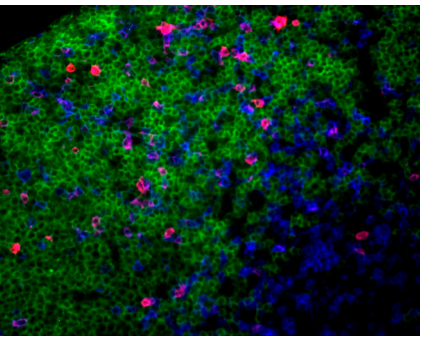


IL-4–expressing CD4+ cells (red) that accumulate in B cell follicles (green) appear to become follicular T cells.

Follicular T-to-be

Helper T (Th) cell identity may not be for life. According to a pair of studies from Zaretsky et al. (page 991) and King and Mohrs (page 1001), Th2 cells can turn into follicular T cells when duty calls.

Many immunologists consider each Th cell subset to be its own distinct class. The same is true of follicular T cells, $CD4^+$ cells found in the B cell follicles and germinal centers of lymph nodes. Yet here, two independent research teams found that Th2 cells morph into follicular T cells in response to worm infections. "What we previously believed to be rigid effector T cell compartments might in fact be rather plastic," says Edward Pearce, senior author of the Zaretsky et al. study.

The consensus has been that Th2 cells respond to worm infections by making IL-4, which helps B cells produce protective antibodies. Now these groups report that lymph node Th2 cells, which express IL-4 and GATA-3 like bona fide Th2 cells, gain follicular T cell attributes in response to parasitic worm infections. In addition to their follicular location, the cells expressed defining characteristics of follicular T cells, including IL-21, CXCR5, and ICOS.

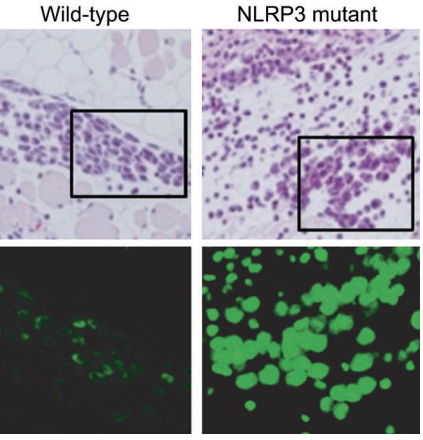
Follicular T cells and B cells relied on one another. The T cells that expressed follicular T cell markers weren't found outside of the follicle and, according to Zaretsky et al., their development from Th2 precursors depended on intact germinal centers. King and Mohrs show that antibody synthesis in response to a worm infection was impaired in the absence of follicular T cells and the IL-4 they produced.

The ability to become a follicular T cell may not belong to Th2 cells alone. A study recently published in *Nature Immunology* showed that follicular T cells expressed either IL-4 or the Th1 cytokine IFN-γ in a setting designed to trigger a mixed Th1/Th2 response.

The classical rule is that Th2 cells promote IgG1 and IgE production by secreting IL-4, and Th1 cells promote IgG2 production with IFN-γ. These new data suggest that it may instead be the follicular helper T cells derived from either Th1 or Th2 cells that drive the production of certain B cell antibody isotypes.

It remains unclear whether other effector T cell subsets can metamorphose, and whether follicular T cells can leave the lymph node and return to their Th2 origins.

Reference: Reinhardt, R.L., et al. 2009. *Nat. Immunol.* 10:385–393.



Neutrophil-rich inflammation (top) and active IL-1β (green, bottom) are increased in mast cells harboring a mutated version of *NLRP3*.

Mast cells master a rash

A hive-inducing villain has been convicted and traced back to its headquarters. On page 1029, Lachmann et al. confirm that IL-1β is the sole cytokine to blame for chronic rashes symptomatic of the genetic disorder CAPS (cryopyrin-associated periodic syndrome). And on page 1037, Nakamura et al. track IL-1β to its surprising source: mast cells.

Drugs that block IL-1 are used to relieve antihistamine-resistant rashes—the type typical of patients with CAPS. However, researchers weren't sure whether IL-1α, IL-1β, or both caused the problem. Lachmann et al. now show that IL-1β alone predicts disease severity. By developing an anti-IL-1β antibody (canakinumab), they found that patients with CAPS have abnormally high levels of circulating IL-1β. Treating patients with canakinumab relieved their rashes within a day, along with other symptoms of the disease, such as fevers, headaches, and joint pain.

In a separate report, Nakamura and colleagues showed that IL-1β localized to mast cells in human skin. Before now, IL-1β was thought to be produced primarily by macrophages. In macrophages, microbial infection stimulates inflammasomes, multiprotein complexes that turn on IL-1β along with other inflammatory cytokines. Within these cells, microbial ligands trigger the synthesis of the IL-1β precursor protein. And a second ATP-triggered signal activates the inflammasome, which then turns on caspase-1, the protease that cleaves the precursor into its active form. Here, Nakamura et al. show for the first time that the same process occurs in healthy mast cells.

A mutation in the gene encoding NLRP3, a component of the inflammasome, causes CAPS. Mast cells expressing mutated NLRP3 were trigger happy, according to Nakamura's study, producing active IL-1β in the absence of an inflammasome-activating signal. When the authors injected mast cells expressing mutant NLRP3 into the skin of normal mice, the mice developed CAPS-like symptoms, including neutrophil recruitment and vascular leakage.

Text by Amy Maxmen
amaxmen@rockefeller.edu

Perhaps a normally benign environmental cue triggers the constitutive production of the IL-1β precursor in patients, suggest Nakamura et al. This might explain why CAPS patients usually develop hives within the first few weeks after birth, when newborn skin is first exposed to microbes and other inflammatory stimuli.

As for canakinumab, it is awaiting approval from regulatory agencies in the US and in Europe for the treatment of CAPS-associated rashes.

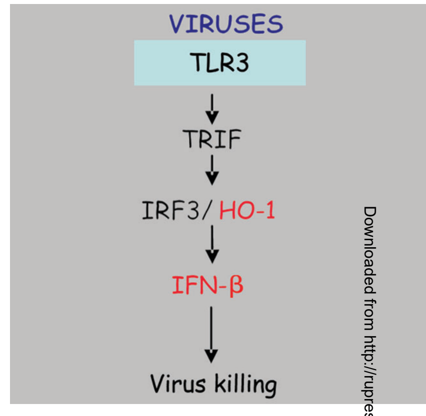
HO-1's versatility

Macrophages need the enzyme heme oxygenase (HO)-1 to produce the antiviral cytokine IFN-β, according to Tzima et al. on page 1167.

For years, HO-1 was best known for its role in dulling inflammation in part by inhibiting the production of proinflammatory cytokines. Now Tzima and colleagues show that HO-1 can also incite inflammation in the face of viral infection. In response to signals from the TLR3/4 and RIG-I/MDA5 pathways, HO-1 formed a complex with the transcription factor IRF3, allowing IRF3 to migrate to the nucleus and trigger IFN-β and chemokine production. By contrast, HO-1 was not needed for MAPK/NF-κB–mediated cytokine production in response to TLR3/4 signals.

Mice with HO-1–deficient macrophages could not make the IFN-β that they needed to clear a viral infection. Likewise, mice with EAE, an autoimmune disorder similar to multiple sclerosis, were worse off without HO-1 unless they were given an exogenous dose of IFN-β. Until now, researchers had assumed that HO-1 directly suppressed auto-inflammation by generating carbon monoxide, which shuts off the production of inflammatory cytokines.

Whether HO-1's effect on IFN-β synthesis requires its enzymatic activity, or its ability to bind to other proteins, remains to be seen. Learning more about HO-1's role in the antiviral pathway is essential to understanding how it elicits innate responses one moment and quells inflammation the next. Future studies are also needed to determine whether HO-1 is required for the production of IFN-β from other cell types.



HO-1 is required for macrophage production of IFN-β.

Bulldozing angiogenesis

Blocking the vessel-promoting cytokine M-CSF may be a promising way to fight cancer. Without it, diseased vessels can't grow but healthy ones can, according to Kubota et al. on page 1089.

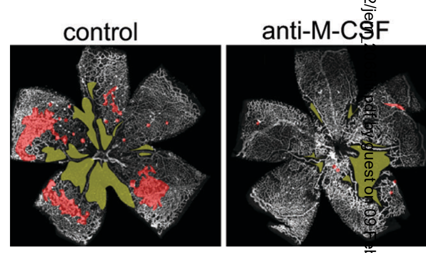
Many cancer treatments work by disrupting angiogenesis, the formation of new blood vessels that feed growing tumors. Agents that block the angiogenic factor VEGF have shown promise in human clinical trials, but recent studies in mice show that when treatment stops, tumor growth rapidly resumes. Now, Kubota and colleagues find that blocking M-CSF suppresses tumor growth, even after treatment subsides.

Kubota and his team compared the efficacy of M-CSF inhibitors to VEGF inhibitors in a mouse model of osteosarcoma, a bone tumor that expresses high levels of M-CSF. Three weeks of anti-VEGF treatment suppressed tumor growth, but the tumors bounced back when the drug treatment was curtailed. However, tumor growth in mice on a similar regiment of anti–M-CSF remained suppressed in the absence of drug.

Another important distinction between the two inhibitors was the type of vessel growth affected. In mice with injury-induced retinopathy, blocking VEGF inhibited pathological vessel growth but also stunted the recovery of healthy vessels. Blocking M-CSF, on the other hand, impeded only pathological angiogenesis, allowing healthy vessels to recover.

The anti–M-CSF treatment had a lasting effect on pathological angiogenesis, most likely because the extracellular matrix surrounding cancerous vessels was damaged, robbing the tumors of a scaffold on which to grow. And without M-CSF to beckon macrophages responsible for matrix repair, the diseased vessels could not recoup. Meanwhile, the extracellular scaffold of mice treated with anti-VEGF remained intact.

Whether or not other types of cancer rely more on M-CSF, rather than VEGF, for their vascular repairs remains unknown.



Blocking M-CSF after eye injury inhibits pathological vessel growth (red) but spares healthy vessel growth (decreased yellow).