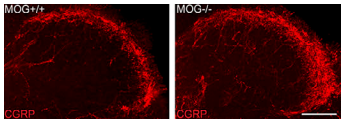
In This Issue

Text by Ben Short
bshort@rockefeller.edu

Myelin goes to great pains to regulate NGF



Spinal cord sections show an increased sprouting of pain fibers (red) in MOG-deficient mice (right), when compared with control animals (left).

A component of the myelin sheath surrounding spinal cord axons regulates the growth of neighboring unmyelinated neurons by sequestering NGF, von Büdingen et al. reveal.

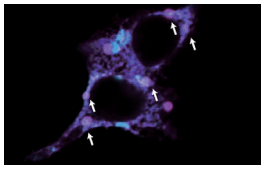
Oligodendrocytes form an insulating myelin sheath around the axons of central nervous system neurons. This sheath is lost in multiple sclerosis and other demyelinating diseases, but it's unclear why this often results in chronic pain, since most pain-sensing (nociceptive) neurons are not myelinated to begin with. Von Büdingen et al. found that the myelin sheath can bind and sequester NGF, a growth factor that promotes the growth and survival of nociceptive neurons.

Specifically, NGF bound with high affinity to myelin oligodendrocyte glycoprotein (MOG), a protein expressed on the outer surface of the myelin sheath. Mice lacking MOG displayed an increased sprouting of nociceptive fibers in their spinal cords, suggesting that MOG might usually limit the growth of these neurons by lowering the local concentration of free NGF.

Other neurotrophic factors, like BDNF and NT-3, can be sequestered by truncated versions of their receptors. Although MOG is unrelated to the NGF receptor TrkA, its extracellular region folds into a similar Ig-like domain. MOG's ability to limit nociceptive fiber sprouting and pain sensation is likely to be lost in multiple sclerosis patients. MOG's function may also be important following peripheral nerve injury, when increased levels of NGF are produced within the central nervous system. The authors now want to test these ideas by developing better mouse models of neuropathic pain and examining these in the context of demyelination.

von Büdingen, H.-C., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201504106

Inflammation gets TRIM'd back by autophagy



TRIM21 (magenta) induces the formation of puncta (arrows) containing ULK1 (cyan) and the autophagy substrate IRF3 (blue).

Kimura et al. describe how TRIM family proteins specifically target key inflammatory regulators for degradation via the autophagy pathway.

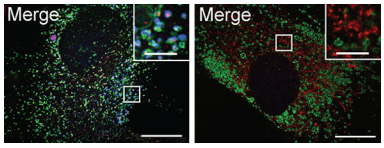
Although autophagy can nonselectively degrade cytoplasmic components by engulfing them in a double-membraned autophagosome and delivering them to lysosomes, the pathway can also act with much greater precision to target specific proteins for destruction. Specific receptors are required to link target proteins to the autophagy machinery, but only a handful of receptors have been identified to date. TRIM proteins are a large family of candidate autophagy receptors, and Kimura et al. found that several members of this family, including TRIM20 and TRIM21, induce autophagy in response to the cytokine IFN-γ.

TRIM20 targeted for degradation several subunits of the inflammasome—an activator of the inflammatory cytokine IL-1β—by linking them to multiple autophagy regulators, including the autophagy-initiating proteins Beclin 1 and ULK1, and the Atg8 family of autophagosome assembly factors. TRIM21, in contrast, coupled a similar set of autophagy regulators to the transcription factor IRF3, an activator of type I IFN responses.

TRIM21 is associated with autoimmune diseases, such as Sjögren syndrome, in which type I IFN signaling is hyperactivated, whereas mutations in the gene encoding TRIM20 are linked to familial Mediterranean fever. Several of these disease-linked mutations disrupted TRIM20's ability to form a complex with ULK1 and induce inflammasome degradation. These TRIM protein–mediated precision autophagy pathways may therefore be crucial for limiting inflammatory responses in vivo.

Kimura, T., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201503023

Progranulin takes an alternate route to lysosomes



Compared with a control cell (left), the localization of progranulin (red) to lysosomes (green) is abolished in a fibroblast (right) lacking prosaposin (blue).

Zhou et al. reveal that the disease-related protein progranulin gets a "piggyback" ride to lysosomes by binding to another lysosomal protein, prosaposin.

Mutations in the gene encoding progranulin cause the neurodegenerative diseases frontotemporal lobar degeneration and neuronal ceroid lipofuscinosis. Although progranulin can be secreted from cells to act as a neurotrophic factor, the protein is also required inside cells to maintain the function of lysosomes. Progranulin is targeted to these organelles by the sorting receptor sortilin but is only partially mislocalized in sortilin-deficient neurons, suggesting that it can also reach lysosomes via a different route.

Zhou et al. found that progranulin binds to prosaponin, another protein that can either be secreted or delivered to lysosomes. Progranulin's localization to lysosomes was partially reduced in neurons lacking prosaposin, and completely abolished in prosaposin-deficient fibroblasts, a cell type that expresses hardly any sortilin. Ectopically expressing sortilin, however, restored progranulin's localization to fibroblast lysosomes, indicating that the sortilin and prosaposin trafficking pathways operate independently of each other.

Prosaposin promoted the delivery of both secreted and newly synthesized progranulin to lysosomes, in part by linking the protein to the cation-independent mannose 6-phosphate receptor. Another sorting receptor, LRP1, was also required for the prosaposin-dependent retrieval of secreted progranulin.

It remains to be seen exactly what progranulin does once it is delivered to lysosomes. Senior author Fenghua Hu is also interested in whether prosaposin and progranulin influence each other's function, both inside and outside the cell.

Zho, X., et al. 2015. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201502029