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Translational machinery and translation regulation in axon regeneration

Homaira Nawabi*, Stephane Belin*

Over the centuries, the regeneration field has been puzzled by the dual response of the central nervous system (CNS—brain, spinal cord, cranial nerves I and II) and the peripheral nervous system (PNS that refers to all the nerves that innervate muscles, skin, organs, bones among others). Even Ramón y Cajal had noticed that an injury to the PNS often leads to axon regrowth, in contrast to the CNS. This PNS ability is explored during spectacular surgeries where chopped limbs could be grafted back. Some of these patients are even able to recover complex functions such as playing the piano after double hands graft (Grenoble University Hospital, France, 2017). In contrast, CNS axons are not able to regenerate after an insult. This is true in cases of neurodegenerative diseases (Alzheimer's or Parkinson's diseases for example) as well as in traumatic injuries (such as spinal cord injury). These insults lead to neuronal circuit disruption and neuronal apoptosis. As no treatment is available yet, patients endure irreversible loss of motor, cognitive and/or sensory functions that considerably impair their quality of life. Thus, understanding molecular mechanisms underlying axon regeneration and finding new therapeutic strategies are critical for patients, families, and public health.

Promoting neuronal intrinsic capabilities to promote axon regeneration: For many years, lack of CNS regenerative capabilities remained enigmatic. Major investigations focused on the role of extrinsic inhibitory factors. Indeed, the CNS environment is a significant source of axon growth inhibitors with the glia scar, chondroitin sulfate proteoglycan expression, and myelin debris-associated molecules at the lesion site. However, the modulation of these factors did not achieve the expected regeneration outcome, pointing out other key intrinsic growth modulators. Now it has become clear that neurons participate in CNS regenerative failure in addition to extrinsic factors (He and Jin, 2016). Indeed, the activation of specific molecular pathways, within neurons, unlocked to some extent axon growth. The first evidence of CNS ability to regenerate came upon mTOR pathway activation specifically in neurons after the deletion of its inhibitor Phosphatase and TENsin homolog. mTOR is a protein kinase that controls cellular metabolism, catabolism, immune responses, autophagy, survival, proliferation, and migration, to maintain cellular homeostasis. This molecular pathway, mostly through mTORC1, regulates protein translation by the phosphorylation of the ribosomal protein S6 (RPS6)

and the translation factor 4EBP1. Indeed, it has been shown that RPS6 and 4EBP1 phosphorylation mostly activate global protein synthesis. mTOR activation induces axonal regeneration in the optic nerve as well as in different cortico-spinal tracts (He and Jin, 2016). However, alone, mTOR pathway modulation is not able to promote full circuit formation. This major breakthrough highlights that axon regeneration is a multilayer process relying on different levels of regulation and multiple molecular mechanisms, as several other molecules have been validated to promote axon regeneration. Particularly, regulations covering epigenetics and transcription modulations have been widely explored using next-generation sequencing approaches. Thus, mainly transcription factors have been identified to promote axon regeneration from a few micrometers to several millimeters. However, in the mature CNS, distances matter as tissues and organs have bigger sizes compared to the embryonic stage when these circuits are physiologically built. Thus, regenerative axons have to cover longer distances to reach their postsynaptic partners. Therefore, combinatorial strategies have been deployed to achieve long-distance regeneration allowing regenerating axons to reach their distant targets (He and Jin, 2016). Interestingly, all these approaches have in common to activate somehow protein translation, mainly through the mTOR pathway, showing that this process is essential to build new neuronal circuits. Moreover, recent studies deciphering different neuronal responses to injury, strongly suggest that neurons showing high levels of phosphorylated ribosomal protein S6 are more likely to respond to the activation of pro-regenerative programs (Duan et al., 2015). The phosphorylation of this specific ribosomal protein is interpreted as a read out of active translation in cells. In the retina, only retina ganglion cells (RGC) project their axons to form the optic nerve. Over the course of development, RPS6 phosphorylation decreases within RGC. It has been correlated with the loss of regenerative capabilities. Within the mature retina, only alpha-RGC and the intrinsically photosensitive RGC maintain high levels of phospho-RPS6 and these neurons are the ones that are the most resilient to injury and are able to regenerate their axons. Therefore, protein synthesis appears as a fundamental process during regeneration. However, specific protein synthesis and more broadly translation regulation have been poorly explored compared to transcription regulations. In addition, neurons are highly compartmentalized cells with a cell body often located far away from

their axon. Thus, local translation appears as a key mechanism allowing neurons to respond to stimuli such as an injury or guidance factors. This process has been mainly studied through local translation in the PNS (Dalla Costa et al., 2021). It has been shown that axon lesion induces modulation of calcium concentrations that will trigger local translation of pro-regenerative pathways, including local translation of mTOR itself (Dalla Costa et al., 2021). We will not go into further details as local translation during axon regeneration has been covered recently in other reviews (Dalla Costa et al., 2021). Instead, we will explore recent insights on the role of translation during nervous system regeneration.

Protein translation mechanisms: Protein translation represents the last step of gene expression, following the very well-studied transcriptional step. Protein synthesis is a highly ordered mechanism involving several components orchestrating the translation of mRNA into proteins. The ribosome, the main effector of translation, is composed of the complex interaction of 80 ribosomal proteins (RP) and 4 ribosomal RNAs (rRNAs). These proteins and rRNA are distributed into 2 ribosomal subunits: the small 40S and the large 60S in eukaryotes. When assembled, they form the 80S ribosome that actively translates mRNA. Ribosome activity could be modulated by RP post-translation modifications. The first uncovered of such regulation is RPS6 phosphorylation. To date, it remains one of the most studied ribosomal modifications. rRNA could also undergo chemical modifications with pseudo-uridylation and 2'-O-methylations, that contribute to ribosomal activity and the selection of mRNA to be translated. Besides ribosomes, translation factors also participate in the translation process. Three classes of factors have been specified according to their role in each step of the translation. Translation initiation is the process of assembly of ribosomes on the mRNA for scanning the start codon (AUG). It requires at least 13 core initiation complexes (eIF1 to eIF5; for eukaryote Initiation Factor). The next step is translation elongation, which allows the formation of the polypeptidic chain. This step requires at least three complexes: eEF1, eEF2, and eEF3 (for eukaryote Elongation Factor). Finally, the termination step allows the ribosomes to release from the mRNA and start a new translation cycle. This step remains poorly understood compared to the first two and only two factors have been identified so far: eRF1 and eRF3 (for eukaryote Release Factor). Finally, recent data suggest the existence of a ribosome-interactome. Proteins, different from translation factors, can interact with the ribosome and might participate in protein synthesis regulation (Simsek et al., 2017). They are not always required but have been identified in specific translation paradigms. For example, Simsek et al. (2017) showed that PKM is a ribosome-associated protein only found in ribosomes interacting with the endoplasmic reticulum and controls the translation



of mRNA destined to the endoplasmic reticulum. They also found that UFL1 protein is part of the ribo-interactome to induce post-translational modification of the ribosome. Altogether the ribosome and its interacting factors form the translational complex.

The translational complex is usually described as being the same and therefore neutral in the regulation of protein synthesis. Surprisingly, a growing body of evidence shows that it is involved actively in the translation process by modulating its composition (specific protein-ribosome interactions, presence or not of translational factors, modification of ribosomal protein stoichiometry or post-translational modifications) to match cellular specific needs. In developing cells or during the cancer process, for example, cell metabolism is increased, correlating with increased amounts of ribosomes and translation machinery. When cells, especially mature neurons reach their steady state, they need less protein synthesis. Thus, they hold fewer ribosomes.

Control of translation machinery to modulate axon regeneration:

Interestingly, recent data show modulation of translational complex composition, during degeneration/regeneration, impacts protein synthesis quality and axonal growth capabilities.

Besides local translation, modulation of protein synthesis in mature neuron cell body is also implicated in axon regeneration. Dorsal root ganglion (DRG) neurons that project their axons to form the sciatic nerve show great regenerative ability. It has been shown that sciatic nerve injury leads to an increase in RPS6 phosphorylation. However, the exact contribution of RSP6 in regeneration remains elusive. This protein has 5 serine residues (S235, S236, S240, S244, and S247) that could be potentially phosphorylated. Usually, S235/236 and S240/244 are phosphorylated in pairs, while S247 phosphorylation is understudied due to the lack of molecular tools. Decourt and colleagues (Decourt et al., 2023) showed that in DRG neurons, RPS6 phosphorylation is critical for axon regeneration (Figure 1). Indeed, in mice expressing an unphosphorylatable form of RPS (all the Serine residues have been replaced by Alanine residues), sciatic nerve regeneration is impaired. Moreover, this system offers the possibility to assess CNS regeneration as well. It has been shown that a prior injury to the sciatic nerve enhances the regeneration of the central branch of the DRG that forms the dorsal column in the spinal cord. This process is called the preconditioning effect. At the cellular scale, neurons show a drastic phenotype whether they have been isolated from naive or injured animals. In intact conditions, DRG neurons present short and ramified neurites. In contrast, when these neurons are put in culture after sciatic nerve injury, they have long neurites with few ramifications. In cultures from the mice expressing an unphosphorylatable form of RPS, the preconditioning effect is inhibited. As hinted by this experiment, RPS6 phosphorylation inhibition

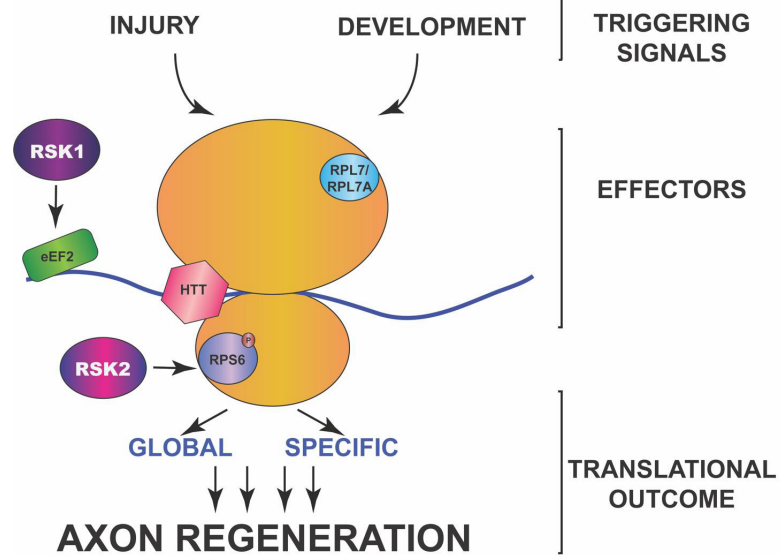


Figure 1 | Implication of translational complex during regeneration.

Schematic summarizing recent advances in understanding translational regulation during axon regeneration. On the left side, there are injury-related modifications, and on the right side, the developmentally regulated changes. Created with Adobe Illustrator. eEF2: Eukaryotic elongation factor 2; HTT: huntingtin; RPL7: ribosomal protein L7; RPS6: ribosomal protein S6; RSK1-2: p90 ribosomal S6 kinase 1-2.

leads to dorsal column regeneration failure (Decourt et al., 2023). These phenotypes could be rescued only when RPS6 phosphorylation is restored on S235/236, suggesting that S240/244 and S247 phosphorylations might not be involved in the regenerative process. Surprisingly RPS6 phosphorylation in this particular context is not dependent on the mTOR pathway but rather on the RSK (p90 ribosomal S6 kinase) family. There are 4 isoforms of RSK (1 to 4) expressed in mammals with high homology. In DRG, RSK2 and 3 show a strong expression while RSK1 is mildly expressed. Upon sciatic nerve injury, RSK3 expression remains stable while RSK2 is strongly upregulated. RSK1 is slightly upregulated in a subset of DRG neurons (Decourt et al., 2023). RSK3 modulation does not impact the regenerative outcome. In contrast, *in vitro* and *in vivo* modulation of RSK2 expression shows that RSK2 is the kinase controlling RPS6 phosphorylation on Ser235/236, therefore regulating axon regeneration both in the CNS and PNS. Regenerating axons are able to reach their final targets in the paw skin conveying sensitive functional recovery. Functional recovery is suggested to involve synaptic plasticity in the spinal cord (Decourt et al., 2023). RPS6 phosphorylation was initially thought to control the translation of 5' TOP mRNA (i.e. mRNA containing 5' Terminal OligoPyrimidine motif in their sequence allowing translation under stress conditions). However, this finding has been invalidated. More recent work suggests that RPS6 phosphorylation is linked with the translation of mRNA according to their Open Reading Frame length (Bohlen et al., 2021). Thus, promoting the translation of short coding DNA sequence mRNA by Phospho-RPS6 could explain the pro-regenerative outcome: indeed, many pro-regenerative targets (such as Rheb or KLF

for example) have short coding DNA sequence. However, it remains to be clearly demonstrated.

In the same line, Mao et al. (2022) showed that RSK1 is also involved in axon regeneration. As described for RSK2, RSK1 is also able to enhance sciatic nerve regeneration and can promote optic nerve regeneration to some extent when combined with mTOR activation. RSK1 is known to control protein translation by modulating the activity of elongation factor eEF2. Thus, the authors show that the expression of eEF2 is able to rescue axon regeneration in the PNS in the context of RSK1 knockdown. In order to understand the precise control of RSK1-eEF2 on translation regulation, they performed parallel transcriptome and translatoome analysis. By comparing the level of transcripts in cells with the level of mRNA associated with the ribosome, the analysis defined which mRNA is specifically regulated by this pathway at the translational level. 2111 mRNAs show positive results for specific translation regulation induced by RSK1. From this list, authors showed that RSK1 promotes the translation of pro-regenerative mRNAs such as IGF or BDNF, supposedly by a mechanism linked to the translational factor eEF2 (Mao et al., 2022). However, the exact mechanisms by which eEF2 controls mRNA translation remain to be determined.

Altogether these results suggest that each member of the RSK family controls a different aspect of protein synthesis. RSK2 regulates directly ribosomal activity through the phosphorylation of a ribosomal protein, while RSK1 modulates translation factors and promotes the translation of pro-regenerative mRNA. It would be interesting to decipher mRNAs that are translated upon RPS6

post translation modifications and to what extent they overlap with the ones regulated by RSK1 (Figure 1).

Axon regeneration could also be induced, to some extent, by modulating directly RP expression. Single-cell profiling of developing and mature RGC shows, as expected, a downregulation of ribosomal protein expression in mature neurons (Xing et al., 2023). Interestingly axon injury triggers the upregulation of these proteins. Indeed, all RPS and RPL show an increased expression (up to half of their developmental expression level) even 2 weeks post injury. However, this upregulation is not sufficient to reinstate developmental stage-associated axonal growth. Thus, authors focused on one ribosomal protein: Ribosomal Protein L7 (RPL7) or its isoform RPL7A. RPL7 has been previously reported to be involved in neurodevelopmental and neurodegenerative diseases. Two weeks after optic nerve injury a modest regeneration has been observed upon RPL7 or RPL7A overexpression in mature retina (Figure 1). However, mechanisms underlying RPL7 induced regeneration remain elusive. Indeed, there is no evidence about changes in the composition of RGC ribosomes after RPL7 overexpression. Thus, the role of RPL7 within the ribosome on translation control and/or a potential extra-ribosomal role of RPL7 cannot be discriminated. Further investigations are required to understand the potential impact of RPL7 on translation regulation.

Protein synthesis could also be regulated by the interaction of specific factors with the translation machinery. The analysis of neuronal response to axon injury (Belin et al., 2015), as well as neural progenitor cell grafting induced regeneration in the lesioned spinal cord (Poplawski et al., 2020) experiments, revealed that the Huntingtin (HTT) protein is an important signaling hub after CNS injury and neuronal plasticity. Recently, it has been shown that the native HTT protein was a major actor in axon regeneration via the regulation of protein synthesis (Schaeffer et al., 2023). Interestingly in WT animals, axon injury induces an HTT decrease at the mRNA and protein levels. In contrast, when axon regeneration is achieved, through mTOR activation in the CNS or the PNS, the HTT level of expression is maintained. These results suggest a correlation between HTT expression and the regenerative outcome. Thus, to evaluate the extent of HTT contribution to regeneration, HTT has been deleted in the context of induced regeneration, upon mTOR activation. HTT deletion completely inhibits axon growth in the optic nerve, without impairing neuronal survival or the phosphorylation of RPS6. Thus, authors analyzed HTT interactome to understand its role in axon regeneration. Surprisingly a major category of HTT interactants appears to be the translation machinery. HTT protein interacts both with the small and large subunits of the ribosome, independently of the presence of mRNA. This interaction does not control global translation

(as shown by puromycin incorporation in MEF cells or RGC upon HTT deletion). Surprisingly, HTT deletion influences which mRNAs are associated with the ribosome (Figure 1). The comparison of the mRNA loaded on the ribosome (the ones that are actively translated) and total mRNA revealed that HTT participates in the selection of 115 mRNAs to be translated. Among the regulated mRNAs, there is the transcription factor Tox2. This family of transcription factors is known to regulate axon growth during development. By multiple approaches, authors demonstrated that when HTT is not associated with the ribosome, Tox2 mRNA is more associated with monosomes in cells. It is suggested that mRNA association to monosomes leads to translation repression. Thus, HTT deletion induces Tox2 mRNA translation inhibition. In addition, overexpression of Tox2 when HTT is deleted restores axon regeneration. As a mirror effect, knocking down Tox2 via ShRNA, decreases axon growth when mTOR is activated. These results suggest that HTT control of mature axon growth is regulated at least in part through a translational regulation of Tox2. Interestingly, when HTT is mutated in the context of Huntington's disease, the protein synthesis is repressed through ribosome stalling on the mRNA (Eshraghi et al., 2021). It appears that native and mutant HTT proteins regulate protein synthesis with different modalities.

To conclude, recent advance in the regeneration field points out the contribution of translational regulation in this process. In addition, this control on protein synthesis is linked to translational machinery modifications to directly participate in the selection of key mRNA to be translated. These data open a new field of investigation to decipher mechanisms of CNS regeneration and repair.

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Additional file: Open peer review report 1.

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P-Reviewer: Song Y; C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y

OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research

Manuscript NO: NRR-D-24-00313

Title: Translational machinery and translation regulation in axon regeneration

Reviewer's Name: Yuanquan Song

Reviewer's country: USA

COMMENTS TO AUTHORS

In this manuscript, the authors provide a deep dive into the mechanism of the translational control of axon regeneration both in the PNS and CNS. More specifically, they focus on the key factors that are recently implicated, including RPS6, RSK1/2, RPL7 and HTT. The content is appropriate for the Perspective, but a number of issues need to be fully addressed.

Major concerns

1. While limited by the format, there are some key citations that should be included. Page 1, Line 16-17 - citations for the mentioned surgeries should be added. Will be helpful to add some key reviews for the CNS inhibitory environment. Add reference to the discussion on modulation of translational complex composition during degeneration/regeneration and its impact on axon growth. Add citations for the preconditioning effect.
2. P1, line 35, the phrasing makes it sound like neurons themselves are the only factor affecting CNS regenerative failure. Please revise.
3. Section 1, need to clarify what effect the phosphorylation actually has on translation.
4. Section 2 "protein translation mechanisms" appears not closely related to the topic in focus, and can be significantly shortened.
5. P2, line 55, what are these different translational paradigms?
6. The "composition" modulation is mentioned 3 times, but it is not clear what the changes are.
7. It is confusing as it is stated that "RPS6 phosphorylation inhibition leads to dorsal column regeneration" on P3 line 32.
8. P3, line 41, in what way is RSK1 modulated?
9. P3, line 48 "The underlying mechanisms are suggested to be the synaptic plasticity in the spinal cord." This sentence does not seem to be well integrated. There may be a gap.
10. P3, line 49, what is 5' TOP mRNA and how is it relevant?
11. P4, line 7, what mechanism links pro-regenerative mRNAs to eEF2?
12. P5, line 2, elaborate on the Tox2 function and monosome.
13. For the Figure, it may be helpful to separate development and injury, so that the injury induced changes in the main players are more evident. It will also be helpful to add the mechanism involving RSK1 and RSK2.
14. The point that native and mutant HTT proteins regulate protein synthesis with different modalities (Figure 1) is not reflected at all in Figure 1.

Minor concerns

The manuscript should be thoroughly checked. There are numerous grammatical and other errors throughout the manuscript. Listed here are just a fraction of them.

1. P1, line 13, add accent mark to Ramón.
2. P1, line 19, change to "Alzheimer's" and "Parkinson's".
3. P1, line 48, change to "relying".
4. P1, line 51 "Particularly, regulations covering epigenetics and transcription modulations has" "have".
5. P2, line 3, check the citation!

6. P2, line 27 "Protein translation represents the last step of genetic expression" "gene expression".
7. P2, line 40 "participate to translation process" "participate in the translational process".
8. P2, line 52 "participate to" "participate in".
9. P2, line 60 "cells metabolism" "cell metabolism".
10. P3, line 2 "hold less ribosomes" "hold fewer ribosomes".
11. P3, line 4 "recent piece of data shows modulation of translational complex composition during degeneration/regeneration process" "recent data show modulation of the translational complex composition during axon degeneration/regeneration".
12. P3, line 23 "sciatic nerve enhance the regeneration" "sciatic nerve enhances the regeneration".
13. P3, line 28 "when these neurons a put in culture after sciatic nerve injury, they present long neurite with few ramifications" "when these neurons are put in culture after sciatic nerve injury, they present long neurites with few ramifications".
14. Miss spelling of "dependant".
15. P3, line 38 "show a strongly expression" "show a strong expression".
16. P3, line 43 "In contrast, in vitro and in vivo modulation of RSK2 expression show that" "In contrast, in vitro and in vivo modulation of RSK2 expression shows that".
17. P3, line 46 "in the paws skin" "in the paw skin".
18. P3, line 49 "was initially thought to control" "thought".
19. P3, line 51 "according their ORF" "according to".
20. Full name for CSPG, TOP, ORF, CDS, RPL.
21. P3, line 59 "RSK1 is also able to sciatic nerve regeneration" "RSK1 is also able to enhance sciatic nerve regeneration".
22. P4, line 4 "level of transcript" "level of transcripts".
23. P4, line 5 "2111 mRNA show" "2111 mRNAs show".
24. P4, line 7 "pro-regenerative mRNA such" "pro-regenerative mRNAs such as".
25. P4, line 14 "to decipher mRNA that are" "to decipher mRNAs that are".
26. P4, line 18 "developing and mature RGC" "developing and mature RGCs".
27. P4, line 56 "influence which mRNA are" "influence which mRNAs are".
28. P4, line 59 "115 mRNA to be translated. Among the regulated mRNA" "115 mRNAs to be translated. Among the regulated mRNAs".
29. P4, line 61 "By multiple approach" "By multiple approaches".
30. P5, line 5, change to "Huntinton's".
31. P5, line 7 "ribosomes stalling on" "ribosome stalling on".
32. P5, line 10 "advance in regeneration field" "advance in the regeneration field".
33. P5, line 14 "open new field of investigation" "open a new field of investigation".