REGULATION OF BLOOD VESSEL GROWTH IN TUMORS AND WOUNDS

H. Brem[1], G. Tamavokopulis[1], D. Tsakayannis[1], I. Gresser[2], A. Budson[1], and J. Folkman[1]

[1]The Ohio State University Hospital, Dept. of Surgery, Children's Hospital and Harvard Med. School, Columbus, Ohio, USA
[2]Groupe de Laboratories de l' Institut de Recherches Scientififiques sur le Cancer, Villejuif, France

We previously reported the identification of a novel fungal-derived angiogenesis inhibitor, AGM-1470, a member of a family of: "angioinhibins" (Nature 348:555, 1990). We now show that AGM-1470 inhibits tumor growth of more than 15 animal tumors as well as human tumors in athymic mice, suppresses metastasis, does not induce drug resistance and has very low toxicity with long-term administration. Alpha/beta interferon (murine), also an angiogenesis inhibitor, potentiates the anti-tumor effects of AGM-1470. These experimental findings and its implications in wound healing and tumors will be discussed. Examples are as follows:

Inhibition of primary tumor: Mean tumor volume of mice with Lewis lung tumors was, treated/control (T/C)=0.35, with untreated tumors having a mean weight of 5.7±0.5 grams. Lewis lung tumors were treated with AGM-1470 and/or murine alpha/beta interferon 200,000 units. This combination resulted in an additive antitumor (TC/0.2) and antimetastatic activity.

Resistance studies: *In vivo*: 10 consecutive tumor passages in mice that were treated with AGM-1470 resulted in 57-72% reduction in tumor volume. Pretreatment of mice for 100 days before tumor implantation did not effect the subsequent T/C. *In vitro*: The dose to obtain half maximal inhibition (50 pg/ml) and the time to confluence (8 days), did not change after 8 consecutive serial passages of capillary endothelial cells with AGM-1470.

Wound healing: Wound healing is angiogenesis dependent. After linear wounds were made (n=160), AGM-1470 given on post wound days 0-10 (every other day) resulted in tensile strengths of: 2.47±0.25 and 7.73±1.4 lbs compared to saline controls of 4.72±0.66 and 13.3±0.77 lbs assayed on days 7 (P=0.014) and 12 post incision, respectively (P=0.017). In contrast, treatment with AGM-1470 for 20 days prior to wounding did not significantly effect wound healing.

Time-dependent expression of bFGF during wound healing: Basic fibroblast growht factor (bFGF) is a ubiquitous, mitogenic and potent angiogenic molecule. An increase in endogenous bFGF occurred during the healing of full thickness murine wounds (n=204). The peak level of bFGF in the wound as measured by ELISA or heparin affinity chromatography occurs between days 10-14 post wounding. AGM-1470 decreased the concentration of bFGF in the day 10 wounds by 55±12%.

Copyright © 1994. Springer. All rights reserved.

Angiogenesis : Molecular Biology, Clinical Aspects, edited by Michael E. Maragoudakis, et al., Springer, 1994. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/nyulibrary-ebooks/detail.action?docID=3085528.
Created from nyulibrary-ebooks on 2024-05-22 13:01:56.

Conclusions: (1) The biological properties of AGM-1470 provide a paradigm of the potential therapeutic efficacy of antiangiogenic therapy for solid tumors and their metastases; (2) Such therapy is likely to be long-term, of low toxicity, equally effective in males or females, independent of immune status, and potentiated when two angiogenesis inhibitors are administered together; (3) Tumor resistance did not develop *in vivo* after prolonged antiangiogenic therapy with AGM-1470; (4) The angiogenesis inhibitor, AGM-1470, suppresses wound healing in a time dependent manner; (5) AGM-1470 does not effect wound healing if given before, or five days after the wound is made; (6) Endogenous bFGF concentrations peak in the wound during days 10-14. This elevation appears to follow the influx of endothelial cells into the wound. These results suggest that invading vascular endothelium may contribute additional bFGF to the wound over and above the level of bFGF that is present in the wound before neovascularization; (7) AGM-1470 decreased the peak bFGF concentration in the wound suggesting that neovascularization significantly contributes to the amount of endogenous bFGF in the wound.

Copyright © 1994. Springer. All rights reserved.

Angiogenesis : Molecular Biology, Clinical Aspects, edited by Michael E. Maragoudakis, et al., Springer, 1994. ProQuest Ebook Central, http://ebookcentral.proquest.com/lib/nyulibrary-ebooks/detail.action?docID=3085528.
Created from nyulibrary-ebooks on 2024-05-22 13:01:56.