

ANGIOSTATIN and ENDOSTATIN SCIENTIFIC ABSTRACTS

The following abstracts indicate that ANGIOSTATIN or ENDOSTATIN are effective against mouse, hamster, bovine and human cancer cells:

Haematologica 1999 Jul;84(7):643-50

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Therapeutic potentials of angiostatin in the treatment of cancer.

The discovery of specific endothelial inhibitors such as angiostatin and endostatin not only increases our understanding of the functions of these molecules in the regulation of physiological and pathological angiogenesis, but also provides an important therapeutic strategy for cancer treatment. Recent studies have demonstrated that the angiostatin protein significantly suppresses the growth of a variety of tumors in mice. However, the dosages of angiostatin protein used in these animal studies seem to be too high for clinical trials. In addition, repeated injections and long-term treatment with angiostatin are required to reach its maximal antitumor effect. In this article, I will discuss several alternative approaches that may become feasible to move angiostatin therapy from animal experiments into the clinic. In particular, I will emphasize the therapeutic potentials of angiostatin gene therapy and more potent angiogenesis inhibitors that are related to angiostatin.

Annu Rev Med, 1998, 49:, 407-24

Angiogenesis and tumor metastasis.

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Angiogenesis, the recruitment of new blood vessels, is an essential component of the metastatic pathway. These vessels provide the principal route by which tumor cells exit the primary tumor site and enter the circulation. For many tumors, the vascular density can provide a prognostic indicator of metastatic potential, with the highly vascular primary tumors having a higher incidence of metastasis than poorly vascular tumors. Tumor angiogenesis is regulated by the production of angiogenic stimulators including members of the fibroblast growth factor and vascular endothelial growth factor families. In addition, tumors may activate angiogenic inhibitors such as angiostatin and endostatin that can modulate angiogenesis both at the primary site and at downstream sites of metastasis. The potential use of these and other natural and synthetic angiogenic inhibitors as anticancer drugs is currently under intense investigation. Such agents may have reduced toxicity and be less likely to generate drug resistance than conventional cytotoxic drugs. Clinical trials are now underway to develop optimum treatment strategies for antiangiogenic agents.

Nat Med, 1996 Jun, 2:6, 689-92

Angiostatin induces and sustains dormancy of human primary tumors in mice.

O'Reilly MS; Holmgren L; Chen C; Folkman J Department of Surgery, Children's Hospital, Boston, Massachusetts, USA.

There is now considerable direct evidence that tumor growth is angiogenesis-dependent. The most compelling evidence is based on the discovery of angiostatin, an angiogenesis inhibitor that selectively instructs endothelium to become refractory to angiogenic stimuli. Angiostatin, which specifically inhibits endothelial proliferation, induced dormancy of metastases defined by a balance of apoptosis and proliferation. We now show that systemic administration of human angiostatin potently inhibits the growth of three human and three murine primary carcinomas in mice. An almost complete inhibition of tumor growth was observed without detectable toxicity or resistance. The human carcinomas regressed to microscopic dormant foci in which tumor cell proliferation was balanced by apoptosis in the presence of blocked angiogenesis. This regression of primary tumors without toxicity has not been previously described. This is also the first demonstration of dormancy therapy, a novel anticancer strategy in which malignant tumors are regressed by prolonged blockade of angiogenesis.

Nat Biotechnol 1999 Apr;17(4):343-8

Systemic inhibition of tumor growth and tumor metastases by intramuscular administration of the endostatin gene.

Blezinger P, Wang J, Gondo M, Quezada A, Mehrens D, French M, Singhal A, Sullivan S, Rolland A, Ralston R, Min W GeneMedicine, Inc.,
The Woodlands, TX 77381-4248, USA.

Tumors require ongoing angiogenesis to support their growth. Inhibition of angiogenesis by production of angiostatic factors should be a viable approach for cancer gene therapy. Endostatin, a potent angiostatic factor, was expressed in mouse muscle and secreted into the bloodstream for up to 2 weeks after a single intramuscular administration of the endostatin gene. The biological activity of the expressed endostatin was demonstrated by its ability to inhibit systemic angiogenesis. Moreover, the sustained production of endostatin by intramuscular gene therapy inhibited both the growth of primary tumors and the development of metastatic lesions. These results demonstrate the potential utility of intramuscular delivery of an antiangiogenic gene for treatment of disseminated cancers.

Cell, 1997 Jan, 88:2, 277-85

Endostatin: an endogenous inhibitor of angiogenesis and tumor growth.

O'Reilly MS; Boehm T; Shing Y; Fukai N; Vasios G; Lane WS; Flynn E; Birkhead JR; Olsen BR; Folkman J
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We previously identified the angiogenesis inhibitor angiostatin. Using a similar strategy, we have identified endostatin, an angiogenesis inhibitor produced by hemangioendothelioma. Endostatin is a 20 kDa C-terminal fragment of collagen XVIII. Endostatin specifically inhibits endothelial proliferation and potently inhibits angiogenesis and tumor growth. By a novel method of sustained release, *E. coli*-derived endostatin was administered as a nonrefolded suspension. Primary tumors were regressed to dormant microscopic lesions. Immunohistochemistry revealed blocked angiogenesis accompanied by high proliferation balanced by apoptosis in tumor cells. There was no toxicity. Together with angiostatin data, these findings validate a strategy for identifying endogenous angiogenesis inhibitors, suggest a theme of fragments of proteins as angiogenesis inhibitors, and demonstrate dormancy therapy.

J Clin Invest, 1998 Mar, 101:5, 1055-63

Expression of angiostatin cDNA in a murine fibrosarcoma suppresses primary tumor growth and produces long-term dormancy of metastases.

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Tumor growth and metastasis are angiogenesis dependent. Previously, we reported that angiostatin, a potent angiogenesis inhibitor, produced by a primary Lewis lung carcinoma suppressed its growth of lung metastases (O'Reilly, M.S., L. Holmgren, Y. Shing, C. Chen, R.A. Rosenthal, M. Moses, W.S. Lane, Y. Cao, E.H. Sage, and J. Folkman. 1994. *Cell*. 79:315-328). Now we show that a shift of balance of tumor angiogenesis by gene transfer of a cDNA coding for mouse angiostatin into murine T241 fibrosarcoma cells suppresses primary and metastatic tumor growth in vivo. Implantation of stable clones expressing mouse angiostatin in C57Bl6/J mice inhibits primary tumor growth by an average of 77%. After removal of primary tumors, the pulmonary micrometastases in approximately 70% of mice remain in a microscopic dormant and avascular state for the duration of the experiments, e.g., 2-5 mo. The tumor cells in the dormant micrometastases exhibit a high rate of apoptosis balanced by a high proliferation rate. Our study, to our knowledge, for the first time shows the diminished growth of lung metastases after removal of the primary tumor, suggesting that metastases are self-inhibitory by halting angiogenesis. Our data may also provide a novel approach for cancer therapy by antiangiogenic gene therapy with a specific angiogenesis inhibitor.

Cancer Res 1999 Jul 15;59(14):3308-12

Liposomes complexed to plasmids encoding angiostatin and endostatin inhibit breast cancer in nude mice.

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Gene therapy transfer of angiostatin and endostatin represents an alternative method of delivering angiogenic

polypeptide inhibitors. We examined whether liposomes complexed to plasmids encoding angiostatin or endostatin inhibited angiogenesis and the growth of MDA-MB-435 tumors implanted in the mammary fat pads of nude mice. We determined that plasmids expressing angiostatin (PCI-Angio) or endostatin (PCI-Endo) effectively reduced angiogenesis using an in vivo Matrigel assay. We then investigated the efficacy of these plasmids in reducing the size of tumors implanted in the mammary fat pad of nude mice. Both PCI-Angio and PCI-Endo significantly reduced tumor size when injected intratumorally ($P < 0.05$). Compared to the untreated control group, the mice treated with PCI-Angio and PCI-Endo exhibited a reduction in tumor size of 36% and 49%, respectively. In addition, we found that i.v. injections of liposomes complexed to PCI-Endo reduced tumor growth in the nude mice by nearly 40% when compared to either empty vector (PCI) or untreated controls ($P < 0.05$). These findings provide a basis for the further development of nonviral delivery of antiangiogenic genes.

Cancer Res, 1997 Dec, 57:23, 5277-80

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