This Week in The Journal

Knocking out KLF9 Improves Retinal Axon Regeneration

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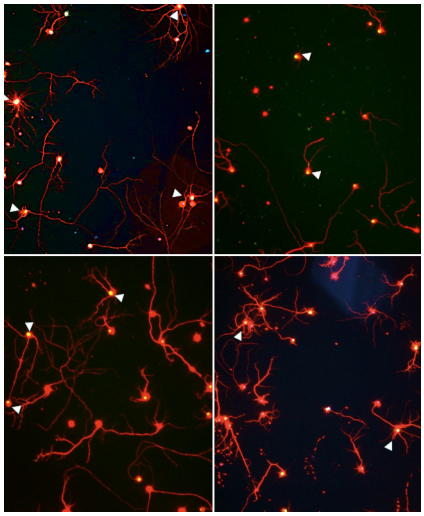
(see pages 9632–9644)

Damage to axons in the CNS typically leads to permanent loss of function, because unlike peripheral nerves, most CNS axons fail to regenerate in mature mammals. This failure is partly attributable to the presence of inhibitory molecules and scar tissue at the lesion site, but even if this inhibitory region is bridged by growth-promoting graft tissue, few axons regenerate. This suggests that factors intrinsic to axons hinder regeneration. Indeed, when axons reach their targets, the growth cones at their tips—where growth occurs during development—disappear, and synaptic terminals develop in their place. At the same time, changes in transcriptional programs ensure neurons devote more energy to synaptic activity and less on the production of proteins and membrane for continued growth. These developmental changes are driven partly by Krüppel-like transcription factors (KLFs), some of which promote and some of which inhibit neurite growth. Manipulating expression of these proteins might therefore enhance regeneration. In fact, overexpressing KLF7 or knocking out KLF4 have both been shown to promote regeneration of optic nerve axons after nerve crush in animal models (He et al. 2016 Neuron 90:437).

Apara et al. now report that KLF9—which is strongly upregulated in parallel with the developmental loss of growth potential in retinal ganglion cell (RGC) axons—also contributes to the inability of these axons to regrow after nerve crush in rats. Although expression of KLF9 did not change after nerve crush, knocking down KLF9 in RGCs increased neurite outgrowth *in vitro* and *in vivo*. Additional experiments revealed that KLF9 is phosphorylated by the kinase JNK3. Preventing this phosphorylation by mutating the phosphorylation site or interfering with KLF9–JNK3 interaction reduced the ability of KLF9 to suppress RGC axon growth, and it resulted in greater axon regeneration after nerve crush injury *in vivo*.

These results indicate that suppressing KLF9 activity facilitates regeneration of RGC axons, and thus might be used to promote functional recovery after CNS nerve injury. Identifying axon-growth-related genes that are regulated by KLF9 might further expand the list of possible targets for such treatments. Importantly, these treatments might also promote sprouting and growth of spared axons, further improving the chances for functional recovery after nerve injuries.



Expressing KLF9 in RGCs (upper right) reduced axon growth compared to controls (upper left), but this effect was prevented when the JNK3 interaction domain of KLF9 was deleted (bottom right) or the phosphorylation site was mutated (bottom left). See Apara et al. for details.

Sphingolipids Promote α-Synuclein Aggregation

Yumiko V. Taguchi, Jun Liu, Jiapeng Ruan, Joshua Pacheco, Xiaokui Zhang, et al.

(see pages 9617–9631)

Glycosphingolipids, constructed by adding sugar chains to the lipid ceramide, are present in the outer leaflet of plasma membranes, where they often cluster in lipid rafts and likely contribute to signal transduction. Glycosphingolipids are broken down in lysosomes by a series of glycosidases, which cleave successive sugar molecules, leaving a core of ceramide linked to galactose or glucose (Schnaar et al. 2017 doi:10.1101/glycobiology.3e.011); these final sugar moieties are removed from ceramide by β-galactosylceramidase or glucocerebrosidase 1 (GCase1), respectively.

Mutations in *GBA1*, the gene encoding GCase1, cause Gaucher disease, which affects multiple organ systems; they are also the most common risk factor for Parkinson's disease (PD). The link to PD likely stems from the fact that loss of GCase1 leads to accumulation of α-synuclein, the protein that aggregates in neurons of people with PD. But how GCase1 deficiency promotes α-synuclein aggregation has remained unclear. Some have proposed that loss of *GBA1* leads to lysosomal dysfunction, while others have proposed that mutant GCase1 interacts directly with α-synuclein to induce its aggregation.

In the absence of GCase1, glucosylceramide can be broken down by other enzymes to produce glucosylsphingosine, sphingosine, and sphingosine-1-phosphate, but nonetheless, glucosylceramide and these metabolites accumulate in the cytoplasm of *GBA1*-deficient cells. Because α-synuclein interacts with lipid membranes, Taguchi et al. hypothesized that one of these accumulating lipids promotes α-synuclein aggregation. Indeed, all four lipids promoted the formation of α-synuclein oligomers and/or fibrils *in vitro*, and when these oligomers were added to neurons derived from human induced pluripotent stem cells, the oligomers generated by glucosylsphingosine or sphingosine caused aggregation of endogenous α-synuclein. Furthermore, in *GBA1*-deficient mice that expressed PD-linked mutant α-synuclein, greater accumulation of glucosylceramide was associated with greater α-synuclein pathology and earlier death.

These results suggest that sphingolipid species that accumulate as a result of GCase1 deficiency promote α-synuclein aggregation. This might contribute to the onset of Parkinson's disease in some patients. Notably, GCase1 activity decreases with age even in people without *GBA1* mutations, so sphingolipid-induced α-synuclein aggregation might contribute to sporadic cases of Parkinson's disease as well. If so, stimulating GCase1 activity might be an effective treatment for the disease.

This Week in The Journal was written by Teresa Esch, Ph.D.