APPLICATIONS OF ANGOGENESIS RESEARCH

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The study of the inhibition of tumor growth by tumor mass has led to the discovery of several angiogenesis inhibitors including angiotatin, endostatin, and antiangiogenic antithrombin. All three are potent and specific inhibitors of angiogenesis. Angiotatin is an internal fragment of plasminogen and endostatin is a C-terminal fragment of collagen XVIII. A change in conformation of antithrombin after cleavage of the molecules reactive C-terminal loop confers antiangiogenic activity. The discovery of angiotatin and antiangiogenic antithrombin provide further evidence that the clotting and fibrinolytic pathways are directly involved in the regulation of angiogenesis.

In vivo, systemic therapy with these agents induces a virtual complete blockade of angiogenesis and potently inhibits tumor growth. To date, all tumors tested in vivo have been potently inhibited and no evidence of resistance to therapy has been demonstrated even after prolonged administration. Prolonged therapy with high doses of angiotatin, endostatin, or antiangiogenic antithrombin leads to regression of established tumors and can induce tumor dormancy. The tumor dormancy is defined by a high rate of tumor cell proliferation balanced by apoptosis and a virtual complete blockade of angiogenesis. Further, the antiangiogenic and anti-tumor activities of human recombinant angiostatin and endostatin are strongly synergistic in vivo. No toxicity has been observed in any mice treated even after prolonged therapy at high dose with any of these agents. When these antiangiogenic agents are combined with cytotoxic agents or radiation therapy in the treatment of malignancies improved anti-tumor efficacy and diminished toxicity is observed.

To determine if angiogenesis suppression would induce drug resistance, mice with several types of cancer were treated with cycled endostatin therapy. Mice were treated for several months without any evidence of resistance to therapy or toxicity. After several cycles of therapy, tumor dormancy of lung and prostate carcinomas, fibrosarcomas, melanomas, and leukemia persisted indefinitely off therapy. Prolonged continuous therapy with high dose endostatin also induced self-sustained tumor dormancy. In a model of spontaneous dormancy of metastatic disease, mice implanted with melanoma were apparently cured by surgical resection of a primary tumor. However, histological analysis of the lungs of the mice revealed persistent microscopic metastases that remain dormant even with no adjuvant therapy. Tumor dormancy in these models can persist for the normal life span of the mice. However, the dormant tumors can be reactivated by repeated locoregional injury, transplantation of the tumor to another site on the same mouse, or by systemic treatment with transforming growth factor beta 1 and basic fibroblast growth factor. Further studies of these and other models may help to identify the mechanism of tumor dormancy and to determine why recurrence can be observed in cancer patients after a prolonged disease free survival and may allow for the design of better therapeutic strategies.

Based upon these and other studies, the endothelial cell can now be considered as one gatekeeper capable of regulating tumor growth. Endostatin and angiotatin are both currently in Phase I clinical trials in cancer patients and antiangiogenic antithrombin is in preclinical development.