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Neuron

A Systems-Level Analysis of the Peripheral Nerve Intrinsic Axonal Growth Program

Highlights

- We identify a transcriptional program observed after PNS, but not CNS injury
- This program links known signaling pathways via a core set of transcription factors
- We experimentally and bio-informatically validate several network predictions
- We use the core transcriptional profile to identify a drug that promotes regeneration

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In Brief

Chandran et al. employ systems approaches to study PNS regenerative capacity after injury. They identify core networks and show that this program is observed after PNS, but not after CNS, injury. Utilizing networks, they identify a drug that promotes CNS regeneration.

Accession Numbers

GSE30691
GSE26350
GSE2884
GSE33175
GSE21007
GSE19701

Chandran et al., 2016, Neuron *89*, 956–970
March 2, 2016
http://dx.doi.org/10.1016/j.neuron.2016.01.034

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A Systems-Level Analysis of the Peripheral Nerve Intrinsic Axonal Growth Program

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http://dx.doi.org/10.1016/j.neuron.2016.01.034

SUMMARY

The regenerative capacity of the injured CNS in adult mammals is severely limited, yet axons in the peripheral nervous system (PNS) regrow, albeit to a limited extent, after injury. We reasoned that coordinate regulation of gene expression in injured neurons involving multiple pathways was central to PNS regenerative capacity. To provide a framework for revealing pathways involved in PNS axon regrowth after injury, we applied a comprehensive systems biology approach, starting with gene expression profiling of dorsal root ganglia (DRGs) combined with multi-level bioinformatic analyses and experimental validation of network predictions. We used this rubric to identify a drug that accelerates DRG neurite outgrowth in vitro and optic nerve outgrowth in vivo by inducing elements of the identified network. The work provides a functional genomics foundation for understanding neural repair and proof of the power of such approaches in tackling complex problems in nervous system biology.

INTRODUCTION

The regenerative capacity of the injured adult mammalian CNS is extremely limited, which leads to permanent neurological deficits following CNS injury. In contrast, injured axons in the adult mammalian peripheral nervous system (PNS) maintain the capacity to regenerate, providing potential for functional recovery after peripheral nerve injury (Abe and Cavalli, 2008; Ramón y Cajal et al., 1991). The failure of CNS axons to regenerate is due to many factors, primarily a lack of induction of a cell-intrinsic growth capacity after injury (Afshari et al., 2009; Giger et al., 2010) and the presence of extrinsic inhibitory effects (Filbin, 2003; Yiu and He, 2006), both mechanisms supported by many lines of experimental evidence (Hoffman, 2010; Neumann and Woolf, 1999; Sun et al., 2011; Yiu and He, 2006). The concept that specific intrinsic molecular differences contribute to the divergent neuronal growth states after PNS and CNS injuries is supported by the manipulation of individual candidate genes induced in neurons by PNS, but not CNS, injury, which can promote limited CNS regrowth after injury (Hoffman, 2010; Neumann and Woolf, 1999; Sun et al., 2011). The relative importance of intrinsic neuronal signals during injury in CNS regeneration failure (Sun and He, 2010) is highlighted by the very limited axon regeneration observed even after eliminating combinations of known extrinsic inhibitory signals (Yiu and He, 2006). Furthermore, a conditioning lesion of the peripheral axon of dorsal root ganglion (DRG) neurons in the PNS increases the intrinsic growth state of the neurons sufficiently to enable the regeneration of their central axons in the CNS (Neumann and Woolf, 1999).

One of the intrinsic molecular mechanisms contributing to the regenerative process is the retrograde transport of injury signals to the cell body of the neuron, leading to expression of regeneration-associated genes (RAGs; Abe and Cavalli, 2008). For example, injured PNS axons activate RAGs such as *Atf3*, *Jun*, *Hsp27*, *Sprr1a*, *Gap43*, and genes involved in the JAK-STAT3 pathway, whereas injury to CNS axons does not result in the activation of these RAGs (Afshari et al., 2009). Axonal injury also induces local activation and retrograde transport of several MAPKs, including ERK (Hanz et al., 2003; Perlson et al., 2005) and JNK (Cavalli et al., 2005; Lindwall and Kanje, 2005), while