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Mechanisms of neurite repair

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Abstract

Upon receiving injury signals, neurons can activate various pathways to reduce harm, initiate neuroprotection, and repair damaged neurite without cell death. Here, we review recent progresses in the study of neurite repair focusing on neuronal cell-autonomous mechanisms, including new findings on ion channels that serve as key regulators to initiate neurite repair and intrinsic signaling pathways and transcriptional and post-transcriptional factors that facilitate neurite repair. We also touch upon reports on how dendrites may be affected upon axotomy and how the regeneration potential in injured neurites might be maximized.

Introduction

There are many types of injury or insults that can cause damages to neurons such as traumatic brain injury (TBI), spinal cord injury (SCI), neurological diseases, optic nerve injury, stroke, and ischemia [1–4]. How to respond to these insults and repair damages is a lifelong task for maintaining the mature nervous system functions. Depending on the types and the degree of insults, neurons have a variety of strategies to deal with them [2].

The process of neurite repair includes regrowth of neurites, formation of new synapses, and re-association of regenerated neurites with their synaptic partners. Unfortunately, inhibitory environment in the mature nervous system, especially in the central nervous system (CNS), normally restricts growth of differentiated neurons and makes neurite repair difficult [1–5]. Both non-cell autonomous and cell-autonomous factors can contribute to the inhibition of neurite repair. For examples, non-cell autonomous molecules released from neighboring cells such as glia cells prohibit regenerated neurite from innervating the correct targets [1,4,5]. As part of the cell-autonomous regulations, inactivations of developmental growth programs hinder neurite regrowth in mature neurons [1,3,6•,7].

In order to overcome restrictions on neurite repair, neurons need to reverse the inhibitory state to active growth in response to injury. Here, we review recent progress in elucidating mechanisms of neurite repair involving ion channels, signaling pathways, transcriptional and post-transcriptional regulations. The interactions between dendrites and axons within an

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Conflict of interest statement

Nothing declared.

injured neuron and strategies to optimize the outcome in neurite repair are also discussed in the review.

Ion channels

Ion channels are transmembrane proteins that allow ions to pass across the cell membrane. They are important for controlling the excitability of neurons and are involved in many aspects of developmental programs including neurite outgrowth and plasticity [8]. Are ion channels also involved in neurite repair? Recent studies of TRPV1, Piezo, voltage gated calcium channels (VGCCs) and potassium channels reveal the underlying mechanism for how regulation of ion flux could have impact on neurite repair upon insults.

Nociceptive ion channels transduce noxious stimuli and are important for pain sensation. Inhibition of TRPV1, a nociceptive ion channel, was found to reactivate the axon growth in sensory neurons through an increase of intracellular calcium and activation of the PKA pathway in nociceptive neurons [8]. The authors did not observe significant improvements in axon regeneration following sciatic nerve crush. It is conceivable that improvement in axon regeneration by manipulating TRPV1 may be masked by neurons without TRPV1 expression that also send their axons into the sciatic nerve, given that only a small subpopulation of sensory neurons express TRPV1. Interestingly, receptors involved in nociceptive stimulation also play roles in neurite repair. Activation or inhibition of ORL1, a nociception receptor, was reported to reduce or enhance axon regeneration, respectively, through a ROCK-dependent mechanism [9].

Mechanosensitive ion channels transduce mechanical forces and can induce downstream signaling pathways to modulate cellular responses, including neurite outgrowth. Song *et al.* found that mechanosensitive ion channels are involved in neurite repair. They reported that Piezo, a Ca^{2+} permeable mechanosensitive cation channel, inhibits axon regeneration in *Drosophila* sensory neurons as well as mammalian corneal sensory neurons through calcium signaling, nitric oxide (NO) synthase and cGMP-dependent kinase PKG [10•].

The voltage-gated calcium channel (VGCC) subunit Alpha2delta was identified as a negative regulator of axon growth and injury-dependent regeneration in cultured DRG neurons [11]. Systemic administration of Pregabalin (PGB), a gabapentinoid that selectively binds to VGCC Alpha2delta1/2 subunits and blocks calcium influx, could improve axon regeneration of dorsal column axons following SCI *in vivo*; the sooner PGB is applied, the better axons regenerate[11].

Electrical stimulation, which affects electrical signaling in neurons, has been shown to enhance axon regeneration after axon injuries [12–14]. The improvement in axon regeneration by electrical stimulation is likely through upregulation of regeneration-associated gene (RAG) expression in injured neurons [15]. The importance of electrical signaling has recently been reported for dendrite regeneration as well. The blockade in electrical activity by overexpressing the inward rectifier K^+ channel Kir2.1 could inhibit dendrite regeneration following severing of dendrites in *Drosophila* sensory neurons [16]. It

will be interesting to find out whether electrical activity also induces the RAG expression or affects other signaling pathways for dendrite regeneration.

Intrinsic signaling pathways

Intrinsic growth capacity is critical for the success in neurite repair following injury. Various signaling pathways including mammalian target of rapamycin (mTOR) pathway have been reported to promote those neurons that are not readily regenerative to re-enter the active growth state [17–19]. A recent study reported that translation of mTOR could be regulated locally in response to injury signals, which then controls the synthesis of retrograde injury signaling molecules important for intracellular communication between axons and soma [20••]. Exploring how local RNA, including mTOR mRNA, are targeted to the injury sites and identifying the targets of mTOR for local translation can provide us more insights regarding the roles of mTOR in neurite repair [21]. Using acute optic nerve injury to induce dendrite degeneration in mouse retinal ganglion cells (RGCs), Agostinone *et al.* found that activations of mTOR triggered by insulin can promote dendrite regeneration. They further showed that mTOR complex1 and mTOR complex2 are involved in dendrite repairs for dendrite branching and coverage area, respectively [22•]. The injured RGCs partially regain the lost electrophysiological properties with the aid of insulin [22•]. It remains to be determined whether insulin-mediated regeneration and protection can facilitate the recovery at the behavioral level as well. The requirement of mTOR in dendrite repair has also been reported in the adult zebrafish RGCs [23].

Lin28a/b are RNA-binding proteins involve in cell growth and reprograming. With their partners, let-7 microRNAs, Lin28a/b participate in sensory axon regeneration [24]. In the CNS, Lin28 can potentiate insulin-like growth factor-1 (IGF1) responsiveness in injured RGCs, which can lead to robust axon regeneration beyond the effect of Lin28 or IGF1 alone [25]. By restricting Lin28 expression in specific types of neurons in the eye, Zhang *et al.* found that Lin28-dependent IGF1 regulation of RGCs is non-cell autonomous. The IGF1 responsiveness of RGCs is controlled by the Lin28 expression in amacrine cells, which are inhibitory neurons innervating RGCs [25]. Study in *Caenorhabditis elegans*, however, showed that IGF1 is deleterious for the dendrite degeneration in adult PVD polymodal neurons while mutation in daf-2, an IGF receptor ortholog, can prevent declines in the dendrite regeneration during aging [26].

14-3-3 adaptors are hubs for cell signaling that function in neural development and axon guidance. Kaplan *et al.* found that stabilization of the 14-3-3 protein interactions by fusicoccin-A (FC-A) could facilitate axon outgrowth and regeneration [27]. They identified the stress response regulator GCN1 protein as one of the binding partners of 14-3-3 protein and showed that FC-A-induced neurite outgrowth requires turnover of GCN1 [27].

Besides the upstream regulators in the intrinsic growth programs, downstream effectors are also critical for neurite repair, especially those that regulate cytoskeleton dynamics [4,28]. Tedeschi *et al.* demonstrated that direct manipulation of actin depolymerizing factor (ADF)/cofilin can induce axon regeneration which depends on the actin-severing activity [29]. Thrombospondin-1 (Thbs1) and muscle LIM protein (MLP) are found to be RAGs [30,31].

MLP improves axon extension by cross-linking F-actin in filopodia, axonal growth cones [31]. Thbs1 enhanced regeneration is dependent on syndecan-1, a known THBS1-binding protein [30]. Neuronal-specific β-tubulin isoform Tubb3 controls the microtubule dynamic in the growth cones and has a specific role in determining the rate of peripheral axon regeneration and the functional recovery in DRG neurons after sciatic nerve crush [32]. These studies suggest that manipulations of downstream effectors is also a promising way to induce neurite repair.

Transcriptional and post-transcriptional regulations

Manipulations of transcription factors or epigenetic process could help to re-establish the growth capacity in mature neurons by regulating expression of RAGs or developmental neurite growth programs [3,4]. Sox11, a transcription factor, is one of the RAGs and can promote axon regeneration in adult RGCs through reactivating other developmental axon growth programs [33••]. Induction of axon regeneration by Sox11 is cell type specific as overexpression of Sox11 actually kills α-RGCs [33••]. In DRG neurons, Silc1, a long noncoding RNAs (lncRNA), facilitates upregulation of Sox11 upon injury and maintains Sox11 expression levels in the adult brain through cis-acting regulation [34]. Contributions of lncRNAs in regulatory programs of transcriptional responses to injury provide another handle to manipulate the expression of RAGs. Upregulation of Ascl1, also a transcription factor, promotes axon growth in DRG neurons [35].

Epigenetic processes silence gene expression by modifying the chromatin architectures including DNA methylation. Studies of dynamic changes in the chromatin modifications during development and upon physiological stimuli have begun to reveal the potential of epigenetically regulating neurite repair [3,7,36•,37]. A study from Weng *et al.* reported that Ten-eleven translocation methylcytosine dioxygenase-3 (Tet3), a DNA demethylation mediator that can oxidize 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and other derivatives, is responsible for injury-induced DNA demethylation and expression of RAGs upon axotomy of adult DRG neurons [6•]. Tet signaling is also required for inducing axon regeneration in the adult CNS with the specific involvement of Tet1 but not Tet3 [6•]. Roles of PIWI-interacting RNA (piRNA) pathway in neurite repair were recently discovered. piRNA factors, PRDE-1 and PRG-1/PIWI can inhibit the axon regeneration following laser axotomy through post-transcriptionally gene silencing [36•]. It remains an open question whether piRNAs are also involved in regulations of developmental axon growth.

Roles of epitranscriptomic regulations on RNA metabolism and protein translation in the neural development and neurite repair have just begun to be elucidated [38,39•]. N^6-methyladenosine (m^6A) modifications of the transcripts of RAGs and some protein translation machinery components were found to change upon injury in the adult mouse DRG neurons [39•]. Moreover, loss of the epitranscriptomic regulations through m^6A methylations attenuates protein translation of tagged transcripts, which in turn ameliorates axon regeneration [39•].

Beyond repair at the site of injury

Upon injury, besides the site of injury, other parts of the neuron are likely to be influenced too as a result of this intracellular communication. However, how the injured sites affect other parts of neurons or *vice versa* following injuries remains unexplored.

Dung and Hammarlund reported an interesting phenomenon in *C. elegans* DA-9 neuron, where axotomy of DA-9 neurons not only results in reduction in axon length but also induced ectopic synaptic vesicle localization to the dendrite [40••]. Aberrant release of the ectopic synaptic vesicles suppresses the behavioral recovery after axon regeneration [40••]. This study provides evidence that repair of dendritic dysregulation is also important for full functional recovery following axon injury. Dendrite degeneration and retraction accompanying axotomy in RGCs is another example of secondary injury effects and has been used as a model for dendrite degeneration and regeneration [22•]. Using adult zebrafish RGCs as a model, Beckers *et al.* found a counteractive interplay between axons and dendrites involving mTOR and matrix metalloproteinases (MMPs) after optic nerve crush where dendrite degeneration is a prerequisite for efficient axon regrowth [23]. Dendritic microtubule polarity was found to be dynamic following axotomy in *Drosophila* sensory neurons. The speed of conversion of microtubule polarity in dendrite differs depending on the distance between injury sites and soma and the microtubule polarity changes faster following proximal axotomy than after distal axotomy [41].

Communication within neurons is important for integrating the information they received and for determining what to relay onto post-synaptic neurons. While studies usually focus on repairing the part of neurite that was directly injured, it is largely unknown what is happening away from the primary injury site. Future works investigating the secondary injury effects in response to the insults and how these subsequent events could change outcomes of the primary injury or overall functional recovery will help us to uncover the missing pieces necessary to accomplish neurite repair.

Some strategies for improving neurite repair

Various repair mechanisms discovered recently are sufficient to restore at least part of the structure or functional deficiency following injury. Unbiased searches for novel molecules responsible for neurite repair continue to shed light on the mechanisms underlying neuroregeneration [42,43]. Could we maximize the benefit by combining all or several of them at once for treatment hopefully for a synergetic effect?

Anderson *et al.* found that manipulating a combination of three factors, including neuron intrinsic growth capacity, growth-supportive substrate, and chemoattraction, can have the most robust improvements in axon regrowth, and the chemoattraction seemed to be the key for guiding axons to regrow across complete SCI lesions in the adult CNS [44••]. The regenerated axons can form synaptic connections and show recoveries in conduction of electrical signals but not behavioral functions [44••]. Lack of myelination was proposed to be one of the limitations for functional recovery after axon regeneration [45]. It will be interesting to see if introducing the voltage-gated potassium channel blocker 4-

aminopyridine (4-AP) known to further improve conduction in regenerated axons lacking myelination can further boost the improvements in the behavioral functions [45]. The rehabilitation trainings may also help to integrate the rewired circuits into the functional networks [44••,45].

The epigenetic or epitranscriptomic regulations and intrinsic signalings also function together to control neurite repair. Combinations of Tet3 knockdown or Lin28 overexpression with PTEN knockdown showed additive effects in improving axon regeneration [6•,24], while knockdown of methyltransferase like 14 (Mettl14), a component of m^6A methyltransferase complex critical for epitranscriptomic regulation, reduced the PTEN deletion-induced axon regeneration [39•].

It is critical to determine how to combine factors known to improve neurite repair together for the best therapeutic outcomes. It can lead to additive or harmful effects depending on the timing, cell types, and many other factors. The case of Sox11 and PTEN is a good example.PTEN deletion alone enhances axon regeneration selectively in α-RGCs [17,18]. Combining PTEN deletion with Sox11 overexpression could unlock the restriction on PTEN deletion-dependent improvement in axon regeneration and boost the axon regeneration in non α-RGCs [33••]. However, the combination of PTEN deletion and Sox11 overexpression was not able to stop Sox11 from killing the α-RGCs [33••]. These results suggest that distinct neuron types may differ in their intrinsic capacity to regenerate upon injuries and one should be cautious when combining a set of pro-regeneration molecules in different circumstances and cell types.

Closing remarks

Understanding how neurons take on challenges from environments and recover could guide us to develop therapeutic strategies to facilitate neurite repair after injury or diseases (Figure 1). The idea to learn from the early developmental stage where neurons undergo active growth is intriguing and has driven many interesting studies to uncover potential targets as discussed in this review. We should not only focus on restorating the primary injury sites of neurons but consider to rescue both primary and secondary deficits of damaged neuron within the whole circuit. It is also important to bear in mind that the right combinations of factors for enhancing neurite repair may vary depending on the cell types. By taking all these considerations into account, we could potentially overcome difficulties to translate the success in cellular repair to functional recovery in clinical therapeutics.

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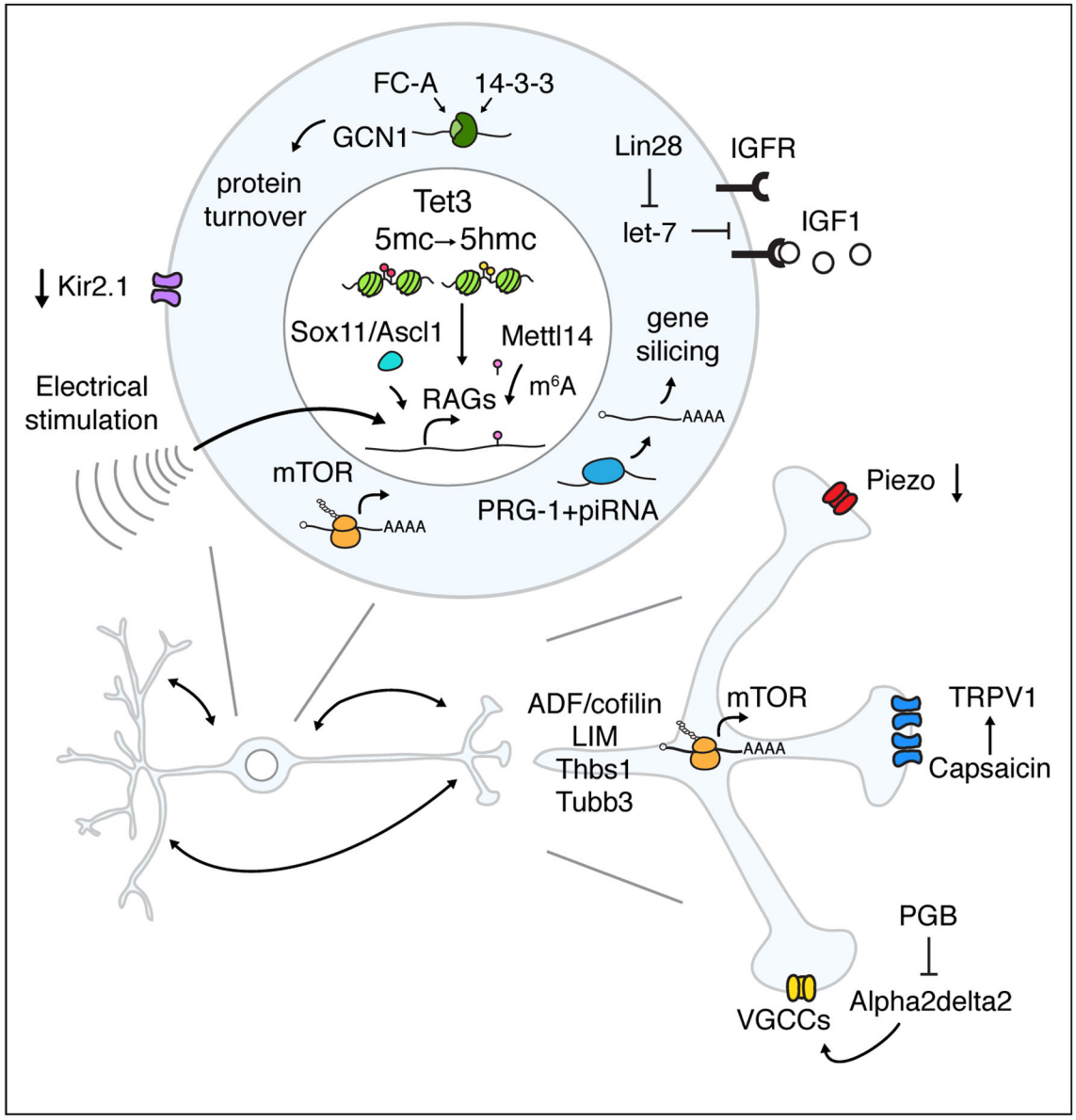

Figure 1.

Summary of cell-autonomous regulations that can improve neurite repair.

Schematic illustration of mechanisms of neurite repair discussed in this review.