IN THE NEWS

Abandoned survivors

A new report has criticized the haphazard nature of post-treatment care for the 10 million cancer survivors in the United States. Care is often inadequate because health plans only cover the initial cancer therapy, according to *From Cancer Patient to Cancer Survivor: Lost in Transition*, published by the National Academy of Sciences.

"We do a great job in addressing the acute need, but when patients get 3, 4, 5 years and beyond, they continue to experience issues and problems and may feel neglected" said Anne Meisner, of the Cancer Treatment Centers of America (http://www.bloomberg.com, 8 November 2005). These problems include not only recurrence, but also side effects of both cancer and therapy, such as depression, infertility, osteoporosis and leukaemia.

In addition, many people find themselves uninsurable or discriminated against at work. Janlori Goldman, of Columbia University, said, "Federal law is not entirely clear about whether employers can discriminate against a person who currently has cancer, has had cancer in the past or has a genetic predisposition to it" (http://www.ap.org, 7 November 2005).

The oncology community has welcomed the report, which addresses the angst of survivors such as Patricia Grullion, who said "I was given a clean bill of health, but nobody gave me any real plan for the future, or any thoughts about what I could expect physically or emotionally" (http://www.nytimes.com, 8 November 2005).

Patrick Goymer

IMMUNOTHERAPY

Do natural born killers specialize?

Natural killer T (NKT) cells can induce tumour regression in mouse models, but NKT cells can also suppress cell-mediated anti-tumour immune responses. The reason for these contrasting effects is not well understood. Now, Nadine Crowe and colleagues show that functionally distinct subsets of NKT cells exist *in vivo* and that their existence could help to explain why only some NKT cells have anti-tumour effects.

In previous studies, the authors showed that NKT cells derived from the liver can promote anti-tumour immune responses in two model systems: mice injected with the 3-methylcholanthrene-induced sarcoma cell line MCA-1, and mice injected with the melanoma cell line B16F10. Using these models, it was shown that mice that lack T-cell receptor (TCR) α-chains that contain Jα18 (denoted TCR Jα18), which are deficient in NKT cells, are more susceptible to tumour growth. In both tumour models, the ability of the NKT cells to promote anti-tumour responses was dependent on their production of interferon-γ. Previous reports have shown that there are at least two phenotypically distinct subsets of NKT cells in mice and humans — $CD4^+$ and $CD4^-$ NKT cells — and that these subsets show differential cytokine production *in vitro*. To test the idea that NKT-cell subsets are functionally distinct, as well as phenotypically distinct, the authors isolated NKT cells from the spleen, thymus and liver, then adoptively transferred these cells to TCR Jα18-deficient mice that had been injected with MCA-1 cells.

EPIGENETICS

Dangerous unmarked genes

Loss of imprinting (LOI) at specific loci has been implicated in several cases of tumorigenesis, probably as a result of imbalanced expression of potential imprinted tumour-suppressor genes and oncogenes. Previous studies have only demonstrated that LOI is associated with tumorigenesis, not that it causes it. Nor have they addressed the consequences of a global LOI, merely the consequences of single-gene LOI or imbalanced imprinting (having an entirely maternally or paternally imprinted genome). Now, Rudolf Jaenisch and colleagues have demonstrated that global LOI leads to tumour formation.

They used conditional mutants of DNA methyltransferase to transiently remove methylation from mouse embryonic stem (ES) cells. When methylation was restored, imprinting patterns were lost — the maternal and paternal genomes were no longer differentially methylated. The authors derived fibroblasts from these ES cells and found that they were immortalized, grew at an increased rate and resisted inhibition by transforming growth factor-β, a cytokine that inhibits the growth of various cell types.

Several tumour suppressors, such as *Igf2r*, *Tsp1* and *Cdkn1c*, were underexpressed in the fibroblasts, and oncogenes, such as *Peg3*, *Peg5* and *Igf2*, were overexpressed. When the non-imprinted fibroblasts were injected into immunodeficient mice there was some tumorigenesis, compared with none in the controls. However, when the fibroblasts were also transfected with constitutively active *RAS*, tumorigenesis was much faster. The authors suggest that this is because RAS and LOI cooperate to form tumours.

Chimeric mice that were created from a mixture of non-imprinted and normal ES cells all had tumours by 18 months of age, in contrast to the controls in which there was only one case of tumour formation. All the tumours in the chimeric mice were

Only the liver-derived NKT cells could completely inhibit tumour growth, and this protection was found to be provided mainly by the $CD4^-$ population of NKT cells. The inability of thymus-derived NKT cells to confer protection was not a consequence of their impaired survival after transfer, because they were easily detectable in the liver and other organs for at least 1 week after transfer.

Because it was possible that liver-derived NKT cells were preferentially activated in the MCA-1 model, the authors then tested various NKT-cell subsets in the B16F10 model. In this model, liver-derived NKT cells transferred to B16F10-inoculated TCR Jα18-deficient mice that were treated with the pan-NKT-cell-activating molecule α-galactosylceramide (α-GalCer) could inhibit the formation of lung metastases. Similar to the MCA-1 model, spleen- and thymus-derived NKT cells were less effective than liver-derived NKT cells at preventing tumour growth, and the $CD4^-$ subset of liver-derived NKT cells was more potent at promoting the anti-tumour response than was the $CD4^+$ NKT-cell subset. However, these differences did not seem to result from differences in interferon-γ production, as liver-derived NKT cells that were isolated from mice deficient in interleukin-4 (IL-4) were considerably better at protecting against the formation of metastases than were their wild-type counterparts, and thymus-derived NKT cells from these mice were also protective. This indicates that IL-4 production by NKT cells could antagonize the ability of these cells to mediate tumour rejection. However, because wild-type, liver-derived NKT cells produce similar amounts of IL-4 to wild-type, thymus-derived NKT cells, it is not clear why thymus-derived cells cannot confer this protection.

This study demonstrates the existence of functionally distinct subsets of NKT cells *in vivo*, and highlights the importance of addressing which NKT-cell subsets have the most efficient anti-tumour response when considering NKT-cell-based anti-tumour therapies.

Elaine Bell, Chief Editor,
Nature Reviews Immunology

References and links

ORIGINAL RESEARCH PAPER Crowe, N. Y. *et al*. Differential antitumor immunity mediated by NKT cell subsets *in vivo*. *J. Exp. Med.* **202**, 1279–1288 (2005)

derived from the non-imprinted cells. Importantly, tumours were not seen in the offspring of the chimaeras, as imprinting is reset during gametogenesis.

Imprinting is therefore an epigenetic tumour-suppressing phenomenon. When imprinting is lost, cells are immortalized through the inappropriate regulation of both tumour suppressors and oncogenes. Further genetic alterations are then required for full transformation.

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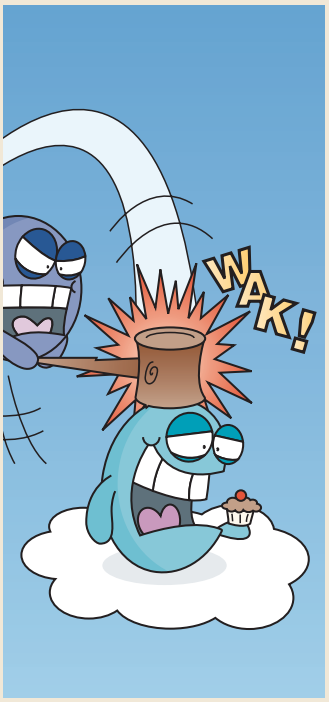

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IN BRIEF

SMALL MOLECULES

BRAF mutation predicts sensitivity to MEK inhibition.

Solit, D. B. *et al*. *Nature* 6 Nov 2005 (doi: 10.1038/nature04304)

Gain-of-function mutations in Ras or Raf family members are found in most human cancers. Both of these signalling molecules activate the mitogen-activated protein kinase kinase 1 (MAP2K1, also known as MEK)–extracellular regulated kinase (ERK) pathway. This paper shows that tumours with mutations in BRAF are highly and selectively sensitive to small-molecule MEK inhibitors, and offer a rational therapeutic strategy for targeting this genetically defined tumour subtype.

TARGETED THERAPIES

Oncogenic pathway signatures in human cancers as a guide to targeted therapies.

Bild, A. H. *et al*. *Nature* 6 Nov 2005 (doi: 10.1038/nature04296)

Bild and colleagues show that gene expression profiles in tumour cells can be identified that reflect the activation status of several oncogenic pathways. These signatures can be used to identify similar patterns of pathway deregulation in a large panel of various human cancers, and these patterns have a prognostic value. Applying the same expression patterns to cancer cell lines predicted their sensitivity to targeted therapies, indicating that these signatures might be a useful guide to choosing targeted therapies in tumour treatment.

PROGNOSTIC MARKERS

A microRNA signature associated with prognosis and progression in chronic lymphocytic leukemia.

Calin, G. A. *et al*. *New Engl. J. Med*. **335**, 1793–1801 (2005)

Can microRNA (miRNA) profiles be used as prognostic markers in chronic lymphocytic leukaemia (CLL)? Analysis of 94 samples of CLL cells for the differential expression of 190 miRNA genes identified a 13 gene miRNA expression signature that is associated with prognostic factors and disease progression. Mutations in the miRNA transcripts were common and might have functional importance.

CELLULAR ADHESION

Focal adhesion kinase promotes the aggressive melanoma phenotype.

Hess, A. R. *et al*. *Cancer Res*. **65**, 9851–9860 (2005)

Metastases in malignant melanoma remain a significant barrier in the treatment of this disease. Mary Hendrix and colleagues investigated the function of focal adhesion kinase (FAK) in promoting melanoma metastasis. They found that FAK is phosphorylated on its key tyrosine residues Tyr397 and Tyr576 in aggressive melanomas only, and that this correlates with increased invasive and migrational properties, as well as increased cellular plasticity. Expression of a kinase-dead FAK abrogated these effects, indicating that FAK-mediated signalling pathways might be viable targets in malignant melanoma.