The idea that angiogenesis plays a major role in tumor growth has rapidly been incorporated into the dogma of cancer control. Even while researchers were creating new antiangiogenic drug therapies, imaging researchers were seeking ways to visualize angiogenesis for better use of those drugs. Now there are numerous angiogenic inhibitors in clinical use; however, despite a large body of literature on dynamic computed tomography, magnetic resonance imaging, microbubble ultrasonography, single photon emission computed tomography, and PET, advanced imaging has so far had little influence. However, a new generation of imaging agents targeting the molecules involved with angiogenesis offers new promise.

Much attention has been focused on the $\alpha_v\beta_3$ integrin as a target for angiogenesis imaging. Integrin imaging agents were first tested in humans by Haubner et al (2). GE Medical Systems and Siemens recently introduced similar integrin imaging probes in humans (3). Now, Mittra et al, in this issue of Radiology (1), describe the first use in humans of FPPRGD2, an integrin imaging agent that they tested successfully in five volunteers. The results suggest that FPPRGD2 is a safe and effective agent with excellent imaging characteristics. The authors are to be congratulated on clearing this hurdle. Needless to say, ahead lays the long and arduous journey to clinical approval. But why has so much attention been paid to integrins?

**The Science**

Integrins are composed of heterodimeric proteins (4) expressed in various...
combinations of α and β chains on the cell membrane. Although the integrin family is large, αβ₃ integrin has been singled out because it is expressed on activated endothelial cells during angiogenesis and appears to literally “integrate” the cytoskeletal matrix to the extracellular matrix. Some tumor cells—particularly melanoma, glioma, and renal cell carcinoma—and inflammatory cells also express αβ₃ on their surface, where the role of the integrin is to promote cell migration.

The αβ₃ integrin has a binding pocket where the peptide sequence arginine-glycine-aspartic acid (known by the amino acid “code,” RGD) binds with high affinity and thus activates the integrin. Linear peptides such as RGD are short lived in plasma and must be stabilized or “cyclized” in such a way that they can then be labeled with ¹⁸F. The various imaging agents that have been introduced in humans for imaging αβ₃ integrins differ in how they approach this chemical synthesis, which in turn, influences how the agent is taken up and excreted.

In the molecular chain of events leading to angiogenesis, αβ₃ integrin formation is an end product. This is helpful because there are multiple mechanisms by which new vessels can be generated; inhibition of one pathway can lead to compensation by another. An imaging agent that targets the “final common pathway” of angiogenesis would be more widely useful than a highly specific agent that is relevant only under certain circumstances; integrins hold promise clinically, precisely because they seem to be part of this final common pathway.

**The Practice**

**Clinical use:** How would an imaging agent be used? The two most commonly suggested uses are the selection of patients for antiangiogenic therapy and the monitoring of patients receiving such therapies. This presumes that uptake of the imaging agent reflects αβ₃ integrin activity, that such activity is modulated by drug therapies, and that such modulation is relevant to patient outcomes. There is evidence in animals that at least the first two presumptions are true. Battle et al (5) recently demonstrated that use of the angiogenic inhibitor, sunitinib, led to rapid decreases in signal with use of the labeled integrin imaging agent, fluociclatide. If integrins are mandatory for angiogenesis, then they should be good indicators for drug efficacy. So far, the evidence is encouraging but confined to that based on findings in mice. The next big step is to use these agents in clinical trials of angiogenic inhibitors. This is complicated because many angiogenic inhibitors are now combined with chemotherapy agents. Additionally, because tumors and inflammatory cells express integrins on their surface, changes in integrin expression could have ambiguous meanings (6). Assessing angiogenesis will be challenging but ultimately critical if these agents are to be used.

**Future opportunities and challenges:** The current generation of integrin imaging agents comprises small molecules that have one fluorine atom per molecule. Since vessels represent about 5% of the volume of a tumor, angiogenesis imaging may be signal limited. However, nanoparticles “decorated” with multiple RGD motifs and containing one more PET emitter could provide higher signal and limit the biodistribution to the vessels (4). Unbound nanoparticles, which are slow to clear the plasma, must be distinguished from specific binding to the endothelium. In addition to integrins, there are numerous other targets of angiogenesis that are being exploited for imaging, including one or more of the vascular endothelial growth factors (VEGFs), VEGF receptors, matrix metalloproteinases (involved in tissue remodeling), hypoxia-related factors such as carbonic anhydrase IX, and hypoxia-inducible factor. Much work is needed to determine the value of these targets.

Of course, the “elephant in the room” is the investment in human and financial resources needed to bring such an agent to clinical fruition. The current economics of molecular imaging dictate that angiogenesis imaging be paired with therapies to be cost effective. Many modern targeted therapies are extremely expensive, and imaging looks very attractive as a means of sorting out who is likely to benefit and whether it is time to switch therapies. More judicious selection of the right “arrow” from the growing oncologic “quiver” is a noble goal for molecular imaging. The steps taken by Mittra et al in demonstrating transition to human testing place us closer to this goal.

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**References**