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**Protecting sight with F4/80**
On page 1615, Lin and colleagues show that an adhesive glycoprotein is essential to prevent the immune system from reacting to environmental antigens encountered by the eyes. The authors show that this glycoprotein, known as F4/80, induces CD8+ regulatory T (T reg) cells thus protecting the eye and perhaps other immune-privileged sites from immune attack.

The F4/80 glycoprotein was first described over two decades ago and has since served as a sensitive marker of resident tissue macrophages. However, this protein had no identified function or ligand. Previous studies by this group showed that F4/80- antigen presenting cells (APCs) carry antigens from the eye to the spleen. Once there, the APCs induce the development of CD8+ T reg cells, which in turn inhibit the activation of pathogenic CD4+ T cells and B cells.

Lin et al. now show a direct role for the F4/80 protein in tolerance induction, as mice lacking this protein fail to generate CD8+ T reg cells after ocular antigen challenge. Although the mechanism is unknown, the structure of F4/80—with adhesive epidermal growth factor domains at one end and a 7-transmembrane spanning domain at the other—suggests that it may be involved in cell–cell or cell–matrix interactions and may also trigger intracellular signaling. The presence of F4/80+ cells in other immune privileged sites, such as the brain and placenta, and its exclusion from T cell zones in the spleen suggests that F4/80 expression and immune activation may be mutually exclusive. JEM

**Fueling CD4+ T cells**
CD4+ T cells continuously monitor antigen levels in their environment and adjust their expansion accordingly, as shown on page 1555. Obst and colleagues demonstrate that when antigen runs out, CD4+ T cell proliferation stops dead in its tracks.

CD8+ T cells have been argued to undergo multiple rounds of cell division and to acquire effector function after only a brief encounter with antigen. Whether CD4+ T cells behave similarly remains controversial. Previous studies—mostly performed in vitro—have produced evidence both for and against a need for prolonged antigen stimulation for sustained CD4+ cell proliferation.

Obst et al. tackled this question in vivo by making a mouse in which expression of a CD4+ T cell epitope could be turned on and off using an antibiotic-inducible promoter. Using this on–off model, they showed that antigen withdrawal resulted in the rapid cessation of CD4+ T cell proliferation, even in the presence of an inflammatory stimulus. CD4+ T cells stimulated in vivo for 48 hours divided only once if transferred into an antigen-free host. This suggested that CD4+ T cells, unlike CD8+ T cells, require continued presence of antigen for continued activation.

The need for persistent antigen by CD4+ T cells may reflect a threshold of signaling molecules that is required for continued activation of the cell. Experiments to test this idea are underway. The authors also plan to test CD8+ T cell activation in a similar system to determine whether the rules governing the proliferation of these cell subsets are truly distinct. JEM

**Deconstructing IκB kinase**
On page 1677, Ruocco et al. show that the formation of bone-resorbing osteoclasts is crippled when the β subunit of the NF-κB–activating IκB kinase (IKK) complex is missing. The absence of IKKβ also protected mice against inflammatory-induced bone loss, a complication of inflammatory diseases such as rheumatoid arthritis (RA) that is caused by excessive activation of osteoclasts.

The osteoclast growth factor RANKL (receptor activator of NF-κB ligand) activates the transcription factor NF-κB, which promotes osteoclast development. NF-κB activation requires the upstream IKK complex (IKKα, β, γ), which releases NF-κB from its inhibitor protein. Although a recent report showed that the IKK complex is required for osteoclast development, the relative importance of the two catalytic subunits of IKK (α, β) in this process remained unclear.

Ruocco et al. now show that mice lacking IKKβ were unable to generate osteoclasts and developed severe osteopetrosis (increased bone formation), whereas those lacking IKKα activity had no apparent bone abnormalities. The IKKβ-deficient mice failed to transmit RANKL signals and had increased TNF-induced apoptosis in osteoclast precursors. Osteoclast formation was partially restored in mice that lacked both IKKβ and the type 1 TNF receptor.

IKKβ-deficient mice were also resistant to inflammatory bone loss and this resistance was dependent on TNF-derived signals. Thus the authors suggest that drugs designed to block IKKβ may prevent bone loss in patients. However, they caution that such drugs, if developed, should perhaps not be combined with anti-TNF therapy (commonly used to treat RA) as the combination may not be effective. JEM

The glycoprotein F4/80 (brown) is required for the induction of CD8+ T reg cells that prevent immune attack on the eye.

The β subunit of the IκB kinase complex is required for inflammation-induced bone loss (arrows).