Prevention and Treatment of Lymphatic Metastasis by Antilymphangiogenic Therapy

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Cancer cells escape a tumor by two primary routes—blood vessels and lymphatic vessels—to establish distant metastases. Thus, it seems reasonable to hypothesize that blocking the growth of new blood vessels (angiogenesis) and lymphatic vessels (lymphangiogenesis) will inhibit hematogenic and lymphogenic metastases, respectively. An impressive array of preclinical studies has demonstrated prevention and suppression of hematogenic metastases by antiangiogenic and antivascular approaches. Whether antilymphangiogenic and antilymphatic approaches will yield similar results for lymphogenic metastases remains to be seen. Both vascular endothelial growth factor (VEGF)-C and VEGF-D induce angiogenesis (1,2) and lymphangiogenesis (1,3–5) in tumors and are associated with lymphogenic metastasis in a variety of human tumors (6). Last year Stacker et al. (1) presented the first direct evidence for the prevention of lymphatic metastasis from a tumor grown in the mammary fat pad by blocking VEGF-D. In this issue of the Journal, He et al. (7) report similar findings in subcutaneously grown tumors that lack VEGF-D by blocking VEGF-C. Although Stacker et al. (1) used a blocking antibody against VEGF-D, He et al. (7) used a receptor-antibody fusion protein (VEGFR-3-Ig fusion protein) that can trap both VEGF-C and VEGF-D. The receptor-antibody was generated in vivo by cancer cells engineered to secrete soluble VEGFR-3-Ig or by the liver infected by an adenovirus expressing VEGFR-3-Ig. In both studies, treatment was initiated within a day after tumor implantation, before the primary tumor became established, and lymph nodes were examined for metastatic lesions 4–6 weeks later. Blocking VEGF-C or VEGF-D suppressed lymphangiogenesis associated with the primary tumor and regional lymph node metastasis. These are exciting and timely findings that raise many important questions about the biology and potential treatment of lymphatic metastases.

First, how do VEGF-C and VEGF-D alter tumor biology to promote lymphatic metastasis? The current study used an ectopic (subcutaneous) model of lung cancer and found an association between lymphatic vessel density (measured as lymphatic vessel endothelial hyaluronan receptor [LYVE]-1-positive structures) and lymph node metastases in one of two tumor lines. Another recent study (4) used orthotopically grown tumors engineered to overexpress VEGF-C and found an increased diameter of functional lymphatic vessels in the tumor margin and a greater number of lymph node metastases compared with mock-transduced controls. Thus, by increasing the surface area of lymphatic vessels, VEGF-C and VEGF-D increase the opportunity for metastatic spread through lymphatic vessels. VEGF-C and VEGF-D may also serve as a survival factor for endothelial cells of newly formed or co-opted lymphatic vessels in a tumor (5). Furthermore, He et al. (7) show that trapping VEGF-C only inhibits lymphatic metastasis without affecting hematogenic lung metastasis. Some investigators have recently proposed that lung metastases from VEGF-C-overexpressing breast tumors could be secondary to lymph node metastases (8). This study does not support this hypothesis. The differential regulation of lymphogenic versus hematogenic metastases by VEGF-C and VEGF-D may be a function of the proteolytic processing of these molecules (5), which in turn may be governed by host–tumor interactions (6).

Second, what is the clinical evidence to support the use of lymphatic markers to predict lymphatic metastasis? Both VEGF-C and VEGF-D are associated with increased lymphatic metastasis in some human tumors (6). However, there is a lack of correlation between lymphatic metastasis and the density of a variety of lymphatic markers for a number of human malignancies (Table 1), including human lung cancer, which is the subject of this preclinical study by He et al. (7). Many animal studies including this one, show a positive association between the density of lymphatic markers and lymphatic metastasis (1,3,4,7,8). Is this discordance between preclinical and clinical findings a result of the limitations of the animal models used or of the nonspecificity of current lymphatic markers? Is it possible that the markers available at present are unable to distinguish between functional and nonfunctional lymphatic vessels (Fig. 1) (4), leading to these contradictory results? Lymphatic metastasis can occur in tumors that lack intratumor functional lymphatics, suggesting that functional lymphatics in the tumor margin are responsible for lymphatic dissemination (4). Therefore, microlymphangiography in patients coupled with lymphatic identification by molecular markers is needed to provide clearer insight into lymphatic metastasis in humans.

Third, how can antilymphangiogenic therapy be translated to the clinic? The work presented by He et al. (7), and that of Stacker et al. (1), clearly shows that lymphatic metastasis can be prevented by anti-VEGF-C and anti-VEGF-D therapy given before the establishment of the primary tumor. However, by the time most tumors are detected clinically, they are already established, and metastatic cells may have already spread to the nearby lymph nodes or distant organs. Therefore, preclinical studies that initiate treatment after the primary tumor is established and lymphatic spread has occurred are now needed to build the basis for clinical trials of antilymphangiogenic therapy. Moreover, additional molecular players other than VEGF-C and VEGF-D may be involved in determining the clinical end points. After all, metastasis is a multistep process (29) in which cancer
cells must detach from their neighbors, invade the surrounding extracellular matrix, enter the blood/lymphatic vessels, survive in the lumen, attach at a distant site, extravasate, migrate, proliferate, and recruit new vessels. It is likely that VEGF-C and VEGF-D are key players for some tumors and not for others. As the techniques for detection of various proteolytically processed forms of VEGF-C and VEGF-D become widely available, we may be able to preselect tumors that are VEGF-C or VEGF-D dependent and to design appropriate interventions. The future of cancer treatment may involve a combination of agents that block the different steps of metastasis and that are tailored to individual patients on the basis of their proteomic profile. The work by He et al. (7) is an important step in this direction.

**REFERENCES**


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