EDITORIAL

New insights in the modulation of tumor angiogenesis

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Angiogenesis is an important event in both physiological and pathological conditions. Under physiological conditions, angiogenesis is tightly controlled, however, increased production of angiogenic stimuli and/or reduced production of angiogenic inhibitors leads to abnormal neovascularization, such as occurs in cancer, chronic inflammatory disease, diabetic retinopathy, macular degeneration and cardiovascular disorders.

Starting with Judah Folkman's hypothesis that tumor growth is angiogenesis-dependent, this area of research now has a solid scientific foundation. Several clinical studies have shown a positive correlation between the number of vessels in many solid and hematologic tumors and metastasis formation and/or disease prognosis. During tumor angiogenesis, in addition to the formation of new blood vessels from pre-existing ones, it has been proposed that endothelial progenitor cells (EPCs), residing in the adult bone marrow, are recruited by tumor-secreted factors to sites of neovascularization where they are incorporated into growing vessels. However, the actual contribution of EPCs to tumor angiogenesis remains controversial.

Whereas conventional chemotherapy, radiotherapy, and immunotherapy are directed against tumor cells, antiangiogenic therapy is aimed at the vasculature of a tumor, in the hope of either causing tumor regression or keeping tumors in a state of dormancy. For these reasons, antiangiogenic tumor therapy has generated much interest in preclinical and clinical assessment. Nevertheless, even though numerous compounds inhibit angiogenesis, few of them have proved effective *in vivo*, and only a couple of agents have been able to induce tumor regression.

It has been estimated that over 10,000 cancer patients worldwide have received experimental forms of antiangiogenic therapy. However, the results from these clinical trials have not shown the dramatic antitumor effects that were expected following preclinical studies. This discrepancy is likely to be due, in part, to preclinical models where agents were administered to small, fast growing, highly angiogenic tumors, whereas their efficacy in clinical trials has almost exclusively been tested in late stage, well established cancers, which were well vascularized and less likely to be dependent upon new vessel formation. Additionally, preclinical and clinical data have shown the possibility that tumors may acquire resistance to antiangiogenic drugs or may escape antiangiogenic therapy *via* compensatory mechanisms. From the results obtained so far in clinical trials, it can be concluded that the future clinical success of angiogenesis inhibitors will be related to their use in combination with chemotherapy or radiotherapy.

Use of neutralizing antibodies and other inhibitors has demonstrated that blockade of vascular endothelial growth factor (VEGF) alone can substantially suppress tumor growth and angiogenesis in several experimental models. This has led to the development of the neutralizing anti-VEGF antibody bevacizumab, the first FDA-approved antiangiogenic molecule. Currently, most of the FDA-approved drugs, as well as those in phase III clinical trials, target a single proangiogenic protein. However, multiple angiogenic molecules may be produced by tumors, and tumors at different stages of development may depend on different angiogenic factors for their blood supply. Therefore, blocking a single angiogenic molecule might have little or no impact on tumor growth. Multi-targeted tyrosine kinase inhibitors, such as sorafenib and sunitinib, which block several tyrosine kinase receptor-mediated pathways, represent a novel approach to angiosuppression. Also, the discovery of the importance of inflammatory cells infiltrating the tumor stroma in promoting angiogenesis raises the possibility of therapeutically targeting these cells instead of the proangiogenic factors they secrete. The clinical challenges facing the development of antiangiogenesis treatments include finding biological markers that would help to identify subsets of patients more likely to respond to a given antiangiogenic therapy, determining optimal dosing, detecting early clinical benefit or emerging resistances, and deciding whether to change therapy in second-line treatments.

An ideal angiogenesis inhibitor should be orally bioavailable with acceptable short- and long-term toxicity, and have a clinically useful antitumor effect. Moreover, carefully constructed clinical trials with valid endpoints need to be undertaken. Finally, cancer genomics and proteomics are likely to identify novel, tumor-specific endothelial targets, and accelerate drug discovery. With the advent of specific and potent new agents, oncologists have a variety of direct and indirect antiangiogenic agents to choose from when designing therapy protocols.

This special issue of *European Cytokine Network* was prepared in order to highlight some aspects of the process of angiogenesis and the molecular mechanisms involved, and to discuss some agents that have been shown to inhibit angiogenesis. We express our gratitude to all our colleagues who have contributed to this issue.

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