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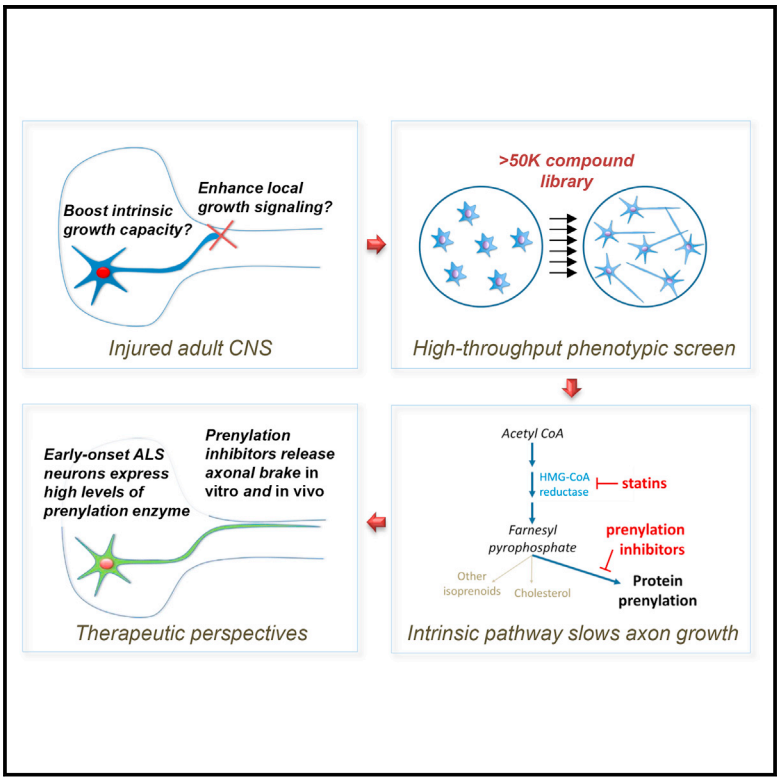
Cell Reports

Protein Prenylation Constitutes an Endogenous Brake on Axonal Growth

Graphical Abstract



Highlights

- Statins are the most potent enhancers of neurite elongation in vitro
- Statins and protein prenylation inhibitors promote CNS axon regeneration in vivo
- Motor neurons of early-onset ALS patients express high levels of prenylation enzyme
- Prenylation inhibitors provide a potential therapeutic approach for CNS regeneration

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In Brief

Using a high-throughput phenotypic screen, Li et al. identify statins and inhibitors of protein prenylation as potent neurite-outgrowth-promoting agents. High levels of prenylation enzyme are found in patients with earlier-onset forms of ALS. Prenylation may limit axonal growth in both normal and pathological situations.

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Protein Prenylation Constitutes an Endogenous Brake on Axonal Growth

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SUMMARY

Suboptimal axonal regeneration contributes to the consequences of nervous system trauma and neurodegenerative disease, but the intrinsic mechanisms that regulate axon growth remain unclear. We screened 50,400 small molecules for their ability to promote axon outgrowth on inhibitory substrata. The most potent hits were the statins, which stimulated growth of all mouse- and human-patient-derived neurons tested, both in vitro and in vivo, as did combined inhibition of the protein prenylation enzymes farnesyltransferase (PFT) and geranylgeranyl transferase I (PGGT-1). Compensatory sprouting of motor axons may delay clinical onset of amyotrophic lateral sclerosis (ALS). Accordingly, elevated levels of *PGGT1B*, which would be predicted to reduce sprouting, were found in motor neurons of early- versus late-onset ALS patients postmortem. The mevalonate-prenylation pathway therefore constitutes an endogenous brake on axonal growth, and its inhibition provides a potential therapeutic approach to accelerate neuronal regeneration in humans.

INTRODUCTION

Axonal growth is an essential step in the formation of neural circuits during normal development. In cases of traumatic brain injury or neurodegenerative disease, axonal damage is among the first morphological manifestations, and suboptimal regeneration is thought to be a major contributor to the low rates of functional recovery. Enhancing axonal regeneration in a controlled manner in patients with spinal cord injury may allow them to regain key lost functions; similar treatment in patients with amyotrophic lateral sclerosis (ALS) has the potential to increase muscle strength over the course of the disease. Over the past few decades, we have gained considerable insight into the extrinsic factors and intrinsic signaling mechanisms that affect directional choices taken by the axon growth cone and govern its reduced ability to advance in the damaged CNS (Alizadeh et al., 2015). However, we still have little knowledge of the cell-intrinsic mechanisms that drive axonal forward growth.

Over the past few decades, much insight has been gained into the low regenerative capacity of the adult CNS (Liu et al., 2011; Yiu and He, 2006). Most studies have focused on extrinsic factors that restrict axon regeneration (Filbin, 2003; Thiede-Stan and Schwab, 2015). Three growth inhibitors—myelin-associated glycoprotein (MAG), Nogo, and oligodendrocyte myelin glycoprotein—act through a common receptor complex containing the ligand-binding Nogo-66 receptor (NgR) and its