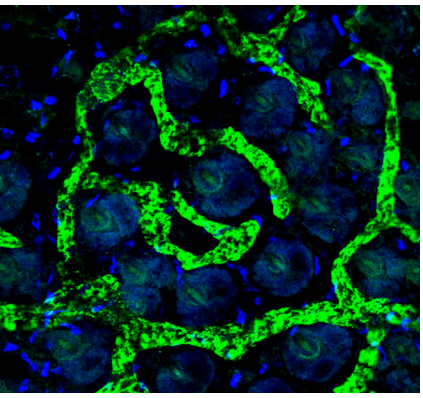


Mast cells (blue) secrete TNF-containing particles that are carried to distant lymph nodes though lymphatic vessels (green).

Mast cells' message in a particle

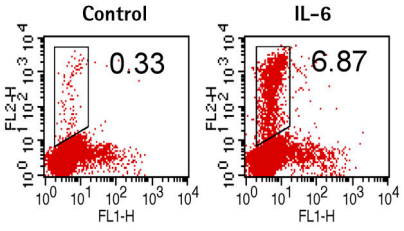
Mast cells know how to maintain long-distance relationships. Rather than sending diluted, mixed signals, they dispatch concentrated messages to distant contacts bound in tightly wrapped packages, according to Kunder et al.

Many cells secrete soluble molecules that help maintain the body's physiology. For example, β cells in the pancreas release large quantities of insulin into the circulation to control blood glucose levels. Here, Kunder and colleagues discover an alternative form of signal transport that comes in handy when signaling molecules are short lived or produced in small quantities.

This group previously found that TNF secreted by tissue mast cells reached draining lymph nodes quickly and was required for the nodes to expand in response to infection. But no one knew how this short-lived cytokine traveled from the periphery to remote lymph nodes without being diluted or degraded along the way.

The new study reveals that mast cells activated in the foot pads of mice released insoluble heparin-based particles that contained TNF. The particles entered lymphatic vessels, presumably through gaps in lymphatic endothelial cells, and drained into regional lymph nodes. After the particles entered, the lymph nodes doubled in size, indicating that TNF had been released. Soluble TNF injections had little effect on lymph nodes. Likewise, without TNF, the particles had no effect.

The particles protect TNF from dilution and degradation as it travels to the lymph node, suggests senior author Soman Abraham. "If Aspirin wasn't enteric coated," he explains, "you'd have to take an awful lot of it for it to work." How the particles release their contents once in the lymph node remains unknown.



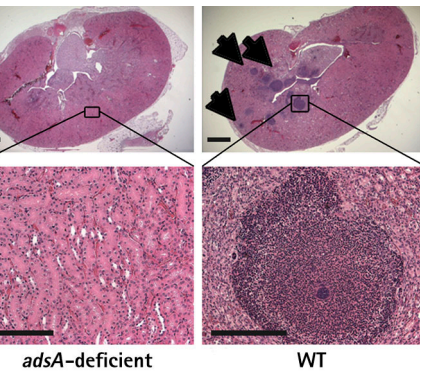
IL-6 alone induces IL-17 production in the absence of the Th1- and Th2-promoting transcription factors T-bet and STAT-6.

Revising the Th17 recipe

Contrary to popular belief, TGF-β doesn't directly induce Th17 cells. Here, Das et al. show that the cytokine merely paves the way for Th17s by blocking their antagonists.

The consensus among immunologists has been that TGF-β, along with IL-6, is a key ingredient in Th17 cell differentiation. But Das and colleagues find that in the absence of Th1 and Th2 cells, IL-6 alone can do the job. Naive $CD4^+$ T cells from mice lacking the essential Th1 and Th2 transcription factors STAT-6 and T-bet produced copious IL-17 in response to stimulation with IL-6. And adding TFG-β to the mix had no effect.

The double-knockout mice developed severe EAE—an MS-like disease driven by Th17 cells. Their symptoms could be reversed by blocking IL-17 or IL-6, but not by blocking TGF-β. TGF-β inhibited Th1 and Th2 differentiation by downregulating the expression of the essential Th1 and Th2 transcription factors STAT-4 and GATA-3. With the competing subsets shut down, Th17s flourished.



Staph infections caused fewer kidney abscesses (arrows) without *adsA*.

How staph thwarts attack

Staphylococcus aureus stifles its host's immune response by producing an immunosuppressive molecule, report Thammavongsa and colleagues.

The new study reveals that without the cell wall enzyme adenosine synthase A (AdsA), most staphylococci fail to thrive and cause severe disease in mice. The gene encoding AdsA contains a 5′-nucleotidase domain, making it similar to a family of mammalian enzymes that convert adenosine monophosphate into adenosine. Adenosine has many immune-dampening effects including blunting T cell proliferation, inhibiting cytokine production, and blocking neutrophil degranulation and superoxide production. Bacterial isolates expressing AdsA were previously associated with invasive disease in humans, but the connection between AdsA and pathogenesis wasn't understood.

Now it appears that at least two strains of staph (including one methicillin-resistant strain) and the anthrax pathogen *Bacillus anthracis* use AdsA to tap into the adenosine system. Bacteria with intact *adsA* survived longer in whole blood from rodents and humans than did *adsA*-deficient bacteria. And mice infected with *adsA*-deficient strains cleared infection

Text by Amy Maxmen
amaxmen@rockefeller.edu

quickly and rarely developed the abscesses characteristic of progressive staph infections. The virulence of *adsA*-deficient staph could be regained by genetically restoring the enzyme. With AdsA around, adenosine levels were higher, presumably allowing staph to escape destruction by neutrophils.

Manipulating the adenosine pathway may turn out to be a widespread phenomenon, as the authors also identified putative 5′-nucleotidase–encoding genes in a variety of gram-positive bacteria.

Runx: T reg cell keeper and creator

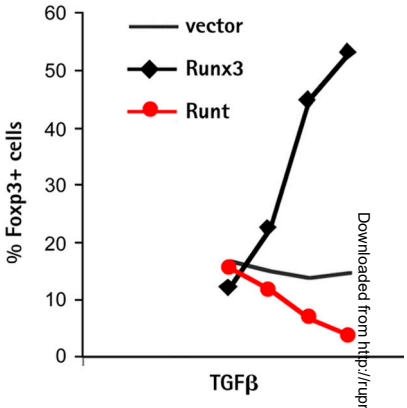
Runx transcription factors help dictate the fate of T cells as they become $CD4^+$ or $CD8^+$ T cells in the thymus, and Th1 or Th17 cells in the periphery. Now, according to Bruno et al., Runx proteins also guide regulatory T (T reg) cell fate.

Runx proteins have been shown to bind to the canonical T reg cell transcription factor Foxp3. Together, the two regulate (and primarily inhibit) the expression of target genes, such as the Th17-promoting transcription factor Ror-γt. Now Bruno and colleagues reveal that Runx proteins also help induce and maintain Foxp3 expression in mature $CD4^+$ T cells.

Inducible T reg cells relied on Runx proteins to express Foxp3. Blocking the proteins reduced the number of these cells, and ablating an indispensable subunit of Runx protein complexes, *Cbfb*, diminished Foxp3 expression in natural T reg cells. Runx proteins bound directly to the Foxp3 promoter in T reg cells, but not in naive $CD4^+$ T cells because of locus inaccessibility.

Another group recently reported that Runx/Cbfb complexes control the expression of Foxp3 in natural T reg cells in vivo. Without *Cbfb*, mice were susceptible to autoimmune disease. However, this study did not investigate a role for Runx proteins in T reg cell induction.

The relative contributions of Runx1 and Runx3 to Foxp3 regulation remain to be dissected. And because Runx proteins interact with so many genes, the authors are also curious to know how else these proteins may fine-tune T reg cell function.



Runx promotes Foxp3 expression during T reg cell induction in response to TGF-β.

Pro-fibrotic SNPs

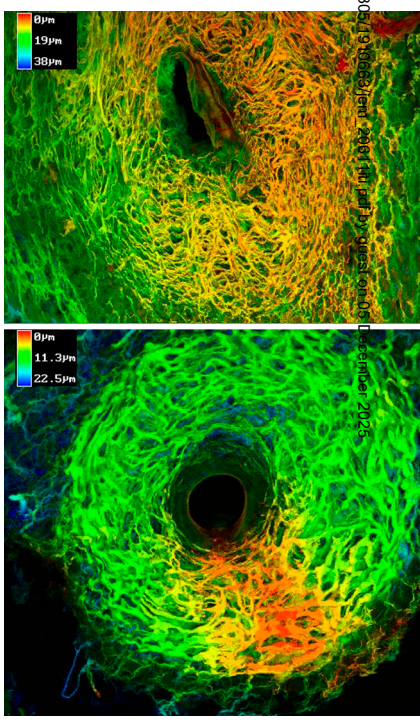
Five to ten percent of people infected with schistosome worms rapidly develop severe liver fibrosis. Here, Dessein and colleagues uncover single nucleotide variations in a growth factor gene that correlate with this life-threatening condition.

Most schistosome eggs pass into the intestines of their human hosts, but some become lodged in the liver. The body responds by producing inflammatory cytokines and repairing the subsequently damaged liver tissue with extracellular matrix proteins. However, in some people, the repair response leads to hepatic fibrosis as matrix proteins build up, plugging vessels and obstructing blood flow. Clinicians have noted that these fibrotic tendencies often run in families.

Here, Dessein et al. survey populations at risk for schistosome infection, including Chinese fishermen and farmers, Sudanese farmers, and Brazilian villagers living near schistosome-infested waters. In each population, they identified single nucleotide polymorphisms (SNPs) near the gene encoding connective tissue growth factor (CTGF) that were associated with severe liver fibrosis. One SNP in particular was common to all populations. This group and others had previously found that schistosome-related hepatic fibrosis was under the control of a major locus at chromosome 6q23. This region contains two candidate susceptibility genes, *CTGF* and *IFNGR1*, and the authors had previously found that *IFNGR1,* which encodes part of the interferon-γ receptor, was also linked to fibrosis.

The fibrosis-associated SNPs resulted in CTGF proteins that bound more readily to nuclear factors, suggesting that these variants likely affect how CTGF, a known mediator of pro-fibrotic activities, regulates the transcription of downstream genes. Previous studies in rats revealed that inhibiting CTGF reduces fibrosis. And many patients with fibrosis express excess CTGF.

Ten to thirty percent of the people in this study harbored deleterious *CTGF* SNPs. To understand why these variants have been maintained across populations over time, the group is now studying whether these alterations provide protection from other infectious diseases.



ENRIQUE LENZI

Fibrotic granulomas can build up around schistosome eggs trapped in the liver.