OncoTargets and Therapy

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REVIEW

Molecular and Cellular Machinery of Lymphatic Metastasis in Breast Cancer

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Abstract: Breast cancer is one of the most common malignant tumours in women worldwide. A primary route for breast cancer cells to disseminate is through regional lymphatic vessels and nodes. Cancer cell-induced lymphangiogenesis plays a crucial role in lymphatic metastasis and is associated with poor survival of breast cancer. Advances in molecular biology have led to the identification of biomarkers associated with lymphangiogenesis and lymphatic metastasis, including lymphatic vessel endothelial cell (LVEC) markers and tumour microenvironment markers, such as vascular endothelial growth factor receptor 3 (VEGFR3), podoplanin (PDPN), and lymphatic endothelial hyaluronan receptor-1 (LYVE1). LVEC molecular markers play a profound role in both the formation of new lymphatic vessels and the invasive expansion of primary tumour. Abnormal expression of LVEC markers may contribute to lymphatic vessel disease and/or metastasis of cancer cells through the lymphatic system. These molecular markers may present a potential for targeted therapies and precision diagnostics for managing lymphatic metastasis in breast cancer. This review aims to provide a comprehensive summary of the current understanding of the molecular and cellular machinery underlying lymphatic metastasis in breast cancer, with a particular focus on the lymphangiogenic markers and their role in the lymphatic dissemination.
Keywords: lymph node metastasis, lymphangiogenesis, lymphatic vessel endothelial cell, biomarkers and breast cancer

Introduction

The lymphatic metastasis commonly occurs in breast cancer with an incidence in the range of 23.8%~35.4% in the early stages of the disease.[1–3] The main reason for the failure of regional therapy is that recurrence in the regional lymph nodes can progress to advanced disease, leading to a failure of initial treatment, including regional therapy. The metastatic status of lymph nodes is an independent prognostic factor and the survival declines with the number of involved lymph nodes increasing.[4] Therefore, the lymph node metastasis is still an important basis in the current 8th edition of the American Joint Committee on Cancer staging as a guidance not only for strategies for regional treatment but also the systemic therapy. The lymph node metastasis is associated with tumor size, gender, and other clinical factors. Large tumors are more prone to lymph node metastasis than small-sized tumors, draining lymphatic vessels from mammary glands are shorter in male than female, with a result of higher frequency of lymph node metastasis in male breast cancer patients.[1,3,4]

Sentinel lymph node biopsy (SLNB) is a technique that can accurately detect lymph node metastasis in breast cancer.[1–3,5] Sentinel lymph node (SLN) is the first station of lymph nodes colonised by metastatic breast cancer cells. The involvement status of SLN can provide key clinical pathological information for appropriate regional and systemic treatment.[1–3,5] In the clinical practice, lymphatic tracers are used to identify the location of SLN, such as radionuclide-labeled sulfur colloids, blue dye, and indocyanine green.[6] Patients with clinical negative axillary lymph nodes were recommended to SLNB to avoid unnecessary removal of axillary lymph nodes and reduce the occurrence of upper extremity lymphedema with improved quality of life.[2,3] It has been shown that thymidylate synthase has a two-fold higher expression in the metastatic SLN in comparison with non-metastatic lymph nodes in early breast cancers.[7] Extra

Received: 28 October 2024
Accepted: 23 January 2025
Published: 4 February 2025

cellular matrix proteins caveolin-1, collagen α-1, desmin, fibrillin-1, and microfibrillar associated glycoprotein 4 have been identified as potential biomarkers for SLN.[8] Cai S identified that POU5F1/Oct-4 expression levels in breast cancer tissues were significantly higher in the SLN with metastasis.[9] These biomarkers can potentially be developed as a diagnostic tool to assess SLN status to guide surgical intervention in early breast cancer.

The lymphatic system consists of lymphatic vessels and lymphatic structures, and the lymphatic vessels connect lymph nodes in different regions. The tumour associated lymphangiogenesis plays an important role in lymphatic metastasis of breast cancer and is associated with worse survival.[10] The lymphatic vessel invasion and the lymphatic vessel density are pathological manifestations of both peritumour and intratumour lymphangiogenesis that are used to evaluate tumor malignancy in clinical pathology.[11] Similarly, tumour angiogenesis could be a predictive and prognostic biomarker, which is stimulated by vascular endothelial growth factors.[12] These new blood vessels provide the required resources for advanced and rapid development of the tumor and also provide direct links with the vascular system of the tumor, facilitating metastatic invasion and dissemination through blood circulation[13] which is associated with poor survival in patients with early and advanced breast cancer.[14–16]

Although current clinical diagnosis techniques can detect and target most lymphatic metastasis, an improvement is highly demanded due to the poor specificity, high false-negative rate, and detection of micrometastases. Biomarkers have been identified for lymphangiogenesis and lymphatic metastasis, such as the lymphatic vessel endothelial cell (LVEC) associated markers.[7,17] The molecular markers of LVEC play a profound role during the formation of new lymphatic vessels and the spread of cancer cells through lymph nodes. The aim of this review is to summarise current knowledge of the molecular and cellular machinery of lymph node metastasis in breast cancer and emerging evidence of novel targeted therapies.

Lymphangiogenesis, Lymphatic Vessel Endothelial Cell (LVEC) Markers and Clinical Evaluation of Lymphangiogenesis

Lymphangiogenesis

Lymphangiogenesis is a process of formation of new lymphatic vessels that is vital for the spread of cancer cells through the lymphatic system, particularly the regional lymph nodes. Newly formed lymphatic vessels by LVECs near the primary tumour not only provide additional draining vessels for excessive interstitial fluid but also form a route for cancer cells to disseminate to regional lymph nodes. The majority of LVECs in the tumour associated with lymphangiogenesis are derived from pre-existing lymphatic vessels, while a few LVECs originate from the vascular endothelial cells (VECs) and the myeloid-derived lymphatic endothelial cell progenitor (M-LECP).[18,19]

The VECs derived from LEC progenitors in the cardinal vein can differentiate into LVECs, which subsequently form the basic sac structure of newly formed lymphatic vessels. LVECs that develop from the VECs through an active budding mechanism, where LEC progenitors are interconnected via VE-cadherin-expressing junctions.[20]

M-LECPs are developed from the bone marrow (BM) derived immature myeloid precursors that can be recruited by a tumor via blood circulation.[18] M-LECPs recruited by the tumor can then differentiate into LVECs, which can be integrated into the newly formed lymphatic vessels into or near the tumour.

The tumours associated with new lymphatic vessels are frequently inflamed and dilated. Peritumoral lymphatic vessels serve as a functional route for the dissemination of cancer cells, while intratumoral lymphatic vessels are commonly sparse, dysfunctional, collapsed with a long narrow or atretic shape being unfavorable for both lymphatic draining and migration of cells.[21]

In the process of lymphangiogenesis, the specific lymphangiogenic factors and markers expressed by LVEC in a primary tumour can coherently regulate the transition and the migration of cells that consequently promote the formation of new lymphatic vessels.

Lymphatic Vessel Endothelial Cell (LVEC) Markers and Regulators of Lymphangiogenesis

A number of markers have been identified for the LVEC cells. The expression and function of these markers can be regulated by certain growth factors and cytokines in the process of lymphangiogenesis (Figure 1).

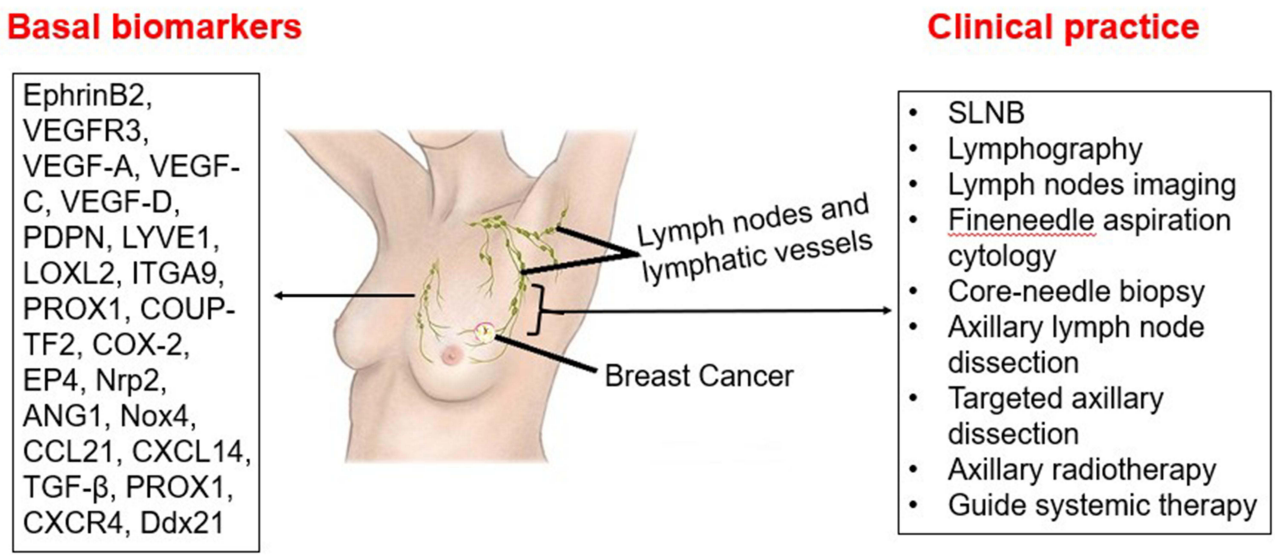

Figure 1 Detection of regional lymph node metastasis and disease management. Shown are lymphangiogenic markers, approaches of detection of the lymph node metastasis including sentinel lymph node biopsy (SLNB), and therapies. Partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 Unported license.

Vascular endothelial growth factor receptor-3 (VEGFR3; also known as FLT4) is a tyrosine kinase receptor and can be activated by VEGFC and VEGFD. VEGFR-3 is an important transmembrane protein in LVEC being highly expressed at the early conformation stage of embryonic blood vessels and highly expressed in LVEC and some fenestrated endothelia at later stages of embryonic development.[12] It is also expressed by cancer cells and regulates migration of cancer cells in addition to its direct involvement in the lymphangiogenesis as its expression by LVECs. VEGFR3 mutations lead to hereditary lymphoedema type I in humans.[22]

Podoplanin (PDPN; also known as T1A, T1A2, GP36, OTS-8, or AGGRUS) is a transmembrane glycoprotein, which controls plasticity of podocytes, which can influence functions of LVECs.[23] PDPN promotes LVEC adhesion, migration, and tubulogenesis in vitro.[24] PDPN is highly expressed in the tumour stroma and mediates tumour associated macrophages (TAM), promoting the growth and migration of LVECs. *PDPN*-knockout mice die perinatally and have malformed lymphatic vessels and impaired tissue drainage.

Lymphatic endothelial hyaluronan receptor-1 (LYVE1; also known as XLKD1) is a transmembrane receptor that binds to glycosaminoglycan hyaluronan.[25] LYVE1 is strongly expressed in all embryonic LVECs but is restricted to lymphatic capillaries in matured embryos.[26] It is one of the receptors identified for an extracellular matrix glycosaminoglycan hyaluronan (HA) in the lymph vessel wall and is considered a unique marker for lymphatic vessels.[27]

The ephrinB2 is an essential regulator of lymphangiogenesis and is associated with PDZ domain effectors.[26] EphrinB2 is a membrane receptor being highly expressed in the arterial endothelium and the endothelial cells of collecting lymphatic vessels.[26,28] EphrinB2-knockin mice that expressed ephrinB2 but lack PDZ domain exhibited defects in the development of lymphatic systems, such as lack of linkage of primary lymphatic capillary plexus into hierarchical vessel networks, and luminal valves.[26] This suggests that ephrinB2 is also an important marker of LVECs involved and that the expression of ephrinB2 is associated with longer survival in breast cancer patients.

CXC receptor 4 (CXCR4, CD184) is an important transmembrane receptor and is expressed in LVEC and cancer cells.[29] As a chemotactic mediator, CXCR4 can be induced by stromal-derived-factor-1 (SDF-1, also known as CXCL12) to promote the migration and invasion of breast cancer cells, thus being involved in the development of lymphatic vessels around tumors, and subsequent lymph node metastasis.[30]

Hsp90alpha is an intracellular regulator of LVEC in the process of lymphangiogenesis.[31] Hsp90alpha transmits the pro-lymphangiogenic signal via lipoprotein receptor-related protein 1 (LRP1) from the cell membrane. LRP1 upregulates the expression of AKT to coordinate the function of LVECs.[31]

https://doi.org/10.2147/OTT.S503272

Lysyl Oxidase-like protein 2 (LOXL2) is an important regulatory molecule for the crosslinking of collagen and elastin in the extracellular matrix. LOXL2 is also a promotive factor in the progression of cancer by accelerating angiogenesis and lymphangiogenesis.[32] LOXL2 activates AKT and ERK pathways to induce VEGFR3 expression that subsequently promotes migration and tube formation of LVECs. Additionally, LOXL2 can also upregulate HIF-1α expression to activate tumor associated fibroblasts, which release VEGF-C and SDF-1α to promote lymphangiogenesis.[32]

Integrin α9 (ITGA9) is one of the integrin subunits that plays a profound role in migration, invasion, adhesion, angiogenesis, and lymphangiogenesis in cancer. Upregulation of ITGA9 has been revealed in LVECs during the embryonic development of lymphatic valve leaflet through an interaction with fibronectin-EIIIA.[33]

Prospero-related homeobox-1 (PROX1) is a transcription factor and located in the nuclei of LVECs being pivotal for cell differentiation and proliferation during the development of the liver, pancreas, lens, and retina. PROX1 has an important role in regulation of LVEC differentiation and metastatic dissemination. PROX1 defection could destroy the progress of lymphangiogenesis and lead to death in mice.[34]

Chicken ovalbumin upstream promoter transcription factor 2 (COUP-TF2; also known as Nr2f2) is a transcription factor implicated in developmental lymphangiogenesis. COUP-TF2 regulates the biological function of PROX1 in LVEC that promotes the proliferation and migration toward VEGF-C by inducing the expression of cyclin E1 and VEGFR3, respectively. The endogenous PROX1 and COUP-TF2 physically interact in LVECs and that both PROX1 and COUP-TF2 bind to the endogenous cyclin E1 promoter.[18]

Cyclooxygenase (COX)-2 promotes interactions between breast cancer cells and LVEC leading to lymph node metastasis. COX-2 induces the expression of prostaglandin (PGE2) which can subsequently bind to PGE receptors (EP, in particular EP4) expressed by both tumor cells and LVECs.[35] Upon the activation of EP4, VEGF-C/D expression can be upregulated to stimulate LVEC sprouting, thus facilitating lymphangiogenesis in addition to its promotive effect on migration of cancer cells.[35]

Neuropilin-2 (Nrp2) is a transmembrane glycoprotein receptor for VEGFA and VEGFC and has an important role in lymph node metastasis of breast cancer. Yasuoka H et al found that Nrp2 mediated an upregulation of CXCR4 expression in breast cancer cells, while an anti-Nrp2 treatment repressed CXCR4 expression.[36]

Angiopoietins 1 (ANG1) and angiopoietins 2 (ANG2) can promote the proliferation and migration by the Tie1/2 signaling pathway in LVECs. ANG1 can upregulate the expression of VEGFR-3 to trigger formation of sprouts and vessels, which can rescue lymphatic defects in Ang2-knockout mice.[37]

LVECs are influenced by various factors throughout development, which can be assessed as biomarkers for predicting lymphangiogenesis. Additionally, LVEC markers may serve as potential therapeutic targets for preventing tumour-associated lymphangiogenesis and lymphatic metastasis in breast cancer. By analysing the expression of these markers, lymphatic metastasis can be detected and addressed within the context of distinct activated signalling pathways, potentially identifying micrometastases in regional lymph nodes or lymphatic vessels.

Clinical Evaluation of Lymphangiogenesis

Lymphatic vessel invasion (LVI) and lymphatic vessel density (LVD) are important indicators for the evaluation of lymphangiogenesis in clinical practice. The two indicators are correlated with the spread of breast cancer cells through lymphatic vessels.[38] LVI provides a greater chance for tumour cells to enter the local lymphatic vessel from primary lesion and increases the possibility of distant metastasis, which leads to poor survival in patients.[39] LVD is associated with the involvement status of lymph node, the expression of VEGF-C, and the prognosis of survival in breast cancer.[40] Both LVI and LVD are important for the prediction of relapse, disease management and subrecommend of treatment, and frequency of follow-up.

PDPN, CD34, and D2-40 are used to evaluate the status of lymphatic vessels around primary cancer by immuno-histochemical stain in clinical practice. High LVD and LVI were the significant indicators of DFS in patients with pN0/chemotherapy/trastuzumab-therapy.[38] Ito M et al found that LVI positive cases were more frequently associated with lymph node metastasis than LVI negative cases (58.8% vs 28.8%, $P<0.05$).[11] Zhang et al found that LVD was higher in peritumoral than in intratumoral (77.9%, 397/515 vs 40.07%, 240/599) and both LVDs were positively associated with

metastasis in lymph node.[41] Wahal SP et al also found that LVD was significantly increased in peritumoral with positive lymph node compared to negative ($P < 0.001$).[42]

Lymphangiogenesis markers and regulators for their predictive potential in lymph node metastasis of breast cancer, relapse, distant metastases, and survival. Identification of candidate genes that are associated with the lymphangiogenesis and vital for the spread of cancer cells through the lymphatic vessels.

Breast and kidney-expressed chemokine (BRAK) is also known as CXCL14 and has an important role in tumour immunology, particularly in the tumour microenvironment.[43] BRAK overexpression in cancer cells promotes the growth of vessels and monocytes.[44] Elevated expression of BRAK has been observed in breast cancer cell lines and breast cancers with lymph nodes metastasis.[45] This suggests that BRAK may serve as a diagnostic marker for lymphangiogenesis and lymph nodes involvement.

In breast cancer patients, PDPN-expressing macrophages (PoEMs) have been associated with the formation of tumor-associated lymphatic vessels, lymph node metastasis, and distant organ metastasis.[46] PDPN expression in cancer-associated fibroblasts (CAFs) has been proposed as an indicator of poor prognosis in patients with invasive breast carcinomas representing a highly aggressive subgroup.[47] Tanaka Y et al found that PDPN-positive status in CAFs was associated with higher levels of Ki-67 (>30%), higher stromal tumor-infiltrating lymphocytes, progesterone receptor-negative status, and shorter disease-free survival (DFS) and disease-specific survival (DSS).[48] PDPN expression in CAFs can be an independent predictor of poor prognosis in patients with HR+/HER2- breast cancer being node-negative at the diagnosis.

Plasma Hsp90alpha has been identified as a lymphangiogenesis marker and plays an important role in the regulation of lymphatic tube formation. Hou Q et al found that Hsp90alpha could increase LVD in breast cancer mouse models and promote lymphangiogenic activity of LVECs in breast cancer cell lines.[31] Level of plasma Hsp90alpha was increased in the cases with sentinel lymph node metastasis, which was reduced with a treatment using Hsp90alpha neutralizing antibody. Therefore, Hsp90alpha has been used to evaluate the metastatic status of regional lymph nodes in patients with breast cancer.[31]

LOXL2 has been shown to be a predictor for lymph node metastasis as the expression of LOXL2 is positively correlated with LVD and tumor malignancy in patients with breast cancer. In animal studies, LOXL2-overexpressing breast cancer cells significantly promoted lymphangiogenesis and lymph node metastasis, whereas a knockdown of LOXL2 suppressed both processes.[32] LOXL2 is a candidate target for anti-lymphangiogenesis and anti-metastasis therapies in breast cancer, although it is yet to be further evaluated.

Increased expression of ITGA9 has been evident in breast cancer.[18] Wang Z et al found that high expression of ITGA9 is associated with significantly worse distant metastasis-free survival and recurrence free survival in TNBC patients.[49] Targeting ITGA9 with nanoparticle-mediated delivered siRNA can inhibit tumor associated angiogenesis, tumor growth, and metastasis in TNBC tumors.[49] ITGA9 may serve as a biomarker for the diagnosis of lymph node metastasis and a potential therapeutic target for anti-tumor target therapies.

COUP-TFII (Chicken Ovalbumin Upstream Promoter Transcription Factor II) is correlated with aggressive biological behavior and a worse prognosis for breast cancer patients. Volk-Draper L et al demonstrated that the expression levels of COUP-TFII were higher in patients with breast cancer and associated with M-LECP.[18] Nagasaki S et al found that the COUP-TFII took part in the process of lymph node metastasis, which was an independent prognostic factor for DFS and OS.[50]

Nrp2 is associated with the regulation of CXCR4 expression, lymph node metastasis, and poor prognosis in patients with breast cancer. The expression of Nrp2 can be used as a prognostic predictor for local recurrence, distant metastases, and long-term survival in breast cancer.[51] Nrp2 may be used as a novel target for precise therapy in the future clinical studies.

These indexes and molecules associated with the lymphangiogenesis have predictive potential for relapse, distant metastasis, and survival in breast cancer. The clinical evaluation of lymphangiogenesis with these indexes and markers also provides more information to clinicians to judge the degree of malignancy and make decisions for subsequent disease management and treatment.

Role of Cancer Invasion and Adhesion in Lymphatic Dissemination

In addition to the lymphangiogenesis, invasion and adhesion of cancerous cells are critical for the dissemination through lymphatic vessels in breast cancer. The first step in lymphatic dissemination is the loss of cancer cell–cell cohesion ability, which enables the cancer cells to migrate through the breast duct basement membrane and dissociate from the situ site of primary tumor mass.[11,52] Subsequent invasion of the surrounding stroma by changes in the cell–matrix interaction.[52] The second step of lymphatic dissemination is tumor cell intravasation through the lymphovascular wall into the lymphatic circulatory system. In this process, malignant tumor cells release the cellular factors that could degrade the extracellular matrix with a coherent alteration of proteins for their migration and invasion.[19] The third step of lymphatic dissemination is tumor cell extravasation from the lymphatic system. There are many signal molecules participating and coordinating the process of lymph node metastasis.

In addition to the loss or weakened cell–cell adhesion, epithelial mechanical transition process (EMT) also plays an important role in the enhanced migration and invasion of cancer cells during local and distant dissemination.[53] The cytoskeleton of breast cancer cells is often reorganized to facilitate migration. For example, active formation of the filopodia and lamellipodia can add stress to the cell–cell cohesion, thus facilitating dissociation of cancer cells.[54,55] Furthermore, another essential cellular protrusion, invadopodia, is pivotal for cancer cells to migrate through the walls of lymphatic vessels.[56]

Activation of EGFR signalling can promote invasion and is positively involved in the progress of lymphatic dissemination. For example, upon the activation of the EGFR pathway by EP4 can induce the formation of invadopodia to enhance invasive capability of breast cancer cells.[57] EP4 can also be activated by PGE2, which can then increase invasion and adhesion of breast cancer cells and subsequent lymphatic dissemination.[58]

Inflammation and immunity in tumour are also actively involved in the lymphangiogenesis and dissemination of cancer cells through lymph nodes. Inflammatory responses not only release promotive factors for oncogenesis but also result in an interruption of epithelium structure and its barrier function.[59] After inflammation-associated endothelial injury, cancer cells cross endothelial weakness into lymphatic vessels surrounding tumours and local lymph nodes.[59] Furthermore, inflammation-associated LVECs can impair the maturation of dendritic cells and the tumour immunity microenvironment. Cancer-associated fibroblasts derived from inflammation can also enhance the function of adhesion and migration of both LVECs and cancer cells to promote lymphangiogenesis and lymphatic metastasis.[60]

The invasion and adhesion of breast cancer is an essential condition for lymphatic dissemination and could accelerate the progress of lymphangiogenesis. Invasion and adhesion molecules play important roles in the chemotaxis of tumour-associated lymphatic vessels and the induction of cancer cell dissemination through lymph nodes.

Cancer Cell Coordinated Lymphangiogenesis Including Direct Effect on LVEC and Indirect Effect on the LVEC via Tumour Environment

Breast cancer cells can have a direct effect on LVEC by releasing lymphatic vessel-associated growth factors, such as VEGFA, VEGFC, and VEGFD. These growth factors could promote the formation of new lymphatic vessels surrounding the primary tumour. It can also enhance the invasiveness and dissemination of cancer cells to the local lymph nodes.[61–64] On the other hand, VEGFR-3 expressed by LVECs is vital for their response to VEGFC and VECFD released from the cancer cells and consequently resulted lymphangiogenesis. Furthermore, cancer cells could stimulate LVEC to produce VEGFR-3, which could regulate the induction of lymphatic metastasis.[65] Furthermore, other factors, such as the expression of receptors on cell membrane and lymphatic flow rate also affect the dissemination of tumour cells to lymph nodes.[66–68].

Breast cancer cells can also elicit indirect effects on LVEC via tumour microenvironments including tumour-associated fibroblasts (TAF), TAM. TAF is an important component of the peritumoral stroma and accumulates in the lymph nodes being positive for metastasis.[69] TAF produces and releases various cytokines to promote tumor growth and lymphangiogenesis.[70] Cytokines commonly secreted from TAF are transforming growth factor beta 1 (TGF-β1) and CXCL12. TGF-β1 can reciprocally induce the activation of TAFs, which releases VEGFs to stimulate LVECs and subsequent lymphangiogenesis in breast cancer.[71] It has also been shown that TGFβ1 canactivate RhoA cascade signaling

in LVECs, leading to cell contraction and increased permeability of lymphatic vessels in an in vivo triple-negative breast cancer murine model.[72] CXCL12 is an important lymphoid chemokine that is expressed on the luminal side of endothelial venules. CXCL12 promotes invasion and migration of breast cancer cells towards lymphatic vessels by interacting with C-C chemokine receptor 7 (CCR7).[30]

TAM is one of the most abundant inflammatory cells in the microenvironment surrounding tumours and also releases multiple factors to participate in the development of lymphatic vessels.[73] TAM expresses NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) and releases interleukin-1beta (IL-1β). NLRP3 inflammasome activates S1P receptor 1 (S1PR1) signaling pathway which can stimulate the proliferation and migration of LVECs thus to promote lymphangiogenesis and dissemination of cancer cells.[74] TAM can also be stimulated by breast cancer cells in addition to the impact of their released TGF-β1 one LVECs.[75]

Above all, cancer cells and the tumour environment are essential for the lymphangiogenesis and lymph node metastasis by orchestrating a supportive environment for the cancer cells for their dissemination (Figure 2).

Novel Therapy of Targeting Lymphatic Metastasis Including Targeting Cancer Cells, Lymphangiogenesis, Potential Development of Conventional Therapies

The key molecules involved in lymphatic metastasis are not only predictors of survival and prognosis but also serve as targets for developing novel therapy. Developing novel therapies against lymphatic metastasis, LVECs can be targeted to prevent lymphangiogenesis and dissemination of cancer cells through lymphatic vessels. Table 1 summarizes the recent ongoing clinical trials of novel therapy for targeting lymphatic metastasis.

The therapeutic application of CCR7 inhibitors is extremely promising in the control of recurrence and metastasis of local lymph nodes. CCR7 is expressed in various lymphocytes and multiple cancer cells that take part in lymphocytes homing to lymph nodes and tumor cells migration.[76,77] Anti-CCR7 siRNA can decrease the number of metastasis in the colon carcinoma xenograft model.[78] In a prostate cancer cell line, CCR7 knockdown could inhibit proliferation,

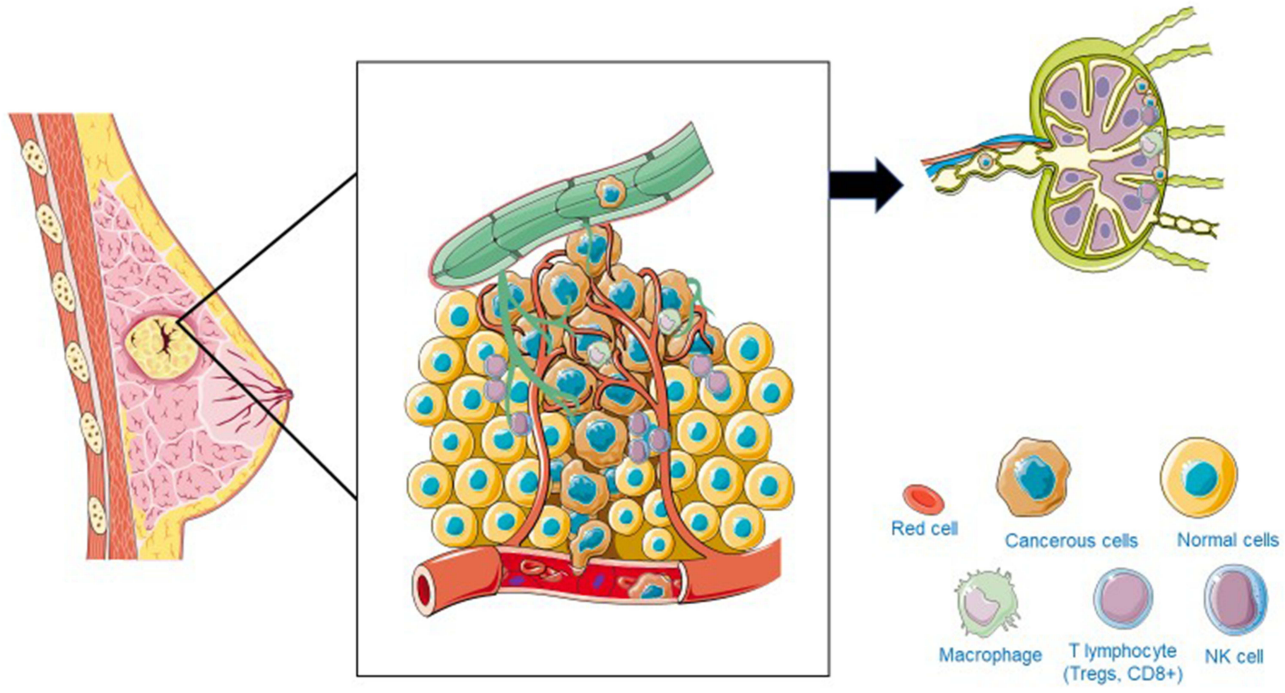

Figure 2 Breast cancer cells dominated process of dissemination and crosstalk in the tumour microenvironment during the process of lymph node metastasis. It was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 Unported license.

https://doi.org/10.2147/OTT.S503272

Table 1 Shows Ongoing Clinical Trials of Novel Therapy for Targeting Lymphatic Metastasis

Target	Specific Agent	Treatment	Tumour Types	Clinical Trial No. and Phase
VEFG2	Apatinib	Apatinib monotherapy	Sarcoma	NCT04072042/II
VEGF2	Apatinib	Drug: Apatinib Drug: Camrelizumab Procedure: Radical surgery Radiation: Post-operative radiotherapy/ chemoradiotherapy	Oral cancer	NCT04393506/I
VEGF	Bevacizumab	Drug: Serplulimab and Bevacizumab injection	Advanced Lung Adenocarcinoma	NCT05675033/II
PDPN	Maackia amurensis seed lectin	Drug: MASL Other: Placebo	Squamous Cell Carcinoma of Head and Neck	NCT04188665/I

migration, and invasion.[79] The knockdown of CCR7 in breast cancer cells can inhibit tumour cell dissemination into the vessels of zebrafish embryos.[80]

Scavenger receptor class A member 5 (SCARA5) is a candidate anti-oncogene which is expressed on the surface of multiple tumour cells.[81] Downregulated of SCARA5 was associated with a poor prognosis in breast cancer. Overexpression of SCARA5 can inhibit proliferation, colony formation, invasion, and migration of breast cancer cells. Additionally, the SCARA5 overexpression resulted in a downregulation of VEGF-C, which plays a vital role in both lymphangiogenesis and lymphatic metastasis.[82] JQ1 (bromodomain-extra-terminal domain inhibitor) plus GSK2801 (bromo adjacent to zinc finger 2A/B domain inhibitor) could upregulate the expression of SCARA5 in triple negative breast cancer cell lines.[83] However, their therapeutic potential for preventing lymphatic metastasis is yet to be further evaluated.

Plant extracts have been found to have some effects on tumor growth and migration, such as 6,8-Diprenylgenistein (6,8-DG), total saponins of panaxnotoginseng (PNS). 6,8-DG inhibited the expression of VEGFA to suppress the signaling pathway of VEGF-A/VEGFR-2 in cancer cells that could reduce lymphangiogenesis and dissemination of cancer cells.[84] Therefore, 6,8-DG could be a novel and valuable therapeutic agent for the prevention and treatment of lymphatic metastasis of tumor cells. PNS, a traditional Chinese medicine for cardiovascular disease in China, increases the expression of VEGFC, which can activate ERK1/2 and PI3K pathways to promote lymphangiogenesis.[85] PNS might be a novel therapeutic agent for lymphatic metastasis in breast cancer but still requires further verification.

Some fungal extracts also have anti-tumour and anti-lymphangiogenesis effects. A typical example is AD0157, which is derived from the fermentation broth of the marine fungus *Paraconiothyrium* sp. HL-78-gCHSP3-B005. A study using human breast cancer xenograft model in mice has shown that AD0157 can decrease tumour-associated lymphangiogenesis and prevent the dissemination to regional lymph nodes by inducing apoptosis in LVECs and inhibiting signal transduction through VEGFR-3/-2, ERK1/2, and AKT pathways, which could influence the lymphatic metastasis.[86]

Conclusions

Lymphangiogenesis plays a critical role in lymphatic metastasis and is linked to poor survival outcomes in breast cancer. Increasing numbers of biomarkers associated with lymphangiogenesis and lymphatic metastasis are being identified through clinical tissue studies. Molecular markers of LVECs are essential for lymphatic vessel formation as well as for the invasion, migration, and proliferation of primary breast cancer cells. A deficiency in a specific LVEC molecular marker could lead to lymphatic vessel disorders or hereditary lymphedema, which may influence the progression of breast cancer.

Targeting these molecular LVEC markers presents a promising strategy for treating lymphatic metastasis in breast cancer patients. However, inhibiting a single biomarker can impact systemic functions and increase the risk of side

effects. Therefore, precise targeting of specific molecules or pathways warrants further research and development to achieve more effective and precise therapies for regional lymphatic metastasis in breast cancer.

Disclosure

The authors report no conflicts of interest in this work.

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