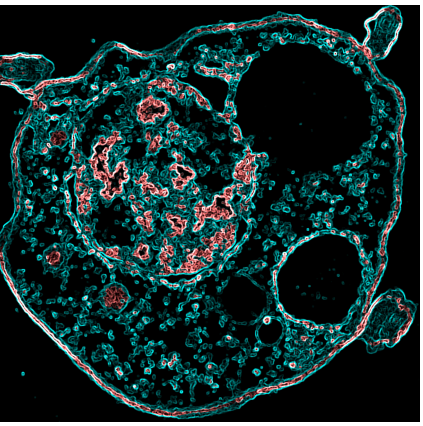


Ingestion of the entire TLF complex causes trypanosomes to swell and burst.

Triple punch against trypanosomes

Fat cooperation keeps sleeping sickness at bay, say Molina-Portela et al. (page 1721). The authors find that all three components of a human high density cholesterol complex are needed to kill disease-causing trypanosomes.

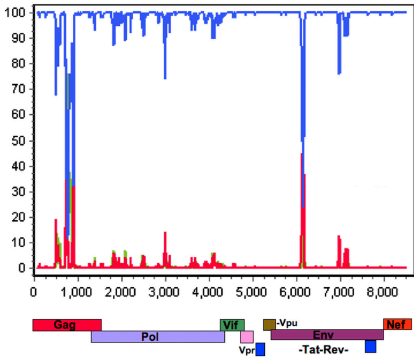
Trypanosomes cannot synthesize their own fats, so they feed on the host's portion, which in humans and some other primates includes a cholesterol complex known as the trypanosome lytic factor (TLF). Because TLF is toxic to parasites that lack a specific resistance gene, it acts as a Trojan horse that kills the bug from within. Of the three lipoproteins in TLF, only apolipoprotein (apoL)-1 has been credited for TLF's killing power, via its ability to drill pores into the parasite's membrane that cause the invader to swell and burst.

The group's initial results supported the single-fat toxicity idea; mice engineered to produce only the apoL-1 component of TLF survived otherwise lethal infections. But when plasma from these mice was transferred into normal infected mice, the recipients did not completely clear the parasite; animals that were infused with plasma containing all three TLF components did.

Mouse plasma that contained only apoL-1 had 10% of the lytic activity of whole human plasma. The authors speculate that this feeble but detectable killing capacity might be due to apoL-1's association with endogenous mouse lipoproteins that are similar to other TLF elements.

The other two TLF components might enhance killing by increasing the uptake of apoL-1 by the parasite. One is thought to be a ligand for the parasite's fat-binding receptor, and the other might direct the delivery of the complex to the lysosome, whose acidic environment helps activate apoL-1.

Some trypanosome varieties have a resistance protein that hook to apoL-1's C terminus, which has led to the idea that a version of apoL-1 lacking this domain might provide broad resistance to the parasites. But the authors now dismiss this idea, as mice that expressed the truncated lipid were still susceptible.



Different HIV strains in one individual that recombine (red/blue overlap) at immune-targeted sites escape T cell attack.

HIV switches to escape

On page 1789, Streeck et al. reveal that a second HIV strain is encouraged by the host's immune pressures to recombine with an earlier strain. Thus thwarted, the immune system fails to keep the new strain in check.

Most HIV-infected individuals initially develop a strong $CD8^+$ T cell response against multiple epitopes, including those found within HIV's Gag and Env proteins, some of which eventually develop escape mutations. In one HIV-infected individual, the authors found, new $CD8^+$ T cells quickly developed against such mutated epitopes while the original T cells waned. Viral levels remained low in the patient, suggesting that the variant-specific T cells controlled the mutant HIV strain.

But this control was broken by an apparent second infection in the individual. Soon after it entered the host, the second strain recombined with the first. In the resulting strain, the authors found switched sequences at the immune-targeted Gag and Env sites. The switch provided the new strain with the original version of the first, before the escape mutations occurred. This allowed viral levels to reach an all-time high by facilitating viral escape from the $CD8^+$ T cell responses that were dominant prior to the second infection. The second strain might distinguish between available strains and choose the right one for recombination. More likely, however, viruses lucky enough to acquire the right bits of Gag or Env might simply be spared by the weakened T cell response.

$CD8^+$ T cells were eventually regenerated against the switched epitopes, and viral levels decreased. But this control was also short lived; a second recombination event at the same regions—this time with the mutated version of the first strain—raised viral levels. The findings suggest that, like escape mutations, recombination is a trick that HIV uses to stay a step ahead of the immune system.

Selective signaling

Two receptors that trigger platelet activation relay their signals via different residues on the same adaptor, according to Bezman et al. (page 1775).

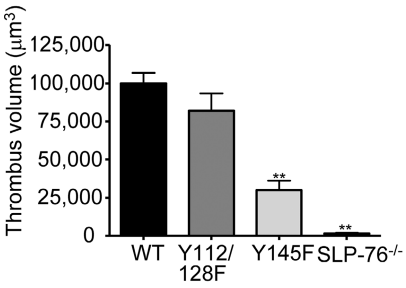
In platelets, the SLP76 adaptor scaffolds a signaling complex that activates platelets via two receptors: the GPVI immunoreceptor and the $\alpha IIb\beta 3$ integrin. Three tyrosines at the SLP76 amino end—Y145, Y112, and Y128—constitute a major part of the molecule's business end.

Text by Hema Bashyam
hbashyam@rockefeller.edu

SLP76 works best in platelets when all three are phosphorylated, and mutations at all three tyrosines block platelet activation. Bezman et al. now find that the tyrosines selectively transmit signals from one or the other receptor.

This partiality became evident when the group created mutant mice defective either in Y145 or in both Y112 and Y128. Platelets from the Y145 mutants did not spread, aggregate, or degranulate—effects mediated by GPVI signals. These defects were associated with an inability to recruit and activate the known downstream molecules PLCγ2 and Vav1. These defects were milder in platelets from the dual mutant, which bound to both PLCγ2 and Vav1, but these cells were less sticky and did not form stable clots—effects attributed to αIIbβ3.

In T cells, mutations in any of the three SLP76 tyrosines cause defective T cell receptor signaling. But T cells that express two forms of SLP76—one mutated at Y112/128 and the other at Y145—remain functional, suggesting that the mutant SLP76s team up to recruit all the necessary molecules. Bezman et al. did not observe such complementation in platelets, however. T cells, which have many more immunoreceptors than platelets, might form larger signaling complexes in which different mutants are more likely to meet up and rescue each other.



Mutation of one SLP76 tyrosine residue (Y145), but not others (Y112/Y128), impairs platelet function and clotting in mice.

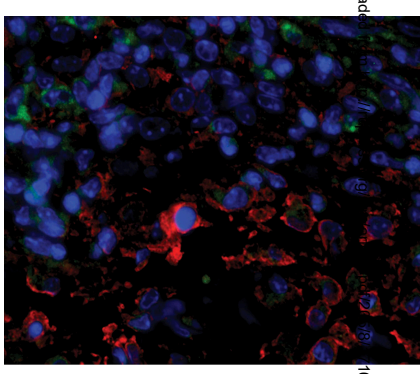
*Twist*ed control

Over-stimulated T helper (Th)-1 cells keep themselves in check by activating an internal brake, say Niesner et al. (page 1889).

Th1 cells activated by self-antigens can cause chronic inflammation, as seen in autoimmune diseases such as diabetes and rheumatoid arthritis. Niesner et al. were searching for genes that are highly expressed in such chronically activated Th1 cells in mice and discovered a transcriptional repressor called *twist1*. Now, the authors show that repeatedly activated Th1 cells avoid turning deadly by turning on *twist1*, which then inhibits NF-κB–dependent cytokine production.

Absent in naive mouse T cells, *twist1* was switched on when these cells were stimulated with antigen in the presence of the Th1 polarizing cytokine IL-12 but not the Th2 cytokine IL-4. IL-12 activates the transcriptional activator STAT4, which then bound to and activated the *twist1* promoter. Subsequent antigen stimulation increased twist1 expression in the Th1 cells, dampening their inflammatory cytokine production. The delayed induction of *twist1* probably gives Th1 cells a chance to initiate inflammation before they are shut down.

An infusion of *twist1*-deficient Th1 cells worsened arthritis in mice, whereas a shot of Th1 cells overexpressing *twist1* ameliorated disease. Before this finding can be clinically exploited, a twist in the human *twist1* story needs to be sorted out: Th1 cells found in the diseased tissues of patients suffering from arthritis or chronic gut inflammation had plenty of twist1. Whether human twist1 also acts as a brake and, if so, how these disease-associated Th1 cells bypass it remains to be seen.



Knockdown of *twist1* increases the production of TNF (red) in the arthritic joints of mice.

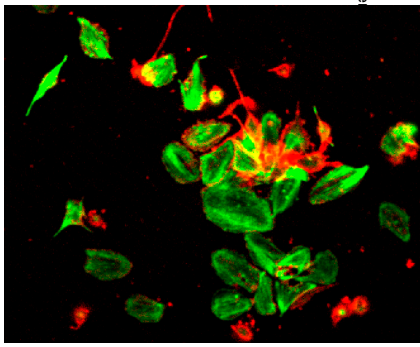
Cranking out healthy platelets

On page 1917, Nishikii et al. produce a plethora of platelets by picking perfect stem cell progenitors and preventing shearing of the platelets' activating receptors.

Platelets for therapeutic use are currently filtered from donated blood, which increases the risk of infections and other side effects in patients who need frequent transfusions. Scientists have been trying to generate platelets from embryonic stem cell (ESC) lines instead, but their efforts have so far been stymied by two problems.

First, ESCs cultured with stromal cells produce a tiny platelet population that is quickly drowned out by other cell lineages. Nishikii et al. resolved this issue by using ESCs that had already differentiated into platelet-committed hematopoietic stem cells, which express the clot-promoting αIIbβ3 receptor.

The second and more worrying problem is that the ESC-derived platelets don't aggregate properly. This defect was previously seen in vivo in long-lived platelets whose matrix-binding receptors had been sheared off by matrix metalloproteinases (MMPs). The group found that this also happened in vitro, and platelets cultured with MMP inhibitors formed clots in vitro and enhanced tissue repair in injured mice. This approach awaits testing in humans.



MMP inhibitors help maximize the numbers and function of cultured platelets (green) expressing integrin receptors (red).