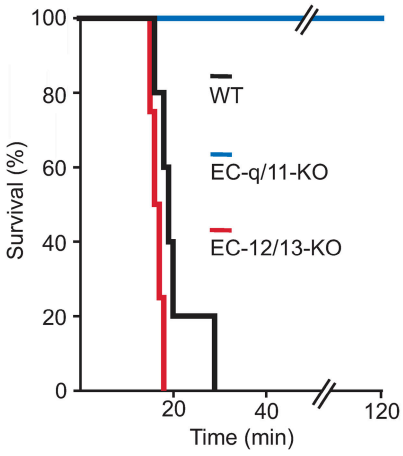


Mice without endothelial G_q/G_{11} survived allergen-induced shock.

Life after shock

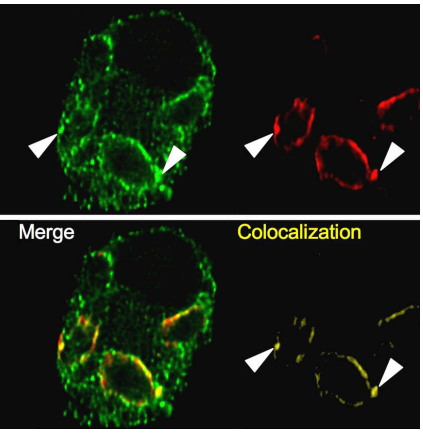
Lethal shock is subverted by crippling a family of G proteins in endothelial cells, according to Korhonen and colleagues on page 411.

Bee stings or other allergens can cause anaphylactic shock in severely allergic individuals by triggering mast cell activation and the release of anaphylactic mediators like histamine and platelet activating factor (PAF). At high enough levels, these mediators cause blood pressure to drop precipitously and vessels to leak, eventually leading to shock. Although much is known about causes and consequences of anaphylaxis, the precise pathogenic pathways remain murky. Here, investigators find that shock was sidestepped in mice whose endothelia lacked the G protein go-betweens G_q/G_{11}.

Many anaphylactic mediators act through G protein–coupled receptors, which link to downstream signaling molecules via G proteins, including G_q/G_{11}, G_{12}/G_{13}, and G_i. Here, G_q/G_{11} turned out to be vital for opening the endothelial barrier and activating endothelial cells during an allergic reaction. Without G_q/G_{11}, there was no phosphorylation of myosin light chain, which allows endothelial cells to retract from one another. G_q/G_{11} was also needed for the production of nitric oxide, a known mediator of anaphylactic shock.

On the other hand, endothelium-specific ablation of G_{12}/G_{13}, which activates the Rho/Rho-kinase pathway, had no effect on allergen-induced shock. And the effects of disabling G_i remain to be seen.

An endothelium-specific antagonist of a downstream player such as G_q/G_{11} could improve treatment for people at risk of allergen-induced shock. Epinephrine injections can be given only after anaphylaxis has begun, and upstream inhibitors of PAF have been ineffective. A pharmacological G_q/G_{11} inhibitor has already been developed and awaits testing in preclinical trials.



Antigen hand-off may occur when the ER (green) membrane fuses with the vacuole surrounding *T. gondii* (red). Arrowheads indicate fusion.

Toxo has a ticket to ride

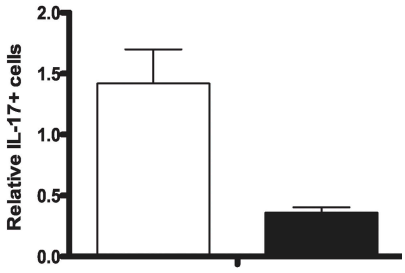
A vacuole encapsulating a parasite of warm-blooded animals shuttles peptides for cross-presentation in a report from Goldszmid and colleagues on page 399.

Pathogens that get sequestered in host cell vacuoles pose a paradox to immunologists. Although they are kept out of their host cells' cytoplasm, where MHC class I T cell epitopes are normally generated, many still elicit a $CD8^+$ T cell response. Here, Goldszmid et al. use *Toxoplasma gondii*, a vacuole-trapped bug, to understand how exogenous peptides in dendritic cells move into the cytoplasm in a poorly understood process known as cross-presentation.

Their findings differ from earlier claims that phagasome membranes fuse to the ER to transfer antigens from the vaccuole to class I molecules in the ER. Instead of a phagosome delivery, the authors show that the parasite-containing vacuole fused directly to the ER and presumably allowed antigens to pass between the organelles.

The previous experiments on ER delivery used phagocytosed ovalbumin-coated latex beads as model antigens. This group now moves one step closer to reality by tracking the process using infection with *T. gondii* expressing a peptide from ovalbumin. The authors hope their model will eventually be verified with unmanipulated *T. gondii* epitopes.

Proof for vacuole–ER fusion could be provided by blocking the fusion event, but the signals that initiate fusion are completely unknown. Goldszmid speculates that the parasite itself initiates the signal because it benefits from the generation of a $CD8^+$ T cell response, which permits host survival. By being ingested, *T. gondii* infects more than one animal in its lifetime. Therefore, the parasite is better off sparing the life of its initial, rodent host until a fat cat comes along.



Gfi-1 expression (black) blunts Th17 development.

Fine-tuning helper Ts

If the transcriptional repressor Gfi-1 attended a dinner party, it would prevent its host from pairing a heavy red wine with a delicate fish. On page 329, Zhu et al. show how Gfi-1 (growth factor independent 1) stops helper T cells from secreting the wrong type of cytokine.

What cytokines a T cell produces helps determine the outcome of an infection. Naive CD4+ T cells differentiate according to the problem at hand. They tend to differentiate into type 2 helper T cells (Th2) when extracellular parasites lurk, Th1 when the culprit is intracellular, Th17 cells after invasion by bacteria and fungi, or regulatory T (T reg) cells when an inflammatory response requires dampening. Gfi-1 helps control that differentiation decision, show Zhu et al. Or as senior author William Paul says, "It keeps cells on the straight and narrow."

This team previously reported that Th2-inducing cytokines, such as interleukin (IL)-4, induce Gfi-1, which then amplifies the Th2 response by triggering proliferation. Now they find that

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Gfi-1 also dampens the cells' tendencies toward the Th17 and T reg cell lineages. Gfi-1 inhibited production of IL-17 and blocked the expression of CD103, which is found on certain T reg cells. In a model of autoimmunity, mice that lacked Gfi-1 developed a preponderance of CD103-expressing T reg cells, thus delaying the onset of disease.

The protein prevented gene expression by binding to loci in the genes encoding IL-17 and CD103. Gfi-1 binding triggered histone modifications—most likely via its known interaction with the LSD1 histone demethylase—thus turning off gene expression. Gfi-1 expression was repressed by the cytokine TGFβ, which drives Th17 and T reg cell differentiation, allowing induction of those cells when needed.

Examining expression of Gfi-1 in various human infections may help explain why the balance of cell types can sometimes be tipped in the wrong direction.

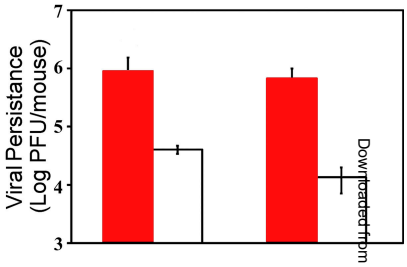
Virus-friendly Th17s

On page 313, Hou et al. expose a traitor. Cells producing the cytokine interleukin (IL)-17 protect a virus instead of their host. These results may help explain how chronic viruses, like HIV, establish a long-term foothold.

High levels of IL-17–secreting helper T (Th17) cells coincide with a number of chronic infections, but their role in disease pathogenesis is variable. Th17 cells help protect the body against certain bacterial infections, but they exacerbate tissue damage in autoimmune diseases. Hou et al. now catch IL-17 helping virus-infected cells survive.

Antigen presenting cells infected with the CNS-invading virus Theiler's murine encephalitis virus (TMEV) drove naive T cells toward a Th17 cell fate by secreting IL-6, show the authors. In turn, the IL-17 produced by those cells up-regulated anti-apoptosis genes, allowing infected cells to skirt suicide as well as assassination by killer T cells.

Other groups have shown that IL-6 promotes Th17 responses by triggering a positive feedback loop with IL-17. Here the authors show how TMEV manipulates that loop. Mice that produced higher levels of IL-6 and IL-17 after infection developed more severe disease than did resistant mice, in which protective Th1 responses predominated. Overproduction of IL-17 has been reported during early HIV infection in humans and herpes simplex virus in mice. Now that Hou et al. reveal that IL-17 promotes viral infection, chances are it's playing a similarly insidious role in other chronic infections.



Virus levels are boosted in the presence of IL-17 (red bars).

Bound to arthritis

Among the autoantibodies detected in patients with rheumatoid arthritis, none indicate the disease as reliably as those that bind to citrullinated proteins. On page 449, Uysal et al. now suggest that these popular biomarkers not only signal the presence of disease, but help to induce it.

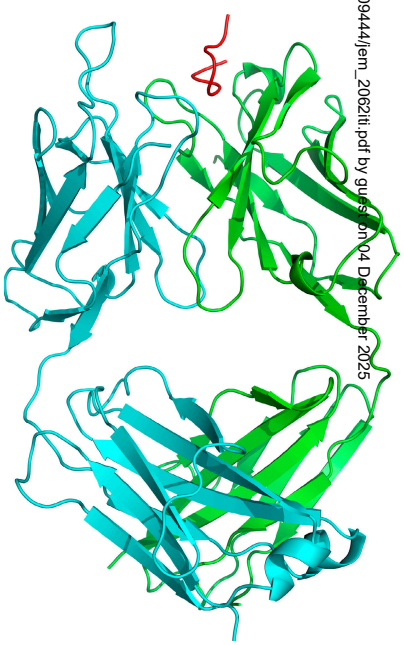
The inflamed cartilage and soft tissue in arthritic patients' joints consist mainly of type II collagen. Previous studies showed that those collagenous proteins are partially citrullinated—in other words, some of their arginine residues have been replaced by citrulline. The presence of antibodies targeting citrullinated proteins diagnoses arthritis with 99% accuracy. And because they are often detected before arthritic symptoms set in, Uysal et al. suspected that they might help generate joint destruction.

The authors now confirm the disease-inducing role of antibodies targeting citrullinated collagen epitopes. Injecting these antibodies into normal mice resulted in disease, and injecting them into arthritic mice worsened disease. According to Uysal et al., disease induction relates to how these antibodies bind their target.

By assessing the crystal structure of one antibody-citrullinated protein complex, the authors show that the antibody recognizes citrulline, rather than some other part of the modified protein. This direct binding suggests that the antibodies might cross-react with other proteins known to be citrullinated in arthritic joints, such as fibrinogen and fillagrin, thus exacerbating inflammation.

The numbers of citrulline-specific antibodies may soar soon after citrullinated proteins evoke an immune response. Mixed in with these antibodies are others that react to noncitrullinated collagen epitopes. The authors speculate that the latter antibodies might present collagen epitopes to T cells. And in turn, collagen-specific T cells could provide help for B cells that recognize either modified or unmodified collagen, creating a vicious cycle that culminates in collagen attack and cartilage destruction.

Why citrulline triggers an immune response in the first place and why that reaction is joint-specific in arthritis remain key questions. Because citrullinated proteins lurk behind several other human diseases, such as psoriasis and multiple sclerosis, understanding how these antibodies interact with their targets may help unravel the pathenogenicity of multiple maladies.



Structure may explain how antibodies to citrullinated proteins enhance arthritis.