TUMORIGENESIS

RapTOR strikes again

Rapamycin, the immunosuppressant inhibitor of the kinase TOR, is in clinical trials for the treatment of several different cancers, but the exact mechanism by which this drug prevents tumour growth is unclear. In the June issue of *Nature Medicine*, William Sellers and colleagues show that a rapamycin analogue inhibits prostate tumour growth by two independent pathways in mice — induction of mitochondrial-mediated apoptosis and inhibition of proliferation through the downregulation of the transcription factor Hif-1.

TOR kinase activity can be regulated by the oncogenic serine/threonine kinase AKT. When targeted to the mouse ventral prostate, transgenic Akt drives the development of prostate intra-epithelial neoplasia. Sellers and colleagues show that in these mice complete inhibition of Tor activity by the oral rapamycin derivative RAD001 induces a return to normal cell morphology within the intraluminal tissue of the prostate epithelium. The authors noted not only an increase in apoptotic cells within the regressing tumours, but also a concomitant inhibition of proliferation.

So how does Tor inhibition both induce apoptosis and inhibit proliferation? The authors addressed this by crossing the transgenic-Akt mice with mice specifically expressing human BCL2 in the ventral prostate. BCL2 prevented the apoptotic death of cells following treatment with the rapamycin analogue, indicating that the mitochondrial apoptosis pathway is important for part of the rapamycin-mediated efficacy in this tumour model. However, BCL2 expression did not reverse the rapamycin-mediated inhibition of proliferation.

Which genes drive Akt-mediated proliferation? The authors used an intricate series of microarray- and computer-based technologies to show that the hypoxia-responsive protein Hif-1α is upregulated in both the Akt- and Akt/BCL2-expressing tumours and that its activity is suppressed in RAD001-treated mice. Although others have published links between HIF-1α, TOR and AKT previously, the mechanism by which TOR regulates HIF-1α activity remains unclear.

Data from this mouse model indicates that human prostate cancer cells that overexpress BCL2 or that have TOR-independent activation of HIF-1α could be resistant to TOR inhibitors. More importantly, the current evaluation of RAD001 in patients with advanced prostate cancer might not prove informative without a corresponding analysis of tumour genotype.

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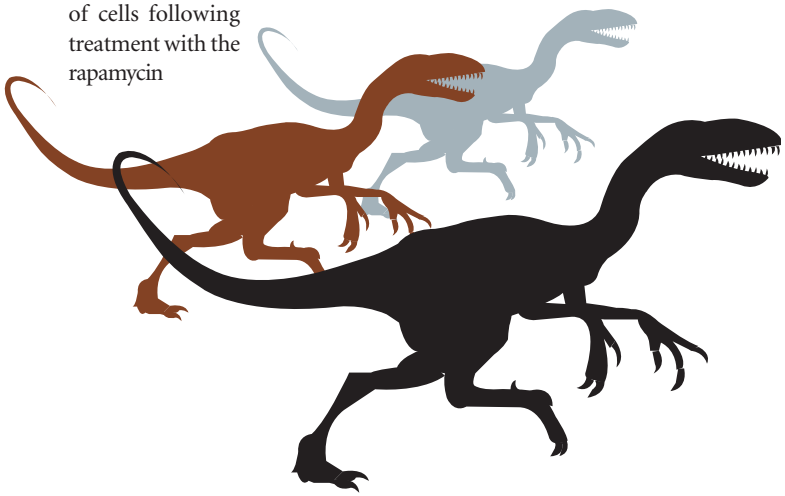
References and links

ORIGINAL RESEARCH PAPER Majumder, P. K. *et al*. mTOR inhibition reverses AKT-dependent prostate intraepithelial neoplasia through regulation of apoptotic and Hif1 dependent pathways. *Nature Med*. **10**, 594–601 (2004)

FURTHER READING Denmeade, S. R. & Isaacs, J. T. A history of prostate cancer treatment. *Nature Rev. Cancer* **2**, 389–396 (2002)



IN BRIEF

METASTASIS

Hypoxia induces adhesion molecules on cancer cells: a missing link between Warburg effect and induction of selectin-ligand carbohydrates.

Koike, T. *et al*. *Proc. Natl Acad. Sci. USA* **101**, 8132–8137 (2004)

Metastatic spread through blood vessels requires tumour cells to express carbohydrate selectin ligands that mediate their adhesion to endothelial cells, allowing them to enter the vasculature. Koike *et al.* show that hypoxia induces increased expression of selectin ligands and the enzymes involved in their synthesis in colon cancer cells, and that this requires hypoxia-inducible transcription factors.

PROGNOSTIC MARKERS

Prognostic significance of a short sequence insertion in the MCL-1 promoter in chronic lymphocytic leukemia.

Moshynska, O. *et al*. *J. Natl Cancer Inst.* **96**, 673–682 (2004)

Moshynska *et al.* identified *MCL1* promoter insertions in peripheral-blood lymphocytes from 18 of 57 patients with chronic lymphocytic leukaemia (CLL). These led to increased expression of the anti-apoptotic MCL1 protein, a member of the BCL2 family. *MCL1* promoter insertions were associated with poor response to chemotherapy and decreased survival, indicating a potential use in identifying high-risk CLL patients.

CHEMOSENSITIVITY

Alkylating DNA damage stimulates a regulated form of necrotic cell death.

Zong, W.-X. *et al. Genes Dev.* 14 May 2004 (doi:10.1101/gad.1199904)

Alkylating agents induce tumour-cell death, even in cells that lack components of the apoptotic machinery. Zhong *et al.* show that these drugs induce necrosis in apoptosis-resistant cells due to the activation of the DNA-repair protein PARP, which causes depletion of ATP within the cell. This outcome only occurs in cells — including most cancer cells — that maintain ATP production via aerobic glycolysis, indicating that the metabolic status of cells specifies their fate in response to alkylating agents.

THERAPEUTICS

Suramin inhibits death receptor-induced apoptosis *in vitro* and fulminant apoptotic liver damage in mice.

Eichhorst, S. T. *et al. Nature Med.* 16 May 2004 (doi:10.1038/nm1049)

Suramin, a derivative of urea, is a chemotherapeutic agent, but its effect on apoptosis is unknown. Eichhorst *et al.* show that suramin inhibits CD95-mediated cell death and under certain circumstances will inhibit chemotherapy-induced apoptosis. This indicates that the use of suramin as a chemotherapeutic agent — based on its ability to inhibit cytokine signalling — needs to be re-evaluated.