INNATE IMMUNITY

Help from 'friendly' bacteria

Commensal gut bacteria have many beneficial effects for the host, including competition with pathogens and induction of the development of gut-associated lymphoid tissues. Now, Benson *et al.* add another function to this list by showing that the gut microbiota acts as an adjuvant to induce immunity to *Toxoplasma gondii*.

In mice *T. gondii* is sensed by Toll-like receptor 11 (TLR11) on dendritic cells (DCs), which secrete interleukin-12 (IL-12) to activate $CD4^+$ T helper 1 (T_H1) cells; these then produce interferon-γ (IFNγ) to kill the parasite. However, *TLR11* is a pseudogene in humans, so a different mechanism must operate. To investigate this, the authors infected wild-type mice and *Tlr11*$^{-/-}$ mice with *T. gondii*. When the mice were infected orally (which mimics natural infection in humans) the production of IL-12 by DCs was reduced but not abolished in *Tlr11*$^{-/-}$ mice; by contrast, IL-12 secretion following intraperitoneal infection required TLR11. Furthermore, $CD4^+$ T cells from *Tlr11*$^{-/-}$ mice could still produce IFNγ when the mice were infected orally but not following intraperitoneal infection. These findings indicate that the mucosal immune system can initiate immune responses to *T. gondii* in the absence of TLR11.

Based on these findings, the authors speculated that either DCs directly detect *T. gondii* in a TLR11-independent manner or the gut microbiota indirectly stimulates DCs to activate T_H1 cell-mediated immune responses. DCs isolated from the intestine of *Tlr11*$^{-/-}$ mice could not detect the parasite *in vitro*, indicating that TLR11 is required for this process. However, depletion of the gut microbiota in *Tlr11*$^{-/-}$ mice abolished the production of IL-12p40 (a component of IL-12) by DCs and subsequent immune responses to the parasite. Therefore, commensal gut bacteria must indirectly stimulate immune responses against the parasite in the absence of TLR11. This TLR11-independent activation of immune responses was found to result in reduced immunopathology compared with TLR11-dependent stimulation, with wild-type mice showing marked immune-mediated damage in the small intestine and significantly higher mortality than *Tlr11*$^{-/-}$ mice.

So how do commensal gut bacteria trigger adaptive immune responses against *T. gondii*? Oral infection of mice lacking TLR9 or both TLR2 and TLR4 (which are used by DCs to sense bacteria) resulted in a marked decrease in IFNγ production by $CD4^+$ T cells. These TLRs signal through myeloid differentiation primary response protein 88 (MYD88), lack of which (in *Myd88*$^{-/-}$ mice) abolished IL-12p40 production following oral or intraperitoneal infection with *T. gondii*. Together, these observations suggest that commensal bacteria stimulate TLR2 and TLR4, or TLR9, of DCs, which signal through MYD88 to mediate DC activation and the induction of T_H1 cell-mediated immunity against *T. gondii*. Further studies will be required to determine how DCs differentiate between commensal and pathogenic bacteria, and how commensal bacteria induce parasite-specific T cell responses without triggering an antibacterial immune response.

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> “commensal gut bacteria must indirectly stimulate immune responses against the parasite in the absence of TLR11.”

ORIGINAL RESEARCH PAPER Benson, A., Pifer, R., Behrendt, C., Hooper, L. V. & Yarovinsky, F. Gut commensal bacteria direct a protective immune response against *Toxoplasma gondii*. *Cell Host Microbe* **6**, 187–196 (2009)