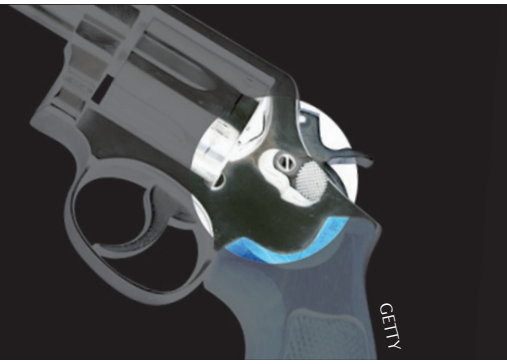
MUCOSAL IMMUNOLOGY

A safety catch to prevent intestinal inflammation



Constant contact with commensal microorganisms is tolerated with the help of a safety mechanism that makes the induction of T helper 17 (T_H17) cells more difficult at mucosal surfaces than systemically, according to new research. A unique population of intestinal dendritic cells (DCs) increases the cytokine requirements for T_H17 cell induction in the gut by tipping the balance in favour of the development of regulatory T (T_{Reg}) cells.

In vitro assays have indicated that interleukin-6 (IL-6) — together with transforming growth factor-β — is a necessary differentiation factor for T_H17 cells. However, the authors showed that memory T cells from the spleens of *Il6*$^{-/-}$ mice and wild-type mice secreted similar amounts of IL-17 and had similar levels of expression of the T_H17 cell master regulator RORγt. By contrast, T_H17 cell lineage commitment in the intestinal lamina propria was defective in *Il6*$^{-/-}$ mice, and this correlated with an increase in the number of T_{Reg} cells. These data indicate that IL-6 is required for T_H17 cell differentiation in the intestines, but not in the spleen, and that this requirement might involve the balance between T_H17 cells and T_{Reg} cells.

Adoptively transferred naive T cells expressing a dominant-negative form of the IL-6 receptor could differentiate into T_H17 cells in the spleen and the liver but not in the lamina propria or the lungs. This indicates that IL-6 is a mucosal tissue-specific priming factor for T_H17 cells. In support of this, oral bacterial infection of *Il6*$^{-/-}$ mice failed to generate T_H17 cells in the mesenteric lymph nodes or the lamina propria, whereas intraperitoneal injection of bacteria leading to a systemic infection resulted in comparable T_H17 cell priming in the spleen in *Il6*$^{-/-}$ and wild-type mice.

The tissue-specific role of IL-6 was shown to depend on differences in the DC populations. In particular, CD103^{hi} DCs are absent from the spleen but constitute ~20% of intestinal DCs. Previous reports have shown that CD103^{hi} DCs preferentially induce T_{Reg} cells, and in this study these DCs could not induce T_H17 cells with or without IL-6. When the CD103^{hi} DCs were depleted from the lamina propria DC population of *Il6*$^{-/-}$ mice, the remaining DCs could induce T_H17 cells in a similar manner to splenic DCs. The results indicate that CD103^{hi} DCs are dominant over CD103^{-} DCs in preventing the IL-6-independent priming of T_H17 cells; this effect was shown to be mediated by their production of retinoic acid, which favours the generation of T_{Reg} cells.

In summary, in the presence of retinoic acid production by CD103^{hi} DCs in the gut, the highly pro-inflammatory cytokine IL-6 — expression of which might indicate pathogen invasion — is necessary for overcoming the 'regulatory' microenvironment that normally tolerates commensal bacteria, thereby allowing the induction of T_H17 cells. In the spleen, which is normally sterile, the requirements for T_H17 cell induction are less stringent and IL-6 is not required. However, the authors showed that IL-1 is necessary for T_H17 cell induction in the spleen, as well as in the lamina propria of the gut.

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ORIGINAL RESEARCH PAPER Hu, W. *et al.* Priming microenvironments dictate cytokine requirements for T helper 17 cell lineage commitment. *Immunity* 1 Dec 2011 (doi:10.1016/j.immuni.2011.10.013)