Chapter 1

LYMPHANGIOGENESIS IN HEALTH AND DISEASE – AN OVERVIEW

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Abstract: The blood and lymphatic vascular networks combine to facilitate immune function and maintain tissue fluid homeostasis in the body. Although these two systems share many common structural and molecular features, recent advances in our understanding of the molecular control of the lymphatics have identified distinct molecular pathways responsible for the formation and function of the lymphatic network. These advances have led to the characterisation of lymphatic-specific markers and growth factors which control lymphatic development and function. Insights gained from in vitro and in vivo studies over the past decade have highlighted the importance of the lymphatic system in human diseases such as lymphedema, inflammatory disorders and cancer. The lymphatic vasculature is an important route for the metastatic spread of tumor cells, and recent studies based on animal models of cancer indicated that lymphangiogenic growth factors, secreted by tumor cells or components of the tumor stroma, can induce formation of new lymphatic vessels in the vicinity of a primary tumor. These studies, as well as clinicopathological data, suggest that this process of tumor lymphangiogenesis can be associated with enhanced metastatic spread – hence tumor lymphangiogenesis is being explored as a therapeutic target for restricting the metastatic spread of cancer.

Key words: Lymphangiogenesis · Growth factors · Growth factor receptors · Metastasis · Cancer

The characterization of the anatomy and physiology of the lymphatic system has been ongoing over centuries, however, advances during the past decade in identifying molecular markers of the lymphatics have accelerated this process (see chapter by Shields and Swartz). The lymphatic vasculature begins as blind-ended, thin-walled
capillaries that collect extravasated fluid and cells from tissues. The lymph fluid then drains into pre-collecting lymphatics, located in the deep dermis, which in turn drain into the collecting lymphatics located in the subcutaneous tissue. The collecting lymphatics, which are invested with smooth muscle cells and pericytes, are capable of propelling lymph fluid, are studded with lymph nodes and coalesce into lymphatic trunks which drain lymph fluid back to the blood circulation via intra-thoracic ducts [1, 2]. The lymphatic vasculature plays crucial roles in immune function, tissue fluid homeostasis and the absorption of dietary fat.

The development of the lymphatic vascular system during embryogenesis begins with sprouting of lymphatic endothelial precursor cells from the cardinal vein, giving rise to the lymph sacs – lymphatic endothelial cells then sprout from these sacs to form the primary lymphatic plexus, and further sprouting, proliferation and migration generates the lymphatic networks of tissues and organs [3] (see chapter by Johnson and Oliver). Differentiation of lymphatic endothelial cells to generate the distinct types of lymphatic vessels is an important aspect of lymphatic development. Elegant developmental studies, utilizing traditional and emerging animal models of embryonic development (see chapter by Hogan and Schulte-Merker), have mapped the initial events in the formation of the lymphatics, as well as of blood vessels, showing their origins in the embryo. Some of the early markers of the lymphatic system such as Prox-1 [4], podoplanin [5], and vascular endothelial growth factor receptor-3 (VEGFR-3) [6, 7] are important for the development or function of the lymphatics [8]. VEGF-C and VEGF-D are significant as they are ligands for VEGFR-3 [9–11], which are capable of inducing lymphangiogenesis when delivered to adult tissues [12, 13]. VEGF-C is indispensable for development of the lymphatic vasculature during embryogenesis [14].

The metastatic spread of tumor cells from the primary tumor to establish metastases at distant sites in the body is the most lethal aspect of cancer. The importance of the lymphatic vasculature in the metastatic spread of cancer has been appreciated for centuries, and the extent of lymph node metastasis is a major determinant for prognostic assessment and planning of treatment (see chapter by Faries and Morton). Recently, the involvement of tumor lymphangiogenesis in lymph node metastasis has become an important focus of study, and the molecular mechanisms underlying lymph node metastasis are being revealed (see chapter by Rinderknecht and Detmar). The VEGF-C/VEGF-D/VEGFR-3 signalling axis is closely linked to the formation and function of the lymphatics in cancer [15]. Initial studies showed that over-expression of VEGF-C or VEGF-D in mouse tumor models led to formation of lymphatic vessels in and/or around the primary tumor, and to increased metastatic spread to regional lymph nodes, as well as increased tumor growth in some cases [16–18]. Some of the underlying mechanisms are schematically shown in Fig. 1.1. Furthermore some of these effects could be inhibited by antibodies [18–20], soluble receptors [21, 22] or small molecule protein tyrosine kinase inhibitors [23] which targeted signalling via VEGF receptors. These experiments were further substantiated by clinicopathological data showing a correlation of VEGF-C or VEGF-D expression levels in human primary tumors with clinical parameters and patient outcomes [24]. Significantly, these correlations were seen over a range of different tumor types including tumors originating from the colon, lung, breast,