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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As mentioned by Dr Gurwitz, there are extensive changes in expression of growth factors such as vasoactive intestinal peptide (VIP), galanin and brain-derived neurotrophic factor (BDNF) in the CNS associated with exercise. In addition, other studies have shown that levels of nerve growth factor (NGF), insulin derived growth factor 1 (IGF-1) and fibroblast growth factor (FGF) are elevated in response to running[2–4]. Physical activity can also change neurotransmitter levels in the brain (for a review, see Ref. 5). Exercise influences cholinergic parameters, affecting choline uptake in the hippocampus and the cortex, and enhances the activity of opioid systems. Furthermore, monoamines such as norepinephrine and serotonin are activated by physical activity.

Some of these changes, such as the increase in FGF mRNA, appear to be transient[3] whereas elevated BDNF gene expression can last for several weeks. More research pertaining to the time-course of exercise-induced changes in gene expression is needed. In particular, effects of exercise on molecules implicated in animal models of human disease should be monitored.

Could favorable CNS drug targets be missed by the routine use of inactive laboratory rodents? Will voluntary physical exercise allow laboratory rodents to be better animal models for human neurological and psychiatric diseases?

It is likely that drug targets are missed by the use of inactive rodents and that inclusion of an exercise paradigm would make rodents better models for human disease. Indeed, in a recent study, we researched adult hippocampal neurogenesis in a mouse model for the neurodegenerative disease ataxia telangiectasia (AT)[1]. We found that, although these mice have a higher rate of cell proliferation under baseline conditions, ultimately less neurons are formed. The deficient neurogenesis can be overcome in part by housing these mice with a running wheel (Fig. 1). Had this study been done under sedentary conditions alone, the effect of the loss of ataxia telangiectasia mutated (ATM) on the genesis of new neurons would have been obscured.

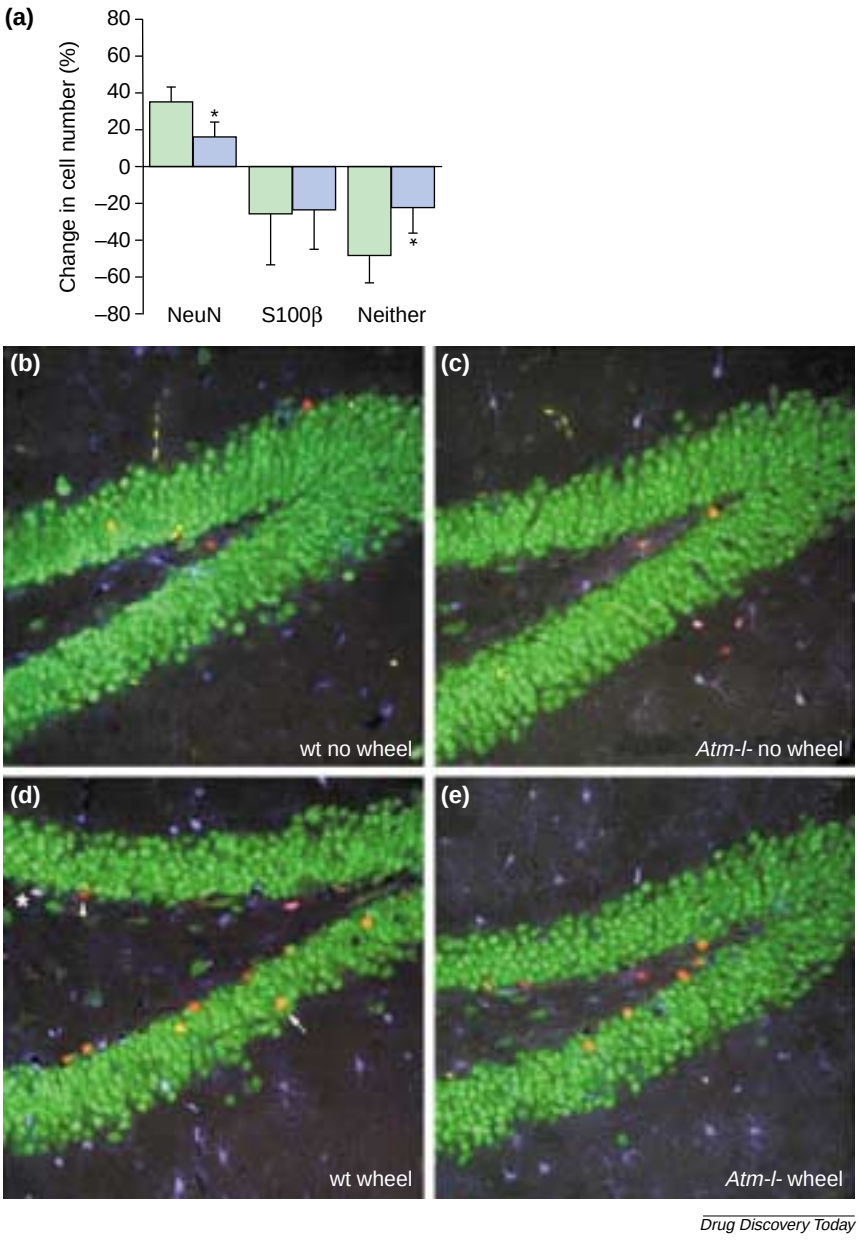

Figure 1. Effects of wheel running on neurogenesis in the adult mouse hippocampus (a brain region that is important for learning and memory). Ataxia telangiectasia (AT) mutant mice show a reduced increase in the number of neurons that differentiate and survive in response to running compared with wild-type (wt) mice. (a) The percent increase or decrease in cells labeled with a marker for dividing cells, or with bromodeoxyuridine (BrdU) that stains for neuronal (NeuN) or glial (S100β) markers, or were marker-negative (neither) in wild-type (green) and ATM knockout (blue) mice. Representative dentate gyrus of the hippocampus sections from (b) wild-type and (c) ATM knockout mice in the absence of running wheels and (d) wild-type and (e) ATM knockout mice with running wheels. Green staining represents neurons; blue staining represents glia; red staining indicates BrdU (arrowhead). Co-labeling of BrdU and neurons is orange (arrow) and co-labeling of glia and BrdU is pink (*) (*P <0.01)[1].

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Should running wheels be implemented in standard laboratory protocols for laboratory rodents in drug development research? What other measures could be applied to ensure that they are allowed the best levels of physical activity for serving as human disease models?

In general, addition of running wheels would be beneficial for drug studies and could lead to a broader interpretation of study results. Moreover, addition of running wheels or treadmills is straightforward, and the distance and frequency of running can be conveniently monitored. However, modeling of specific human diseases might require environmental conditions that do not necessarily include running wheels. For example, studies of motor impairments might preclude running. Thus, depending on the research question, the environmental conditions in which the animals are housed could be modified.

References

1 Allen, D.M. *et al.* (2001) Ataxia telangiectasia mutated is essential during adult neurogenesis. *Genes Dev.* 15, 554–566

2 Carro, E. *et al.* (2000) Circulating insulin-like growth factor I mediates effects of exercise on the brain. *J. Neurosci.* 20, 2926–2933

3 Gomez-Pinilla, F. *et al.* (1997) Physical exercise induces FGF-2 and its mRNA in the hippocampus. *Brain Res.* 764, 1–8

4 Neeper, S.A. *et al.* (1995) Exercise and brain neurotrophins. *Nature* 373, 109

5 van Praag, H. *et al.* (2000) Neural consequences of environmental enrichment. *Nat. Rev. Neurosci.* 1, 191–198

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