



Binding VEGF-C/D- VEGFR-3 Signaling to Inhibit Tumor Lymphangiogenesis and Lymphatic Metastasis

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Abstract: The vascular endothelial growth factor-C/ vascular endothelial growth factor receptor-3 (VEGF-C/ VEGFR-3) signaling axis plays an important role in lymphangiogenesis. Lymphangiogenesis is the formation of lymphatic vessels from preexisting vessels. VEGFR-3 is a receptor that regulates lymphatic vessel development, where VEGF-C is the protein that acts on its VEGFR-3 receptor to promote lymphangiogenesis. Restriction of this signaling pathway using a soluble (non-membrane bound) decoy receptor of VEGFR-3 to trap and keep VEGF-C from binding to endogenous membrane bound VEGFR-3 can decrease tumor lymphangiogenesis and lymphatic metastasis. As VEGF-C is a key growth factor responsible for inducing lymphangiogenesis, a chimeric recombinant protein composed of VEGF-C binding domains of VEGFR-2 and VEGFR-3 was developed as a therapeutic agent that inhibits lymphangiogenesis.

Background: The process of new blood vessel formation and lymphatic vessels is the definition of angiogenesis and lymphangiogenesis respectively. Angiogenesis is a key trait for vasculature, development and growth of all types of tumors, along with vascular endothelial growth factor (VEGF) being its primary regulator in vessel formation. An important indication of tumor aggressiveness for most human malignancies are from the spread of tumor cells by lymphatic vessels to local lymph nodes. This constant manifestation, alongside the predictable genomic fidelity of endothelial cells and VEGF creates a straight and constant targeting of VEGF an important antitumor method. Lymphatic vessels comprised of groups of tumor cells often occur at the margin of malignant tumors; however, lymphatic vessels have been believed to be absent from tumors themselves. Numerous studies have established the significance of the lymphatic system as a path for tumor propagation and that metastasis is heightened by VEGF-C via an escalation in tumor lymphangiogenesis.

Appearance of VEGF-C arises in a range of human tumors such as most the common locations as the colon, eye, gastric, lung, thyroid, breast, and squamous cell cancers such as, neuroblastomas, mesotheliomas, melanomas and sarcomas. Amplified expression of its receptor VEGFR-3 has been noticed in lymphatic endothelial neighboring to cancer cells and in lymph nodes comprised of carcinoma metastases. Additionally, expression of VEGF-C mRNA has newly been revealed to link with the frequency of metastasis to lymph nodes in prostate, colorectal, breast, thyroid, lung and gastric cancers. Manifestation of VEGF-D or VEGF-C by tumor cells in transgenic or xenograft animal models of cancer steered to an intensification in the abundance of lymphatic vessels at the margin of and occasionally inside the chief tumor, endorsed spread of tumor cells to lymph nodes and, in some prototypes, enabled distant organ metastasis. As we can see, the growth over tumor and cancer cells is strongly enabled by the presence of VEGF-D and VEGF-C.

Results: A decoy VEGF-C receptor was produced and purified from Chinese hamster ovary (CHO) cells. The decoy receptor's affinity for VEGF-C was confirmed through enzyme-linked immunosorbent assay (ELISA) and surface plasmon resonance (SPR) assays. We showed that the decoy receptor reduced VEGFR-3 activation and decreased migration of lymphatic endothelial cells in vitro. We are in the process of establishing a mouse metastasis model using 4T1 murine breast cancer cell line to test the therapeutic potential of the decoy receptor.

References:

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