REVIEW ARTICLE

Interplay between Inflammatory Responses and Lymphatic Vessels

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Lymphatic vessels are routes for leukocyte migration and fluid drainage. In addition to their passive roles in migration of leukocytes, increasing evidence indicates their active roles in immune regulation. Tissue inflammation rapidly induces lymphatic endothelial cell proliferation and chemokine production, thereby resulting in lymphangiogenesis. Furthermore, lymphatic endothelial cells induce T cell tolerance through various mechanisms. In this review, we focus on the current knowledge on how inflammatory cytokines affect lymphangiogenesis and the roles of lymphatic vessels in modulating immune responses.
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Keywords: Lymphangiogenesis, Lymphatic vessels, Inflammation, Immune responses

INTRODUCTION

Lymphatic vessels (LVs) exist in most vascularized organs (1). LVs contribute to fluid homeostasis by absorbing tissue fluid and draining it into the venous circulation (2-4). In addition to fluid homeostasis, LVs are also important for immune surveillance (5). In contrast to blood vessels, lymphatic capillaries are connected by monolayers of lymphatic endothelial cells (LECs) and discontinuous basement membrane; thus, dendritic cells (DCs) can migrate into LVs (6,7). Furthermore, LVs in lymph nodes (LNs) and peripheral tissues are highly plastic; hence, LVs undergo proliferation or remodeling during various pathological conditions such as inflammation (8-11).

Recent studies have revealed that lymphangiogenesis during inflammation influences the extent of inflammation and immune responses by modulating leukocyte migration and inducing T cell tolerance. In this review, we will describe the inflammatory mediators that affect lymphangiogenesis and the tolerogenic roles of LVs during immune responses.

FACTORS AFFECTING LYMPHANGIOGENESIS DURING INFLAMMATION

Several factors regulate lymphangiogenesis (Table I). However, here, we focus only on those factors that have been investigated both *in vivo* and *in vitro*. Of them, vascular endothelial growth factors (VEGFs), mainly produced by macrophages are the most well-known and well-studied pro-lymphangiogenic factors. VEGF-C/D and VEGF-A have been reported to induce lymphangiogenesis in various inflammatory models (12-14). Blocking the VEGF receptor tyrosine kinase inhibits proliferation and tube formation of umbilical vein endothelial cells and LECs *in vitro*. Furthermore, in a transgenic

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Abbreviations: LV, lymphatic vessel; LEC, lymphatic endothelial cell; DC, dendritic cell; LN, lymph node; VEGF, vascular endothelial growth factor; LT, lymphotoxin; IL, interleukin; HGF, hepatocyte growth factor; FGF, fibroblast growth factor; IFN, interferon; TGF, transforming growth factor

Table I. Inflammatory mediators which have pro- and anti-lymphangiogenic activity

| Factor	Animal model	Reference
Pro-lymphangiogenic factors		
VEGFs	Overexpression of VEGFs induce lymphangiogenesis in the skin	(12-14)
LTs	Ectopic expression of LTs induce lymphangiogenesis in the thyroid	(16, 17)
IL-8	IL-8 promotes lymphatic regeneration in the lymphedema model	(17)
IL-17	IL-17 induces corneal lymphangiogenesis in autoimmune dry eye disease	(23)
HGF	HGF promotes lymphatic regeneration in the lymphedema model	(18)
FGF-2	FGF-2 implanted in the mouse cornea stimulates lymphangiogenesis	(20)
Anti-lymphangiogenic factors		
IFN-γ	IFN-γ inhibits lymphangiogenesis in LPS induced inflammation	(24)
TGF-β	Inhibition of TGF-β accelerates lymphangiogenesis in chronic peritonitis	(26)
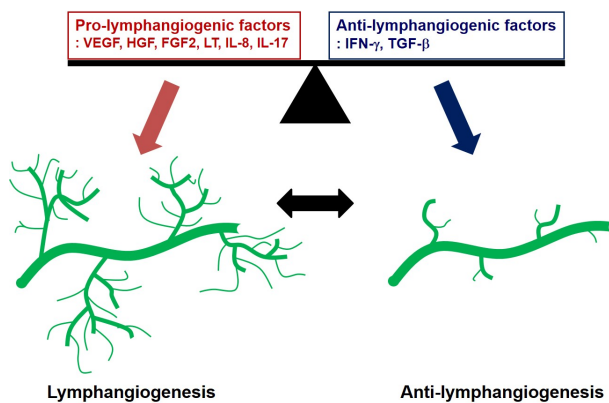
Figure 1. The lymphangiogenic balance between pro-lymphangioge-nic factors and anti-lymphangiogenic factors regulates lymphatic vas-cular homeostasis. Lymphangiogenesis under pathophysiological conditions is associated with increased pro-lymphangiogenic factors and/or decreased anti-lymphangiogenic factors.

mouse model of psoriasis, treatment with a VEGF receptor tyrosine-kinase inhibitor reduces the number of LVs in the skin (15).

In addition to VEGFs, lymphotoxin (LT)-α and LT$\alpha_1\beta_2$ are involved in lymphangiogenesis during infection and lymphoid organ formation. Ectopic expression of LTα promotes the de-velopment of LVs within tertiary lymphoid organs. In addi-tion, genetic deletion of LT$\alpha_1\beta_2$ or LTα abrogates develop-ment of LVs in the inflamed thyroid (16,17).

Furthermore, interleukin (IL)-8 and hepatocyte growth fac-tor (HGF) promote proliferation and tube formation of LECs without activating VEGF signaling *in vitro*. IL-8 and HGF pro-mote formation of LVs and improve amelioration of lymphe-dema in an experimental lymphedema model (18,19).

Fibroblast growth factor (FGF)-2 also exhibits pro-lym-

phangiogenic activity in the mouse cornea (20). Moreover, FGF-2 induces lymphangiogenesis via both direct and indirect effects. FGF-2 binds LECs and induces proliferation and mi-gration *in vitro* (21). Furthermore, recent findings suggest that FGF-2 interacts with VEGF-C to induce additional pro-lym-phangiogenic activity (22).

Similarly, IL-17 from type 17 T helper (Th17) cells induces lymphangiogenesis in an autoimmune dry eye disease model. IL-17 directly promotes growth of LVs by inducing increased expression of VEGF-D and proliferation of LECs *in vitro*. Furthermore, *in vivo* blockade of IL-17 in a model of Th17 dominant autoimmune ocular disease results in a reduction in corneal lymphangiogenesis (23).

By contrast, some inflammatory cytokines have been re-ported to show anti-lymphangiogenic activity. Interferon (IFN)-γ, which is mainly produced by Th1 cells, inhibits LV formation in an LPS-induced inflammation model. Notably, resolution of increased LVs is dependent on IFN-γ in this model. Furthermore, IFN-γ production by T cells suppresses lymphatic-specific genes in LECs and causes reduction of LV formation *in vitro* (24).

In addition, in thioglycollate-induced peritonitis and in a lymphedema model, inhibition of transforming growth factor (TGF)-β promotes LV formation (25). Expression of LEC markers, including LYVE-1 and Prox1, is inhibited by TGF-β but is enhanced by a TGF-β type I receptor inhibitor (26).

Therefore, the balance of pro- and anti-lymphangiogenic factors could determine the nature of LVs in various in-flammatory conditions (Fig. 1). LVs are involved in immune responses; thus, these results imply that controlling these fac-tors could be a good tool to control lymphangiogenesis and immune responses.

CROSSTALK BETWEEN IMMUNE CELLS AND LYMPHATIC VESSELS

LVs provide pathways for DCs and lymphocyte migration to LNs, thus facilitating inflammation or possible immune tolerance (7,27). For leukocyte trafficking, adhesion molecules like intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 are induced on LECs. Moreover, various chemokines are produced by LECs during inflammation (28,29). Of them, CCL21, which binds to CC-chemokine receptor 7 (CCR7) expressed on DCs and T cells, is the primary determinant of leukocyte migration to LNs (30-32). CXCL12 also enhances the migration of CXCR4-expressing leukocytes (33). Furthermore, CX3CL1 was reported to enhance DC transmigration across LECs to LNs (34). Therefore, although CCL21 has a major role in DC migration during inflammation, the expression of other LEC adhesion molecules and chemokines also contributes to migration (29).

In addition to the ability of LECs to control leukocyte trafficking through adhesion molecules, LECs control immune responses via their functions as professional antigen presenting cells (APCs). LECs in LNs constitutively express major histocompatibility complex (MHC)-II molecules. Moreover, they endocytose and cross-present antigens in context with MHC-I molecules to T cells (35-37). However, LECs do not express co-stimulatory molecules such as CD80, CD86, OX40L, or 4-1BBL, thus fail to induce T cell activation and proliferation (38,39). Although the lack of co-stimulatory molecules on LECs implies immunological tolerance, further study is needed to elucidate the exact roles of LECs in CD4 T cell activation.

Recently, it was reported that LECs affect not only CD4 T cell tolerance but also CD8 T cell tolerance. LECs express peripheral tissue antigens (PTA) that are restricted to specific tissues such as skin, gut, pancreas, and central nervous system (40-44). Furthermore, LECs induce deletion or abortive proliferation of PTA-specific CD8 T cells through a lack of co-stimulation or engagement with inhibitory molecules such as PD-L1 (38,45-48). Other co-stimulatory molecules such as HVEM or CD48 are constitutively expressed; thus, their expression suggests that LECs may have immune regulatory roles in steady state as well as in inflammatory conditions (49).

CONCLUSION

So far, we have discussed inflammation, LV formation, and

immune regulation. Different pro- and anti-lymphangiogenic factors are produced by different inflammatory stimuli, and their overall effects determine the extent of lymphangiogenesis. Furthermore, although LECs promote leukocyte migration and enhance immune responses, LECs also attenuate T cell-mediated immune responses by mediating tolerance. LECs attract lymphocytes and DCs through cell adhesion molecules and chemokines. In addition, LECs induce CD8 T cell tolerance through PD-L1 and lack of co-stimulatory molecules. However, mechanisms of CD4 T cell tolerance and roles of other inhibitory molecules on LECs need to be investigated. Finally, controlling lymphangiogenesis could be a novel therapeutic strategy to regulate autoimmunity, enhance tumor immunotherapy, and reduce transplantation rejection.

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CONFLICTS OF INTEREST

The authors have no financial conflict of interest.

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