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Liposome-delivered angiostatin inhibits breast cancer growth and metastasis

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Keywords

Angiostatin, breast cancer, liposome, transgenic

Introduction

Angiogenesis, the growth of new blood vessels, is required for tumours to grow and metastasise. Control of angiogenesis is complex. It is believed that human tumours have the ability early in their natural history to produce factors which 'switch' on angiogenesis. This opens up the possibility of inhibiting tumour growth through inhibiting angiogenesis. One such anti-angiogenic factor is angiostatin, which has already been shown to have significant antitumour growth effect in laboratory animals. How to deliver angiostatin to the tumour, when to initiate therapy and which administration schedule is most effective remain unknown.

Aims

To assess the ability of liposome-delivered angiostatin to impact upon tumour growth and metastases in a transgenic mouse model of breast cancer.

Comments

This very interesting and important study examines the impact of liposomally-delivered angiostatin in the murine transgenic model of breast cancer. This model has the advantage of being relatively similar to its human counterpart, with tumours developing slowly in an immunocompetent host. The authors found that angiostatin could be easily delivered to the tumour and, more importantly, that the angiostatin affected tumours at sites distant to the injection. In addition, no pulmonary metastases developed in treated mice, a finding one would expect to see if angiostatin does in fact prevent tumour angiogenesis. Interestingly, when treatment commenced at a later time point, when tumours were already clinically detectable, the growth retardation effect of angiostatin was less. This suggests that there may be an optimal time point for the initiation of anti-angiogenic therapies, and this might be when tumour burden

is minimal (ie in the adjuvant setting, after surgery). Obviously a lot more work is required but anti-angiogenesis is certainly an exciting antitumour strategy.

Methods

Angiostatin cDNA was added to a liposomal transfection agent for injection into MMTV (mouse mammary tumour virus)-neu transgenic mice. There were two sets of experiments, each performed on 2-month-old mice. In the first, the angiostatin was injected into both breasts every 15 days until the mice were 5 months old 'bilateral mice'. In the second, only the right breast was injected 'unilateral mice'. A separate experiment began treatment from age 2.5 months, when tumours are already clinically detectable. At the age of 5 months, mice were sacrificed, and tumours were analysed. The analysis consisted of tumour weight, histopathological examination, tumour vessel density (measured using standard antibody technique with the rat antimouse CD31 antibody), and assessment of angiostatin DNA and RNA. Eight control mice were injected with empty liposomes, and a further five mice were injected with liposomes carrying a grossly deranged endostatin cDNA.

Results

Angiostatin expression was detected in injected tumours at the time of sacrifice, but not in the non-injected tumours of control mice or in the non-injected tumours in unilateral mice. Tumour weight differed significantly between the treated and the control mice. The tumour weights were far less in treated mice whether or not they were directly injected, which implies that the angiostatin exerted a systemic effect, not just a local one. Comparison of tumour weights between the two angiostatin-treated groups showed no significant difference. Tumours in mice treated with angiostatin from age 2.5 months weighed less than those of control mice, but more than those of the mice treated with angiostatin from age 2 months. This suggests that a delay in treatment may affect the outcome. Tumours from mice treated from age 2 months showed a significant decrease in vessel density, and there were no pulmonary metastases detected, whereas six of the eight control mice demonstrated pulmonary metastases. Comparison of tumour weight, with weights recorded in previous experiments with other gene-therapy approaches, demonstrated that angiostatin appears to have the greatest impact in slowing tumour growth.

Discussion

Liposome-delivered angiostatin has a significant impact upon primary tumour growth and also inhibits the appearance of pulmonary metastases in the transgenic model of breast cancer. It appears to work in a systemic fashion, and there is the suggestion that optimal anti-tumour effect occurs with early administration.

Additional information

Previous work has shown the anti-angiogenic effects of angiostatin.

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