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ORIGINAL PAPER

The inflammatory response of lymphatic endothelium

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Abstract Lymphatic vessels have traditionally been regarded as a rather inert drainage system, which just passively transports fluids, leukocytes and antigen. However, it is becoming increasingly clear that the lymphatic vasculature is highly dynamic and plays a much more active role in inflammatory and immune processes. Tissue inflammation induces a rapid, stimulus-specific upregulation of chemokines and adhesion molecules in lymphatic endothelial cells and a proliferative expansion of the lymphatic network in the inflamed tissue and in draining lymph nodes. Moreover, increasing evidence suggests that inflammation-induced changes in the lymphatic vasculature have a profound impact on the course of inflammatory and immune responses, by modulating fluid drainage, leukocyte migration or the removal of inflammatory mediators from tissues. In this review we will summarize and discuss current knowledge of the inflammatory response of lymphatic endothelium and of inflammation-induced lymphangiogenesis and the current perspective on the overall functional significance of these processes.

Keywords Inflammation · Lymphatic endothelial cells · Lymphangiogenesis · Leukocyte migration · Chemokines · Drainage

Introduction

Lymphatic vessels (LVs) are present in most vascularized tissues. By absorbing excess tissue fluid and returning it to the blood vascular circulation, LVs essentially contribute to tissue fluid homeostasis [1, 2]. Moreover, LVs transport soluble antigen and leukocytes and therefore are important for immune function [3]. Afferent LVs begin as blind-ended capillaries, which give rise to collecting vessels that eventually merge and connect with draining lymph nodes (dLNs) (Fig. 1a). Initial lymphatic capillaries are composed of oak-leaf shaped lymphatic endothelial cells (LECs) that are connected by discontinuous, button-like cell junctions [4]. This setup gives rise to characteristic flaps, which represent the prime sites of leukocyte and fluid entry into LVs [4, 5]. By contrast, collecting LVs are ideally adapted for the transport of lymph; here, cuboidal LECs are tightly connected by continuous, zipper-like cell junctions. Moreover, collecting LVs contain valves and are surrounded by a continuous basement membrane and a smooth muscle cell layer [1].

Research of the last 15 years has revealed that the lymphatic network in peripheral tissues and in LNs is highly plastic and undergoes substantial changes under pathologic conditions [1, 2]. For example, tissue inflammation induces rapid, stimulus-specific changes in LEC gene expression and a stimulus-specific expansion and remodeling of the lymphatic network. In humans, inflammation-induced lymphangiogenesis has been reported for psoriasis [6], rheumatoid arthritis [7], inflammatory bowel disease [8], atherosclerosis [9], chronic airway inflammation [10] as well as for transplant rejection [11, 12] and lymphedema [13]. Furthermore, recent animal studies have revealed that inflammation-induced lymphangiogenesis directly impacts the course of inflammatory and immune responses, by modulating fluid drainage, leukocyte migration or the removal of inflammatory mediators from tissues [10, 14–19]. Increasing evidence also suggests that LVs and LECs directly crosstalk with the immune system and

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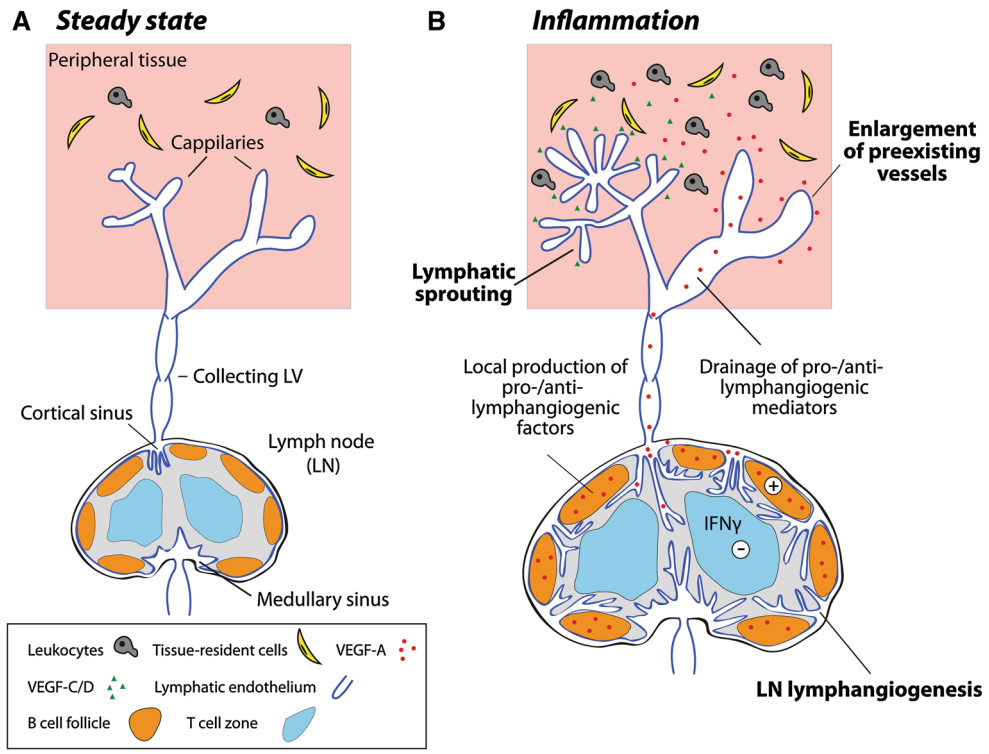

Fig. 1 Inflammation-induced lymphangiogenesis in peripheral tissues and in dLNs. **a** Anatomy of the lymphatic vasculature at steady state: afferent LVs are composed of initial capillaries and collecting vessels. The lymphatic network in LNs mainly comprises the subcortical and medullary sinus. **b** During tissue inflammation, lymphangiogenic growth factors, such as VEGF-C/D or VEGF-A, are secreted by tissue-infiltrating leukocytes or by stromal cells. These factors induce a proliferative growth of the lymphatic vasculature by lymphatic sprouting or enlargement of preexisting vessels. At the same time, lymphangiogenesis occurs in dLNs. LN lymphangiogenesis-inducing factors are either produced locally (e.g. VEGF-A produced by B cells) or drained to the LN from the inflamed tissue. Depending on the type of inflammatory response induced, LN lymphangiogenesis may be counterbalanced by inhibitory factors (i.e. IFNγ produced by activated T cells)

are involved in antigen presentation and tolerance induction in LNs [20–22]. The latter processes have been the focus of excellent recent reviews [23, 24] and therefore will not be discussed in further detail.

In this review we will introduce the best characterized mediators of inflammatory lymphangiogenesis and summarize current knowledge about inflammation-induced gene expression changes in LECs. Furthermore, we will focus on the morphologic and structural changes of LVs in inflamed tissues and in dLNs. Finally, we will summarize how inflammation-induced lymphangiogenesis and lymphatic remodeling are thought to impact the inflammatory process, by modulating leukocyte trafficking, fluid drainage and chemokine levels in inflamed tissues.

Mediators of inflammation-induced lymphangiogenesis

The best-studied mediators of inflammation-induced lymphangiogenesis are vascular endothelial growth factor (VEGF)-C and VEGF-A, which are produced by stromal cells like keratinocytes or fibroblasts as well as by leukocytes in inflamed tissues [1, 2, 25]. Particularly macrophages are a major source of VEGF-A and VEGF-C [26–28]. In various inflammatory models, depletion of macrophages was shown to significantly reduce lymphangiogenesis [26–29]. Notably, macrophages may also physically contribute to lymphangiogenesis by up-regulating lymphatic marker genes and incorporating into LVs [11, 29]. Besides VEGF family members, also other leukocyte-derived cytokines contribute to inflammation-induced lymphangiogenesis (Table 1). For example, lymphotoxin (LT)α and $LT\alpha\beta_2$ have been implicated in inflammatory lymphangiogenesis during infection or tertiary lymphoid organ formation [30, 31]. Similarly, interleukin 17 (IL-17) was shown to induce lymphangiogenesis in a mouse model of ocular autoimmunity [32], whereas IL-8 promoted LV regeneration and reduced post-surgical lymphedema formation [33]. Interestingly, also some inflammatory cytokines with anti-lymphangiogenic activity have been identified (Table 1). For example, IFNγ, a mainly T cell-derived cytokine, reportedly inhibits LECs in vitro and in vivo [34–36]. Moreover, inhibition of transforming growth factor beta (TGFβ) was shown to

Table 1 Inflammatory mediators with documented pro- or anti-lymphangiogenic activity

Mediator	Lymphangiogenic activity	In vitro (1) In vivo (2)	References
VEGF-C	+	1 & 2	[72, 105]
VEGF-A	+	1 & 2	[72, 105]
LTα	+	2	[31]
$LT\alpha\beta_2$	+	1 & 2	[30, 106]
IL-17	+	1 & 2	[32]
IL-8 (CXCL8)	+	1 & 2	[33, 107]
HGF	+	1 & 2	[108]
IL-3	+	1	[66]
FGF-2 (bFGF)	+	1 & 2	[65]
LPS	+	1 & 2	[61, 66]
CXCL12	+	1 & 2	[59]
S1P	+	1 & 2	[109]
TNFα	−	1	[35]
IL-27	−	1	[60]
IFNα	−	1	[34]
IFNγ	−	1 & 2	[34–36]
TGFβ	−	1 & 2	[37, 38]
CXCL10/11	−	1	[60]

Various inflammatory mediators have been shown to induce or inhibit lymphangiogenesis in vitro or in vivo. Lymphangiogenic activity: (+) pro-lymphangiogenic activity, (−) anti-lymphangiogenic activity. In vitro/in vivo activity: (1) shown to modulate LEC in vitro proliferation, migration, or tube formation, (2) shown to modulate lymphangiogenesis in vivo. *HGF* hepatocyte growth factor, *S1P* sphingosine-1-phosphate

enhance lymphangiogenesis in thioglycollate-induced peritonitis [37] and to induce lymphangiogenesis and lymphatic drainage in a murine lymphedema model [38]. Overall, the balance of pro- and anti-lymphangiogenic cytokine expression appears to determine the extent and nature of inflammation-induced lymphangiogenesis. This generates a very flexible system, in which tailored lymphangiogenic responses are initiated, depending on the type of inflammatory immune response elicited.

Inflammation-induced changes in LEC gene expression

In vitro many inflammatory mediators, such as growth factors, cytokines or pathogen-derived molecules induce LEC proliferation, migration or tube formation and therefore exert a pro-lymphangiogenic activity (Table 1). Conversely, other mediators appear to rather suppress these processes or to mainly modulate the gene expression phenotype of LECs. For example, inflammatory cytokines such as TNFα, IFNγ, IL-1 induce no or little LEC proliferation [35], but are strong inducers of inflammatory chemokines and adhesion molecules like ICAM-1 and VCAM-1, which participate in leukocyte trafficking [35, 39–41]. In fact, leukocyte trafficking via afferent LVs is typically enhanced in the context of inflammation [3, 42, 43].

Adhesion molecules

Inflammatory signals have been shown to modulate the expression of ICAM-1 and VCAM-1 [39, 40], P-selectin [40], E-selectin [39, 44], L1CAM [45], ALCAM [46] or CAR [47] in LECs. While some of these molecules contribute to lymphangiogenesis [46, 47], others mediate leukocyte trafficking via afferent LVs [39, 45, 48]. Particularly inflammation-induced ICAM-1 or VCAM-1 were shown to be important for dendritic cell (DC) transmigration into [39, 48] and migration within LVs [49]. LVs in resting tissues express very low levels of ICAM-1 and VCAM-1, but these adhesion molecules are strongly upregulated in LECs during tissue inflammation. This might explain why DC migration in absence of inflammation occurs independently of ICAM-1 or VCAM-1 binding integrins [50]. By contrast, blockade of ICAM-1, VCAM-1 or of the DC-expressed integrin LFA-1 significantly reduced DC migration to dLNs in the context of skin inflammation [39, 48]. Interestingly, interactions between LEC-expressed ICAM-1 and DC-expressed Mac-1 (CD11b) occurring in the process of DC migration to dLNs were also shown to modulate the maturation state and function of DCs [51].

Chemokines

Various chemokines are upregulated in LECs in response to inflammatory signals (Table 2). The chemokine with the best documented role in leukocyte trafficking into LVs is CCL21, which attracts CC-chemokine receptor 7 (CCR7) expressing leukocytes, such as DCs or T cells [3]. Tissue inflammation was shown to upregulate CCL21 protein expression in vivo [40]. Moreover, TNFα, VEGF-C as well as transmural flow were identified as inducers of CCL21 expression in LECs [42, 52, 53] (Table 2). Interestingly, a substantial fraction of CCL21 is stored intra-cellularly in vesicles of the Trans-Golgi Network [40, 54]. In vitro treatment of LECs with TNFα was shown to induce rapid secretion of CCL21 from its intracellular stores [55], but it is still unclear how tissue inflammation affects CCL21 secretion in vivo. Interestingly, also neutrophil migration via afferent LVs, which occurs during acute inflammation, is mainly CCR7-dependent [56]. Similarly, CCR7 expression was shown to be the main determinant of regulatory and effector T cell migration into LVs during acute inflammation [3, 43]. However, the CCR7-dependence of T cell migration into lymphatics appears to be less strong in

Table 2 Inflammatory mediators inducing chemokine expression in LECs

Inflammatory stimulus	Chemokines induced	Comment	Ref.
in vitro			
TLR ligands (TLR2/3/4/6/8/9)	CCL5, 20, 21; CXCL8/9/10/11/12	*stimulus-specific responses*	[41]
TLR ligands (TLR1/2/3/4/6/9)	**CCL2/5 CXCL8**	*stimulus-specific responses*	[62]
LPS	CCL2/3/5/7/8/20 CXCL1/3/5/6/8		[44]
LPS	**CCL2/5 CX3CL1**		[61]
TNFα	**CCL2/5**/20/21 CXCL2/5 **CX3CL1**		[39]
TNFα	**CCL21**		[55]
TNFα / IFNγ	**CCL2/7 CXCL5/9/10**		[40]
MDP / LTA	**CCL2/7 CXCL5**		[40]
Transmural flow	**CCL21**		[53]
VEGF-C	**CCL21**		[52]
in vivo			
LPS injection	**CCL2**	*peritoneal inflammation*	[61]
CHS response to DNFB	**CXCL12**	*skin inflammation*	[57]
CHS response to oxazolone	CCL**2**/7/8/**21** CXCL**1**/5/**9**/10	*skin inflammation*	[40]
CFA injection	CCL2/7/**21** CXCL5	*skin inflammation*	[40]
VEGF-C	**CCL21**	*Intradermal injection*	[52]
TNFα	**CCL21**	*Intradermal injection*	[42]
Lymph flow	**CCL21**	*lymphedema or overhydration*	[53]
Pancreatic islet inflammation	CCL2, CCL21 CXCL10	*mouse model of autoimmune diabetes*	[110]

Various inflammatory stimuli have been shown to induce chemokine expression in LECs in vitro or in vivo. *Chemokines written in bold font*: protein expression reported. *Chemokines written in regular font*: mRNA expression reported

MDP muramyl dipeptide, *LTA* lipoteichoic acid, *DNFB* dinitrofluorobenzene

the context of chronic inflammation [43], suggesting a role for other inflammation-induced chemokines or other chemotactic molecules under this condition.

Besides CCL21, various other chemokines are upregulated in LECs in response to inflammatory signals (Table 2), but thus far only two further chemokines have been shown to support leukocyte migration into afferent LVs. Inflammation-induced CXCL12 reportedly enhanced the migration of CXCR4-expressing dermal DCs and Langerhans cells to dLNs [57]. Moreover, LEC-expressed CX3CL1 (fractalkine) was recently shown to support DC transmigration across lymphatic endothelium and the overall trafficking process from inflamed tissue to dLNs [58]. On the other hand, experiments performed in $CCR7^{-/-}$ mice revealed that DC migration to dLNs remained strictly CCR7-dependent in the context of skin inflammation [40]. Thus, although CCL21/CCR7 signaling remains of key importance for DC migration during inflammation, also other LEC-expressed chemokines contribute to this process, possibly by affecting distinct steps in the migration cascade.

In analogy to the role of chemokines in angiogenesis, increasing evidence suggests that inflammation-induced chemokines may be involved in the regulation of lymphangiogenesis. For example CXCL12 reportedly induces lymphangiogenesis in vitro and in vivo [59]. Similarly, CXCL8 (IL-8), which is upregulated in LECs in response to various inflammatory stimuli, reportedly enhances lymphangiogenesis [33, 41]. By contrast, inflammation-induced CXCL10 and CXCL11 (Table 2) were shown to exert anti-lymphangiogenic activity in vitro [60]. It has also been suggested that the upregulation of chemokines might serve to indirectly support lymphangiogenesis. In a murine peritonitis model, inflammation-induced chemokine expression in LECs was responsible for the attraction and association of macrophages with LVs, what in turn induced lymphangiogenesis by macrophage-derived lymphangiogenic growth factors [61].

Stimulus-specific changes in LEC gene expression

Several studies have revealed that many changes in LEC gene expression occur in a highly stimulus-specific manner [35, 39–41, 62]. For example, performing gene expression analyses of LECs isolated from inflamed or resting murine

ear skin we have recently observed that inflammation elicited by a contact hypersensitivity (CHS) response to oxazolone or by CFA injection induced a similar degree of tissue swelling, but a differential upregulation of inflammatory chemokines (Table 2) and of adhesion molecules (e.g. ICAM-1, P-selectin) [40]. Stimulus-specific upregulation of chemokines and of ICAM-1 or VCAM-1 was also observed in other studies when treating LECs in vitro with different cytokines or with Toll-like receptor (TLR) ligands [35, 39–41, 62]. It is likely that stimulus-specific upregulation of trafficking molecules serves to fine-tune leukocyte migration or other chemokine-induced responses in LECs in the context of the ongoing immune response.

Inflammation also modulates the expression of lymphatic marker genes in a stimulus-specific manner. Various stimuli reportedly induce down-regulation of the hyaluronan receptor LYVE-1 in LECs [10, 40, 63]. The significance of this down-regulation is presently unclear, but recent findings suggest that loss of LYVE-1 may alter LEC barrier function [64]. Interestingly, LYVE-1 was also shown to bind and to enhance the activity of fibroblast growth factor-2 (FGF2), an inflammation-induced factor with reported lymphangiogenic activity [65]. Also the transcription factor Prox-1 and its target gene VEGFR-3 were shown to be down-regulated in LECs in the context of CHS-induced skin inflammation [15, 40]. By contrast, Prox-1 and VEGFR-3 expression remained constant during tissue inflammation induced by CFA injection [40], whereas both genes were upregulated in LVs in a mouse model of thioglycollate-induced peritonitis [66]. It is perceivable that modulation of Prox-1 affects lymphatic differentiation, whereas changes in VEGFR3 expression likely affect LEC responsiveness towards inflammation-induced VEGF-C.

Inflammation-induced changes in afferent LVs

Inflammation leads to a rapid dilation of LVs in tissues [1, 67, 68]. Additionally, the size of the lymphatic network increases due to proliferative expansion [68–70]. This may feature a proliferative enlargement of preexisting vessels [67] or the sprouting of new LVs [27, 28, 66] (Fig. 1b). Interestingly, the extent of lymphangiogenic sprouting versus expansion of preexisting vessels appears to depend on the lymphangiogenesis-inducing stimuli. VEGF-A was shown to mainly induce LV enlargement [71, 72], whereas VEGF-C induced sprouting lymphangiogenesis [72, 73]. Besides changing lymphatic morphology, persistent inflammation may also alter the typical organization of lymphatic cell junctions [4]. In a model of chronic airway inflammation induced by infection with *Mycoplasma pulmonis*, the characteristic button-like cell junctions were replaced by continuous, zipper-like junctions [74]. The functional significance of this conversion is not known, but it is likely that these structural differences affect lymphatic drainage or leukocyte migration.

Inflammation-induced changes in the lymphatic network in dLNs

Inflammation-induced lymphangiogenesis does not only affect the inflamed tissue but also extends to dLNs [36, 68–70, 75] (Fig. 1b). In a mouse model of skin inflammation induced by immunization with complete Freund's adjuvants (CFA), LN lymphangiogenesis was mainly driven by VEGF-A secreted from LN-resident B cells. By contrast, in a mouse model of chronic skin inflammation induced by a CHS response to oxazolone, LN lymphangiogenesis was shown to be mediated by VEGF-A that was drained to the LN from its production site in the inflamed skin [68]. Different from nodal B cells, activated T cells appear to have a negative impact on LN lymphangiogenesis. IFNγ secreted by activated T cells reportedly inhibits LN lymphangiogenesis and limits the size of the lymphatic network in the LN T cell area in steady state and in inflammation [36, 75]. Thus, it appears that depending on the inflammatory stimulus and the type of immune response induced, the pattern and extent of LN lymphangiogenesis may vary. As a further illustration of this hypothesis; lipopolysaccharide (LPS) injection into the skin was shown to promote LN lymphangiogenesis, whereas injection of the T cell mitogen concanavalin-A did not increase the lymphatic vasculature in the dLN, although both agents accounted for potent inflammatory reactions at the site of injection [36].

Intriguingly, experiments in mouse models of lymphedema have revealed that lymphedema formation was reduced and lymphatic regeneration and drainage were enhanced in mice devoid of T cells [75] or upon depletion of $CD4^+$ T cells [76]. The latter findings suggest that T-cell-derived mediators might also negatively impact lymphangiogenesis and LV function outside of the LN. Regarding to functional significance of inflammation-induced LN lymphangiogenesis, experimental evidence suggests that this process serves to regulate leukocyte migration to and from LNs. In the context of CFA-induced inflammation, VEGFR-2- and VEGFR3-mediated blockade of LN lymphangiogenesis was shown to reduce DC migration to dLNs [69] as well as lymphocyte egress via efferent lymphatics [70]. On the other hand, LECs in LNs have been shown to present antigen to T cells and to participate in tolerance induction [21, 22]. Thus, it is likely that LN lymphangiogenesis directly modulates the induction of adaptive immunity in LNs [23, 24].

Role of afferent LVs in modulating inflammatory and immune responses

Several studies have shown that tissue inflammation not only alters LV morphology but also changes lymphatic function, for example the capacity of LVs to mediate leukocyte migration or to drain tissue fluids [10, 14–19]. Such changes in LV function profoundly impact the persistence or resolution of tissue inflammation. In the following sections, the impact of alterations in LV immune and drainage functions on the inflammatory response shall be discussed in greater detail.

Leukocyte trafficking

Besides removing tissue fluids and inflammatory mediators, the lymphatic network is also thought to contribute to the downregulation and resolution of inflammation by facilitating tissue exit of leukocytes. For example, regulatory T cells have been identified as a major cell type emigrating from inflamed skin to dLNs, where they are thought to downregulate cutaneous immune responses [77]. Moreover, the clearance of tissue-infiltrating macrophages via LVs has been discussed as an important step in the resolution of inflammation [78, 79], but also contradicting data exist on this topic [80].

On the other hand, tissue exit of leukocytes via LVs may also enhance the inflammatory process. For example, an activated and expanded lymphatic network is known to increase the migration of antigen-presenting DCs to dLNs, what may support the induction of adaptive immunity [16, 69]. This is particularly relevant during organ transplantation, where studies in humans have revealed a positive correlation between lymphangiogenesis and transplant rejection [11, 12]. Moreover, in animal models, blocking lymphangiogenesis was shown to significantly reduce DC migration and graft rejection [16–19]. However, organ transplantation represents a special condition, in which lymphatic connectivity with dLNs need to be formed *de novo*, and additionally strong alloimmune responses may be induced. By contrast, in the context of endogenous tissues with preexisting lymphatic vasculature and immune connectivity with dLNs, blockade of inflammation-induced lymphangiogenesis was shown to exacerbate the inflammatory response, likely due to the enhancement of tissue edema [10, 14, 15].

LV drainage

Increasing evidence suggests that lymphatic drainage is frequently compromised in the context of chronic inflammation, such as in psoriasis [81, 82] or Morbus Crohn [83, 84]. However, in animal models, both inflammation-induced enhancement and reduction of lymphatic drainage has been observed. For example, injection of LPS [27], reportedly enhanced lymphatic drainage in the skin, whereas in the diaphragm drainage was reduced in a model of LPS-induced peritonitis [28], suggesting that the response of the lymphatic vasculature to an inflammatory stimulus might not be uniform but organ-specific. However, such organ-specific differences, have not been studied in great detail thus far. By contrast, an abundant literature indicates that the nature of the inflammatory stimulus has a great impact on lymphatic drainage function. For example, in the skin, LV drainage reportedly was reduced in the context of CHS- [85, 86] and UVB-induced [15, 87] skin inflammation, whereas skin inflammation induced by transgenic overexpression of interleukin-4 [88] lead to enhanced lymphatic drainage. Several studies have also shown that VEGF-A-induced lymphangiogenesis generated less functional LVs as compared to lymphangiogenesis induced by VEGF-C and VEGF-D [15, 71, 87, 89]. In general, activation of the VEGFR-3 pathway appears to be an effective way of stimulating productive lymphangiogenesis and stimulating lymphatic drainage: genetic overexpression or injection of recombinant VEGF-C was shown to alleviate UV-B or CHS-induced acute and chronic skin inflammation [15, 89, 90] as well as chronic inflammatory arthritis [91], likely by enhancing lymphatic drainage function. By contrast, inhibition of VEGFR-3 signaling impaired lymphatic growth and exacerbated inflammation in mouse models of airway inflammation [10], inflammatory arthritis [14] or chronic skin inflammation [15], likely by promoting tissue edema formation.

Many inflammatory mediators are known to enhance permeability of BVs, but only few in vivo reports about effects on LV permeability exist. Nitric oxide (NO) and VEGF-A were shown to contribute to the leakiness of dermal LVs in the context of UV-B-induced inflammation [87, 92]. In vitro, inflammatory mediators such as TNFα, IL-1, histamine, thrombin and VEGF-C were shown to decrease the barrier function of LEC monolayers [35, 93, 94]. Moreover, inflammation was also shown to impact the pumping function of lymphatic collectors. Specifically, various inflammatory mediators, such as histamine, prostaglandins or NO were shown to reduce lymphatic pumping [95–97], whereas VEGF-C enhanced pumping [98].

Chemokine scavenging

In addition to passively draining tissue fluids and inflammatory mediators, LVs have been shown to actively remove chemokines from inflamed tissues. In particular, the chemokine scavenging receptor (CSR) D6, which is expressed by LECs and is upregulated during inflammation [99], was shown to be important for the resolution of tissue inflammation [100, 101]. D6 internalizes and degrades

inflammatory chemokines (i.e. CCL2, 3, 5, 8, 12, 17, 22), thereby accelerating their elimination from tissues. Moreover, it was recently proposed that D6 functions to ensure selective presentation of CCL21 on LECs, by suppressing inflammatory chemokine binding and accumulation. In inflamed tissues of D6-deficient mice, a massive association of myelomonocytic cells around LVs was observed, leading to obstructed lymphatic drainage and reduced DC migration to dLNs [100]. Thus far, only the function of D6 in LECs has been analyzed. However, it was recently reported that another CSR, namely the CXCL11- and CXCL12-binding CXC chemokine receptor 7 (CXCR7), was upregulated in inflamed LVs [102]. Thus, it is likely that besides D6, further CSRs contribute to the inflammation- and immune-modulating functions of LVs.

Conclusion

Over the last 15 years a lot of progress has been made in understanding how tissue inflammation alters gene expression in LECs as well as LV morphology and function. The emerging view is that the inflammatory response of the lymphatic endothelium and its impact on LV functionality is very much *stimulus-specific* and *context-dependent*. Depending on the inflammatory stimulus and the resulting immune response, different pro-/anti-lymphangiogenic mediators are produced in the tissue. This generates a unique milieu, which impacts the inflammatory response of LECs and the overall nature and extent of lymphangiogenesis. Such *stimulus-specific* changes in the lymphatic vasculature may greatly influence LV functionality, such as fluid drainage and leukocyte trafficking. Recent data also indicate that the same inflammatory stimulus may have different effects on LV function in different organs [27, 28]. The latter might be explained by the fact that clear morphologic [103] and gene expression [104] differences exist between LVs in different body parts. However, many of these differences are only now starting to be unraveled. By contrast, already to date abundant evidence suggests that the impact of lymphangiogenesis on tissue inflammation is very much *context-dependent.* Lymphangiogenesis occurring within transplanted organs (e.g. cornea [16, 17], heart [18], pancreatic islands [19] or kidney [11, 12]) has been shown to exacerbate tissue inflammation, supposedly by re-establishing connectivity with the immune system in the dLNs and hence contributing to the rejection process. On the other hand, various recent studies reveal that in tissues with a pre-established LV network (e.g. the skin [89], lung [10] or joints [14, 91]) productive, in particular VEGF-C-mediated, lymphangiogenesis contributes to the resolution of inflammation, supposedly by promoting tissue drainage. Thus, stimulation or inhibition of lymphangiogenesis could represent an attractive novel therapeutic strategy for reducing chronic inflammation or transplant rejection, respectively.

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Conflict of interest The authors declare no competing financial interests.

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