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Review

Mechanobiology of lymphatic contractions

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ABSTRACT

The lymphatic system is responsible for controlling tissue fluid pressure by facilitating flow of lymph (i.e. the plasma and cells that enter the lymphatic system). Because lymph contains cells of the immune system, its transport is not only important for fluid homeostasis, but also immune function. Lymph drainage can occur via passive flow or active pumping, and much research has identified the key biochemical and mechanical factors that affect output. Although many studies and reviews have addressed how tissue properties and fluid mechanics (i.e. pressure gradients) affect lymph transport [1–3] there is less known about lymphatic mechanobiology. As opposed to passive mechanical properties, mechanobiology describes the active coupling of mechanical signals and biochemical pathways. Lymphatic vasomotion is the result of a fascinating system affected by mechanical forces exerted by the flowing lymph, including pressure-induced vessel stretch and flow-induced shear stresses. These forces can trigger or modulate biochemical pathways important for controlling the lymphatic contractions. Here, I review the current understanding of lymphatic vessel function, focusing on vessel mechanobiology, and summarize the prospects for a comprehensive understanding that integrates the mechanical and biomechanical control mechanisms in the lymphatic system.

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Contents

1. Lymphatic anatomy and network topology

Blood microvasculature is somewhat permeable to water and proteins, and a fraction of the circulating plasma extravasates into tissue wherever there is a transmural pressure driving force. This can establish pressure gradients that extend from the blood vessels to the lymphatic system, allowing for flow of plasma through the tissue, into the lymphatics. The process of flushing the extravascular space with plasma is likely useful for conditioning the extracellular matrix and providing biomechanical signals to cells, but it relies on proper pressure distribution in the tissue: if the pressure in the lymphatic bed is not lower than that in the surrounding tissue – at least transiently – then there is accumulation of pressure and fluid, resulting in edema.

The lymphatic system is responsible for maintaining proper tissue-fluid balance [4] and organizing the immune response. Fluid from the tissue first enters blind-ending lymphatic capillaries, termed *initial lymphatics* (Fig. 1). The initial lymphatic walls are formed by overlapping endothelial cells that act as one-way valves to allow fluid into the vessels, but not out [5,6]. Initial lymphatics pass the fluid to *collecting lymphatics*, which constitute a system of variable-demand, distributed pumps [7]. Distinct compartments (lymphangions) within each collecting lymphatic vessel are defined by intraluminal luminal one-way valves [8–10]; lymphangions can

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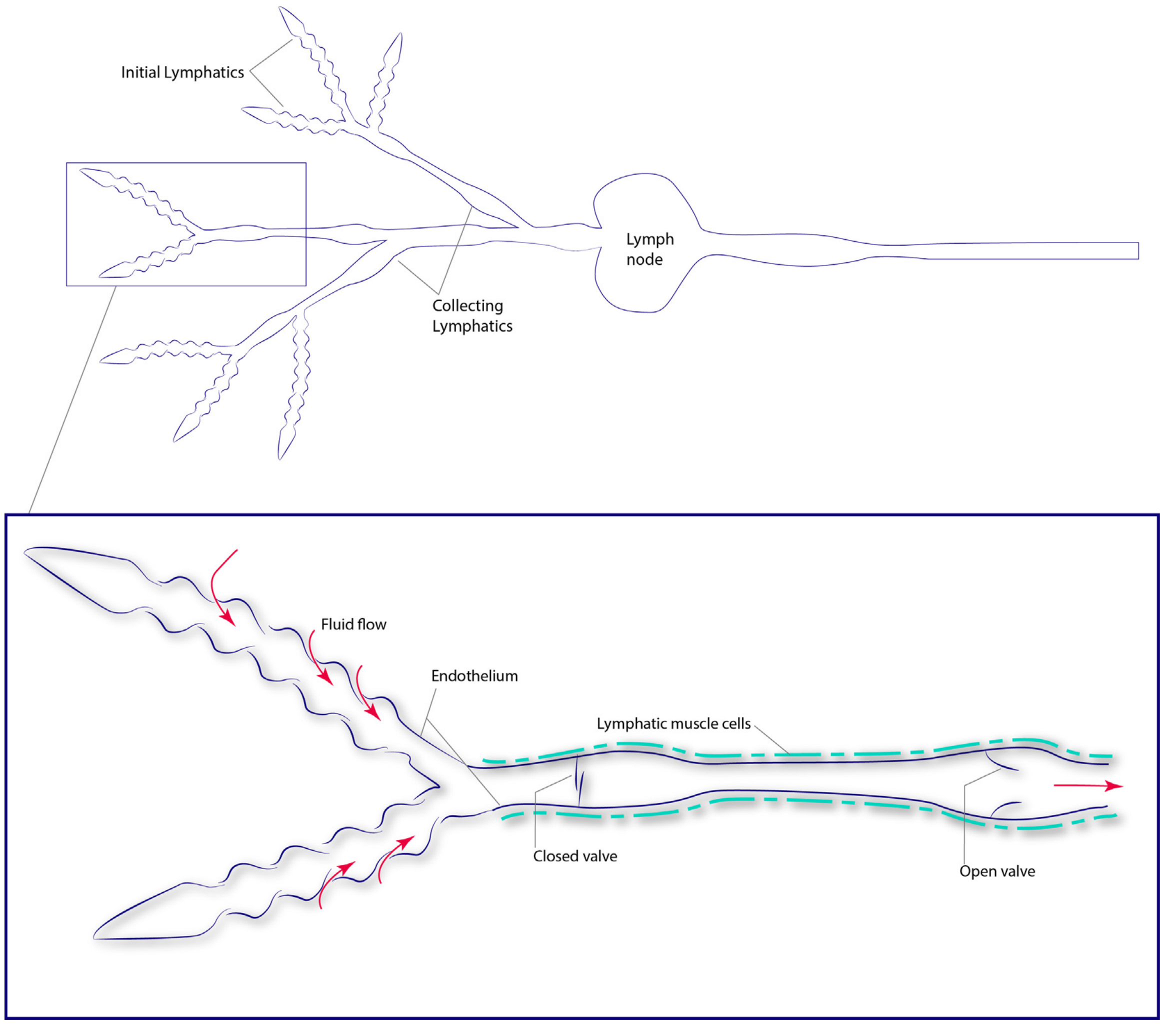

Fig. 1. Lymphatic network topology and anatomy.

drive flow via contractions of their muscle-invested walls. The collecting lymphatic vessels are arranged in a converging tree-like network, and lymph nodes are distributed throughout, so that lymph passes through them on the way back to the blood circulation [5].

However, active lymphatic pumping is not always operational, and deficient lymphatic pumping is involved in multiple clinical problems, including metabolic disorders [11], local immunocompromise [12,13], and lymphedema (fluid accumulation in tissue). The lymphatic system is also involved in cancer progression, as entry of metastatic cancer cells into the lymphatic system can result in lymph node metastases. Thus, the lymphatic system is central to a variety of pathological processes.

A key question is how a connected network of pumps (lymphangions) can coordinate the contractions to move fluid efficiently back to the large veins. In the diverging arterial network of the cardiovascular system, flow is achieved by a single, central pump (the heart), and only relatively small (but important) local adjustments of diameters are able to achieve correct flow distribution to the capillaries. The inverse problem, which exists in the converging lymphatic network, is more difficult. One-way valves must be arranged appropriately, and individual contractions coordinated along vessels and at branch points so that the system does not "fight against itself".

Therefore, an overarching communication system might exist to provide the necessary coordination of the contractions. Although many studies have delineated the various mechanical and chemical perturbations that affect phasic contractions, there are still questions about their role in organizing the contractions.

2. Lymphatic contractions: calcium dynamics, pacemaker potentials and mechanobiology of stretching

To actively move fluid, the lymphangions have to contract, increasing local fluid pressure, which closes upstream – and opens downstream – valves. The contractions are driven by Ca^{2+} fluxes from extracellular and intracellular stores, which operate through myosin light chain kinase (MLCK) to allow binding of actin with the myosin light chain crossbridges, generating force [14–17].

To control lymphatic pumping on the larger scale, there needs to be synchronization of the calcium dynamics [18]. Coordination of the pumping should lead to a decrease in pressure pulses over the network, and indeed this is observed, especially with high lymph flow states. This implies that the active pumping is organized so that pressure pulses are smoothed as the lymph moves up the lymphatic tree [19]. Conceptually, there are many possible modes in which the contractions might synchronize. For example, in a series of lymphangions, all the odd numbered segments might contract at the same time that the even numbered segments are relaxing (Fig. 2A). This would serve to move the fluid effectively in "bucket brigade" style. Alternatively, two lymphangions might contract together, moving fluid downstream to the next pair

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