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Experimental Translational Research Using siRNA to Target Vascular Genesis in Inhibition of Mammary Cancer Metastasis

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According to the International Agency for Research on Cancer (IARC), an estimated 1,384,000 patients world-wide were diagnosed with breast cancer in 2008 and 458,000 women died of the disease [1]. Breast cancer mortality is largely due to metastasis; this is the biggest issue in cancer therapy. To delay disease progression and prolong patient life, metastasis must be conquered.

Cancer cells spread through the body by different mechanisms, such as direct invasion of surrounding tissue, dispersion of cells *via* the blood vascular system (*i.e.*, hematogenous metastasis), and/or dissemination by means of the lymphatic system (*i.e.*, lymphatic metastasis). Lymph node metastasis is one of the most important adverse prognostic factors in breast carcinoma [2]. An adequate blood supply is required to sustain the uncontrolled cell proliferation characteristic of malignant tumors, and tumorigenesis and metastasis have both been associated with angiogenesis [3]. Thus, members of the vascular endothelial growth factor (VEGF) family, which promote the formation of new blood and lymphatic vessels in tumor tissues and enable the spread of tumor cells [4], have come under particular scrutiny. Within the VEGF family, VEGF-A is also known to exert a crucial role in tumor angiogenesis [3], while both VEGF-C and VEGF-D have been reported to induce lymphangiogenesis *via* activation of the VEGF receptor-3 (VEGFR3) expressed on lymphatic endothelial cells [5,6]. In animal models, VEGF-C and VEGF-D have also been shown to enhance lymphangiogenesis and associated lymphatic metastasis [7-13], while clinical studies have demonstrated overexpression of either VEGF-C or VEGF-D associated with lymph node metastasis and poor prognosis in breast cancer patients [14-17].

Within the past several years, RNA interference has become the most widely used technology for gene silencing. A popular therapeutic concept involves knockdown of target mRNA expression by gene silencing using vectors expressing short interfering RNA (siRNA). In order to suppress mammary cancer metastasis by vascular spread, siRNA was used in several studies performed in our laboratory. Using a particular murine mammary cancer cell line producing a metastatic spectrum similar to that seen in human breast cancers, we demonstrated inhibitory effects on lymph node metastasis by siRNA expression vectors targeting *Vegf-c* [18,19] or *Vegf-a* [20] using *in vivo* gene electrotransfer in an immunocompetent mouse mammary cancer model. However, *Vegf-d* siRNA therapy did not prove effective in our mammary cancer model [19] (Note: analogous genes in the mouse are referenced in italics with the first letter only capitalized).

In clinical studies performed by Currie et al., [21] no association between VEGF-D and lymph node metastasis was found in human breast cancer [21], while another group of investigators linked high expression of VEGF-A and VEGF-C, but again not VEGF-D, with poor prognosis [22]. More recently, another clinical study demonstrated that only tumor-derived VEGF-C induced pre-metastatic sentinel node lymphangionenesis in primary breast cancer [23]. In addition, we recently reported that a new splicing variant, endogenous soluble vascular endothelial growth factor receptor-2 (es*Vegfr*-2) inhibits VEGF-C function [24] and metastasis in a mouse model of metastatic mammary cancer [20].

Even though gene therapy targeting vascular genesis using *Vegf-c* and *Vegf-a* silencing was able to inhibit mammary cancer metastasis in our animal model, there are many issues to be addressed in a human application, including the method of gene introduction, delivery of a gene to a specific target organ, patient safety and so on. Recently, the molecule Akt is garnering attention as the key downstream effector of phosphatidylinositol-3-kinase (PI3K). Akt activation (phosphorylation) induces oncogenic signaling for such functions as vascular genesis, cell proliferation, cell growth, migration, anti-apoptosis, *etc*. A new avenue in cancer therapeutics is development of drugs that induce Akt dephosphorylation as another possible way to inhibit metastasis. In the trend towards primary and adjunctive use of natural products, we found α-manogstin, an extract of the pericarp of the mangosteen-a fruit native to Southeast Asia-induces Akt dephosphorylation and inhibition of vascular genesis, and results in inhibition of metastasis in our mouse model of mammary cancer model [25,26]. These data support our conclusion that targeting vascular genesis (in particular, lymphangiogenesis) may have great clinical significance in the treatment of metastatic human breast cancer.

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