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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. JEM

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. JEM

Protease protects from snakes and sepsis

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Germinal centers are free for all

Germinal centers (GCs)—the sites of antibody development—are not exclusive niches for rookie B cells. They are also open to experienced old-timers, according to Bende et al. (page 2655).

GCs are temporary lymph node structures that form during an immune response to help newly activated B cells better recognize an antigen. As they proliferate, the B cells’ antibody-encoding DNA is mutated. The environment of the GC somehow helps select the best new clones, which then differentiate into either memory B cells or cells that secrete high-affinity antibodies.

This transition route from low to high affinity within GCs was thought to be used exclusively by B cells that encounter antigen for the first time. But Bende and colleagues now find that the GCs are hospitable to returning memory B cells as well.

The group dissected GCs out of human lymph nodes and sequenced the antibody-encoding RNA of the resident B cells. A single type of B cell clone was present in several GCs, suggesting that B cells traffic between GCs. Several GCs also contained the offspring of memory B cells that had undergone further mutation. The memory cells might have returned to the GCs for additional improvements upon a second encounter with an antigen.

GCs are known cancer hotspots, as the mutating B cells are vulnerable to chromosomal translocations and other cancer-causing events. These high cancer rates are probably due in part to the repeated visits from memory B cells during recall responses.


T cells learn quickly

Young T cells are fast learners, according to McCaughtry et al. (page 2513). They finish part of their schooling in the thymus in just four days.

Upon entering the thymus, young T cells are first tested for correctly rearranged T cell receptors (TCRs). Those that pass the exam are selected for further training in the thymic medulla. There, T cells that react to self-antigens are killed off. The rest graduate into functional, proliferating adults.

This training program was previously estimated to last for two to three weeks. This notion was based on methods that did not differentiate between young T cells, mature T cells that reentered the thymus, and other thymic TCR-bearing immune cell subsets.

McCaughtry and colleagues now reanalyze the kinetics of T cell training with this distinction in mind. Maturation stages were identified by specific markers and by labeling proliferating cells with BrdU. The results revealed that T cells took just four days to pass through the medulla and enter the circulation.

The team also found that T cells were educated on a first-come, first-served basis. As they passed the first selection test, the cells shut off expression of a fluorescent protein, resulting in a gradual decrease in brightness. Only dim cells expressed receptors that mark exiting cells, suggesting that the emigration follows a first-in, first-out assembly-line pattern.

The authors now want to understand how the plumbing of the thymus helps T cells so rapidly sample the different self-antigens expressed by each epithelial cell.

Regulatory T cells hasten infant AIDS

HIV infection tends to develop into AIDS more quickly in infants than in adults. A study by Hartigan-O’Conner et al. (page 2679) now suggests that more potent infant regulatory T (T reg) cells are to blame.

T reg cells cool down virus-induced immune responses by suppressing activated T cells. It has been suggested that too much suppression allows HIV to get the upper hand. Others, however, have suggested that activated T cell suppression by T reg cells prevents inflammatory T cell cytokines from damaging tissues and thus enhancing disease.

Hartigan-O’Conner and colleagues now show that healthy infant monkeys have more—and more potent—T reg cells than do adult monkeys. When monkeys were infected with SIV—the primate version of HIV—most of the infants rapidly developed AIDS. Their T reg cells suppressed anti-SIV T cell functions, whereas the adult T reg cells did not.

Humans also have more T reg cells during infancy. The authors suspect that, like primate T reg cells, the potency of human T reg cells might also decrease with age. Determining why T reg cell numbers decrease with age and why aging T reg cells lose their steam is the next step. JEM

The offspring of two types of B cell clones (red and yellow) are present in several germinal centers (numbered) in a human lymph node (blue).