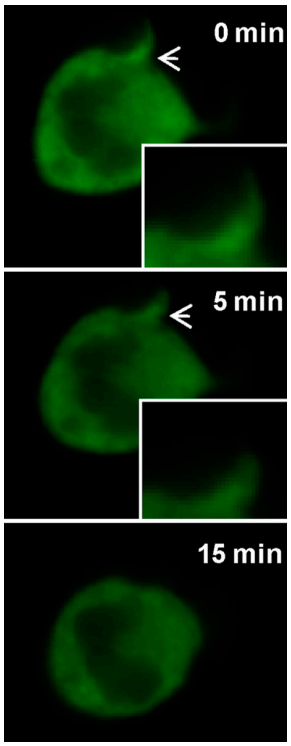
In This Issue



A macrophage grabs but does not swallow a human red blood cell (arrow) carrying CD47.

How to escape from a macrophage

Like a well-trained police dog, a macrophage responds to a signal that means "let go." Tsai and Discher reveal that the signal works by blocking a molecular motor that helps drag bacteria and other potential enemies into the macrophage.

Macrophages sweep up pathogens while leaving our own cells alone. A two-step procedure for recognizing intruders helps avoid misdirected attacks. In the first step, macrophages snare and begin swallowing objects studded with IgG antibodies, which usually latch onto interlopers. But the antibodies are sloppy, sometimes attaching to the body's own cells. So before a macrophage engulfs its target, it also checks for a second form of identification, the protein CD47. If a "self" version of CD47 is present, it induces the macrophage to disengage. How CD47 spurs a macrophage to stop mid-swallow was uncertain.

To find out, Tsai and Discher followed human macrophages as they tangled with human and sheep red blood cells. When a macrophage meets its quarry, actin molecules flock to the contact site and polymerize, extending the cell's membrane around the target. Another protein called nonmuscle myosin also moves in. It contracts to help reel in the partly engulfed object. The researchers found that actin and nonmuscle myosin relocated normally when the macrophages encountered sheep red blood cells, which sport a "foreign" version of CD47. But when the targets were human red blood cells—which carry self CD47—only actin is mobilized.

Further experiments indicated that CD47 exerts its effects through its receptor on macrophages, SIRPα, which in turn indirectly inactivates the myosin by preventing the addition of a phosphate group to the brawny molecule. By shutting down a pulling protein needed to complete phagocytosis, the researchers conclude, self CD47 prevents cells that carry it from being eaten. The team speculates that macrophages benefit from the two-step recognition process because it allows them to restrain a potential troublemaker while checking its credentials. As a result, they are poised to gobble the target if it turns out to be a threat. JCB

Tsai, R.K., and D.E. Discher. 2008. *J. Cell Biol.* 180:989–1003.

Making the wrong connections in epilepsy

A matrix enzyme that helps us learn and remember might also promote epilepsy, as Wilczynski et al. report. The enzyme might clear the way for abnormal links between brain cells.

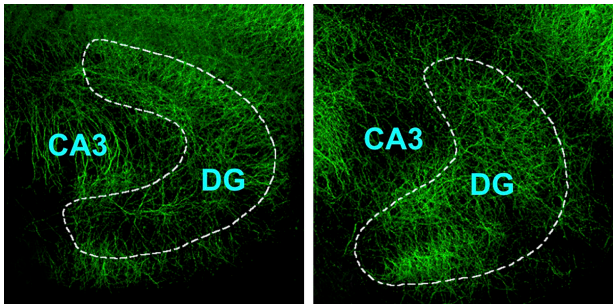
Researchers think that epileptic seizures are the result of aberrant synapses between neurons that create stimulatory circuits. However, the rearrangement of neural circuits, known as synaptic plasticity, also allows learning and memory. Recent studies have shown that the enzyme matrix metalloproteinase 9 (MMP-9), which dissolves the extracellular matrix, is essential for synaptic plasticity. Wilczynski et al. wanted to determine whether MMP-9 also helps spur epilepsy.

The researchers gave rodents either of two drugs that trigger epilepsy. Mice lacking MMP-9 were less likely to start having seizures than were control animals, and their attacks were less severe. The team then tested a line of genetically modified rats they had developed that pump out extra amounts of MMP-9. These rodents were particularly susceptible to seizures.

Two types of synaptic plasticity occurred in mice that made MMP-9. First, the short spines that protrude from dendrites withered. Their shrinkage might open space for new synapses, the researchers speculate. Second, axons sprouted outgrowths called mossy fibers that link up with other cells. MMP-9's absence inhibited both types of plasticity, the researchers found.

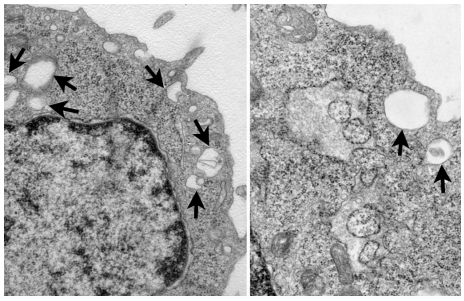
The work indicates that MMP-9 helps provoke epileptic seizures, possibly by rebuilding the extracellular matrix so that neurons can form new connections. MMP-9 is in the right place to perform that job, the team found: it accumulates at brain synapses. The results raise the possibility that drugs to block metalloproteinases, which are under development as cancer treatments, might also work against epilepsy. JCB

Wilczynski, G.M., et al. 2008. *J. Cell Biol.* 180:1021–1035.



Fewer brain synapses sprout after treatment with an MMP-9 inhibitor (left) than in a control (right).

Text by Mitch Leslie
mitchleslie@comcast.net



Endosomes contain either removed bacterial toxins (left) or damaged membrane (right).

Cells' puncture repair kit

A cell with a torn or perforated membrane has to close the breach fast. To heal wounds inflicted by bacteria, cells rely on endocytosis, Idone et al. show.

An injury or even a workout at the gym can tear the plasma membranes of our cells. Earlier work showed that a wounded cell makes repairs through exocytosis, extruding lysosomes whose membranes help close the rip. But this mechanism alone can't explain how cells heal all injuries. Some bacterial toxins and defensive proteins such as the complement system embed themselves in the membrane, forming a pore that can't be closed by exocytosis. Idone et al. wanted to nail down how cells mend these types of perforations.

The team exposed cells to *Streptococcus* toxin that bores into the plasma membrane. Repairs were quick—the membranes resealed in less than 30 seconds. Cells wouldn't have time to disassemble the pores in that time, ruling out one possible mechanism. The team also discounted the possibility that injury-induced blebs on the cell membrane somehow dislodge the pores—cells still healed when the team blocked blebbing.

A third possibility is that cells use endocytosis to remove the pores from the membrane. To test the idea, Idone et al. followed labeled pores that were stuck in the membrane. Within a few seconds, endosomes carrying tagged toxin began showing up inside the cells. The results indicate that injury stimulates the formation of endosomes that engulf pores that have penetrated the membrane. The team also discovered that cells use the same method to excise membrane abrasions. JCB

Idone, C., et al. 2008. *J. Cell Biol.* 180:905–914.

SIRT2 stops cells

Recent work from Pandithage et al. reveals a new pathway for controlling cell movement that involves a cancer enabler and a member of a protein family best known for boosting longevity.

The researchers chanced on the discovery while investigating the oncogene Myc, which is overactive in many tumors. Myc activates cyclin E and cyclin-dependent kinase (CDK)—a protein power couple that pushes cells through the cell cycle. The team wanted to determine what lies downstream of this pair.

One of the pair's targets, they found, is SIRT2, a member of the sirtuin protein family. Sirtuins take part in everything from insulin secretion to transcription and can extend life span in organisms such as nematodes and yeast. The cyclin E/CDK pair and other cyclin/CDK combinations phosphorylate SIRT2 to shut it down, the team found.

SIRT2 cleaves acetyl groups off histones and α-tubulin. As a result of its tubulin effects, SIRT2 destabilizes microtubules. The group found that by preventing microtubule extension, SIRT2 stopped tumor cells from getting a good grip on the substrate—a necessity for crawling. Thus by indirectly shutting off SIRT2, Myc might prompt the migration of cancer cells.

SIRT2 also blocked the protrusion of neurites from brain neurons. The work indicates that this enzyme helps maintain the status quo in cells by regulating microtubule stability. Recent studies implicate SIRT2 in neurodegeneration, which suggests that this pathway could also be involved in illnesses such as Parkinson's disease. JCB

Pandithage, R., et al. 2008. *J. Cell Biol.* 180:915–929.

Origins of mitotic inequality

All cells are not equal, at least when it comes to the length of the cell cycle. Asymmetric distribution of two regulatory proteins in the early embryo helps create these timing differences, Rivers et al. show.

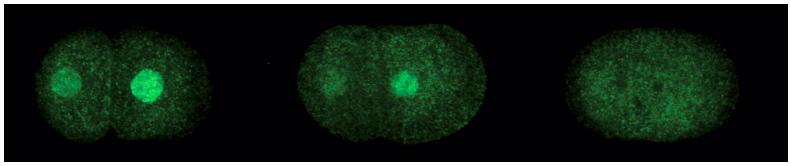
Different cell types often differ in cell cycle length. Take AB and P1, the first two cells of a worm embryo. AB completes its cycle about two minutes sooner than does P1. Researchers knew that Par proteins, which help set up the embryo's polarity, are also responsible for unequal cell cycle times. What they didn't know was how.

Rivers et al. tested whether two key proteins that control the cell cycle, cyclin E and CDC-25.1, were involved. AB and P1 harbored equal amounts of cyclin E, indicating it wasn't responsible for the timing difference. But the levels of CDC-25.1 are higher in the AB cell's nucleus, and the protein builds up faster there, suggesting it drives the asynchrony.

But what causes CDC-25.1 to accumulate in only one cell? One candidate was the polo-like kinase PLK-1, which helps the human counterpart of CDC-25.1 home in on the nucleus. Rivers et al. found that at the one-celled stage, PLK-1 amasses at the anterior end, which becomes AB after the first cell division.

In turn, Par proteins seem to help set up the PLK-1 asymmetry through two other proteins, which control protein degradation. These two proteins might spur the breakdown of an unidentified inhibitor of PLK-1. JCB

Rivers, D.M., et al. 2008. *J. Cell Biol.* 180:877–885.



CDC-25.1 (green) is asymmetrically distributed at the two-cell stage (left and center) but not at the first telophase (right).