

ANGIOGENESIS AND LYMPHANGIOGENESIS IN INFLAMMATION AND CANCER

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Tumor metastasis to regional (sentinel) lymph nodes represents the first step of tumor dissemination in most human cancers and serves as a major prognostic indicator for disease progression. However, little is known about the mechanisms how tumor cells gain entry into the lymphatic system, and it has been generally thought that lymphatic endothelium only plays a passive role during this process and that lymphatic invasion only occurs once stroma-infiltrating tumor cells happen upon preexisting peritumoral lymphatic vessels. In this respect, we have previously shown that tumors can actively induce the formation of lymphatic vessels (leading to the new concept of tumor lymphangiogenesis) (1) and that tumor lymphangiogenesis was correlated with lymph node metastasis in an orthotopic breast cancer model. Our recent studies in human cutaneous malignant melanomas demonstrated the presence of both intratumoral and peritumoral lymphangiogenesis in cutaneous melanoma. They also showed that primary melanomas that later metastasized were characterized by increased lymphangiogenesis – as compared to non-metastatic tumors – and that the degree of tumor lymphangiogenesis can serve as a novel predictor of lymph node metastasis and overall patient survival, independently of tumor thickness (2). Very recently, we found that the extent of lymphatic vessel growth in primary human cutaneous melanomas was the most sensitive parameter for predicting whether these tumors had already metastasized to the sentinel (draining) lymph node at the time of surgery (3).

Moreover, we have recently found - for the first time - that metastatic tumor cells can induce lymphangiogenesis within lymph nodes, furthering their metastatic spread (4). This has led to the new concept of lymph node lymphangiogenesis. Surprisingly, we found that tumor cells can induce lymph node lymphangiogenesis already before they metastasize, giving a new twist to the seed-and-soil hypothesis and suggesting that tumors can prepare lymph nodes for their future arrival (4). We have also been able to isolate and to culture human lymphatic endothelial cells, and to characterize their transcriptional profile in comparison to blood vascular endothelial cells (5). This has enabled us to identify a number of new lymphangiogenic growth factors, including hepatocyte growth factor (6), and to identify Prox1 as a major lymphatic lineage-specific transcription factor (7). Based on these studies, we found that the Kaposi's sarcoma-associated herpes virus (KSHV) is able to reprogram differentiated blood vascular endothelium to adopt a lymphatic phenotype (8). Very recently, we have established the mouse embryonic stem cell-derived embryoid body assay as a new tool for the characterization of potential lymphangiogenesis factors (9). Taken together, tumor lymphangiogenesis has not only emerged as a novel prognostic parameter for the metastatic risk of human cancers, but inhibition of tumor-associated lymphangiogenesis appears to represent an exciting new strategy to inhibit cancer progression. In addition to cancer progression, recent data indicate that lymphangiogenesis and angiogenesis play a major role in mediating and maintaining chronic inflammatory diseases (10, 11).

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