Characterizing Lymphatic Micrometastases

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Metastasis remains the major cause of cancer mortality, but breakthroughs in our understanding of the molecular and cellular mechanisms regulating metastasis have yet to be broadly translated into improved survival rates in patients with metastatic disease. The challenge is how to treat cancer cells that have spread to lymph nodes or distant organs in order to prevent their growth and ideally eradicate them from the body. Most cancer therapies are developed against the primary tumor growing in its native microenvironment. However, it is clear that the local microenvironment in which tumor cells grow greatly affects the growth rate, metabolism, vascularization, and ultimately the response to therapeutic intervention. For instance, antiangiogenic therapy to date has failed to improve overall survival in cancer patients when used in the adjuvant setting. The presence of lymph node metastases dictate treatment decisions, however their reliance on angiogenesis for growth has not been described. Here, we introduce a novel chronic lymph node window (CLNW) model to facilitate new discoveries in the growth and spread of lymph node metastases. Using the CLNW in multiple models of spontaneous lymphatic metastases in mice, we reveal the surprising lack of sprouting angiogenesis during metastatic growth, despite the presence of hypoxia in some lesions. Treatment with two different antiangiogenic therapies showed no effect on the growth or vascular density of lymph node metastases in our models. We confirmed these findings in clinical specimens, including the lack of reduction in blood vessel density in lymph node metastases in patients treated with bevacizumab. We provide pre-clinical and clinical evidence that sprouting angiogenesis does not occur during the growth of lymph node metastases, which reveals a mechanism of treatment resistance to antiangiogenic therapy in adjuvant settings. The targets of clinically approved angiogenesis inhibitors are not active during early cancer progression in the lymph node, suggesting that inhibitors of sprouting angiogenesis as a class will not be effective in treating lymph node metastases.