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 mammalian 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 mammalian 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.