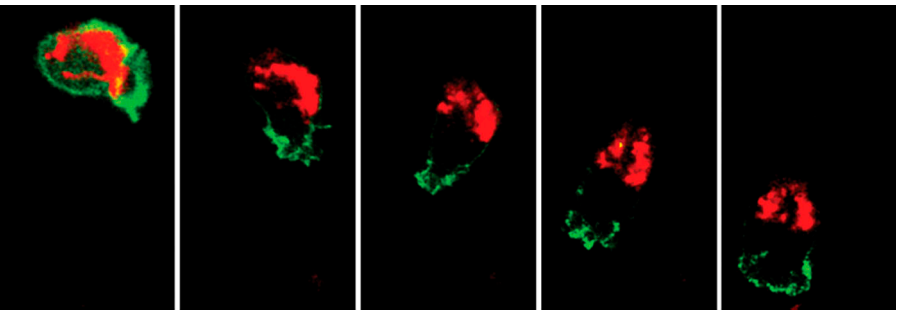
Position of power

Migrating leukocytes are "rear-wheel drive cells," says Antonella Viola. Her group finds that mitochondria, the cell's engines, shift to the back of neutrophils to power cell movement, as revealed in Campello et al. (page 2879).

Mitochondria can accumulate in regions of the cell with high energy demands, such as at the active growth cones of developing neurons and at the neuromuscular synapse. Viola and her team wondered whether mitochondria might also adopt a specific intracellular location in migrating cells. Leukocytes migrate to immunological battlegrounds in response to chemokines, and the team now shows that, in vitro, this chemotaxis is coupled with movement of mitochondria to the rear of the cell, known as the uropod.

Although the leading edge of the leukocyte sends out exploratory protrusions as these cells migrate, the uropod contains both the adhesion machinery and the myosin motors essential for cell movement, explains Viola. The discovery that mitochondria also relocate to the uropod leads Viola to suggest that, in the mechanics of cell migration, the power comes from the push.

Mitochondrial movement along microtubules requires the mitochondria to first divide into smaller, mobile units. By preventing this division, the team revealed that mitochondrial relocation to the uropod was not just coupled with, but necessary for, leukocyte migration.



A migrating leukocyte gets its rear in gear by shifting mitochondia (red) to its back end.

Boosting the mitochondrial energy production in these cells compensated for a lack of relocation, suggesting that mitochondrial movement was required for localizing ATP production at the uropod. Indeed, the team showed that inhibiting mitochondrial, but not cytoplasmic ATP production, reduced activation of myosin motors in the uropod but not elsewhere in the cell.

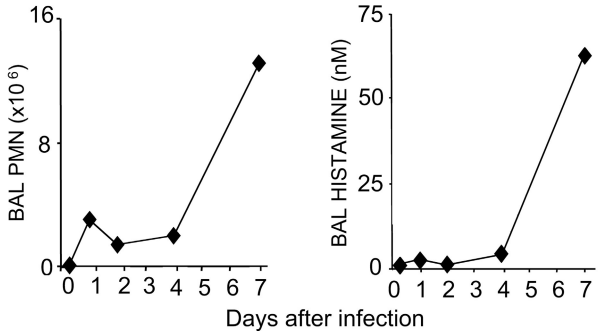
In addition to various leukocytic cell types, migrating human breast cancer cells also relocate their mitochondria to the rear, the team found. This suggests that inhibiting the division of mitochondria, and thus their movement, might be a potential intervention strategy for preventing tumor metastasis. JEM

Hunting for histamine's source

For asthma sufferers, contracting a lung infection can mean hospitalization, but it has never been clear how bugs exacerbate allergic conditions. Xu et al. (page 2907) now show that the major allergic inflammatory mediator—histamine—is also produced in response to infection. But it comes from an unexpected source.

Mast cells together with basophils are considered the major producers of histamine. Because bacterial infection of the lung can lead to asthma attacks more severe than those caused by allergens, Caughey's group hypothesized that histamine might be produced in response to infection and, if indeed it were, that mast cells were likely to be the source.

The team found that, approximately one week after infection with *Mycoplasma pulmonis* bacteria, histamine levels in the lungs of the mice had risen dramatically. However, this increase was observed even if the mice had no mast cells. The team noticed that the rising level of histamine paralleled an increase in the number of neutrophils in the lung. Considering the possibility that these cells might be the source of the histamine, the team depleted neutrophils in the mast cell-deficient mice and, sure enough, observed a concurrent drop in the level of infection-induced histamine.



Rising numbers of neutrophils (left) in the infected lung are the cause of rising histamine (right).

Although neutrophils have previously been reported to produce histamine, their contribution was thought to be small. The vast amount of histamine they produce in response to lung infection—an approximately 50-fold induction—was therefore a surprise, says research leader, Caughey.

The team now plans to see whether other bacteria induce a similar increase in the production of histamine, and whether high histamine levels are also a feature of human lung infections. If so, Caughey suggests that antihistamines, not generally considered in the treatment of infection, deserve a second look. JEM

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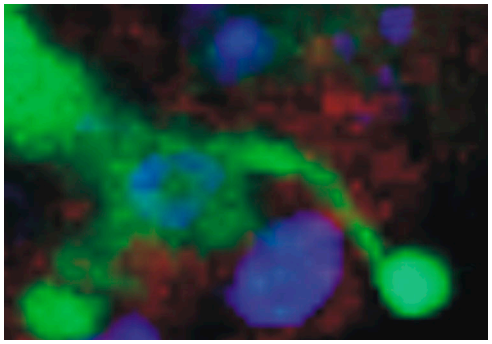
Dynamic DCs of the gut



Dendritic cells (green) reach their finger-like protrusions past the gut epithelia to catch bacteria.

Dendritic cells (DCs) stretch finger-like extensions into the gut to capture bacteria. But, according to Chieppa et al. (page 2841), it is the gut epithelial cells that first recognize the bacteria and then give DCs the tip-off.

Regular sampling of gut bacterial antigens by the immune system is necessary for maintaining tolerance to commensal bacteria and for defending against pathogens. DCs gather bacterial antigens using their extensions, but Chieppa et al. show that these extensions are not a constitutive feature of gut DCs.

Treatment of mice with antibiotics reduced the number of DC extensions in the small bowel, whereas oral infection of mice with *Salmonella* increased their numbers. DC extensions are thus dependent on the presence of the bacteria themselves. Indeed, live imaging using intravital microscopy showed that DC extensions begin to emerge from the gut wall following bacterial exposure and remain protruded for 10–40 min before retracting with their quarry.

Recognition of bacteria by innate immune cells is often dependent on Toll-like receptors (TLRs). Recent studies reveal that gut epithelial cells also have TLRs, and the group show here that mice lacking specific epithelial but not DC TLRs failed to extend DC processes across their gut wall in response to the relevant bacterial stimuli. Although the team does not yet know how epithelial cells alert the DCs, the gut barrier function of the epithelial cells makes them the perfect choice to be the first to perform identity checks on gut bacteria. JEM

Get Syk and get cycling

Rampant proliferation of pre–B cells in leukemia can be caused by overly active proto-oncogenes such as c-Myc. Wossning et al. (page 2829) now discover that this c-Myc surplus is driven by a tyrosine kinase called Syk. But even with lots of c-Myc, pre–B cells still need Syk to cycle.

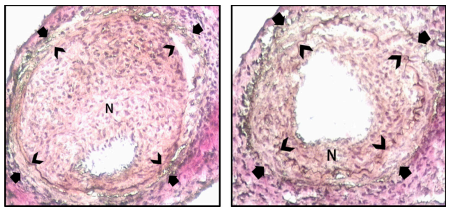
B cell proliferation and differentiation must be tightly controlled to avoid the release of immature, nonfunctional cells into the circulation. The proliferation is driven by the pre–B cell receptor (pre-BCR), which activates Syk. Syk's role in proliferation is murky: it is overexpressed in some types of lymphoma and leukemia cells, yet it activates a known tumor suppressor and is down-regulated in certain malignant cancers.

To sort through this confusion, Wossning et al. overexpressed Syk in pre–B cells, which transformed the cells into an overproliferative, undifferentiated state. A Syk-specific inhibitor reversed this phenotype. The team thus concludes that Syk is a proto-oncogene rather than tumor suppressor, at least in this cell type.

The group also found that Syk promoted c-Myc expression. The addition of more c-Myc was all that was needed to transform pre–B cells, yet this transformation was reversed by Syk inhibition. Furthermore, c-Myc expression did not transform pre–B cells that lacked the pre-BCR. Together, these results indicate that Syk must be turning on other necessary proliferative or survival signals—perhaps Bcl-2 family members—in addition to c-Myc.

The finding that transformation resulting from either too much Syk or too much c-Myc can both be blocked with a Syk inhibitor suggests that a variety of B cell proliferative disorders might respond to this type of treatment. JEM

FSAP reduces risk of repair



After vascular injury, repair is restricted in the presence of FSAP (right) to prevent narrowing of the blood vessel.

Overenthusiastic repair of damaged blood vessels could cause a fatal blockage. Sedding et al. (page 2801) report that the normal repair-restricting function of factor VII activating protease (FSAP) is disrupted by a common mutation. People carrying the mutation might thus be more at risk of vessel narrowing.

Approximately 5% of the population carries an *FSAP* polymorphism linked to cardiovascular disease. The authors' previous in vitro evidence suggested that wild-type FSAP, a plasma protein, limits vessel repair processes in part by inactivating PDGF-BB—a growth factor which promotes the proliferation and migration of blood vessel wall cells during repair.

The team isolated and characterized the mutated form of FSAP and discovered that although its ability to bind PDGF-BB was unaltered, it failed to cleave the protein efficiently. Wild-type human FSAP reduced vascular cell proliferation and accumulation at sites of injury in a mouse model—most likely by reducing PDGF-BB activity. The mutant protein, however, provided no such restraint, suggesting that people possessing the mutation might generate excessive scar tissue during vessel repair.

Vessel narrowing occasionally recurs after surgical repair. If, as the team suspects, recurrence correlates with the FSAP polymorphism, then screening cardiovascular patients for the mutation might identify those at risk. JEM