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Spotlight

Antiviral immunity rewired for axon regeneration

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In *Neuron*'s January 18th issue, Wang et al.[1] report that activating the immune signaling IFNγ-cGAS-STING axis promotes axon regeneration in both the peripheral and central nervous systems. Their findings uncover the coordination mechanism of neural innate immune responses for axon regeneration.

Traumatic injury in the adult central nervous system (CNS) can lead to devastating consequences such as paralysis. Axon regeneration is manifested as the process of axon regrowth and the subsequent re-innervation of target regions following injury. In contrast to the limited axonal regeneration capacity of the CNS, such as retinal ganglion cells (RGCs), the peripheral nervous system (PNS) exemplified by dorsal root ganglion cells (DRGs) is capable of regenerating axons after nerve damage. Therefore, the distinct and shared machinery has been intensively interrogated to inform the therapeutic strategies in the CNS. Mammalian target of rapamycin (mTOR), signal transducers and activators of transcription 3 (STAT3), suppressor of cytokine signaling 3 (SOCS3, a negative regulator of Janus kinase/STAT pathway), and phosphatase and tensin homologue (PTEN, a negative regulator of mTOR and STAT3) represent such outstanding candidates identified.[2,3] In parallel, innate immune responses have been primarily studied for their protective roles against pathogen invasions. However, recent studies have unveiled that the neural immune response is elicited upon nerve damage and is critically involved in nerve repair and injury-associated pathophysiology. For instance, the cGAS-STING signaling axis, comprising the synthase for the second messenger cyclic GMP-AMP (cGAS) and the cyclic GMP-AMP (cGAMP) receptor stimulator of interferon genes (STING) and the ciliary neurotrophic factor (CNTF)-STAT3 signaling axis can be engaged upon nerve injury to mediate neuroimmune reactions.[4,5] Understanding and harnessing their regulatory functions in the repair program to its full power have emerged as a viable therapeutic option.

To search for the molecular targets in axon regeneration, Wang and colleagues carried out a functional screening utilizing the DRG replating assay.[1] Out of 84 preselected phosphatases, protein tyrosine phosphatase non-receptor type 2 (*Ptpn2*) was identified among 5 candidates, knockdown of which promoted axon regrowth. Of particular importance, RGCs showed more regenerating axons post nerve injury when PTPN2 was inhibited pharmacologically or abrogated genetically.

Next, the authors went on to explore the signaling cascade that involves PTPN2. When *Ptpn2* was deleted in DRGs, transcriptome analysis showed that the injury-induced genes were significantly enriched in the categories related to host defense responses such as induction of interferon-stimulated genes (ISGs). When testing the ligands that may enhance the axon regeneration of RGCs upon *Ptpn2* deletion, they observed that interferon γ (IFNγ) showed robust phenotypes. Endogenous IFNγ can be detected in the vitreous humor, and knocking down the receptor subunit *Ifngr1* or *Ifngr2* suppressed *Ptpn2* deletion-induced axon regeneration, supporting the important role of endogenously produced IFNγ.

To understand how IFNγ may stimulate axonal regeneration, the RGCs were sorted following retrograded labeling of axons. ISGs showed the most prominent induction upon *Ptpn2* deletion in the presence of exogenous IFNγ. When accessing the downstream signaling events, *Ptpn2* deletion appeared to sustain phosphorylated STAT1 much longer than wild-type controls. Notably, investigations of CNTF and PTEN pathways show that their effector components STAT3 and mTOR functioned independently from IFNγR-STAT1 for axonal regeneration.

When probing the interconnection between PTPN2, STAT1, and ISGs, the authors tested the involvement of the cGAS-STING pathway. cGAS and STING belong to the family of ISGs transcriptionally induced by interferons. cGAS senses double-stranded DNA (dsDNA) and synthesizes cGAMP, which binds to and activates STING.[6] Interestingly, cGAS was upregulated in a STAT1-dependent manner. Meanwhile, DNA damage was detectable in a small percentage of RGCs after nerve injury, but the percentage increased drastically upon *Ptpn2* deletion even in the absence of injury. Further, cGAS or STING deletion blocked the regenerating effect mediated by *Ptpn2* knockdown.

Lastly, they turned back to the PNS to probe the IFNγ-STAT1 axis in axon regeneration. Interestingly, the mRNA and protein of IFNγ were highly inducible in axons by nerve injury. Further examination showed that IFNγ was locally translated in axons. Different from the CNS where neurons exhibited cGAS expression, cGAS was induced in Schwann cells and blood cells in the PNS. Those non-neuronal cells generated cGAMP and signaled to neuronal STING in a *trans*-cellular manner. Mechanistically, cGAS-STING activation regulated the production of regenerating associated genes (RAGs) and local microtubule dynamics to promote axon regeneration. Collectively, in the periphery, the neurons and non-neuronal cells are coordinated to promote axonal growth.

In sum, Wang et al. have elucidated how innate immune signaling contributes to axon regeneration (Figure 1). Importantly, the findings have raised many unresolved questions and enlightened our pursuit of axon regeneration intervention. At present, CNS axon regrowth can be induced following modulation of pro-growth signaling pathways in injured neurons or alteration of extrinsic factors that inhibit axon re-extension, but few of them have achieved complete recovery. Multiple layers of antagonizing mechanisms seem to ensure axon regrowth quiescence. In this scope, neuron autonomous and non-autonomous mechanisms are to be exploited simultaneously to alter neuronal homeostasis and the tissue microenvironment when maximizing structural and functional recovery. In addition to traumatic injuries, neurodegenerative diseases are inflicting an expanding population including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Intriguingly, axonal damages often precede soma degeneration and represent a key feature in neuron degeneration. Designing ways to promote axon regeneration stand as an immediate option. Admittedly, our current understanding of axon regeneration and neuroimmune response is limited and perplexing. Taking the cGAS-STING pathway as an example, mice lacking STING exhibit hypersensitivity to nociceptive stimuli in the sensory neurons[7]; loss of functional STING protects mice from α-synuclein pre-formed fibril (α-Syn PFF)-induced motor deficits and dopaminergic neuron loss[8]; cGAS-STING activation serves as a critical determinant of TAR DNA-binding protein 43 (TDP-43)-associated pathology in ALS[9]; and STING activation affects neuropathology in Niemann-Pick disease type C (NPC).[10] As a result, caution should be taken when tackling pathological conditions involving neuroinflammation. Reinvigorating the axonal regeneration program while at the same time restraining detrimental consequences remains a daunting challenge and a unique opportunity.

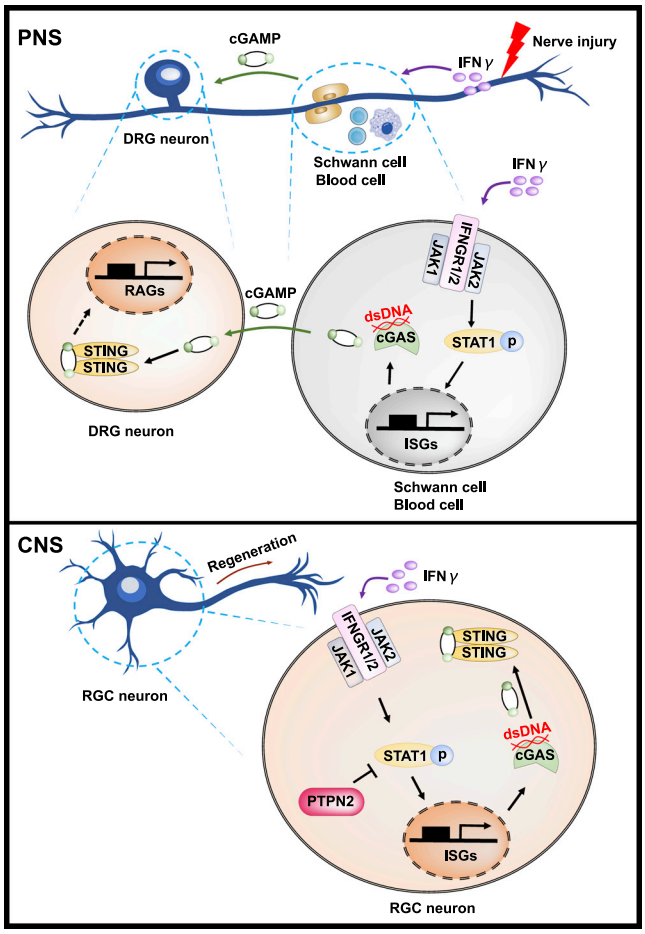

Figure 1. Activating the immune signaling IFNγ-cGAS-STING axis promotes axon regeneration in both the PNS and the CNS

Post nerve injury of DRG neuron, IFNγ is locally produced within the axons and acts on the Schwann cells and blood cells in the injury zone via its receptor complex IFNGR1/2, leading to upregulation of ISGs. cGAS is thereby induced in the non-neuronal cells and generates cGAMP to activate neuronal STING in *trans*, which then initiates the transcription of RAGs to promote axon regeneration. In the RGC neurons, IFNγ combined with *Ptpn2* ablation can activate the IFNγ-cGAS-STING pathway and boost axon regeneration.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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