■ CARDIOVASCULAR DISEASE

Taking aim at Lp(a)

The lipoprotein Lp(a) not only is a risk factor for cardiovascular disease but also has a causal role in promoting disease. As a first step toward an Lp(a)-lowering therapy, Indumathi Chennamsetty *et al.* have discovered that the nuclear hormone receptor FXR directly represses expression of the gene encoding one of the proteins making up Lp(a), apoA (*J. Clin. Invest.* doi:10.1172/JCI452777).

The serendipitous observation that individuals with biliary obstruction have very low Lp(a) levels, which rise after surgery to correct the obstruction, provided the first clue that bile acids might regulate Lp(a). In mice expressing human apoA, the researchers found that treatment with bile acids led to lower circulating Lp(a) levels. Bile acids are FXR activators, and their effect on Lp(a) was abolished in mice lacking FXR. In human hepatic cells and primary mouse hepatocytes, FXR bound the promoter of the gene encoding apoA and repressed its transcription.

As noted by the authors, ongoing clinical trials of FXR agonists to treat liver disease may provide an early opportunity to test whether such compounds can reduce Lp(a) levels in humans.—*MB*

■ IMMUNOLOGY

Tinker and tailor T cell fate

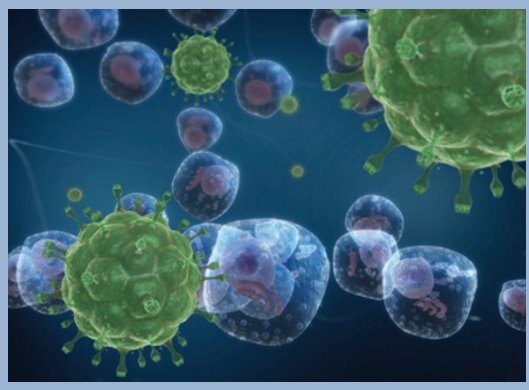
During the immune response to infection, $CD8^+$ T cells can be directed to develop into effector T cells or memory T cells by various stimuli. Two studies now identify inflammatory chemokine receptors and uncover mechanisms that can direct these fate decisions, which may have clinical implications for promoting memory T cell development in vaccine strategies.

Makoto Kurachi *et al.* (*J. Exp. Med.* **208**, 1605–1620) reveal the importance of Cxcr3 in T cell fate decisions in mice. After infection, antigen-specific *Cxcr3*$^{-/-}$ $CD8^+$ T cells failed to contract, leading to a huge expansion of the memory cell component. The *Cxcr3*$^{-/-}$ $CD8^+$ T cells did not cluster in the marginal zone of the spleen early after infection, so they failed to receive the inflammatory stimuli present in this region that allow them to become effector T cells. The authors therefore suggest that the proximity of the T cells to inflammatory cytokines is important for determining their fate.

In a second paper, Jacob E. Kohlmeier *et al.* (*J. Exp. Med.* **208**, 1621–1634) confirm that Cxcr3 regulates memory T cell development and also show that Ccr5 is involved. These two receptors help traffic T cells to infected sites, and, consistent with this, the authors found that *Cxcr3*$^{-/-}$ *Ccr5*$^{-/-}$ $CD8^+$ T cells differentially localized within the lung compared with wild-type cells. This altered localization hindered the ability of the T cells to reencounter antigen in the lung, thus directing them along the memory pathway, with addition of exogenous antigen allowing T cell activation and effector development. This study highlights antigen exposure at peripheral sites as another mechanism for regulating T cell fate.—*MS*

INFECTION

Modeling the elite



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The mechanisms by which HIV-1 infection is controlled—but not eradicated—in less than 1% of infected but untreated individuals are not fully understood. Ivona Pandrea and colleagues now report on a new model of SIV infection of rhesus macaques that may help elucidate the immune mechanisms of viral control in these 'elite controllers' (*PLoS Pathog.* 7, e1002170).

Using an SIV derived from acute infection of African green monkeys (SIVagm.sab), the researchers infected 12 rhesus macaques and monitored the infection for more than 6 years in some of the animals. Although infection with SIVagm.sab initially paralleled that of both macaque SIV and HIV-1 infections, with substantial replication in both lymphoid and nonlymphoid tissues, high plasma and intestinal viral load, elevated immune activation, and severe $CD4^+$ T cell depletion in the intestinal lamina propria, plasma viral load of SIVagm.sab declined to undetectable by 3 months. $CD4^+$ T cell counts and levels of immune activation also returned to baseline by 4 years after infection in these monkeys. Moreover, all 12 macaques controlled the infection without any significant association with major histocompatibility complex type or host restriction factors.

$CD8^+$ T cell responses are thought to participate in control of HIV-1 infection in human elite controllers, but proof of this is still needed. To address the role of $CD8^+$ T cells in their model, the researchers depleted $CD8^+$ cells in three of the monkeys that had controlled SIVagm.sab infection. Their depletion triggered viral rebound and increased $CD4^+$ T cell activation and loss. Subsequent recovery of $CD8^+$ T cell numbers decreased viral load and increased numbers of $CD4^+$ T cells, indicating that $CD8^+$ cells indeed suppress viral replication in these animals. This model may serve as a useful tool to study the immune mechanisms harnessed by elite controllers to keep HIV-1 infection at bay.—*AF*

A new therapy for asthma

A monoclonal antibody against interleukin-13 (IL-13) shows therapeutic benefit in people with asthma, report Jonathan Corren *et al.* in *The New England Journal of Medicine* (doi:10.1056/nejmoa1106469).

IL-13 participates in the pathogenesis of asthma, particularly in patients who do not respond to standard therapy with glucocorticoids. In response to IL-13, bronchial epithelial cells secrete a protein known as periostin, which acts on epithelial cells and fibroblasts, contributing to the airway remodeling characteristic of asthma.

Corren *et al.* conducted a randomized, double-blind, placebo-controlled trial of lebrikizumab, an antibody to IL-13, in 219 patients with asthma with suboptimal response to glucocorticoids. They found that the forced expiratory volume (the primary endpoint of the trial) increased in the treated group compared to subjects given a placebo. This increase was more apparent in individuals with high levels of periostin, which could become a biomarker to identify those patients more likely to respond to this therapy.

The results of this trial warrant follow-up studies with larger groups of patients to confirm the therapeutic effect of lebrikizumab.—*JCL*