In This Issue

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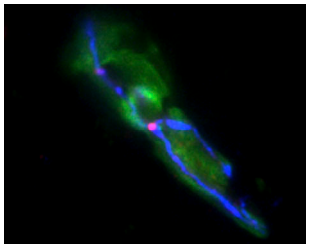
LSR puts its seal on brain endothelial cells



LSR (red) is enriched at the tight junctions formed between three neighboring brain endothelial cells (green), whereas occludin (blue) localizes to bicellular junctions.

Sohet et al. demonstrate that the tricellular tight junction protein LSR helps form the blood–brain barrier during embryogenesis.

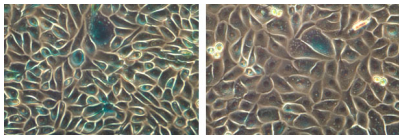
The blood–brain barrier protects neurons from the contents of the circulatory system and relies, in part, on the formation of tight junctions between the endothelial cells lining the blood vessels of the central nervous system. Mice lacking the tight junction protein claudin 5, for example, develop a leaky blood–brain barrier and die shortly after birth. But, because claudin 5 is expressed in all endothelial cells, it remains unclear why blood vessels in the brain are so much more impermeable than the blood vessels supplying other tissues.

Sohet et al. were interested in a protein called LSR that, in epithelial tissues, localizes to tight junctions at the points where three neighboring cells contact one another. LSR was also enriched at the tricellular tight junctions of central nervous system endothelial cells, the researchers found, but wasn't expressed in the blood vessels of other mouse tissues. LSR was expressed in brain endothelial cells at the time—embryonic day E14.5—that the blood–brain barrier became impermeable to small molecules. In mice lacking LSR, however, the barrier failed to seal before the animals died at E15.5.

The blood–brain barrier is often disrupted by neurological injury or disease. Sohet et al. found that LSR was down-regulated in the leaky brain blood vessels generated in mouse models of both multiple sclerosis and stroke. The authors now want to investigate how this down-regulation occurs and whether preventing it can help maintain the blood–brain barrier's integrity.

Sohet, F., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201410131.

NORE1A erects a senescence barrier to tumorigenesis



Activated Ras induces cell senescence (marked by β-galactosidase staining, blue) in the presence (left), but not the absence (right), of NORE1A.

The Ras effector NORE1A induces cell senescence and suppresses tumorigenesis by promoting the acetylation of p53, Donninger et al. reveal.

Activating mutations in the Ras GTPase drive cell proliferation, but their ability to promote tumorigenesis is limited by the fact that they also induce cells to exit the cell cycle and become senescent. How Ras induces senescence, and how this pathway is disrupted in cancer cells, is largely unknown. Donninger et al. examined the role of the tumor suppressor NORE1A, a scaffold protein that binds to active Ras.

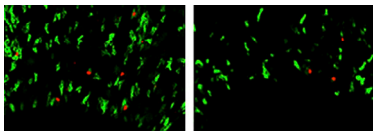
Overexpressing NORE1A induced cell senescence, whereas knocking down the protein inhibited senescence and enhanced the transformation of cells expressing activated Ras. Donninger et al. found that Ras promoted NORE1A's association with a kinase called HIPK2, and this interaction was required for senescence induction.

NORE1A, in turn, promoted HIPK2's association with the tumor suppressor p53. HIPK2 can phosphorylate p53 to induce the transcription of proapoptotic genes such as *Bax*. But the kinase can also recruit enzymes that acetylate p53 and promote the expression of genes, like $p21^{CIP1}$, that induce cell senescence. Donninger et al. found that NORE1A suppressed the former pathway and enhanced the latter. Accordingly, human tumors lacking NORE1A showed decreased levels of p53 acetylation.

NORE1A therefore mediates Ras-induced cell senescence, and the loss of this protein may be a critical step in tumorigenesis. Senior author Geoffrey Clark is now interested in whether NORE1A and related proteins allow Ras to regulate the acetylation of other proteins besides p53.

Donninger, H., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201408087.

Hedgehog induces a gut reaction



In *Drosophila* midguts treated with DSS, the number of proliferating cells (red) is reduced (right) when Hh signaling is inhibited in enteroblasts (green).

Tian et al. reveal how Hedgehog (Hh) signaling prompts intestinal stem cells to proliferate in response to injury.

Just like in mammalian intestines, cells in the *Drosophila* midgut constantly turn over and are replaced by intestinal stem cells (ISCs), which divide to produce enteroblasts that subsequently differentiate into more specialized cell types. ISC proliferation is up-regulated upon intestinal injury, and Tian et al. found that Hh signaling drove this response, even though the pathway was not required for normal, homeostatic ISC proliferation.

Feeding flies with the detergent DSS damaged their guts and, via the JNK signaling pathway, induced production of the Hh ligand. Surprisingly, Hh didn't drive ISC proliferation by acting directly on the stem cells themselves. Instead, Hh prompted enteroblasts to up-regulate the cytokine Upd2, which stimulated ISC proliferation by activating the JAK–STAT signaling pathway. Knocking down Upd2 or inhibiting the Hh pathway in enteroblasts suppressed DSS-induced ISC proliferation.

Senior author Jin Jiang now wants to determine whether Upd2 is a direct transcriptional target of the Hh pathway and to investigate whether there is any crosstalk with the Hippo pathway, which also regulates ISC proliferation in response to intestinal injury.

Tian, A., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201409025.