New hope for matrix metalloproteinase inhibitors in cancer therapy ▼

The recent article by Foda and Zucker in *Drug Discovery Today*[1] is a timely reminder of the complexities of the matrix metalloproteinase (MMP) field. The authors make the point that MMPs could just as readily be termed 'angiogenesis proteinases' or 'growth factor proteinases'. MMPs are certainly important mediators of extracellular matrix degradation, but it is also now apparent that MMPs and related proteinases act on growth factors and their receptors. The article also highlights some of the subtleties of the invasive process. The historical model of cancer cells aggressively destroying surrounding tissue is not only over-simplistic, but it is impractical. A cancer is as dependent as any tissue on the existence of a functional architecture. It is perhaps more productive to think of the cancer as reorganizing the local tissue environment to suit its own needs. This is done in the face of the body's own response to the cancer. Untangling the myriad of interactions and responses continues to provide scientists with new avenues of research.

The breakdown of the extracellular matrix by proteinases will release growth factors as well as matrix fragments with cytokine properties. Foda and Zucker note that MMPs might be responsible for the production of anti-angiogenic protein fragments such as angiostatin. This raises the troubling possibility that in some situations, treatment of cancer with MMP inhibitors could actually promote tumour growth. This was certainly the concern when a large randomized trial of the MMP inhibitor BAY129566 in patients with small-cell lung cancer (SCLC) was prematurely closed because of interim data, which revealed a significant increase in both disease progression and mortality in the treated group when compared with placebo[2].

Fortunately, this result does not appear to be a general feature of the treatment of SCLC with MMP inhibitors. Recent results from two large randomized trials (334 and 555 patients) of the MMP inhibitor, marimastat, in patients with this cancer revealed no benefit from MMP inhibitor treatment but also no adverse effect on disease progression or survival [British Biotech (2001) Reports of clinical studies with matrix metalloproteinase inhibitors in cancer. *Press Release* 13 February]. More encouragingly, a randomized trial of marimastat in patients with gastric cancer has provided the first demonstration of clinical benefit for this class of compound. A significant increase in progression-free survival was demonstrated in the patient group as a whole, and a significant increase in overall survival was noted for patients with locally advanced disease and for patients who had previously benefited from chemotherapy[3].

These first encouraging results were much needed in a field where several drug development programmes have been discontinued because of a lack of efficacy or tolerability problems. As we begin to understand more of the complex interactions between structural matrix proteins, cell signalling proteins and proteinases in the process of cancer invasion and spread, we should expect to be able to develop more potent and effective anti-invasive drugs, with improved side effect profiles.

References

1 Foda, H.D. and Zucker, S. (2001) Matrix metalloproteinases in cancer invasion, metastasis and angiogenesis. *Drug Discov. Today* 6, 478–482

2 Hughes, S. (1999) Bayer drug casts shadow over MMP inhibitors in cancer. *Scrip Daily News Alert*, 40301

3 Fielding, J.F. *et al.* (2000) A randomised, double-blind, placebo-controlled study of marimastat in patients with inoperable gastric adenocarcinoma. *Proc. Am. Soc. Clin. Oncol.* 19, 240a

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Are drug targets missed owing to lack of physical activity? – Reply ▲

Initial letter: Gurwitz, D. (2001) *Drug Discov. Today* 6, 342–343

Response from Henriette van Praag, Carrolee Barlow and Fred H. Gage

In his letter, Dr Gurwitz provides convincing evidence that animal housing conditions can regulate CNS function. In particular, a lack of exercise is suggested to alter production of proteins such as neurotrophins as well as result in impairments in cognitive function. As Dr Gurwitz suggests, confinement of laboratory animals without opportunity for exercise could result in unrealistic animal models for drug discovery research. Here is how we see the answers to Dr Gurwitz's outstanding questions:

How similar are mice and humans in their need for regular physical activity?

Both humans and rodents benefit from exercise. However, it should be noted that in humans as well as in rodents, there is variability in the need and motivation for physical activity. The basis for these individual differences in frequency and intensity of exercise could be genetic. For example, when housed with a running wheel, some strains of mice will run every night for several kilometers, whereas others will run much less or sometimes not at all. Apart from inter-strain differences, intra-strain variation is also found. For example, a recent study showed that the 129SvEv mouse strain will run between 24 and 4710 m per night[1].

To what extent is CNS gene expression modified in docile mice or rats compared with physically active laboratory rodents? Are changes in gene expression in active animals transient or long-lasting, and how do they affect the suitability of these animals to model human diseases?

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