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IMMUNOTHERAPY

Soluble ligands—a new approach to cancer therapy

Immune cells, including natural killer (NK) cells, recognize transformed cells and eliminate them in a process termed immunosurveillance, which is mediated by the presence of activating receptors, such as natural killer group 2 member D (NKG2D) on the NK cells. The transformed cell upregulates the expression of NKG2D ligands, triggering the NK-cell response. However, tumour cells evade immunosurveillance by shedding membrane ligands that bind to the NKG2D receptor, desensitizing the immune cells. In this context, the research group led by David Raulet set out to investigate the impact of soluble NKG2D ligands, focusing on the mouse ligand Mult1, which is commonly upregulated in primary tumours. They uncovered a surprising new mechanism, showing that the cleavage of Mult1 activates NK cells.

Using murine models of cancer and mouse tumour cell lines, "we have demonstrated that tumours secreting soluble Mult1 induce the activation of NK cells that results in their increased killing activity and tumour rejection," says Raulet. In these conditions, the amount of NKG2D on the surface of NK cells was increased. They propose that soluble Mult1 competitively blocks the NKG2D receptor, preventing its association with the membrane bound form of the ligand and thus reversing the global desensitization process of the NK cells.

The discovery of this mechanism highlights a new avenue for cancer immunotherapy—using soluble ligands to restore antitumour immunity. "Depending on the mechanism of action of soluble ligands, antibodies against specific NKG2D ligands, or NKG2D itself, may also have therapeutic effects," says Raulet.

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Original article Deng, W. *et al.* A shed NKG2D ligand that promotes natural killer cell activation and tumor rejection. *Science* doi:10.1126/science.1258867