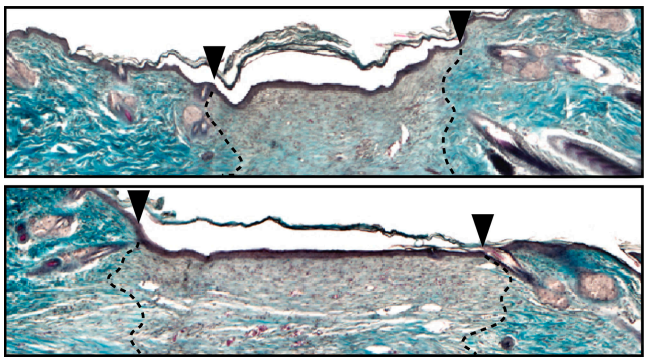


Treating skin wounds (blue) with osteopontin antisense DNA (top) reduces the size of scars (area between arrows).

Scar-free healing

Mending wounds quickly while keeping them scar-free is not an impossible task. Mori et al. (page 43) find that shutting down a protein called osteopontin does the trick.

Scars form when the inflammatory response that protects skin wounds against invading microbes induces the release of chemokines, which recruit fibroblasts. These cells then generate swathes of collagen to provide a new matrix for epithelial cells to close the wound. But all that new collagen stands out from the surrounding skin. It is also more than a cosmetic blight: scarring in injured organs can cause organ damage when the new collagen hardens.

Mori et al. previously found that injuries healed faster, without scarring, in knockout mice that lack neutrophils, macrophages, and mast cells. These mice are unable to mount a normal inflammatory response and fail to recruit fibroblasts to the wound. The mice had lower levels of osteopontin, a structural protein required for bone formation, which is secreted by the wound fibroblasts during inflammation.

The group now finds that suppressing osteopontin alone in healing wounds accelerates repair and reduces scarring. The researchers treated skin wounds on mice with a gel containing osteopontin antisense DNA. The resulting reduction in osteopontin levels increased the regeneration of blood vessels around the wound and sped up tissue reconstruction. These wounds had a sparser collagen matrix that might allow blood vessels to grow unimpeded.

Treated wounds also contained fewer macrophages, which the authors found normally amplify osteopontin production and inflammation via cytokine secretion. The team has yet to test whether this reduction in macrophage numbers increases the risk of infection.

How osteopontin beefs up scar tissue is still unclear. The collagen matrix within the gel-treated wounds was composed of thinner collagen fibrils, suggesting that osteopontin somehow directs either the synthesis or assembly of collagen during the repair process. JEM

Helping lymphocytes to move on

Try as it might to pull itself forward, an immune cell will go nowhere unless a myosin also pushes it from behind, report Morin et al. (page 195).

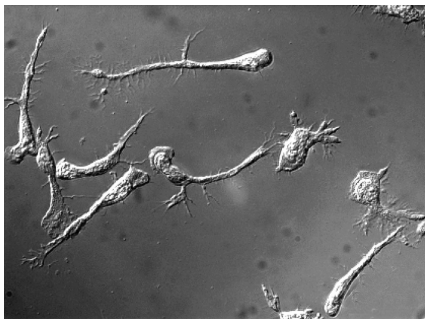
An immune cell holds onto the underlying matrix or another cell with the help of membrane receptors called integrins. When the cell receives a chemokine signal, the integrins change shape, allowing them to grab onto their ligands on target cells. Using the traction provided by these integrin links, the now sticky cell elongates a leading edge in the direction of migration and is trailed by a uropod—the back end of the cell.

The cell moves ahead when the integrins deactivate and the integrin-ligand bonds in the uropod are broken. The forces that unstick the uropod to allow forward propulsion are unknown.

Morin et al. hunted for these forces by looking for proteins that bind to a T cell integrin called LFA-1 in cells that are getting ready to move. They found a nonmuscle form of the myosin motor called MyH9, which is known to be required for immune cell migration. Images and videos showed that this actin-based motor docked with LFA-1 in the uropod but not in the leading edge.

Cells that were treated with a myosin inhibitor or a myosin-specific siRNA froze into comet shapes with extended uropods that failed to detach. The motor's action thus seems to break LFA-1's hold on its ligand.

Even without the myosin, the uropod integrins were already in an inactive form, as shown by their failure to bind antibodies specific for active integrins. Clusters of these inactive integrins, however, still formed weak bonds with their ligands. The positioning of the myosin near these weak attachments might allow the motor to pop them apart via actin contraction.



Cells elongate but are unable to detach their tails when the MyH9 myosin is blocked.

The mechanism that inactivates integrins in the uropod is not yet known. It is possible that integrins deactivate as they drift farther from the activating chemokine signal at the cell's leading edge.

How the myosin distinguishes between active and inactive LFA-1 is another question that still needs an answer. JEM

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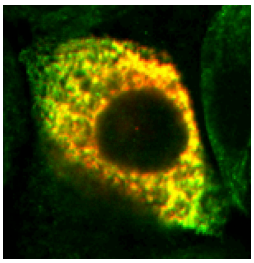


EVERs keep zinc out of the nucleus by trapping zinc transporters (green) at the ER (red).

Block the zinc, starve the virus

Zinc might strengthen our immune systems and fortify our bones, but it also helps a cancer-causing skin virus take hold, according to Lazarczyk et al. (page 35).

Most people harbor within their skin a human papillomavirus (HPV) subtype called HPV EV. Although this virus is usually harmless, certain infected individuals develop wart-like skin lesions that eventually grow into tumors. These rare, susceptible individuals have mutated versions of ER membrane proteins known as EVER1 and EVER2.

Lazarczyk et al. now show that normal versions of EVER proteins counter the virus by depriving the cell's nucleus of zinc—a known transcription booster. Zinc is shuttled into the nucleus by a transporter called ZnT-1. But the team found that EVERs bound and retained ZnT-1 at the ER, thus keeping the level of zinc in the nucleus low.

Cells containing mutated versions of EVERs had abnormally high levels of nuclear zinc, which activated proproliferation transcription factors, thus increasing the host cell's ability to seed tumors. Adding back functional EVERs reduced cellular proliferation. As the extra zinc also activated cellular transcription factors required for viral replication, EVERs might normally block viral replication as well.

Unlike HPV EV, the group found, other HPVs fought back against EVER proteins. One version that causes genital cancer, for instance, manufactured a protein that disrupted the EVER–ZnT-1 complex and freed zinc for nuclear entry. JEM

New vaccines may provide full coverage

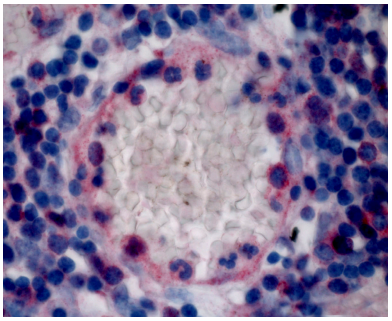
On page 117, Giefing et al. report the discovery of two new vaccine candidates that might protect humans against all 90 versions of a deadly bacterium.

This bacterium, *Pneumococcus*, invades the lungs, blood, and eventually brain to cause pneumonia, sepsis, and meningitis, respectively. Surface proteins from this bug are currently being used as vaccines to induce the body to produce protective antibodies. But these vaccines, which comprise proteins from only a few types of *Pneumococcus,* are not effective against other variants, due to extreme sequence diversity in the surface proteins.

Giefing et al. now identify two bacterial antigens that are nearly identical among all pneumococcal strains and that induce potent antibodies in vivo. The authors hunted for conserved bacterial antigens that would be exposed on the pathogen during disease. Antibodies isolated from exposed but healthy humans and from those recovering from infection were used to identify pneumococcal proteins that were targeted by the protective antibody response.

Both of the newly identified antigens induced antibodies that protected immunized mice against several other pneumococcal variants. The antigens might be potent targets because they come from a protein that is essential for bacterial growth and survival and thus unlikely to mutate. The team is currently testing their vaccines in clinical trials. JEM

An inflammation-enhancing virus



HCMV induces infected cells to produce leukotrienes (pink) that attract more inflammatory cells (dark blue).

A dormant virus that is awoken by inflammation enhances this potentially dangerous immune response to remain active, say Qiu et al. (page 19).

The human cytomegalovirus (HCMV) switches off its own replication after infection to stay off the immune system's radar. Unlike other dormant viruses that require a weakened immune system to reactivate, HCMV thrives amidst a roaring immune response. The virus replicates when its host cells—monocytes and other inflammation-causing cell types—proliferate. These cells produce cytokines such as TNF that directly stimulate the promoters of some HCMV genes.

Active HCMV infections are thus commonly found within the inflamed tissues of patients suffering from chronic inflammatory diseases, such as atherosclerosis. But whether the reactivated virus is just a lucky beneficiary of local inflammation or actively perpetuates inflammation was under debate.

Qui et al. now find that HCMV enhances inflammation by coercing nearby noninflammatory cells to join the fray. Smooth muscle cells isolated from inflamed tissues harbored active HCMV and produced leukotrienes—powerful proinflammatory lipids. Leukotriene production had been thought to be restricted to immune cells. How the virus reprograms the previously harmless muscle cells to become inflammatory is not clear.

The virus's escalation of inflammation probably amplifies its own growth and spread; smooth muscle cells, monocytes, and other HCMV host cells migrate when activated and might thereby seed new sites of viral activity. JEM