In an *in vivo* model, treatment with rosiglitazone was shown to inhibit tumour growth in athymic nude mice that were inoculated subcutaneously with GH3 cells — tumour weight was markedly lower in treated mice compared with control mice after 4 weeks. Importantly, rosiglitazone could also inhibit the growth of already established tumours of αT3 cells.

As oral rosiglitazone has already been approved for use in humans in the United States (for the treatment of type-2 diabetes), this drug could be safer and more effective than going under the knife for patients with non-functioning adenomas or with hormone-secreting pituitary tumours that are unresponsive to current drug therapies.

Kirsty Minton

References and links

ORIGINAL RESEARCH PAPER Heaney, A. P., Fernando, M. & Melmed, S. PPAR-γ receptor ligands: novel therapy for pituitary adenomas. *J. Clin. Invest*. **111**, 1381–1388 (2003)

FURTHER READING Heaney, A. P., Fernando, M., Young, W. & Melmed, S. Functional PPAR-γ receptor represents a novel therapeutic target in Cushing's disease. *Nature Med.* **11**, 1281–1287 (2002)

vector-expressing cells again localized to the tumours, but on exposure to gancyclovir, were quickly cleared. At the end of the treatment phase, these tumours were much smaller and their vascular density was almost fivefold less than control tumours. There were no signs of myelotoxicity in treated mice.

DePalma *et al*. also checked to see if the transduced haematopoietic cells homed to other sites of neo-angiogenesis, such as to healing wounds. They found that after partial hepatectomy, *Tek/GFP*-expressing cells localized to the granulation tissue that surrounds regenerating hepatic lobules. This cancer treatment might therefore disrupt wound-healing in patients.

The authors conclude, however, that haematopoietic cells are a useful vehicle for delivering gene-based therapies to tumours. The bone-marrow-derived cells that associate with the developing tumour vasculature will have to be better characterized, but other reagents designed to target these cells might be developed as antitumour agents.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER DePalma, M., Venneri, M. A. & Naldini, L. Targeting exogenous genes to tumor angiogenesis by transplantation of genetically modified hematopoietic stem cells. *Nature Med*. **9**, 789–795 (2003)

FURTHER READING Rafii, S. *et al*. Vascular and haematopoietic stem cells: novel targets for anti-angiogenesis therapy. *Nature Rev. Cancer* **2**, 826–835 (2003)

WEB SITE

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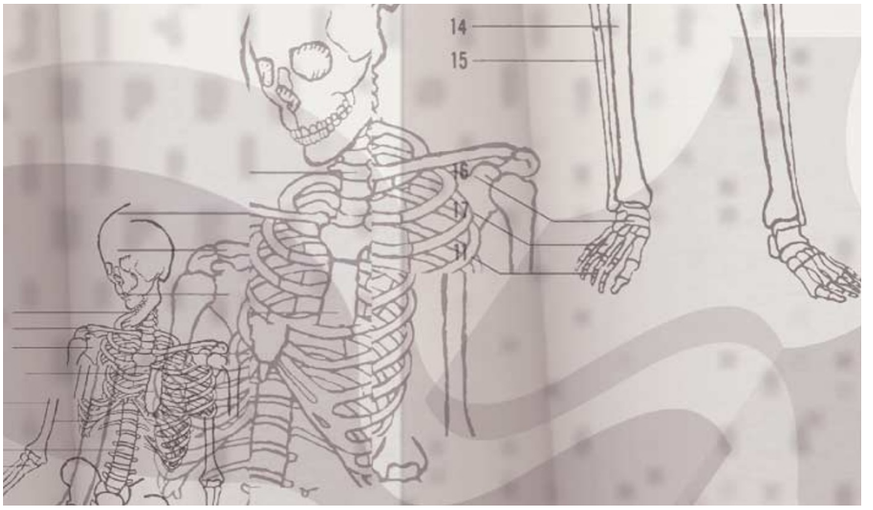

ANGIOGENESIS

Skeletal links

When tumours become large and hypoxic, cancer cells activate hypoxia-inducible factor (HIF), leading to transcription of vascular endothelial growth factor (VEGF) and other factors that promote angiogenesis. Mabjeesh *et al*. now show that the antitumour agent 2-methoxyestradiol (2ME2) — known to have anti-angiogenic properties — dysregulates HIF and that this function is linked to disruption of the microtubule cytoskeleton.

2ME2 is a naturally occurring derivative of oestradiol and preliminary results from Phase I and II trials in patients with breast and prostate cancer have shown promising antitumour responses. In investigating its effects in human prostate cancer and breast cancer cell lines, the authors observed that 2ME2 decreased the levels of the alpha subunit of HIF1 (HIF-1α), leading to reduced expression of HIF-1α target genes, including VEGF. Exposure of cells to cycloheximide — which blocks new protein synthesis — caused a similar rate of decrease in HIF-1α levels in both 2ME2-treated and -untreated cells, indicating that 2ME2 inhibits synthesis but not stability of HIF-1α. To examine the effect on protein translation further, the authors carried out ^{35}S-methionine labelling experiments and showed that HIF-1α synthesis was higher in untreated cells compared with 2ME2-treated cells 15 minutes after labelling. In addition, use of a proteasome inhibitor led to an increase of HIF-1α levels in untreated cells but did not restore the inhibitory effect of 2ME2 on HIF1. Together, these data indicate that 2ME2 probably inhibits HIF-1α protein synthesis rather than enhancing its degradation.

It has previously been shown that 2ME2 binds to tubulin and depolymerizes microtubules in both endothelial and tumour cells *in vitro*. So, is there a link between the effects of 2ME2 on the cytoskeleton and its effects on HIF-1α? Under hypoxia, cells treated with 2ME2 showed dose-dependent depolymerization of microtubules, and this disruption was necessary before a significant decrease in accumulation of HIF-1α in the nucleus was seen compared with untreated cells.

To study the effect of the drug's activity on tumour microvascular density, mice bearing orthopically growing breast tumours were treated with doses of 2ME2 that are known to be efficacious *in vivo*. A dose-dependent reduction in tumour volume and a clear decrease in microvessels was seen with drug treatment. A laser-scanning confocal microscopy technique using an antibody against tubulin revealed that the microtubules of the treated tumour cells in the mice were depolymerized in a dose-dependent manner and aberrant mitotic spindles were seen in nearly every cell. In addition, disruption of microtubules also occurred in endothelial cells of vessels associated with the tumours.

So, at concentrations that inhibit tumour growth and vascularization *in vivo*, 2ME2 effectively depolymerizes tumour microtubules. The authors also showed that other microtubule-targeting antitumour agents — vincristine and paclitaxel — inhibit HIF-1α, further supporting evidence of a link between disruption of the microtubule cytoskeleton and repression of HIF-1α, leading to downregulation of VEGF and inhibition of angiogenesis.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPER Mabjeesh, N. J. *et al*. 2ME2 inhibits tumor growth and angiogenesis by disrupting microtubules and dysregulating HIF. *Cancer Cell* **3**, 363–375 (2003)

WEB SITE

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