T-CELL RESPONSES

Directing responses in death

It is well established that different combinations of cytokines drive the differentiation of $CD4^+$ T cells into specialized effector-cell subsets. For example, both transforming growth factor-β (TGFβ) and interleukin-6 (IL-6) are required for the generation of IL-17-producing T helper 17 (T_H17) cells, and IL-23 supports the clonal expansion of these cells. These conditions can be easily recreated *in vitro*, but it is not clear what events trigger the simultaneous production of these cytokines *in vivo*. Now, Torchinsky *et al.* show that infected apoptotic cells induce dendritic cells (DCs) to establish the ideal conditions for T_H17-cell differentiation *in vivo*.

Drawing on the knowledge that phagocytosis of apoptotic cells by DCs induces TGFβ production and that microbial components induce IL-6 production following Toll-like receptor (TLR) activation, the authors investigated whether concomitant ligation of TLRs during phagocytosis leads to the production of both cytokines simultaneously. Indeed, when DCs were cultured with apoptotic neutrophils that were infected with *Escherichia coli* or apoptotic B cells carrying the TLR4 ligand lipopolysaccharide (LPS), they secreted more TGFβ and IL-23 than DCs cultured with LPS alone; IL-6 was produced in all cultures at similar levels. Importantly, incubation of naive $CD4^+$ T cells with media from cultures of DCs that had phagocytosed LPS-containing apoptotic B cells led to the efficient generation of T_H17 cells, as indicated by the secretion of IL-17A and expression of the T_H17-cell-lineage-specific transcription factor RORγt (retinoic acid receptor-related orphan receptor-γt). By contrast, T_H17 cells did not develop in T-cell cultures containing media from DCs that had phagocytosed apoptotic B cells not carrying TLR ligands. Instead, regulatory T (T_{Reg}) cells expressing forkhead box P3 (FOXP3) developed in these cultures, which is consistent with the known immunosuppressive nature of apoptotic cell clearance. Addition of IL-6 to these cultures restored IL-17A secretion and impaired FOXP3 expression, indicating that the specific combination of signals from TLR ligands and apoptotic cells enables DCs to favour the generation of T_H17 cells rather than T_{Reg} cells.

The use of a pan-caspase inhibitor and *Il6*$^{-/-}$ DCs confirmed that LPS-containing B cells must be apoptotic and DCs must be able to produce IL-6 to support T_H17-cell development. A requirement for TLR signalling in the DCs was also confirmed with the use of DCs that lacked TLR signalling adaptor proteins or TLR4; media from cultures of TLR-signalling-deficient DCs that had phagocytosed infected apoptotic neutrophils or LPS-containing apoptotic B cells supported the development of T_{Reg} cells rather than T_H17 cells.

Next, the authors investigated whether blockade of apoptosis impairs T_H17-cell development *in vivo* during infection of mice with the enteric pathogen *Citrobacter rodentium*, which is known to cause apoptosis of intestinal epithelial cells and trigger T_H17-cell responses. Treatment of infected mice with a pan-caspase inhibitor markedly diminished the T_H17-cell response. Similarly, infection with a mutant strain of *C. rodentium* that cannot trigger apoptosis failed to induce the characteristic T_H17-cell response.

So, these data indicate that the presence or absence of TLR ligands in apoptotic cells dictates whether DCs that take up these cells direct the generation of T_H17 or T_{Reg} cells. In addition, these findings suggest that pathogens triggering significant levels of apoptosis could preferentially induce T_H17-cell immunity.

Lucy Bird

ORIGINAL RESEARCH PAPER Torchinsky, M. B. *et al.* Innate immune recognition of infected apoptotic cells directs T_H17 cell differentiation. *Nature* **458**, 78–82 (2009)
FURTHER READING Stockinger, B. Cause of death matters. *Nature* **458**, 44–45 (2009)