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REVIEW ARTICLE

Beyond Lymph Nodes: Emerging Insights into Lymphatic Remodeling as a Driver of Tumor Spread and Immune Escape

Deepalakshmi Mani[1], Arun Kanniyappan Parthasarathy[1*]

Beyond its original functions in tissue fluid clearance and immune surveillance, the role of lymphatic remodeling in the progression of cancer has come to the fore. The microenvironment of the lymphatics promotes tumor cell dissemination, lymph node metastasis and systemic spread due to dynamic structural and functional changes that occur within the lymphatic vessels. All these factors, including tumour-derived growth factors, inflammatory mediators, extracellular matrix remodeling and stromal/immune cell interactions, contribute to lymphangiogenesis and lymphatic dysfunction. These changes can create physical pathways for the metastasis to occur and create an immune escape niche through modulation of antigen presentation, immune cell trafficking, and T-cell activity. The new advances in molecular biology, imaging technologies and single-cell sequencing have uncovered the intricate mechanisms that underlie lymphatic remodeling and uncovered novel therapeutic targets. Several strategies are being investigated to enhance cancer therapeutic responses, focusing on lymphangiogenic signaling pathways, immune checkpoint modulation and tumor lymphatic microenvironment. This review summarizes the current knowledge about the proper role of lymphatic remodeling in the process of tumor metastasis and immune evasion, new biomarkers and future therapeutic approaches.

Keywords: Lymphatic remodelling; Lymphangiogenesis; Tumor metastasis; Immune escape; Tumor microenvironment

*[1]*Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty, The Nilgiris, Tamil Nadu, India*
Corresponding authors
Correspondence: Dr. Arun Kanniyappan Parthasarathy, □: kparun@jssuni.edu.in

0.1 List of Abbreviations

Abbreviation	Full Form
APC	Antigen-Presenting Cell
CAF	Cancer-Associated Fibroblast
CCL	Chemokine (C-C Motif) Ligand
CCR	Chemokine (C-C Motif) Receptor
DC	Dendritic Cell
ECM	Extracellular Matrix
EMT	Epithelial–Mesenchymal Transition
FDA	Food and Drug Administration
FGF	Fibroblast Growth Factor
HIF	Hypoxia-Inducible Factor
IFN-γ	Interferon Gamma
IL	Interleukin
LEC	Lymphatic Endothelial Cell
LN	Lymph Node
LNM	Lymph Node Metastasis
LYVE-1	Lymphatic Vessel Endothelial Hyaluronan Receptor-1
MDSC	Myeloid-Derived Suppressor Cell
MHC	Major Histocompatibility Complex
NK	Natural Killer
PD-1	Programmed Cell Death Protein-1
PD-L1	Programmed Death-Ligand 1
PROX1	Prospero Homeobox Protein-1
TAM	Tumor-Associated Macrophage
TGF-β	Transforming Growth Factor Beta
TME	Tumor Microenvironment
Treg	Regulatory T Cell
VEGF	Vascular Endothelial Growth Factor
VEGF-C	Vascular Endothelial Growth Factor-C
VEGF-D	Vascular Endothelial Growth Factor-D
VEGFR-3	Vascular Endothelial Growth Factor Receptor-3

1 Introduction

In addition to its role in the maintenance of tissue fluid homeostasis, in the transport of dietary lipids and in the regulation of immune surveillance by immune cells and antigens that are trafficked to regional lymph nodes, the lymphatic system is an integral part of the circulatory and immune systems (1, 2). In general, the lymphatic vessels were considered as passive channels for the spread of metastasis cells to draining lymph nodes. Recent advances, however, have significantly changed this view in the last ten years and shown that the structure and function of lymphatic vessels is dynamically remodeled during tumor progression (3, 4). Lymphatic remodeling plays a key role in the dissemination of tumors, immune regulation and therapeutic responses, making it a hallmark of the cancer process. **Figure 1**

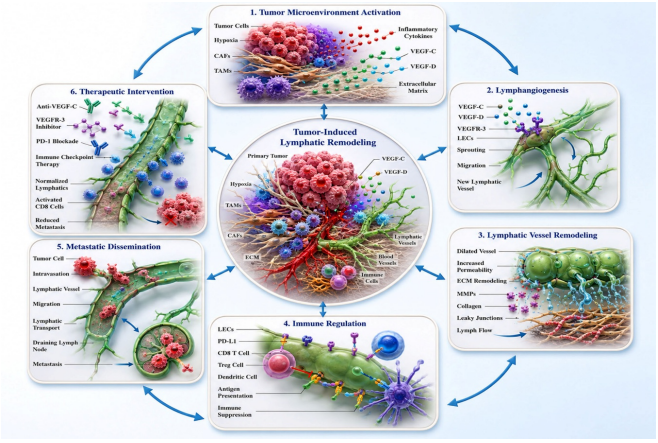

Fig. 1 Schematic illustrating tumor-induced lymphatic remodeling, from tumor microenvironment activation and lymphangiogenesis to vessel remodeling, immune regulation, metastatic dissemination, and therapeutic interventions targeting lymphatic signaling and metastasis.

Lymphatic remodeling involves a range of biological changes such as lymphangiogenesis, vessel enlargement, increased permeability, ECM remodeling, and changes in the function of the cells that line the lymphatics (5, 6). A significant number of these adaptations are a result of interactions between tumor cells and the tumor microenvironment. Malignant cells produce lymphangiogenic factors, like vascular endothelial growth factor-C (VEGF-C), and vascular endothelial growth factor-D (VEGF-D), that bind to VEGFR-3 receptors that are expressed by the lymphatic endothelial cells, leading to the development and progression of lymphatics (7, 8). At the same time, inflammatory cytokines and chemokines, hypoxia, cancer associated fibroblasts and tumor associated macrophages exacerbate these remodeling events, resulting in the formation of structurally abnormal, highly invasive lymphatic vessels.

In addition to their role as conduits for the metastatic spread of disease, remodeled lymphatics play an active role in immune escape (9, 10). Lymphatic endothelial cells have unique immunomodulatory properties such as antigen presentation, expression of immune check molecules and regulation of dendritic cell and T-cell trafficking. The remodeling of the lymphatics induced by a tumor leads to immune tolerance by favoring the recruitment of regulatory T cells, the suppression of the cytotoxic lymphocytes and the induction of expression of inhibitory molecules like PD-L1. As a result, the reconfigured lymphatic system creates an immunosuppressive niche that allows tumor cells to survive without being recognized and eliminates by the immune system and helps metastatic colonization (11, 12).

The last decade has seen tremendous advances in technology, such as single-cell RNA sequencing, spatial transcriptomics, multiplex imaging and high-resolution intravital microscopy, which has significantly improved our understanding of the molecular and cellular heterogeneity of the LEc in cancer progression(13, 14). In recent years, many new technologies have emerged, including single-cell RNA sequencing, spatial transcriptomics, multiplex imaging and high-resolution intravital microscopy, which has greatly enhanced our understanding of the molecular and cellular heterogeneity of LEc during cancer progression. These have uncovered novel pathways, stromal interactions, and metabolic changes that control lymphatic remodeling. Furthermore, they have uncovered significant variability between tumor types, and pointed out that specificity of genetic, molecular and microenvironmental characteristics of cancer has impact on lymphatic remodeling.

The increasing awareness of the role of lymphatic remodeling as an active regulator of lymphogenous metastasis has therapeutic potential. Pharmacological (inhibiting lymphangiogenic pathways), signaling (modulation of lymphatic endothelial cell), and normalization (restoring lymphatic function) strategies and combination approaches using anti-lymphangiogenic agents and immune checkpoint inhibitors are actively being explored in preclinical and clinical studies(15). These strategies aim at not only curbing the spread of metastases but also at reinvigorating efficient anti-tumoral immunity and improve the efficacy of already used cancer treatment.

This review offers an in-depth analysis of the mechanisms underlying the remodeling of the lymphatic system in cancer, highlighting both its pro-tumorigenic and immune evasive properties. It also outlines new molecular markers, novel therapeutic targets, recent advances and future areas of research that may lead to better cancer prevention of metastasis and patient care. **Table 1**

Table 1 Summary of normal lymphatic functions, tumor-induced remodeling mechanisms, molecular mediators, immune alterations, clinical consequences, and emerging therapeutic strategies targeting lymphangiogenesis, immune evasion, and metastatic progression in cancer.

Aspect	Normal Lymphatics	Tumor-Induced Change	Key Mediators	Biological Impact	Therapeutic Focus
Function	Fluid balance, immunity	Lymphatic remodeling	VEGF-C, VEGF-D	Enhanced metastasis	Anti-lymphangiogenic therapy
Vessel Structure	Stable vessels	Enlargement, permeability	VEGFR-3 signaling	Tumor cell invasion	Vessel normalization
Tumor Microenvironment	Homeostatic	ECM remodeling, inflammation	CAFs, TAMs, cytokines	Lymphangiogenesis	Microenvironment targeting
Immune Regulation	Immune surveillance	Immune suppression	PD-L1, Tregs	Immune escape	Checkpoint inhibitors
Molecular Insights	Limited heterogeneity	Dynamic cellular changes	scRNA-seq, spatial transcriptomics	Biomarker discovery	Precision medicine
Clinical Relevance	Tissue homeostasis	Metastasis and therapy resistance	Combined pathways	Poor prognosis	Combination immunotherapy

2 Molecular Basis of Lymphatic Remodeling

2.1 *Physiology of the Tumor Lymphatic System*

The lymphatic vasculature regulates tissue fluid balance, plays a role in the absorption of dietary lipids and coordinates the immune surveillance by transporting immune cells and antigens to the lymph nodes(16, 17). In healthy tissues, PROX1, VEGFR-3 and LYVE-1 are well regulated signaling pathways that maintain the integrity of vessels by the lymphatic endothelial cells (LECs). Throughout the progression of the tumor, this physiological equilibrium is disturbed, and a steady exposure occurs to inflammatory cytokines, hypoxia and the tumor cells stimulate growth factors. As a result, it causes changes in normal lymphatic vessels and makes them abnormal to aid cancer progression (18, 19). The understanding of the basis of the physiology of the lymphatic vessels is key to understanding the pathological remodeling of lymphatic vessels in tumor microenvironments.

2.2 *Molecular Drivers of Lymphangiogenesis*

The key molecules involved in regulation of tumor-associated lymphangiogenesis are vascular endothelial growth factor-C (VEGF-C) and vascular endothelial growth factor-D (VEGF-D) which activate the receptor of lymphatic endothelial cells, VEGFR-3 (20, 21). In addition there are other mediators that further promote lymphatic expansion such as fibroblast growth factors, platelet-derived growth factors, angiopoietins, transforming growth factor-β and hypoxia-inducible factor-1α. These signals are further enhanced by the release of pro-lymphangiogenic cytokines by cancer-associated fibroblasts and tumor-associated macrophages as well as the remodeling of extracellular matrix components (22, 23). These molecular pathways work together to create a huge network of lymphatics that promotes tumour dissemination. In recent years, transcriptomic analyses have led to the discovery of novel regulators of lymphangiogenesis that could be targeted for inhibiting metastasis progression (24, 25).

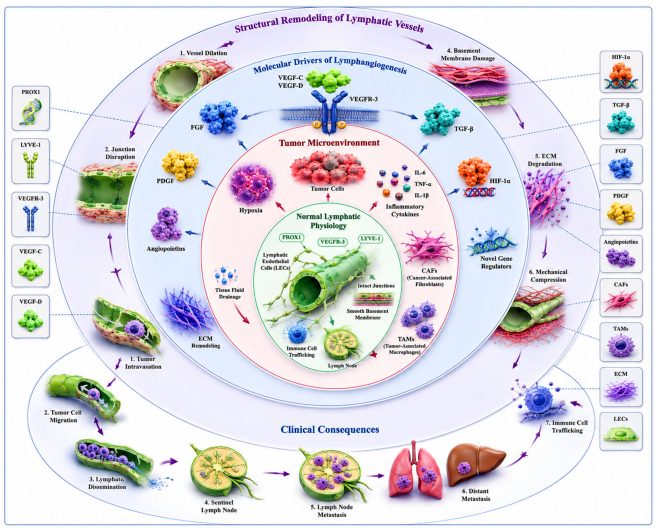

Fig. 2 Concentric schematic illustrating tumor lymphatic remodeling, highlighting normal lymphatic physiology, molecular drivers of lymphangiogenesis, structural vascular alterations, and clinical consequences leading to tumor dissemination, lymph node metastasis, and distant metastatic progression.

2.3 *Structural Remodeling of Lymphatic Vessels*

The changes in the vessels include dilation, increased permeability, disruption of the basement membrane, disruption of endothelial junctions and degradation of the extracellular matrix. Such changes in structure lessen the physical obstacles that block entry of tumor cells into vessels of the lymphatics (26, 27). Applying these concepts to the case of malignant cells, increased vessel diameter and impaired intercellular junctions enhance the intravasation of malignant cells in efficient ways, and also allow immune cell trafficking(28). Tumour cells inducing mechanical forces due to tumour growth and matrix stiffness also influence the architecture of lymphatics (14, 29). Advanced imaging shows that remodeled lymphatics have irregular shapes and impaired drainage, which provide good conditions for the metastasis of Tumors. Structural remodeling is thus an important step in the progression of cancer. **Table 2**

Table 2 Summary of physiological, molecular, and structural mechanisms driving tumor-associated lymphatic remodeling, highlighting major signaling pathways, vessel alterations, biological consequences, and potential therapeutic targets that contribute to cancer metastasis.

Aspect	Normal State	Tumor-Induced Change	Key Molecules	Biological Effect	Clinical Significance
Lymphatic physiology	Fluid balance, immune surveillance	Homeostasis disrupted	PROX1, VEGFR-3, LYVE-1	Vessel dysfunction	Supports tumor progression
Growth signals	Controlled lymphangiogenesis	Excess lymphatic growth	VEGF-C, VEGF-D	LEC proliferation	Increased metastasis
Microenvironment	Balanced signaling	Cytokines, hypoxia, CAF/TAM activation	HIF-1α, TGF-β, FGFs	Pro-lymphangiogenic niche	Enhanced tumor spread
Vessel structure	Intact endothelium	Dilated, permeable vessels	ECM proteases, angiopoietins	Easier tumor entry	Lymphatic invasion
Mechanical remodeling	Normal matrix tension	Matrix stiffness, vessel distortion	ECM components	Altered drainage	Facilitates dissemination
Therapeutic targets	Stable lymphatics	Dysregulated pathways	VEGFR-3, VEGF-C/D	Targeted inhibition	Reduced metastatic potential

3 Lymphatic Remodeling in Tumor Progression

3.1 *Lymphatic Routes of Tumor Dissemination*

Many epithelial malignancies, such as breast cancer, melanoma, gastric cancer, colorectal cancer and head and neck cancers, are often the first cancer to become metastatic via the lymphatics (30, 31). The tumor cells take advantage of the following properties of the lymphatic capillaries: discontinuous basement membrane, loose junctions of the endothelial cells and low shear stress. CCR7 expressing tumour cells and CCL21 secreted by the lymphatic endothelial cells promote directionality of tumour cell migration through the chemokine interaction (17, 32). After invading the lymphatics, tumour cells then invade the systemic circulation, and colonise regional lymph nodes. This sequential spread brings up a point: that metastasis is not just the passive spread through the lymphatic system, but an active process. **Figure 3**

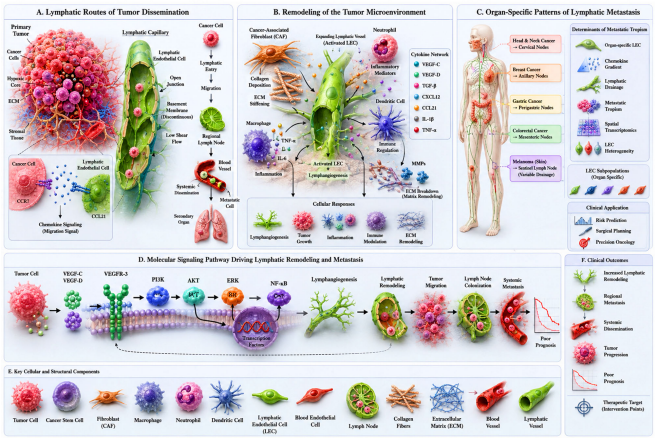

Fig. 3 Lymphatic remodeling promotes tumor dissemination through CCR7–CCL21 signaling, stromal activation, inflammatory cytokines, extracellular matrix remodeling, lymphangiogenesis, organ-specific lymphatic metastasis, and molecular pathways driving tumor progression and poor clinical outcomes.

3.2 *Remodeling of the Tumor Microenvironment*

Lymphatic remodeling has a profound effect on the tumour microenvironment through controlling stromal interactions, inflammatory responses and extracellular matrix dynamics (33, 34). Activated fibroblasts produce matrices of collage that are stiffer and activate lymphangiogenesis. At the same time, the macrophages, neutrophils and dendritic cells secrete cytokines that also alter the behaviour of the lymphatic endothelial cells. Such interactions result in an autostimulatory inflammatory environment that fosters tumor growth and vascular remodelling (35, 36). Lymphatic vessels expand while at the same time breaking down the extracellular barriers with MMPs. As a result, the tumor microenvironment undergoes dynamic remodeling, closely associated with the dynamic remodeling of the lymphatics.As such, the tumor microenvironment is tightly coupled with the remodel of the lymphatics (27, 37).

3.3 *Organ-Specific Patterns of Lymphatic Metastasis*

Each type of malignancy has a specific pattern of metastasis to the lymph nodes that is the result of the tissue-specific molecular signatures and lymphatic drainage pathways (13, 38). The nodal metastasis of breast cancer is common to axillary nodes while that of gastric carcinoma is along perigastric nodes. Lymphatic dissemination of melanoma is very variable and related to the site of the primary lesion (14, 39). The phenotype of the lymphatics in the organs and the expression of chemokines affect the tropism of metastasis. Recent spatial transcriptomic research indicates that there is some degree of heterogeneity within the population of LECs in different organs, suggesting that the metastatic efficiency of LECs within organs is controlled by the local microenvironment (40). These observations could help to predict which patients are at risk of having a metastasis and help plan the surgery. **Table 3**

Table 3 Summary of lymphatic remodeling mechanisms, molecular mediators, tumor microenvironment changes, organ-specific metastatic patterns, and their clinical significance in predicting lymphatic dissemination and improving personalized cancer management.

Aspect	Mechanism	Key Molecules/ Cells	Biological Effect	Cancer Examples	Clinical Significance
Lymphatic invasion	Entry through permeable lymphatic capillaries	Tumor cells, LECs	Initial metastatic spread	Breast, melanoma	Early nodal metastasis
Chemotactic migration	CCR7–CCL21 signaling	CCR7, CCL21	Directed tumor migration	Breast, colorectal	Target for anti-metastatic therapy
Tumor microenvironment remodeling	Stromal and inflammatory activation	Fibroblasts, macrophages, MMPs	ECM remodeling, lymphangiogenesis	Multiple solid tumors	Promotes tumor progression
Lymphatic vessel expansion	VEGF-mediated lymphangiogenesis	LECs, VEGF-C/D	Increased lymphatic density	Gastric, head & neck	Facilitates dissemination
Organ-specific metastasis	Tissue-specific drainage and chemokines	Organ-specific LECs	Selective lymph node colonization	Breast, gastric, melanoma	Guides surgical planning
Clinical implications	Biomarker-based risk prediction	Spatial transcriptomics	Improved prognosis assessment	Solid malignancies	Personalized therapeutic strategies

4 Lymphatic Remodeling and Immune Escape

4.1 *Immune Regulation by Lymphatic Endothelial Cells*

The lymphatic endothelial cells actively control adaptive and innate immune responses, through antigen handling, secretion of cytokines and trafficking of immune cells (41, 42). They play a role in peripheral immune tolerance under physiological conditions, and promote the migration of dendritic cells to the draining lymph nodes. These regulatory functions are modified by tumor-associated lymphatic remodeling through the regulation of the expression of adhesion molecules, chemokines and immune checkpoint ligands (43, 44). As a result, the lymphatic endothelial cells are recruited to actively contribute to the creation of an immunosuppressive environment which supports tumor persistence (45, 46). The mechanisms of these have changed the way that lymphatic vessels are viewed; as a passive conduit to a dynamic immune regulator. **Figure 4**

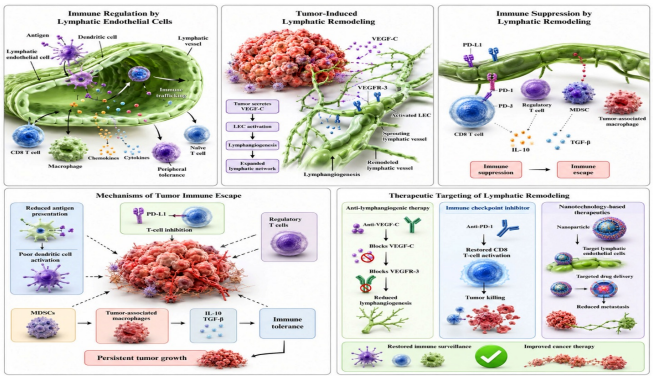

Fig. 4 Three-dimensional graphical abstract illustrating lymphatic endothelial immune regulation, tumor-induced lymphatic remodeling, immune escape mechanisms, and therapeutic targeting strategies, highlighting VEGF-C/VEGFR-3 signaling, PD-L1-mediated immunosuppression, nanotechnology, and immune checkpoint inhibition to suppress metastasis and restore antitumor immunity.

4.2 *Mechanisms of Tumor Immune Escape*

Tumors take advantage of remodelling of lymphatics to escape immune surveillance by several complementary mechanisms(20, 47). Up-regulation of PD-L1 on the LYE inhibits activation of cytotoxic T cells and the up-regulation of recruitment of regulatory T cells leads to immune tolerance. Myeloid-derived suppressor cells and tumor-associated macrophages also mediate tolerance to tumors by producing other immunosuppressive cytokines, such as IL-10 and TGF-β. Impaired antigen presentation leads to suboptimal T-cell priming in DLNs. These changes have a combination of effects that contribute to an 'immune-privileged' tumor environment in which there is a functional immune system but tumor growth can proceed (48, 49).

4.3 *Therapeutic Targeting of Lymphatic Remodeling*

The lymphatic remodeling is a novel strategy for the prevention of metastasis and improvement of cancer therapy. Preclinical studies have shown that inhibitors of VEGF-C/VEGFR-3 signalling inhibit lymphangiogenesis and the lymph node metastasis (11, 50). However, combination therapies combining anti-lymphangiogenic agents (ALG) with immune checkpoint inhibitors (ICI) have shown synergic therapeutic effects against the tumor eliminating two targets at once and reducing metastasis dissemination at the same time by reestablishing immune surveillance (12, 51). There are two approaches that have been developed with nanotechnology that enhance the specificity towards the lymphatic endothelial cells, namely drug delivery systems and antibody directed therapeutics (14). Further clinical trials are needed to fine-tune treatment regimens, to find predictive biomarkers and to minimise side effects of lymph node-specific therapies. **Table 4**

Table 4 Summary of lymphatic endothelial immune regulation, tumor-induced immune escape mechanisms, and emerging therapeutic strategies targeting lymphatic remodeling to suppress metastasis, restore immune surveillance, and improve anticancer treatment outcomes.

Aspect	Lymphatic Endothelial Cell (LEC) Function	Tumor-Induced Change	Immune Consequence	Therapeutic Target	Expected Benefit
Antigen presentation	Maintains peripheral tolerance	Impaired antigen presentation	Weak T-cell priming	Immune restoration	Enhanced antitumor immunity
Immune checkpoints	Regulates immune activation	PD-L1 overexpression	Cytotoxic T-cell inhibition	PD-1/PD-L1 inhibitors	Restored T-cell function
Immune cell trafficking	Directs dendritic cell migration	Altered chemokine expression	Reduced immune surveillance	Chemokine modulation	Improved immune infiltration
Immunosuppressive cells	Balanced immune regulation	Increased Tregs, MDSCs, TAMs	Immune tolerance	Immunomodulatory therapies	Reduced tumor immune escape
Lymphangiogenesis	Maintains lymphatic homeostasis	VEGF-C/VEGFR-3 activation	Enhanced metastasis	Anti-VEGF-C/VEGFR-3 agents	Decreased lymphatic spread
Targeted therapy	Supports lymphatic function	Tumor-associated remodeling	Persistent immunosuppression	Nanomedicine + immune checkpoint inhibitors	Improved therapeutic efficacy

5 Future Directions

Future research should aim to uncover the molecular heterogeneity of LECs in various types of tumor using a single-cell multi-omics, spatial transcriptomics and artificial intelligence enabled data integration approach. New imaging technologies that can capture the processes of lymphatic remodeling in real time will enable better understanding of the dynamics and response to therapy of metastasis. The potential for development of selective therapeutic treatments for lymphatics, patient stratification based on markers, and combination therapy of immunotherapies with anti-lymphangiogenic agents are all promising approaches. Furthermore, there is a need for standardised experimental models and longitudinal clinical trials to confirm novel biomarker discovery, treatment timing and to ensure successful translation of discovery in the laboratory to precision oncology.

6 Discussion

As emerging proof demonstrates, lymphatic remodeling is a complex biological mechanism with multiple functions affecting the dissemination of cancer, immune function and response to therapy. Remodelling of lymphatic vessels isn't just a passive drainage, but regulates the interaction between malignant cells, stromal cell and immune cells. While there has been great success in molecular identification of regulators, there are still many molecular pathways that are not well understood and may be type-specific. The clinical translation is also difficult due to the heterogeneity of tumors, and the lack of predictive markers. Multidisciplinary strategies combining molecular biology, immunology, bioengineering and computational approaches will pave the way for the rapid development of personalized strategies for targeting remodeling of the lymphatic system.

7 Conclusion

The ability of cancer to disseminate to distant organs and to escape immune surveillance has come to be known as lymphatic remodeling, and is now recognized as a key factor in the progression of cancer. The lymphoid system is remodeled into a dynamic component of tumour biology by structural modifications, molecular signalling pathways and immune regulation. The last decade has seen significant advances in technology that have led to a better understanding of these complicated interactions, and the discovery of new therapeutic targets. Combining targeted therapy, conventional chemotherapy and immunotherapy with targeting of the remodeling of the lymphatics has the great potential to limit the metastatic burden and increase patient's survival. Ongoing translation will be key in realizing the impact of mechanistic understanding in the development of translationally impactful interventions that will improve precision cancer management in the clinic.

7.1 CRediT Author Statement

Deepalakshmi Mani, Arun Kanniyappan Parthasarathy conceptualization of the study, drafted the manuscript and designed the figures, and manuscript review and editing. All authors reviewed the manuscript.

7.2 Declaration Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Conflicts of Interest

All authors declare that there are no conflicts of interest associated with the publication of this manuscript.

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Notes and references

1 Eichin D, Takeda A, Pessia A, Laakkonen JP, Kankainen M, Imhof BA, et al. Breast cancer remodels lymphatics in sentinel lymph nodes. Nature Communications. 2025;16(1):10117.

2 He M, He Q, Cai X, Zhu L, Zhang Y. Role of lymphatic endothelial cells in the tumor microenvironment. Cancer Cell International. 2021;21(1):278.

3 Hu X, Deng Q, Ma L, Li Q, Chen Y, Liao Y, et al. Meningeal lymphatic vessels regulate brain tumor drainage and immunity. Cell Research. 2020;30(3):229-43.

4 Huang Y-C, Hsu C-L, Chuang H-C, Chang Y-J, Chen Y-J, Huang P-H. Single-cell transcriptomic profiles of lung pre-metastatic niche reveal neutrophil and lymphatic endothelial cell roles in breast cancer. International Journal of Molecular Sciences. 2023;24(1):690.

5 Kalucka J, de Rooij LPMH, Goveia J, Rohlenova K, Dumas SJ, Meta E, et al. Single-cell transcriptome atlas of murine endothelial cells. Cell. 2020;180(4):764-79.e20.

6 Karakousi T, Moro A, Halin C. Lymphatic vessels in the age of cancer immunotherapy. Nature Reviews Cancer. 2024;24(10):673-90.

7 Kuonqui KG, Zhang J, Srinivasan RS. Dysregulation of lymphatic endothelial VEGFR3 signaling in disease. Cells. 2023;12(24):2788.

8 Peng M, Yang H, Liu J, Zhou Y, Wang Y, Li J, et al. Dual FGFR and VEGFR inhibition synergistically restrain lymphangiogenesis and improves antitumor immunocompetence in intrahepatic cholangiocarcinoma. Journal of Gastroenterology. 2023;58(11):1111-27.

9 Secker GA, Harvey NL. Regulation of VEGFR signalling in lymphatic vascular development and disease: An update. International Journal of Molecular Sciences. 2021;22(14):7760.

10 Sibler E, He Y, Ducoli L, Rihs V, Sidler P, Puig-Moreno C, et al. Immunomodulatory responses of subcapsular sinus floor lymphatic endothelial cells in tumor-draining lymph nodes. Cancers. 2022;14(15):3602.

11 Song E, Mao T, Dong H, Boisserand LSB, Antila S, Bosenberg M, et al. VEGF-C-driven lymphatic drainage enables immunosurveillance of brain tumours. Nature. 2020;577(7792):689-94.

12 Sun M, Angelillo J, Hugues S. Lymphatic transport in anti-tumor immunity and metastasis. Journal of Experimental Medicine. 2025;222(3):e20231954.

13 Takeda A, Salmi M, Jalkanen S. Lymph node lymphatic endothelial cells as multifaceted gatekeepers in the immune system. Trends in Immunology. 2023;44(1):72-86.

14 Viúdez-Pareja C, Kreft E, García-Caballero M. Immunomodulatory properties of the lymphatic endothelium in the tumor microenvironment. Frontiers in Immunology. 2023;14:1235812.

15 Xiang M, Grosso RA, Takeda A, Pan J, Bekkhus T, Brulois K, et al. A single-cell transcriptional roadmap of the mouse and human lymph node lymphatic vasculature. Frontiers in Cardiovascular Medicine. 2020;7:52.

16 Bokhari SMZ, Akhtar S, Shahzad M, Raza A, Khan MI. Vascular endothelial growth factor-D (VEGF-D): An angiogenic and lymphangiogenic factor in cancer. International Journal of Molecular Sciences. 2023;24(17):13560.

17 Dieterich LC, Detmar M. Lymphatic vessels in cancer. Physiological Reviews. 2022;102(4):1837-79.

18 Geldhof V, Cheng H-W, Nair R, Giannarelli C, Van de Velde M, Carmeliet P. Single cell atlas identifies lipid-processing and immunomodulatory endothelial cells in healthy and malignant breast. Nature Communications. 2022;13(1):5511.

19 He M, He Q, Cai X, Chen Z, Lao S, Deng H, et al. Role of lymphatic endothelial cells in the tumor microenvironment—A narrative review of recent advances. Translational Lung Cancer Research. 2021;10(5):2252-77.

20 Jalkanen S, Salmi M. Lymphatic endothelial cells of the lymph node. Nature Reviews Immunology. 2020;20(9):566-78.

21 Ji H, Castillo S, Zhang Y, Li X, Alitalo K. Lymph node metastasis in cancer progression. Signal Transduction and Targeted Therapy. 2023;8(1):367.

22 Kalucka J, de Rooij L-APMH, Goveia J, Rohlenova K, Dumas SJ, Meta E, et al. Single-cell transcriptome atlas of murine endothelial cells. Cell. 2020;180(4):764-79.e20.

23 Kuonqui KG, Jackson DG. Dysregulation of lymphatic endothelial VEGFR3 signaling in disease. Cells. 2024;13(1):68.

24 Leong SP, Naxerova K, Keller L, Pantel K, Witte M. Molecular mechanisms of cancer metastasis via the lymphatic versus the blood vessels. Clinical & Experimental Metastasis. 2022;39(1):159-79.

25 Munir H, Mazzaglia C, Shields JD. Stromal regulation of tumor-associated lymphatics. Advanced Drug Delivery Reviews. 2020;161-162:75-89.

26 Paik DT, Tian L, Lee J, Sayed N, Chen IY, Rhee S, et al. Integrated single-cell atlas of endothelial cells of the human lung. Circulation. 2021;144(4):286-302.

27 Rezzola S, Sigmund EC, Halin C, Ronca R. The lymphatic vasculature: An active and dynamic player in cancer progression. Medicinal Research Reviews. 2022;42(1):576-614.

28 Yang Y, Cao Y. The impact of VEGF on cancer metastasis and systemic disease. Seminars in Cancer Biology. 2022;86(Part 3):251-61.

29 Suárez L, Rodríguez-Ruiz ME, Rouzaut A. The lymphatic endothelium in the context of radioimmuno-oncology. Cancers. 2023;15(1):21.

30 Che Q, Wang C, Zheng S, Zhao K, Liu M. Single-cell sequencing and spatial transcriptomics reveal functional plasticity of lymphatic endothelial cells in disease. ENT Updates. 2026;16(2):14-26.

31 Chen J-M, Luo B, Ma R, Luo X-X, Chen Y-S, Li Y. Lymphatic endothelial markers and tumor lymphangiogenesis assessment in human breast cancer. Diagnostics. 2022;12(1):4.

32 Fujimoto N, He Y, D'Addio M, Tacconi C, Detmar M, Dieterich LC. Single-cell mapping reveals new markers and functions of lymphatic endothelial cells in lymph nodes. PLOS Biology. 2020;18(4):e3000704.

33 He M, He Q, Cai X, Chen Z, Lao S, Deng H, et al. Role of lymphatic endothelial cells in the tumor microenvironment—A narrative review of recent advances. Translational Lung Cancer Research. 2021;10(5):2252-77.

34 Karinen S, Hujanen R, Salo T, Salem A. The prognostic influence of lymphatic endothelium-specific hyaluronan receptor 1 in cancer: A systematic review. Cancer Science. 2022;113(1):17-27.

35 Miyasaka M. A short review on lymphatic endothelial cell heterogeneity. Inflammation and Regeneration. 2021;41(1):32.

36 Montenegro-Navarro N, García-Báez C, García-Caballero M. Molecular and metabolic orchestration of the lymphatic vasculature in physiology and pathology. Nature Communications. 2023;14(1):8389.

37 Roberts LM, Perez MJ, Balogh KN, Mingledorff G, Cross JV, Munson JM. Myeloid derived suppressor cells migrate in response to flow and lymphatic endothelial cell interaction in the breast tumor microenvironment. Cancers. 2022;14(12):3008.

38 Sibler E, He Y, Ducoli L, Keller N, Fujimoto N, Dieterich LC, et al. Single-cell transcriptional heterogeneity of lymphatic endothelial cells in normal and inflamed murine lymph nodes. Cells. 2021;10(6):1371.

39 Yusof KM, Rosli R, Abdullah M, Avery-Kiejda KA. The roles of non-coding RNAs in tumor-associated lymphangiogenesis. Cancers. 2020;12(11):3290.

40 Zhang S, Wang H, Xu Z, Bai Y, Xu L. Lymphatic Metastasis of NSCLC Involves Chemotaxis Effects of Lymphatic Endothelial Cells through the CCR7–CCL21 Axis Modulated by TNF-α. Genes. 2020;11(11):1309.

41 Cousin N, Cap S, Dihr M, Tacconi C, Detmar M, Dieterich LC. Lymphatic PD-L1 expression restricts tumor-specific CD8+ T-cell responses. Cancer Research. 2021;81(15):4133-44.

42 Deng H, Zhang Y, Zhang Y, Liu X, He J. Current status of lymphangiogenesis: Molecular mechanism, immune regulation, and therapeutic intervention. Cancers. 2023;15(4):1169.

43 Dieterich LC, Tacconi C, Ducoli L, Detmar M. Lymphatic vessels in cancer. Physiological Reviews. 2022;102(4):1837-79.

44 Francis DM, Manspeaker MP, Schudel A, Sestito LF, O'Melia MJ, Kissick HT, et al. Blockade of immune checkpoints in lymph nodes through locoregional delivery augments cancer immunotherapy. Science Translational Medicine. 2020;12(563):eaay3575.

45 Garnier L, Pick R, Montorfani J, Sun M, Brighouse D, Liaudet N, et al. IFN-γ-dependent tumor-antigen cross-presentation by lymphatic endothelial cells promotes their killing by T cells and inhibits metastasis. Science Advances. 2022;8(23):eabl5162.

46 He M, He Q-H, Cai X, Chen Z, Lao S, Deng H, et al. Role of lymphatic endothelial cells in the tumor microenvironment—A narrative review of recent advances. Translational Lung Cancer Research. 2021;10(5):2252-77.

47 Li X, Zhai J, Shen Y, Zhang T, Wang Y, He Y, et al. Tumor-derived IL-8 facilitates lymph node metastasis of gastric cancer via PD-1 up-regulation in CD8+ T cells. Cancer Immunology, Immunotherapy. 2022;71(12):3057-70.

48 Louie DAP, Oo D, Leung G, Lin Y, Stephens M, Alrashed O, et al. Tumor-draining lymph node reconstruction promotes B cell activation during E0771 mouse breast cancer growth. Frontiers in Pharmacology. 2022;13:825287.

49 Mehrara BJ, Greene AK, Rockson SG. The emerging importance of lymphatics in health and disease. Journal of Clinical Investigation. 2023;133(17):e171582.

50 Paillasse MR, Sanchez P, Marionneau-Lambot S, Maurel C, Joubert N, Corlu A. Targeting tumor angiogenesis with the selective VEGFR-3 inhibitor SAR131675. Cancers. 2022;14(24):6136.

51 Suárez L, Ferrando M, Rubiolo JA, Vega FM. The lymphatic endothelium in the context of cancer: From basic biology to therapeutic opportunities. Cancers. 2023;15(1):21.