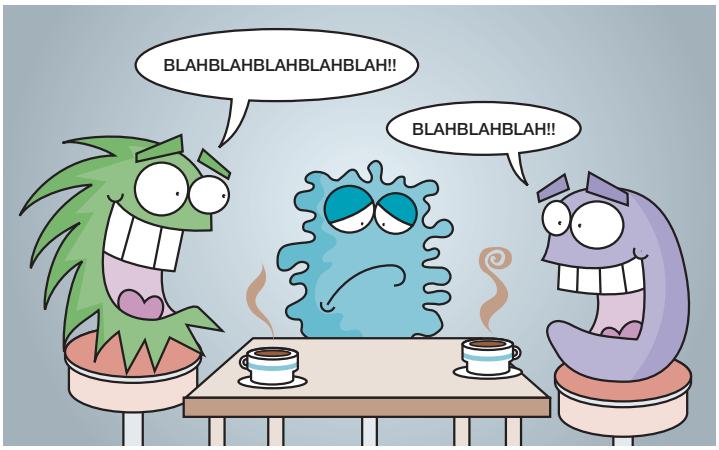
T-CELL RESPONSES

Cutting out the middle man



New research published in *The Journal of Immunology* shows that antigen-presenting cells such as dendritic cells (DCs) are not always required to link innate immune signals through Toll-like receptors (TLRs) to adaptive T-cell responses. This study showed that TLR expression by T cells can lead to direct effects of pathogen-associated molecular patterns (PAMPs) on adaptive immunity.

Stimulation of TLRs on DCs results in DC maturation and induces the upregulation of MHC and co-stimulatory molecules and the production of pro-inflammatory cytokines. The mature DCs in turn present antigen to, and stimulate, T cells. However, in this study, activated mouse $CD4^+$ T cells were also shown to express TLRs, indicating the possibility of a direct effect. Specifically, purified $CD4^+CD25^-$ T cells expressed mRNA encoding TLR3 and TLR9 but not TLR2 and TLR4. In the absence of suitable monoclonal antibodies to detect TLR protein, the mRNA results were confirmed by stimulation with the TLR3 ligand poly(I:C) and the TLR9 ligand CpG-containing DNA. These ligands induced nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) activation in the activated T cells, in contrast to the TLR4 ligand lipopolysaccharide.

Having shown that T-cell TLR3 and TLR9 are functional in terms of signalling, Laurence Turka and colleagues looked at the downstream effects. They showed that stimulation with poly(I:C) or CpG-containing DNA increased the survival of a purified population of activated $CD4^+$ T cells *in vitro*. The increase in viable cell number occurred without any change in proliferation. When activated T cells were stimulated with poly(I:C) or CpG DNA and then adoptively transferred into congenic hosts, survival was also increased *in vivo* compared with unstimulated cells, as indicated by an increased percentage of transferred T cells in the host spleen and an increased proliferative response to restimulation with the cognate antigen. Therefore, TLR signalling in T cells might improve memory responses by promoting the survival of T cells after primary stimulation.

Using specific inhibitors, the T-cell survival response mediated by TLRs was shown to depend on NF-κB but not MAPK activation. Consistent with previous knowledge of TLR signalling, CpG-DNA-mediated survival through TLR9 depended on the adaptor molecule MyD88, whereas poly(I:C)-mediated survival through TLR3 did not. This indicates that both MyD88-dependent and -independent pathways can activate NF-κB to mediate increased survival in T cells. The end result of these two pathways was upregulation of expression of the anti-apoptotic molecule $BCL\text{-}X_L$.

The authors speculate that the ability of T cells to respond directly to PAMPs, without using DCs as an intermediary, might be one way in which we have evolved to deal with pathogens that try to evade the immune system by inhibiting DC function.

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References and links

ORIGINAL RESEARCH PAPER Gelman, A. E., Zhang, J., Choi, Y. & Turka, L. A. Toll-like receptor ligands directly promote activated $CD4^+$ T-cell survival. *J. Immunol.* **172**, 6065–6073 (2004).