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Mechanical forces and lymphatic transport

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ABSTRACT

This review examines the current understanding of how the lymphatic vessel network can optimize lymph flow in response to various mechanical forces. Lymphatics are organized as a vascular tree, with blind-ended initial lymphatics, precollectors, prenodal collecting lymphatics, lymph nodes, postnodal collecting lymphatics and the larger trunks (thoracic duct and right lymph duct) that connect to the subclavian veins. The formation of lymph from interstitial fluid depends heavily on oscillating pressure gradients to drive fluid into initial lymphatics. Collecting lymphatics are segmented vessels with unidirectional valves, with each segment, called a lymphangion, possessing an intrinsic pumping mechanism. The lymphangions propel lymph forward against a hydrostatic pressure gradient. Fluid is returned to the central circulation both at lymph nodes and via the larger lymphatic trunks. Several recent developments are discussed, including evidence for the active role of endothelial cells in lymph formation; recent developments on how inflow pressure, outflow pressure, and shear stress affect the pump function of the lymphangion; lymphatic valve gating mechanisms; collecting lymphatic permeability; and current interpretations of the molecular mechanisms within lymphatic endothelial cells and smooth muscle. An improved understanding of the physiological mechanisms by which lymphatic vessels sense mechanical stimuli, integrate the information, and generate the appropriate response is key for determining the pathogenesis of lymphatic insufficiency and developing treatments for lymphedema.

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Introduction

The mammalian lymphatic system has an important role in overall health, collectively through its contributions to extracellular fluid and protein homeostasis, lipid transport, and immunity. Lymphatic insufficiency causes lymphedema, which in its worst form is a deforming and debilitating disease with severe swelling throughout the body. Mild forms of lymphedema are more prevalent, and certain populations, like cancer survivors, are at risk for development of lymphedema (Beesley et al., 2007; Petrek et al., 2001). As with all living tissues, organs, and organ systems, a key characteristic of the lymphatic system is its ability to detect and respond to a variety of physical and chemical cues in order to optimize function under varying conditions. Lymph flow can vary widely, with 10- to 15-fold changes recorded,

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when standing up from a supine position, and as high as 63-fold by foot warming in standing individuals (Olszewski et al., 1977). Others have reviewed the impact of mechanical forces on lymphatic development and lymphangiogenesis in detail (Planas-Paz and Lammert, 2013; Wiig and Swartz, 2012). This review will highlight recent advances to our understanding of how lymphatic vessels optimize lymph flow in response to mechanical forces.

Organization of the lymphatic system

Lymphatics are organized as a vessel tree (Fig. 1), with the most distal, blind-ended vessels serving as the site where interstitial fluid enters the system to form lymph. Terms to describe these blind-ended vessels include lymphatic capillaries (based on fluid exchange function), terminal or peripheral lymphatics (both based on location at the end of the vascular tree), and initial lymphatics (based on being the site of lymph formation). The initial lymphatics are thin-walled vessels composed of a single layer of endothelial cells, with an incomplete basement membrane. They typically form interconnected networks with features that are tissue specific, like the blind-ended lacteals inside intestinal villi (a comprehensive review of tissue-specific initial lymphatic networks is featured in Schmid-Schonbein, 1990). The diameters of initial lymphatics vary widely depending on tissue and species. The smallest initial lymphatics reported are the lacteals within rat intestinal villi, as small as 5–15 μm in specimens fixed and viewed by electron microscopy, or 15–30 μm when filled with fluid and viewed by intravital microscopy (Lee, 1979; Ushiki, 1990). Much larger initial lymphatic diameters, as high as 450 μm, have been observed in the bat wing (which are also exceptional in that they possess a smooth muscle layer) (Webb and Nicoll, 1944). Rat mesenteric and human skin initial lymphatics typically fall within ranges of 25–50 and 35–70 μm, respectively (Fischer et al., 1996; Zweifach and Prather, 1975).

The endothelial cells of initial lymphatics feature specialized intercellular junctions, described as “buttons” that give each cell an “oak leaf” shape (Baluk et al., 2007; Murfee et al., 2007). These button junctions display an alternating pattern of the adhesion proteins VE-cadherin and PECAM-1, forming overlapping leaflets of cell membrane between adjacent cells (Baluk et al., 2007), and are thought to act as microscopic one-way valves, termed primary valves, that favor entry of fluids, macromolecules, and lymphocytes into the lymphatic lumen (Murfee et al., 2007; Schmid-Schonbein, 1990; Trzewik et al., 2001). In addition to this paracellular route of fluid entry, the initial lymphatic endothelial cells have significant expression of the water channel aquaporin-1, suggesting transcellular water transport across the initial lymphatic may contribute to lymph formation (Gannon and Carati, 2003).

The initial lymphatic vessel segments coalesce into larger, collecting lymphatics. The collecting lymphatics are distinguished by having both endothelial and smooth muscle layers, and an adventitia that can contain fibroblasts, connective tissue, MHC-II + antigen presenting cells, nerves that innervate the vessel, and vasa vasorum (Bridenbaugh et al., 2013; Schmid-Schonbein, 1990; Zawieja et al., 2008). While the lymphatic smooth muscle cell organization varies between species, in general the amount of smooth muscle increases when moving centrally along the lymphatic tree. The functional importance of the smooth muscle layer is that it establishes both a vessel tone and a phasic contractile cycle that drives lymph flow (von der Weid, 2001; Zawieja et al., 2008). Another important feature of collecting lymphatics is their organization into segments, termed lymphangions, which have unidirectional valves at each end. These valves, which are bicuspid flaps composed of endothelial cells and connective tissue, prevent backflow of lymph. This is of particular importance in humans standing upright, in which lymph must flow against a significant hydrostatic gradient. These luminal unidirectional valves are referred to as “secondary valves” to distinguish them from the microscopic leaflets between endothelial cells of initial lymphatics (Schmid-Schonbein, 1990; Zawieja et al., 2008). The transition from initial lymphatic to collecting lymphatic is easily distinguishable in some tissues, like mesentery. However, in the skin, an intermediate network of lymphatics known as precollectors lies between the initial and collecting lymphatics. Notable features of precollectors is the appearance of secondary valves, yet there is no smooth muscle layer or phasic contractions (Schmid-Schonbein, 1990). Also, the precollector endothelial

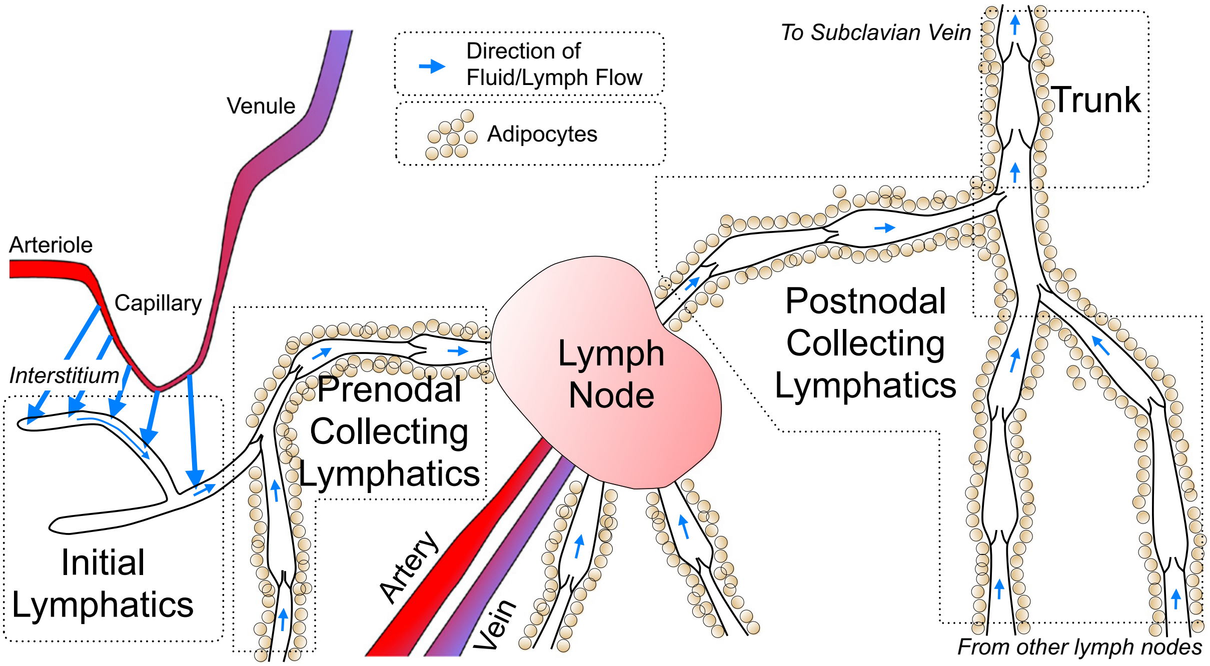

Fig. 1. Schematic view of lymph formation and transport. The interstitial fluid formed by capillary filtration moves toward initial lymphatics (large blue arrows). This fluid then moves along the initial lymphatic network into contractile prenodal collecting lymphatics (small blue arrows). The collecting lymphatics frequently are surrounded by adipocytes and bring lymph to one or more lymph nodes, where some of the lymph fluid is lost to the blood circulation. A single postnodal collecting lymphatic exits a lymph node, eventually coalescing with other collecting lymphatics into a larger lymph trunk. The two largest, main trunks of this vascular tree (thoracic duct, right lymph duct) empty into the left and right subclavian veins, respectively.