Anti-VEGF Therapy Modulates Immune Cell Infiltration and Function in Multiple Breast Cancer Models

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Breast cancer is the most frequently diagnosed malignancy in women in North America. Advancements in standard treatment regimens have improved the overall outlook for breast cancer patients in recent years; however, 40,000 women a year succumb to this disease. Breast cancer is initiated when mammary epithelial cells acquire mutations in genes that regulate cell proliferation, survival, polarity, and differentiation. However, a growing body of evidence indicates that the stromal cell response to these malignant cells participates in tumorigenesis and is required for the tumor to advance past the hyperplastic stage.

Angiogenesis, or expansion of the existing vascular network, is required for the growth of solid tumors. For this reason, tumor angiogenesis is an attractive target for tumor therapy. Many of the current anti-angiogenic therapies target vascular endothelial growth factor-A (VEGF). VEGF binds to and activates two primary VEGF receptors, VEGFR1 and VEGFR2. VEGFR2 is the primary angiogenic receptor, while the function of VEGFR1 is less defined. It is important to note that the VEGFRs are expressed on endothelial cells, tumor cells and on many host immune cells. Therefore, to better understand the biology of anti-VEGF therapy it is important to consider the effects of VEGF on all VEGFR-positive cells in the tumor microenvironment.

In the present study, immune cell infiltration and function were analyzed following anti-VEGF therapy. Inhibition of VEGF:VEGFR2 signaling with r84 or mouse-chimeric (mcr84) decreases tumor-associated myeloid-derived suppressor cells and increases mature dendritic cells in multiple models of breast cancer. In contrast to other immunosuppressive cell types, an increase in anti-inflammatory macrophage infiltration was observed following treatment with mcr84, corresponding to an increase in the cytokine pleiotrophin (PTN). Once expressed, PTN stimulates the phosphorylation of anaplastic lymphoma kinase on tumor associated macrophages. These macrophages promote anti-inflammation, angiogenesis, immune tolerance, and metastasis. Importantly, these phenomena can be inhibited using the receptor tyrosine kinase inhibitor crizotinib, Furthermore, the combination of mcr84 and crizotinib decreased metastatic burden in animals with already disseminated disease.

These findings suggest that mcr84 is a valid clinical candidate in breast cancer and its combination with crizotinib has the potential to reduce metastastic burden in patients with already disseminated disease.