostasis by collecting excess tissue fluid and returning it to the venous circulation. It also plays an essential role in the absorption and transport of dietary fat. Furthermore, lymphatics serve as the main conduits of antigens and antigen-presenting cells from the periphery to lymph nodes and are thus crucial for immune surveillance and acquired immunity.[1–4]

Lymphatic vascular research was impeded by a lack of knowledge about the markers and signaling pathways specific to the lymphatic vasculature. From 1995 to 1997, however, it was shown that vascular endothelial growth factor receptor (VEGFR)-3 is expressed in the lymphatic endothelium and that its ligand vascular endothelial growth factor (VEGF)-C promotes lymphangiogenesis.[5,6] This finding identifying signaling pathways specific to the lymphatic vasculature and subsequent discoveries of other specific markers for lymphatic endothelial cells (LyECs), such as lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1),[7] prospero homeobox protein 1 (Prox1),[8] and podoplanin,[9] significantly advanced lymphatic vascular research. As a consequence, it is now recognized that lymphatic vessel dysfunction plays an important role in the pathogenesis of various diseases.

However, in the liver, the lymphatic vascular system has been little explored. This review will provide an overview of the structure, function, and markers of the lymphatic vascular system as well as factors associated with lymphangiogenesis in the liver, highlighting both new findings and areas needing further study.

Structure of the Hepatic Lymphatic Vascular System

This section will address the structure of the lymphatic vascular system in general, followed by structural features specific to the liver. A detailed description of the anatomic structure of the lymphatic and hepatic lymphatic vascular systems is available in other review articles.[3,10–12]

Anatomy of the Lymphatic Vascular System

Lymphatic capillaries. Lymphatic fluid originates from plasma components leaked from blood capillaries into the interstitium and then enters lymphatic capillaries, which are blind-ended, thin-walled vessels consisting of a single layer of LyECs. Lymphatic capillaries are not covered by pericytes or smooth muscle cells and lack basement membranes.[13,14] They are highly permeable, with discontinuous "button-like" junctions through which interstitial fluid, macromolecules, and immune cells can be transported.[15] LyECs have anchoring filaments that are mainly composed of emilin-1 and fibrillin and bind LyECs to the surrounding extracellular matrix.[14,16,17] These filaments keep lymphatic vessel

Abbreviations used in this paper: CCl_4, carbon tetrachloride; EHE, epithelioid hemangioendothelioma; HA, hyaluronan; HBx Ag, hepatitis B x antigen; HCC, hepatocellular carcinoma; IFN, interferon; IL, interleukin; LSEC, liver sinusoidal endothelial cell; LyEC, lymphatic endothelial cell; LYVE-1, lymphatic vessel endothelial hyaluronan receptor 1; mTOR, mammalian target of rapamycin; NO, nitric oxide; Prox1, prospero homeobox protein 1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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lumens open, facilitating fluid intake in conditions of tissue swelling.

Collecting vessels. Lymphatic capillaries coalesce into collecting vessels, which are covered with smooth muscle cells and have basement membranes.[14] Collecting vessels lack the discontinuous junctions typical of lymphatic capillaries and are thus much less permeable. Collecting vessels can be divided into smaller functional units called lymphangions that have unidirectional bicuspid valves at each end.[18] The phasic contraction of smooth muscle cells covering lymphangions enables collecting vessels to act as pumps to drive lymphatic flow. Stimulation of smooth muscle cells causes depolarization of cell membrane and opens Ca^{2+} channels, resulting in Ca^{2+} influx and smooth muscle cell contraction. Smooth muscle cells also have stretch-activated Ca^{2+} channels that facilitate phasic contraction.[19,20] On the other hand, LyECs produce the vasodilator nitric oxide (NO) in response to shear stress from fluid flow, counteracting Ca^{2+}-dependent contraction.[21,22] Spatiotemporal alterations of Ca^{2+} and NO levels are thereby believed to modulate the phasic contraction of lymphangions.[23]

Lymph nodes and lymph trunks. Collecting vessels connect to 1 or more lymph nodes. Antigen-presenting cells including dendritic cells and macrophages in lymphatic fluid interact with lymphocytes in lymph nodes, facilitating adaptive immune responses. After reaching primary lymph nodes, lymphatic fluid flows to secondary central lymph nodes, tertiary central lymph nodes, and finally lymph trunks.[24] Lymphatic fluid from the left side of the body, abdomen, and lower limb ultimately drains into the thoracic duct, the largest lymphatic vessel, which is connected to the left subclavian vein (Figure 1), whereas lymphatic fluid from other

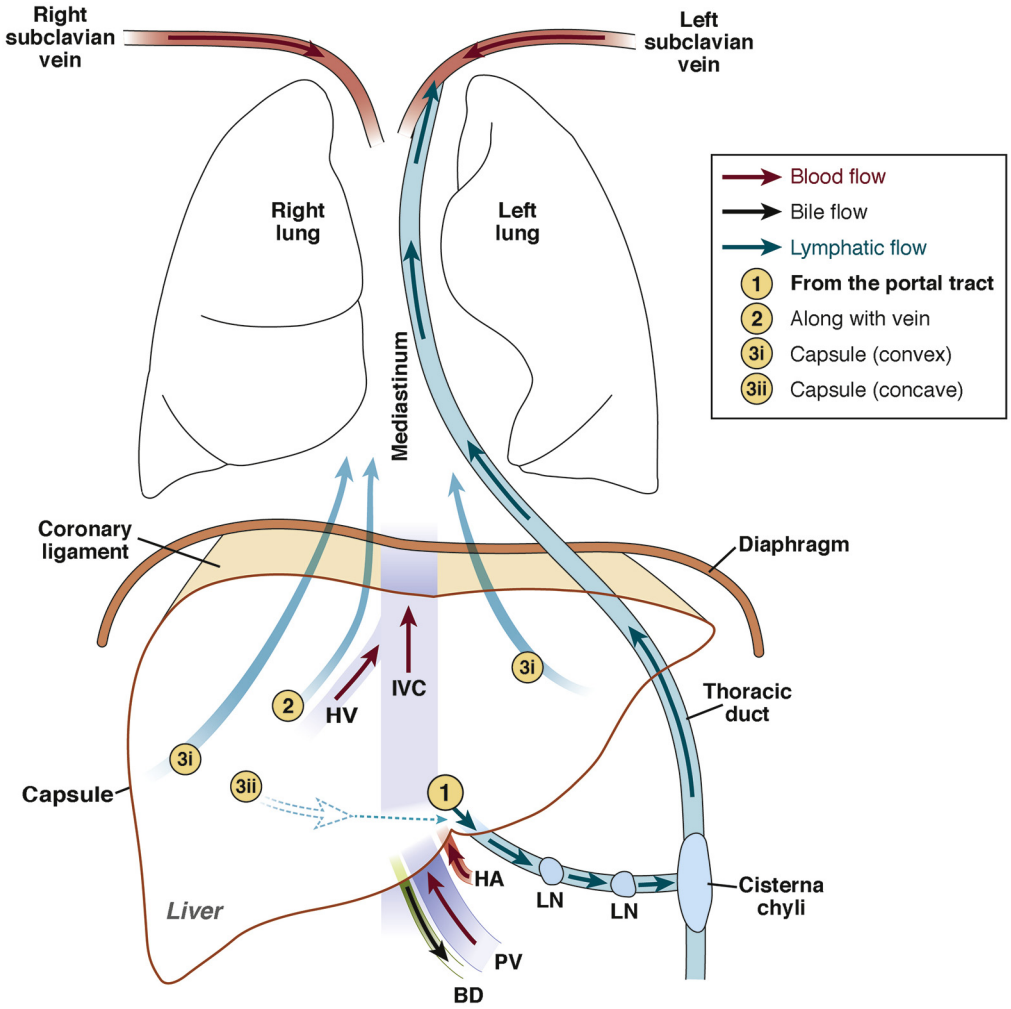

Figure 1. Schematic diagram of macro-anatomy of hepatic lymphatic vascular system. (*1*) Lymphatic capillaries in the portal tract coalesce into collecting vessels, which drain to lymph nodes at the hepatic hilum and the lesser omentum. Efferent lymphatic vessels (LV) from these lymph nodes connect to celiac lymph nodes, which drain to the cisterna chyli, the enlarged origin of the thoracic duct. Lymphatic fluid through the thoracic duct drains to the left subclavicular vein and returns to the systemic blood circulation. (*2*) Lymphatic vessels along the central vein (CV) converge into large lymphatic vessels along the hepatic vein (HV), which then traverse along the inferior vena cava (IVC) through the diaphragm toward mediastinal lymph nodes. (*3*) Lymphatic fluid running underneath the capsule of the convex surface of the liver (*3i*) drains to mediastinal lymph nodes through the coronary ligament, whereas that of the concave surface (*3ii*) drains to lymph nodes of the hepatic hilum and regional lymph nodes. BD, bile duct; HA, hepatic artery; LN, lymph node; PV, portal vein.