Role of lymphangiogenesis and lymphatic vessel microenvironment in metastatic progression

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The lymphatic vasculature is an important pathway for dissemination of most solid tumors and presence of metastases in the lymph nodes remains one of the key prognostic criteria. Despite the apparent clinical significance of lymphatic spread, it is not understood whether the presence of metastases in lymphatics is only an indicator of aggressive disease or whether the lymphatic system directly contributes to metastatic progression. We have demonstrated that the induction of lymphangiogenesis in the primary tumor increases regional and distant metastases. Moreover, induction of lymphangiogenesis at the distant site, in the lung, leads to the colonization of the lung through the pulmonary lymphatics and rapid progression of metastatic disease. Metastases in pulmonary lymphatics exhibit rapid growth and they are not hypoxic despite the absence of angiogenesis. Furthermore, metastases in lymphatics exhibit remarkably low rate of cell death. We have recently discovered that the soluble factors made by lymphatic endothelium protect melanoma and breast cancer cells from death by inducing metabolic adaptations in cancer cells. Lymphatic endothelial cells (LECs) promoted survival of tumor cells under stress by improving mitochondrial function in tumor cells and by inducing metabolic shift to maintain redox homeostasis and promote cellular energy production. I will present recent advances in our understanding of the mechanisms by which lymphatic vessels, and in particular lymphatic endothelium, impact metastasis.