IN THE NEWS

Weighty consequences

"Study hailed as convincing in tying fat to cancers", claimed the headline in *The New York Times* (24 April 2003), after a comprehensive long-term study by the American Cancer Society (ACS) concluded that excess body weight contributes to cancer deaths.

The study — published in the *New England Journal of Medicine* (24 April 2003) — estimates that 90,000 annual cancer deaths in the USA alone could be prevented if people maintained normal body weight. These results "…reflect the combined influence of body-mass index [BMI] both on the incidence of cancer and on survival…", according to the study's lead researcher Dr Eugenia Calle (*ACS News Room*, 13 May 2003), and the link "was the rule more than the exception". The higher the BMI — a measure of weight in relation to height — the greater the risk of cancer death, which, according to Dr Calle, "could account for 14% of all deaths from cancer in men and 20% of those in women" (*The Guardian*, 13 May 2003).

These statistics are worrying, given that obesity rates in Western countries are dramatically increasing. "What's clear is that large studies of this sort — and this is the biggest and best to date — show very clearly this is a major health problem…", said Dr Robert Mayer for the American Society of Clinical Oncology (*The Washington Times*, 24 May 2003). In light of these findings, Dr Calle is adamant that "…we need to make maintaining a healthy weight a national priority now" (*USA Today*, 23 May 2003).

Emma Croager

ANGIOGENESIS

Low pressure warning

Just as low air pressure indicates bad weather is approaching, low oxygen tension in tumour tissue is bad news for cancer patients, as it indicates poor prognosis and an increased risk of developing metastases. So, although anti-angiogenic compounds can inhibit growth of solid tumours by reducing blood-vessel formation, the hypoxia that this causes promotes tumour-cell invasiveness. But how is this possible? In the April issue of *Cancer Cell*, Pennacchietti and colleagues show that expression of the MET tyrosine kinase — the receptor for hepatocyte growth factor (HGF) encoded by the *MET* proto-oncogene — is induced by low oxygen tension, activating a programme of invasive growth.

Pennacchietti *et al.* found that *MET* mRNA expression increased in normal and tumour cell lines that were cultured under hypoxic conditions — 3% oxygen or 100 μM cobalt chloride — and this was followed by a similar increase in MET protein levels. Cobalt chloride is known to mimic hypoxia by stabilizing the hypoxia-inducible transcription factor HIF-1α. As multiple binding sites for HIF-1α are found within the *MET* promoter, the authors used luciferase reporter assays to show that hypoxia — and wild-type HIF-1α — activates transcription of *MET*. So, what effect does hypoxia have on *MET* expression *in vivo*? The authors identified hypoxic regions within tumour sections using HIF-1α-specific antibodies and found high levels of MET within these poorly vascularized areas. By contrast, regions expressing low levels of MET were highly vascularized and negative for HIF-1α expression.

It is clear that hypoxia induces *MET* expression *in vitro* and *in vivo*, but what is the biological significance of this? Immunoprecipitation assays using anti-MET and anti-phosphotyrosine antibodies showed that although hypoxia had little effect on the phosphorylation of MET, it considerably increased MET activation in response to HGF signalling. Similarly, activation of GAB1 — a key signal transducer of MET — was also increased under hypoxic conditions, indicating that hypoxia amplifies the HGF signalling cascade. Activation of this pathway in cancer is known to give rise to metastases and the authors used a collagen invasion assay to show that although hypoxia markedly amplifies the invasive effects of HGF, hypoxia alone was also sufficient to induce invasion.

So, there are two possible explanations — either hypoxia acts via a mechanism unrelated to MET, or hypoxia-induced MET overexpression sensitizes cells to extremely low levels of HGF present in the culture medium. Under normoxic conditions, overexpression of wild-type MET in cell lines closely reproduced the invasive effect of hypoxia in collagen invasion assays, whereas expression of a kinase-inactive form of MET completely prevented this, showing that activation of MET was, in fact, necessary for cellular invasion to occur. These results were confirmed using RNA interference experiments, in which inhibition of MET expression blocked cellular responses to HGF in normoxic and hypoxic conditions. Treating tumours with anti-angiogenic drugs might kill tumours, but at the same time cancer cells are being encouraged to escape. Combination therapy with MET inhibitors might help to overcome this problem.

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References and links

ORIGINAL RESEARCH PAPER Pennacchietti, S. *et al*. Hypoxia promotes invasive growth by transcriptional activation of the *met* protooncogene. *Cancer Cell* **3**, 347–361 (2003)

WEB SITE

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