Cell Reports
Report

The Phr1 Ubiquitin Ligase Promotes Injury-Induced Axon Self-Destruction

Elisabetta Babetto,[1] Bogdan Beirowski,[2] Emilie V. Russler,[1] Jeffrey Milbrandt,[2,3] and Aaron DiAntonio[1,3,*]
[1]Department of Developmental Biology
[2]Department of Genetics
[3]Hope Center for Neurological Disorders
Washington University School of Medicine, St. Louis, MO 63110, USA
*Correspondence: diantonio@wustl.edu
http://dx.doi.org/10.1016/j.celrep.2013.04.013

SUMMARY

Axon degeneration is an evolutionarily conserved process that drives the loss of damaged axons and is an early event in many neurological disorders, so it is important to identify the molecular constituents of this poorly understood mechanism. Here, we demonstrate that the Phr1 E3 ubiquitin ligase is a central component of this axon degeneration program. Loss of Phr1 results in prolonged survival of severed axons in both the peripheral and central nervous systems, as well as preservation of motor and sensory nerve terminals. Phr1 depletion increases the axonal level of the axon survival molecule nicotinamide mononucleotide adenyltransferase 2 (NMNAT2), and NMNAT2 is necessary for Phr1-dependent axon stability. The profound long-term protection of peripheral and central mammalian axons following Phr1 deletion suggests that pharmacological inhibition of Phr1 function may be an attractive therapeutic candidate for amelioration of axon loss in neurological disease.

INTRODUCTION

Axon degeneration is a hallmark of many neurological disorders including neuropathies and neurodegenerative diseases. An active and evolutionarily conserved mechanism drives axon loss (Wang and Barres, 2012), so inhibiting this process is an attractive therapeutic target for treating a wide range of neurological disorders. Acute severing of axons leads to a process commonly referred to as Wallerian degeneration, consisting of axon breakdown, glial and macrophage responses, and clearance of myelin debris (George and Griffin, 1994). Wallerian degeneration is delayed for at least a week by the ectopic expression of the Wallerian degeneration slow (Wld^S) protein, which acts via a gain-of-function mechanism requiring the axonal relocalization of its active component nicotinamide mononucleotide adenylyltransferase, NMNAT1 (Babetto et al., 2010; Sasaki et al., 2009a). Axon degeneration occurs not only in response to trauma, but also occurs in metabolic, inflammatory, and hereditary neuropathies as well as neurodegenerative diseases (Vargas and Barres, 2007). Remarkably, expression of Wld^S or axonal NMNAT can delay axon loss in many of these disease models suggesting the existence of a general axon loss program (Wang and Barres, 2012).

While ectopic expression of NMNAT orthologs can delay axon loss, the endogenous mechanisms that promote axon degeneration are largely unknown. Others and we have recently identified neuron intrinsic pathways that promote axon death (Miller et al., 2009; Osterloh et al., 2012; Wakatsuki et al., 2011; Wishart et al., 2012) and have designed screens to identify additional components (Bhattacharya et al., 2012; Fang et al., 2012; Gerdts et al., 2011). In a hypomorphic mouse mutant of dual-leucine zipper kinase (DLK), we demonstrated axon protection for at least 52 hr after axotomy and identified JNK and SCG10 as downstream signaling effectors (Miller et al., 2009; Shin et al., 2012). However, only deletion of the sterile alpha- and armadillo-motif-containing protein (SARM) protein confers Wld^S-comparable axon protection in mice for days after peripheral nerve transection, yet its mechanism of action remains unknown (Osterloh et al., 2012). To advance our understanding of the endogenous processes orchestrating axon death, it is thus necessary to identify essential components of the degeneration program and to define the underlying mechanisms.

PHR (PAM-Highwire-Rpm-1) ligases are an evolutionarily conserved family of large E3 ubiquitin ligases that are central regulators of multiple aspects of axonal biology. Mutations of PHR orthologs from worms to mice lead to dramatic defects in the development of synapses and axons (Bloom et al., 2007; Culican et al., 2009; D'Souza et al., 2005; Lewcock et al., 2007; Schaefer et al., 2000; Wan et al., 2000; Zhen et al., 2000). Recent work in invertebrates demonstrates that PHR proteins also accelerate the regenerative response following nerve injury (Nix et al., 2011; Xiong et al., 2010) and delay synapse loss in genetic models of cytoskeletal instability (Massaro et al., 2009). The involvement of Phr1 (also known as Mycbp2) in fundamental aspects of axon biology prompted us to test the role of Phr1 in axon degeneration in mice. Here, we demonstrate that Phr1 is a central component of the axonal degeneration program. Excision of Phr1 in adult mice leads to long-term preservation of peripheral nervous system (PNS) and CNS axons, and Phr1 promotes the self-destruction of injured axons by limiting the availability of the essential axonal maintenance factor NMNAT2. This identifies Phr1 as a candidate therapeutic target for inhibiting axonal loss due to trauma and disease.