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The Increasing Role of Lymphangiogenesis in Mammary Cancer Metastasis

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Abstract

The researchers till now have been more focused on the mechanisms of angiogenesis in tumor metastasis. The lack of specific lymphatic markers has been a constraint in establishing the role of lymphatics in tumor metastasis in the past. With the advent of few novel lymphatic markers i.e Podoplanin, Prox 1, LYVE-1, vascular endothelial growth factor receptor-3 (VEGFR-3) and its growth factors VEGF-C and VEGF-D, the research on lymphangiogenesis and lymphatics as a mode of tumor metastasis has picked up. The purpose of this mini-review is to make the researchers aware about the role played by the lymphatics and the process of lymphangiogenessis in mammary cancer metastasis.

Keywords: Lymphangiogenesis; Lymphatic Markers; Mammary Tumor Metastasis

Introduction

French surgeon Le Dran [1] in the sixteenth century, first noted that cancers of the breast that spread to axillary lymph nodes had significantly worse survival outcomes than those that were localized only to a primary tumor. Some 200 years later, Halsted [2] performed the radical excision of both the primary breast cancer and the metastatic lesions in the axillary lymph nodes [3]. The next major clinical development regarding lymphatics in cancer occurred in the 1950s, when clinicians began to use radioisotope injections to better understand which regional lymph node groups drain different parts of the body [4], thus identifying the potential routes of cancer metastasis via the lymphatic vasculature. The lymphatic system is a vascular network of thin-walled capillaries and larger vessels lined by a continuous layer of endothelial cells, which drain lymph from the tissue spaces of most organs and return it to the venous system for recirculation. Although much information has been gained regarding the normal and pathological growth of the vascular system [5], The lack of specific lymphatic markers made it difficult to elucidate the development of the lymphatic system. Consequently, the study of the formation of the lymphatic vasculature and its possible role in tumor metastasis has been neglected in the past, and the understanding of the precise manner by which neo-lymphangiogenesis occurs was not fully clear.

The 1990's saw the adaptation of lymphatic mapping for the prediction of each patient's lymphatic drainage from a specific tumor, and for identification of the 'sentinel lymph node' (i.e. the lymph node most likely to contain spreading cancer cells) within the lymphatic drainage basin [6]. The same decade also yielded the discovery of lymphatic-specific molecular markers to identify lymphatic vessels, which were hitherto histologically indistinguishable from blood vessels [7]. The advent of these techniques led to the realization that lymphatics are fundamental to cancer metastasis, particularly carcinomas, and many other pathological processes, and has thus generated intense clinical and scientific interest in the lymphatic vasculature as a potentially valuable therapeutic target [8]. The major cause of cancer mortality is the metastatic spread of tumor cells that can occur via multiple routes, including the lymphatic vasculature. The lymphatic vessels play a major role in cancer biology, as the spread of tumor cells to lymph nodes implicates the lymphatics as an important route of metastasis and is often an early event in metastatic disease. Lymphatic capillaries are identified by the fact that they are lined by a single layer of endothelial cells, which are characterized by poorly developed junctions with frequent large gaps between cells. These loose junctions readily permit the passage of large biological macromolecules, pathogens and migrating cancer cells. Unlike blood capillaries, lymphatic capillaries lack a continuous basement membrane, and are devoid of pericytes [9]. The migration of tumour cells and their presence in local lymph nodes is significant for the staging of cancer, hence the relevance of sentinel lymph node biopsy for planning of therapeutic strategies [10].

Lymphangiogenesis and Lymphatic Markers

Lymphangiogenesis is the formation of new lymphatics which facilitates cancer progression through a series of sequential processes that include dissemination and invasion into surrounding stromal tissues from a primary tumor, penetration into lymphatic walls and implantation in regional lymph nodes, extravasation,

seeding and proliferation in the parenchyma of target organs [11]. Traditionally the role of lymphangiogenesis in cancer metastasis has been underestimated. However, the study and understanding of the lymphatic system has been revolutionized in recent years by the discovery of proteins that are specifically expressed on the lymphatic endothelium and serve as markers for it [12]. These lymphatic markers include LYVE-1, a lymphatic endothelial receptor for hyaluronan, Prox1, a homeobox gene (master gene), involved in regulating early lymphatic development, podoplanin, a glomerular podocyte membrane mucoprotein found on lymphatic endothelium, but not in blood vessels and the VEGFR-3 a trans membrane tyrosine kinase receptor predominantly expressed on the lymphatic endothelium. VEGFR-3 has also been shown to control the development and growth of the lymphatic system by binding to a polypeptide vascular endothelial growth factor growth (VEGF), precisely VEGF-C and VEGF-D [13].

With the discovery of novel lymphatic markers, it has now become possible to explore the relationship between lymphangiogenesis and tumor metastasis. Progress has been made in understanding the role of lymphangiogenesis in cancer metastasis in several human neoplasms, including breast cancer [14] and sparsely in feline mammary tumour [15]. However, there appears to be meager information on this aspect in the canine mammary tumor, although it is regarded as a good model for human breast cancer. Banerji et al. [7] described hyaluronan (HA) binding molecule, LYVE-1, which was identified as a major receptor for HA on the lymph vessel wall. The deduced amino acid sequence of LYVE-1 was predicted similar to the CD44 HA receptor. LYVE-1 was the first lymphatic specific HA receptor to be characterized. Conventional PCR, DNA sequencing, plasmid synthesis, and real-time quantitative PCR were used by Cunnick et al. [14] for measurement of lymphangiogenesis using LYVE-1 marker. LYVE-1 is a novel and specific lymphatic marker in breast cancer tissue.

Schoppmann et al. [16] used immune-staining for the specific lymphatic endothelial marker podoplanin, originally identified as a podocyte membrane protein in the renal corpuscle, and revealed that lymphangiogenesis occurred in many breast tumors. Skobe et al. [17] using LYVE-1, demonstrated the occurrence of intratumoral lymphangiogenesis in human breast cancer. He also concluded that over-expression of VEGF-C in breast cancer cells vigorously increased intratumoral lymphangiogenesis, resulting in significantly enhanced metastasis to regional lymph nodes. Akishima et al. [18] raised a polyclonal antibody against human LYVE-1 for detecting lymphatic vessels using immune histo chemistry in normal and pathological tissues. LYVE-1 expression was confined to the endothelial surface of lymphatic vessels but was not expressed on the endothelium of blood vessels. Karkkainen et al. [13] opined that vascular endothelial growth factor receptor-3 (VEGFR-3), largely found in adult lymphatic endothelium, specifically bound to and was activated by lymphatic growth factors VEGF-C and VEGF-D. Van der et al. [19] compared different immuno-histo chemical markers (podoplanin, LYVE-1 and Prox-1) with several histomorphometric variables for lymphatic vessels and concluded that podoplanin was the most suitable for staining peritumoral and intratumoral lymphatic vessels in both inflammatory and non-inflammatory breast carcinomas.

Cunnick et al. [20] quantified lymphangiogenesis by measuring mRNA expression by Q-PCR of seven lymphatic markers (LYVE-1, VEGFR-3, VEGFR-2, Prox1, Podoplanin, 5'nucleotidase, VEGF-C, VEGF-D) from 153 frozen archived breast samples. The findings revealed that lymphangiogenesis was higher in breast cancer than in normal breast tissue. Yan et al. [21] demonstrated lymphangiogenesis in breast carcinoma by RT-PCR and immune-staining for VEGF-C and VEGF-D. They further inferred that there was a close correlation between clinico-pathological parameters, metastasis and progression with lymphangiogenesis in breast cancer. Podoplanin expression increases in the early stages of tumourigenesis, but diminishes during later stages of tumor progression, thus supporting the fact that podoplanin has a larger role in the initiation than the progression of cancers [22]. More recently, several studies have furthered the role of lymphatics and lymphangiogenesis in breast cancer metastasis [23-26].

Conclusion

The lymphatic vascular system has an important role in the maintenance of tissue fluid homeostasis, intestinal lipid absorption and immune surveillance in that it recruits and transports immune cells from peripheral tissues to the regional lymph nodes. The lymphatic system plays an important role in modulating inflammatory diseases and in promoting metastasis to lymph nodes and further beyond. Lymphatics serve as the most common pathway of initial dissemination of cancer cells via afferent vessels following routes of natural lymphatic drainage. The discovery of various lymphatic markers has facilitated the study of role of lymphatics in tumor metastasis. But the comparative evaluation of pre-existing lymphatic vessels vis-à-vis intratumoral and peritumoral neo-lymphangiogenesis in mammary cancer metastasis is a subject of further investigation.

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