Attacking angiogenesis has recently moved to the front lines of the fight against cancer (1–3). People are not killed by their primary tumors, especially by tumors that have not developed their own blood supply. Recruitment of a blood supply by the primary tumor is especially devious, as it not only nourishes the primary tumor, but provides an escape route for those tumor cells that can invade the blood vessels and travel to distant sites. Primary breast tumors with a high content of blood vessels are at increased risk of metastasis (4), and in sections of such tumors it is often possible to see cells at the start of their metastatic journey invading the primary tumor-associated vasculature.

By focusing specifically on the adhesion molecule repertoire characteristic of endothelium during angiogenesis, Cheresh and his colleagues have now put forward the αvβ3 integrin extracellular matrix (ECM) receptor as a candidate for anti-angiogenic and therefore anti-tumor therapy (5). The αvβ3 integrin is a promiscuous ECM receptor, which recognizes several ligands found in subendothelial and stromal ECM, including fibronectin, vitronectin, thrombospondin, and fibrinogen. Brooks et al. (6) reported previously that endothelial cells express αvβ3 strongly in periods of angiogenesis, for example, during development and wound healing, and in response to angiogenic factors. However, this integrin is minimally expressed on mature quiescent endothelial cells or even on most other normal mature tissues.

In this issue of The Journal, Brooks et al. (5) first show that expression of αvβ3 is high in blood vessels associated with human breast carcinoma tissue and low in vessels present in normal and fibrocystic breast tissue. The authors then document that interference with αvβ3 function reduces both the formation of a tumor-associated vasculature, and tumor size in a human skin/SCID mouse tumor model. In these experiments, MCF-7PB cells, (an αvβ3-negative derivative of the MCF-7 human metastatic breast tumor cell line) were injected intradermally into full thickness human neonatal foreskin transplanted onto SCID mice (7). When evaluated after 5 wk, the MCF-7PB cells formed solid tumors that contained an extensive network of human blood vessels. However, systemic introduction of the LM609 anti-αvβ3 monoclonal antibody 2 wk after tumor cell injection, greatly reduced tumor size at 5 wk: many anti-αvβ3 treated animals had no palpable tumors at all. Those tumors which did form were significantly smaller than control antibody–treated tumors, contained many fewer blood vessels, and had smooth margins. In contrast the margins of the larger control tumors showed evidence of stromal invasion, and tumor cells were frequently detected within the tumor-associated vessel network. Thus, the breast tumors that did form in the anti-αvβ3–treated animals did not display the angiogenic or invasive phenotypes thought to favor subsequent metastasis.

Although no data are shown, the authors report a similar inhibition of angiogenesis by LM609 after introduction of melanoma cells into the human skin/SCID model. Thus, anti-αvβ3 therapy may be applicable to a variety of tumor types. Significantly, these studies, together with previous work by the authors (6, 8), showing that LM609 ligation of αvβ3 on endothelium not only stops vessel outgrowth, but induces unscheduled apoptosis of existing αvβ3-positive endothelial cells, suggest that therapies mimicking the αvβ3 antibody might be cytotoxic, as well as cytostatic for human tumor-associated vasculature.

These promising findings will now have to be expanded to more relevant animal models for breast cancer and other kinds of tumors. Furthermore, LM609, which is an αvβ3-specific mouse monoclonal antibody, will have to be modified before use as a therapeutic agent in humans. Generating humanized antibodies or peptide mimetics that retain the ability to block both αvβ3 function and induce vascular cell death are promising possibilities. In fact, recent studies using a humanized version of the 7E3 antibody that recognizes the integrin β3 subunit (and therefore the platelet integrin, αIIbβ3, as well as αVβ3), has been tested successfully in humans as a therapeutic against restenosis after balloon angioplasty (9). Importantly, the antibody treatment appeared to have no side effects, other than very minor bleeding due to its blockade of platelet αIIbβ3. Since LM609 is completely specific for αVβ3, even those side effects should not be present if a humanized version of this antibody is tested as a tumor antiangiogenic therapeutic.

Several other therapeutic agents that target tumor angiogenesis have been reported, including angiostatin (3), platelet factor-4, and analogs of fumagillin (reviewed in references 1 and 2), although their modes of action are not well understood in all cases. The addition of the αVβ3 integrin as a possible target for blocking tumor angiogenesis in humans is a welcome development indeed. An extensive base of knowledge has developed over the past decade that provides insights into how integrins contribute to regulating gene expression, cell growth, and survival, as well as cell attachment and migration. This body of work should promote increasingly rapid progress in producing effective therapeutic agents targeted to αvβ3, and perhaps to other integrins, not only in cancer but in other disease states as well.

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Editorial

Starve a Tumor: Therapeutic Advice for Breast Cancer?