

The Lymphatic Vasculature as a Double Agent in Cancer Progression

While the blood vasculature delivers oxygen, nutrients, and fluid to tissues throughout the body, the lymphatic vasculature instead collects and filters this fluid back into the circulation. During this process, the lymphatics pass the fluid through local lymph nodes where immune cells sample the draining fluid for the presence of pathogens. If pathogens are detected, the immune cells in the lymph node will become activated and travel out of the node to mount an immune response. In this manner, the lymphatic vessels act as immune highways, providing direct routes of travel for activated immune cells to find and eliminate harmful pathogens. These pathogens can include bacteria, viruses, and even abnormal human cells including cancer.

For decades, the lymphatics were thought to play a passive role in cancer progression. This role was limited to providing a physical “escape route” for cancer cells to metastasize to local lymph nodes, much like the vessels act as highways for immune cells. However, recent evidence increasingly shows that lymphatic vessels are active players in cancer progression. For example, as tumors grow, they secrete large volumes of fluid that drain into the lymphatic vasculature. In response to this drainage, new lymphatic vessels grow around the tumor (Figure 1). These additional vessels create even more “escape routes” for metastasizing tumor cells and increase the delivery of fluid from the tumor to the lymph nodes. The delivery of certain biochemical factors in tumor-derived fluid to lymph nodes has been shown to suppress the ability of these nodes to mount effective immune responses. This is one of many mechanisms that cancer uses to evade the immune system during tumor progression and metastasis.

Given the role of the lymphatic vasculature in promoting metastasis and suppressing the immune response, inhibiting the formation of lymphatic vessels has been proposed as a new form of anti-cancer therapy. So far, pre-clinical mouse studies show that inhibiting the formation of new vasculature reduces the rate of metastasis. However, surprisingly, these studies also found that treatment reduced how well immunotherapies work. The investigators determined that just as lymphatic vessels provide an “escape route” for metastasizing tumor cells, they also provide an “entry route” for activated immune cells resulting from immunotherapy treatment. These findings highlight the complex and sometimes counterintuitive interactions that exist between tumors, the lymphatic vasculature, and the immune system. Moving forward, the degree of lymphatics around a tumor may not only be used as an indicator of metastasis risk, but also as a marker to predict how well a patient will respond to immunotherapy.

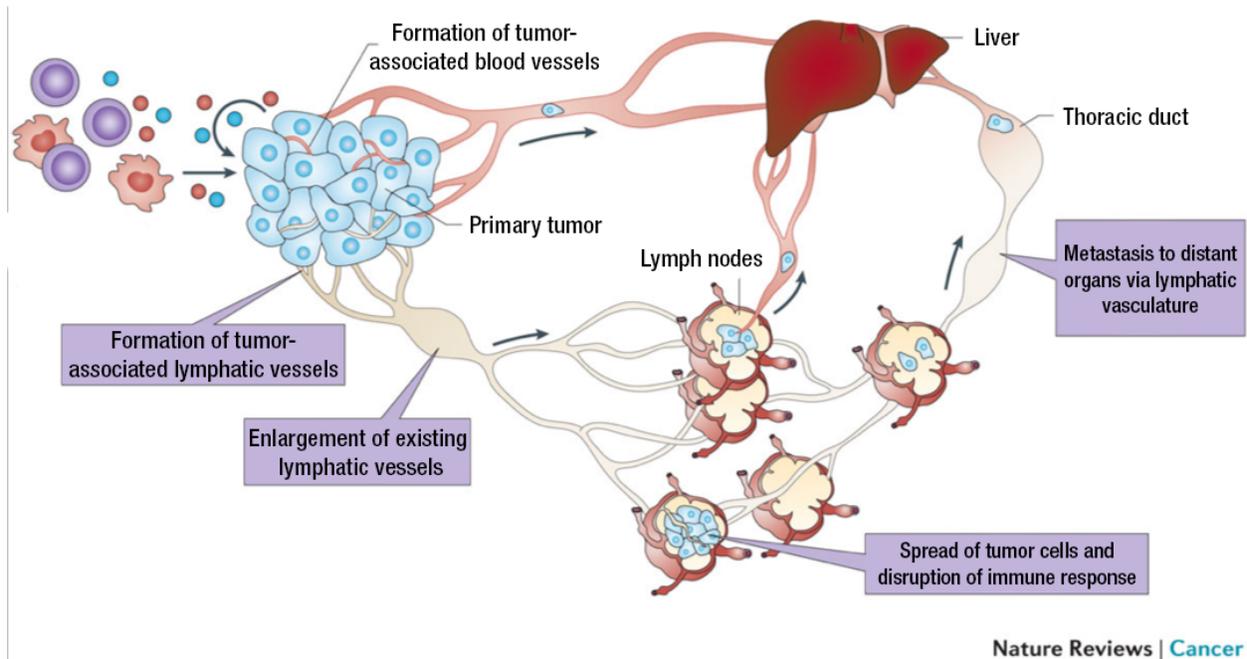


Figure 1. Tumor-lymphatic interactions. Adapted from Stacker et al. (2014).

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