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Current topics of physiology and pharmacology in the lymphatic system

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Abstract

We have reviewed physiological significance of rhythmical spontaneous contractions of collecting lymph vessels, which play a pivotal role in lymph transport and seem to control lymph formation through changing the pacemaker sites of the rhythmic contractions and contractile patterns of the lymphangions. A characteristic feature that the rhythmic pump activity works in vivo physiologically under the specific environment of lower oxygen tension in lymph (25–40 mm Hg) has been evaluated. With the characteristic feature, generation of endogenous nitric oxide (NO) from lymphatic endothelial cells and/or activation of ATP-sensitive potassium channels (K_{ATP}) are reviewed to play crucial roles in the regulation of lymph transport at physiological or pathophysiological conditions. Chemical substances released from malignant tumor cells and tumor-derived parathyroid hormone-related peptide (PTHr-P) are also shown to cause a significant reduction of lymphatic pump activity through generation of endogenous NO and activation of K_{ATP} channels. Finally, we have discussed physiological significance and roles of the lower oxygen tension in lymph, generation of endogenous NO, and activation of K_{ATP} in lymph formation, lymph transport, and the functions of lymph nodes.

Keywords: Lymphatic system; Spontaneous contraction; Lymphatic endothelial cell; Oxygen tension; Nitric oxide; Prostaglandins; Reactive oxygen radicals; K_{ATP} channel; Tumor-derived chemical substance; ATP; Adenosine; PTHr-P

Abbreviations: ACh, acetylcholine; AM, acetoxymethyl ester; ATP, adenosine triphosphate; bFGF, basic fibroblast growth factor; $[Ca^{2+}]_i$, intercellular concentration of calcium ions; COX, cyclo-oxygenase; Dil-Ac-LDL, 1,1-diocadecyl 1-3,3,3′,3′-tetramethylindo-carbocyanine perchlorate-labeled acetylated low-density lipoprotein; D_{max}, maximum diameter; D_{min}, minimum diameter; DMPX, 3,7-dimethyl-1-proparglyxanthine; DPCPX, 8-cyclopentyl-1, 3-diprophylxanthine; EDD, end-diastolic diameter; EF, ejection fraction; EGM-2, endothelial growth medium-2; ESD, endsystolic diameter; ET, endothelin; F, frequency of lymph pump activity; FITC, fluorescein 5′-isothiocyanate; GTP, guanosine tri-phosphate; 5-HT, 5-hydroxytryptamine; K_{ATP} channel, ATP-sensitive potassium channel; LEC, lymphatic endothelial cell; LLC, Lewis lung carcinoma; L-NAME, N^{ω}-nitro-L-arginine; L-NMMA, N^{G}-monomethyl-L-arginine; LYVE-1, lymphatic vessel endothelial hyaluronan receptor; NO, nitric oxide; NOS, nitric oxide synthase; ODQ, 1*H*-[1,2,4,]Oxadiazolo[4,3-*a*]quinoxalin-1-one; PDGF, platelet-derived growth factor; PFI, pump flow index; PG, prostaglandins; PO_2, partial pressure of oxygen; Prox-1, prosperorelated homeobox 1; PTHr-P, parathyroid hormone-related peptide; ROS, reactive oxygen radicals; SLN, sentinel lymph node; SNP, sodium nitroprusside; STD, spontaneous transient depolarization; SV, stroke volume; TX, thromboxane; VEGF, vascular endothelium growth factor; VEGFR, vascular endothelium growth factor receptor.

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1. Introduction

The functions of lymph vessels and lymph nodes as a tissue drainage system and an immuno-surveillance have been recognized for well over a century. In general, in all parts of the body the large lymph vessels act as means for return to the circulation of fluid that leaks out of blood capillaries into the tissues, especially plasma protein, that leak out of the venules and can not be reabsorbed directly back into the circulation. The terminal vessels of the lymphatic system are very minute lymphatic capillaries that lack, in contrast to blood capillaries, fenestrations, a continuous basal membrane and pericytes; instead, these vessels are lined with a continuous, single layer of overlapping endothelial cells that form loose intercellular junctions. These characteristics make the lymphatic capillaries highly permeable to large macromolecules; pathogens and migrating cells. Lymph returns to the venous circulation through the thoracic duct and the collecting lymph vessels, which contain a muscular layer and adventitial layer.

Located along the lymph trunks are lymph nodes through which the lymph flows. These nodes act as filters to remove particular matter from the lymph before it flows into the circulation. The reticuloendothelial cells of the lymph nodes phagocytize most of the particulate matter, and they form immune bodies against such invading agents as bacteria, toxins, and so forth (Yoffey & Courtice, 1970; Guyton et al., 1975).

On the other hand, interest in basic lymphatic research has radically increased in the past few years. It may be, in part, related to the identification of lymph vessel with specific markers such as lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1), prospero-related homeobox 1 (Prox-1), podoplanin, and vascular endothelial growth factor receptor 3 (VEGFR3) and growth factors such as VEGF C and D. The hot debate about tumor-mediated lymphangiogenesis also contributes to the development of basic lymphatic research (Oliver, 2004). Malignant tumors can directly activate lymphangiogenesis and lymphatic metastasis (Karpanen et al., 2001; Mandriota et al., 2001; Skobe et al., 2001; Stacker et al., 2001; Wigle et al., 2002).

Metastasis of most cancers mainly occurs through the lymphatic system, and the extent of lymph node involvement is a useful prognostic indicator. Thus the status of the regional lymph node is known to remain the most powerful predictor of survival in women with invasive breast cancer, and this status is used to make treatment decisions (Morrow 1996; Baxter et al., 1996). Therefore Morton et al. (1992) for melanoma and Giuliano et al. (1994) for breast cancer proposed originally a procedure, in which lymphatic drainage from primary tumors can be mapped to the regional lymph nodes. With the mapping, they established a concept of sentinel lymph node(s) (SLN) that is the first node(s) draining the primary tumor in the lymphatic network. This SLN is the presumptive initial site of the lymphatic metastasis of carcinoma cells and the histological characteristics of the SLN reflect those