TUMORIGENESIS

Stress and cancer

DOI:
10.1038/nrc1986

URLs

β_2-adrenergic receptor
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=154

ovarian cancer
http://www.cancer.gov/cancertopics/types/ovarian

VEGF
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=7422

Chronic stress has been suggested to increase tumour growth, but the mechanism has remained unclear. Anil Sood and colleagues have now shown that β-adrenergic signalling mediates increased angiogenesis and tumour growth in a mouse model.

The authors used nude mice that had been inoculated with human ovarian carcinoma cells, and the mice were stressed by being immobilized for several hours a day. Stressed mice had a three–fourfold increase in the number of tumour nodules and tumour weight; they also had more metastases. These results were replicated using other tumour cell lines and another method of stressing the mice.

The stressed mice had larger adrenal glands and greater sympathetic nervous system activity than the controls, so the authors investigated whether the effect of stress on tumour growth is mediated by β-adrenergic receptors. An agonist for β_2-adrenergic receptor and a general β-adrenergic receptor agonist increased tumour nodule number and tumour weight in a similar manner to chronic stress. Moreover, a β-adrenergic antagonist could reverse these effects and the effects of chronic stress itself. By contrast, β_1-adrenergic receptor agonists had no effect.

To confirm that the effect of stress is mediated by β_2-adrenergic receptors, the authors screened other ovarian cancer cell lines to find ones that were negative for the gene that encodes this receptor. They identified two such lines and found that stress had no significant effect on nodule number or tumour size. They also confirmed that it was the β_2-adrenergic receptors expressed on the human tumour cells rather than normal mouse cells that were important, as the effect could be reversed with RNA interference that was specific for the human mRNA, and therefore did not affect the host cells.

As stress and β_2-adrenergic receptor agonists led to increased angiogenesis, the authors looked at the expression of vascular endothelial growth factor (VEGF) and found that it was upregulated. By using activators and inhibitors of adenylyl cyclase and protein kinase A (PKA), they showed that β_2-adrenergic receptors increase VEGF expression through the cAMP–PKA pathway.

These results show one way in which stress increases tumour growth, though they do not rule out other mechanisms being involved in different circumstances. They also suggest that targeting angiogenesis by blocking β_2-adrenergic receptor signalling could be useful in ovarian cancer therapy.

Patrick Goymer

ORIGINAL RESEARCH PAPER Thaker, P. H. *et al.* Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nature Med.* 23 July 2006 (doi:10.1038/nm1447)

© 2006 Nature Publishing Group