The biological significance of lymphangiogenesis in human tumours

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Abstract

Increasing evidence indicates that lymphangiogenesis in cancer is an important factor in promoting tumour progression and metastasis. The discovery of immunohistochemical markers for lymphatic vessels' identification as well as the characterization of lymphatic-specific growth factors and receptors afforded insight into the mechanisms involved in new lymphatic vessel formation and the process of lymphatic-borne metastasis. Quantitative assessment of lymphangiogenesis in malignant tumours has emerged as a promising prognostic indicator, although there are conflicting results on the impact of lymphatic vessel density to predict lymph nodal metastases and overall survival. Solid tumours were recently found to induce new lymphatic vessel growth in draining lymph nodes before the onset of metastasis and therefore lymphangiogenesis in the lymph nodes has gained great interest. This review highlights advances in our understanding of the mechanisms by which lymphangiogenesis in tumours and lymph nodes enhances metastases and reports the potential implications of these developments in cancer therapeutics.

Keywords cancer; lymphangiogenesis; lymphatic endothelial cells; lymphatic vessels; lymph nodes; metastasis; VEGF-C; VEGF-D; VEGFR-3

Introduction

The lymphatic vascular system mediates tissue fluid homeostasis by providing an important route for fluid and protein transport, serves as conduit for fat absorption from the gut and for the transport of lymphocytes and antigen-presenting cells to regional lymph nodes where specific immune responses are initiated. Interest in basic lymphatic research was recently boosted by the increasing evidence that the lymphatic vasculature plays an active role in the lymph nodal and systemic metastasis of human cancer. The discovery of various molecular markers allowing the distinction of blood and lymphatic vessels as well as the characterization of lymphatic-specific growth factors and receptors afforded insight into the mechanisms of tumour lymphangiogenesis. Furthermore, genome-wide analyses of the lymphatic endothelial transcriptome, contemporary technological advances in microscopic imaging of lymphatics and the availability of an increasing number of sophisticated *in vitro* and *in vivo* models have greatly facilitated the unravelling of lymphatic biology and lymphatic-borne metastases. This expanded knowledge, focus of the present review, offers promise for the development of novel cancer therapies specifically targeting dissemination through the lymphatic network.

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Development of the lymphatic system

In contrast to the blood vascular system, the lymphatic system is open ended and serves as a drainage system by collecting interstitial fluid, proteins and macromolecules in the periphery and by transporting them back to the subclavian veins in the nuchal region. In the gut, lymphatic vessels also play an important role in the uptake of dietary fats. Furthermore, lymphatic vessels attract antigen-presenting cells and other immune cells from peripheral tissues to the draining lymph nodes. The lymphatic vascular system is composed of peripheral capillaries, collecting vessels, lymph nodes, larger trunks and the thoracic duct. The lymphatic capillaries are lined by a single, non-fenestrated layer of overlapping endothelial cells, and — in contrast to blood vessels — lack a continuous basement membrane as well as pericyte or smooth muscle cell coverage. Lymphatic endothelial cells (LECs) are connected to the surrounding extracellular matrix by specialized fibrillin-containing anchoring filaments, which represent the major means of vessel stabilization. These features prevent the vessels from collapsing during changes in interstitial pressure and facilitate the uptake of soluble tissue components. A rise in external pressures causes interendothelial valves to open, thus allowing fluid to enter the capillary lumen.[1]

The major molecular determinants that control the step-wise process of lymphatic competence, commitment, differentiation and maturation are illustrated in Figure 1. It is agreed that Prox1 is a key transcription factor in lymphatic vessel development, and its expression confirms lymphatic identity whereas vascular endothelial growth factor (VEGF)-C/VEGF receptor(VEGFR)-3 provide essential signals for sprouting.[2,3] The earliest event in lymphatic development is the expression of the homeobox transcription factor Prox1 in a subpopulation of lymphatically competent endothelial cells at one side of the embryonic cardinal vein, by a yet unidentified initiating signal.[4] Prox1 is required for lymphatic development, since Prox1 null mice do not develop a lymphatic vascular system, whereas blood vessels seem to be unaffected.[5] Prox1 overexpression in human vascular endothelial cells suppresses blood vessel-specific genes and upregulates lymphatic endothelial specific cell transcripts.[6] This original Prox1 positive lymphatic vessel serves as the lymphatic ''stem'' for further sprouting lymphatic capillaries, which would eventually be remodelled into the lymphatic vascular tree.[7] VEGF-C also plays an essential role during early lymphatic development. VEGF-C activates the VEGFR-3 that is expressed on early embryonic blood vessels and on lymphatic endothelium. VEGF-C is an essential chemotactic and survival factor during lymphangiogenesis and is required for the sprouting of the first lymphatic vessels from embryonic veins.[2] In VEGF-C null mice,

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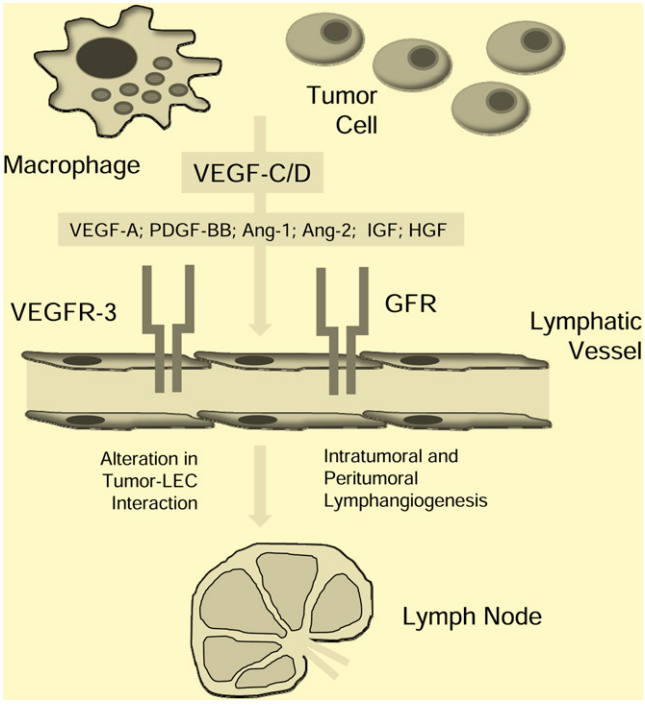
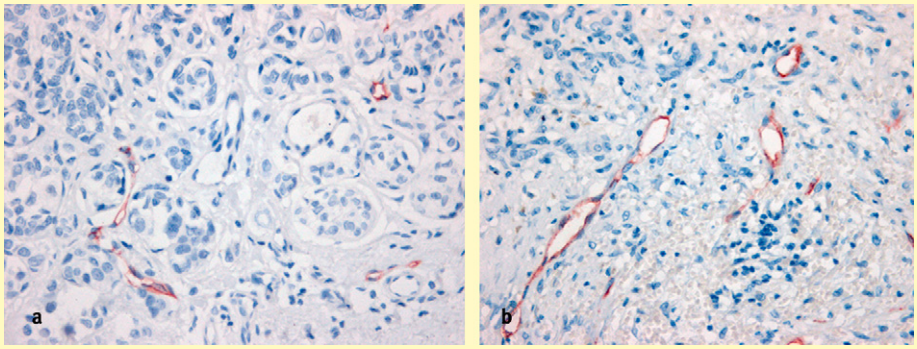


Figure 1 The process of lymph node metastasis. Both tumour cells and tumour-associated macrophages express lymphangiogenic factors. The peritumoural or intratumoural lymphangiogenesis increases the lymphatic area within or close to the tumour tissues that in turn is thought to facilitate access of tumour cells into the lymphatic network. Lymphatic invasion by tumour cells is also facilitated by chemotactic lymphatic endothelial cell secretions, including CCL21. GFR, receptors for various growth factors.

the endothelial cells that bud off the cardinal vein are committed to the lymphatic lineage, but they are unable to sprout or to form lymphatic vessels.[2] The distinct role of VEGFR-3 during embryonic lymphatic development is currently difficult to assess because VEGFR-3 null mice die during early development due to cardiovascular failure.[8] *VEGFR-3* deletion leads to defects in blood vessel remodelling and embryonic death at mid-gestation, suggesting an early blood vascular function.[8] In normal adult tissues, VEGFR-3 expression is largely restricted to the lymphatic endothelium.[9] However, VEGFR-3 expression has also been detected on some blood capillaries associated with tumour neovascularization or with wound granulation tissue[10]; therefore VEGFR-3 alone is not a sufficiently specific marker for lymphatic vessels. LYVE-1, a homologue of the blood vascular endothelium-specific hyaluronan receptor CD44, is expressed on blood endothelial cells early in the phase of lymphatic competence[3] and it associates with lymphatic and lymph node endothelia throughout the development towards terminal differentiation. LYVE-1 is the first marker of lymphatic endothelial competence during development, in the mature vasculature, LYVE-1 expression remains high in lymphatic capillaries while being downregulated in the collecting lymphatic vessels.[11] However, additional molecules, including the mucin-type glycoprotein podoplanin, neuropilin-2 and angiopoietin-2 play major roles in the further maturation of the developing lymphatic system. Likely, additional signalling systems are essential for both the early and late stages of lymphangiogenesis. For example, the Notch, Ephrin, and Netrin signalling pathways might regulate LEC sprouting, patterning and remodelling as they do on blood vessel endothelial cells.[12] Recently, collagen and calcium-binding EGF domain-1 and VEGF-C were demonstrated acting at the level of both angiogenic sprouting and lymphangiogenic budding from venous endothelium during embryogenesis.[13] Ccbe1 was necessary for lymphangiogenesis, although no genetic evidence was found that it is a component of either the VEGF-C—VEGFR-3 signalling or SOX18—Prox1 transcriptional pathways, suggesting that Ccbe1 defines an independent regulator of lymphangioblast budding, which might work as an extracellular guidance molecule.[13]

Lymphangiogenic growth factors and their receptors

Because of their common origin, lymphangiogenesis as well as angiogenesis relay on the interplay of several growth factors and receptors (Figure 2). Members of the VEGF family, VEGF-C and VEGF-D, are thus far the best characterized lymphangiogenic factors that bind the VEGFR-3 specifically expressed on LEC, and the VEGF-C/VEGF-D/VEGFR-3 axis constitutes the signal transduction system for lymphatic endothelial cell growth, migration, and survival.[14,15] In addition to VEGF-C and VEGF-D, also VEGF-



Imaging of lymphatic vessels immunostained with D2-40 in primary cutaneous melanoma at intratumoural **a** and peritumoural location **b**. In peritumoural location, lymphatic vessels are often seen in contiguity with a mononuclear cell inflammatory infiltrate.

Figure 2

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