IN BRIEF

IMMUNE REGULATION

Homomultimeric complexes of CD22 in B cells revealed by protein–glycan cross-linking.

Han, S. *et al*. *Nature Chem. Biol.* **1**, 93–97 (2005)

CD22 is a B-cell co-receptor that functions as a negative regulator of B-cell-receptor signalling. The activity of CD22 is regulated by other cell-surface glycoproteins expressed by the B cell that bind CD22 and mask its ligand-binding domain; these are known as *cis* ligands. Han *et al*. developed a method to identify the *cis* ligands that regulate CD22 activity *in situ*. B cells were cultured in the presence of sialic-acid analogues (which become incorporated into the cell-surface glycoproteins) that become crosslinked to any bound molecules after exposure to ultraviolet light. Although glycoproteins such as CD19, CD45 and IgM could bind CD22 *in vitro*, they were not CD22 *cis* ligands *in situ*. Instead, CD22 was found to form homomultimers, indicating that CD22 functions as its own *cis* ligand.

IMMUNODEFICIENCY

Mutations in *TNFRSF13B* encoding TACI are associated with common variable immunodeficiency in humans.

Salzer, U. *et al*. *Nature Genet.* 10 Jul 2005 (doi:10.1038/ng1600)

TACI is mutant in common variable immunodeficiency and IgA deficiency.

Castigli, E. *et al*. *Nature Genet.* 10 Jul 2005 (doi:10.1038/ng1601)

Two studies in the August issue of *Nature Genetics* present evidence of a role for the tumour-necrosis-factor receptor (TNFR)-family member TACI in two human immunodeficiency syndromes, common variable immunodeficiency (CVID) and IgA deficiency. Salzer *et al*. identified homozygous and heterozygous mutations in the gene encoding TACI (*TNFRSF13B*) in 13 individuals with CVID (both sporadic and familial forms). TACI, which is expressed by B cells, has been shown to induce immunoglobulin class switching after binding either of its ligands, BAFF and APRIL. Accordingly, individuals with mutations that abrogated binding of APRIL had impaired B-cell proliferation and defective class switching in response to interleukin-10 and APRIL or BAFF. As a result, these individuals had humoral immunodeficiency characterized by low serum IgM level and impaired IgG and IgA production, making them susceptible to recurrent bacterial infections. Lymphoproliferation and signs of autoimmunity were also evident in TACI-deficient individuals — similar to features seen in *Tnfrsf13b*$^{-/-}$ mice. Castigli *et al*. identified mutations in the same gene in individuals with either CVID or IgA deficiency. Similarly, in response to ligation with APRIL, they observed defective IgG and IgA secretion by B cells from individuals with CVID or IgA deficiency. But only IgA secretion was defective when these cells were stimulated with BAFF. The common genetic basis of CVID and IgA deficiency has long been suspected, as these disorders have been shown to coexist within families.

NATURAL KILLER CELLS

DNA damage link to innate immunity

In a study published in *Nature*, Stephan Gasser and colleagues report that DNA damage initiates a cellular-signalling pathway that alerts the immune system to the presence of potentially dangerous cells.

NKG2D (natural-killer group 2, member D) is an activating receptor that is expressed at the surface of natural killer (NK) cells and CD8$^+$ T cells. NKG2D recognizes ligands that are upregulated by diseased cells, leading to the lysis of these cells, but regulation of the expression of NKG2D ligands is poorly understood. In this study, the authors studied ovarian epithelial cell lines. NKG2D ligands were not expressed in culture by cells that had been transformed, as detected using an NKG2D tetramer, but they were expressed when the transformed cells were injected into the ovaries of mice and developed into tumours. So, transformation *per se* is not sufficient to induce upregulation of ligand expression.

Next, the authors subjected the transformed ovarian epithelial cells to various cellular stresses, including changes in pH, changes in oxygen concentration, and heat shock. However, the cells expressed NKG2D ligands only after exposure to ionizing radiation, inhibitors of DNA replication or chromatin-modifying reagents, all of which activate a major DNA-damage-response pathway that is initiated by the protein kinases ATM (ataxia telangiectasia mutated) and/or ATR (ATM- and RAD3-related). These treatments also induced NKG2D-ligand expression by normal adult fibroblasts. Other treatments, such as with ultraviolet light or the chemotherapeutic reagent cisplatin, also induced NKG2D-ligand expression by these fibroblasts. The role of ATR in upregulation of NKG2D-ligand expression was confirmed in three ways: by inhibiting ATR and ATM using caffeine, by blocking ATR expression using small interfering RNA and by showing that fibroblasts deficient in ATR could not upregulate expression of NKG2D ligands in response to genotoxic stress. Regulation of ligand expression did not depend on arrest of the cell cycle or on induction of cell-death pathways.

This study shows that DNA damage alerts cells of the immune system to attack damaged self cells, and it is possible that this mechanism also operates to trigger immune responses to virally infected cells. It remains to be established whether this mechanism can account for at least some of the effects of chemotherapy and radiation therapy, but the signalling pathway that involves ATR and/or ATM could become a target for the development of new therapeutics for cancer.

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References and links

ORIGINAL RESEARCH PAPER Gasser, S., Orsulic, S., Brown, E. J. & Raulet, D. H. The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor. *Nature* 3 Jul 2005 (doi:10.1038/nature03884)