Immune Potential Untapped: Leveraging the Lymphatic System for Cancer Immunotherapy

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ABSTRACT

Over the past decade, our understanding of the role of the lymphatic vasculature in tumor progression has evolved from it being a passive participant, as a first step along Halsted's path of sequential metastasis, to a potentially active regulator of antitumor immune surveillance. These new data, however, seemingly support paradoxical predictions for cancer immunotherapy; on one hand that enhanced lymphatic involvement augments antitumor immune surveillance and on the other, drives immune evasion and metastasis. The potential to leverage lymphatic biology for the benefit of clinical immunotherapy, therefore, requires a mechanistic understanding of how the lymphatic vasculature interacts with functional immune responses during disease progression and in the context of relevant immunotherapy regimes. In this review, I dissect the promise and challenge of engaging the lymphatic system for therapy and suggest important avenues for future investigation and potential application.

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Introduction

It is a central tenant of biology that structure informs function. For immunotherapy, this manifests in the hypothesis that targeting tissue architecture, in concert with intrinsic leukocyte biology, will provide orthogonal therapies that improve access, persistence, and functionality of antitumor immune responses. The hematogenous and lymphogenous vasculatures provide important influx and efflux routes respectively, linking peripheral tumors to systemic organs and lymph nodes (LN), and thereby govern the systemic distribution of immunologic information (e.g., antigens and leukocytes). Although the concept of vascular targeting (e.g., blood vessel normalization for improved drug and leukocyte delivery to tumors) has gained some traction, immunotherapeutic strategies to target or leverage the lymphatic vasculature have lagged. As such, the immune potential of the lymphatic system remains largely untapped.

The lymphatic vasculature is a unidirectional network of specialized vessels that facilitates the movement of fluid, leukocytes, and lipids out of tissues and regulates tissue homeostasis. Structured along a functional hierarchy, initial lymphatic capillaries are blunt-ended vessels lined by a single layer of endothelial cells and lack both a continuous basement membrane and muscle cell investment. As a function of their naïve, open structure, initial lymphatic capillaries are the presumed site of fluid and cell uptake. Uptake of fluid and macromolecules by capillaries forms lymph, which is transported through precollecting vessels and then into collecting vessels where a continuous basement membrane, muscle cell investment, and specialized valve structures prevent retrograde flow. These vessels feed a larger system that recycles and recirculates effector molecules, leukocytes, and signals from peripheral tissues and LNs back into the hematogenous circulation. The specialized structure of the lymphatic system and the homeostatic signals that maintain it have been reviewed (1).

Over the past 20 years, new data indicate that the lymphatic vasculature plays a functional role across the spectrum of health and disease. We have learned that in addition to its well-known role in maintaining fluid homeostasis and antigen transport (2), the lymphatic vasculature actively contributes to peripheral tolerance, dietary lipid absorption, and stem cell maintenance (1). In cancer, despite the prevailing view that lymphatic vessels were excluded from the tumor parenchyma and dysfunctional, seminal work in the early 2000s, causally linked the growth factors, VEGF-C and VEGF-D, with tumor-associated lymphangiogenesis (proliferation to form new vessels) and LN metastasis (3, 4). These data positioned tumor-associated lymphatic vessels as functional drivers of tumor progression by providing paths for regional metastasis. More recently, however, the field extended these data and challenged the assumption that lymphatic vessels are simply passive conduits for metastatic tumor cells. Instead, tumor-associated lymphangiogenesis is considered a causal factor in tumor immune surveillance by the host (5–8). This establishes an interesting paradox, whereby tumor-associated lymphangiogenesis may be at once tumor-promoting and tumor-suppressive. Reconciling the paradox that these data have established is a necessary step towards untapping their therapeutic potential. To do this, we must understand the extent to which lymphatic vessels are active participants in the molecular and transport phenomena that define their function, or whether it is the simple presence or absence of physical vessels that is sufficient to explain both the immune and metastatic phenotypes observed *in vivo*. We recently reviewed the known mechanisms of active afferent lymphatic transport and their impact on peripheral tissue immunity (9). In this brief perspective, we focus on putting these mechanisms in the context of cancer and discuss three therapeutic strategies that have emerged: (i) the regulation of lymphatic output to control the flux of fluid, cells, and antigens from tumors to their draining LNs; (ii) the modulation of mechanisms of peripheral lymphatic–immune cross-talk in order to promote lymphocyte accumulation and function in tumors; and (iii) the leveraging of lymphatic transport to reinvigorate LN immune potential for systemic immune surveillance (**Fig. 1**).

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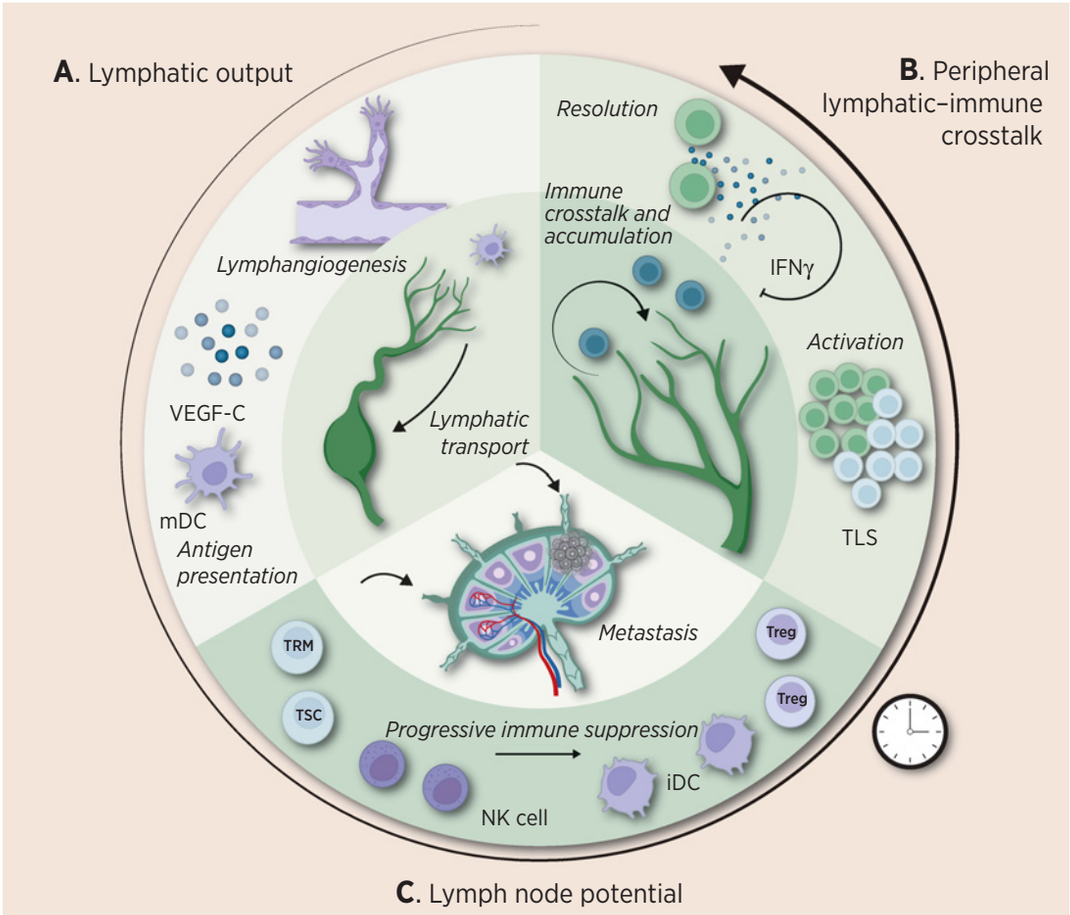

Figure 1.

Leveraging the lymphatic system for immunotherapy. Over the last decade and more, the lymphatic vasculature has emerged as a critical coordinator of host immune responses. Although many mechanistic details remain to be defined, a framework is emerging for leveraging the lymphatic system for immunotherapy. **A,** Lymphatic Output. Defined as the flux of fluid, mature DCs (mDC), and antigen from tumors to draining LNs, increasing lymphatic output (e.g., fluid, mDC, antigen) through VEGF-C–induced lymphangiogenesis inflames tumor microenvironments and potentiates response to immunotherapy in preclinical models. Limitations of this approach remain the potential promotion of regional metastasis. **B,** Peripheral lymphatic-immune cross-talk. Defined as the coupling of lymphatic vessel function to lymphocyte accumulation and function in peripheral tissues, a focus on these mechanisms of cross-talk (e.g., IFNγ) may lead to functional shifts in intratumoral immune repertoires independent of lymphatic proliferation. **C,** LN potential. Independent of their function in peripheral tissue, lesion-associated lymphatic vessels provide a path toward immunologically primed, but immunosuppressed LNs that may be leveraged for immune reinvigoration and regional tumor control. The reversibility of immune failure in draining LNs must be determined to guide patient selection and clinical application in the neoadjuvant and adjuvant setting. Understanding the relevance for each of these lymphatic-dependent processes across time and as a function of tumor progression will be necessary for their effective targeting in the clinical setting. Treg, regulatory T cell; iDC, immature dendritic cell; TSC, stemlike $CD8^+$ T cell.

Lymphatic Output

Lymphatic transport is necessary for antigen presentation in draining LNs and the rapid activation of protective adaptive immune responses (2). Antigen delivery via lymph is mediated in large part by activated dendritic cells (DC) that access peripheral lymphatic vessels and migrate to draining LNs where they present to naïve and memory T cells. One hypothesis that has emerged is that increasing the number of tumor-associated lymphatic vessels could enhance this first step of immune surveillance. Consistent with this hypothesis, VEGF-C overexpression in syngeneic models of murine melanoma promotes a hyper-inflammatory response leading to increased tumor-promoting and tumor-suppressive mechanisms (5). Conversely, the complete absence of a dermal lymphatic vasculature protects implanted melanomas from host surveillance, leading not only to a reduction in the adaptive immune infiltrates, but also to a surprising depletion of innate effectors (8). This apparent lymphatic-dependent priming of intratumoral inflammation and adaptive immunity suggests that the lymphangiogenic microenvironment could synergize with immunotherapy. Consistent with this idea, VEGF-C/VEGFR3 signaling enhances response to immunotherapy in preclinical models of melanoma (6) and glioblastoma (7). The relevance of these findings is further supported by human data in both melanoma and glioblastoma, where there is a positive correlation between *VEGF-C* expression, markers of the lymphatic endothelium (e.g., *LYVE1*, *PDPN*, *CCL21A*), and T-cell inflammation (6–8, 10). Interestingly, high density of both lymphatic vessels and granzyme B^+ cells correlates with the lowest risk for distant metastasis in colorectal cancer and long-term survival (11).

These data support the conclusion that increasing either the rate, or absolute quantity of, information flow out of tumors boosts immune surveillance and primes the tumor microenvironment for response to immunotherapy.

Importantly however, VEGFR3 is not restricted to the lymphatic endothelium, and hyper-physiologic levels of VEGF-C likely impacts other neighboring cell types, notably myeloid cells and the blood vasculature, which may play a part in the remodeled immune responses seen in these models. Therefore, to what extent the immunologic changes observed above are directly dependent on changes in lymphatic vessel density as opposed to VEGF-C–dependent activation of lymphatic vessels and the surrounding microenvironment remains unclear. These mechanistic uncertainties paired with the causal relationship between VEGF-C, lymphangiogeneis, and metastasis (3, 5) makes the therapeutic relevance of a VEGF-C–dependent approach in the clinic unclear. It is possible that in the context of neoadjuvant therapy, lymphangiogenic tumors might be preselected as likely responders or that lymphatic transport could be stimulated to enhance local immune communication and LN responses. Alternatively, other molecular mediators of tumor-associated lymphangiogenesis and growth-independent lymphatic vessel activation (e.g., adhesion molecules and chemokines) may provide more effective targets in the clinic. As these hypotheses are tested, the important question remains as to whether immune and metastatic potential can ever be functionally uncoupled *in vivo* and in patients.

One recent approach leveraged VEGF-C to potentiate a therapeutic antitumor vaccine given at a site distant from an established preclinical tumor (12). Administration of VEGF-C at a distant vaccination site may mitigate concerns of enhanced metastatic potential in the tumor itself while leveraging lymphangiogenesis to enhance DC migration to LNs and invigorate potent antitumor immune responses. In the study, a VEGF-C–overexpressing, irradiated B16F10 melanoma cell vaccine activated lymphangiogenesis at the subcutaneous implantation site and boosted systemic tumor control and immunologic memory compared with control vaccines (12). Interestingly, in both this vaccine approach (12) and in VEGF-C–overexpressing murine melanomas (6), observations of epitope spreading indicate that boosting lymphatic and LN engagement may broaden the antitumor T-cell repertoire, leading to more durable systemic control and antitumor memory. Whether epitope spreading is simply a function of more presentation driven by lymphangiogenesis, or something else, remains to be determined.

Peripheral Lymphatic–Immune Cross-talk

As a challenge to the idea that *de novo* lymphangiogenesis is required to enhance immune surveillance, dermal lymphatic vessels in Vaccinia virus infected skin do not undergo significant lymphangiogenesis and the absolute numbers of DCs that migrate to LNs in response to infection are not significantly different than steady state (2). Despite this, Vaccinia virus is a successful vaccine vector that drives potent protective cellular and humoral immune responses. These observations suggest that the preexisting lymphatic vasculature is sufficient to support adaptive immunity in the right context. Instead of proliferating, the dermal initial lymphatic capillaries undergo an infection-dependent process of junctional tightening, termed zippering, that restricts fluid transport, sequesters virus, and seems to optimize $CD8^+$ T-cell priming and expansion (13). Rather than depending on VEGF-C/VEGFR3, lymphatic zippering in skin is dependent on type I IFN (2) and VEGFR2 (13), pointing to contextual cues as key drivers of diverse lymphatic responses to inflammation. These data suggest a complementary hypothesis, that rather than viewing lymphatic vessels as tubes to expand or contract and boost the quantity of signal transported, we may consider how lymphatic vessels are activated and harness this knowledge to tune the quality of immune surveillance and peripheral immune function.

If this hypothesis holds, one would expect there to be mechanisms that govern a switch between lymphatic-intrinsic suppressive and immune-potentiating activity. Although the VEGFR2 signals described above may represent an immune-potentiating signal, interstitial IFNγ has emerged as a potent activator of suppressive function in peripheral lymphatic vessels. In inflamed skin, IFNγ induces local expression of the immune checkpoint molecule PD-L1 (10) and antigen presenting machinery (e.g., MHCII; ref. 14). Loss of IFNγR specifically in lymphatic vessels enhances $CD8^+$ T-cell accumulation and spontaneous T cell–dependent tumor control, and similarly, lymphatic deletion of IFNγR during cutaneous viral infection exacerbates T-cell accumulation and skin pathology (10). These data indicate that IFNγ sensing by the peripheral lymphatic vasculature may facilitate a switch towards immune resolution and return to homeostasis; however, the mechanisms through which IFNγ signaling in peripheral lymphatic vessels limits peripheral $CD8^+$ T-cell responses remain incompletely understood. Although stromal PD-L1 can contribute to T-cell dysfunction in the tumor microenvironment and lymphatic vessels exhibit high levels of PD-L1 expression in response to IFNγ (10), IFNγ-dependent upregulation of MHCII also promotes local induction of regulatory T cells that may impair $CD8^+$ T-cell function (14). Therefore, IFNγ signaling in lymphatic vessels may directly regulate immune suppressive antigen presentation by lymphatic endothelial cells (LEC). Collectively, these data suggest an interplay between accumulating cytotoxic immunity and LEC function, such that IFNγ acts as a functional switch to support local immune suppression and immune escape. Finally, the accumulation of $CD8^+$ T cells, as well as other leukocytes, in tumors may directly depend on the probability of their recirculation through an activated lymphatic vasculature. Functional $CD8^+$ T cells do in fact exit tumor microenvironments via associated lymphatic vessels (15), however, the mechanisms that regulate T-cell exit and its impact on ongoing antitumor immune responses remains largely unexplored.

The concept of peripheral lymphatic–immune cross-talk in tumors may be of particular interest when considering the formation of lymphocyte aggregates and tertiary lymphoid structures (TLS) in tumor microenvironments. The presence of TLS is correlated with response in patients, and yet the organizing principles that initiate their formation and maintenance remain poorly understood. Lymphatic vessels are a rich source of chemokines that regulate cellular infiltration and may initiate the formation of these structures. VEGF-C enhances LEC expression of CCL21, a homeostatic chemokine that governs LN structure and function. Overexpression of CCL21 in murine melanomas generates a reactive LN-like stroma, high endothelial venule–like blood vessels, and naïve T-cell infiltrates that may suggest the early emergence of a TLS-like structure (16). Similarly, overexpression of VEGF-C in murine melanoma (6) and VEGF-C boosted vaccines (12) promotes $CCR7^+$ infiltrates, including naïve T cells, which indicates potential for naïve T-cell priming directly in peripheral tissue. These data suggest the potential for lymphatic remodeling, growth, and growth-independent activation (e.g., chemokine production), to impact tumor infiltrates and thereby tumor immune surveillance. A relationship between peripheral tissue lymphatic vessels and lymphocyte aggregates is further supported by observations in the colonic lamina propria that aggregates induced by immunogenic commensal

bacteria associate closely with CCL21-expressing lymphatic capillaries (17). In addition, stemlike T cells, which are critical for response to immunotherapy, are found proximal to MHCII-enriched, lymphatic niches in renal cancer (18). Despite their proximity, however, whether activation of the lymphatic vasculature is causal for initiation and maintenance of some or all of these tumor-associated aggregates remains to be carefully determined. In support of a causal relationship, however, TLS initiate at sites of disrupted lymph flow in chronic inflammation. In a TNF-driven model of colon inflammation, lymphatic valve dysfunction catalyzes lymphocyte aggregation, which further disrupts fluid flows to exacerbate intestinal inflammation and drive progressive disease (19).

It is therefore becoming evident, that either instead of or in concert with proliferative lymphangiogenesis, microenvironment-induced lymphatic activation states may impact the functional intratumoral immune repertoire. Moving these ideas forward to clinical application, however, requires a deeper understanding of the basic molecular mechanisms that govern lymphatic adaptation and maladaptation in relation to tumor progression and response to immunotherapy. These mechanistic insights could provide new therapeutic strategies that follow recent advances in vascular targeting focused on inducing novel functional states that interface with ongoing peripheral tissue immune responses (20).

Lymph Node Potential

Ultimately, tumor-associated lymphatic vessels connect developing tumors, at their earliest stages, to sentinel, draining LNs. Despite the fact that draining LNs are the main sites for *de novo* adaptive immune initiation, they are also coopted to seed early regional metastatic outgrowth in many types of solid tumors. The historical, Halstedian view of LN metastasis is that it provides a depot for systemic metastasis. However, direct hematogenous metastasis, either coincident with or instead of lymphogenous metastasis, also drives progression; the preference for one route over the other is likely tumor type specific. Consistent with this idea, recent large-scale trials have failed to show long-term survival benefit with immediate complete LN dissection, which likely indicates that systemic dissemination is an early event in tumor evolution. What may reconcile these hypotheses, however, is the observation that both prior to tumor seeding and as a function of LN metastasis itself, tumor-draining LNs are progressively immune-suppressed. LN immune suppression may not only permit initial regional spread, but also dampen systemic immune surveillance and thereby enable distant tumor progression (recent review; ref. 21). Recent evidence indicates that LN metastasis depends on sequential suppression of innate [natural killer (NK) cell] and adaptive immunity ($CD8^+$ T cells) where IFNs play a critical role (22). Interestingly, upon establishment, LN tropic melanoma cells activate expansion of LN regulatory T cells in a TGF-β–dependent manner. LN-expanded regulatory T cells are sufficient to drive systemic immune suppression and ultimately facilitate metastatic seeding in lungs (22). These data provide some of the first functional evidence for a direct impact of the sentinel LN in systemic tumor progression. The specific expansion of LN regulatory T cells, as well as many other mechanisms of LN maladaptation to tumor drainage, are likely candidates for immune potentiation and reinvigoration. It may be possible, therefore, to leverage lymphatic transport to unlock LN immune potential in the neoadjuvant and adjuvant settings.

Proof of principle for the hypothesis that sentinel LNs can be reinvigorated for improved systemic control comes from multiple studies that have explored topical, intratumoral, and intranodal immunotherapy. In one such clinical study, local adjuvant treatment leveraged lymphatic transport to deliver the TLR9 agonist, CpG, to sentinel LNs in patients with early-stage I to II melanoma prior to sentinel LN biopsy (23). Adjuvant CpG delivered intradermally at the primary tumor resection site prior to sentinel LN biopsy activates LN DCs and NK cells, leading to boosted peripheral tumor-reactive $CD8^+$ T cells. Despite the small number of patients in the study, a significant reduction in occult metastases was observed in the adjuvant treated group relative to controls, which correlated with improved recurrence-free and distant metastasis–free survival over more than 88 months of follow-up (23), perhaps indicating rapid control of existing LN metastases. Most interestingly, this level of regional tumor control was achieved in only the 7 days between administration and LN biopsy, hinting at the presence of effector cells poised for rapid tumor control upon appropriate stimulation. Recent evidence indicates that the LN harbors potent populations of resident memory T cells (T_{RM}) with potential to mediate local tumor control (24) and stem-like $CD8^+$ T cells that reinvigorate in response to checkpoint blockade and replenish the intratumoral repertoire (25). Although the mechanisms that generate and maintain these specific T-cell populations in draining LNs remains incompletely understood, they may provide important targets to reinvigorate and mobilize antitumor immune responses in patients.

Whether increasing tumor burden will limit the therapeutic utility of the sentinel LN remains to be determined. Analyses of sentinel LN leukocyte populations in patients with melanoma suggest a progressive inhibition of DC maturation, reduced NK-cell cytotoxic function, and loss of T-cell proliferative potential as a function of micrometastasis and increasing primary tumor burden (26). These changes, in addition to the accumulation of regulatory T cells, are consistent with others recorded in breast, colorectal, and hepatocellular cancers (21). Interestingly, $CD69^+CD8^+$ T cells, which would include the LN T_{RM} that are predicted to be capable of rapid, local tumor control and seem to be associated with improved long-term outcomes (24), appear to be lost as a function of metastatic progression (26). What might drive the loss of this population with metastatic LN outgrowth remains unclear, though the concomitant clonal expansion of an effector memory and progressively dysfunctional $CD8^+$ T-cell population (26) may indicate similar mechanisms of antigen-dependent T-cell dysfunction as seen in the periphery. It still, however, remains unknown how tumor-specific T-cell populations in LNs are impacted by metastatic outgrowth, or if metastatic growth itself indicates a fundamental failure of these populations within the LN specifically. Mechanistic studies that model the relevant clinical treatment paradigms are necessary to define the point of LN failure, if it exists, to ultimately guide clinical course of care.

So, Good or Bad?

The need to label tumor-associated lymphatic vessels good or bad clearly oversimplifies a complex problem. Like other structural components of the tumor microenvironment (e.g., blood vessels and fibroblasts), lymphatic vessels undergo temporal and spatially resolved adaptations and maladaptations that can restrict or contribute to tumor progression. These structural and functional remodeling events occur across anatomical sites and directly impact the efficacy of the cancer–immunity life cycle and both regional and distant metastatic potential. Moving forward, the extent to which we may leverage the lymphatic system for clinical care will depend upon a deeper mechanistic understanding for how to uncouple immunity and metastasis. If tapped, however, the immune potential stored within the lymphatic system may enable early immune reinvigoration to interrupt tumor progression and ultimately limit distant disease.

Authors' Disclosures

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