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Review

Connexins in lymphatic vessel physiology and disease

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ABSTRACT

Connexins are transmembrane proteins that form gap junction- and hemi-channels. Once inserted into the membrane, hemi-channels (connexons) allow for diffusion of ions and small molecules (<1 kDa) between the extracellular space and the cytosol. Gap junction channels allow diffusion of similar molecules between the cytoplasms of adjacent cells. The expression and function of connexins in blood vessels has been intensely studied in the last few decades. In contrast, only a few studies paid attention to lymphatic vessels; convincing *in vivo* data with respect to expression patterns of lymphatic connexins and their functional roles have only recently begun to emerge. Interestingly, mutations in connexin genes have been linked to diseases of lymphatic vasculature, most notably primary and secondary lymphedema. This review summarizes the available data regarding lymphatic connexins. More specifically it addresses (i) early studies aimed at presence of gap junction-like structures in lymphatic vessels, (ii) more recent studies focusing on lymphatic connexins using genetically engineered mice, and (iii) results of clinical studies that have reported lymphedema-linked mutations in connexin genes.
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1. Introduction

Connexins form a protein family consisting of 21 members in humans and 20 members in mice [1,2]. These transmembrane proteins form hexamers in either the endoplasmic reticulum (ER) or the Golgi apparatus that, once inserted in the membrane, can function as a hemi-channel (connexon) or as part of a gap junction channel (Fig. 1). Connexons allow diffusion of small soluble molecules (<1000 Da, e.g. ATP, Ca^{2+}, cAMP and IP_3) from the cytosol to the extracellular space and *vice versa* [3]. Gap junctions permit diffusion of similarly sized molecules between the cytoplasms of adjacent cells [4]. Most cell types express connexins and many cells express more than one connexin subtype. Their (patho-)physiological contribution to intercellular communication and synchronization of tissue responses in, for example, the brain, heart, arterial endothelium and glomeruli has been extensively studied. The results of these studies have been summarized elsewhere in excellent reviews (see e.g. [5–9]). However, their *in vivo* expression in lymphatic vessels has only recently been established and their function in lymphatics remains elusive [10,11].

2. Anatomy and physiology of lymphatic vessels

Components of the lymphatic system have already been reported by Hippocrates (an ancient Greek physician) and the anatomy of the lymphatics was characterized almost completely in the 19th century [12]. The lymphatic vasculature is composed of a branched network of capillaries and collecting lymphatic vessels that are present in most organs (Fig. 2) [13–15]. Unlike capillary blood vessels, lymphatic capillaries are blind-ended. Anchoring filaments attach the lymphatic endothelial cells (LECs) of the capillary to the extracellular matrix (ECM) and prevent vessel collapse under the conditions of increased interstitial pressure. Small capillaries drain into pre-collecting and collecting vessels, which join the thoracic duct or the right lymphatic trunk. Ultimately, lymph is returned to venous circulation at the junctions with subclavian vein. Lymphatic capillaries have sparse and discontinuous basement membrane and they lack pericytes. In contrast, collecting lymphatic vessels are covered with continuous basement membrane and smooth muscle cells (SMCs). Collecting lymphatic vessels are composed of series of functional units, called lymphangions, separated by intraluminal valves. Lymphatic valves are necessary for ensuring unidirectional lymph flow; they consist of two semilunar leaflets, covered on both sides by a specialized endothelium anchored to the ECM [16]. High lymph pressure upstream of a valve opens the valve and enables lymph flow,

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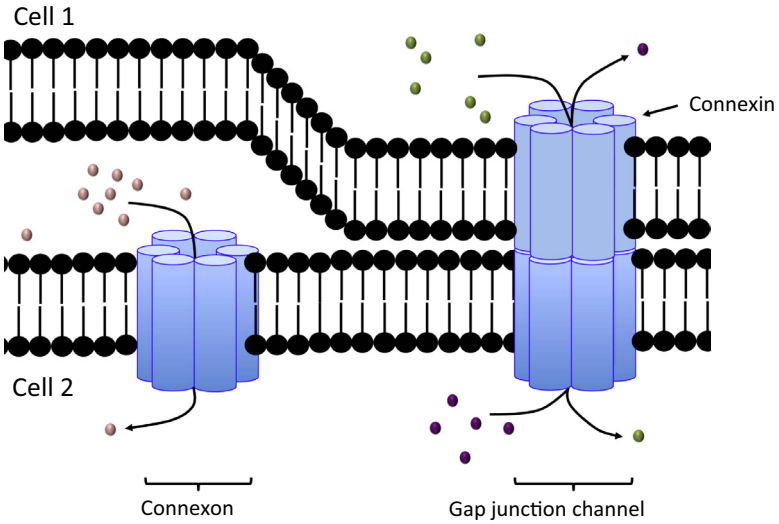

Fig. 1. Schematic structure of connexins, connexons and gap junction channels. Connexins are transmembrane proteins that are inserted in the membrane as hexamers. These hexamers can function as hemichannels, or connexons, which allow diffusion of small molecules from the cytosol towards the extracellular space or *vice versa*. Alternatively, a connexon can dock to a connexon expressed by a neighbouring cell to form a gap junction channel. Gap junction channels allow direct intercellular exchange of small molecules.

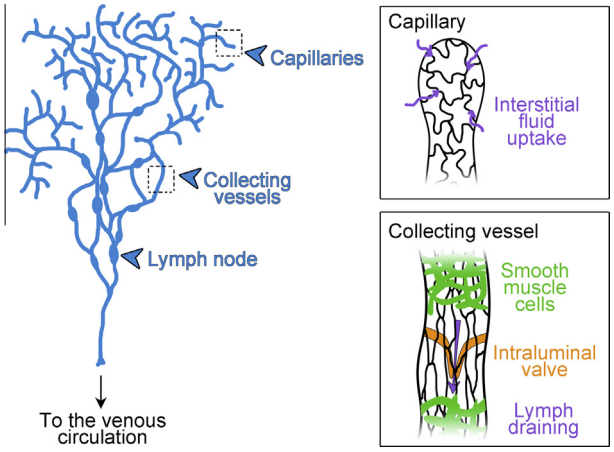

Fig. 2. Anatomy of the lymphatic vasculature. Lymph is collected by lymphatic capillaries which lack a basement membrane and have discontinuous intercellular junctions. Subsequentely, the lymph flows via pre-collecting lymphatic vessels into lymphatic collecting vessels. Collecting lymphatic vessels have a basement membrane, are surrounded by smooth muscle cells and contain intraluminal lymphatic valves that ensure unidirectional lymph flow. After being filtered by lymph nodes along its way, the lymph returns to the blood circulation at points where larger lymphatic trunks empty into veins in the jugular region.

whereas the flow in reverse direction pushes the leaflets against each other thereby closing the valve. Opening and closure of valves thus depend on periodic changes of fluid pressure gradients within collecting vessels. Lymph propulsion along the lymphatic network is regulated by rhythmic compression and expansion of lymphatic vessels by surrounding tissues and intrinsic pump forces, generated by the spontaneous phasic contractility of SMCs that cover each lymphangion. SMC contractions are controlled by nitric oxide, which regulates the lymphatic pump, as well as by hormones and prostanoids [17,18]. The primary function of the lymphatic system is thus to provide an accessory route for getting the excess of interstitial fluid resulting from (blood) capillary filtration (approx. 3 - liters per day) returned to the blood.

The lymph flows through nodes on its way to returning to the blood. Lymph nodes are organized structures of lymphoid tissue, located at intervals along the lymphatic system, containing follicles of densely packed B and T lymphocytes. The number and size of the follicles in a lymph node may expand tremendously upon encountering a foreign antigen. The lymph transports antigen-presenting cells, e.g. dendritic cells, from peripheral tissues to the lymph nodes where an immune response is initiated. In fact, afferent lymph vessels enter at all parts of the periphery of the lymph node, the lymph penetrates through the substance of the lymph node, and is drained out by an efferent lymph vessel. These vessels export immune effector cells and humoral response factors into the blood circulation [13]. Similarly, tumor cells metastasize through the lymphatic vessels to draining lymph nodes. Tumor-draining sentinel lymph nodes are nowadays generally accepted as prognostic marker for the severity of disease, in particular for breast cancer and melanomas [19].

Finally, lymphatic vessels are also important in lipid metabolism, as lymphatic capillaries in the villi of the small intestine (lacteals) take up dietary lipids in the form of chylomicrons and transport them to the blood circulation via the thoracic duct [20]. Lacteals are also crucial for the uptake of lipid soluble vitamins A, D, E and K from the digestive system. Additional emerging roles that link lymphatic vasculature to the control of cardiovascular function and disease include reverse transport of cholesterol [21,22] and control of hypertension [23]. In summary, the anatomy of lymphatic vessels is firmly established and the role of lymphatics in the transport of interstitial fluid, immune cells and lipids is well recognized.

3. 'Early' evidence for presence of gap junctions and connexins in the lymphatic system

As mentioned before, connexins can form connexons and full gap junction channels. As such, connexins can be involved in autocrine and paracrine signaling and can also allow for direct gap junctional intercellular communication (GJIC). Moreover, it is increasingly recognized that the connexin interactome involves not only other connexins but also non-connexin proteins such as endothelial nitric oxide synthase (eNOS) in blood endothelial cells [24], the zona occludens-1 (ZO-1) in cardiomyocytes and other cells [25,26] and mitochondrial proteins in hepatocytes [27]. Indeed, connexin-mediated protein–protein interactions can regulate the function of such non-connexin proteins (e.g. eNOS) [24].

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