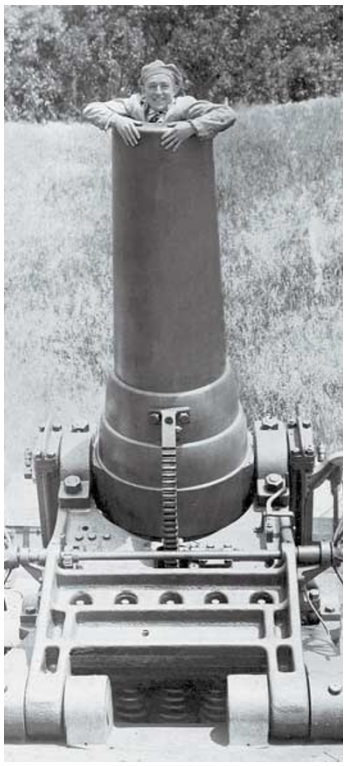
TUMORIGENESIS

Survivin death



Survivin is an inhibitor of apoptosis protein (IAP) — a group of proteins known to inhibit caspases, the proteolytic components of the apoptotic pathway. However, survivin also regulates mitosis, leading to conflicting reports about which of these functions is crucial during tumorigenesis. Dario Altieri and colleagues have now found that some survivin localizes to the inter-mitochondrial membrane space in tumour cells and that this localization accelerates tumorigenesis *in vivo*.

In rat insulinoma cell lines, survivin is expressed in the cytoplasm and does not accumulate in the mitochondria; so, Altieri and co-workers infected these cells with green fluorescent protein (GFP)-tagged survivin that was either targeted to the mitochondria or expressed in the cytoplasm as normal. These cells and control cells expressing mitochondria-targeted GFP only were injected into immunocompromised animals. Mitochondria-targeted survivin resulted in the formation of solid tumours, but cytosolic survivin inhibited tumour growth compared with the control GFP-expressing cells. Further analysis showed that all the tumours had a similar proliferative index, but that tumours with mitochondria-targeted survivin had a very low apoptotic index compared with both GFP controls and tumours expressing cytosolic survivin. Indeed, tumours expressing cytosolic survivin had an increased apoptotic index, explaining the slow net growth of these tumours *in vivo*.

So how do these results correlate with survivin function? Altieri and colleagues show that survivin is released from mitochondria during apoptosis, resulting in the inhibition of caspase-9 activation, the effector caspase required to regulate mitochondria-mediated apoptosis, but precisely how survivin inhibits caspase-9 activation remains unclear. Previously, overexpression of cytosolic survivin has been shown to induce increased spindle-microtubule stability and potential disruption of spindle checkpoints. So the authors hypothesize that in their system cytosolic survivin is having a similar effect, leading to increased apoptosis. In addition, the authors show that survivin does not localize to mitochondria in normal cells and might specifically accumulate in the mitochondria in tumour cells in response to cellular stress.

Survivin is highly expressed in a range of human tumours and correlates with both accelerated relapse and chemotherapy resistance; therefore, molecular antagonists of survivin have been developed and are approaching Phase 1 clinical trials. Whether these molecules have specific effects against mitochondria-localized survivin remains to be seen.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPER Dohi, T. *et al.* Mitochondrial survivin inhibits apoptosis and promotes tumourigenesis. *J. Clin. Invest.* **114**, 1117–1127 (2004)

IN BRIEF

MELANOMA

Dead cells in melanoma tumors provide abundant antigen for targeted delivery of ionizing radiation by a mAb to melanin.

Dadachova, E. *et al. Proc. Natl Acad. Sci. USA* **101**, 14865–14870 (2004)

The pigment melanin is normally found in melanosomes, but Dadachova *et al.* hypothesized that in rapidly growing melanomas, melanin would be released from cells and could be targeted for delivery of cytotoxic radiation by antibodies against melanin. Treating mice bearing melanoma xenografts with such a therapy inhibited tumour growth and prolonged survival. The authors suggest that the radiation is delivered to adjacent viable tumour cells by bystander effects.

MOUSE MODEL

Dissecting tumor maintenance requirements using bioluminescence imaging of cell proliferation in a mouse glioma model.

Uhrbom, L., Nerio, E. & Holland, E. C. *Nature Med.* 24 Oct 2004 (doi:10.1038/nm1120)

Eric Holland and colleagues have produced a novel transgenic mouse for imaging the loss of the retinoblastoma pathway and proliferative activity of glioma cells over time using a luciferase gene controlled by the *E2F1* promoter. They show that platelet-derived growth factor (PDGF)-induced gliomas are dependent on both activation of the PDGF receptor and TOR signalling.

THERAPEUTICS

Suppression of the Shh pathway using a small molecule inhibitor eliminates medulloblastoma in *Ptc1*$^{+/-}$*p53*$^{-/-}$ mice.

Romer, J. T. *et al. Cancer Cell* **6**, 229–240 (2004)

Using a mouse model of medulloblastoma, Romer *et al.* showed that a small-molecule inhibitor of the sonic hedgehog (SHH) signalling pathway suppressed several genes that are highly expressed in medulloblastoma. This resulted in decreased tumour-cell proliferation, an increase in cell death and complete eradication of tumours. These findings support the development of SHH antagonists for the treatment of medulloblastoma.

ERRATUM

PREDICTIONS ARE CIRCULATING

Nature Reviews Cancer **4**, 751 (2004)

In this Trial Watch article, we should have said that the technique CellSearch was developed by Immunicon. Veridex commercializes products incorporating this technology in the cancer field.