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Multiple roles of lymphatic vessels in tumor progression

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Sentinel lymph node metastasis is a prognostic indicator for systemic tumor spread in many types of cancers, and tumor lymphangiogenesis correlates with reduced survival. Consequently, lymphatic vessels have been suggested to promote tumor progression in multiple ways. Tumor lymphangiogenesis occurs both in primary tumors and at distant (pre-) metastatic sites, and facilitates lymphatic invasion and tumor cell dissemination. Lymphatic vessels have also emerged as regulators of tumor immunity, transporting tumor antigens to lymph nodes and directly interacting with immune cells. Furthermore, lymphatic vessels might provide a 'lymphovascular' niche contributing to the maintenance of stem-like tumor cells that are tightly related to tumor recurrence. Thus, targeting tumor lymphangiogenesis or specific lymphatic-associated functions might represent a promising approach to inhibit tumor progression.

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Introduction

The lymphatic system is a unidirectional, blind-ended vascular network consisting of lymphatic capillaries and larger collecting vessels as well as secondary lymphoid organs such as lymph nodes (LNs). It is essential to maintain fluid homeostasis, to absorb dietary lipids, as well as to transport immune cells and soluble antigens from peripheral tissues towards lymph nodes and the central circulatory system [1]. Lymphatic capillaries are composed of a single layer of oak leaf-shaped lymphatic endothelial cells (LECs) that are loosely connected by 'button-like' junctions and covered by a discontinuous basement membrane. Lymphatic capillaries merge to form larger precollecting and collecting vessels, which finally drain into the thoracic and the right lymphatic duct that join the blood circulation via the subclavian vein. Lymphatic collectors possess tight 'zipper-like' junctions between adjacent LECs, a continuous basement membrane, valves to prevent backflow, and they are covered by a layer of smooth muscle cells and supporting pericytes [2].

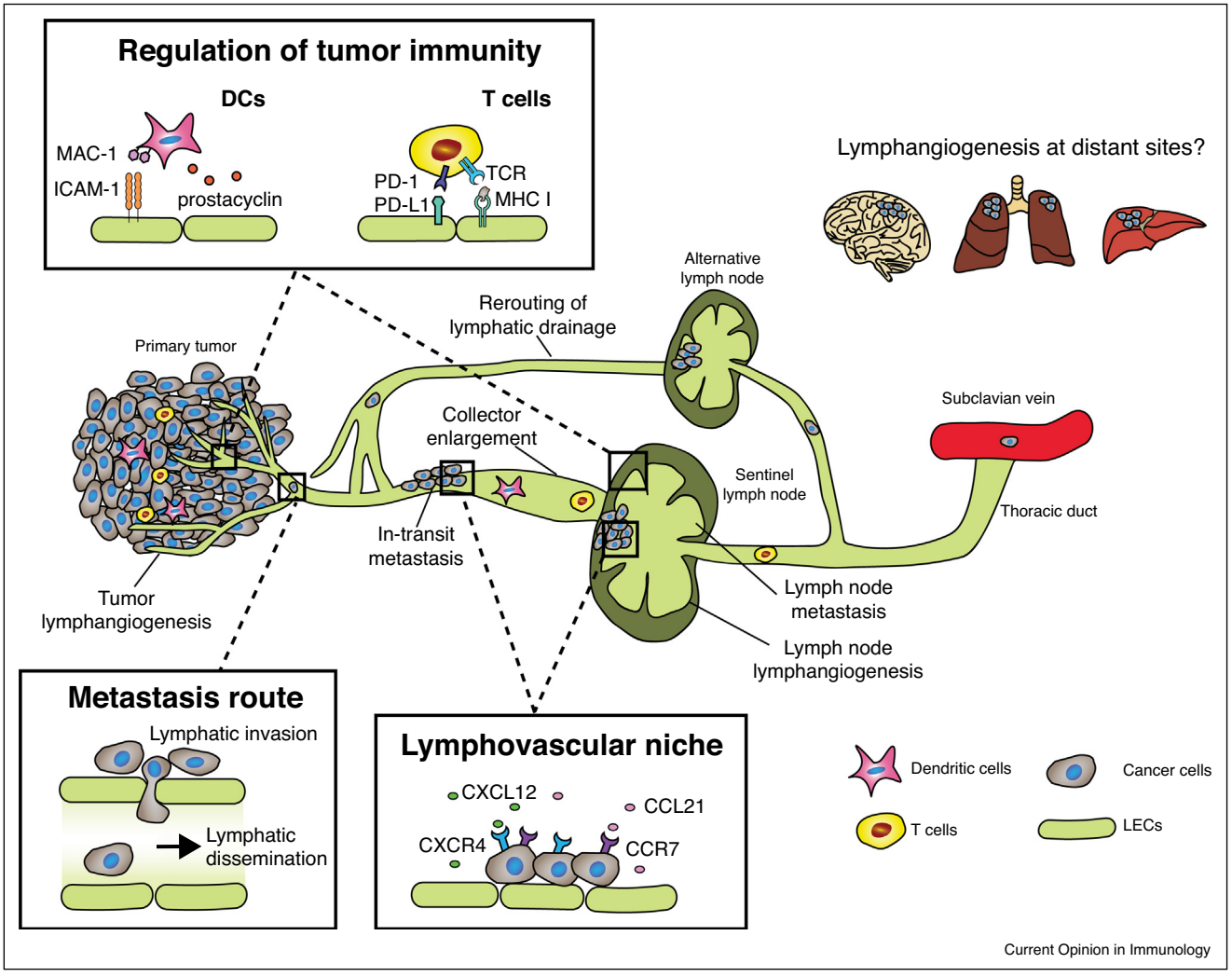
Lymphatic vessels have been shown to be actively involved in tumor progression (Figure 1). In many cancer types, the presence of tumor cells in sentinel LNs is regarded as a predictor for poor patient outcome. Expression of lymphangiogenic growth factors, high lymphatic vessel density, and high incidence of lymphatic invasion are typically associated with LN metastasis and reduced survival [3,4,5•]. In this review, we discuss tumor-associated lymphatic remodeling as well as potential mechanisms how lymphatic vessels promote tumor progression.

Lymphatic vessels as routes for metastasis

Despite the clear correlation between LN metastasis and poor outcome in many types of cancer [3,5•], it has been a matter of debate for many years whether LN metastasis does in fact contribute to distant organ metastasis, or whether it is merely a reflection of the general capacity of a tumor to disseminate via the blood stream [6]. Surgical removal of regional LNs reduced the rate of local recurrence but did not extend the overall survival of patients suffering from breast cancer or melanoma, as compared to regular clinical follow-up with resection of newly diagnosed LN metastases [7,8,9•]. Importantly, however, recent studies in colorectal and prostate cancer indicate that tumor cells derived from metastatic foci in LNs can indeed contribute to distant organs [10••,11••,12••], confirming the importance of lymphatic vessels as a metastatic route for the distant spread of tumor cells.

Lymphatic vessels frequently undergo extensive remodeling during tumor progression, which facilitates lymphatic dissemination [3]. Lymphangiogenic factors such as vascular endothelial growth factor (VEGF)-C are released by cancer cells and stromal cells and stimulate the proliferation and migration of LECs, inducing sprouting of lymphatic vessels and enlargement of existing vessels, which increases the potential lymphatic contact surface with tumor cells. VEGF-C has also been reported to weaken lymphatic junctions, which further facilitates lymphatic invasion by tumor cells [13]. In most carcinomas, major expansion of lymphatic vessels occurs at the tumor-stroma interface, whereas in malignant cutaneous melanomas, it may also occur inside the tumor mass [14].

Figure 1



Schematic representation of the principal roles of lymphatic vessels in tumor progression. Tumor lymphangiogenesis is induced in primary tumors and at (pre-) metastatic sites, which facilitates the entry of tumor cells into lymphatic vessels and their dissemination. The enlargement of lymphatic collectors increases lymph flow and sentinel LN metastasis. Upon obstruction of the regular lymphatic flow path, rerouting of lymphatic vessels may lead the lymph and metastatic cells to alternative LNs. Besides transporting tumor antigens to LNs, lymphatic vessels also regulate tumor immunity by direct interactions with DCs and T cells. LECs reduce DC activation via MAC-1/ICAM-1 interactions or via release of anti-inflammatory prostacyclin under inflammatory conditions, and suppress T-cell responses by upregulation of PD-L1 and presentation of tumor antigens. Furthermore, by secreting CXCL12 and CCL21, LECs may attract and maintain CXCR4 or CCR7 expressing stem-like tumor cells.

Besides the lymphatic vessels at the site of the primary tumor, lymphatic collectors, which drain away from the tumor towards sentinel LNs, also undergo substantial remodeling induced by lymphangiogenic factors. Enlargement of collecting lymphatics due to LEC proliferation and structural remodeling of smooth muscle cells results in an increased flow rate and increased sentinel LN metastasis [4,15,16]. Extensive lymphangiogenesis is also observed within the sentinel LNs in many cancer types. Lymphatic remodeling within tumor draining LNs was found to occur even before tumor cells in the LNs were detectable, properly driven by soluble factors drained from the primary tumor. Expanded lymphatic networks in LNs have been suggested to represent a 'premetastatic niche' that promotes colonization of the LNs by metastatic cells [17,18]. Once LN metastases reach a certain size, they may furthermore obstruct nodal sinuses and block the regular lymphatic flow path, resulting in collateral vessel remodeling and re-routing of the lymph flow. This has been demonstrated in experimental melanoma studies [19]. Importantly, re-routing of lymph flow from the original draining LN to alternative nodes may lead to erroneous identification of sentinel LNs in cancer patients.