T CELLS

TLRs deliver a direct hit to T_H17 cells

Toll-like receptors (TLRs) generally promote adaptive immune responses indirectly by activating innate immune cells. Now, new research shows an unexpected direct role for TLR2 signalling in T cells themselves, promoting the differentiation and proliferation of T helper 17 (T_H17) cells.

Microarray and flow cytometry analyses of various T cell subsets showed that T_H17 cells express high levels of TLR2 and its dimerization partners, TLR1 and TLR6, with levels being higher than in T_H1 and T_H2 cells but lower than in macrophages and interleukin-17 (IL-17)-producing γδ T cells. In support of a functional role for TLR expression in T cells, purified naive $CD4^+$ T cells cultured in T_H17-polarizing conditions in the presence of the TLR2 agonist Pam3Cys-Ser-Lys4-trihydrochloride (Pam3CSK4) showed a marked increase in IL-17 production, as well as upregulation of mRNA encoding the T_H17 cell-associated transcription factors retinoic acid receptor-related orphan receptor-γ (RORγ) and interferon-regulatory factor 4 (IRF4). Pam3CSK4 had no effect in cultures of *Tlr2*$^{-/-}$ T cells.

In addition to directly promoting T_H17 cell differentiation, the authors showed that TLR2 activation in naive T cells, T_H17 cells, memory T cells and γδ T cells enhanced their proliferation *in vitro*, even in the absence of T cell receptor stimulation. IL-23 was found to synergize with TLR2 agonists in the proliferation of these subsets, as well as in the production of IL-17 by T_H17 cells.

To explore the role of TLR2 signalling in the regulation of T_H17 cells *in vivo*, the authors reconstituted immunodeficient mice with wild-type or *Tlr2*$^{-/-}$ $CD4^+$ T cells and injected them with myelin oligodendrocyte glycoprotein in complete Freund's adjuvant to induce experimental autoimmune encephalomyelitis (EAE). Surprisingly, compared with mice reconstituted with wild-type T cells, mice receiving *Tlr2*$^{-/-}$ T cells were largely resistant to EAE induction, showing much reduced cellular infiltration of the central nervous system with fewer cells producing IL-17 or interferon-γ.

So, in addition to the well known role of TLR signalling in the activation of innate immune cells, TLR2 ligands can act directly on T cells and modify adaptive immune responses that contribute to the pathogenesis of autoimmune disease.

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ORIGINAL RESEARCH PAPER Reynolds, J. M. *et al.* Toll-like receptor 2 signaling in $CD4^+$ T lymphocytes promotes T helper 17 responses and regulates the pathogenesis of autoimmune disease. *Immunity* 29 Apr 2010 (doi:10.1016/j.immuni.2010.04.010)