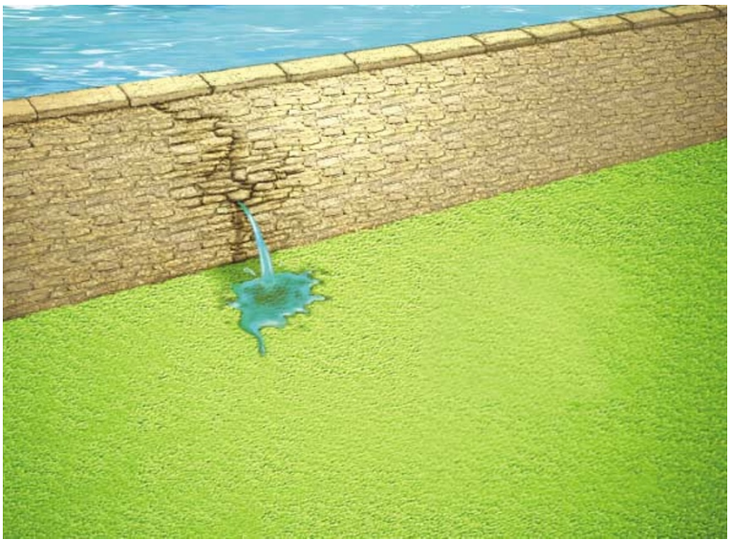
THERAPEUTICS

Breaking down barriers



One of the reasons that brain tumours are such a challenge to treat is because of the difficulties in delivering anticancer drugs across the blood–brain barrier. In fact, the brain is a sanctuary for metastases from tumours that respond to cytostatic drugs, such as paclitaxel, in other parts of the body. In the November issue of the *Journal of Clinical Investigation*, Fellner *et al.* report an approach to overcome this barrier, allowing paclitaxel to enter the brain and reduce the size of brain tumours.

Paclitaxel is used to treat various tumours, but it is not always effective because it is a substrate for the multidrug-resistance protein P-glycoprotein (P-GP) — a transporter that pumps drugs out of cells. Fellner *et al.* investigated whether P-GP was expressed in the brain, where it might transport paclitaxel and other drugs away from central nervous system (CNS) tumours. They found that P-GP is expressed at high levels in intact rat and human brain capillaries at the luminal surface of the endothelium — a location that could restrict permeation of drugs into the CNS. When human glioblastomas were transplanted into the brains of mice, the blood vessels that developed within the tumours also expressed high levels of P-GP.

Previous studies have shown that animals with reduced P-GP function accumulate P-GP substrates in the brain, so the authors checked to see whether blocking this transporter increased paclitaxel entry into the CNS. They showed that intravenous administration of the P-GP blocker valspodar increased the levels of fluorescently labelled paclitaxel in the brains of mice. Furthermore, co-administration of valspodar with paclitaxel reduced the growth of human glioblastomas by 90%, whereas treatment with

ANGIOGENESIS

Stemming the flow

A tumour without a blood supply — like flora and fauna in a valley that is deprived of its source of water — is unlikely to survive, and this makes inhibiting angiogenesis an attractive antitumour strategy. Andreas Niethammer and colleagues now report a novel antitumour approach — inhibiting the growth of endothelial cells in the tumour vasculature using an oral DNA vaccine.

The authors first constructed a DNA vaccine encoding mouse Vegf receptor 2 (Flk1) carried by an attenuated bacterium, *Salmonella typhimurium*. They showed that when mice were challenged with melanoma, colon carcinoma or non-small-cell lung cancer cells 2 weeks after receiving the last of three vaccinations with the *Flk1* vaccine, development of subcutaneous tumour growth was suppressed. Even 10 months after their last vaccination, mice still had greatly reduced tumour growth compared with controls that were vaccinated with an empty vector. The experimental animals that were challenged with lung carcinoma also had a marked decrease in the development of spontaneous lung metastases, and vaccinated mice that were challenged with a lethal dose of CT-26 colon carcinoma cells survived four times longer than mice that were vaccinated with an empty vector.

The problem with this model is that the tumour challenge was given after vaccination, which is not representative of what would happen in a therapeutic setting. So, Niethammer *et al.* injected mice with CT-26 cells 10 days before giving the *Flk1* vaccine, when they had already established lung metastases. All of the treated mice survived and growth of the established metastases was greatly reduced — all of the control mice died.

So, the *Flk1* vaccine has an impressive impact on tumour-cell growth, but what is the mechanism of cell kill? Anti-angiogenesis effects of the *Flk1* vaccine that were independent of tumour cells were shown in a Matrigel assay — vascularization was markedly reduced in Matrigel plugs of mice that were immunized with the *Flk1* vaccine versus the empty control vaccine. The authors hypothesized that the vaccine triggered a T-cell-mediated immune response against proliferating endothelial cells, as Flk1 is often overexpressed on these cells in the tumour vasculature. They observed a marked upregulation of several T-cell activation markers when splenocytes were incubated with cells expressing Flk1, and showed that *in vivo* depletion of $CD8^+$ T cells, before challenging the vaccinated mice with CT-26 tumour cells, resulted in severe impairment of the antitumour response, with extensive tumour growth and development of metastases.

This novel strategy of inhibiting the tumour blood supply might overcome problems that limit the effectiveness of therapies that target the tumour cell *per se*, such as genetic instability and heterogeneity of tumours cells, and using a DNA vaccine overcomes the usual lack of stimulation of an immune reponse by tumour cells.

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References and links

ORIGINAL RESEARCH PAPER Niethammer, A. G. *et al.* A DNA vaccine against VEGF receptor 2 prevents effective angiogenesis and inhibits tumor growth. *Nature Med.* 4 Nov 2002 (doi:10.1038/nm794).

WEB SITE

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