Research Roundup

Bacteria tear down microtubules

Many invasive bacteria let themselves into host cells, not bothering to wait for an invitation. So far, known effector proteins that allow bacteria to enter work by rearranging actin dynamics. But new research from Sei Yoshida, Chihiro Sasakawa (University of Tokyo, Tokyo), and colleagues reveals that Shigella bacteria have another trick up their proverbial sleeves. They destabilize microtubules (MTs) to promote their own phagocytosis.

Shigella uses the Type III secretion system to deliver a set of its effector proteins into cells it plans to invade. Some of these proteins act in well-known ways to modulate the actin cytoskeleton. For instance, IpaA binds the focal adhesion protein vinculin, and this complex promotes actin depolymerization. But the group focused on VirA, which acts independently of other effectors. Shigella lacking VirA are 70–80% less invasive than wild-type bacteria.

The authors found that VirA bound α/β-tubulin heterodimers and destabilized MTs in vitro and in vivo. Destabilization led to membrane ruffling around the bacterium, an effect that was dependent on the activation of Rac1. Sasakawa is not yet sure how VirA binding causes MT instability. Bound heterodimers may be held less stably in the MT lattice, or VirA might compete with MTs for binding to tubulin heterodimers. VirA homologues exist in other bacteria, including E. coli, indicating that a wide range of pathogens may alter MT dynamics to aid in their invasion.

Reference: Yoshida, S., et al. 2002. EMBO J. 21:2923–2935.

Stable globin needs a partner

In the absence of a binding partner, such as when β-globin is mutated in β-thalassemia, the unstable α-globin protein tends to form toxic inclusion bodies. Molecular chaperones that stabilize hemoglobin have been proposed to exist, but have not been found, until now. Anthony Kihm, Mitchell Weiss, and colleagues (University of Pennsylvania, Philadelphia, PA) have now identified a protein that protects α-globin until it can find β-globin and form hemoglobin A (HbA).

This chaperone-like protein, AHSP, was identified in a screen for genes induced by the transcription factor GATA-1, which promotes erythrocyte differentiation. Many genes were induced by GATA-1, but Weiss found AHSP particularly interesting because it was strongly and specifically expressed in RBCs and had no known function. Screens for protein–protein interactions revealed that AHSP bound to α-globin, but not to β-globin or HbA.

AHSP prevented α-globin precipitation in cells and in vitro. In mice lacking AHSP, erythrocytes contained inclusion bodies and turned over more rapidly than in wild-type mice. “The phenotype of the knock-out mice was relatively mild, probably because red cells do a good job of balancing the amount of α- and β-globin they produce,” says Weiss. “So, AHSP is not absolutely essential when things are good, but may become more important when things aren’t going so well.”

Thus, AHSP could be a genetic modifier of β-thalassemia. Patients with this disease suffer twofold from a lack of β-globin—they are unable to make enough HbA for good respiratory capacity, and they have an excess of toxic, free α-globin. If a drug could be made to mimic AHSP, it might help offset free α-globin toxicity. This could decrease transfusion requirements in some patients.

Reference: Kihm, A.J., et al. 2002. Nature. 417:758–763.

Arteries play follow the leader

Arteries branch and extend in an intricate pattern worthy of a Michelangelo painting. But it’s more like a tracing than an original work of art, according to new results from Yoh-suke Mukouyama, David Anderson (California Institute of Technology, Pasadena, CA), and colleagues. They find that the original artwork is the nerve network.

Anderson’s group observed that peripheral nerves in the limbs of mice are aligned along arterial vessels. More than a coincidental association, the presence of these nerves actually specified arterial differentiation. When nerves were misrouted, arteries became similarly patterned along the altered nerve route. Veins, on the other hand, were not affected. “Nerves in limbs go where the action is, to muscle and skin,” says Anderson. “There’s a lot of metabolic activity there that needs oxygen. So it makes sense that arteries would take the same path taken by nerves.”

Nerve cells probably direct arterial organization and formation by secreting the endothelial mitogen VEGF. In vitro, VEGF induced arterial differentiation of endothelial cells, and mutant mice that lack Schwann cells and whose arteries and nerves had lost their association also had reduced expression of VEGF in their nerve cells. Anderson plans to confirm VEGF involvement in this process by examining mice that completely lack VEGF expression in peripheral nerves.

Reference: Mukouyama, Y., et al. 2002. Cell. 109:693–705.