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Review

Research status of regenerative difficulties after central nervous system injury

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ABSTRACT

Multiple studies have shown that permanent functional disabilities caused after nerve damage are mainly due to the limited ability of damaged neurons in the central nervous system (CNS) to regenerate axons and re-establish functional connections. Most axons in the CNS of adult mammals cannot reactivate their intrinsic growth program after injury, making axonal regeneration difficult when damaged. This article provides a systematic review of the response processes following CNS injury and the factors affecting repair and regeneration, focusing on the molecular mechanisms that regulate the regeneration of damaged axons, in hopes of offering new insights for the repair of CNS injuries.

Contents

1. Introduction

In adult mammals, nerve damage is a prevalent condition, with the primary causes including neurodegenerative diseases, autoimmune disorders, physical injuries, inflammation, and viral infections [1–3]. The repair and regeneration of axons in the central nervous system (CNS) following injury differ across species and pathways. In mature mammals, neural regeneration is generally impaired [4,5], and damaged neurons typically do not undergo self-repair [4]. To promote regeneration and repair, researchers have transplanted embryonic neurons into injured regions of the adult mammalian CNS, where they can extend new axons toward distal

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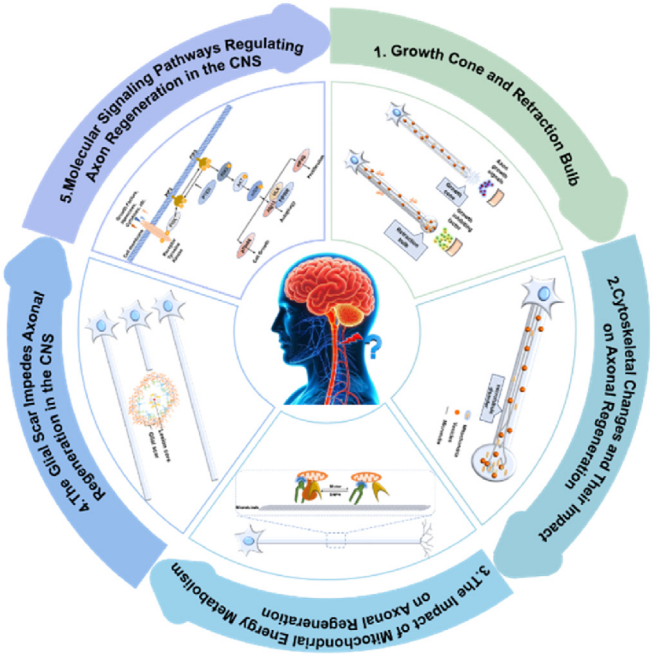
sites. However, this regenerative process ceases as the neurons mature [6]. Taylor's research demonstrated that when the optic nerve axons of opossums are injured before day 12 post-birth, retinal ganglion cells (RGCs) regenerate. However, if the injury occurs after day 12, regeneration does not occur [7]. Current theories on the challenges of CNS regeneration predominantly focus on the loss of intrinsic and extrinsic growth capabilities [8], alterations in cytoskeletal dynamics [9], epigenetic changes, cell death, and the disruption of functional connectivity [6]. This article provides a comprehensive review of the current mechanisms involved in axonal repair and regeneration within the CNS, aiming to offer new insights into strategies for repairing CNS injuries (Scheme 1).

2. Growth cone and retraction bulb

The growth cone is a specialized structure located at the tip of a neuron's axon or dendrite, responsible for sensing and integrating environmental cues to direct axonal and dendritic growth. It consists of a central domain enriched with microtubules and a peripheral domain rich in actin filaments [10] Regeneration and sprouting are two primary mechanisms of axonal growth following CNS injury [11,12]. Regeneration (Fig. 1) is defined as the formation of a growth cone at the injured axonal tip, which sustains distal growth over an extended period. Regeneration includes the regrowth of axons or dendrites, synaptic reconstruction, and the response of glial cells and associated structures, such as myelin. On the other hand, sprouting (Fig. 1) refers to the extension of new branches from an existing axon into a new neural region. Both regeneration and sprouting contribute to the recovery of neural function [13–15].

Axonal repair and extension are similar to the processes of growth and development; however, they are more complex because new growth cones must form from severed or crushed axons. The growth cone is considered the primary regulator of axonal growth, and its ability to form new growth cones at the injury site is a critical determinant of axonal regeneration [16–18] In the peripheral nervous system (PNS), axonal sprouting occurs at the proximal end of the injured axon, forming a new growth cone [17]. In this region, mitochondria accumulate to provide energy, and microtubules are organized to extend the cytoskeleton, enabling the growth cone to sense and interpret environmental cues, promoting appropriate growth along its trajectory and facilitating peripheral nerve regeneration (Fig. 2). However, in the CNS, axons lack intrinsic regenerative capacity. The microtubule structure in CNS is unstable and disordered, leading to retraction at the distal axon, which forms a ball-like structure. Mitochondria concentrate at the retraction site. After axonal injury, the proximal axoplasm leaks and swells, forming a non-regenerative counterpart to the growth cone, known as the "retraction ball" (Fig. 2) [19] This retraction ball is a crucial structure in the failure of regeneration following CNS injury [19,20].



Scheme 1. Repair mechanisms associated with central nervous system injury. 1. The growth cone can promote nerve regeneration, while the retraction bulb leads to impaired nerve regeneration. 2. After central nervous system injury, pathological cytoskeletal dynamics lead to microtubule disorder, resulting in damaged mature neurons lacking regenerative capacity. Controlling the arrangement of microtubules can effectively enhance the regenerative ability of damaged mature neurons. 3. Mitochondrial damage caused by central nervous system injury leads to insufficient energy in the damaged axons. Regulating the distribution of mitochondria in the axons is crucial for axonal regeneration. The distribution of mitochondria in the axons primarily relies on two molecular motors, dynein and kinesin, as well as the anchoring mechanism involving SNPH. 4. The glial scar is made up of reactive astrocytes (orange), NG2 glia (green) and microglia (bule) that form a tight barrier around the lesion core, or area of severe tissue damage. The lesion core contains blood-borne macrophages (gray) and stromal cells (yellow). Injured axons fail to grow through the glial scar. 5.PTEN-mTOR pathway is an extensively studied signaling cascade involved in neuronal regeneration.

3. Cytoskeletal changes and their impact on axonal regeneration

In addition to supporting axonal tip movement and providing structural integrity to neurons, the cytoskeleton also facilitates the active transport of proteins, vesicles, and organelles along the axon. Following nerve injury, microtubules in the retraction balls do not form the typical, tightly organized parallel bundles observed in growing axons. Instead, they disassemble and lose directional orientation within the retraction ball. This results in dynamic microtubule polymerization, which contributes to pathological cytoskeletal dynamics and microtubule disorganization. As a result, mature, damaged neurons exhibit a lack of regenerative capacity. Regulating microtubule organization has been shown to enhance the regenerative potential of these neurons [21]. Several studies have demonstrated that both the formation of retraction balls and

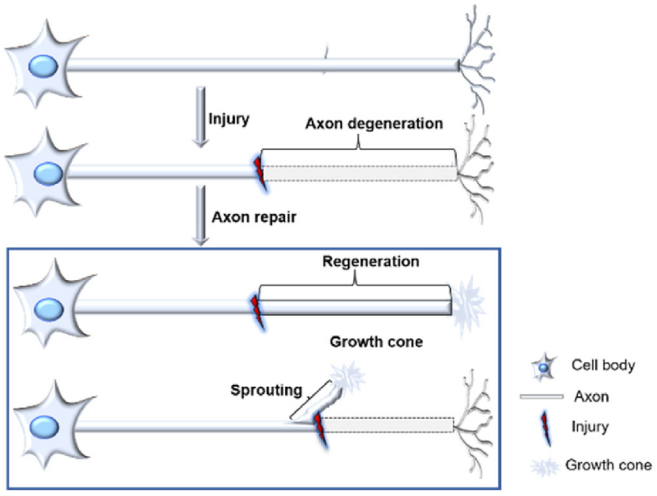


Fig. 1. The two main forms of axon growth after CNS injury: regeneration and sprouting.

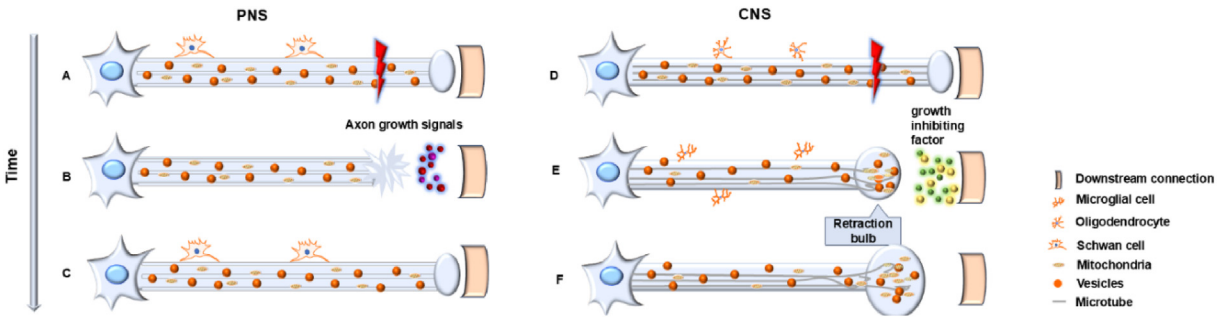


Fig. 2. The formation process of growth cone and retraction bulb at the end of axons after PNS and CNS axonal injury. A. Normal PNS axons, axon function is active. B. After axonal injury, the growth cone was formed at the end of PNS axon, which was effectively prolonged by membrane transport, energy and dynamic cytoskeleton. C. During repair and regeneration, PNS axons continued to elongate rapidly until they were found and connected to the target. D. Normal CNS axons, axon function is active. E. After axonal injury, CNS microtubules were disordered, terminal retraction bulbs were formed, and mitochondria were more concentrated on retraction bulbs. F. As the injury progressed, the retraction bulb at the end of the CNS axon further increased.

the failure of neuronal regeneration are linked to microtubule disorganization. The misdirected microtubules serve as intrinsic inhibitors of axonal regeneration [3,22]. An ordered microtubule arrangement following axotomy can prevent the formation of retraction balls and promote axonal growth, even in the face of significant growth limitations in the CNS [23]. Paclitaxel has been shown to facilitate axonal growth in the CNS by promoting microtubule polymerization. It induces the organized alignment of microtubules at the axonal tip, thus inhibiting retraction ball formation. In contrast, the microtubule destabilizer nocodazole causes microtubule disorganization, converting growth cones into retraction balls and inhibiting axonal growth [22,24,25]. In conclusion, enhancing microtubule formation and stabilizing the cytoskeletal structure in the CNS represents an effective strategy for reducing retraction ball formation and promoting axonal regeneration in the adult CNS [26].

4. The impact of mitochondrial energy metabolism on axonal regeneration

Mitochondria plays a crucial role in axonal regeneration, serving as essential cellular powerhouses required for neuronal growth, survival, function, and post-injury regeneration [27,28]. Axonal injury induces a strong stress response, which leads to mitochondrial depolarization [29,30]. Mitochondrial depolarization, in turn, causes transport defects and energy deficits, both of which contribute to the failure of axonal regeneration following nerve injury [31]. After axonal injury, mitochondrial damage, reduced mitochondrial transport in mature neurons, and increased energy consumption collectively result in an energy deficit in the damaged axon. Therefore, in response to the energy consumption and homeostatic changes that occur following neuronal injury, the regulation of mitochondrial distribution and movement within the axon plays a pivotal role in axonal regeneration post-injury [32]. Long-distance mitochondrial transport is driven by ATP-dependent, microtubule (MT)-based molecular motors, including kinesin, a plus-end-directed motor protein, and dynein, a minus-end-directed motor protein [33,34]. Kinesin motors move mitochondria in the anterograde direction toward the distal axon, while dynein motors mediate retrograde transport toward the cell body. In addition to motor-driven transport, axonal mitochondria also rely on anchoring mechanisms [35]. Syntaphilin (SNPH) anchors axonal mitochondria to microtubules, preventing mitochondrial transport [36]. The movement of mitochondria can switch between motility and anchoring in response to changes in cellular energy metabolism (Fig. 3). In the CNS, most axonal mitochondria remain stationary, with only a small proportion being mobile. Proper transport of mitochondria to growth cones during axonal regeneration after injury ensures that metabolically active regions receive sufficient ATP. Due to the limited diffusion capacity of ATP through long axons, mitochondria are the primary source of ATP for assembling new growth cones and supporting axonal regeneration. When mitochondrial dysfunction occurs, energy supply is reduced, leading to local energy deficits, while the release of toxic reactive oxygen species (ROS) and apoptotic factors exacerbates axonal damage [37]. Enhancing mitochondrial transport can reduce the damage caused by dysfunctional mitochondria and meet local energy demands [28]. Studies have shown that reducing SNPH expression or increasing Miro 1 expression can enhance mitochondrial transport, thereby promoting axonal regeneration [31].

The axonal mitochondria contain transport and anchoring functions to achieve the balance of axonal energy. Directed kinesins in mitochondria can transport mitochondria to distal axons, while directed dynein can transport mitochondria to the cell body. In the axons of the CNS, most mitochondria remain quiescent, and a small fraction of the mitochondria can move. This is controlled by anchoring proteins SNPH.

5. The glial scar impedes axonal regeneration in the central nervous system

Factors that hinder regeneration in the CNS primarily include myelin debris from damaged axons and astrocytes, as well as contributions from fibroblasts, extracellular matrix (ECM) components, and microglia [20,38,39]. In the PNS, Schwann cells (the myelin-forming glial cells) collaborate with blood-derived macrophages to clear myelin debris through TAM (Tyro 3, Axl, Mer) receptor-mediated phagocytosis and autophagy [40]. Rapid clearance of peripheral myelin debris is crucial for successful axonal regeneration and functional recovery; however, the molecular mechanisms underlying this process remain poorly understood [41,42]. In contrast to the response in the PNS, CNS injury results in the prolonged persistence of myelin debris, lasting for months or even years, which serves as a significant molecular barrier to repair in the brain and spinal cord [43,44]. The failure to clear myelin debris impedes axonal regeneration through the damaged region, thereby obstructing the restoration of neural circuits.

A major barrier to regeneration in the CNS is the formation of glial scars around the lesion site [45,46]. Glial scars are a cellular response to CNS injury, in which proliferating reactive astrocytes, NG2 glial cells, and microglia create a dense boundary around severely damaged regions or the lesion core. This core is composed of a mixture of fibroblasts, pericytes, ependymal cells, and macrophages originating from the surrounding vasculature [47]. After

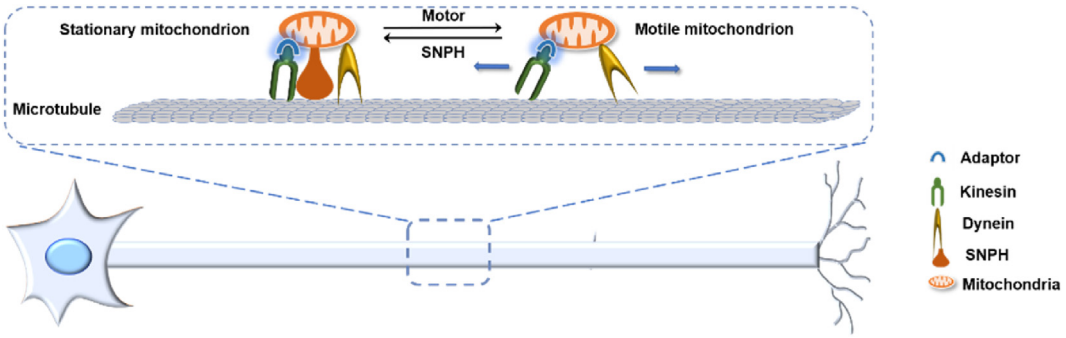


Fig. 3. Motor/adaptor and Anchor proteins have opposite effects in the mitochondria. 1. Long-distance axonal mitochondrial transport is driven by microtubule (MT)-based molecular motors: kinesin and dynein. Kinesin motors move mitochondria in the anterograde direction toward the distal axon, while dynein motors mediate retrograde transport toward the cell body. Axonal mitochondria also deploy an anchoring mechanism in addition to motor-driven transport. 2. Syntaphilin (SNPH) anchors axonal mitochondria to microtubules, preventing mitochondrial transport. In central nervous system (CNS) axons, most mitochondria remain stationary, while approximately 20–30 % are motile. 3. Motile mitochondria can become stationary and stationary ones can be remobilized. The balance of motile versus stationary axonal mitochondria depends on the relative action of the motor/adaptor and SNPH.

spinal cord injury, astrocytes involved in scar formation upregulate genes such as chondroitin sulfate proteoglycans (CSPG) and the repulsive axon guidance protein Slit 232, CSPG has been shown to inhibit axonal regeneration in vitro [48]. In addition to impairing axonal growth, glial scars also hinder endogenous myelin regeneration [49,50]. The inhibitory properties of glial scars are largely attributed to the high concentrations of inhibitory proteins, including CSPG and myelin-associated proteins. However, some studies challenge the view that glial scars inhibit axonal regeneration. One perspective suggests that the formation of acute astrocytic scars may help limit inflammation and protect neural tissue [51,52]. Preventing the formation of astrocytic scars, reducing scar-forming astrocytes, or ablating chronic astrocytic scars has not been successful in promoting spontaneous regeneration of corticospinal, sensory, or serotonergic axons after severe spinal cord injury (SCI) [53]. Furthermore, a series of studies conducted by the Sofroniew laboratory over the past decade has shown that preventing astrocytic scar formation following CNS injury does not enhance regenerative capacity [53,54]. In fact, selectively eliminating proliferating astrocytes or blocking STAT3 signaling specifically in astrocytes can lead to increased axon degeneration [8].

6. Molecular signaling pathways regulating axon regeneration in the central nervous system

A growing body of evidence suggests that axonal growth and regenerative capacity in mammals are governed by genomic regulation [55]. The expression of specific pro-regenerative transcription factors in mature neurons can promote axon regeneration and collateral sprouting following CNS injuries [56–58]. Even without therapeutic intervention, some damaged RGC axons can initiate spontaneous regeneration [59]. According to Leibinger's report, this spontaneous regenerative repair is mediated by ciliary neurotrophic factor (CNTF), which activates STAT3 (signal transducer and activator of transcription 3) [60]. Furthermore, activation of the gp130-JAK-STAT3 pathway transmits damage signals to the nucleus, initiating gene transcription and regulating the axonal regeneration response [61,62]. SOCS3 and KLF4, intrinsic inhibitors of this signaling pathway, can suppress the regeneration of damaged RGC axons [63].

The protein phosphatase and tensin homolog (PTEN)—mammalian target of rapamycin (mTOR) pathway (Fig. 4) is another extensively studied signaling cascade involved in neuronal regeneration. PTEN deletion enhances downstream PI3K signaling, counteracting the reduction of mTOR signaling and protein synthesis in damaged neurons, thereby promoting axon regeneration (Fig. 4) [64] When optic nerve compression causes the death of approximately 80 % of RGCs, knocking down PTEN expression in RGCs increases cell survival and promotes retinal axon regeneration [65]. Beyond RGCs, activation of mTOR activity has been shown to promote regeneration of other types of CNS axons. In PTEN-silenced adult mice, damaged corticospinal tract axons can undergo robust regeneration [66].

PTEN is a negative feedback regulator of the phosphatidylinositol 3-kinase (PI3K)–AKT–mTOR signaling pathway. When an extracellular membrane growth factor, hormones, cytokines, etc. ligand binds to a receptor tyrosine kinase, receptor dimerization and activation of PI3K, PI3K phosphorylates PIP2 into PIP3, and then PIP3 activates PDK1, PDK1 activates AKT, finally, the mTOR is activated. After mTOR activation, cell growth, autophagy and proliferation can be regulated.

In addition to the well-established mechanisms of neuronal regeneration discussed earlier, several other signaling pathways have recently gained attention. For example, deletion of Dual leucine zipper kinase (Dlk) significantly enhances the viability of RGCs [67]. Overexpression of the transcription factor Sox11 has been shown to promote long-distance axon regeneration in certain RGC types [68]. Brain-derived neurotrophic factor (BDNF), through its specific receptor, tropomyosin receptor kinase B (TrkB), plays a

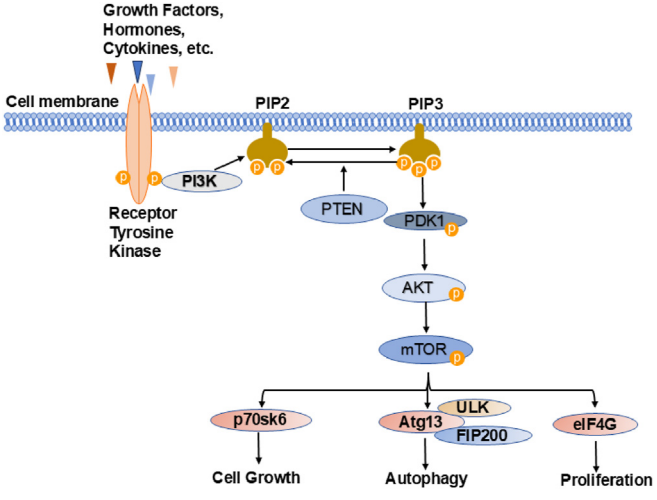


Fig. 4. PTEN-mTOR Mechanism diagram.

pivotal role in neuronal survival, structural remodeling, and plasticity [69]. Additionally, a study by Ju demonstrated that CXC chemokine receptor 2 (CXCR2) is crucial in demyelinating diseases. Inhibition of CXCR2 promotes oligodendrocyte precursor cell differentiation and remyelination through the PDE10A/cAMP/ERK1/2 signaling pathway [70]. Xue's research found that knockout of myosin II A/B enhances optic nerve regeneration. This effect is mediated by Lin28a overexpression, which alters gene expression in RGCs, and when combined with the myosin II A/B knockout, it produces an additive effect that further promotes optic nerve regeneration [71]. Many genes that are active during development and promote axon growth are downregulated in the adult CNS, complicating neuronal regeneration. Investigating the molecular mechanisms behind this downregulation could enable the regulation of relevant gene expression in the mature nervous system, thereby facilitating the repair of damaged neurons.

7. Conclusion

In contrast to the PNS, the mammalian CNS is characterized by several factors that impede axonal regeneration following injury [72]. This review focuses on key regulatory factors and molecular signaling pathways that have recently attracted considerable attention. These factors and pathways collectively influence axonal regeneration and sprouting, playing a critical role in the regeneration of axons and the restoration of functional connections in CNS.

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Declaration of competing interest

There are no conflicts of interest in this study.

All authors have read and approved this version of the article, and due care has been taken to ensure the integrity of the work. Neither the entire paper nor any part of its content has been published or has been accepted elsewhere. It is not being submitted to any other journal.

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