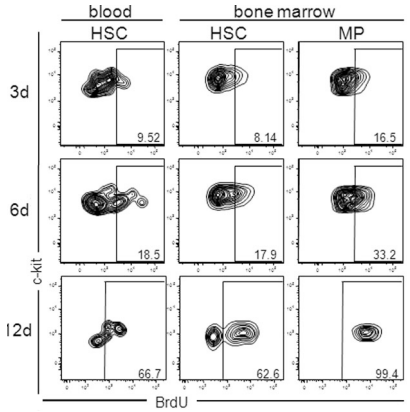


After 12 days, many hematopoietic stem cells in circulation hadn't incorporated BrdU, meaning that they didn't divide before leaving the bone marrow.

Vacant spots for stem cells

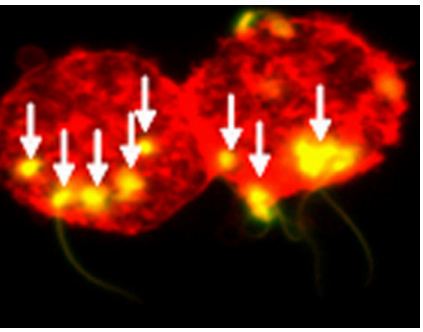
Like cars circling city blocks on Saturday night, stem cells stand a good chance of finding a parking spot in bone marrow if they circulate long enough. Hematopoietic stem cells frequently leave their niches, freeing up space for other stem cells to enter, report Bhattacharya et al.

Their finding explains a paradox posed by bone marrow transplantations that replaced recipients' blood supplies without radiation treatment. Radiation treatments are normally used in part to clear a recipient's malfunctioning stem cells, thus freeing up limited stem cell space. And although studies suggest that stem cells exit their niches periodically, researchers have thought that the cells first underwent mitosis, leaving a replacement in their wake.

By labeling cells with BrdU, however, the team found that not all hematopoietic stem cells divide before they exit the bone marrow. And they appear to go away often, as one to five hematopoietic stem cells were found in the blood stream of mice at any particular time. The cells circulated for about five minutes—meaning that more than 1,000 stem cells enter circulation each day.

Steady stem cell egress could account for the authors' finding that transplantation was enhanced when mice were given small numbers of donor stem cells repeatedly over seven days as compared with a single large dose.

Although hematopoietic stem cells appear to return to their niche, the extent to which this happens is unknown, as are the signals that drive the cells out or welcome them in. If the factors coordinating this process can be better understood, induced vacancies could provide an alternative to radiation treatments and their accompanying side effects. **AM**



Spermatozoa (arrows) transmit HIV when they attach to dendritic cells (red).

HIV sticks to sperm

Sperm, and not just the fluid it bathes in, can transmit HIV to macrophages, T cells, and dendritic cells (DCs), report Ceballos and colleagues. By infecting DCs, which carry the virus and potently pass it to T cells, sperm may play a leading role in spreading HIV.

During sexual intercourse, HIV-infected men transmit HIV through their semen, which carries free-floating virus as well as HIV-infected leukocytes. Traces of HIV have been detected on sperm as well, but the role they play in viral transmission has been a matter of debate. After all, men with vasectomies can transmit HIV. Now, Ceballos et al. show that HIV attaches to the surface of sperm and that these HIV carriers pass on the virus to DCs and other HIV targets.

Sperm express molecules known to interact with HIV's envelope, such as heparan sulfate and mannose receptors. The authors show that HIV relies on heparan sulfate to attach to sperm, but not mannose receptors as previously predicted.

Once attached, the virus was transmitted from sperm to DCs in culture. The DC receptors CD4 and DC-SIGN were required for transmission, suggesting that DCs pick up the virus by binding to sperm rather than by ingesting them. DCs matured after interacting with the sperm, producing tolerance-promoting cytokines like interleukin-10. The authors speculate that this immune-suppressing profile, versus an inflammatory profile, might also help the virus spread.

Sperm might reach DCs by passing through microabrasions in the vaginal or anal lining that often form during intercourse, suggest the authors. Or they might contact the finger-like projections of DCs that extend to the surface of mucosal linings. Furthermore, the team found that a slightly acidic pH, similar to the pH in the vagina after sex, promoted HIV–sperm binding and the subsequent rate of sperm-related DC infection. **AM**

Mapping TB resistance

The first genetic resistance factor for tuberculosis (TB) infection is now reported by Cobat et al. The group has identified one locus that determines whether an individual will respond to the TB skin test and a second that controls the extent of that response. The results suggest that one major genetic locus controls innate resistance to the pathogen in humans.

Two-thirds of the global population is infected with *Mycobacterium tuberculosis*, the agent responsible for TB. Yet the disease only manifests in about 10% of infected individuals. To find genetic variants controlling susceptibility to infection, the authors studied 128 families in Cape Town, South Africa, where TB is highly endemic.

Although most subjects were likely to have been exposed to *M. tuberculosis*, about 40% did not show delayed type hypersensitivity (DTH) in a skin antigen test. This strong resistance mapped to a

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6-Mbp chromosome region, 11p14. This locus may unveil cellular mechanisms that might one day be manipulated to prevent TB—an important goal given the recent rise in drug-resistant strains.

The second locus, in the 2.9-Mbp 5p15 region, segregated with differing extents of positive DTH responses. These genetic factors might contribute to whether an infected individual keeps the bacterium dormant or develops the disease. The same chromosomal region is associated with susceptibility to sarcoidosis, an immune disorder of persistent inflammation that is often associated with TB.

A candidate 5p15 gene is a solute carrier (SLC) family member. A human SLC member called *NRAMP1* is known to influence granuloma responses to mycobacteria, and loss of the mouse *SLC6A3* protein reduces DTH response to ovalbumin. **NL**

At junctions, Gα tears and Gβγ repairs

A team of G protein subunits have opposing agendas during thrombin-induced increases in lung vessel permeability, show Knezevic and colleagues. Once separated, Gα and Gβγ subunits act to open and close, respectively, cell–cell adhesions. The findings implicate the Gβγ pathway in deadly disorders causing persistently leaky vessels.

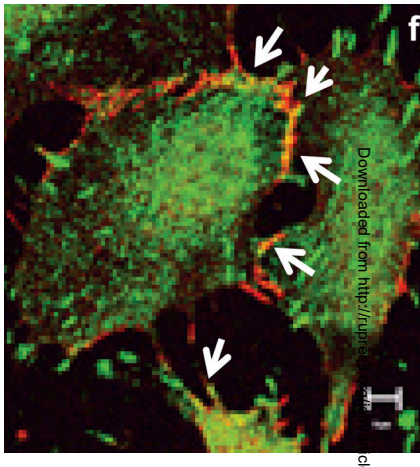
A transient opening of endothelial cell–cell adhesion allows immune cells to infiltrate tissue and fight infection and injury. Thrombin instigates this opening by cleaving the G-protein-coupled PAR1 receptor. Upon subsequent G-protein dissociation, the Gα subunit initiates RhoA- and MLCK-mediated cell contraction, which pulls apart cell–cell adhesions called adherens junctions, thus creating leaky vessels.

The group's research now shows that freed Gβγ works to undo Gα's efforts. By blocking expression of the main endothelial Gβ isoform, Knezevic et al. found that loss of Gβγ prevented the resealing of adherens junctions, which typically occurred two to three hours after their opening.

Interaction partners of Gβγ that are also known to regulate adherens junctions include Focal Adhesion Kinase (FAK) and the scaffolding protein RACK1. The group had previously shown that FAK suppresses the RhoA cell contraction pathway. They now show that Gβγ is required for FAK activation after thrombin exposure.

Without thrombin, Gβγ associated with RACK1 in endothelial cells. But with thrombin, the group saw, Gβγ left RACK1 and joined FAK and its kinase, Fyn. What controls the system's timing, such that Gα undoes junctions well before Gβγ rezips them, is not yet clear.

Mice lacking Fyn were unable to turn on FAK and had problems resolving fluid leakage into their lungs upon PAR1 activation. This edema was lessened with the transduction of a version of FAK that mimics its phosphorylation. The findings identify a potential new therapy target for the treatment of acute respiratory distress syndrome (ARDS), which kills tens of thousands of patients in the US every year. **NL**



FAK (green) and Gβγ help reseal endothelial adherens junctions (red) that are opened by Gα upon thrombin exposure.

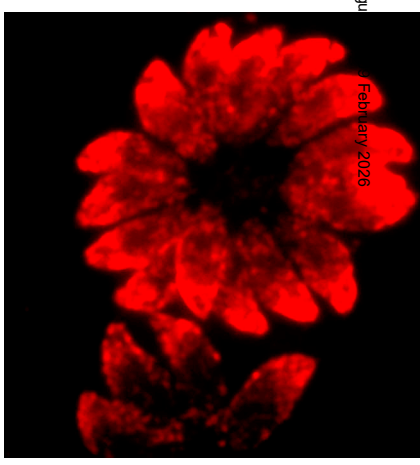
Toxoplasma hosts ROP'd into STAT3 activation

A lone amino acid change determines success or failure for strains of *Toxoplasma gondii*, say Yamamoto et al. The group identifies a kinase mutation that thwarts one strain's ability to activate Stat3 and halt the host immune response.

T. gondii comes in three chief flavors: types I, II, and III. Unfortunately for types II and III, their genetic differences severely cripple infectivity. The genetic changes in type II parasites disable *T. gondii's* ability to down-regulate protective host cytokines by turning on the Stat3 transcription factor. Exactly how the type I parasite activates Stat3 was unknown, but a polymorphism was recently mapped to a gene encoding a secretory organelle kinase called ROP16. And inserting type I ROP16 into type II parasites helped them activate Stat3.

Yamamoto et al. have now created a type I strain that lacks ROP16. Like normal type II parasites, the type I mutant failed to activate Stat3 and as a result induced host cytokines. Expression of ROP16 in mammalian cells, on the other hand, pumped up STAT3 activity by triggering its phosphorylation and nuclear translocation.

ROP16 kinase activity was necessary for Stat3 activation, and in vitro evidence suggested the phosphorylation may be direct, as ROP16 directly bound to and phosphorylated Stat3. The group found that a single leucine-to-serine substitution in type II ROP16 disabled Stat3 activation. The residue is not essential for kinase activity, but in silico modeling suggested the serine creates a misshapen active site. **NL**



CÉRÈDE, O, ET AL. 2009. *J. EXP. MED.* 201:453–463.

A polymorphism in the *Toxoplasma gondii* (shown) ROP16 kinase prevents host activation of STAT3 and thereby cripples the infectivity of the type II strain of the parasite.