IN BRIEF

ANTIGEN PRESENTATION

The dominant role of CD8$^+$ dendritic cells in cross-presentation is not dictated by antigen capture.

Schnorrer, P. *et al. Proc. Natl Acad. Sci. USA* **103**, 10729–10734 (2006)

Mouse splenic CD8$^+$ dendritic cells (DCs) are unique in their ability to present exogenous antigen by MHC class I molecules, a process known as cross-presentation. However, it was not known, until now, if this ability is due to a difference in antigen-capturing ability or if this cell population has specialized machinery for this process. Schnorrer *et al.* examined the uptake and presentation of different forms of a model antigen by the three main splenic DC subsets and found that all subsets captured comparable amounts of antigen and presented it on their MHC class II molecules. Therefore, the ability of CD8$^+$ DCs to cross-present antigen cannot be attributed to a difference in their ability to capture antigen, indicating that this cell type must have specialized machinery for cross-presentation.

REGULATORY T CELLS

Heat shock protein 60 enhances CD4$^+$CD25$^+$ regulatory T cell function via innate TLR2 signalling.

Zanin-Zhorov, A. *et al. J. Clin. Invest.* **116**, 2022–2032 (2006)

How are the regulators regulated? This paper shows that heat-shock protein 60 (HSP60) can increase the suppressive activity of human CD4$^+$CD25$^+$ regulatory T (T_{Reg}) cells. Treatment of purified T_{Reg} cells with HSP60 before stimulation with CD3-specific antibody enhanced their ability to suppress both pro-inflammatory cytokine secretion by and proliferation of CD4$^+$CD25$^-$ effector T cells in co-culture. The HSP60-derived peptide p227 had a similar effect. The effects of HSP60 or p227 on the T_{Reg} cells were mediated through Toll-like receptor 2 (TLR2), as TLR2-specific blocking antibody abrogated the effects. The mechanism of suppression by HSP60-treated T_{Reg} cells required both cell–cell contact, through interactions with cytotoxic T-lymphocyte antigen 4, and the inhibitory cytokines transforming growth factor-β and interleukin-10. So, signals from an innate receptor delivered by a self-protein might regulate adaptive immune responses.

IMMUNE RESPONSES

Interleukin 12p40 is required for dendritic cell migration and T cell priming after *Mycobacterium tuberculosis* infection.

Khader, S. A. *et al. J. Exp. Med.* **203**, 1805–1815 (2006)

Adaptive T-cell immunity to respiratory infections depends on the migration of dendritic cells (DCs) from the lung to the draining lymph nodes and their subsequent activation of T cells. For effector T-cell development, these DCs must produce interleukin-12 (IL-12)p70, which is made up of IL-12p35 and IL-12p40. Khader *et al.* investigated whether there might be an independent role for IL-12p40 in lung-DC migration and CD4$^+$ T-cell activation following *Mycobacterium tuberculosis* infection, given that there is early secretion of IL-12p40 during lung inflammation. They found that the migration of IL-12p40-deficient DCs from the lungs of *M. tuberculosis*-exposed mice was defective and that these cells were not able to activate naive CD4$^+$ T cells *in vivo*; treatment of the DCs with IL-12p40 homodimer, however, restored these properties. Khader *et al.* have defined a novel and important role for IL-12p40 in the initiation of the lung's adaptive immune response to pathogen challenge.

INNATE IMMUNITY

Gut feeling

How intestinal immune cells discriminate between pathogenic and commensal bacteria in the gut has troubled immunologists and microbiologists alike for decades. Might the answer lie in the selective expression of Toll-like receptors (TLRs) by cells in the lamina propria, as described by Shizuo Akira and colleagues in a recent *Nature Immunology* paper?

TLR5 recognizes the flagella of both Gram-positive and Gram-negative bacteria and has been shown to be expressed mainly on the basolateral surface of intestinal epithelial cells. It is not, however, expressed by conventional splenic dendritic cells or macrophages, which implies an important role for TLR5 in the detection of invasive flagellated bacteria in the gut. In this study, the authors observed that CD11c$^+$ cells in the intestinal lamina propria preferentially express TLR5 and not TLR4.

Gene-expression analysis showed that, following stimulation of CD11c$^+$ lamina propria cells with flagellin, the expression of pro-inflammatory cytokines such as interleukin-6 (IL-6) and other immune-related proteins was induced. Interestingly, expression of the regulatory cytokine IL-10 was not induced, indicating that the response to flagellin is immunostimulatory and not tolerogenic.

By generating *Tlr5*-knockout mice, the authors then studied the role of TLR5 in response to commensal (*Enterobacter cloacae*) versus pathogenic (*Salmonella enterica* serovar Typhimurium) bacteria *in vivo*. Although wild-type CD11c$^+$ lamina propria cells produced copious amounts of IL-6 in response to *S. typhimurium*, only low levels were induced by *E. cloacae*. Importantly, the response to the pathogenic bacteria was TLR5 dependent, as *Tlr5*$^{-/-}$ CD11c$^+$ lamina propria cells failed to respond. This was in contrast to the response by wild-type CD11c$^+$ splenic cells, which, although they lack TLR5 expression, responded to both

CYTOKINES

Involvement of IL-1 in IL-17 production

Recently, there has been much interest in the differentiation and expansion of interleukin-17 (IL-17)-producing T cells, owing to the importance of these cells in the development of autoimmune diseases. Now, new research published in *The Journal of Experimental Medicine* has implicated IL-1 in the induction of this T-cell population.

IL-23 has previously been associated with the induction of experimental autoimmune encephalomyelitis (EAE) through promoting the differentiation of IL-17-producing T cells. However, while examining cytokine production following immunization, Sutton *et al.* observed a defect in IL-17 production by antigen-specific T cells in IL-1 receptor type I-deficient (*Il1r1*$^{-/-}$) mice. To investigate this observation, they examined the development of EAE in these mice.

While all wild-type mice developed severe EAE following immunization with myelin oligodendrocyte glycoprotein (MOG) and adjuvant, most *Il1r1*$^{-/-}$ mice did not develop any clinical signs. In addition, stimulation of spleen cells from *Il1r1*$^{-/-}$ mice with MOG peptide *in vitro* resulted in dramatically reduced IL-17 production compared with cells from wild-type mice. By contrast, the production of IL-10, IL-6 and tumour-necrosis factor (TNF) was unaffected.

These data indicate an important role for IL-1 in promoting the production of IL-17 by antigen-specific T cells *in vivo*. Interestingly, *Il1r1*$^{-/-}$ mice developed EAE following transfer of MOG-specific T cells isolated from wild-type mice that had developed EAE, which suggests that IL-1 might be dispensable for the development of EAE after the induction of IL-17-producing T cells.

Stimulation of CD4$^+$ and CD8$^+$ T cells from wild-type, but not *Il1r1*$^{-/-}$, mice

S. typhimurium and *E. cloacae* in a TLR4-dependent manner.

So, how does the absence of this immune response in *Tlr5*$^{-/-}$ mice affect the outcome of infection with *S. typhimurium*? Surprisingly, *Tlr5*$^{-/-}$ mice survived infection with an otherwise lethal dose of *S. typhimurium*. This was probably due to the involvement of TLR5 in the transport of the bacteria from the gut to the blood and therefore in establishing lethal systemic infection, as fewer bacteria could be detected in the mesenteric lymph nodes and spleen of infected *Tlr5*$^{-/-}$ mice than infected wild-type mice.

Therefore, although selective expression of TLRs by cells in the lamina propria provides an elegant way of avoiding responses to commensal bacteria, pathogenic bacteria might have evolved ways to use this to their advantage.

Lucy Bird

ORIGINAL RESEARCH PAPER Uematsu, S. *et al.* Detection of pathogenic intestinal bacteria by Toll-like receptor 5 on intestinal CD11c^{+} lamina propria cells. *Nature Immunol.* 9 July 2006 (doi:10.1038/ni1362)

with IL-23 induced low levels of IL-17 production *in vitro*, but this was dramatically enhanced by the addition of either IL-1α or IL-1β. IL-1 alone did not directly induce cytokine production by T cells, suggesting that IL-1 synergizes with IL-23 to induce IL-17 production by T cells. TNF is involved in the development of certain T-cell-mediated autoimmune diseases and is a major target of therapeutic intervention. Here, TNF was shown to synergize with IL-23 to induce IL-17 production by splenocytes in an IL-1-dependent manner.

Together, these data suggest that IL-1 is a crucial factor in the induction of IL-17-producing antigen-specific T cells *in vivo*, which are involved in the development of experimental autoimmune disease.

Olive Leavy

ORIGINAL RESEARCH PAPER Sutton, C., Brereton, C., Keogh, B., Mills, K. H. G. & Lavelle, E. C. A crucial role for interleukin (IL)-1 in the induction of IL-17-producing T cells that mediate autoimmune encephalomyelitis. *J. Exp. Med.* **203**, 1685–1691 (2006)

APOPTOSIS

Demise of activated T cells

Apoptosis is an essential process for the control of immune responses, eliminating reactive T cells following their activation-driven expansion in response to an infectious agent. The mitochondrial apoptotic pathway is regulated by the B-cell lymphoma 2 (BCL-2) family of proteins, and BCL-2 homology 3 (BH3)-only proteins regulate the initiation stage of apoptosis. It is thought that the initiation of activated-T-cell death occurs through the activation of the BH3-only protein BIM (BCL-2-interacting mediator of cell death) at the end of the immune response. An unrelated but also important observation is that the transcription factor BCL-3 has been shown to delay the apoptosis of activated T cells in an adjuvant-dependent manner. Georg Häcker and colleagues now pull together some of these observations to help clarify how activated-T-cell death might be regulated.

Forced expression of BCL-3 prolonged the survival of activated T cells in culture, confirming that BCL-3 does have a function in the regulation of T-cell death. Subsequently, the authors compared the gene-expression patterns of activated T cells from BCL-3-deficient and wild-type mice, and found that BIM expression was slightly increased in *Bcl3*$^{-/-}$ T cells. BIM activation was also accelerated in the absence of BCL-3. Bauer *et al.* concluded that BCL-3 exerts its anti-apoptotic effect mostly, and possibly exclusively, by blocking BIM activation.

The authors conditioned activated T cells for autonomous survival by adding medium from lipopolysaccharide (LPS)-activated dendritic cells (DCs) during T-cell-receptor stimulation. They found that although the conditioned medium induced BCL-3 expression in the activated T cells, BCL-3 was not the sole mediator that promoted the survival of these cells. Because BCL-3 seemed to function by inhibiting BIM activation, could there be a BIM-independent pathway leading to activated-T-cell death?

Bauer *et al.* considered PUMA (p53-upregulated modulator of apoptosis), another BH3-only protein, to be a promising candidate because PUMA-deficient T cells survive longer in culture. Activated T cells from *Puma*$^{-/-}$ mice did show increased survival compared with wild-type T cells, although not to the same extent as *Bim*$^{-/-}$ mice. The survival of these cells, like those from *Bim*$^{-/-}$ mice, was also increased when they were activated in the presence of supernatant from LPS-stimulated DCs.

In an effort to identify candidate soluble factors in the medium from LPS-stimulated DCs, Bauer *et al.* tested individual cytokines for their ability to prime T cells for survival in the presence of mitogen. The cytokines interleukin-1 (IL-1), IL-7 and IL-15 effected this priming, even in the absence of BIM and PUMA. These findings prompted the authors to propose that a pathway(s) is activated during activated-T-cell apoptosis that can initiate the activation of BIM and PUMA, but that this pathway(s) can be inhibited by the presence of adjuvants.

These results have helped to clarify how BIM, PUMA and adjuvant-dependent stimuli interact in the activated-T-cell death pathway, and should have implications for T-cell homeostasis and autoimmunity.

Sharon Ahmad

ORIGINAL RESEARCH PAPER Bauer, A. *et al.* The NF-κB regulator Bcl-3 and the BH3-only proteins Bim and Puma control the death of activated T cells. *Proc. Natl Acad. Sci. USA* **103**, 10979–10984 (2006)