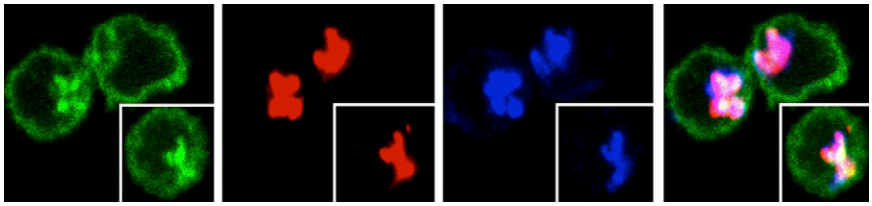
In This Issue



Myosin II drives the clustering of MHC vesicles (green) and endocytotic vesicles (red) containing antigen (blue) in B cells.

Myosin mobilizes MHC

A cellular contraction brings antigens together with the MHC molecules that will present them, say Vascotto et al. (page 1007).

Vesicles containing endocytosed antigen and those containing MHC class II molecules come together in the cell to form specialized antigen-processing lysosomes. To investigate the mechanics of this union, Vascotto and colleagues followed events in real time by live cell microscopy.

They were surprised to see that B cells contracted soon after activation with antigen. This contraction was coupled with a clustering of MHC class II toward the center of the cell, where immunofluorescence revealed that antigen vesicles also cluster.

Cell contraction relies in part on myosin II activation. Antigen stimulation of B cells led to myosin II activation. Inhibiting myosin II blocked the cell contraction, the clustering of the vesicles, and antigen presentation at the cell surface. Endocytosis of the antigen, however, remained unaffected, indicating that general cell paralysis was not to blame.

Upon B cell stimulation with antigen, MHC molecules become hooked to the contractile actomyosin network through an interaction between myosin II and the cytosolic tail of the MHC class II chaperone, called the invariant chain. In cells lacking the invariant chain, MHC class II–containing vesicles did not cluster. Antigen-containing vesicles also did not cluster in these cells, but the authors have yet to explain this failure.

Myosin II might directly transport MHC class II vesicles along actin filaments, although MHC class II vesicles were reported to travel along microtubules in other cell types. Exactly how myosin II relocates MHC class II vesicles is currently under investigation. JCB

Bending membrane to form filopodia

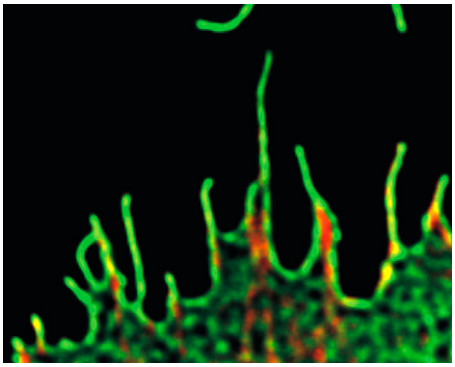
A filopodia-promoting protein domain deforms membranes by a similar mechanism but in the opposite direction of an endocytosis-promoting domain, report Mattila et al. (page 953).

These filopodia-inducing IM domains are found in cytoskeletal scaffolding proteins such as missing-in-metastasis and IRSp53. Sites of membrane deformation, including filopodial protrusions, are often associated with bundles of actin filaments. Previous results suggested that the IM domain contributes to filopodium formation by bundling actin, but Mattila and colleagues now dispute this result.

The authors find that the IM domain only bundles actin at unnaturally low ionic strengths, at which point the domain tends to form aggregates. The IM domain also did not colocalize with actin bundles in cells, but instead was observed at the plasma membrane surrounding the bundle.

The membrane association makes more sense, according to the authors, because the IM domain shows structural homology to another protein domain, BAR, that binds and deforms membranes.

BAR domains have a curved, banana-like structure and interact with the plasma membrane through residues on the banana's inside curved edge. IM domains have a similar although less curved structure. Here, the authors map IM's membrane-interacting residues to its outside curved edge. This opposite geometry explains why BAR proteins promote endocytotic invaginations, whereas IM domain proteins promote filopodial protrusions.



IM domains (green) push out filopodia by binding and deforming the membrane, not by bundling actin (red).

The geometry of IM's membrane binding also predicts that IM domains would bend membranes into filopodial tubules of ~95nm diameter—closely fitting with the size of IM-induced tubules that the team observed by electron microscopy.

Filopodium formation was dependent on IM domains interacting with $PI(4,5)P_2$-rich membrane regions. It is yet unclear, however, whether $PI(4,5)P_2$ enrichment is a cause or coincidence of IM's membrane binding. Filopodium formation was also dependent on IM domains binding to actin. Thus, although IMs do not appear to regulate the bundling of actin, their membrane deformation activity is connected to actin dynamics to enable filopodial growth and stability. JCB

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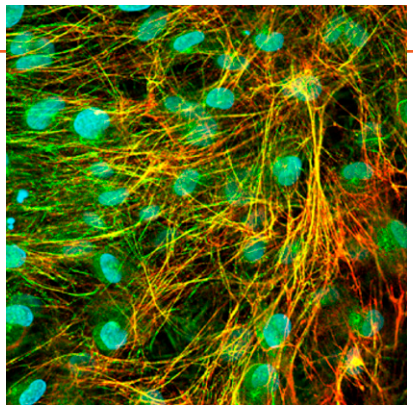


Fibulin-5 (red) promotes elastic fiber (green) development to keep skin springy.

Fibulin-5 for youthful skin

A loss of tissue elasticity leads to wrinkles and more serious age-related problems, such as emphysema and vascular defects. On page 1061, Hirai et al. report that youthful elastic fibers are assembled by an extracellular matrix protein that slips away with age.

Mice that lack this matrix protein, called fibulin-5, have loose, wrinkled skin, vascular abnormalities, and emphysema, all of which are thought to be due to their disorganized and fragmented elastic fibers.

Elastic fibers are composed of an inner core of cross-linked elastin surrounded by a microfibril envelope. Hirai et al. now show that fibulin-5 generates elastic fibers by promoting aggregation of the elastin precursor, called tropoelastin, its deposition onto microfibrils, and its cross-linking into mature elastin.

A naturally occurring truncated version of fibulin-5 that did not associate with microfibrils was unable to promote elastic fiber assembly. This truncated version accumulated with age, while the full-length, microfibril-associating version diminished.

The shorter version of fibulin-5 is formed by the action of a serine protease, which cleaves off the NH_2-terminal region of the full-length protein. The team is currently investigating the identity of this protease and trying to determine why it promotes more cleavage with age. JCB

Macrophages boost hair growth

For a healthy head of hair, activate your macrophages. Besides their role in host defense, these immune cells also promote hair growth, according to a report on page 903 by Osaka et al.

New and rapid hair growth is a by-product of the wound response in mice. The team now finds that this hair growth requires a wound-activated protein kinase called ASK1.

ASK1 was necessary for the up-regulation of a number of immune response factors in wounded skin, including many that are expressed in macrophages. The team found that macrophage recruitment to the wound site and macrophage activation were both significantly reduced in mice lacking ASK1. Transplantation of activated macrophages into the skin of ASK1-lacking mice promoted hair growth even in the absence of wounding.

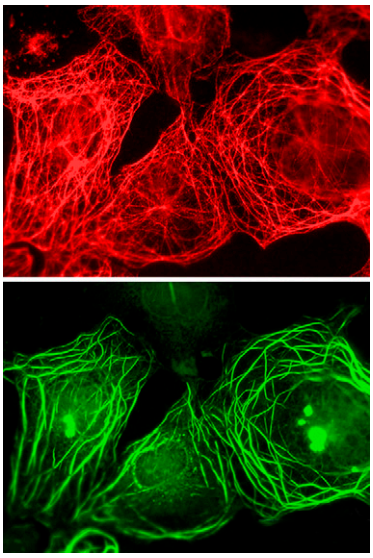
Although wounding is not necessarily linked to the induction of hair growth in humans, one of the common treatments for alopecia does activate macrophages. The team is currently attempting to purify hair growth–promoting factors that are produced from activated macrophages in the hope of designing more effective drugs to treat alopecia.

Until then, the authors do not recommend a head injury as a home remedy. JCB

Spastin pulls tubulin out of shape

It's easier to snap a twig with two hands than one, and the same goes for snapping microtubules. By binding to tubulin in two places, a microtubule-severing protein can exert the force necessary to pull the polymer apart, according to White et al. (page 995).

Microtubule-severing spastin is a member of the AAA ATPase family, which often breaks down multiprotein complexes. The team now shows that spastin, like other AAAs, forms ring-shaped hexamers. They find that spastin must use two different binding domains—one on the outside of the ring and one on the loop domains inside the ring—to lock onto tubulin and cause severing.



Microtubules (red) are bound but not broken by spastin (green) when one hand of spastin is mutated.

The spastin ring is too small to fit around the whole microtubule. Instead, the team shows, spastin binds to two spots on the microtubule, one of which they identify as the extreme COOH-terminal amino acids of the tubulin tail that sticks out from the surface of the microtubule polymer. The authors found that spastin only bound to the polymerized form of tubulin. They therefore suggest that spastin, by grabbing hold of two parts of tubulin, might pull the protein into a conformation that would release tubulin from the microtubule polymer as well as from spastin itself.

Some AAAs, such as those of the proteasome, unfold and thus destroy their targets. Other AAAs pull off individual components from multiprotein complexes, thus allowing the components to be reused. The team is currently trying to determine which of these mechanisms spastin uses. JCB