TUMOUR IMMUNOLOGY

Disarming defences

Tumours might evade the immune response by secreting soluble MHC class-I-chain-related protein A (MICA), which downregulates expression of the receptor NKG2D on host immune cells and impairs the antitumour response, according to a report by Groh *et al.* in *Nature*.

NKG2D is expressed by natural-killer (NK) cells, γδ T cells and $CD8^+$ αβ T cells, and ligand binding results in NK-cell activation and the co-stimulation of effector T cells. NKG2D ligands include MICA and MICB, which are expressed as a result of stress (such as viral infection or transformation). Tumour cells frequently express MIC, so might be recognized and destroyed by NKG2D-expressing host immune cells.

However, the immune system often fails to recognize MIC-expressing tumour cells, so the authors questioned whether NKG2D is functionally impaired on host effector T cells. First, the expression of NKG2D by T cells from MIC^+ and MIC^- tumours was analysed. Cell-surface expression of NKG2D by $CD8^+$ T cells isolated from tumour-infiltrating lymphocytes (TILs) and peripheral-blood mononuclear cells (PBMCs) from MIC^+ tumours was reduced compared with that of T cells from MIC^- tumours, and the level of expression decreased with time, indicating that MIC downmodulates NKG2D. Further experiments indicated that MIC-mediated binding of NKG2D on T cells that were exposed to MIC^+ tumour cells resulted in the endocytosis and degradation of this receptor.

Next, Groh *et al.* asked whether MIC proteins are released from MIC^+ tumour cells, as this would explain why both TILs from MIC^+ tumours, which are in direct contact with MIC^+ tumour cells, and PBMCs, which are not, have reduced expression of NKG2D. Experiments showed that MICA is released by MIC^+ tumour cells and shed into the circulation, which indicates that tumour-derived MICA in the peripheral blood of cancer patients might cause the downregulation of NKG2D expression. This was confirmed as serum from cancer patients with MIC^+ tumours, and recombinant, soluble MICA, downmodulate the expression of NKG2D on isolated peripheral-blood $CD8^+$ T cells and on melanoma-antigen-specific $CD8^+$ T-cell clones.

What effect does the downregulation and degradation of NKG2D have on T-cell function? Cytolytic responses and the ability to produce interferon-γ were impaired markedly in $NKG2D^{low}$ $CD8^+$ T cells compared with $NKG2D^{high}$ T cells. Therefore, the release of MIC proteins by tumours impairs effector T-cell function, so compromising the immune responses of cancer patients.

Jenny Buckland, Associate Editor,
Nature Reviews Immunology

References and links

ORIGINAL RESEARCH PAPER Groh, V. *et al.* Deficiencies in NKG2D expression and T-cell functions caused by tumour-derived soluble MIC ligands. *Nature* **419**, 734–738 (2002)

BREAST CANCER

Filling the hole

A hollow, glandular architecture is associated with many highly organized tissues, such as the mammary gland, and apoptosis functions to create this space. Now, the authors of a recent *Cell* paper have used non-transformed MCF-10A mammary epithelial cells in a three-dimensional cell-culture model — a system in which the cells can take on many of the *in vivo* features of breast epithelium — to show that apoptosis is important in maintaining luminal space and that tumour cells must suppress apoptosis to successfully invade the lumen.

On studying cell death during acinar morphogenesis, the authors observed, after 5–8 days in culture, a well-polarized outer layer of cells surrounding a subset of poorly polarized cells. The cells in the interior of the structure — the presumptive luminal space — died after 6–8 days, just before the lumen appeared. A lack of survival-promoting signals from the AKT pathway was implicated in this cell death.

To determine whether lumen formation can occur in the absence of apoptosis, the authors overexpressed the anti-apoptotic proteins BCL2 and BCL-X_L. Although lumen formation was delayed, cells were eventually cleared — possibly by autophagy — and a luminal space formed. Conversely, increased proliferation — induced by overexpressing cyclin D1 or human papillomavirus (HPV) 16 E7 — also did not fill the luminal space. Large amounts of cellular debris and fragmented nuclei provided clues as to why this was — increased cell death was occurring.

So, how do certain oncogenes cause cells to invade the luminal space, as occurs in early epithelial tumours? To address this, the authors cultured MCF-10A cells that stably expressed either cyclin D1 with BCL-X_L or HPV 16 E7 with BCL2, and found that the luminal space of acini in which both the proliferative and anti-apoptotic genes were simultaneously expressed became filled.

It seems, therefore, that only a combination of increased proliferation and decreased cell death can fill the lumen; 'isolated' biological insults that are induced by many cancer genes have little effect on disrupting epithelial architecture. Notably, activated ERBB2, which induces both of these biological activities, can fill the luminal space in this model system; it is also overexpressed in many metastatic breast cancers.

Katrin Bussell, Associate Editor,
Nature Reviews Molecular Cell Biology

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IN THE NEWS

Gene therapy resumes

Despite evidence that a gene-therapy experiment caused a 3-year old boy to develop a leukaemia-like illness, a government advisory panel encouraged the United States Food and Drug Administration (FDA) to reinstate three similar experiments that have been suspended since September, when the child became sick.

The trial involved patients with severe combined immune deficiency (SCID) of the common γ-chain — a rare X-linked disorder in which mature T cells and natural-killer cells fail to develop. Patients received autologous haematopoietic stem cells that had been transduced *ex vivo* with a retroviral vector encoding the common γ-chain. A report published in April 2002 showed that the deficiency had been corrected in 9 out of 11 patients.

Retroviruses are risky gene-therapy vectors because they can insert into the genome in or near an oncogene or tumour-suppressor gene and disrupt its expression or function. In this case, the retroviral vector inserted into the DNA region that regulates the gene *LMO2* — a site associated with a number of T-cell acute-lymphoblastic-leukaemia-specific translocations. The defective immune cells in this patient express *LMO2*, indicating that the retroviral vector activated the gene.

The retrovirus was probably not the sole factor in the boy's illness, as the family has a history of cancer. The National Institutes of Health's Recombinant DNA Advisory Committee is preparing a broad review of the case this December.

Kristine Novak

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