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Neuron

Injury-Induced Decline of Intrinsic Regenerative Ability Revealed by Quantitative Proteomics

Highlights

- Proteomics analysis of intact and injured retinal ganglion cells
- Identification of a molecular network of neuronal injury responses
- c-*myc* as a critical regulator of injury responses and axon regeneration
- Functional interactions between c-*myc* and other known regeneration regulators

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In Brief

Belin et al. used comparative proteomics approaches and revealed a signaling network of injury responses in axotomized retinal ganglion cells and also demonstrated c-myc as a critical regulator of neuronal survival and axon regeneration.

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Injury-Induced Decline of Intrinsic Regenerative Ability Revealed by Quantitative Proteomics

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SUMMARY

Neurons differ in their responses to injury, but the underlying mechanisms remain poorly understood. Using quantitative proteomics, we characterized the injury-triggered response from purified intact and axotomized retinal ganglion cells (RGCs). Subsequent informatics analyses revealed a network of injury-response signaling hubs. In addition to confirming known players, such as mTOR, this also identified new candidates, such as c-*myc*, NFκB, and Huntingtin. Similar to mTOR, c-*myc* has been implicated as a key regulator of anabolic metabolism and is downregulated by axotomy. Forced expression of c-*myc* in RGCs, either before or after injury, promotes dramatic RGC survival and axon regeneration after optic nerve injury. Finally, in contrast to RGCs, neither c-*myc* nor mTOR was downregulated in injured peripheral sensory neurons. Our studies suggest that c-*myc* and other injury-responsive pathways are critical to the intrinsic regenerative mechanisms and might represent a novel target for developing neural repair strategies in adults.

INTRODUCTION

In the adult mammalian CNS, axotomy often triggers neuronal death, and spontaneous axon regeneration rarely occurs. An implicated mechanism is the diminished intrinsic regenerative ability of mature CNS neurons (Fawcett, 2006; Goldberg et al., 2002b; Moore et al., 2009; Park et al., 2008). Based on the differences in axon growth between immature and mature neurons, it has been proposed that the neuronal intrinsic growth ability is lost over the course of development. Therefore, much effort has been made to seek molecular pathways that are differentially expressed during development and in the adult, resulting in the identification of several axon regeneration regulators. For example, in many types of neurons, cAMP levels appear to be higher in the immature neurons, but decline in the mature neurons (Cai et al., 2001; Filbin, 2003). By analyzing the axon growth of retinal ganglion cells (RGCs) from different developmental stages, Goldberg et al. showed a development-dependent decline of axon growth rate, with a dramatic decrease in postnatal RGCs (Goldberg et al., 2002a). Further, recent studies implicated transcription factors from the Krüppel-like family of transcription factors (KLFs) as critical regulators of development-dependent axon growth ability in RGCs (Moore et al., 2009). Interestingly, while KLF7 is downregulated, other members, such as KLF4, are upregulated during development. Importantly, manipulations of these factors could promote the regrowth of injured optic nerve axons and corticospinal tract axons in the adult (Blackmore et al., 2012).

However, ample evidence indicates that even in the adult CNS, many uninjured neurons possess considerable capacity for structural plasticity and collateral sprouting (Holtmaat and Svoboda, 2009; Raineteau and Schwab, 2001). For example, upon incomplete spinal cord injury in the adult, spared axons have been repetitively shown to elaborate spontaneous sprouting responses (Bareyre et al., 2004; Rosenzweig et al., 2010). Furthermore, such sprouting responses could be further enhanced by rehabilitation training (Harel et al., 2013; van den Brand et al., 2012). This is in contrast to no or limited regrowth from injured axons in the adult CNS (Bradke et al., 2012; Goldberg et al., 2002b; Moore et al., 2009; Park et al., 2008; Rossi et al., 2007). Therefore, it is possible that in addition to development-dependent processes, axonal injury-triggered stress responses might contribute to the impaired intrinsic regenerative ability of mature neurons.

While many previous studies documented gene expression changes in different types of injured neurons (Costigan et al., 2002; Michaelevski et al., 2010; Saul et al., 2010; Tanabe et al., 2003; Fischer et al., 2004), pinpointing key molecular pathways that orchestrate neuronal survival and axon regeneration remains a major challenge. One possible reason is that axotomy may impinge on both gene transcription as well as protein translation and degradation. Thus, analyzing the transcriptome may not reflect the full scope of injury-induced changes in neurons.