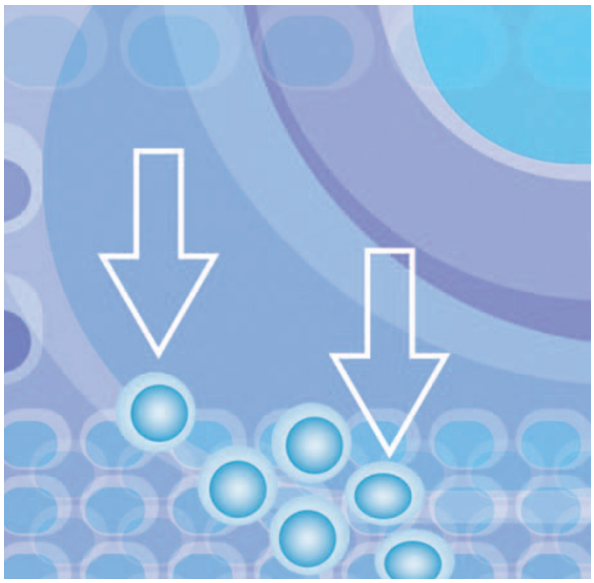
IMMUNOTHERAPY

Suppressing regulatory T cells



The presence of increased numbers of regulatory T (T_{Reg}) cells in cancer patients suppresses an effective anti-tumour immune response. Jens Dannull and colleagues have investigated whether a targeted therapy, aimed at decreasing the numbers of T_{Reg} cells, can improve the response of patients to tumour-based vaccines. Although the number of patients in this preclinical trial was small, the results were promising.

T_{Reg} cells are $CD4^+$ T cells that normally suppress the development of autoimmunity. They express high levels of the interleukin 2 (IL-2) α-chain receptor, CD25, and previous studies in mouse models have shown that targeting CD25 can lead to depletion of T_{Reg} cells. In this study, the authors used human IL-2 conjugated to the catalytic and membrane-translocation domain of diphtheria toxin (DAB_{389}IL-2) as a means to specifically kill T_{Reg} cells in patients with advanced renal cell and ovarian carcinoma.

Initially, the authors carried out *in vitro* experiments on human peripheral blood cells from both healthy donors and cancer patients to determine whether DAB_{389}IL-2 would selectively deplete the T_{Reg} cells. $CD4^+$ $CD25^{high}$ cells were selectively eliminated with no evident effect on other T cells that expressed low or intermediate levels of CD25 (such as memory T cells). However, the presence of active DAB_{389}IL-2 also suppressed the effector T-cell response, indicating

SIGNALLING

Pathway paradox

AKT (or protein kinase B) is a Ser/Thr kinase that has three isoforms (AKT1, AKT2 and AKT3), and it is activated by ligand-stimulated growth-factor-receptor signalling in a phosphatidylinositol 3-kinase (PI3K)-dependent manner. It is an important mediator of many cell-survival and -proliferation signalling pathways, and has a pivotal role in these processes through a number of downstream effectors. The activation or overexpression of the PI3K–AKT pathway is a prominent feature of many human cancers, so the inhibition of AKT is considered to be an attractive therapeutic target. However, two recent papers now identify an unexpected function for the AKT pathway in cancer cells.

Although previous studies have indicated that AKT activation induces cancer-cell invasion, both groups now show, albeit using different mechanisms, that AKT can block cell migration and invasion. As reported in *Molecular Cell*, Yoeli-Lerner and colleagues found that signalling through AKT blocked the activity of the transcription factor NFAT (nuclear factor of activated T cells) by promoting NFAT ubiquitylation — which is mediated, in part, by the E3 ubiquitin ligase HDM2 (human homologue of mouse double minute 2) — and its subsequent proteasomal degradation. The authors acknowledged that other mechanisms might also be involved and cautioned that the three AKT isoforms might not share the same cellular functions.

> “The activation or overexpression of the PI3K–AKT pathway is a prominent feature of many human cancers...”

Indeed, reporting in the *Journal of Cell Biology*, Irie and colleagues identified a different mechanism of AKT-mediated inhibition of cancer-cell invasion, and found an isoform specificity for this effect. The authors initially found that enhanced insulin-like growth factor 1 (IGF1) stimulation induced hyperproliferation and anti-apoptotic activities, which were reversed by downregulating AKT2. Downregulating AKT1, however, enhanced the migration of IGF1-receptor-overexpressing cells, and induced phenotypic changes that were characteristic of an epithelial–mesenchymal transition (EMT). A significant increase in extracellular signal-regulated kinase (ERK) activation, which is involved in many models of EMT, accompanied the phenotypic effects of AKT1 downregulation, and contributed to the induction of migration and EMT.

Together, these studies report that AKT suppresses cell motility and invasion in an isoform-specific manner, and indicate that AKT1 is acting through both NFAT and ERK. These pathways are known to cooperate in immune cells, but further study will be needed to determine whether NFAT and ERK are working on parallel or coupled pathways in cancer cells. These surprising results regarding one of the most well-characterized oncogenes provide new insights into cancer metastasis. Perhaps most importantly, however, they raise questions about the development of inhibitor therapies, and highlight the need for a comprehensive picture of a potential therapeutic drug target before effective treatments can be developed.

Sharon Ahmad, Assistant Editor, Nature Reviews Molecular Cell Biology

ORIGINAL RESEARCH PAPERS Yoeli-Lerner, M. *et al.* Akt blocks breast cancer cell motility and invasion through the transcription factor NFAT. *Mol. Cell* 23 Nov 2005 (doi:0.1016/j.molcel.2005.10.033) | Irie, H. Y. *et al.* Distinct roles of Akt1 and Akt2 in regulating cell migration and epithelial–mesenchymal transition. *J. Cell Biol.* 19 Dec 2005 (doi:10.1083/jcb.200505087)

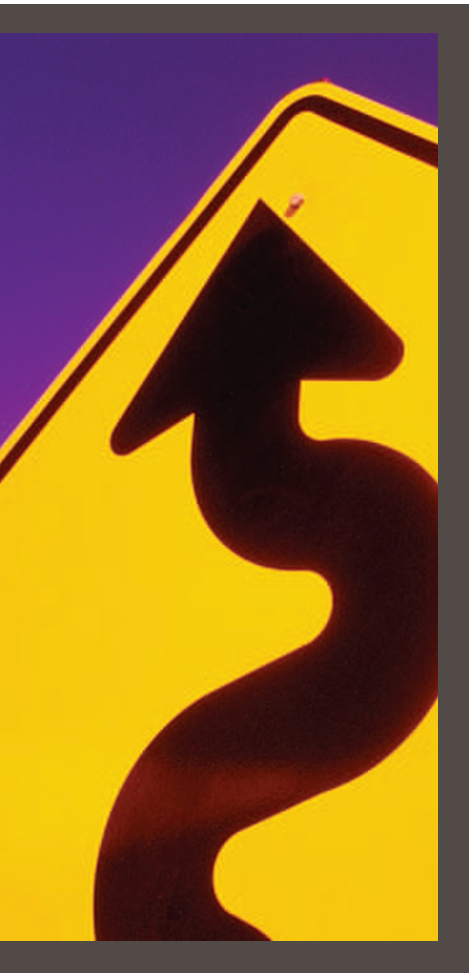
that DAB_{389}IL-2 can only be used in a pre-vaccination setting.

In the clinical study, DAB_{389}IL-2 was given to 7 patients 4 days before administering a vaccine that consisted of dendritic cells that were transfected with tumour cell RNA. DAB_{389}IL-2 significantly reduced the numbers of circulating T_{Reg} cells and therefore increased the numbers of circulating cytotoxic anti-tumour T cells when the vaccine was administered, compared with four patients who were treated with the vaccine alone.

The authors hope that this study will act as a baseline from which to improve and define the strategy of T_{Reg} cell depletion in cancer patients, with a view to achieving anti-tumour immunity with clinical impact.

Nicola McCarthy

ORIGINAL RESEARCH PAPER Dannull, J. *et al.* Enhancement of vaccine-mediated antitumour immunity in cancer patients after depletion of regulatory T cells. *J. Clin. Invest.* 23 Nov 2005 (doi:10.1172/JCI25947)



APOPTOSIS

Taming Puma

Controlling the activity of p53 following DNA damage is essential for the appropriate execution of cell death and the regulation of cell survival. But how does p53 decide whether to induce cell-cycle arrest or apoptosis in different cell types? Reporting in *Cell*, Wen-Shu Wu and colleagues now show that the transcription factor slug determines the fate of haematopoietic progenitors by repressing the gene that encodes puma (*Bbc3*) — a BCL2-homology domain-3 (BH3)-only protein.

Slug (which is encoded by the *Snai2* gene) belongs to the highly conserved slug/snail family of transcription factors, which have numerous roles at different stages of development, from *Caenorhabditis elegans* to humans. In the haematopoietic system, slug functions as a survival factor to protect the progenitor cells from DNA damage. Intriguingly, slug is expressed in stem cells and progenitors of the myeloid lineage, which undergo cell-cycle arrest and DNA repair upon DNA damage, but not in differentiated cells, which undergo apoptosis upon genotoxic stress. So, assuming that slug could provide the switch between cell-cycle arrest and cell death, what might be the mechanism that drives such a decision?

The authors tested the genetic interaction of slug with p53 — the key mediator of DNA-damage-induced apoptosis — and found that slug protects haematopoietic progenitors from DNA-damage-induced apoptosis by antagonizing the p53-mediated apoptotic pathway. As slug contains a potent SNAG transcriptional-repressor domain, it might antagonize p53 by repressing a p53-responsive gene. By using a combination of numerous techniques, Wu and colleagues showed that slug selectively downregulates puma — a downstream effector of p53-induced apoptosis — by binding specifically to a conserved binding site in the first intron of *Bbc3*.

The evidence that slug functions downstream of p53, and the existence of p53-responsive elements in the mouse and human *Snai2* genes, prompted the authors to then test whether slug could be a potential p53 target. *In vitro* experiments indicated that p53 not only interacts with each of the putative p53-responsive elements in *Snai2*, but it directly upregulates slug expression after γ-irradiation. Furthermore, analysis of mice that lacked either slug and p53, or slug and puma confirmed that slug functions downstream of p53 and upstream of puma to control the fate of progenitor cells that are exposed to genotoxic stress *in vivo*.

The ability of slug to transcriptionally repress *Bbc3* has important implications for tumorigenesis — slug is aberrantly expressed in various tumours, and it might contribute to tumorigenesis by repressing the expression of puma or other BH3-only proteins. The authors propose that their findings are also relevant to cancer therapy, as the selective upregulation of slug before cancer treatment might be advantageous for the survival of haematopoietic progenitor cells.

Ekat Kritikou, Locum Associate Editor,
Nature Reviews Molecular Cell Biology

ORIGINAL RESEARCH PAPERS Wu, W-S. *et al.* Slug antagonizes p53-mediated apoptosis of hematopoietic progenitors by repressing puma. *Cell* **123**, 641–653 (2005)
FURTHER READING Zilfou, J. T. *et al.* Slugging it out: fine tuning the p53–PUMA death connection. *Cell* **123**, 545–548 (2005)