IN THIS ISSUE

Protease protects from snakes and sepsis

High blood pressure, sepsis, and snake bites might all be cured by the same antidote, according to Schneider et al. (page 2629).

High blood pressure and septic shock are both enhanced by a 21–amino acid peptide called ET-1. This peptide is secreted by blood vessel cells that have been activated by inflammatory cytokines. ET-1 triggers the contraction of smooth muscle cells that are wrapped around blood vessels, causing blood to flow through the squeezed vessels at a higher pressure. This contraction prevents blood from getting to its target tissues, leading to sepsis-associated organ malfunction.

ET-1 is structurally similar to a snake venom toxin called sarafotoxin. This toxin is lethal to mice that lack a type of immune cell called mast cells. These mice also die when sepsis–causing bacteria enter the abdominal cavity from an injured gut.

High blood pressure, sepsis, and snake bites might all be cured by the same antidote, according to Schneider et al. (page 2629).

High blood pressure and septic shock are both enhanced by a 21–amino acid peptide called ET-1. This peptide is secreted by blood vessel cells that have been activated by inflammatory cytokines. ET-1 triggers the contraction of smooth muscle cells that are wrapped around blood vessels, causing blood to flow through the squeezed vessels at a higher pressure. This contraction prevents blood from getting to its target tissues, leading to sepsis-associated organ malfunction.

ET-1 is structurally similar to a snake venom toxin called sarafotoxin. This toxin is lethal to mice that lack a type of immune cell called mast cells. These mice also die when sepsis–causing bacteria enter the abdominal cavity from an injured gut.

How mast cells protect against sepsis and snake venom, however, was unclear. They express both ET-1 receptors and degradative enzymes that normally destroy pathogens. The authors thus imagined that the mast cells might trap ET-1 (and the toxin) and then degrade it. They focused on mast cells’ most abundant defensive protease, Mc-cpa.

The team now shows that Mc-cpa is indeed the weapon of choice against ET-1 and the toxin. Mice that lack mast cells died within hours after injection with ET-1. Mc-cpa protected mice by snipping and thus disarming the dangerous peptides. Mice that secreted inactive Mc-cpa were as susceptible to sepsis and snake venom as mice that lacked mast cells.

ET-1 is needed for mast cell activation, but its subsequent degradation might limit its long-term destructive effects.

DNA vaccines get a boost

The use of DNA vaccines in humans has been limited by their relatively poor ability to build immunity against pathogens all on their own. Kwissa et al. (page 2733) now find that coinjecting a DNA vaccine with a Toll-like receptor (TLR) ligand activates dendritic cells (DCs) and goads monkeys into putting up a better fight against SIV.

Because they are cheaper and easier to manufacture than recombinant protein vaccines, successful DNA vaccines are in high demand. So far, however, DNA vaccines targeted against malaria, hepatitis B, and HIV have failed to induce a strong immune response in either monkeys or humans.

For various other types of vaccines, TLR ligands are commonly coinjected to improve the patient’s immune response. The ligands activate DCs, which in turn secrete immune-boosting cytokines and enhance the proliferation and activity of T cells. Despite their success in protein vaccines, TLR ligands have not been tested as supplements to DNA vaccines in humans or other primates.

Findings from Kwissa et al. now suggest that TLR ligands may indeed make human DNA vaccines more effective. The authors report that monkeys are better at fighting off SIV infection if their DCs are also activated by a TLR ligand at the time of DNA vaccination. The ligand of choice was TLR-9, which is primarily expressed by a subset of DCs known to boost the numbers of antiviral CD8+ T cells.

This dual injection increased the total numbers of SIV–specific T cells. Many of these cells secreted a broader range of protective cytokines than did T cells from monkeys given only the DNA vaccine. However, the mechanism by which the TLR-9–activated DCs instruct T cells to secrete more types of cytokines is unclear.

In humans, survival from HIV infection is correlated with the numbers of CD4+ T cells—particularly the precursors of virus-fighting effector cells—in the gut. These precursors were more abundant a few weeks after SIV infection in monkeys that were given the coinjection regimen. Whether this stronger protection is also long lasting remains to be tested.

Without the mast cell protease Mc-cpa, most mice die within an hour of being injected with ET-1.