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AUTOIMMUNITY

Too much of a good thing

It's all a question of balance. This recurring theme in immunology ensures appropriate reactivity to harmful/foreign antigens while maintaining tolerance to harmless/self antigens. Thomas Spies and colleagues have now identified another example of this balance by showing that unrestrained activation of a subset of $CD4^+$ T cells has a role in the autoimmune disease rheumatoid arthritis.

Normally, activating isoforms of natural killer (NK)-cell receptors that modulate T-cell reactivity are co-expressed with inhibitory counterparts, which prevent inappropriate activation. It has therefore been suggested that the expression of an activating receptor without an inhibitory counterpart might have a role in autoimmune disease. One such receptor that lacks a known antagonist is NKG2D.

NKG2D is a receptor for the MHC-class-I related chains MICA and MICB, which are normally expressed by the intestinal epithelium only. However, these ligands can be induced in response to stress such as abnormal proliferation. In synovial-tissue sections from patients, the expression of MIC proteins by fibroblasts was associated with expression of the nuclear proliferation marker Ki-67, which indicates that MIC expression is induced by the synovial hyperplasia that is a feature of rheumatoid arthritis.

So, how does ligation of NKG2D by MICA/B contribute to pathology? Rheumatoid arthritis is associated with a subset of $CD4^+CD28^-$ T cells that are rare in healthy individuals, and this study showed that these cells preferentially express NKG2D in the peripheral blood and synovial tissue of patients with rheumatoid arthritis. These T cells produced the pro-inflammatory cytokine interferon-γ (IFN-γ) in response to autologous, but not allogeneic, synoviocytes, and this effect was blocked by an antibody specific for MIC proteins.

Interleukin-15 (IL-15) is known to upregulate the expression of NKG2D by intestinal $CD8^+$ T cells, and this cytokine is present at a high level in arthritic synovia. IL-15 was shown to upregulate the expression of NKG2D by peripheral-blood lymphocytes (PBLs) *in vitro*, and this upregulation was more marked for PBLs from patients with rheumatoid arthritis. Tumour-necrosis factor (TNF) — another cytokine that is involved in the pathogenesis of rheumatoid arthritis — also upregulated the expression of NKG2D.

Normally, soluble MIC ligands (shed from cells by proteolysis) induce the downmodulation of NKG2D and restore the equilibrium. However, in the presence of IL-15 and TNF, receptor downmodulation is prevented. So, T-cell activation is maintained in patients with rheumatoid arthritis, which perpetuates pathology. This indicates that part of the therapeutic effect of agents that target TNF or IL-15 might be due to the restoration of NKG2D downmodulation.

Kirsty Minton

References and links

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