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EDITORIAL

Introduction to the special issue on lymphangiogenesis in inflammation

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Lymphatic vessels are traditionally considered as transporters of fluid, solutes, lipids, and cells from peripheral tissues to lymph nodes and back to the blood circulation, and their dysfunction can lead to lymphedema. However, a renaissance of lymphatic research in the last decade has not only deepened our understanding of the molecular and biomechanical mechanisms underlying lymphatic development and function, but has also enabled us to appreciate the scope of influence that lymphatic vessels wield in many other physiological and pathophysiological processes including metabolism, inflammation, immunity, and tissue repair and remodeling, among others. The potential roles of lymphatic vessels in metabolism continues to intrigue as an increasing number of collaborations have been revealed between lymphatic vessels and adipocytes, and the cross-talk between lymphatic endothelial cells and other stromal cells (particularly in lymph stasis and fibrosis) is being revealed. The importance of biomechanical forces in lymphatic development and function are being discovered. Questions in the field abound and tools to address them are rapidly becoming available. Areas ripe for exploration span multiple disciplines and include understanding how different organs control the development of their respective lymphatic vasculatures, how lymphatic endothelial cells sense and modulate their biochemical environment, how lymphatic vessels contribute to metabolism, and the functional consequences of adult lymphangiogenesis.

Whereas most these areas of focus remain largely unexplored, recent progress has been exceptionally rich in the area of how the lymphatic vasculature influences inflammation and immunity. Tumor-associated lymphangiogenesis has long been correlated with tumor progression and metastasis, but we now know that lymphangiogenesis is also associated with nearly all acute and chronic inflammatory processes, both locally and in the draining lymph node. Furthermore, the last few years have brought to light completely new roles for both lymphatic endothelial cells and their drainage functions in directly modulating adaptive immunity, for example by modulating dendritic cell maturation as well as by directly presenting antigens to T cells to regulate their differentiation programs. Questions in the field include whether lymphangiogenesis negatively or positively affects the development of chronic inflammatory diseases, the resolution of acute inflammation, the rejection of transplanted organs, and the regulation of tumor immunity and autoimmune diseases.

This special issue of *Angiogenesis* aims to highlight the exciting new research focused on lymphangiogenesis in inflammation. Five review articles (ref von der Wied, Detmar, Johnson, Angeli and Halin) give different perspectives of the roles of lymphatic vessels and lymphangiogenesis in inflammation. Lymphangiogenesis in chronic inflammation and cancer is the subject of reviews by Liao and von der Weid ([10.1007/s10456-014-9416-7](https://doi.org/10.1007/s10456-014-9416-7)), Dieterich et al. ([10.1007/s10456-013-9406-1](https://doi.org/10.1007/s10456-013-9406-1)), and Tan et al. ([10.1007/s10456-014-9419-4](https://doi.org/10.1007/s10456-014-9419-4)). Aebischer et al. focuses on the response of lymphatic endothelial cells to inflammatory cues ([10.1007/s10456-013-9404-3](https://doi.org/10.1007/s10456-013-9404-3)), while Johnson and Jackson discuss the regulation of dendritic cell trafficking into lymphatic vessels by the lymphatic endothelium ([10.1007/s10456-013-9407-0](https://doi.org/10.1007/s10456-013-9407-0)).

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This series of review articles is followed by four original research articles exploring lymphatic endothelial cell (LEC) response to inflammatory mediators as well as radiation and photodynamic therapy (PDT)-induced damage. Cromer et al. ([10.1007/s10456-013-9393-2](https://doi.org/10.1007/s10456-013-9393-2)) explores the barrier function of the lymphatic endothelium to bacterial lipopolysaccharide (LPS) as well as inflammatory cytokines and demonstrates that while all tested mediators decrease the LEC barrier function, IFN- γ does so much more than the others. They also show these increases in permeability are dependent on nitric oxide signaling and correlated with changes in VE-cadherin as well as cytoskeletal activation. Hsu et al. ([10.1007/s10456-013-9386-1](https://doi.org/10.1007/s10456-013-9386-1)) explores mechanisms of how IL-6, which is upregulated in many cancers, can induce lymphangiogenesis. Specifically, they report evidence supporting a mechanism whereby IL-6 activates ERK1/2 and p38MAPK in a Src-dependent manner, which in turn results in C/EBP β and p65 binding to the VEGF-C promoter, driving its expression. In this way, IL-6 directly leads to VEGF-C activation and lymphangiogenesis.

Kilarski et al. ([10.1007/s10456-013-9365-6](https://doi.org/10.1007/s10456-013-9365-6)) examines the use of PDT for lymphatic-specific ablation, whereby

photosensitizer is taken up by dermal lymphatic vessels after being injected intradermally and irradiated to destroy lymphatic vessels locally. They determined the dosage effects of both light and photosensitizer on the degree to which lymphatic vessels can be selectively destroyed with minimal damage to blood vessels and interstitial tissue. They also explore mechanisms of lymphatic occlusion and regeneration, demonstrating vessel regeneration by LEC repopulation of previous vessel ‘ghosts’. Finally, Kesler et al. ([10.1007/s10456-013-9400-7](https://doi.org/10.1007/s10456-013-9400-7)) address the question of why some breast cancer patients develop lymphedema after radiation therapy, and present an interesting in vitro study of LEC sensitivity to ionizing radiation. They report that VEGF-C increases the radiosensitivity of LECs by increasing the fraction of LECs in S and G2/M phases, thus increasing DNA damage and driving LEC quiescence and probable dysfunction. This could suggest that patients with pre-existing inflammation, where VEGF-C is upregulated, could predispose them to radiation-induced lymphedema.

We believe these exciting original and review articles highlight the rapidly growing area in angiogenesis research of lymphangiogenesis in inflammation. We hope you enjoy this special issue.