CANCER

Stress can fuel tumour angiogenesis

The possible effects of stress on cancer are a matter of hot debate. While most studies investigating this connection focus on the dampening effects of stress on the immune response to arising tumours, a more direct link has now been uncovered. Reporting in *Nature Medicine*, Thaker *et al.* demonstrate that stress hormones can accelerate cancer progression by affecting tumour angiogenesis, thereby enhancing tumour growth and metastasis, in mouse models of ovarian cancer.

To investigate the stress–cancer link, immune-deficient 'nude' mice were inoculated into the peritoneal cavity with human ovarian cancer cell lines after one week of experimental stress. This was induced using a physical restraint system, in which periodic immobility induces high levels of hypothalamic–pituitary–adrenal and sympathetic nervous system activity that is characteristic of chronic stress. Two weeks after tumour inoculation, there was a marked difference in tumour aggressiveness: stressed mice had two- to threefold more tumour nodules, with similar increases in tumour weight gain, compared with 'unstressed' controls. Furthermore, whereas in control mice tumours were confined to the peritoneal cavity, tumours had spread to the liver and spleen in 50% of the stressed mice. Similar experiments with a different ovarian cancer cell line and in an orthotopic breast cancer model showed that these stress effects were evident in a wide range of tumour cell lines.

At the molecular level, this effect was found to be conveyed by stress-induced tissue catecholamines activating β_2-adrenoreceptors on tumour cells, a receptor overexpressed in most ovarian cancer cell lines. The effect of stress could be mimicked with β_2-adrenoceptor agonists, and blocked with the beta-blocker propanolol. Natural β_2-adrenoceptor-deficient ovarian cancer cell line variants, and tumour cells in which the β_2-adrenoceptor was knocked down by small interfering RNA, were 'immune' to the stress effect, further confirming the central importance of this receptor. Downstream of the β_2-adrenoceptor, it was found that catecholaminergic stimulation induces expression of vascular endothelial growth factor (VEGF) via a cyclic AMP–protein kinase A-dependent pathway. The resulting elevated levels of VEGF led to increased tumour vascularization — and the ovarian cancer cells seem to exploit this pathway to boost their own blood supply.

Although the effects of stress on immunological, neurochemical and endocrinological functions are well known, this is the first report to demonstrate that the neuroendocrine stress response can also directly affect the growth and activity of malignant tissue via hormone receptors on tumour cells. If this mechanism is confirmed in the human setting, it could have exciting therapeutic implications for the management of ovarian cancer and possibly other types of cancer — especially as beta-blockers are safe and readily available. The authors also speculate that other neuroendocrine signalling pathways might modulate tumour cell biology under other circumstances, implying that interventions targeting neuroendocrine function at the level of the CNS could represent a new strategy to protect patients from the detrimental effect of stress on the progression of malignant disease.

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ORIGINAL RESEARCH PAPER Thaker, P. H. *et al.* Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nature Med.* **12**, 939–944 (2006).