INNATE IMMUNITY

Controlling the microflora…

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MyD88
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In mammals, the commensal microflora of the intestine is crucial for normal physiology but also harbours the potential for harm, because inappropriate activation of the immune response by these microorganisms can cause disorders such as inflammatory bowel disease (IBD). Mucosal immune responses to the intestinal microflora are therefore tightly controlled by regulatory cytokines such as interleukin-2 (IL-2) and IL-10. Ruslan Medzhitov and colleagues now reveal that IL-2 and IL-10 regulate the immune response to intestinal commensal microflora by two distinct pathways: one pathway that converges on the Toll-like receptor (TLR)-signalling pathway, and a separate pathway that is TLR independent.

TLRs have an important role in initiating immune responses through the recognition of pathogen-associated molecular patterns at the surface of microorganisms. To find out whether TLRs are implicated in the development of commensal-dependent colitis, the authors crossed mice deficient in either IL-2 or IL-10 (both of which develop spontaneous commensal-dependent colitis) with mice deficient in MyD88 (myeloid differentiation primary-response gene 88) and/or TRIF (Toll/IL-1-receptor-domain-containing adaptor protein inducing interferon-β), which are adaptor molecules in TLR-signalling pathways. Phenotypic analyses of these mice showed that IL-10 negatively regulates the immune response to intestinal microflora by inhibiting the TLR–MyD88-signalling pathway. By contrast, IL-2 inhibits commensal-induced intestinal inflammation by inhibiting TLR-independent pathways.

The colitis that occurs in IL-2-deficient mice and IL-10-deficient mice is characterized by an aberrant T helper 1 (T_H1)-cell response that is elicited by the production of T_H1 cytokines by antigen-presenting cells. However, whereas IL-10 inhibits commensal-induced $CD4^+$ T-cell-mediated inflammation by downregulating MyD88-dependent signalling, aberrant $CD4^+$ T-cell activation persists in mice deficient in both IL-2 and MyD88 despite the absence of T_H1 cytokines. This provides further evidence that microflora can induce intestinal inflammation by fundamentally different mechanisms. The authors propose that decreased activity of naturally occurring regulatory T cells could contribute to the pathology that occurs in mice that are deficient in both IL-2 and MyD88, and they discuss a potential role for IL-27 in causing colitis in the context of IL-2 deficiency.

These studies highlight the complexities of the interactions between intestinal commensal microorganisms and the mammalian immune system, which are reflected in the heterogeneous characteristics of human IBD. Optimal treatment for IBD should therefore take into account these diverse pathophysiological mechanisms.

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