Stopping asthma

Administration of CpG-containing immunostimulatory DNA sequences (ISSs) inhibits airway inflammation in animal models of allergic asthma. In the *Journal of Experimental Medicine*, Hessel *et al.* document ISS-mediated inhibition of airway T helper type 2 (T_H2) cytokine secretion, hyper-responsiveness and eosinophil recruitment. Administration of ISSs impairs allergen-induced airway inflammation but not interleukin 4 (IL-4)– or IL-13-induced inflammation, which indicates an effect on T_H2 activation rather than on T_H2 effector function. Two mechanisms underlie this inhibition. First, intratracheal administration of ISSs prevents expression of costimulatory molecules on airway $CD11c^+$ antigen-presenting cells, thereby rendering them unable to induce T_H2 polarization of local lymphocytes. Second, provision of ISSs prevents anti–immunoglobulin E–induced T_H2 cytokine release from airway Fcε receptor I–positive cells. These results suggest that the anti-inflammatory action of ISS occurs at the earliest stages of the allergic airway response. ***CB***

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Precision block of TNF

Direct inhibition of tumor necrosis factor (TNF) signaling has been achieved via blocking antibodies and is used clinically. The discovery of small-molecule inhibitors, however, has been less successful. In *Science*, He *et al.* describe a small-molecule antagonist of TNF that promotes dissociation of TNF trimers, which are required for binding and activation of TNF receptor 1. *In vitro* experiments demonstrate the specificity of the antagonist for inhibiting TNF- but not IL-1β-induced activation of transcription factor NF-κB. The TNF-antagonist crystal structure indicates displacement of one subunit of the TNF trimer. Incubation of the antagonist with the TNF trimer accelerates TNF trimer dissociation. Initial antagonist-TNF trimer complex formation is confirmed by sedimentation equilibrium centrifugation and quenching of intrinsic tryptophan fluorescence. The results demonstrate a unique antagonist that binds the TNF trimer and promotes dissociation of a single subunit, thereby rendering the TNF dimer–antagonist complex incapable of signaling through TNF receptor 1. *DCB*

Science **310**, 1022–1025 (2005)

Reducing cathespin S

Maturation of major histocompatibility complex (MHC) class II molecules requires cathespin S activity to cleave invariant chain (Ii). IL-6 activation of transcription factor STAT3 somehow inhibits MHC class II antigen presentation. In *Immunity*, Kitamura *et al.* show that IL-6-mediated activation of STAT3 leads to reduced expression of cystatin C, an endogenous inhibitor of cathepsin S, resulting in increased cathepsin S activity. Paradoxically, increased cathepsin S activity results in reduced MHC class II surface expression and decreased abundance of intracellular MHC class II αβ heterodimers, Ii and H2-DM. Dendritic cells treated with IL-6 or IL-10, or those that overexpress cathepsin S, have reduced ability to activate $CD4^+$ T cells *in vitro* and *in vivo*. Thus, IL-6 and IL-10 can dampen immune responsiveness by altering the balance of cystatin C and cathepsin S. ***LAD***

***Immunity* 23, 491–502 (2005)**

Written by Christine Borowski, Douglas C. Braaten and Laurie A. Dempsey.

Runx1 blocks elongation

Runx1, a transcriptional regulator essential for hematopoiesis, is known to act at the *Cd4* silencer to negatively regulate CD4 expression during thymopoiesis, but how silencing occurs remains unclear. In *Molecular and Cellular Biology*, Peterlin and colleagues show that Runx1 inhibits conversion of the RNA polymerase II initiation complex to an elongation complex, thereby blocking transcription of *Cd4*. Specifically, a C-terminal inhibitory domain of Runx1, found between amino acids 371 and 411, inhibits P-TEFb (positive transcription factor b), which consists of cyclin-dependent kinase 9 and C-type cyclins and acts on stalled RNA polymerase II initiation complexes at promoter-proximal pause sites. Although RNA polymerase II complexes can assemble and initiate transcription at the *Cd4* promoter, in the presence of Runx1, only short, prematurely truncated transcripts result. These findings suggest a mechanism by which Runx1 actively suppresses *Cd4* expression. *LAD*

Mol. Cell. Biol. **25**, 10675–10683 (2005)

$CD8^+$ T_{reg} cells

Many types of $CD4^+$ regulatory T cells (T_{reg} cells) have been described. In the *Journal of Immunology*, Endharti *et al.* characterize the mechanism used by $CD8^+$ T_{reg} cells that express CD122 (IL-2 receptor β-chain). These natural T_{reg} cells, like their $CD4^+$ counterparts, inhibit T cell proliferation *in vitro*, but for $CD8^+$ T_{reg} cells the targets of suppression are $CD122^-CD8^+$ T cells. The mechanism of suppression, evaluated *in vitro*, involves a soluble factor that could be blocked by antibody to IL-10. That result is confirmed with *Il10*$^{-/-}$ $CD8^+CD122^+$ T_{reg} cells, which are incapable of suppressing $CD8^+CD122^-$ T cell proliferation. Experiments *in vivo* generally confirm the *in vitro* results, although *Il10*$^{-/-}$ $CD8^+CD122^+$ T_{reg} cells still demonstrate some suppressive capability after adoptive transfer. Thus other, perhaps redundant, mechanisms may explain how $CD8^+CD122^+$ T_{reg} cells suppress $CD122^-CD8^+$ T cells. ***DCB***

***J. Immunol.* 175, 7093–7097 (2005)**

IPC-specific regulator

By secreting massive quantities of type I interferons, plasmacytoid dendritic cells, also called interferon-producing cells (IPCs), alert the immune system to the presence of viruses. The characterization of IPCs has been hampered by their rarity as well as the complexity of the cell surface receptors they express. In *Blood*, Blasius *et al.* identify a sialic acid–binding immunoglobulin-like lectin, siglec-H, as being specifically expressed on mouse IPCs. Siglec-H contains a transmembrane lysine residue required for association with the transmembrane adaptor molecule DAP12; that result is confirmed by the absence of siglec-H from the cell surface of DAP12-deficient IPCs. In response to low concentrations of Toll-like receptor 9 ligands, DAP12-deficient IPCs secrete more interferon-α than do wild-type cells. Coupled with earlier data documenting decreased IPC interferon-α production after siglec-H ligation, these results highlight siglec-H, via its association with DAP12, as a potential modifier of IPC Toll-like receptor 9 responses. *CB*

Blood (17 November 2005) doi:10.1182/blood-2005-09-3746