have so far been described to depend on VAV1 occur in the cytoplasm, so the identification of arginine-methylated VAV1 in the nucleus indicates that VAV1 might have additional functions in T-cell activation: for example, it might modulate the activity of transcription factors.

Further studies are required to determine which T-cell functions are regulated by arginine methylation downstream of CD28 co-stimulation, although initial experiments reported in this paper indicate that this is one mechanism by which T-cell production of interleukin-2 can be regulated. The authors also suggest that, because arginine methylation is a stable protein modification (no enzymes that can remove this modification have been identified so far), arginine methylation downstream of CD28 co-stimulation might contribute to T-cell-fate differentiation decisions.

Karen Honey

References and links

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TUMOUR IMMUNOLOGY

Another way to escape the immune system's watchful eye

It seems that we can learn a thing or two about the immune system from tumours: the genes that they silence might indicate pathways of immune surveillance. Reporting in *Blood*, Marco Colonna and colleagues show that lung cancers frequently silence the tumour-suppressor gene *TSLC1* to escape the cytotoxic activity of natural killer (NK) cells and CD8$^+$ T cells.

***TSLC1* (tumour suppressor in lung cancer 1) encodes a cell-surface protein known as nectin-like 2 (NECL2), which contributes to cell–cell adhesion through homotypic interactions or heterotypic interactions with other nectin or nectin-like proteins. It was thought therefore that the silencing of this gene — a common occurrence in lung cancers — in lung epithelial cells disrupts cell polarity and cell–cell adhesion, favouring neoplastic growth and metastasis. But Colonna and colleagues thought that there might be another reason for its silencing, as they have recently shown that similar proteins, nectin-2 and NECL5, can be recognized by NK cells and activate their cytolytic activity.**

To investigate whether NECL2 is recognized by immune cells, the authors first searched the databases for putative receptors for NECL2, and they came up with a candidate — class-I-restricted T-cell-associated molecule (CRTAM). When cell lines expressing either NECL2 or CRTAM were co-cultured, cell–cell conjugates formed between the NECL2-expressing cells and the CRTAM-expressing cells. These cell–cell interactions could be disrupted by incubation with antibody specific for CRTAM. The interaction between NECL2 and CRTAM was further confirmed by showing that a NECL2–Fc fusion protein could bind the CRTAM-transfected cell line and vice versa.

The authors then showed that CRTAM is expressed by NK cells only after activation: for example, after triggering by PMA (phorbol 12-myristate 13-acetate) and ionomycin or by antibodies specific for NK-cell activating receptors. Similarly, CRTAM expression was detected at the surface of CD8$^+$ T cells only after stimulation through the T-cell receptor. Importantly, CRTAM expression promoted NK-cell lysis of NECL2-expressing tumour cells and increased interferon-γ secretion by CD8$^+$ T cells when co-cultured with a B-cell line expressing high levels of NECL2.

The key question therefore is whether expression of NECL2 by tumour cells allows efficient rejection by NK cells *in vivo*. To test this, mice were injected intraperitoneally with an equal mixture of lymphoma cells that were transfected with either a plasmid encoding NECL2 or a control plasmid and labelled with different amounts of fluorochrome. Before tumour challenge, the mice were stimulated with polyI:C (polyinosinic–polycytidylic acid) to accelerate NK-cell activation. After 48 hours, significantly fewer NECL2-expressing tumour cells than control tumour cells could be recovered from the peritoneal cavity, indicating preferential rejection of these cells. NK cells were crucial for this rejection, because the rejection of NECL2-expressing cells was reduced when mice were depleted of NK cells.

On the basis of these observations, the authors propose that, because NECL2 is normally expressed at epithelial-cell junctions, it might not be readily accessible to the immune system. But, after epithelial cells begin to transform and metastasize, NECL2 could become exposed and induce NK- and T-cell responses. So, NECL2 is another molecular target that allows surveying cytotoxic lymphocytes to distinguish tumour cells from normal cells.

Lucy Bird

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