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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, so impairing the anti-tumour response, according to work by Groh *et al.*, now published in *Nature*.

NKG2D is expressed by natural killer (NK) cells, $\gamma\delta$ T cells and CD8⁺ $\alpha\beta$ T cells, and ligand binding results in NK-cell activation and the co-stimulation of effector T cells. Ligands for NKG2D include MICA and MICB, which are expressed by cells as a result of stress (such as viral infection or transformation). Tumour cells express MIC molecules frequently and, therefore, it follows that these cells might be recognized and destroyed by NKG2D-expressing host immune cells.

However, the immune system often fails to recognize MIC-expressing tumour cells, which led the authors to question 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. The level of expression of cell-surface NKG2D by CD8⁺ T cells isolated from tumour-infiltrating lymphocytes (TILs) and peripheral-blood mononuclear cells (PBMCs) from MIC⁺ tumours was reduced considerably compared with that of T cells from MIC⁻ tumours, and the level of expression decreased with time, which indicates that MIC proteins induce the downmodulation of 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 down-regulation of NKG2D expression. This was confirmed directly by experiments showing that serum from cancer patients with MIC⁺ tumours — as well as recombinant, soluble MICA — downmodulates 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 for 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

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)

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

WEB SITE

Thomas Spies' home page:
<http://myprofile.cos.com/spiesabc5>