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REVIEW

Mechanisms of Cancer Cell Lymphatic Endothelialization in Tumor Lymphangiogenesis and Metastasis: A Comprehensive Review

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Abstract: Cancer cell lymphatic endothelialization refers to the transformation of cancer cells into lymphatic endothelial cells through complex cellular and molecular mechanisms, which involve transdifferentiation of cancer cells and their fusion with endothelial cells, both modulated by multiple signaling pathways. This process reflects a dual phenotype comprising features of both cancer cells and lymphatic endothelial cells. The expression of lymphatic-specific markers, including PDPN, LYVE1, PROX1, and SOX18, serves as molecular evidence of this process. Histopathologically, this phenomenon is manifested through lymphangiogenic mimicry, which can be classified into lymphatic-like, mosaic, and lymphatic types. This study presented a theoretical framework to elucidate the developmental mechanisms driving cancer cell lymphatic endothelialization and provided a new theoretical basis for understanding the cellular origin of tumor-associated neolymphatic vasculature and introduces new pathways for investigating mechanisms of tumor lymphangiogenesis and metastasis, thereby providing potential avenues for clinical treatment strategies.

Keywords: cancer cell lymphatic endothelialization, lymphangiogenesis molecules, lymphangiogenic mimicry, tumor lymphangiogenesis, tumor lymphatic metastasis

Introduction

Solid tumors are composed of tumor cells and stromal cells including lymphatic endothelial cells (LEC), which are mainly viewed as cells forming lymphatic vessels involved in the transport of metastatic and immune cells. In the process of metastasis, tumor cells need to acquire motility features that imply at least a partial epithelial-to-mesenchymal transition and the capacity to degrade the basement membrane. In addition, in the metastasis of lymph node, there were many complex mechanisms through which tumors engage lymphatic transport and condition tumor-draining lymph nodes, such as extracellular vesicles for pre-metastatic niches.

Cancer cell endothelialization has emerged as a key area of research in recent years. This process involves the gradual transformation of cancer cells into endothelial-like cells, contributing to the formation of tumor-associated blood and lymphatic vasculature. These transformations occur through complex cellular and molecular mechanisms, either within the in vivo tumor microenvironment or under controlled in vitro experimental conditions.[1–3] Since these endothelial cells retain certain characteristics of cancer cells, this phenomenon is also referred to as endothelial cell cancerization, representing different perspectives on the initiating and terminal phases of the same biological event. The formation of neovascular and lymphatic structures via cancer cell endothelialization has been observed in various human cancers and animal models. Recent studies indicate that during tumor development, a significant proportion of endothelial cells lining the luminal surfaces of newly formed blood and lymphatic vessels originate from tumor-derived endothelial cells. Specifically, endothelial cells

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formed through cancer cell endothelialization may account for up to 70% of the endothelial population within tumor-associated lymphatic vasculature.[2–4]

Cancer cell endothelialization is broadly classified under epithelial-endothelial transition (EET) and epithelial-mesenchymal transition (EMT).[5–7] Recent studies have shown that cancer stem cells (CSCs) and EET, a subtype of EMT, accelerate vasculogenic mimicry formation by stimulating tumor cell plasticity, remodeling the extracellular matrix and connecting vasculogenic mimicry channels with host blood vessels. However, strict histoembryological and histopathological definitions classify endothelial cells as a subtype of epithelial cells. In contrast, cancer cells may originate from either epithelial or mesenchymal origins. From the perspective of tumor biology, cancer cell endothelialization represents a specialized form of lineage-directed differentiation, whereby malignant cells of epithelial or mesenchymal origin transition into vascular or lymphatic endothelial cell phenotypes. Mirroring angiogenesis, tumour cells were also shown to secrete lymphangiogenic factors that facilitate lymphangiogenesis and metastasis to sentinel lymph nodes. However, the mechanisms underlying the pathologic growth and function of the lymphatic vascular system have remained poorly understood. Given space constraints, this review primarily examines the concept, background, cellular and molecular mechanisms, molecular markers, histopathological characteristics, clinical significance, and targeted therapeutic approaches related to the lymphatic endothelialization of cancer cells derived from epithelial lineages.

Concept and Background of Cancer Cell Lymphatic Endothelialization

Cancer cell lymphatic endothelialization is one of the two recognized forms of cancer cell endothelialization, alongside cancer cell vascular endothelialization. This process involves the transformation of malignant cells into lymphatic endothelial-like cells during tumor progression, presenting a novel perspective on the origin of tumor neolymphatic endothelial structures within tumors and offering insights into tumor-associated lymphangiogenesis and lymphatic metastasis.[1,3,4]

Traditional perspectives in developmental cell biology have posited that somatic cell lineage differentiation is typically unidirectional, non-selective, and irreversible. However, recent research indicates that both normal and malignant cells can exhibit significant cellular plasticity in response to specific internal or external factors. This plasticity enables reprogramming toward alternative differentiation pathways and the potential to transform into one or more distinct cell lineages. Notable examples include squamous metaplasia of cervical columnar epithelium during cell injury repair and the presence of glandular differentiation within squamous cell carcinoma tissues. Such lineage transitions may occur through dedifferentiation, wherein cells revert to a less differentiated state within the same lineage, or through transdifferentiation, where differentiation occurs toward a different cell lineage. These processes are accompanied by coordinated molecular, metabolic, morphological, and functional transitions.[5,7–11] In some instances, these transformations occur bidirectionally, as observed in epithelial-mesenchymal transition (EMT) and mesenchymal-epithelial transition (MET), as well as reciprocal processes of cancer cell endothelialization and endothelial cell cancerization discussed in this review.[1,3,12,13]

Cellular and Molecular Mechanisms of Cancer Cell Lymphatic Endothelialization

The cellular mechanisms underlying cancer cell lymphatic endothelialization encompass two primary forms: the transdifferentiation of malignant cells into lymphatic endothelial cells and the fusion of cancer cells with pre-existing lymphatic endothelial cells. Normal endothelial cell nuclei are strictly diploid, whereas tumor-derived endothelial cells undergoing cancer cell endothelialization exhibit polychromosomal aneuploidy.[1,2] Cancer cells may directly transdifferentiate into lymphatic endothelial cells, or alternatively, dedifferentiate into mesenchymal stem cells before transdifferentiating into lymphatic endothelial cells. Alternatively, cancer cells may fuse with lymphatic endothelial cells, leading to the formation of aneuploid endothelial cells, multinucleated heterokaryotic clusters, and syncytial structures.[14,15] These hybrid cells exhibit features characteristic of both cancer cells and lymphatic endothelial cells. Such phenotypes include the proliferative, migratory, and invasive capabilities typical of malignant cells, as well as behaviors such as sprouting, cord formation, and tubulogenesis.[10,16,17] Moreover, tumor-associated fibroblasts, along with immune cells like lymphocytes and macrophages, influence the process of cancer cell lymphatic endothelialization by releasing growth factors, cytokines, inflammatory mediators, and other signaling molecules into the tumor microenvironment.[3,18–21]

At the molecular level, cancer cell lymphatic endothelialization involves exosome-mediated signaling, transcriptional reprogramming, and the activation of various signaling pathways. Tumor type and individual differences may contribute to varying sensitivity and responsiveness of cancer cells to endothelialization-inducing stimuli. Lymphatic endothelial cells primarily express VEGFR-3 and NRP2, which bind directly or synergistically with the ligands VEGFC-C and VEGF-D, forming key molecular axes that regulate lymphangiogenesis and lymphatic endothelial cell function.[22,23] Several signaling pathways contribute to endothelial cell differentiation, proliferation, sprouting, and migration including NOTCH, MAPK, RhoA, CXCL12/CXCR4, WNT, TEL, BMP, LMO2, ETS variant transcription factor 2, and uPAR pathways, with particular emphasis on hypoxia-inducible factor 1 (HIF-1). Additional pathways include MAPK/AKT, RhoA/Rac, PI3K/FAK, Erk1/2, CD44/c-Met, among others.[10,18,24–26] The interaction between cancer cell-derived syncytin and its receptor on endothelial cells contributes to both the formation and apoptosis of hybrid endothelial structures formed during cancer cell lymphatic endothelialization.[27,28]

Molecular Biological Markers of Cancer Cell Lymphatic Endothelialization

In addition to VEGFR-3 and NRP2, several transmembrane proteins, including PDPN, LYVE1, and nuclear transcription factors such as PROX1, SOX18, have been identified as regulators of lymphatic endothelial cell differentiation. These molecules not only distinguish lymphatic endothelial cells from vascular endothelial cells, but also act as molecular markers indicative of cancer cell lymphatic endothelialization.[29–32] The expression of *LYVE1* marks the onset of lymphatic endothelial cell competence, while the transcription factor *PROX1* plays a role in the preferential formation of lymphatic structures. Additionally, the activation of PDPN and NRP2 is associated with the specialization of lymphatic endothelial cells.[3,33] PDPN and LYVE1 are expressed in the cell membrane, whereas PROX1 and SOX18 are expressed within the nucleus. These markers are temporally regulated, with PROX1 and SOX18 contributing to early stage lymphangiogenic differentiation and PDPN and LYVE1 being more prominently involved in later stages.[34,35] The classification, gene localization, subcellular distribution, and roles of these lymphatic-associated molecules in lymphangiogenesis and lymphatic metastasis are presented in Table 1.

Recent studies have demonstrated that these lymphatic-associated molecules, including PDPN, LYVE1, PROX1, and SOX18, are also highly expressed in various epithelial and mesenchymal malignancies.[36–40] For instance, PDPN is predominantly expressed at the periphery of cancer nests in lung, laryngeal, cervical, skin, and esophageal cancers, and contributes to the formation of filopodia-like membrane protrusions, thereby enhancing matrix penetration in breast

Table 1 Characteristics and Roles of Lymphatic-Associated Molecules in Lymphangiogenesis and Lymphatic Metastasis

Molecule Abbreviation	Molecule Full Name	Gene Location	Number of Amino Acids	Subcellular Distribution	Role in Lymphatic Endothelial Cell Differentiation and Lymphatic metastasis
PDPN	Podoplanin	1p36.21	162	Cell membrane, transmembrane protein	Serves as a lymphatic endothelial cell marker, primarily involved in the later stages of lymphangiogenic differentiation. It is selectively expressed on the surface of lymphatic vessels, but not on vascular endothelial cells. PDPN contributes to tumor cell invasion and lymphatic metastasis. A commonly used monoclonal antibody is commercially available as D2-40.
LYVE1	Hyaluronan(HA) receptor	11p15	322	Cell membrane, transmembrane protein	Lymphatic endothelial cell marker, primarily involved in the later stages of lymphangiogenic differentiation, in the formation of lymphatic capillaries. It binds to hyaluronan (HA) ligands expressed on tumor cell surfaces, facilitating cancer cell lymphatic endothelialization and promoting lymphatic metastasis.

(*Continued*)

Table 1 (Continued).

Molecule Abbreviation	Molecule Full Name	Gene Location	Number of Amino Acids	Subcellular Distribution	Role in Lymphatic Endothelial Cell Differentiation and Lymphatic metastasis
PROX1	Prospero homeobox protein1	lq32.2-lq32.3	737	Cell nucleus, nuclear transcription factor	Serves as a lymphatic endothelial cell marker primarily involved in early lymphangiogenic differentiation. It functions as an upstream transcriptional regulator by binding to the 5' functional regulatory region of the *PDPN* gene, thereby activating its expression. It is an early regulatory factor in the transition of primitive vascular endothelial cells into mature lymphatic endothelial cells, and is related to the density and development of both physiological and tumor-associated lymphangiogenesis.
SOX18	Sex determining region Y box18	20q13.33	1384	Cell nucleus, nuclear transcription factor	Acts as an early lymphatic endothelial cell marker and is the earliest known transcription factor involved in initiating differentiation toward lymphatic endothelial lineage. It binds to and activates the promoter region of the *PROX1* gene, thereby regulating its expression. It plays a critical role in the early stages of cancer cell lymphatic endothelialization and lymphatic metastasis.

cancer cells.[41,42] LYVE1 expression is significantly elevated in breast cancer with lymph node metastasis and is also associated with tumor stage, recurrence, and metastasis in head and neck squamous cell carcinoma and gastric cancer.[43,44] PROX1 expression is notably elevated in breast and colorectal cancer tissues with lymph node involvement.[45] Furthermore, SOX18 expression is upregulated in gastric, ovarian, non-small cell lung, breast, cervical, and squamous cell carcinomas. Functional studies have shown that deletion of the *SOX18* gene leads to a reduction in the incidence of lymph node metastasis rate in breast cancer models.[46,47]

Histopathological Characteristics of Cancer Cell Lymphatic Endothelialization

Previous studies have indicated that tumor cells in human malignant melanoma could mimic vascular endothelial cells to form vascular lumen-like structures containing erythrocytes, a phenomenon termed tumor cell vasculogenic mimicry. This process is recognized as a significant contributor to hematogenous metastasis of tumor cells.[16,18,48–50] Owing to the developmental and structural similarities between lymphatic and blood vessels, the occurrence of tumor cell lymphangiogenic mimicry has more recently been identified. In this context, tumor cells mimic lymphatic endothelial cell behavior by forming lymphatic lumen-like structures, which contain lymphatic components rather than red blood cells. This phenomenon provides the structural foundation for the propensity of tumor cells to undergo lymphatic metastasis and represents a key histopathological feature of cancer cell endothelialization.[1,4,51–54]

Similar to vasculogenic mimicry, lymphangiogenic mimicry consists of three histopathological subtypes, each defined by differences in wall cell composition, pathomorphological manifestations, immunohistochemical profiles, and their relationship with the cancer cell lymphatic endothelialization process, as presented in Table 2.[1,53–55] The subtypes—referred to as the lymphatic-like type, mosaic type, and lymphatic type—represent the initial, intermediate transition, and terminal stages of the endothelialization process, respectively. Comprehensive identification and characterization of these mimicry types can be achieved through the use of immunohistochemical markers, pathological histology, and microscopic imaging. These approaches are further enhanced by techniques such as fluorescence in situ immunohybridization, reverse transcription quantitative polymerase chain reaction (RT-qPCR), and next-generation sequencing. These methods facilitate the detection and confirmation of molecular biological markers and histopathological features associated with cancer cell lymphatic endothelialization.[56]

Table 2 Types of Lymphangiogenic Mimicry: Wall Cell Composition, Histopathological Features, Immunohistochemical Markers, and Association with Cancer Cell Lymphatic Endothelialization

Type	Vascular Wall Cell Composition	Pathomorphological Characteristics	Immunohistochemical Markers	Relationship to Cancer Cell Lymphatic Endothelialization
Type I (lymphatic-like type)	Tumor cells arranged in a lymphatic-like arrangement	Cuboidal or polygonal cells aggregate to form vessel-like walls; basement membrane is intact and rich in laminin and collagen	Positive for epithelial markers (E-Cadherin, Pan-CK, EMA) and lymphatic endothelial markers (PDPN, LYVE-1)	Represents the initial stage, morphology and immunohistochemical markers are predominantly epithelial in nature.
Type II (mosaic type)	Tumor cells and endothelial cells form a composite vessel wall	Vessel wall exhibits a bipartite structure: tumor cells predominate on the luminal side and endothelial cells on the basal side	Co-expression of epithelial and endothelial markers respective to the cell types	Intermediate transition stage, morphological and immunohistochemical features indicate mixed epithelial-endothelial phenotype
Type III (lymphatic type)	Predominantly endothelial cells forming lymphatic vessel-like structures	Thin, flattened, endothelial cells form vessel walls; basement membrane is incomplete or absent; reduced intercellular adhesion proteins and collagen content	Positive for endothelial markers (PDPN, LYVE-1); negative for epithelial cell markers (E-Cadherin, EMA, Pan-CK)	Represents the final stage, morphology and marker expression are predominantly endothelial

Table 3 Classification, Representative Drug Inhibitors and Targeted Mechanisms of Some Antitumor Angiogenesis and Lymphangiogenesis Drugs

Type	Representative Drug Inhibitors	Target Mechanisms
Large molecule single-target monoclonal antibody	Bevacizumab, Ramucirumab, Cetuximab, Pembrolizumab, Olaratumab	Competitively bind to specific receptors, inhibiting signaling pathways such as VEGFR, EGFR, FGFR, RET, PDGFR, resulting in reduced angiogenic activity and vascular formation.[59–61]
Small molecule multi-target tyrosine kinase inhibitors	Sunitinib, Vandetanib, Sorafenib, Lenvatinib, Apatinib, Fruquintinib, Pazopanib, Nintedanib, Regorafenib, Almonertinib, Larotrectinib	Inhibit phosphorylation of receptor and non-receptor tyrosine kinases, thereby suppressing multiple signaling pathways including VEGFR, EGFR, FGFR, Ang (angiopoietin), RET, FLT, TEL, Ab1, and Src, as well as upstream downstream molecular activities within these pathways.[62–64]
Non-tyrosine kinase inhibitors	Everolimus, Sirolimus, Mekinist, Cobimetinib	Inhibit phosphorylation of serine/threonine kinases and mek/erk kinases, thereby blocking the action of angiogenic growth factors and their receptors.[65,66]
Endogenous pan-target inhibitors	Endostatin, Vitaxin, Intravascular lipid	Function through protein modification mechanisms that prevent binding of VEGF and other factors to endothelial cells, inhibiting endogenous angiogenic drivers such as endostatin and anti-integrin pathways.[67,68]
microRNA	miRNA34a, miRNA124, miRNA29, miRNA26a, miRNA206, miRNA16, miRNA276, miRNA143-3p, miRNA218, miRNA9, miRNA375	Suppress the expression and function of pro-angiogenic factors/receptors, cytokines, and matrix metalloproteinases (MMPs), thereby inhibiting tumor neovascularization and lymphangiogenesis.[69,70]
Traditional Chinese Medicine components	Ginsenoside Rh3, Norcantharidin, Curcuminoid, resveratrol, curcumol, Safflower Yellower, Tetramethylpyrazine, Scutellaria barbata flavonoids, Glucose anthocyanin	Interfere with angiogenic signaling pathways and modulate tumor and endothelial cell proliferation, migration, and survival, contributing to the inhibition of tumor angiogenesis and lymphangiogenesis.[71–74]

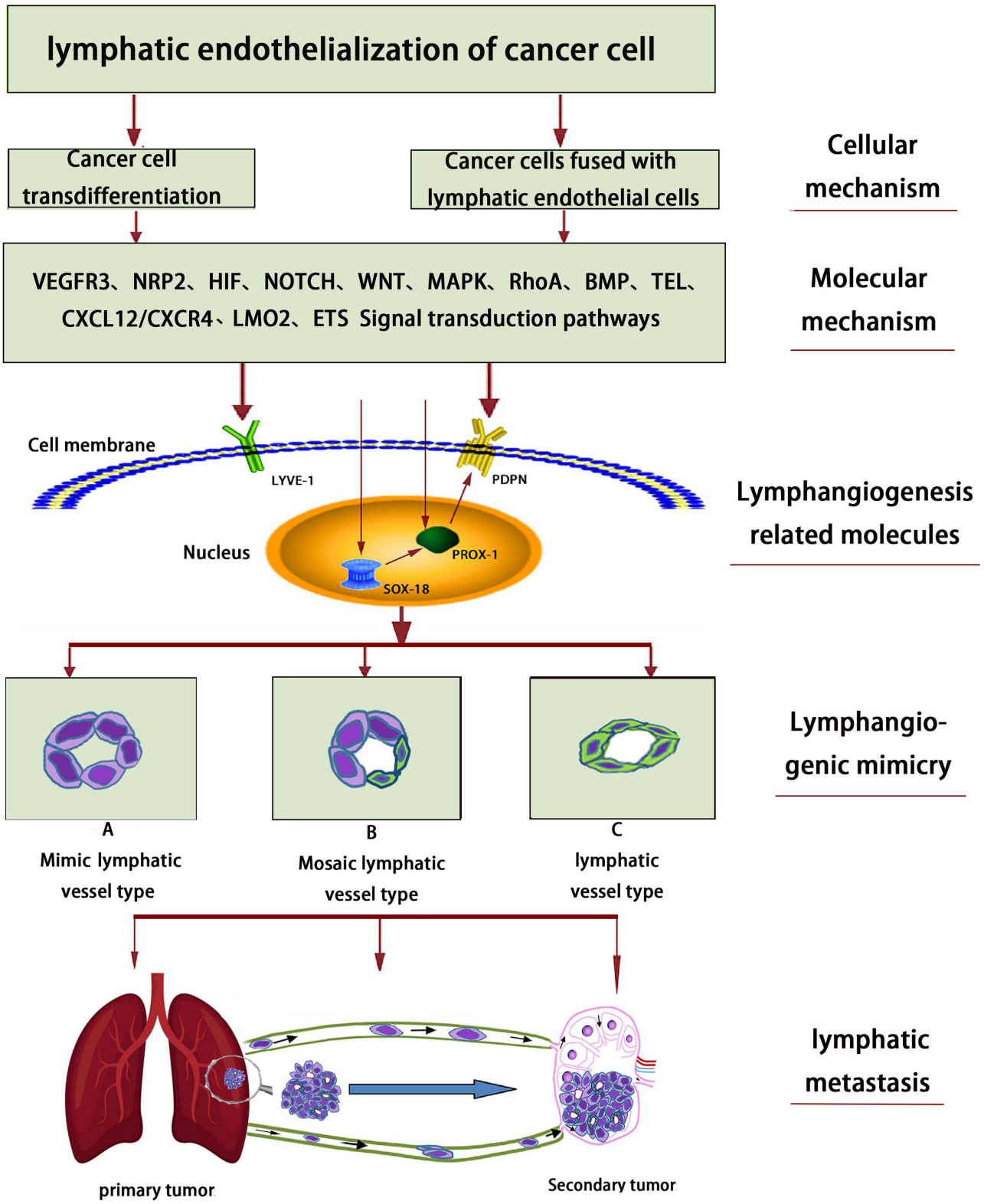

Figure 1 Lymphatic endothelialization of cancer cells and tumor lymphangiogenesis and lymphatic metastasis. A. Mimic lymphatic vessel type B. Mosaic lymphatic vessel type C. lymphatic vessel type—represent the initial, intermediate transition, and terminal stages of the endothelialization process, respectively.

Clinical Significance and Targeted Therapy of Cancer Cell Lymphatic Endothelialization

During tumor-associated lymphangiogenesis, the endothelial lining of neolymphatic vessels is thought to originate from three primary sources. The first includes pre-existing normal endothelial cells within the tumor stroma. The second involves bone marrow-derived endothelial progenitor cells. The third and predominant source comprises tumor-derived endothelial cells formed through the process of cancer cell endothelialization. These tumor-derived endothelial cells are in direct contact with lymphatic fluid, facilitating their detachment and migration to regional sentinel lymph nodes. This facilitates the increase in lymphatic and subsequent hematogenous metastasis rates in patients. Enlargement of regional lymph nodes is often the earliest clinical manifestation of tumors.[3,25] Screening for tumor-derived endothelial cells with aneuploid characteristics in peripheral blood, along with the detection of lymphatic-associated molecular markers and lymphangiogenic mimicry patterns, can improve the early diagnosis of tumor lymphatic metastasis associated with cancer cell lymphatic endothelialization. This approach provides a valuable tool for prognostic assessment and monitoring treatment efficacy in patients with cancer.[1,51]

To date, various targeted therapeutic agents and inhibitors have been employed in clinical, preclinical, and experimental research to address tumor neovascularization and lymphangiogenesis. Table 3 summarizes these agents, including their classifications, representative compounds, and mechanisms of action.[10,16,25,52,57,58] These therapeutic strategies may be utilized either independently or in combination to block endothelial cell proliferation, inhibit angiogenesis and lymphangiogenesis, reduce the likelihood of invasion and metastasis, and minimize side effects. Moreover, engineered nanoparticles (NPs) have emerged as delivery vehicles in overcoming the intricate physiological structure and immunosuppressive microenvironment by facilitating targeted drug to activate T cells directly or indirectly, which could reduce side effects and increase biocompatibility.

Conclusion

In conclusion, cancer cell lymphatic endothelialization represents a novel biological paradigm that offers a unified explanation for the directed transformation of diverse tumor cell types into lymphatic endothelial-like cells. This framework provides a new theoretical basis for understanding the cellular origin of tumor-associated neolymphatic vasculature and introduces new pathways for investigating mechanisms of tumor lymphangiogenesis and metastasis (Figure 1). Of course, due to the existence of tumor heterogeneity, the lymphatic endothelialization ability of cancer cells from different tissues may also vary. Moreover, different tumor cells can have complex and profound impacts on targeted drug therapy, which are reflected in the diversity of treatment responses, the spatial heterogeneity of target expression, the dynamic compensation of signaling pathways, and the influence on the tumor microenvironment, etc. Therefore, on the basis of in-depth research on the mechanism of the occurrence and development of cancer cell lymphatic endothelialization and a comprehensive understanding of its molecular biological and histopathological characteristics and rules, further exploring the in-depth development and application of more precise and effective targeted drugs for cancer cell lymphatic endothelialization for different specific tissue origin tumor types should be the key focus of the next step.

Abbreviations

VEGFR-3, Vascular endothelial growth factor receptor-3; NRP2, Neuropilin-2; HIF1, Hypoxia-inducible factor 1; WNT, Wingless / Integrated; MAPK, Mitogen-activated protein kinase; RhoA, Rho kinase A; PDPN, Podoplanin; LYVE1, Lymphatic Vessel Endothelial Hyaluronan Receptor 1; PROX1, prospero homeobox 1; SOX18, Recombinant Sex Determining Region Y Box Protein 18; CXCL12/CXCR4, C-X-C motif chemokine ligand 12/ C-X-C chemokine receptor type 4; TEL, Telomerase; FLT, Fms-like tyrosine kinase; BMP, Bone Morphogenetic Protein; LMO2, Lim domain only 2; RhoA/Rac, Rho kinase A/Ras-related C3 botulinum toxin substrate; PI3K/FAK, Phosphoinositide 3-kinase / Focal Adhesion Kinase; Erk1/2, Extracellular regulated protein kinases ½; CD44/c-Met, Homing cell adhesion molecule/ MNNG HOS Transforming gene; VEGFR, Vascular Endothelial Growth Factor Receptor; EGFR, Epidermal growth factor receptor; FGFR, Fibroblast Growth Factor Receptor; RET, Receptor Tyrosine Kinase; FGFR, Fibroblast Growth Factor Receptor; Ang, Angiopoietin.

Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author, Jianwu Tang.

Ethics Approval and Consent to Participate

This study did not involve human or animal subjects, and thus, no ethical approval was required. The authors confirm that this review was conducted in accordance with the principles of academic integrity and research ethics.

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Disclosure

The authors declare that they have no competing interests.

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