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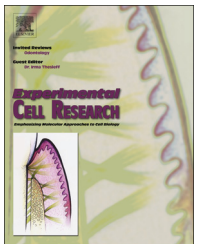

Review Article

Lymphatic function and responses in periodontal disease

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ABSTRACT

Extravasated fluid, proteins and cells are returned into the circulation by lymphatic vessels that are also important in immune cell trafficking. Lymphatic vessels in gingiva are located in lamina propria, and traverse the external surface of the alveolar bone. Lack of gingival lymphatics has been shown to increase the interstitial fluid pressure and fluid volume, thus showing that lymphatics are important for fluid drainage also in this tissue. Gingival lymphatic vessels require continuous signaling by the growth factors VEGF-C and D via their receptor VEGFR-3 for their maintenance, factors that are expressed in the gingival epithelium and also in immune cells in lamina propria. VEGF-C seems to be of critical importance for lymphangiogeneses induced during periodontal disease development. Mice are protected against periodontitis by lymphatics clearing bacteria and bacterial products and promoting humoral immune responses. CCL21, a ligand important for dendritic cell migration, has been found to be downregulated in lymphatics from patients with periodontitis. Such patients may have impaired gingival lymphatic function due to high enzymatic activity and thus loss of structural components in the interstitium. At present there are few studies on the role of lymphatic vessels in periodontal disease making this a rather unexplored field.

Contents

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Introduction

The gingiva is constantly challenged by oral bacteria that are able to induce inflammatory responses which promote increased blood vessels permeability followed by fluid filtration into the interstitium and visible swelling (edema formation) in the tissue. Periodontal disease characterized by bone resorption may develop under certain circumstances if the inflammatory response becomes chronical. The lymphatic vascular system plays an essential role in tissue fluid homeostasis by absorbing fluid and proteins from the tissue and returning it back into the circulation. In addition, lymphatic vessels are highly important for immune function as activated antigen presenting cells, enter the blind-ended lymphatic capillaries, and are transported to lymph nodes for antigen presentation. The lymphatic endothelial cells themselves interplay with immune cells and are active partners in the peripheral tissues inflammatory responses [1]. Lymphatic research has developed rapidly since the first specific lymphatic markers were detected, but so far we have limited information about their role in normal tissue homeostasis in the oral cavity and their role when the tissues become inflamed. Focusing on periodontal tissues, in this article we summarize the knowledge in this field by giving an overview of the role of lymphatic vessels in tissue fluid homeostasis and also their functions as part of the body`s immune system. The lymphangiogenic responses in inflammation are also discussed. We have excluded the dental pulp and pulpal disease with development of apical periodontitis, since it appears that lymphatic vessels do not exist in these areas. The review also points out the direction in the future in the field of periodontal research, but the knowledge is still limited since the area is underinvestigated so far.

Structure and function of lymphatics

The lymphatic system consists of lymphatic vessels and lymphoid organs. Lymphatic vessels return extravasated fluid, proteins and cells back into the circulation and are important in immune cell trafficking and immune response as well as absorption of dietary fat [2,3]. Some avascular tissues such as epidermis, cartilage and cornea and some vascularized organs like brain, dental pulp and the retina are without lymphatics, but all other organs have blind ended lymphatic capillaries, also known as initial lymphatics.

After its formation, the lymph travels through the following channels with increasing size from the tissue to the blood circulation; lymph capillaries (also called initial lymphatics), precollectors (human skin only), collecting vessels, lymph nodes, lymphatic trunks and lymphatic ducts [3], and is returned to the systemic blood circulation in lymphatic-vascular junctions in the cervical area [2,4]. The initial lymphatics are thin-walled, relatively large vessels (10–60 μm [3]) compared with surrounding blood capillaries (5–10 μm [5]). The lymphatic capillaries are composed of a single layer of endothelial cells called lymphatic endothelial cells (LECs), are not covered with pericytes or smooth muscle cells, and have little or discontinuous basement membrane. Interstitial fluid is absorbed unidirectionally into initial lymphatics, and only small and transient pressure gradients estimated to 0.09 mmHg/mm [5] are required for entrance of fluid. Anchoring filaments, consisting of collagen VII [6] connecting elastic fibers in the extracellular matrix and the abluminal part initial lymphatics [7] are important in initial lymph formation by mediating tissue stress like tissue expansion due to increased fluid content in the interstitium. Moreover, contraction of surrounding muscles and arterial pulsations contribute in the initial lymph formation [3,5] by causing expansion and compression of the initial vessels. The specialized structure of the initial lymphatics, having overlapping endothelial cells that are joined together by the junctional protein VE-cadherin in "button-like" patterns [8], may serve as flaps and thus as primary valves that allow one-way absorption of cells, fluid, and proteins.

Lymph is formed from transcapillary fluid filtration, again determined by colloid osmotic (oncotic) and hydrostatic pressure gradients expressed quantitatively as:

$$J_v = L_pA\,[(P_c - P_{if}) - \sigma(COP_c - COP_{if})] \quad (1)$$

also known as the Starling Equation [9]. In Equation 1, J_v is the net capillary filtration, L_p the hydraulic permeability of the capillaries, A the surface area available for filtration and σ the capillary reflection coefficient. $(P_c - P_{if})$ is the hydrostatic pressure difference between plasma in the capillaries (c) and interstitial fluid (if), and $(COP_c - COP_{if})$ the corresponding difference in colloid osmotic pressures. In an unchallenged normal situation, the lymph flow will equal J_v, and thereby the tissue hydration is kept constant. During inflammation, however, the various parameters of Eq. (1) will change as schematized in Fig. 1 and fluid will accumulate.

Whereas initial lymph is propagated by tissue stress, lymph in collecting vessels is moved centrally by spontaneous contractions of the lining smooth muscle cells, a transport that is unidirectional because of one-way valves. Larger collecting vessels are innervated and have pacemaker units [10,11]. The functional units within the collecting lymphatics are called lymphangions. These

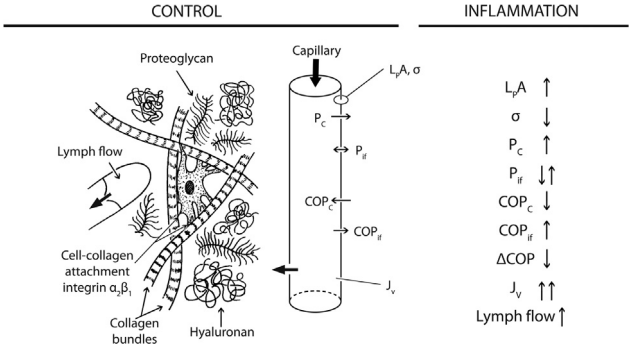

Fig. 1 – Overview of the transcapillary-interstitial fluid exchange system in control situation and during inflammation. Left part (Control): The transcapillary hydrostatic (*P*) and colloid osmotic pressure (COP) determining capillary fluid flux. Subscripts '*c*' and 'if' denote capillary and interstitial fluid, respectively. L_pA and σ are capillary hydraulic conductivity and capillary reflection coefficient, respectively. The capillary net filtration pressure (ΔP) is normally 0.5–1 mmHg and results in a net fluid filtration (J_v) that is removed by lymph flow. Collagen and glycosaminoglycans including hyaluronan are abundant structural components of loose connective tissues. Right part: Presumed changes in pressures and filtration parameters during inflammation. (Reproduced from Wiig [58]).