The two faces of IL-6

Interleukin 6 (IL-6) can signal via the membrane-bound IL-6 receptor (mIL-6R) or can signal in *trans* using a soluble IL-6 receptor (sIL-6R). In the *Journal of Clinical Investigation*, Doganci *et al.* investigate the possible function of these IL-6R signaling components in allergic asthma. Local blockade of sIL-6R in an experimental mouse model of asthma reduces T helper type 2 cytokine production in the lung, whereas local blockade of mIL-6R induces expansion of $Foxp3^+CD4^+CD25^+$ regulatory T cell (T_{reg} cell) populations. These T_{reg} cells express a functional IL-6Rα receptor and show an increased ability to suppress target cells *in vitro*. In addition, an adoptive transfer model shows that these T_{reg} cells can also inhibit $CD4^+CD25^-$ T cell–induced inflammation *in vivo*. These data suggest that the various IL-6 signaling components control the balance between effector T cells and T_{reg} cells in the lung. *JDKW*

J. Clin. Invest. **115**, 313–325 (2005)

Dampening inflammation

The adaptive immune response seems to dampen increases in Toll-like receptor (TLR)–mediated production of proinflammatory cytokines after burn injury. In the *Journal of Immunology*, Lederer and colleagues identify which adaptive immune cells mediate control of this inflammatory response. Burn-injured CD4-deficient splenocytes produced substantially more proinflammatory cytokines in response to TLR2 or TLR4 agonists than do burn-injured CD8-deficient and wild-type splenocytes, which produce amounts equivalent to each other after TLR stimulation. Specifically, adoptive transfer of wild-type $CD4^+CD25^+$ but not $CD4^+CD25^-$ T cells into CD4-deficient mice suppresses injury-induced proinflammatory cytokine production mediated by TLR signaling. These data therefore suggest $CD4^+CD25^+$ T_{reg} cells help control the innate proinflammatory response after injury. *JDKW*

J. Immunol. **174**, 2957–2963 (2005)

Soothing grafts

The use of T_{reg} cells in therapy requires understanding of its antigen specificity. Although *in vitro* experiments suggest bystander suppression by T_{reg} cells is possible, this mode of suppression *in vivo* is unclear. In *Blood*, Karim *et al.* find that T_{reg} cells generated from one strain of mice in the presence of antibody to CD4 and blood from a different mouse strain prevent rejection of a skin graft from the second mouse strain in an alloantigen-specific way. However, when these T_{reg} cells are restimulated with the alloantigens, they can now prevent graft rejection in a bystander way (graft rejection from a third party). The alloantigen used may be noncellular protein derived from a different source, such as human γ-globulin. Notably, graft rejection in this system requires suppression of $CD8^+$ T cells with a subtherapeutic dose of antibody to CD8. Thus, bystander regulation by T_{reg} cells *in vivo* is possible, which therefore has important implications for long-term success in transplantation. *PTL*

Blood (15 February 2005) doi:10.1182/blood-2004-10-2888

T_{reg} cells for baby

Mice seem to develop T_{reg} cells soon after birth, but when humans begin to generate T_{reg} cells is unclear. In the *European Journal of Immunology*, Cupedo *et al.* identify $CD4^+CD25^+$ cells in human fetal thymi as earlier as week 14 of gestation. These cells, which represent 15–20% of the thymic $CD4^+$ population, also express several markers associated with regulatory activity, including GITR, Foxp3 and intracellular CTLA-4. Functionally, these cells show inhibitory activity *in vitro*. This thymic subset first appears at the double-positive stage, coinciding with expression of CD27. Peripheral T_{reg} cells also express CD45RO, indicating that these cells have been activated *in vivo* by encounters with self or maternal antigens. Thus, human fetuses develop functional T_{reg} cells early in gestation, thereby preventing potential lethal immune activity against themselves or their mothers. *LAD*

Eur. J. Immunol. **35**, 383–390 (2005)

Good bugs

Although certain gut bacteria cause inflammatory diseases of the intestine, others, known as 'probiotics', are beneficial. In the *Journal of Immunology*, Di Giacinto *et al.* find that probiotics are beneficial in inflammatory bowel diseases because of the induction of T_{reg} cells. In a recurrent colitis model, administration of probiotics leads to decreased IFN-γ production with a corresponding decrease in mortality. The protection against colitis, which is dependent on IL-10, is transferable with the lamina propria mononuclear cells (LPMCs). In the LPMC population is a subset of $CD4^+$ T cells that expresses surface transforming growth factor-β (TGF-β) and is dependent on IL-10 for expansion. These regulatory cells are in turn dependent on TGF-β for their suppressive activity. Depletion of these regulatory cells from the LPMC populations abrogates their ability to transfer protection against colitis in host mice. Thus, probiotics suppress recurrent colitis through the generation of TGF-β-bearing regulatory cells. *PTL*

***J. Immunol.* 174, 3237–3246 (2005)**

A positive function for IFN-γ

After immunization with collagen, DBA/1 mice succumb to an arthritis-like disease that is exacerbated in interferon-γ receptor (IFN-γR)–deficient mice. In the journal *Arthritis Research & Therapy*, Kelchtermans *et al.* show depletion of $CD4^+CD25^+$ T_{reg} cells from DBA/1 mice increases the severity of and hastens the onset of collagen-induced arthritis similar to the loss of IFN-γR expression in this mouse model. *Ifngr*$^{-/-}$ mice have numbers of T_{reg} cells similar to those of wild-type mice, but after collagen immunization express less Foxp3 and show reduced suppressor activity. However, *in vitro* reconstitution assays show that this occurs because of an altered 'instructive' ability of antigen-presenting cells in the *Ifngr*$^{-/-}$ mice. The suppressive activity of *Ifngr*$^{-/-}$ $CD4^+CD25^+$ T cells is not reduced when wild-type antigen-presenting cells are used. Thus, IFN-γ provides a positive but indirect effect on eliciting peripheral T_{reg} cell activity. *LAD*

Arthritis Res. Ther. **7**, R402–415 (2005)

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