T-CELL DEVELOPMENT

CD40–CD40L crosstalk in T_H17-cell differentiation

Understanding the factors that are involved in the differentiation of T helper 17 (T_H17) cells is currently one of the most active areas of immunological research. Now, Kopf and colleagues add more detail to this picture with the finding that CD40–CD40 ligand (CD40L) crosstalk is required for the differentiation of T_H17 cells *in vitro* and *in vivo*.

The authors first examined the effect of antigen dose on T_H17-cell differentiation and found that a high, but not low or intermediate, antigen dose favours the development of these cells *in vitro*. T_H17-cell differentiation in the presence of a high antigen dose was accompanied by increased CD40L expression and was synergistically enhanced by the presence of pattern-recognition receptor (PRR) ligands — specifically, CpG DNA, curdlan and zymosan.

These PRR ligands upregulated the expression of CD40 and CD86 by dendritic cells (DCs) and induced the production of various cytokines, such as interleukin-6 (IL-6), an effect that was boosted by CD40 ligation. Co-culture of antigen-exposed $CD4^+$ T cells with *Cd40*$^{-/-}$ DCs in the presence of these PRR ligands resulted in impaired T_H17-cell, but not T_H1-cell, differentiation, suggesting a role for CD40–CD40L crosstalk in T_H17-cell differentiation. T_H17-cell differentiation in this setting was restored by the addition of exogenous IL-6. These observations were confirmed *in vivo*: immunization of *Cd40*$^{-/-}$ mice with a high antigen dose and adjuvant resulted in impaired T_H17-cell, but not T_H1-cell, differentiation.

To examine the physiological relevance of CD40–CD40L crosstalk in T_H17-cell differentiation, the authors used a mouse model of experimental autoimmune encephalomyelitis, in which T_H17 cells are thought to have a pathogenic role. Unlike wild-type mice, *Cd40*$^{-/-}$ mice were protected from disease and few effector $CD4^+$ T cells were found in their central nervous system. Although splenic T cells from *Cd40*$^{-/-}$ mice responded to antigen stimulation *ex vivo* (indicating that T-cell priming had occurred in these mice), they did not produce IL-17.

Together, the data show that strong antigenic and pathogenic stimuli synergize to drive T_H17-cell differentiation *in vitro* and *in vivo* by promoting CD40–CD40L crosstalk.

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ORIGINAL RESEARCH PAPER Iezzi, G. *et al.* CD40–CD40L cross-talk integrates strong antigenic signals and microbial stimuli to induce development of IL-17-producing $CD4^+$ T cells. *Proc. Natl Acad. Sci. USA* **106**, 876–881 (2009)