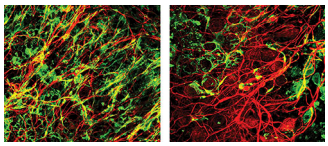
In This Issue

Text by Ben Short
bshort@rockefeller.edu

A vitamin supplement for remyelination



In a control brain slice (left), most axons (red) have regained a myelin sheath (green) eight days after demyelination. But regeneration is impaired in the presence of a VDR inhibitor (right).

de la Fuente et al. reveal how the vitamin D receptor (VDR) promotes the differentiation of oligodendrocyte progenitor cells (OPCs), thereby boosting myelin sheath regeneration.

When central nervous system axons lose their insulating myelin sheath—due, for example, to demyelinating diseases such as multiple sclerosis (MS)—OPCs migrate toward the damage and differentiate into mature, myelin-producing oligodendrocytes. The nuclear receptor retinoid X receptor γ (RXR-γ) promotes OPC differentiation and remyelination, but nuclear receptors generally function as heterodimers, so de la Fuente et al. set out to identify RXR-γ's binding partners.

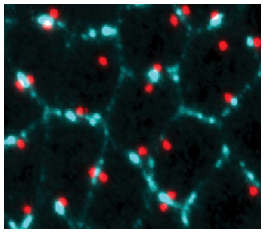
RXR-γ bound to several nuclear receptors, including VDR, in OPCs and mature oligodendrocytes. Inhibiting VDR signaling impaired OPC differentiation and reduced the cells' ability to remyelinate axons ex vivo. Vitamin D, in contrast, boosted OPC differentiation.

Low vitamin D levels have been linked to the onset of MS, and de la Fuente et al.'s findings suggest that the vitamin might also affect the disease's progression by controlling myelin sheath regeneration, a process that declines with age. VDR agonists might therefore be able to enhance remyelination in MS patients. Indeed, the researchers found that VDR was expressed in OPCs and oligodendrocytes present in MS brain lesions.

The team now wants to identify which genes are downstream targets of the RXR-γ–VDR heterodimer. They also want to investigate whether other partners of RXR-γ also play a role in OPC differentiation and remyelination.

de la Fuente, A.G., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201505119

Splicing limits the spread of Crumbs



In *obe* mutant epithelia, centrosomes (red) flank adherens junction clusters (blue), giving the appearance of a division symbol, or obelus.

Vichas et al. reveal that an RNA helicase controls epithelial cell polarity by regulating alternative splicing of the apical membrane protein Crumbs.

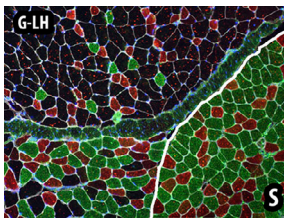
In a genetic screen, Vichas et al. found that mutations in a gene called *obelus* (*obe*) perturbed epithelial cell polarity and intercellular junctions in early *Drosophila* embryos. *obe* mutant cells displayed an expanded apical membrane domain, and their intercellular adherens junctions clustered into single large aggregates instead of becoming evenly distributed across cell–cell interfaces. In addition, centrosomes were in aberrantly close proximity to the clustered junctions.

obe encodes an RNA helicase homologous to human and yeast proteins that are core components of the spliceosome, which catalyzes pre-mRNA splicing. Surprisingly, however, only a few transcripts were differentially spliced in *obe* mutant embryos. One of these encoded the apical membrane determinant Crumbs. In *obe* mutants, *crumbs* transcripts frequently retained an additional exon, increasing the expression of a Crumbs isoform with an extra EGF-like repeat in its extracellular domain. Overexpressing this isoform induced apical expansion, junction aggregation, and centrosome mispositioning similar to *obe* mutants. In contrast, overexpressing the shorter Crumbs isoform that usually predominates in early embryos had only mild effects on centrosome location and a distinct effect on junction organization.

Obelus therefore controls epithelial polarity and adherens junction organization by regulating *crumbs* splicing. It remains to be determined how the inclusion of an additional EGF-like repeat has such a marked affect on Crumbs activity.

Vichas, A., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201504083

Ephrin-A3 typecasts muscle fibers



Ephrin-A3 (green) is specifically expressed in slow myofibers, and is absent from fast fibers expressing myosin IIa (red).

Stark et al. describe how an ephrin ligand repels fast-firing motor axons so that slow muscle fibers can maintain their identity.

Individual skeletal muscles are composed of a characteristic ratio of fast and slow myofibers that express different myosin isoforms and are innervated by fast- or slow-firing motor neurons, respectively. Fiber type is specified cell autonomously during development but is maintained in adult tissue by the fiber's connection to the correct type of motor neuron. How myofibers and motor neurons get appropriately matched up with each other remains unclear.

Stark et al. found that the repulsive guidance cue ephrin-A3 was specifically expressed on slow muscle fibers. Mice lacking ephrin-A3 were born with the same number of slow myofibers as wild-type animals, but, over time, many of these fibers converted to fast myofibers innervated by fast motor axons. On the other hand, misexpressing ephrin-A3 in fast myofibers promoted their conversion to the slow type after their neuronal connections were removed and then allowed to reform.

Ephrin-A3 may therefore help slow myofibers maintain their identity by preventing fast motor neurons from innervating them incorrectly. Accordingly, ephrin-A3's receptor, EphA8, was present near the synaptic terminals of fast motor axons. Surprisingly, however, EphA8 wasn't expressed in the motor neurons themselves but in the terminal Schwann cells that regulate neuromuscular junctions. The researchers now want to investigate how EphA8-expressing Schwann cells specifically recognize fast motor neurons and how ephrin-A3 expression is influenced by factors, such as exercise or aging, that can alter the ratio of slow and fast muscle fibers.

Stark, D.A., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201502036