THERAPEUTICS

Self destruction

Although immune cells infiltrate tumours, they are frequently unable to mount a full-scale attack, because tolerance mechanisms prevent them from destroying cells that express 'self' antigens. Immunization of patients with cancer antigens has only been shown to cause a slight increase in the number of tumour-specific circulating lymphocytes, but has not been observed to promote tumour regression. In the 19 September issue of *Science*, Steven Rosenberg and colleagues describe a new immunotherapy approach that replaces up to 90% of a patients' normal lymphocytes with activated tumour-specific ones, resulting in regression of metastatic melanoma.

Thirteen patients with refractory metastatic melanoma received high levels of chemotherapy to deplete their immune systems, followed by administration of tumour-specific T cells and high doses of the cytokine interleukin (IL)-2. The T cells were initially isolated from the patient's own tumour samples and expanded *in vitro*, and shown to react against melanoma cells. Six of these patients experienced significant regression of metastatic melanoma, whereas four others had mixed responses with significant shrinkage of one or more metastases. The responses lasted for up to 24 months after therapy.

But what tumour antigen activated this immune response? Analysis of peripheral-blood cells isolated from the patients revealed that they contained a large percentage of T cells that specifically recognized the MART1 antigen — a non-mutated differentiation antigen that is expressed by both melanomas and normal melanocytes. The high frequency and extended persistence of individual T-cell clones that react to non-mutated self antigens has not been previously observed in humans.

The authors suggest that this approach succeeded when previous immunotherapy strategies failed because the expanded cultures that were used to treat the patients included both helper and cytolytic T cells. The non-myeloablative conditioning regimen that was used in this study might also have eliminated regulatory cells or other mechanisms that limit lymphocyte expansion.

Five of the patients who underwent tumour regression also experienced autoimmune melanocyte destruction, leading to vitiligo. This study shows, however, that 'self antigens' can be used as targets for human cancer immunotherapy, and, if autoimmunity can be controlled, similar approaches might be useful in treating other cancers and viral diseases.

Kristine Novak

References and links

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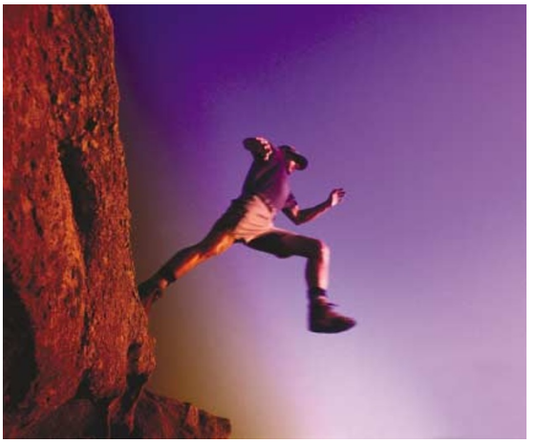
FURTHER READING Pardoll, D. Spinning molecular immunology into successful immunotherapy. *Nature Rev. Immunol*. **2**, 227–238 (2002)

WEB SITE

Steven Rosenberg's lab: http://ccr.cancer.gov/Labs/Lab.asp?LabID=93

APOPTOSIS

Death-defining feat



Most cancer drugs are general cytotoxins that kill cells by means of an undefined mechanism. By studying the ways in which different BCL2-family members regulate the commitment to programmed cell death, Stanley Korsmeyer's group discovered two specific pathways by which a subset of this family, known as the 'BCL2 homology (BH)3-only'proteins, promote apoptosis. In the September issue of *Cancer Cell*, they report that mimetics of regions of these proteins might be some of the first reagents that have been developed to initiate cancer-cell death through genetically defined pathways.

The pro-apoptotic members of the BCL2 family comprise two classes — those that share homology in up to three conserved regions, known as BH 1–3 domains, and the BH3-only proteins, which only share sequence homology with the amphipathic α-helical BH3 domain. The BH3 domain is required for apoptosis induction, and mediates binding of the BH3-only proteins (BID, NOXA, PUMA, BIK, BIM and BAD) to other BCL2-family members.

Letai *et al*. synthesized BH3 peptides from representative BH3-only molecules to test whether these domains, when removed from the context of the intact protein, could induce cell death. Surprisingly, they found that different BH3 domains possessed distinct functions, and could be further categorized into two subgroups. One group, called the 'BID-like' subgroup, activated oligomerization of the pro-apoptotic mitochondrial proteins BAK and BAX, leading to cytochrome *c* release and cell death. This BID-like subgroup also bound to the anti-apoptotic protein BCL2, however, where these peptides were sequestered and unable to function. The other group, known as the 'BAD-like' subgroup, did not activate BAK or BAX, but instead bound BCL2. This binding displaced the sequestered BID-like peptides, freeing them to mediate cytochrome *c* release and apoptosis.

So can these peptides be used to kill cancer cells, which possess many alterations in this entire pathway? The authors linked the peptides to an eight-amino-acid polyarginine chain stretch, to facilitate transport of the peptides across the plasma membrane, and showed that the BID-like peptide induced apoptosis in cultured leukaemia cells. The BAD-like peptide could not kill cells on its own, but seemed to sensitize cells to apoptosis, lowering the concentration of BID-like peptide that is required to induce cell death. These peptides might be used to increase the apoptotic susceptibility of other types of cancer cell, which frequently protect themselves from death by upregulating BCL2.

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WEB SITE

Korsmeyer's lab: http://research.dfci.harvard.edu/korsmeyer/