PERSPECTIVES: CANCER

Targeting Lymphatic Metastasis

Jeffrey E. Gershenwald and Isaiah J. Fidler

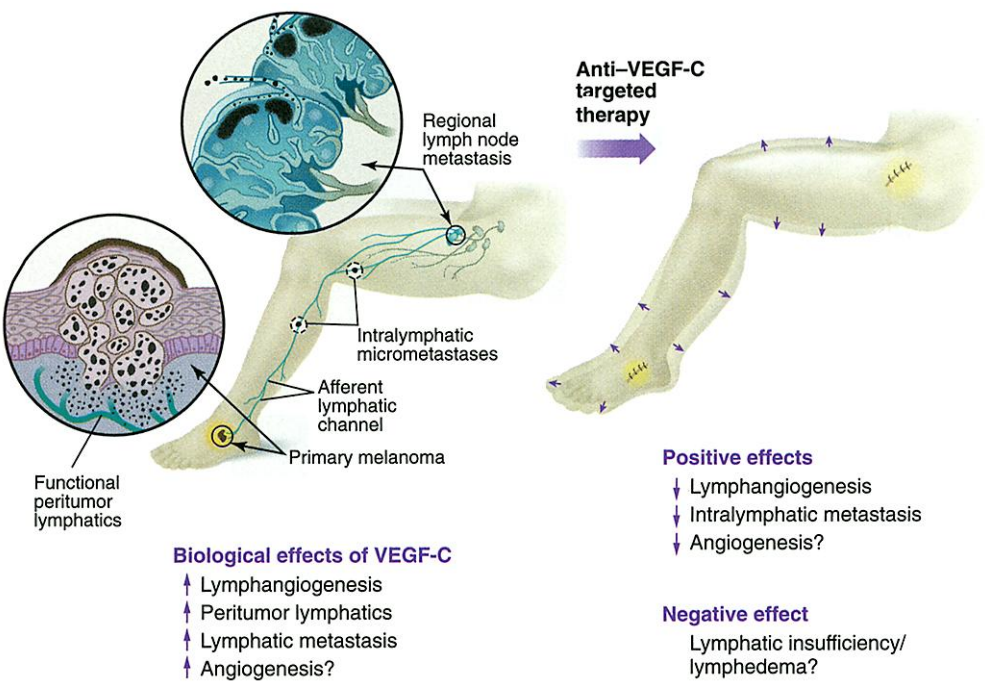
The major cause of death from cancer is dissemination of the primary tumor, leading to formation of metastases that are resistant to conventional chemotherapy. Several factors account for the failure to treat metastases. First, neoplasms are biologically heterogeneous and contain subpopulations of cells with different angiogenic, invasive, and metastatic properties. Second, the process of metastasis selects for a small subpopulation of cells that preexist within a parental neoplasm. Third, and perhaps the greatest obstacle for therapy, is that the outcome of metastasis depends on multiple interactions between metastatic cells and homeostatic mechanisms that the tumor cells usurp (*1*). A better understanding of the molecular events that lead to metastasis and of the complex interactions between metastatic cells and host factors is essential for the design of more effective cancer therapies. To this end, Padera *et al.* (*2*) discuss on page 1883 of this issue the contribution of the lymphatic system to tumor metastasis in the mouse.

To produce a metastasis, tumor cells must complete a series of sequential, interrelated steps. These include growth; neovascularization and lymphangiogenesis (development of new lymphatic vessels); invasion of the host stroma, blood vessels, and lymphatic system; survival in the circulation; arrest in small blood vessels; extravasation (migration out of blood vessels) into the parenchyma of organs; and continuous proliferation, which depends on establishing an adequate blood supply (angiogenesis) (*1*). Early clinical observations suggested that solid tumors (carcinomas) spread primarily via the lymphatic vessels and that mesenchymal (connective tissue) tumors spread mainly through the bloodstream. In truth, the lymphatic and vascular systems have numerous connections that allow disseminating tumor cells to pass rapidly from one system to the other (*3*).

Although the importance of the lymphatic system has been recognized for centuries (*4*), its involvement in the metastatic cascade has taken a back seat to the recent explosive interest surrounding the formation of tumor-associated blood vessels. Fortunately, recent work is beginning to elucidate the molecular mechanisms of lymphangiogenesis and lymphatic metastases. Among the unresolved controversies is the question of whether cancer cells in a primary tumor are transported to regional lymph nodes through intratumor lymphatic vessels (see the figure).

New techniques, such as intradermal administration of vital blue dye and radiolabeled colloid at the periphery of primary tumors, can identify the specific lymph nodes that receive afferent lymphatic drainage from the primary tumor site. These sentinel lymph nodes are the most likely to contain tumor metastases, which are often harbingers of future tumor development at sites distant from the lymph node (*5*). Padera and colleagues apply similar techniques to study lymphatic vessels associated with cutaneous melanomas and fibrosarcomas in mice (*2*). They used functional assays, high-resolution imaging, and immunohistochemical staining to search for lymphatic vessels within these tumors. The two types of tumor expressed different amounts of vascular endothelial growth factor–C (VEGF-C). This growth factor is one of two recently identified VEGF family members—the other is VEGF-D (*6*)—that stimulate formation of new lymphatic vessels. Padera and coworkers present compelling evidence that the center of tumors do not contain functional lymphatic vessels, and that it is lymphatic vessels at the periphery of tumors that are the conduit for metastasis.

Neoplasms are known to be heterogeneous entities containing zones with different properties that contribute to angiogenesis, invasion, and metastasis (*1*). Indeed, immunohistochemical and in situ hybridization analyses of human neoplasms, such as those of colon, stomach, prostate, and lung, reveal that expression by tumor cells of genes regulating angiogenesis and metastasis is more pronounced in the peripheral (proliferative) zones of tumors than in their centers, which are often necrotic (*1*). The new findings show that the location of functional lymphatic vessels follows the same pattern: They are located around human tumors rather than in them (*2*, *7*, *8*). In hu-



The VEGF-C balancing act. (Left) A primary melanoma on the foot is surrounded by lymphatic vessels that connect with the draining (sentinel) lymph nodes. In patients with melanoma metastasis, these sentinel lymph nodes are the most likely conduit for micro- or macro-metastases. Although primary melanomas and regional lymph nodes (containing metastases) can be surgically excised, additional lymphatic metastases may arise from tumor cells arrested within the lymphatic system. VEGF-C stimulates lymphangiogenesis and hence contributes to lymphatic metastasis. **(Right)** Targeted therapy that blocks VEGF-C activity may decrease lymphangiogenesis and hence intralymphatic metastasis, but may also lead to lymphatic insufficiency and possibly lymphedema.

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man cutaneous melanomas, for example, patent (noncollapsed) lymphatic vessels are common at the periphery but not in the center of the tumor (*9*).

The Padera *et al.* study reveals that the expression of VEGF-C in experimental mouse tumors correlates with the incidence of lymph node metastasis (but not pulmonary metastasis, which is dependent on dissemination through the blood). This suggests that VEGF-C may be a potential therapeutic target for treating lymphatic tumor metastases, but there is still much to learn. For instance, does VEGF-C contribute to lymph node metastasis by boosting the number of lymphatic vessels, by promoting hyperplasia or dilatation of peritumoral lymph vessels, or by stimulating angiogenesis (*10*)? Targeting VEGF-C to prevent lymphatic metastasis should be approached with caution because in many patients with visceral neoplasms, metastasis has already occurred by the time of diagnosis.

The homeostasis of body fluids requires an intact lymphatic system and hence fully active VEGF-C. Surgical excision of lymph nodes containing metastases can upset this dynamic equilibrium. The subsequent disruption of lymphatic drainage may result in the accumulation of fluid in the affected extremity, a complication known as lymphedema (see the figure). In a mouse model of congenital lymphedema—caused by an inactivating mutation in the VEGF C/D receptor–3 (VEGFR-3) (*11*)—the symptoms can be abrogated by treatment with VEGF-C gene therapy, which induces lymphangiogenesis. Similarly, inhibition of lymphangiogenesis in transgenic mice expressing soluble VEGFR-3 produces severe lymphedema (*12*). These studies suggest that systemic targeting of VEGF-C (and other lymphangiogenic molecules) could increase the risk of lymphedema in patients.

Any clinical trial involving VEGF-C–targeted therapy should include methods to identify the potential increased risk of undesirable side effects such as lymphedema. Similarly, any trial designed to assess the efficacy of VEGF-C treatment for reversing lymphedema in cancer patients must take into account the possibility that VEGF-C–induced lymphangiogenesis could enhance lymphatic metastasis. A better understanding of lymphangiogenesis is a prerequisite for developing effective targeted therapy for treating cancer patients.

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PERSPECTIVES: GEOLOGY

Flood Basalts—Bigger and Badder

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Flood volcanism is an episodic process whereby vast amounts of mass and energy are transferred from Earth's interior to its surface within a relatively short time. Such events have occurred about a dozen times during the last several hundred million years. There is increasing geochronological evidence that in each of these events, the magma was generated and erupted within 1 to 3 million years or so. The implied magma production rate, on the order of 10^6 km^3/year, is much higher than in Earth's main magma-producing environments at the boundaries between lithospheric plates.

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Increasingly, Earth scientists are trying to establish the causes and consequences of flood volcanism. The Siberian Traps have played a central role in shaping thought on the problem.

More than 20 years ago, Morgan (*1*) posited that this massive mantle belch might have been the first manifestation of a still-active magma source (hot spot) represented by a volcanic island, Jan Mayen, in the North Atlantic. A generalized theory soon linked flood basalts to hot spots created by buoyant, superheated mantle plumes, which were inferred to play a dynamic role in the rifting apart of continents (*2*). A leading alternative to these "plume impact" models holds that flood volcanism results when rifting of the lithosphere causes decompression of the mantle, allowing it to melt and rise buoyantly without requiring anomalous heating.

A volcanic province a million times the area of that shown here (in Kilauea's east rift) lies buried under Siberian sediments.

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The rifting that precedes decompression melting in the latter model cannot happen quickly for mechanical reasons: The lower lithosphere is ductile and does not break rapidly under extension. Pure decompression melting therefore seems less consistent with the observed rapidity of the eruptions than does the plume impact model. On the other hand, there is evidence that crustal extension predates volcanism in some cases, which suggests that at least some aspects of the decompression model are valid. But what initiates extension, if not the dynamic consequences of plume impact? One possibility is edge-driven convection (*3*), hypothesized to originate from discontinuities in lithospheric thickness and properties.

Besides establishing the brevity of flood volcanic events, geochronology has played a key role in defining the vast provinces wherein they occur. A recent example is the central Atlantic magmatic province (CAMP), whose 200-million-year-old remnants are now scattered across eastern North America, northeastern South America, western Africa, and western Europe. It had been hypothesized that CAMP's remnants formed a single contiguous province before the opening of the central Atlantic (*4*), but it was only through precise dating of the dispersed fragments that identification of an extensive flood basalt province was confirmed (*5*).

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