DOI:
10.1038/nri2060

MUCOSAL IMMUNOLOGY

IECs keep the peace

How can a protective immune response occur in the gut, where the immune cells must remain hyporesponsive to commensal bacteria and food antigens? Now, a report published in *Nature* shows that a mediator derived from intestinal-epithelial cells (IECs) regulates immune homeostasis in the gut following exposure to a pathogen.

Previous data have shown that IECs might have a role in the regulation of innate immunity *in vitro*, but the role of these cells *in vivo* was not known. Using a mouse model of intestinal nematode infection with *Trichuris muris*, the authors examined the role of IECs in the regulation of T-cell-mediated inflammation and immunity.

DNA-binding assays showed that in IECs, *in vivo, T. muris* induced the activation of nuclear factor-κB (NF-κB) in an IκB kinase-β (IKKβ)-dependent manner. So, the authors generated mice in which IKKβ was specifically deleted in IECs ($Ikkb^{\Delta IEC}$ mice) to determine the influence of IKKβ-dependent IEC-derived products on the immune response in the gut. $Ikkb^{\Delta IEC}$ mice infected with *T. muris* failed to mount a protective T helper 2 (T_H2)-cell response and clear the pathogen. In addition, the authors observed an increase in the production of the shared p40 subunit of interleukin-12 (IL-12) and IL-23 (known as IL-12/IL-23 p40) by dendritic cells (DCs), as well as interferon-γ (IFNγ) and IL-17 by $CD4^+$ T cells in $Ikkb^{\Delta IEC}$ mice compared with litter-mate control mice.

So, what IEC-derived factor(s) is absent in $Ikkb^{\Delta IEC}$ mice that could result in this dysregulated immune response? Gene analysis showed that the expression of IEC-derived thymic stromal lymphopoietin (TSLP) was significantly reduced in $Ikkb^{\Delta IEC}$ mice compared with wild-type mice. TSLP has previously been associated with the development of type 2 responses, but whether it acts by suppressing the production of pro-inflammatory cytokines or by directly inducing T_H2-cell-associated cytokines is not known. Conditioned supernatant from a mouse IEC line or recombinant TSLP inhibited the production of lipopolysaccharide-induced IL-12/IL-23 p40 production by DCs, indicating that the reduced expression of TSLP by IKKβ-deficient IECs might be responsible for the enhanced production of pro-inflammatory cytokines in infected $Ikkb^{\Delta IEC}$ mice.

To confirm this hypothesis, $Ikkb^{\Delta IEC}$ mice infected with *T. muris* were treated with blocking antibodies specific for IL-12/IL-23 p40 and IFNγ. These mice were able to mount protective T_H2-cell responses that resulted in clearance of the pathogen. The data indicate that in wild-type mice infected with *T. muris*, TSLP limits the production of pro-inflammatory cytokines by DCs and promotes the development of a protective T_H2-cell response. Indeed, mice that lack the TSLP receptor were susceptible to infection with *T. muris*.

Therefore, the IKKβ-dependent production of TSLP by IECs is crucial for regulating intestinal immune homeostasis after exposure to a gut pathogen, by directly influencing innate and adaptive immunity.

Olive Leavy

ORIGINAL RESEARCH PAPER Zaph, C. *et al.* Epithelial-cell-intrinsic IKK-β expression regulates intestinal immune homeostasis. *Nature* 25 February 2007 (doi:10.1038/nature05590)