Helpless without SAP

CD4+ T cells that lack the adaptor protein SAP are little help to B cells, according to Cannons and colleagues on page 1551. But their unhelpful nature does not result from a failure to produce T helper (Th)-2 cytokines, as the authors had previously thought.

The absence of SAP wreaks havoc on the immune system. SAP—the adaptor that links the SLAM family of activating receptors to the downstream signaling protein Fyn—is expressed in most immune cell types and its absence causes a bevy of immune defects.

Mutations in SAP cause a rare disease called X-linked lymphoproliferative disease (XLP), which is characterized in part by extreme susceptibility to Epstein Barr virus (EBV) infection. Those who survive EBV infection often have long-term antibody deficiencies. But Cannons and colleagues put the blame for this not on B cells, but on CD4+ T cells.

Previous studies in SAP-deficient mice revealed defects in both CD4+ T cells and B cells. But whether one cell type is mostly to blame for the glitch in antibody production has been controversial. Here, Cannons and colleagues put the rap squarely on the CD4+ T cells, as transfer of wild-type T cells into SAP-deficient mice restored immunization-induced antibody production, even when the B cells still lacked the adaptor.

The authors suspected (based on previous work with SAP-deficient T cells) that SAP-deficient mice might be unable to secrete antibody-promoting Th2 cytokines, such as interleukin (IL)-4 and IL-10. But when they infected the mice with *Schistosoma mansoni* eggs—a classic Th2 trigger—the mice had no problem producing these cytokines. Antibody production, on the other hand, was still blocked.

The antibody defect was instead traced to changes in the expression of two T cell costimulatory molecules: CD40 ligand (CD40L) and ICOS. In SAP-deficient cells, CD40L expression was increased and ICOS expression was decreased—both changes that have been shown to inhibit antibody production. A decrease in ICOS expression has also been reported on T cells from patients with XLP.

SAP's ability to bind Fyn was dispensable for antibody production, as T cells containing a Fyn binding mutant of SAP still restored antibody production in mutant mice. The authors are now characterizing this previously unrecognized signaling pathway.

Taking advantage of saliva

The bacterium *Anaplasma phagocytophilum* uses a tick protein to help it set up camp in the insect’s salivary glands, according to Sukumaran and colleagues (page 1507).

Many tick-borne pathogens hijack host proteins to establish infection in their tick vector or mamalian host. Previous work by this group, for example, showed that the Lyme disease bacterium *Borrelia burgdorferi* induces the expression of the salivary protein Salp15 in infected *Ixodes scapularis* ticks as they feed. The bacterium then coats itself with Salp15 as it exits the tick, creating a shield against the destructive antibodies encountered in the mamalian host.

Here, Sukumaran and colleagues used a similar approach to study the obligate intracellular bacterium *A. phagocytophilum*, which causes a common and sometimes deadly tick-borne disease in humans called anaplasmosis (formerly granulocytic ehrlichiosis). They found that if *I. scapularis* ticks fed on *A. phagocytophilum*-infected mice, the ticks selectively increased their expression of the salivary protein Salp16.

But in this case, Salp16 was used for protection in the tick, not the mammalian host. Inhibiting Salp16 expression in the tick (using RNAi) reduced the number of bacteria in the insect’s salivary glands, suggesting that Salp16 was needed for the bacterium to establish a foothold in the salivary gland where it resides after migrating from the gut. Once there, however, the bug no longer required Salp16 to maintain its residence. Inhibiting Salp16 had no effect on transmission of the bug to the mouse reservoir or on the initial uptake of the bug (with the blood meal) into the tick gut.

The authors are now trying to determine how Salp16 helps *A. phagocytophilum* to colonize the salivary gland. In the meantime, blocking Salp16 in ticks might provide a way to disrupt the transmission cycle of the pathogen and thus lower the prevalence of disease.
Gut bacteria side-step lymph nodes

Invasive bacteria can take more than one route from the gut to distant organs, say Barnes and colleagues on page 1591.

According to conventional wisdom, pathogenic gut bacteria spread to distant tissues via an orderly march from gut to local lymph nodes (LNs) and then on to distant organs. But some mutant bugs that cannot invade the lymphoid tissues of the gut can still spread, hinting at the existence of an alternative route.

Barnes and colleagues infected mice orally with *Yersinia pseudotuberculosis*. They noted two waves of bacteria that spread to both the spleen and liver in the infected mice. The first wave occurred within 30 minutes of infection and was rapidly cleared from these distant organs. The second began later and stuck around.

Only the second wave of bacteria side-stepped the LNs, as mice lacking Peyer’s patches—the gut lymphoid tissue that bacteria traverse to reach the LNs—developed only late-stage infections in the liver and spleen.

Marking individual bacteria with unique oligonucleotide tags revealed that the bugs entrenched in distant organs were descendants only of those that migrated later, after first replicating in the gut—possibly because replication triggers the expression of virulence factors that protect the bug against the host immune response.

How the disseminating bugs bypass the LNs remains to be determined. Perhaps they piggyback on dendritic cells, which can reach directly across the gut epithelium to grab antigens and then head straight for the circulation. JEM

Neutrophils take the easy way out

To migrate out of blood vessels into inflamed tissues, blood cells must cross both the vessel endothelium and basement membrane (BM). According to Wang and colleagues (page 1519), protein-sparse exit sites in the BM pave the way for this cellular escape.

The signals required for blood cells to adhere to sites of vessel inflammation and to squeeze through endothelial cell (EC) junctions are well defined. But it is unclear how the cells then traverse the tough, underlying network of BM proteins. Migrating cells, such as neutrophils, produce proteases that can cleave BM proteins, which may help the cells drill through the BM.

But Wang and colleagues favor a less destructive model, as drilling holes in the BM could inflict irreversible vessel damage. They now show that steady-state expression of certain (but not all) BM proteins—including laminin 10 and collagen IV—is patchy in small veins, creating discrete areas of low protein expression. Most of these low expression regions were aligned with both EC junctions and gaps between pericytes—structural cells that help synthesize BM proteins. These protein-sparse regions appeared to be the preferred sites for inflammation-induced neutrophil exit.

These data suggest that exiting neutrophils take the path of least resistance, a finding that makes perfect sense to senior author Susan Nourshargh. “If you have a door, you use it,” says Nourshargh. “You don’t blast through the wall.”

How neutrophils find these sites, and whether other cell types use the same exits, is now under investigation. JEM

IL–6 drives T cell proliferation

Hyperresponsiveness to the IL–6 family of cytokines triggers a spontaneous rheumatoid arthritis (RA)–like disease in mice. On page 1459, Sawa and colleagues show that excessive IL–6 signaling drives hyperproliferation of CD4+ T cells, which then attack the joints.

IL–6 has been implicated in RA and other T cell–driven autoimmune diseases. Indeed, a previous study by this group showed that an activating mutation in the gp130 subunit of the IL–6 receptor caused a lymphocyte–driven arthritis in mice. But the mechanism was unclear. The authors now show that disease development in these mice depends on CD4+ T cells, but not on cytolytic CD8+ T cells or antibody-producing B cells.

The CD4+ cells did not appear to cause disease because of an affinity for joint-specific antigens. Rather, the cells simply proliferated excessively in the mutant mice. This hyperproliferation was not the fault of the T cell, as wild-type CD4+ T cells also multiplied excessively and caused disease when transferred into irradiated mutant mice.

Rather, the gp130 mutation caused nonhematopoietic cells to produce excess IL–7—a growth factor that triggers T cell proliferation. This is the first evidence that IL–6 family cytokines can trigger IL–7 production.

These data suggest that IL–6, which is elevated in the serum and joints of patients with RA, might exacerbate disease by inducing IL–7 and thus driving T cell activation. What causes the overstimulated T cells to attack the joints in the first place remains a mystery. JEM