

Lymphatic Anatomy and Physiology

Abhishek K. Goswami, BS¹ Minhaj S. Khaja, MD, MBA² Trevor Downing, MD³ Nima Kokabi, MD¹
Wael E. Saad, MBBCh⁴ Bill S. Majdalany, MD¹

¹Division of Vascular and Interventional Radiology, Department of Radiology and Imaging Sciences, Emory University Hospital, Atlanta, Georgia

²Division of Vascular and Interventional Radiology, Department of Radiology and Medical Imaging, University of Virginia, Charlottesville, Virginia

³Division of Vascular and Interventional Radiology, Department of Radiology, Wake Forest Baptist Medical Center, Medical Center Boulevard, Winston-Salem, North Carolina

⁴Division of Vascular and Interventional Radiology, Department of Radiology, National Institutes of Health, Bethesda, Maryland

Address for correspondence Bill S. Majdalany, MD, Department of Radiology and Imaging Sciences, Emory University Hospital, 1364 Clifton Road NE, Suite AG05, Atlanta, GA 30322 (e-mail: bmajdal@emory.edu).

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Abstract

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- ▶ lymphatic
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Lymphatics have long been overshadowed by the remainder of the circulatory system. Historically, lymphatics were difficult to study because of their small and indistinct vessels, colorless fluid contents, and limited effective interventions. However, the past several decades have brought increased funding, advanced imaging technologies, and novel interventional techniques to the field. Understanding the history of lymphatic anatomy and physiology is vital to further realize the role lymphatics play in most major disease pathologies and innovate interventional solutions for them.

History

The classic tale of Gaspare Aselli's vivisection of a well-fed dog to discover lacteals is often repeated, yet lymphatic history stretches back further. The first recorded discovery of a lymphatic structure was the lymph node in the 5th century BCE by Hippocrates. He found many nodes scattered around the body, calling the fluid contained within "ichor." Aristotle, in the 4th century BCE, described colorless humors called "sanies," potentially being the first description of lymph vasculature. For the next two millennia, many individuals would discover various components and functions of the lymphatic system; Galen (3rd century BCE) with lacteals and the thymus, Paul of Aegina (7th century CE) with infected lymph nodes, Nicola Massa (16th century CE) with renal lymphatic vessels, and Bartolomeo Eustachi (16th century CE) with the thoracic duct. However, it was not until the 17th century physician Gaspare Aselli's well-documented discovery of "venae albae aut lacteae" that the lymphatic system was formally recognized.¹

Aselli, while credited with discovering gut lacteals, mischaracterized the overall flow of lymph, stating it to be from the pancreas, to the liver, and then to the blood. This was corrected several decades later by Jean Pecquet in 1651, who also discovered the cisterna chyli and thoracic duct, and first described the valvular nature of lymphatic vessels. Just 2 years later in 1653, Thomas Bartholin discovered systemic lymphatic vessels outside the gut and liver, thus differentiating systemic lymphatic fluid from mesenteric lymphatic fluid and ultimately naming this fluid "lymph."

Overview of Anatomy and Physiology

The lymphatic system functions as a diffuse network of vasculature that exchanges, transports, and reabsorbs a wide variety of molecules and cells. While the circulatory system utilizes the heart to provide a central motor force, the lymphatic system is propelled by a combination of peripheral osmotic and oncotic forces, smooth muscle within vessel walls, and decentralized muscle contractions throughout the

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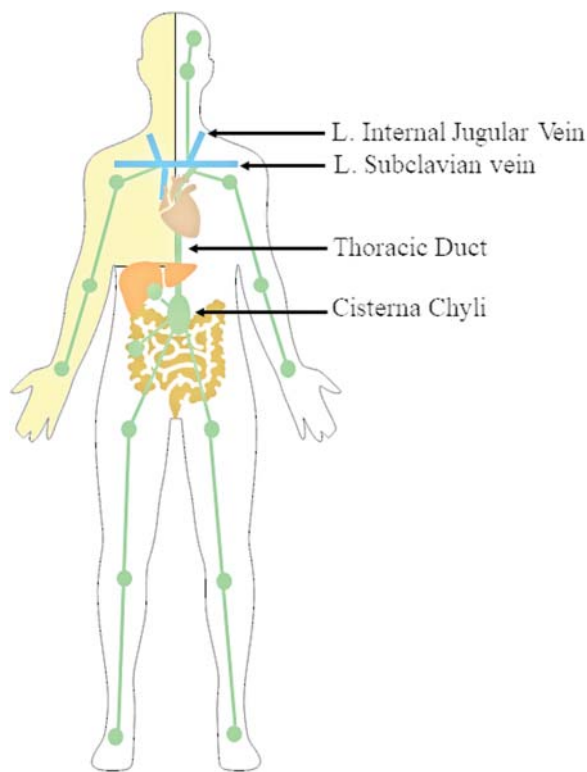


Fig. 1 Overview of lymphatic flow in the body. The lower extremities, left upper extremity, left head, left hemithorax, and subdiaphragmatic organs drain into the cisterna chyli and transit through the thoracic duct emptying into the left venous angle, near the junction of the left internal jugular and subclavian veins. The right upper extremity, head, and hemithorax (drainage pattern shaded yellow) drain to the right lymphatic duct, near the junction between the right internal jugular and subclavian veins.

body. Breslin et al aptly described the analogy best: “[while arteries and] veins [function] like a super highway, lymphatics are slow local roads eventually leading to the heart.”²

The lymphatic system can be thought of as numerous independent compartments that progressively coalesce to empty into the venous circulation. Each compartment serves distinct functions and contains lymph of varying compositions. While the lymphatic system includes lymphoid organs such as the thymus and the spleen, the scope of this article will be limited to the three major lymphatic compartments: soft-tissue/peripheral lymphatics, intestinal lymphatics, and hepatic lymphatics.

Lymph produced from these compartments coalesce into the cisterna chyli, then giving rise to the thoracic duct which ultimately returns fluid to the venous circulation at the junction of the left subclavian and internal jugular veins (→ **Fig. 1**). While this is the classical depiction, numerous smaller lymphovenous connections and anatomical variants exist.

The soft-tissue or peripheral lymphatics are distributed throughout much of the soft tissue across the body and serve numerous physiological purposes, with fluid homeostasis and immunological surveillance being the most well-studied. These functions are standard for all other lymphatic compartments as well.

The intestinal lymphatics include much of the lymphatic vessels draining the small and large intestines (also termed

“lacteals”) and include the intestinal Peyer’s patches. In addition to the classic lymphatic functions, the intestinal lymphatics absorb dietary fats from the intestines and deliver this fat into circulation.

The hepatic lymphatics have historically been difficult to image due to their small caliber, but recent advances in imaging modalities have assisted greatly. Lymph flowing from the liver has the additional function of delivering hepatic proteins synthesized in the liver to the systemic circulation.

Microarchitecture and Microphysiology

Lymphatic flow begins at the arteriovenous-capillary junction. A diminishing, but net positive filtration pressure is present at this junction with an estimated 8 to 12 L of fluid extravasated into the surrounding interstitium daily.²⁻⁴ The lymphatic system is responsible for the majority of fluid resorptive efforts in the body. Small, blind-ended, lymphatic vessels in surrounding tissue termed “initial lymphatic vessels” or “lymphatic capillaries” reabsorb this lost fluid. These initial lymphatic vessels are microscopically arranged in a leaf-like orientation, which function as a one-way valvular structure. They are formed by a single layer of endothelial cells organized on a discontinuous basement membrane^{5,6} (→ **Fig. 2**). Once this fluid has entered the lymphatic system, it is termed “lymph.”

The composition of this early lymph differs widely across the body and is determined by the organ or tissue from which drainage occurs. This initial composition of lymph is typically like that of plasma, consisting primarily of water alongside nutrients, plasma proteins, antigens, humoral factors, and many other components.⁶ Lymph derived specifically from the intestines and liver is termed “chyle” and contains a higher concentration of proteins and chylomicrons—between 0.02 and 0.06 g/mL of proteins, and > 0.01 g/mL of chylomicrons.⁷ This gives chyle a more opaque and milky white appearance as opposed to lymph, which appears clear or lightly translucent.

As lymph flows proximally toward lymph nodes and beyond, initial lymphatic vessels transition into precollecting and then collecting lymphatic vessels. These vessels are lined by lymphatic smooth muscle cells and have continuous tight junctions between vessel cells, limiting flow across the vessel wall.⁸ Within the collecting lymphatic vessel are proper intraluminal bicuspid valves formed from endothelial cells and elastin, termed “secondary lymphatic valves,” which limit retrograde lymph flow.² The length of lymphatic vessel between two valves is termed a “lymphangion” and is the functional unit of the lymphatic system.⁶

Lymph flows proximally by both active and passive mechanisms. Lymphatic smooth muscle cells actively contract in a systematic fashion, while neighboring arterial contractions, smooth and skeletal muscle contractions, and pressure gradients passively assist.⁹⁻¹¹ Lymphangions can contract both independently or synchronously with neighboring lymphangions and are thought to be coordinated by local feedback nervous tissue rather than central nervous system control, given the decentralized nature and speed of coordination.¹²

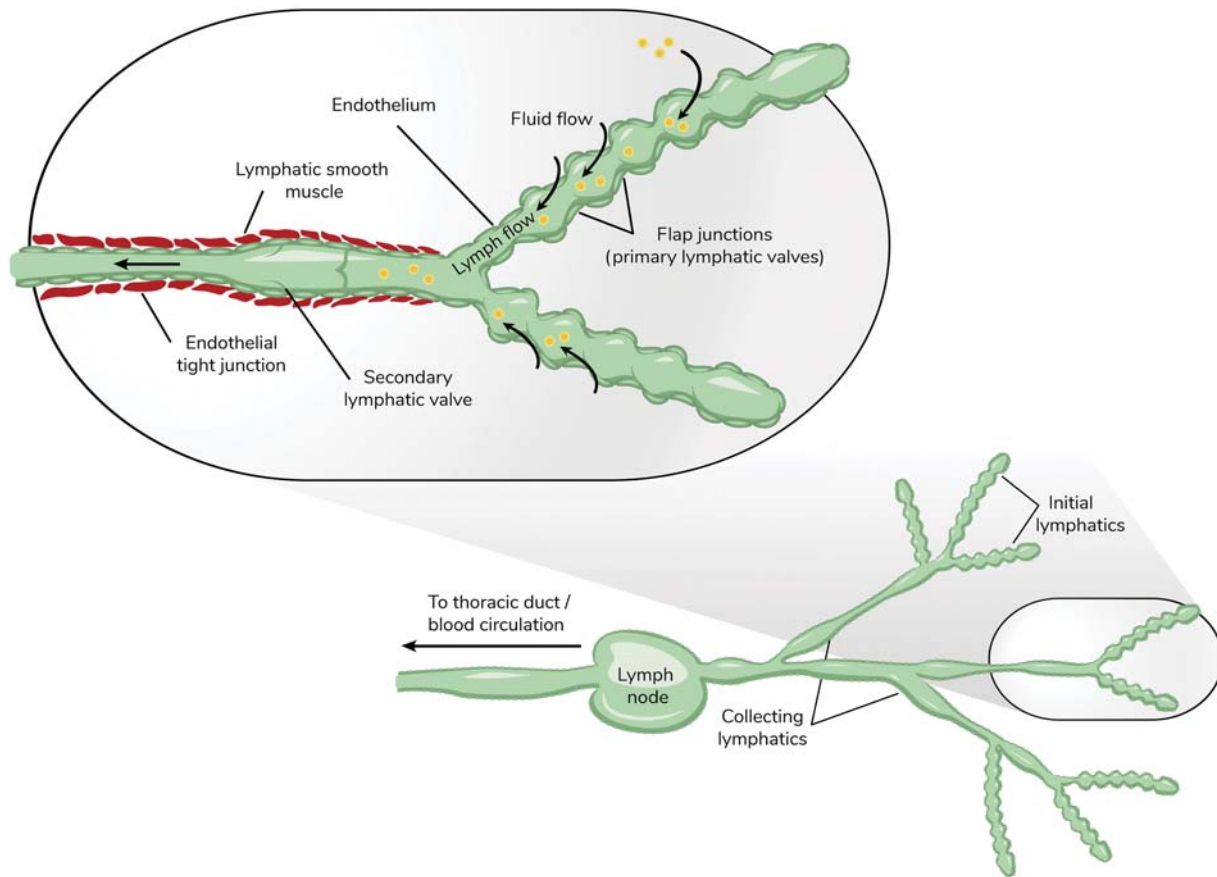


Fig. 2 Diagram of lymphatic microanatomy. Initial lymphatic vessels converge into collecting lymphatic vessels, which flow into lymph nodes. Initial lymphatics have leaky flap junctions allowing fluid to enter while collecting lymphatics have tight junctions surrounded by smooth muscle to propel lymph forward.

As smaller caliber lymphatic vessels (both initial lymphatic vessels and collecting lymphatic vessels) progressively converge into larger vessels, each will flow into lymph nodes. Lymph nodes generally receive multiple afferent vessels and fill several roles, the most studied being immunologic function. The node itself houses lymphocytes (primarily dendritic cells and memory T-cells) to serve as immunologic first responders against infectious and malignant agents. Many cancers spread through the lymphatics, and these drainage pathways are the foundational principles for sentinel node biopsy research.

Lymph nodes also concentrate lymph. Each node has a dedicated artery and vein which allows excess water to be osmotically reabsorbed. This leads to increased postnodal lymphatic oncotic pressure, as approximately 4 L of fluid is reabsorbed at the lymph node level.¹² This aids in overall fluid homeostasis and helps generate some of the driving force for proximal lymph flow.

Cisterna Chyli and Thoracic Duct

Most lymphatic vessels and lymph nodes below the diaphragm coalesce and drain into a central lymphatic sac located at the T12–L2 level termed the “cisterna chyli” (→Fig. 3).¹³ The cisterna chyli is usually 1 to 2 cm long, with an average diameter of 6.7 mm (→Fig. 4).¹³ Given the considerable anatomic variability of the lymphatic system, the cisterna chyli is not always

distinctively present, with one study reporting it in only 52% of cases.¹³ The cisterna chyli serves as a valuable landmark for the lymphatic system and typically receives lymph from the right and left lumbar trunks, the intestinal trunk, and some of the lower intercostal vessels (→Fig. 2). The lumbar trunks receive lymph from the pelvis, kidneys, adrenals, and most of the abdominal wall. The intestinal trunks receive lymph from the gastrointestinal system and will also receive lipid-rich chyle.¹³

After collecting in the cisterna chyli, lymph flows proximally through the thoracic duct, and ultimately empties in the venous circulation at the junction of the left internal jugular and subclavian veins. Like much of the lymphatics, there are many anatomical variants for both the course and the ultimate destination of the thoracic duct. As the largest lymphatic vessel in the body, the thoracic duct is the major lymphatic-venous connection, returning much of the lymph into the systemic circulation.

The thoracic duct begins at the superior aspect of the cisterna chyli and travels cephalad (→Fig. 4). It ascends between the aorta and azygos vein laterally, immediately passing through the aortic hiatus of the diaphragm at the T12 level. As it travels through the posterior mediastinum, the thoracic duct remains anterior to the thoracic vertebrae and intercostal arteries, while staying posterior to the esophagus and pericardium on the right. At the T5 level, it crosses to the left side of the thorax, then running posteriorly to the aorta

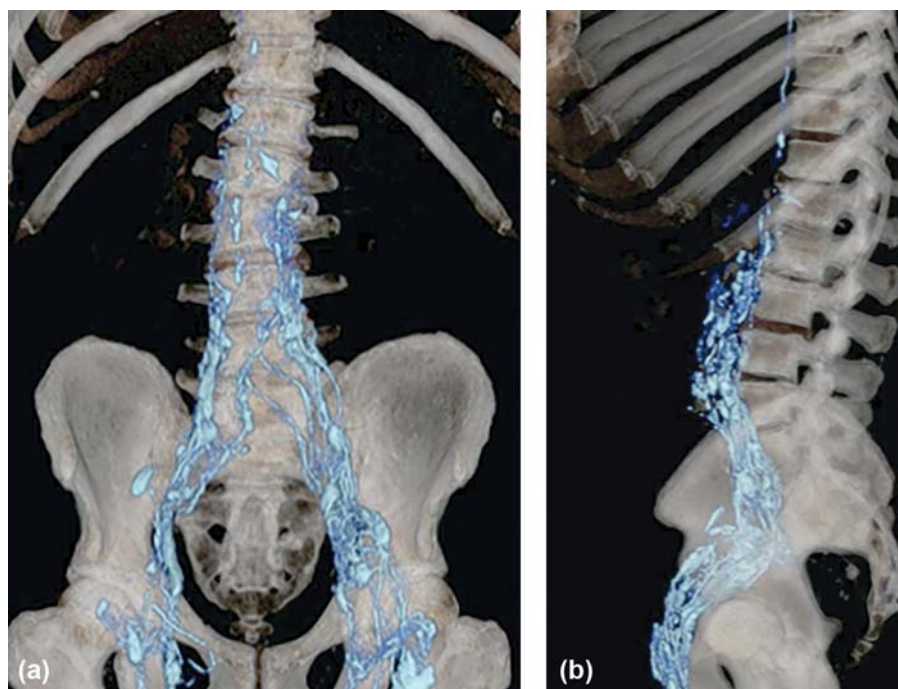


Fig. 3 Volume-rendered CT lymphangiography in coronal (a) and sagittal (b) planes shows coalescing of lymphatic vessels along the pelvic sidewalls to the retroperitoneum overlying the spine.

and subsequent common carotid. The thoracic duct continues to ascend until the C7 level, at which point it descends toward the subclavian and terminates in the venous circulation (► **Fig. 5**).

The thoracic duct, like large caliber arteries, possesses three layers of tissue—intima, media, and adventitia. The media consists of smooth muscle which contracts to assist in lymph flow. Much like other portions of the lymphatic system, the thoracic duct contains predominantly bicuspid valves interspersed throughout to prevent regurgitant flow, especially at lymphatic-venous junctions.¹⁴ The thoracic duct receives all the lymph produced in the body except for the right hemithorax, right head and neck, and right upper extremity. This side of the body has a separate path into the venous circulation via the right lymphatic duct, which similarly empties into the angle between the right subclavian and right jugular trunk (► **Fig. 1**).

Soft-Tissue Compartment

The soft-tissue lymphatic compartment is the most dispersed lymphatic compartment and includes dermal, muscular, and vascular lymphatic networks. The diverse drainage patterns are specific to the respective regions of the body. Soft-tissue lymphatics are important in immune function, fluid resorption, and macromolecular transport.

Dermal lymphatics are especially important for immune function, with skin dendritic cells utilizing initial dermal lymphatics as entry into the lymphatic system. Initial dermal lymphatic tips are found just below the epidermis, forming a two-dimensional polygonal web of initial lymphatic vessels 10 to 20 μm in diameter.^{2,15} From this web, larger lymphatic vessels arise to travel deeper into the dermis as the network

takes on a more three-dimensional appearance, later converging on collecting lymphatics in the subcutaneous layer. As dermal lymphatics progress to larger calibers, their drainage patterns typically follow arterial supply routes (► **Fig. 6**).

Muscular lymphatics assist mostly with fluid resorption and removal of metabolites. During exercise, normal physiology leads to a marked increase in capillary filtration. Consequently, muscular lymphatics show a dramatic increase in lymphatic fluid uptake and flow. Skeletal muscle lymphatics typically follow the arterial distribution for muscular blood supply, with initial muscular lymphatics wrapping around penetrating arterioles or venules within the muscle.² Notably, these lymphatics lack a smooth muscle layer for intrinsic contractile pumping and instead rely on surrounding skeletal muscle contractions to propel their lymph proximally.

Vascular lymphatics are found surrounding major vessels like the aorta, coronary arteries, pulmonary artery, pulmonary vein, and vena cava. Vessels within the thoracic cavity drain to the para-aortic lymph nodes and thoracic duct. These lymphatics are found within the adventitia of the vessel wall and have important lipid removal properties, with several studies demonstrating lymphatic insufficiency leading to atherosclerotic and intimal plaque build-up.¹⁶

Intestinal Lymphatic Compartment

The small and large intestine lymphatics are responsible for fat absorption, immune surveillance, and fluid balance, with the small intestine lymphatics being the most extensive and nuanced network. The initial small intestinal lymphatic vessels are found within the villi of the small intestine and are termed “lacteals” (► **Fig. 7**). Each villus contains a single lacteal surrounded by a dense arteriovenous capillary network, which is

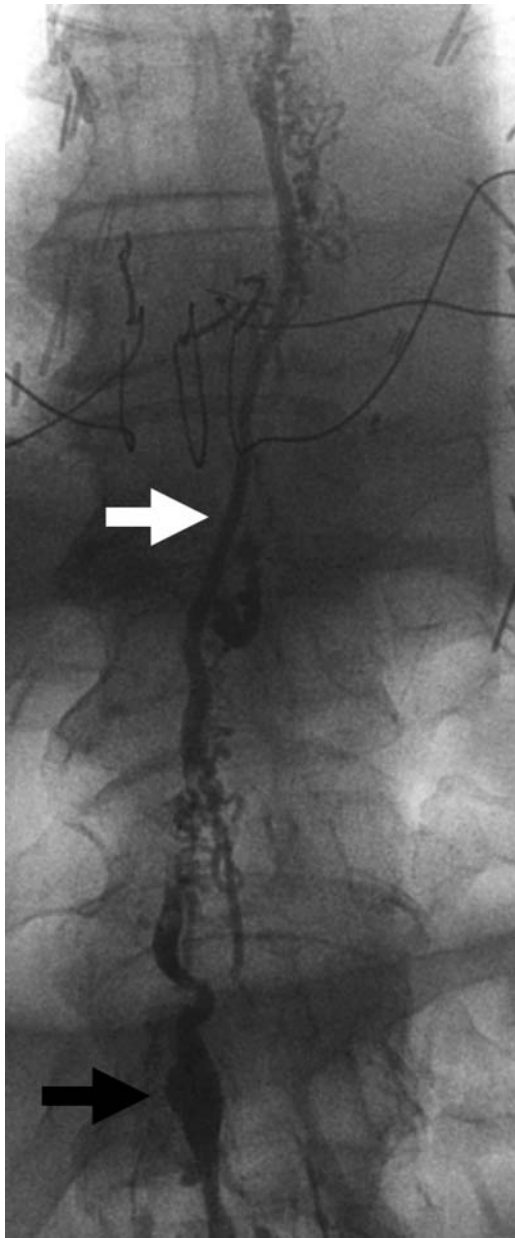


Fig. 4 Radiograph of central lymphatics during lymphangiography reveals a saccular structure at the bottom of the image (black arrow) representing the cisterna chyli, which gives rise to a single main thoracic duct (white arrow), which crosses from right to left as it ascends toward the neck.

responsible for long-chain fatty acid transport. Short-chain fatty acids are metabolized in situ by colonocytes and medium-chain fatty acids are delivered to the liver by the portal vein. Meanwhile, long-chain fatty acids are packaged into chylomicrons and sent into the systemic circulation by small intestinal lymphatics.² These initial lacteals drain into a submucosal lymphatic network which then converges on mesenteric collecting lymphatics.

Mesenteric lymphatics will drain into various lymph nodes, with different intestinal regions draining to different lymph nodes. The drainage patterns typically follow the corresponding intestinal arterial supply. Intestinal regions supplied by the superior mesenteric artery will drain to a cluster of nodes named the superior mesenteric lymph



Fig. 5 Radiograph of the terminal thoracic duct during lymphangiography. The terminal thoracic duct (white arrow) ascends above the left clavicle and has two valves at its communication with the left venous angle (black arrow).

nodes. Likewise, regions supplied by the inferior mesenteric artery will typically drain to a single node named the inferior mesenteric or caudal lymph node.¹⁷ These nodes will eventually drain into the cisterna chyli and thoracic duct, ultimately emptying their lipid-rich contents into the venous circulation for further transport.

The intestinal mucosa contains various gut-associated lymphoid tissue (GALT), also known as Peyer's patches, which screens intestinal contents for harmful microbes. Native immune cells present in this lymphoid tissue differentiate between pathogenic and commensal bacteria. Like lymph nodes in the soft tissue, Peyer's patches house increased numbers of dendritic cells and T-cells. They also contain M-cells, which are gut-specific antigen-presenting cells. The GALT contains most of the body's immunologic cells, with some estimating 70% of all immunologic cells to be found in the GALT.¹⁸

Moreover, novel research has demonstrated the important role intestinal lymphatics play in endocrine signaling, specifically regarding incretin transport. Incretins, major pharmaceutical targets for diabetic treatments, include glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like-peptide-1 (GLP-1). These signaling molecules travel further and at higher concentrations in lymphatics than in blood, providing an exciting target for future drug delivery.^{2,19}

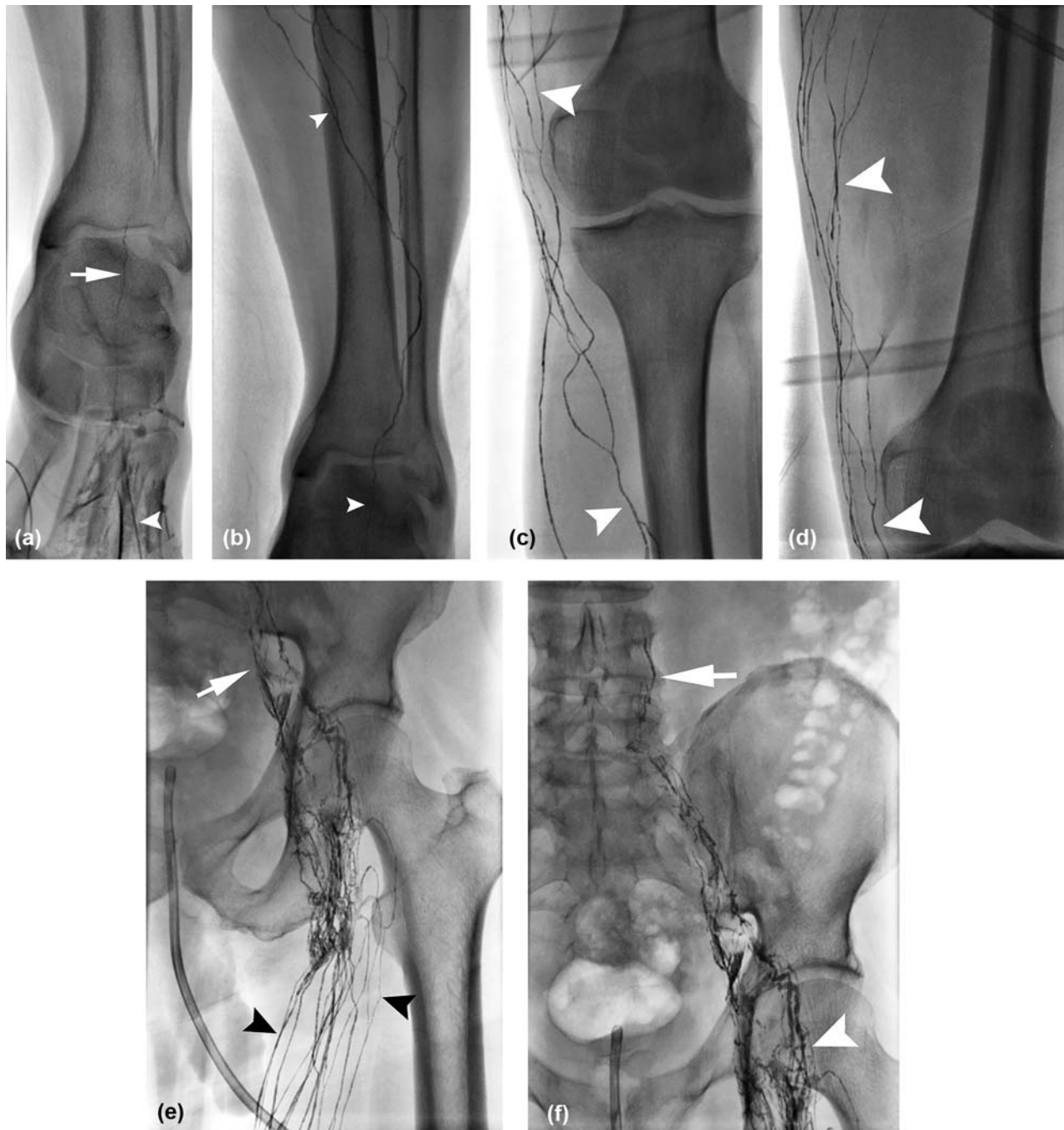


Fig. 6 Pedal lymphangiography of the left leg. (a) A 30-gauge needle (white arrowhead) opacifying a dermal foot lymphatic vessel (white arrow). As ethiodized oil ascends into the (b) lower leg, (c) knee, and (d) thigh, additional channels begin to fill (white arrowheads). All the lymphatic vessels are similar in size. No lymph nodes were visualized from the foot to the thigh. At the level of the pelvis (e), the lymphatic vessels (black arrowheads) converge into inguinal lymph nodes, first seen central to the lesser trochanter, which transmit the dye through multiple lymphatic vessels (white arrow). (f) Interspersed lymph nodes and lymphatic vessels (white arrowhead) are present from the inguinal area, along the pelvic sidewall and into the lumbar lymphatic chain (white arrow).

Hepatic Lymphatic Compartment

Hepatic lymphatics are intimately associated with liver function and lymph supply, producing 25 to 50% of the total lymph in the body.²⁰ The liver receives blood from both the hepatic artery and the portal vein. The hepatic artery delivers fresh, oxygenated blood from the heart, while the portal vein delivers deoxygenated, nutrient-rich blood from the intestinal veins. The classical functional unit of the liver is the

microscopic hexagonal liver lobule. Within each lobule, small branches of the hepatic artery and portal vein join to form hepatic sinusoids, which are small fenestrated capillaries allowing arterial and portal blood to freely mix. The sinusoids are surrounded by functional hepatocytes and between them exists the perisinusoidal space of “Disse.” This space is where nutrients, cells, and fluid are exchanged between blood and hepatocytes and is also where most of the hepatic lymph is formed.²¹ Excess fluid in the space of Disse

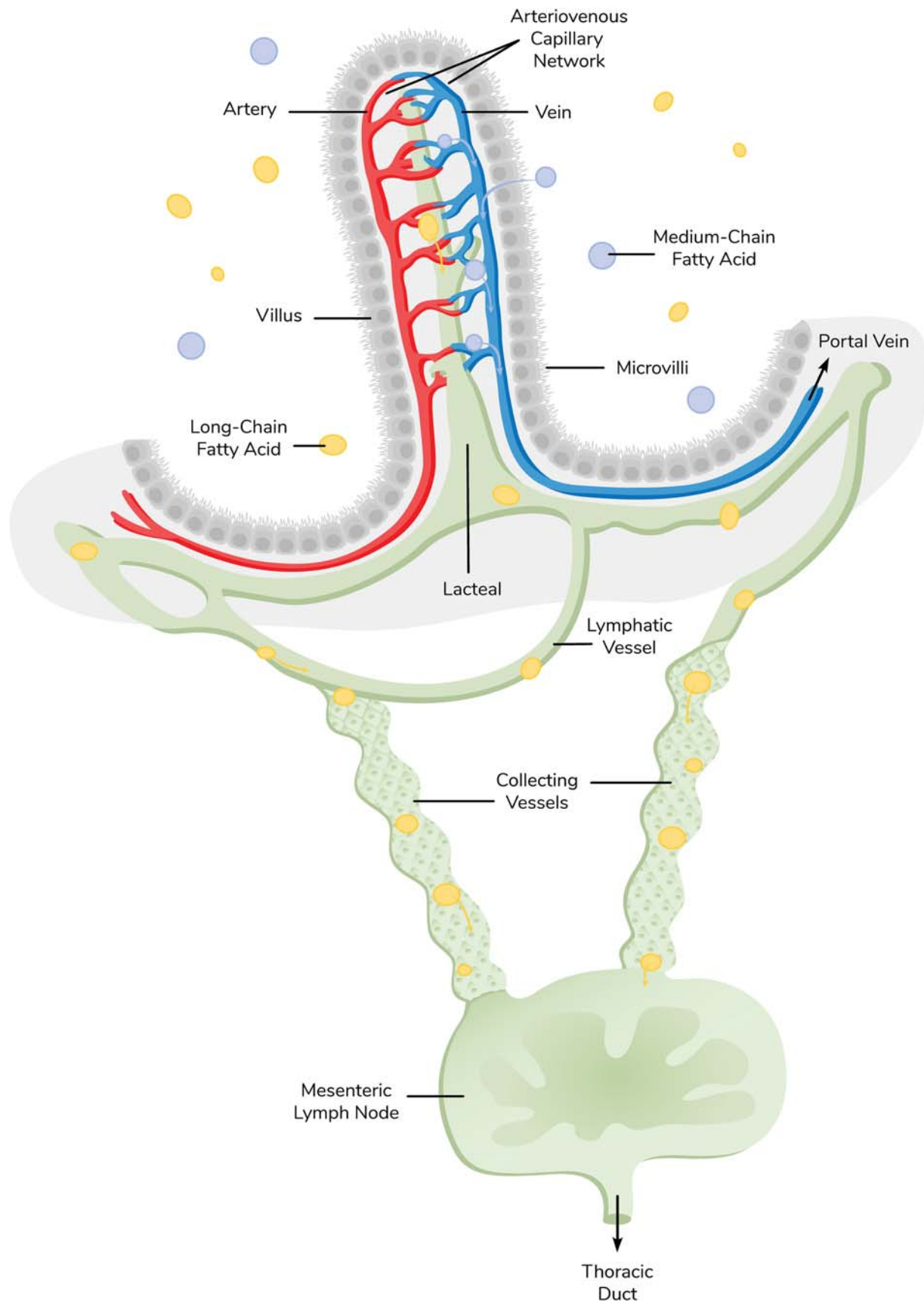


Fig. 7 Schematic showing intestinal microvilli. Each microvillus has an arteriovenous capillary network and a lacteal, with the lacteal absorbing long-chain fatty acids, which are processed into chylomicrons before draining to mesenteric lymph nodes and subsequently the thoracic duct.

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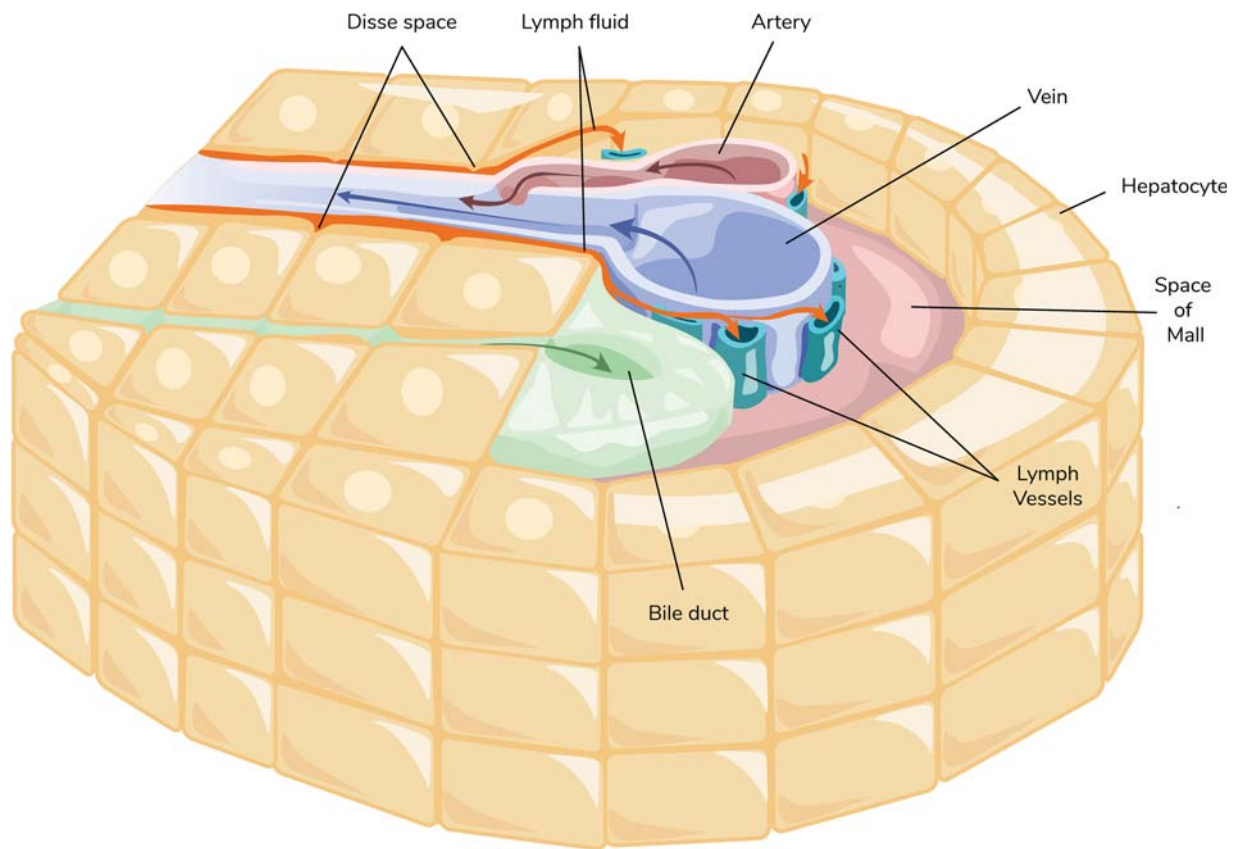


Fig. 8 Diagram of a hepatic sinusoid, depicting origin of hepatic lymph. Blood enters the sinusoid from branches of the portal vein and of the hepatic artery, which allows mixing. Fluid extravasates into the space of “Disse” to flow retrograde, entering initial lymphatic microvessels surrounding the portal vein.

flows between hepatocytes and then along channels parallel to the sinusoids. These channels drain into several initial lymphatic vessels located near branches of the portal vein within each liver lobule (► **Fig. 8**). These lymphatic vessels are named periportal lymphatics due to their proximity to the portal vein.

The hepatic lymphatics are divided into deep and superficial divisions, with some further subdividing the deep division into portal tract lymphatics and sublobular hepatic vein lymphatics. Most hepatic lymph is carried by the deep division, with up to 80% of hepatic lymph originating from portal tract lymphatics.²⁰ The deep hepatic lymphatics drain much of the liver parenchyma, with the portal tract lymphatics and the sublobular hepatic vein lymphatics each, respectively, following the course of the portal triad and hepatic vein (► **Fig. 9**). The portal tract lymphatic division specifically flows to groups of lymph nodes in three regions: near the origin of the superior mesenteric artery, near the hepatic artery and celiac trunk, and near the posterior pancreatic head.²² From these nodes, lymph converges on the para-aortic lymph nodes, which ultimately drain into the thoracic duct.²³ The superficial hepatic lymphatics drain the liver capsule and underlying serosa but is much less systematic or standard in its initial drainage. It also ultimately drains to the thoracic duct.²² These complex hepatic lymph node and lymph drainage patterns are important in preventing hepatic injury, but also leave the liver vulnerable to hepatic

tumor metastases and are hypothesized to be the etiology behind chylous ascites.^{2,23}

Endocrine Lymphatics

The lymphatic system also plays an important, yet often overlooked, role within the endocrine system, with lymphatics extending into the thyroid, pancreas, and gonads.

Like hepatic lymphatics, most solid-organ lymphatics are divided into superficial and deep branches (i.e., lungs, kidneys, heart). The thyroid gland possesses a network of anastomosing lymphatics that both surround the capsule and penetrate between follicles; it has not been shown to extend into the parathyroid glands.² Thyroid lymphatics typically follow the thyroid arterial circulation glands and are functionally significant in thyroid hormone transportation.² Early studies demonstrated thyroid lymph to have an increased thyroxine and thyroglobulin concentration compared with thyroid venous blood and may serve as a reservoir for thyroid hormone.²⁴

Daily pancreatic lymph production is relatively small, and the lymphatic network has not been shown to extend into the islets of Langerhans. However, initial pancreatic lymphatic vessels are found at the exocrine acinar cells and extend to the pancreatic ducts and connective tissue.² Lymph from the pancreas drains either directly into the thoracic duct or to the cisterna chyli.²⁵

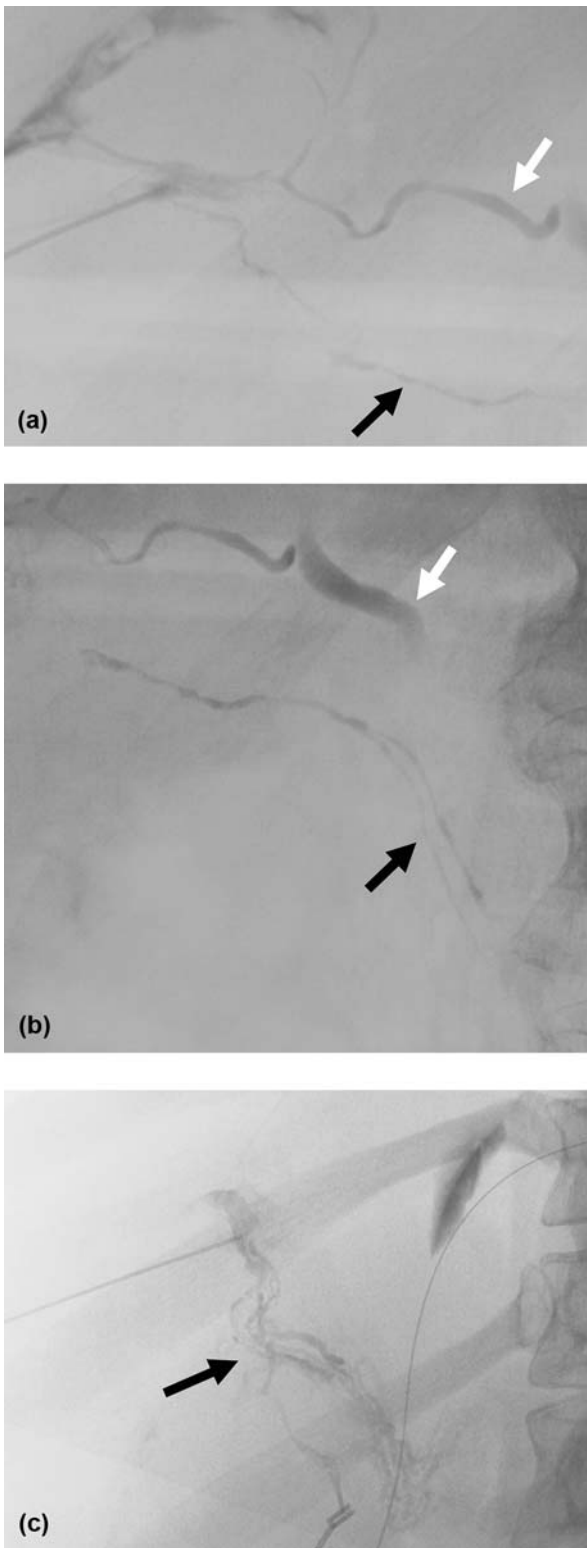


Fig. 9 Hepatic lymphangiography and cholangiography. A 22-gauge needle was passed into the liver and contrast was injected while it was withdrawn, opacifying (a) a peripheral lymphatic vessel (black arrow) and biliary radical (white arrow). (b) The biliary tree (white arrow) becomes larger as it centralizes, while the lymphatics (black arrow) do not markedly enlarge in size and bifurcate. (c) The 22-gauge needle was repositioned centrally in the hepatic hilum and opacified the lymphatics (black arrow), which are tortuous, redundant, and extend to the hepatoduodenal ligament, along the portal vein. Cholecystectomy clips are present at the bottom of the image and a microwire is present in the left hepatic duct and central biliary tree.

Gonadal lymphatics have mostly been studied in animals. Both ovarian and testicular lymphatics have been shown to be extensive in reach and function. Like thyroid lymphatics, gonadal hormones are found at increased concentrations within lymph, similarly implying that gonadal lymphatics may serve as a hormone reservoir. Specifically, ovarian steroid hormones within ovarian lymph are found at higher concentrations than peripheral blood, but lower than ovarian venous blood.² Likewise, testicular lymph was shown to have up to 10 times the concentration of estrone sulfate and dehydroepiandrosterone sulfate relative to testicular venous blood.²⁶ Testicular lymph notably did not show a significant role in testosterone transport or storage.²⁷ Gonadal lymphatic physiology requires additional research to better understand its scope, but its drainage patterns are crucial for interpreting gonadal tumor metastases.

Conclusion

Previously understudied, lymphatics are an emerging frontier in medicine. An understanding of lymphatic anatomy and physiology will further allow for novel lymphatic-based pharmaceuticals and interventions, further transforming treatment paradigms.

Disclosures

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Conflict of Interest

None declared.

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All authors have read and contributed to this manuscript.

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