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Editorial Open Access

Role of Lymphatics in Immunity - Introduction

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Editorial

The lymphatic system consists of a network of vessels connecting peripheral tissues and secondary lymphoid organs. The lymphatics vasculature is involved in the transport of fluid, fatty acids/cholesterol, local waste products, peripheral antigens, and immune molecules and cells throughout the body, and therefore plays critical roles in fluid, lipid, and immune homeostasis. However, while the lymphatic system was initially identified close to 400 years ago, the immune-roles for the lymphatics have only recently been appreciated, following the identification of lymphatic-specific markers. However, the lymphatics are still often perceived as a passive, inert conduit for immune cells and mediators rather than a tightly integrated and active component of the immune system. In addition, the lymphatics are often underrepresented or overlooked in immune studies of human disease.

This special issue of the *Journal of Clinical & Cellular Immunology* is dedicated to the "Role of Lymphatics in Immunity". This collection of review articles addresses the critical immune roles of the lymphatics system and highlights the importance of these immune mechanisms in specific organs and diseases [1-10].

David G. Jackson [4] and Hancock et al. [3] both review different aspects of the lymphatics regulation of dendritic cell migration from the periphery to secondary lymphoid organs. Importantly, dendritic cell migration is different in the steady state and during inflammation and appears to be modified by stimulus-specific activation of both dendritic cells and lymphatic endothelial cells [4]. The important function of the lymphatics appears to also extend beyond regulating the migration of dendritic cells as lymphatic-expressed molecules can additionally mediate dendritic cell activation and effector function [3]. Rouhani et al. [6] focus on the ability of lymphatic endothelial cells to present antigen and mediate T cell tolerance. This process appears to be important for ensuring steady state T cell tolerance, for limiting immune hyperactivity during inflammation, and for mediating tumour immune evasion by inducing tolerance in tumour-reactive T cells [6]. Together, these three reviews highlight evidence that suggests the lymphatics influence adaptive immunity by indirectly modulating the function of dendritic cells (who then regulate T cell function) and by directly influencing T cell function in the lymph node [3,4,6].

A number of articles in this special issue also review the role of the lymphatics in mediating local innate and adaptive immune responses in peripheral sites [1,3,5,7-9]. One lymphatic-dependent mechanism for maintaining local immune homeostasis is the removal of interstitial fluid and cytokines/chemokines from local sites, to allow for the resolution of inflammation and effective wound healing [1,5,7-9]. Interestingly, lymphatic contractility and dilation are central to lymphatic drainage function and can be induced by local immune molecules such as histamine and TNFα, which implies a reciprocal relationship between lymphatic drainage and immunity [5,9]. Furthermore, lymphatic endothelial cells can also directly remove chemokines from the immune microenvironment through their expression of chemokine scavenging receptors, allow for specific control of immune homeostasis [9].

Ying et al. [10] discuss lymphatic regulation of lipid homeostasis and the close links to immunity. Interestingly, alterations in lipid and cholesterol homeostasis can impair lymphatic drainage, while this altered lymphatic function can lead to further alterations in adipose accumulation [10]. As such, lymphatic dysfunction is frequently observed in obesity, hypercholesterolemia, and atherosclerosis and may play a role in the immune dysfunction in these diseases, such as the low-grade inflammation in obesity or the increased susceptibility to infection in hypercholesterolemia [10].

Three articles highlight the importance of the immune roles of the lymphatics from the context of different organ systems [1,5,7]. Chauhan et al. [1] review the role of the lymphatics in corneal inflammation and transplantation. While, the cornea actively maintains an alymphatic (and avascular) state to ensure immune privilege, lymphangiognesis in the cornea occurs in a wide range of conditions including infection, inflammation, and transplantation and appears critically linked to the resolution or progression of these conditions. Mathias et al. [5] review the critical role of the lymphatics in gastrointestinal immune homeostasis and in the pathophysiology of inflammatory bowel disease and food allergy. Finally, Seeger et al. [7] review the importance of lymphangiogenesis in the pathophysiology of renal injury and disease. One recurrent trend from these articles is the apparent ability of the lymphatics to mediate both positive and negative immune-outcomes [1,5,7]. In the eye, the lymphatics appear to be involved in the positive resolution of trauma and infection but also the negative processes of corneal transplant rejection and chronic inflammation in dry eye disease [1]. Similarly, lymphangiogenesis in the kidney helps resolve inflammation in acute tubulointerstitial nephritis, but also negatively mediates graft rejection and chronic diabetic nephropathy [7]. These seemingly contrasting results have been hypothesised to be due to differences in lymphatic function in acute versus chronic disease [7], differences in tissues with or without pre-existing lymphatics [9], and differences due to the disorganized lymphangiogenesis characteristic of some immune diseases [1,5].

The final three articles from this special issue highlight the immune roles of the lymphatics from the context of disease processes [2,8,9]. Vranova et al. [9] review the importance of lymphangiogenesis and lymphatic function in inflammation. Importantly, the lymphatics appear critically linked with all inflammatory conditions and play key roles in mediating the progression or resolution of inflammation [9]. Tian et al. [8] review the immune dysfunction in lymphoedema arising from primary (genetic) or secondary (surgery/filariasis) damage to the lymphatics system. In lymphoedema, impaired lymphatic drainage and the resulting chronic stasis of immune mediators and antigen

presenting cells, results in an immunocompromised local microenvironment, which predisposes the affected site to neoplasms, infections, and other immune conditions [8]. Finally, Francois et al. [2] review the critical role of the lymphatics in mediating cancer metastasis and immune evasion. The authors also draw similarities between lymphangiogenesis during embryonic development and tumourigenesis in order to highlight commonalities and propose potential new targets for therapy.

Collectively, this special issue aims to emphasise the importance of the lymphatics as an active and integrated component of the immune system that is involved in the pathophysiology of nearly all human immune-mediated diseases. This issue also highlights key areas for future research such as the need for a better understanding of the mechanisms underlying lymphatic-mediated immunity and the potential for therapeutics aimed at targeting the lymphatics in human health and disease.

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