Published in final edited form as:

J Neurosci Res. 2017 August ; 95(8): 1525–1527. doi:10.1002/jnr.24069.

Neurodegeneration and Regeneration

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One of the main differences between the adult mammalian's central nervous system (CNS) and peripheral nervous systems (PNS) is the capability to regenerate. It has long been thought that neurons in the CNS do not regenerate after injury. As depicted in Cajal's dogma, "Once development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In adult centers, the nerve paths are something fixed, ended, and immutable. Everything may die. Nothing may be regenerated" (Ramón y Cajal, 1969). Yet, intensive studies over the past few decades have revealed that injured CNS axons can regain their growth ability after manipulating intrinsic and extrinsic factors. Unraveling the mechanisms underlying this phenomenon will greatly advance the neurodegeneration and regeneration field and the development of therapeutic methods.

Unlike the well-regenerating peripheral nerves, CNS axons invariably fail to regenerate after injury, resulting in permanent functional deficits. Researchers and physicians understand that tissues and organs change in many ways after injury or during pathological conditions. After an injury, the formation of scar tissue induced by glia cells and immune response, alters the local anatomical structure (Brosius Lutz and Barres, 2014; Silver et al., 2014). As a physical and molecular wall used to prevent intense inflammation and protect remaining fragile tissue, the scar is an essential part of wound healing after brain and spinal cord injuries (Silver and Miller, 2004). The astroglial component of the scar wall is formed by serial steps: (a) the rapid migration of astrocytes (Fitch and Silver, 1997; George and Griffin, 1994), (b) the proliferation of reactive astrocytes (gliosis) that reside at the lesion margin (Aldskogius and Kozlova, 1998; Bush et al., 1999; Wanner et al., 2013), (c) the accumulation of intermediate filament proteins (predominantly glial fibrillary acidic protein [GFAP]) secreted by reactive astrocytes (Bardehle et al., 2013; Liuzzi and Lasek, 1987; Pekny et al., 1999), (d) the restructuring of the gliotic layer into a mesh-like envelope (Bardehle et al., 2013; Wanner et al., 2013), and (e) the production of a variety of extracellular matrix (ECM) molecules (Busch and Silver, 2007; Yamaguchi, 2000). The physical wall of the gliotic envelope has been considered an unsupportive environment for regenerating axons to overcome. The expression of GFAP, and the upregulation of ECM proteins, including chondroitin sulfate proteoglycans (CSPGs), which are associated with regeneration failure in the injured area (Filous et al., 2010; Yiu and He, 2006). Thus, it is

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CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest.

well accepted that the presence of an inhibitory environment surrounding the injured axons contributes to the CNS axon regeneration failure.

In the last decades, many studies suggest that removing the inhibitory influences alone is not sufficient enough to promote regeneration. Therefore, it can be implied that CNS neurons lose their natural ability to regrow following injury and that their growth capacity in adult neurons is diminished (Liu et al., 2011; Ramón y Cajal, 1969; Sun et al., 2011). Scientists have been searching for the intrinsic molecules responsible for the decrease in the regenerating ability of neurons; and recently, in one of the injury models in the CNS, after an optic nerve crush, a breakthrough was reported in the retinal ganglion cell (RGC). The group, led by Dr. Zhigang He, was the first to find that the deletion of a phosphatase and tensin homolog (PTEN) in mice enabled the regeneration of injured RGC axons (Park et al., 2008). PTEN is a negative regulator of the mammalian target of rapamycin (mTOR), which is responsible for cell growth. During early development, the PTEN expression level is low to ensure cell proliferation, whereas it increases in mature tissue after growth is completed. In order to reconnect with their targets and to achieve functional restoration after injury, the axons need to regrow and then maintain their regenerating capacity. The same group revealed that concurrent activation of mTOR and Janus kinase/signal transducers and activators of transcription (JAK/STAT3) pathways, by double inhibition of PTEN and suppressor of cytokine signaling 3 (SOCS3), are necessary for sustaining long distance axon regeneration in the adult CNS (Sun et al., 2011). Besides the mTOR pathway, augmenting other intrinsic cell-growth promoting factors such as cyclic adenosine monophosphate (cAMP; Cai et al., 1999) or ciliary neurotrophic factor (CNTF; Leaver et al., 2006) could also improve CNS axon regeneration. Currently, additional investigations are focusing on the manipulation of both intrinsic and extrinsic factors to achieve axon regeneration in different injury models. A recent study reported that in addition to triggering the intrinsic growth capacity, the enhancement of neural activity by visual stimulation or using chemogenetics could promote long distance, target specific regeneration of adult retinal axons (Lim et al., 2016). In addition to the RGC neurons in the brain, researchers also induced robust regeneration of CST axons by blocking PTEN signaling, which govern nerve connections and voluntary movement after a spinal cord injury (Liu et al., 2010). Taken together, both inhibitory extrinsic factors and decreased intrinsic capacity that limit axon regeneration in the CNS can be manipulated pharmacologically and genetically to improve axon regrowth and function. Studies in different injury paradigms and animal models of intrinsic control of axon regeneration can be found in a recent review by He and Jin (2016).

Before axons achieve regeneration and functional recovery, understanding how to prevent axonal degeneration and neuronal loss would provide important clinical implications. Besides traumatic injury, axons degenerate in the condition of several neurological diseases, including different neuropathies (diabetes, chemotherapy induced, and hereditary) and neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Huntington's Disease, and amyotrophic lateral sclerosis, etc.; Conforti et al., 2014; Saxena and Caroni, 2007; Wang et al., 2012). Though many studies implicate intracellular events during pathogenesis, including mitochondria dysfunction, mitophagy, and axon transport issues, it is still not absolutely clear how the degeneration occurs. Thus, with a better understanding of

the molecular mechanisms and signaling pathways that regulate it, we can begin searching for therapeutic targets to prevent neuronal degeneration and improve survival.

It is thought that axonal degeneration is regulated by mechanisms distinct from those governing cell body death. Wallerian degeneration is a common form of pathological axonal death, defined as the breakdown of distal segments of severed axons following traumatic injury, likely resulting from a self-destruction program (Coleman, 2005). This process is dramatically delayed by the expression of a gain-of-function mutant protein of Wallerian degeneration Slow (*Wld^S*; Mack et al., 2001) and its component nicotinamide mononucleotide adenylyltransferase (NMNAT; Araki et al., 2004; Vohra et al., 2010). This observation, seen in many different degeneration models besides injury, suggests the existence of a common intrinsic regulatory mechanism of axonal death (Conforti et al., 2014; Wang et al., 2012). Indeed, recent studies have found that mitogen-activated protein kinase (MAPK) cascade is involved in this event (Yang et al., 2015); and dual leucine zipper kinase (DLK, a MAP3K) is an essential component of the injury signaling pathway (Miller et al., 2009; Watkins et al., 2013). Loss of DLK protected distal axons from Wallerian degeneration (Miller et al., 2009) and insult induced retrograde c-jun N-terminal kinase (JNK) signaling (Cavalli et al., 2005; Shin et al., 2012). Genetic deletion of JNK2 and/or JNK3 is sufficient to protect axons from degeneration in many different CNS injury models (Fernandes et al., 2012; Holland et al., 2016; Kuan et al., 2003; Yang et al., 1997; Yang et al., 2015). Interestingly, this MAPK signaling pathway regulated axonal death in Wallerian degeneration is also observed in developmental axonal degeneration (Ghosh et al., 2011; Maor-Nof et al., 2016; Simon et al., 2016). DLK and downstream JNK signaling is retrogradely transported to the cell body after injury or trophic deprivation and initiates a transcriptional program that mediates axonal degeneration, suggesting the important role of soma in this event. Indeed, recent studies have shown that p53 upregulated modulator of apoptosis (PUMA) serves as the convergent point of Akt/Foxo3a and JNK/c-Jun signaling, which is required for axon degeneration following trophic deprivation (Maor-Nof et al., 2016; Simon et al., 2016). However, how the pro-apoptotic signals are delivered from the cell body to distal axon still remains unclear.

In the same paradigm, understanding the pathogenesis of neuronal degeneration at multiple levels, from genes, cells, neuronal circuitry, anatomy and function, would advance our understanding of the fundamental mechanisms underlying the normal function and dysfunction in neurodegenerative disorders. This commentary will cover some topics under the range of neural degeneration and regeneration, in both normal development and disease models. While the issue cannot cover the entire range of subjects in this area, I hope that the ideas presented by the authors may inspire new thoughts, and hopefully further investigations that will advance the field.

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