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 (DAB₃₈₉-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 DAB₃₈₉-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 DAB₃₈₉-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

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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.

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.

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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:10.1016/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)