TOLERANCE

The 'indifferent' thief

This study identifies a new form of tolerance in which $CD8^+$ T cells interact with high affinity with their MHC class-I-restricted epitope on dendritic cells (DCs) but fail to proliferate. Instead, the T cells remove the peptide from the surface of the DC, thereby affecting the activation of other T cells specific for the same epitope.

Goverman and colleagues used a mouse model of the autoimmune disease multiple sclerosis, in which $CD8^+$ T cells express a transgenic T-cell receptor (TCR) specific for an MHC class-I-restricted epitope of myelin basic protein — MBP(79–87) — to look at the mechanisms of tolerance to self-antigens. They created two mouse lines expressing different TCR transgenes (known as 8.6 and 8.8) specific for MBP(79–87).

As expected, 8.6 T cells underwent negative selection in the thymus (central tolerance) and deletion in the periphery (peripheral tolerance) in wild-type mice, which express MBP. However, although 8.8 T cells recognize the same epitope, they were not deleted in the thymus or periphery of wild-type mice, indicating that they have an intrinsic non-responsiveness to MBP. Surprisingly, this was not due to TCR affinity as the 8.8 T cells have a higher affinity than 8.6 T cells for MBP(79–87).

Not only do the 8.8 T cells escape deletion themselves, they can also prevent the deletion of 8.6 T cells. When 8.6 and 8.8 bone marrow from MBP-deficient mice were transferred together into wild-type recipients, bone-marrow-derived 8.6 T cells were no longer deleted in the thymus or periphery. This inhibitory effect of 8.8 T cells was shown to be antigen and epitope specific. Together with the high affinity of 8.8 T cells, this epitope specificity indicated that the mechanism might involve competition for, and removal of, peptide–MHC complexes on DCs. Consistent with this, the proliferation of 8.6 T cells in response to DCs isolated from MBP-expressing 8.8 mice was significantly reduced compared with the response to DCs from non-transgenic mice. Although they were unable to show this 'epitope theft' from DCs directly, all of their results are consistent with a model in which the high-affinity interaction of 8.8 T cells with MBP(79–87) strips this epitope from the surface of DCs.

So, despite their lack of proliferation, 8.8 T cells are not ignorant of endogenous MBP, and it seems that indifference is the new tolerance. However, as this epitope theft inhibits other T cells specific for the same epitope from being deleted, the effects of this phenomenon require further investigation.

Kirsty Minton

References and links

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INNATE IMMUNITY

Cargo-driven phagosome fate

The phagocytosis of microbial pathogens by cells of the innate immune system (such as macrophages) usually results in the induction of inflammatory responses, whereas the engulfment of apoptotic cells during tissue remodelling generally does not. A recent report in *Science* shows that activation of Toll-like receptor (TLR) signalling by bacteria, but not by apoptotic cells, underlies the distinct outcomes of these phagocytic pathways.

After uptake of bacteria by macrophages, phagosomes rapidly fuse with lysosomes (within 30 minutes) to become phagolysosomes, in which bacteria are degraded. To explore the role of TLR signalling in the regulation of this phagosome-maturation pathway, the authors followed the uptake of fluorescent bacteria by wild-type macrophages or those that lacked expression of TLR2 and TLR4, or MyD88 — a crucial TLR-signalling adaptor protein. They found that in the absence of TLRs or MyD88, internalization of bacteria (*Escherichia coli, Staphylococcus aureus* or *Salmonella typhimurium*) was delayed and degradation was less efficient, due to inefficient fusion of phagosomes with lysosomes. By contrast, phagocytosis of apoptotic cells was not affected in the absence of TLRs or MyD88, although the kinetics of phagocytosis of apoptotic cells were slower than the uptake of bacteria by wild-type macrophages — lysosome fusion only occurred after 1.5 to 2 hours. In fact, the rate of phagocytosis of apoptotic cells was similar to the rate of bacterial uptake by TLR-signalling-deficient cells. The authors therefore propose that two rates of phagosome maturation exist: a constitutive rate and a more rapid inducible rate, triggered by TLR signalling.

The authors went on to show that the rate of phagosome maturation depends on the ability of the specific phagosome cargo to trigger TLR signalling. In a single macrophage, bacteria and apoptotic cells are internalized into separate phagosomes; however, phagosomes containing apoptotic cells do not mature faster in macrophages that also have bacteria-containing phagosomes or in macrophages stimulated by the TLR4 ligand lipopolysaccharide, indicating that the inducible rate of maturation is phagosome autonomous.

Finally, using specific inhibitors, they show that the p38 mitogen-activated protein kinase that is activated downstream of TLRs is required for accelerated phagosome maturation triggered by bacteria. The authors suggest that the TLR–MyD88–p38 signalling pathway might be disrupted by some intracellular bacteria that avoid phagolysosomal fusion and the subsequent recognition by the innate and adaptive immune systems.

Lucy Bird

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