local autoreactive T cells that had previously ignored epithelial self-antigens. IFN-γ and RbAp48 were also found in epithelial cells of patients with Sjögren’s syndrome.

Professional APCs seem to be required to start or maintain autoimmunity when estrogen levels are normal, as transferring T cells from transgenic lymph nodes into nontransgenic mice initiated gland cell destruction only if APCs were included. But epithelial cells may be self-sufficient APCs in the absence of estrogen; T cells from the transgenic mice were enough to cause disease in mice whose ovaries had been removed. NL

Beekeepers show way to allergen tolerance

Beekeepers are the new, improved mouse model for immune responses to allergens, according to a study from Meiler et al. (page 2887). The fleeting tolerance of these intrepid honey lovers to bee antigens is now revealed to require a Jekyll-and-Hyde set of T cells that go from attack to suppressive mode and back again.

It’s an immunologist’s dream. By the very nature of their jobs, unprotected beekeepers are voluntarily and repeatedly injected with high doses of bee antigen—an average of 13 antigen-loaded stings in the first week of honey-harvesting season alone, according to the study. And in just these seven days, the beekeepers developed an immune tolerance that was noticeable in both skin reactions and T cell responses.

T cells that started out proliferation-happy in response to bee antigen became much more subdued soon after the season began. The authors traced this change to cytokine alterations: within a week, T cells that had made mostly IFN-γ started making more IL-10, which tempers immune reactions. IL-10–producing cells curbed the in vitro proliferation of other T cells in response to bee antigen.

The cytokine switch, the authors found, was initiated through the histamine pathway. As with many allergens, bee venom induces mast cells to unload histamine. In vitro experiments with the beekeepers’ T cells revealed that histamine induced IL-10 production and T cell lethargy, both of which required the H2 histamine receptor.

The beekeepers’ tolerance was lost within two months of season’s end, unveiling a relatively short lifespan of T cell suppression. The cycle repeated at the onset of the next season, so beekeepers have little to worry about. But allergy sufferers, who may be defective in this IL-10 response, might be less enthused, because the findings suggest that successful therapies involving allergen-specific immunotherapy probably require considerable perseverance. NL

Reviving the attack against HIV

Researchers breathe life into exhausted T cells in a study on page 2763.

HIV beats the immune system in part because killer T cells stop fighting the virus. PD-1, a T cell inhibitory protein that normally prevents over-inflammation, was recently associated with chronic HIV. Now Jones et al. identify another manipulated manager, TIM-3.

When CD4+ T cells express the glycoprotein TIM-3, proliferation and cytokine production are suppressed. Because disruption of TIM-3 is known to induce hyperactive inflammatory responses, as seen in autoimmune diseases like multiple sclerosis, Jones et al. predicted that the opposite might be true in HIV infection. The team assessed T cells from HIV patients and found that high levels of the protein indeed corresponded to a heavy viral load.

TIM-3–expressing CD4+ and CD8+ T cells from HIV-infected patients secreted far less interferon (IFN)-γ and TNF than did cells without TIM-3. And blocking TIM-3’s ligand reversed this effect. Although the effect of blocking TIM-3 and PD-1 is similar, these molecules were found on distinct populations of CD8+ T cells.

Half of the participants undergoing antiretroviral therapy maintained high TIM-3 expression, even after their viral loads diminished, suggesting to the authors that TIM-3 upregulation may be irreversible in some individuals. And obstructing its signals could be an important means of controlling the underlying virus that persists despite therapy.

Many of the steps between the virus and TIM-3 manipulation aren’t yet known, and it appears that HIV isn’t the only T cell exhauster. Learning how to revive tired cells might therefore help patients with other chronic infections as well. AM