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AUTOIMMUNITY

The bug eye bandits

> “the activation of autoreactive T cells by commensals may contribute to the development of an array of autoimmune diseases”

S.Bradbrook/NPG

Autoimmune uveitis is major cause of human blindness and is thought to be driven by retina-specific T cells. As the eye is an immune-privileged site, it has been unclear how T cells become activated to respond to retinal antigens. Rachel Caspi and colleagues now show that the activation of pathogenic T cells in a mouse model of uveitis is dependent on the intestinal microbiota.

Many patients with uveitis show immune responses to retinal proteins that are uniquely expressed in the eye. To explore how peripheral T cells become activated to respond to these sequestered antigens, the authors had previously developed a novel mouse model of uveitis — the R161H mouse. These mice express a transgenic T cell receptor (TCR) specific for interphotoreceptor retinoid-binding protein (IRBP; also known as RBP3), which is an autoantigen associated with uveitis, and they spontaneously develop uveitis around the time of weaning. In the present study, the authors set out to determine the triggers of disease development in R161H mice. They found that young R161H mice with no overt disease had high percentages of T cells with an activated or memory phenotype in the intestine but not in peripheral lymphoid tissues, including the eye-draining lymph nodes. Experiments using reporter mice to assess the levels of TCR signalling in R161H mice also suggested that T cells are activated in the intestine before the onset of uveitis.

The authors suspected a possible role for the intestinal microbiota in priming pathogenic T cell responses. In keeping with this, treatment of R161H mice with a broad-spectrum antibiotic cocktail delayed the development and reduced the extent of eye inflammation. A similar attenuation of uveitis was seen in germ-free R161H mice. Compared with wild-type mice, R161H mice showed a marked increase in the frequency of interleukin-17A (IL-17A)-producing $CD4^+$ T cells in the intestine. Of note, IL-17A has previously been associated with the pathology of autoimmune uveitis. The authors also found that in R161H mice, IRBP-specific T cell populations contained higher proportions of $IL\text{-}17A^+$ cells than T cell populations that were not specific for IRBP. These $IL\text{-}17A^+$ T cells were still detected in R161H mice that lacked IRBP expression, indicating that the endogenous protein is not required for their induction.

Further studies using different reporter systems confirmed that IRBP-specific T cells undergo active TCR signalling in the intestine. Importantly, backcrossing with TCRα-deficient mice indicated that the R161H mice signal through their clonotypic receptor rather than through a second TCR. The authors were not able to identify the exact intestinal antigens involved in the activation of the IRBP-specific T cells; however, a series of experiments suggested that these T cells are responding to a protein component from the microbiota. Finally, the authors showed that R161H T cells cultured with components of the gut microbiota induced uveitis when transferred into wild-type recipients, whereas R161H T cells that were cultured alone did not promote disease development in this system.

This study adds to our growing understanding of how the intestinal microbiota can affect immune responses at distal sites. The authors suggest that the activation of autoreactive T cells by commensals may contribute to the development of a range of autoimmune diseases, including uveitis.

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ORIGINAL RESEARCH PAPER Horai, R. *et al.* Microbiota-dependent activation of an autoreactive T cell receptor provokes autoimmunity in an immunologically privileged site. *Immunity* **43**, 343–353 (2015)