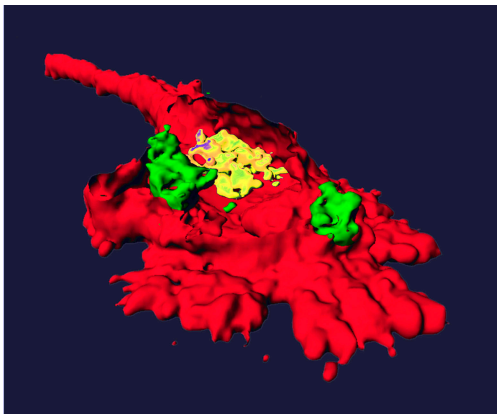


Airway dendritic cells (red) capture lipids from pollen grains (green) and present them on MHC CD1 molecules to lipid-reactive T cells.

Pollen power

On page 295, Agea and colleagues show that airway dendritic cells (DCs) help trigger allergic responses by capturing phospholipids from the surface of pollen grains and presenting them to lipid-reactive T cells. This is the first report of human T cells that recognize lipids derived from an environmental allergen. Thus, according to senior author Fabrizio Spinozzi, "the concept of the allergen should be extended to all pollen membrane structures," not just proteins.

T cell responses to allergens have traditionally focused on $CD4^+$ T helper 2 (Th2) cells, which recognize peptides derived from protein allergens. Generating Th2 responses, however, requires the time-consuming processes of antigen processing and presentation, whereas allergic T cell responses develop very rapidly. Spinozzi thus suspected that something faster was at work.

Spinozzi's group now shows that phospholipids present on the surface of pollen grains bind to CD1 molecules on airway DCs, which then trigger lipid-reactive T cells to proliferate and produce cytokines. DCs that had been chemically fixed could still stimulate T cells, suggesting that the lipids could be captured directly from the pollen grains and did not require processing by the DC.

These lipid-specific T cells were most prevalent during allergy season and were rarely found in nonallergic individuals. In addition, greater numbers of CD1-expressing DCs were found in the airways of allergic individuals, which may help explain why nonallergic people don't respond to pollen-derived lipids in the same way. JEM

Dangerously golden

The pathogenic bacterium *Staphylococcus aureus* has a colorful resistance mechanism. According to Liu and colleagues on page 209, the gold color of *S. aureus* is not just for show; the molecules that give the bug its golden hue also help it resist attack by neutrophils.

The characteristic gold color of *S. aureus* sets it apart from its avirulent relatives, which are mostly unpigmented. The color reflects the production of antioxidant molecules called carotenoids—similar to those originally isolated from carrots and touted for their ability to boost the immune system and decrease tumor growth in humans. Despite the connection between color and virulence of *S. aureus*, a functional link had never been investigated.

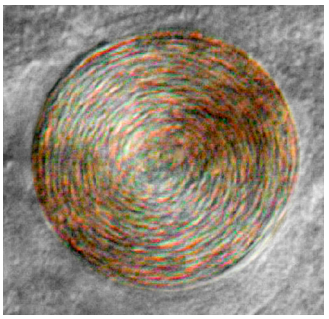
Liu and colleagues now show that these pigmented molecules can also help *S. aureus* resist the hosts' immune defenses. Carotenoids produced by *S. aureus* defused the reactive oxygen species (ROS) that normally help neutrophils kill bacteria. Expression of these pigments rendered the normally colorless *Streptococcus pyogenes* golden and more virulent. And *S. aureus* that were robbed of the ability to make carotenoids could no longer resist neutrophil attack and were less pathogenic in mice.

The protective effect of the carotenoids on the bacteria was a function of their antioxidant activity, as wild-type bacteria had no advantage over carotenoid-deficient bacteria in mice whose neutrophils lacked the ROS-producing machinery. The authors suggest that drugs that inhibit carotenoid synthesis might be useful for treating *S. aureus* infections, which are often resistant to traditional antibiotic treatment. JEM

Malaria held captive

Malaria sporozoites that lack a certain protease get trapped in their cyst-like breeding ground (the oocyst), as shown by Aly and Matuschewski (page 225). Unable to break free, these captive parasites turn in helpless circles inside the oocyst and their life cycle halts.

Malaria-causing parasites (*Plasmodium* species) have a complex life cycle that includes several distinct stages of intracellular growth in vertebrate and mosquito hosts. Movement from one stage to the next requires exit from one host cell and entry into another. Invasion of target cells has been shown to require parasite-encoded proteases that, by poorly defined mechanisms, allow the bug to penetrate cell membranes. Parasite exit from target cells has been even less well-studied.



Malaria sporozoites that lack egress cysteine protease 1 get trapped inside the oocyst (shown) in the mosquito midgut.

Aly and Matuschewski now identify a cysteine protease that is selectively expressed at the late sporozoite stage, just before sporozoite release and entry into the mosquito salivary glands. Elimination of this protease from the parasite caused mature sporozoites to become trapped inside the oocyst, a protective compartment forged from the basal lamina of the mosquito midgut where the sporozoites divide and grow. There they commenced an unusual circular motion, the significance of which is not yet understood.

These data suggest that *Plasmodium* egress is an active process that requires the protease—dubbed egress cysteine protease 1—to actively break down the oocyst wall, rather than a passive one in which the oocyst simply ruptures once it is filled to capacity. JEM

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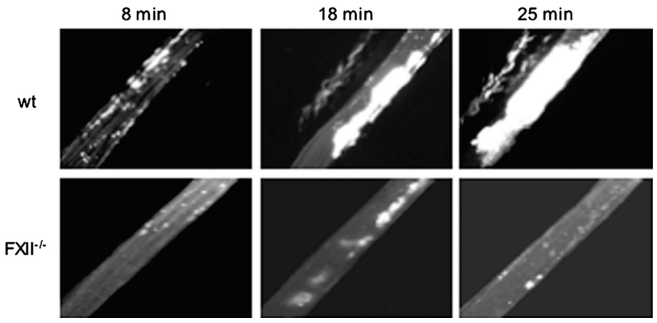
Clotting revisited

On page 271, Renné and colleagues show that the absence of a clot-promoting protein in mice keeps arteries from clogging with no risk of excessive bleeding. These data challenge the decades-old belief that this protein—called factor XII (FXII) or Hageman factor—has no impact on clotting in vivo.

Blood clotting depends on the sequential activation of proteins, called clotting factors, that culminates in the production of fibrin—the protein that forms the meshwork of the clot. This process must be tightly regulated, as too little clotting can lead to bleeding disorders and too much clotting can lead to blood vessel blockage, which triggers strokes and heart attacks.

Deficiencies in some blood clotting proteins, such as tissue factor and factor VII, result in fatal bleeding disorders. But deficiencies in FXII are not associated with abnormal bleeding, and thus this factor has long been considered dispensable for normal clotting.

Renné and colleagues now reexamine a role for this clotting factor in FXII-deficient mice. As they had previously reported (and similar to the situation in humans), these mice developed no spontaneous bleeding disorders. However, the FXII-deficient mice were less likely to develop blocked arteries (thrombosis) in response to induced vessel injury. Thrombosis formation was initiated normally in the FXII-deficient mice, but the clots were unstable and detached from the vessel wall before they could grow large enough to impede blood flow, suggesting that FXII is required not to initiate, but rather to propagate, the clotting reaction.



Vessel-blocking thrombus formation (white) in damaged mesenteric vessels is prevented in the absence of coagulation factor XII (bottom panels).

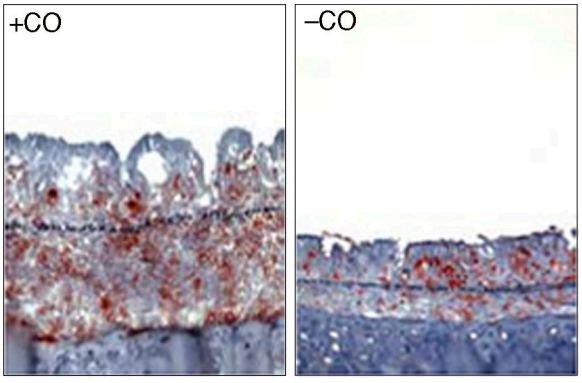
Consistent with these findings, elevated plasma levels of FXII in humans have been associated with increased coronary artery disease, and lower levels with protection. Thus the authors suggest that drugs that inhibit FXII might be useful in treating heart disease without increasing the risk of spontaneous bleeding. FXII-driven fibrin formation thus appears to be essential for pathological thrombus formation. The beneficial effects of this pathway, however, remain mysterious. JEM

Breathing easy with carbon monoxide

Ancient Greek philosophers extolled moderation in all things. On page 283, Minamoto and colleagues show that carbon monoxide (CO) inhalation is no exception. In a mouse model of trachea transplantation, inhaled CO—in moderation—prevented the development of lethal obstructive airway disease.

CO gas is both a toxic air pollutant and a normal byproduct of cellular heme metabolism. Although CO is well-known for its role as an asphyxiant, recent studies have revealed its virtues, which include anti-inflammatory and anti-apoptotic effects on a variety of cell types. CO has also been shown to inhibit the rejection of xenogeneic heart transplants in rats.

Minamoto et al. now add to that list of virtues by showing that treating mice with low-dose inhaled CO reduced the T cell infiltration and airway obstruction that develops after allogeneic tracheal transplantation. The benefits of endogenous CO were evident based on comparisons with mice that received grafts lacking the CO-synthesizing enzyme hemoxygenase-1 (Hmox-1), which developed more severe disease than mice that received wild-type grafts.



Inhaled carbon monoxide reduces T cell (brown) invasion of the airways following allogeneic tracheal transplantation.

This group previously showed that the development of post-transplant airway obstruction requires the expression of inducible nitric oxide synthase (iNOS). They now find that CO counterbalances the production of nitric oxide by inhibiting the activation of the transcription factor NF-κB, which drives the expression of iNOS.

This came as a surprise to the authors, as most other known effects of CO depend on activation of the MAP kinase or cyclic GMP signaling pathways. Further experiments are required to determine how CO inhibits NF-κB activation. But in the meantime, these data suggest that increasing endogenous CO levels might be therapeutic in transplant patients who develop a lethal, and currently untreatable, complication of lung transplantation called obliterative bronchiolitis. JEM