

Outgrowing IRAK-4

Humans outgrow their need for a TLR-activated kinase, according to a new study by Ku et al. (page 2407). The kinase helps protect young children from specific pathogens but is expendable in adults.

The TLRs are part of an early infection warning system that recognizes microbial intrusion. Many activated TLRs recruit a kinase called IRAK-4, which switches on immune-boosting transcription pathways.

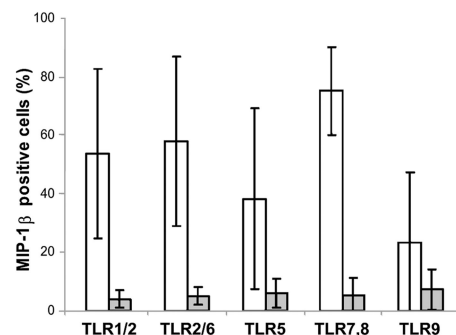
In mice, IRAK-4 is thought to be a crucial cog in innate defense, as mice of all ages lacking the kinase are vulnerable to many different viruses, bacteria, and fungi. But the human version now appears to be less comprehensive.

The new study examined 28 patients with IRAK-4 mutations. Immune cells from these patients' blood failed to produce inflammatory cytokines in response to TLR ligation. During infancy and childhood, these patients experienced repeated, sometimes lethal infections mainly with *Streptococcus pneumoniae* and *Staphylococcus aureus*. Resistance to other pathogens might stem from TLRs that bypass IRAK-4,

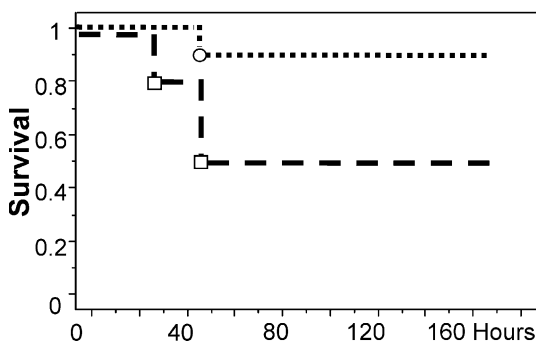
including possibly TLR3 and TLR4, or from non-TLR pathways.

About half of the young children succumbed to the bacterial infections. But the patients' resistance improved with age, and older children consistently survived infections. The impact of IRAK-4 deficiency might fade as the adaptive immune network, particularly memory responses by T and B cells, kicks in later in life.

It is unclear why IRAK-4 deficiency preferentially opens the door for some invasive bacteria but not other pathogens. The team has previously identified defects in other innate immunity factors that render patients susceptible to just one pathogen. A mechanistic explanation for this selectivity is yet to be found. **JEM**



Human dendritic cells that lack IRAK-4 (gray bars) do not produce inflammatory cytokines in response to most TLR signals.



Mice are protected from sepsis-induced death by an APC variant that lacks its anticlotting activity (circle).

Improving survival after sepsis

The only drug that can save patients from severe sepsis carries a risk of internal bleeding. Kerschen et al. (page 2439) have now engineered a variant version that offers the same benefits as the original but minimizes the risk.

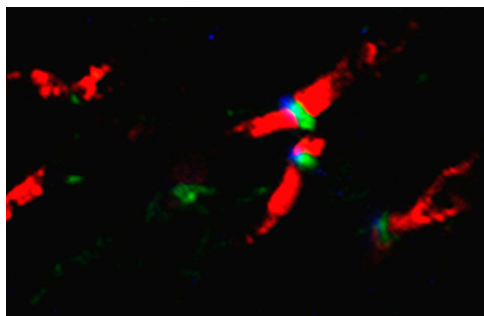
Sepsis is a system-wide inflammation that occurs when an infecting microbe enters the bloodstream. The inflammation is meant to fight the pathogen, but it also triggers widespread clotting. Clotting proteins, in turn, reinforce inflammation by activating oxidants and proteases, ultimately causing organ failure. Because the exact cause of death in sepsis patients is unknown, scientists don't know what problem to target when designing an effective therapy.

Antiinflammatory agents such as steroids and cytokine antagonists have failed as therapies. So too have anticlotting agents. The only treatment that has had any degree of success is activated protein C (APC).

APC is both a clot-busting enzyme and a signaling molecule that blocks apoptosis, inflammatory cytokine production, and immune cell recruitment. APC is therefore thought to work against sepsis by breaking the inflammation/clotting cycle. But patients dosed with APC can experience internal bleeding thanks to the drug's anticlotting activity.

Kerschen and colleagues now test whether APC might still be effective but less dangerous if its anticlotting activity is reduced. They engineered an APC variant that was 90% less effective at stopping clotting. This variant was just as good as normal APC at saving septic mice, suggesting that the protective effect of APC did not stem from its anticlotting function but from its signaling ability.

Exactly why APC's antiinflammatory signaling activity succeeds in treating sepsis where other antiinflammatory drugs have failed is unclear, but this might be due to its broader effects on both the inflammatory and apoptotic pathways. **JEM**



Antibodies (green) against neurofascin bind to the unmyelinated nodes of Ranvier (blue) in axons (red).

Axon-attacking antibodies

Axons have an Achilles' heel that antibodies can attack to cause multiple sclerosis (MS), Mathey et al. show on [page 2363](#).

MS is triggered when T cells breach the blood-brain barrier and produce inflammatory cytokines that activate myelin-scavenging macrophages, causing damage to the myelin sheath. Myelin-specific antibodies that enter the brain in the T cells' wake enhance the destruction of the sheath and exacerbate disease. Researchers have blamed this myelin destruction for the neurological problems of patients with MS. But in some patients, damage happens not just to the myelin, but to the axons themselves. Because myelin can be replaced, axon damage is now considered to be the cause of permanent disability.

Mathey et al. now find that some MS patients have antibodies that attack the parts of axons known as the nodes of Ranvier. These nodes must be myelin free to allow clusters of voltage-gated ion channels to propagate action potentials.

The newly identified antibodies recognized a structural node protein called neurofascin-186 (NF-186). The antibodies interrupted neurotransmission in tissue sections and worsened disease symptoms by damaging axons in a rat model of MS.

Higher levels of these antibodies were found in patients who have a particularly degenerative version of the disease. The study included only a small number of patients, but if the trend continues in larger groups, the authors will then test whether getting rid of antibody-producing B cells or filtering the antibodies out of the patients' blood might halt disease progression. [JEM](#)

T cells raise the tension

The price of immunity might be high blood pressure, as data from Guzik et al. ([page 2449](#)) suggest.

High blood pressure—or hypertension—is triggered by angiotensin II. This hormone instructs the kidneys to retain salt and the brain to release stress hormones. It also activates oxidases that generate free radicals, which narrow blood vessels and cause plaques to grow and harden the arteries.

Recent evidence suggests that angiotensin II might also get the immune system into the tension-raising act. Patients with immune systems weakened by immunosuppressive drugs or HIV infection have low blood pressure, which can skyrocket when they go off the drugs or start taking antiviral medications. One set of lymphocytes, the T cells, are the likeliest culprits, as they bear angiotensin II receptors and the same dangerous free radical-generating enzymes.

Guzik et al. now find that angiotensin II activates T cells to raise blood pressure. Mice that lack lymphocytes failed to develop hypertension after angiotensin II injection unless T cells were put back in. The hormone, they found, increased the T cells' ability to attach to and infiltrate blood vessel walls. The cells congregated in the underlying fatty tissue and secreted the inflammatory cytokine tumor necrosis factor (TNF), which further activates free radical production in the surrounding cells. Blocking TNF blunted hypertension.

The authors propose that T cells infiltrating the kidney and the brain might also amplify angiotensin II's damaging effects in these organs. [JEM](#)

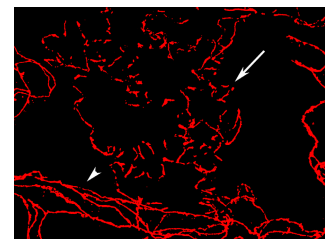
Buttoned-up vessels

A study by Baluk et al. ([page 2349](#)) reveals how the organization of junctional proteins might keep endothelial cells in lymphatic vessels buttoned up but still allow fluid and cells to enter.

Lymph flows through a network that starts out as tiny vessels and then widens into collecting ducts. But how lymph gets from the blood into lymph vessels through the endothelial barrier is unclear. One model suggests that endothelial cells lack junctions and thus glide apart under mechanical stress. Another proposes that junctions break down to permit fluid entry and then reseal.

Baluk et al. did not favor either idea, as junctions are required to maintain vessel structure, and their breakdown and reconstruction spell excessive wear and tear on the vessel. The team traced the expression of junctional proteins in lymphatic vessels in mouse airways and found that the proteins formed continuous zipper-like structures in collecting ducts. In the tiny vessel entryways, however, they were organized into button-like clumps at the corners of adjacent endothelial cells.

The flaps between the buttons probably allow fluid to enter, but the authors are not sure whether cells also crawl in through these openings. In the lymph networks of mice whose airways were inflamed, leukocytes sidled alongside the buttoned openings rather than the zippered ends. But the team is yet to catch cells in the act of creeping through. [JEM](#)



A junctional protein (red) clumps (arrows) at lymph vessel entryways but is continuous (arrowheads) in the lower collecting ducts.