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Review Article

Neurodegeneration and axonal mRNA transportation

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Abstract: The prevalence of neurodegenerative diseases is accelerating in rapidly aging global population. Novel and effective diagnostic and therapeutic methods are required to tackle the global issue of neurodegeneration in the future. A better understanding of the potential molecular mechanism causing neurodegeneration can shed light on dysfunctional processes in diseased neurons, which can pave the way to design and synthesize novel targets for early diagnosis during the asymptomatic phase of the disease. Abnormal protein aggregation is a hallmark of neurodegenerative diseases which can hamper transportation of cargoes into axons. Recent evidence suggests that disruption of local protein synthesis has been observed in neurodegenerative diseases. Because of their highly asymmetric structure, highly polarized neurons require trafficking of cargoes from the cell body to different subcellular regions to meet the extensive demands of cellular physiology. Localization of mRNAs and subsequent local translation to corresponding proteins in axons is a mechanism which allows neurons to rapidly respond to external stimuli as well as establishing neuronal networks by synthesizing proteins on demand. Axonal protein synthesis is required for axon guidance, synapse formation and plasticity, axon maintenance and regeneration in response to injury. Different types of excitatory and inhibitory neurons in the central and peripheral nervous systems have been shown to localize mRNA. Rising evidence suggests that the repertoire of localizing mRNA in axons can change during aging, indicating a connection between axonal mRNA trafficking and aging diseases such as neurodegeneration. Here, I briefly review the latest findings on the importance of mRNA localization and local translation in neurons and the consequences of their disruption in neurodegenerative diseases. In addition, I discuss recent evidence that dysregulation of mRNA localization and local protein translation can contribute to the formation of neurodegenerative diseases such as Alzheimer's disease, Amyotrophic Lateral Sclerosis, and Spinal Muscular Atrophy. In addition, I discuss recent findings on mRNAs localizing to mitochondria in neurodegeneration.

Keywords: Neurodegeneration, Alzheimer's disease, mRNA localization, axon, axonal transportation

Introduction

Neurodegenerative diseases (NDD) are a major public health concern worldwide. As lifespan is increasing and the population is aging, the prevalence of NDD is increasing globally [1]. NDD are a group of neurological diseases and disorders such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD), Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Dementia (FTD), Spinal Muscular Atrophy (SMA), Spinocerebellar Ataxia (SCA), and dementia with Lewy bodies. Patients with NDD demonstrate various symptoms, such as memory loss, motor problems, language and communication impairment, breathing difficulties, eating and swallowing problems, and eventually, in severe cases, death [2-6]. While they can have different clinical manifestations, NDD share some common features such as the progressive course of the disease, aging as a risk factor, and atrophy of the brain tissue in different anatomical regions due to irreversible neuron loss [7]. Currently, no definitive cure exists for NDD. However, various behavioural, psychological, and neurological treatment plans are used to manage symptoms and slow down the progression of the disease. With technological, medical and biological advances over the past few decades, growing evidence suggests that a cohort of genetic, cellular, and functional neuron network dysregulation can result from, and cause neuronal and cognitive impairments observed in NDD. Protein misfolding, oligomerization and aggregation in the neuron are the main factors initiating pathological abnormalities responsible for NDD [8]. For example, aggregation of amyloid-beta (Aβ) is present in AD and tau aggregates in AD and frontotemporal dementia [7]. Alpha-synuclein

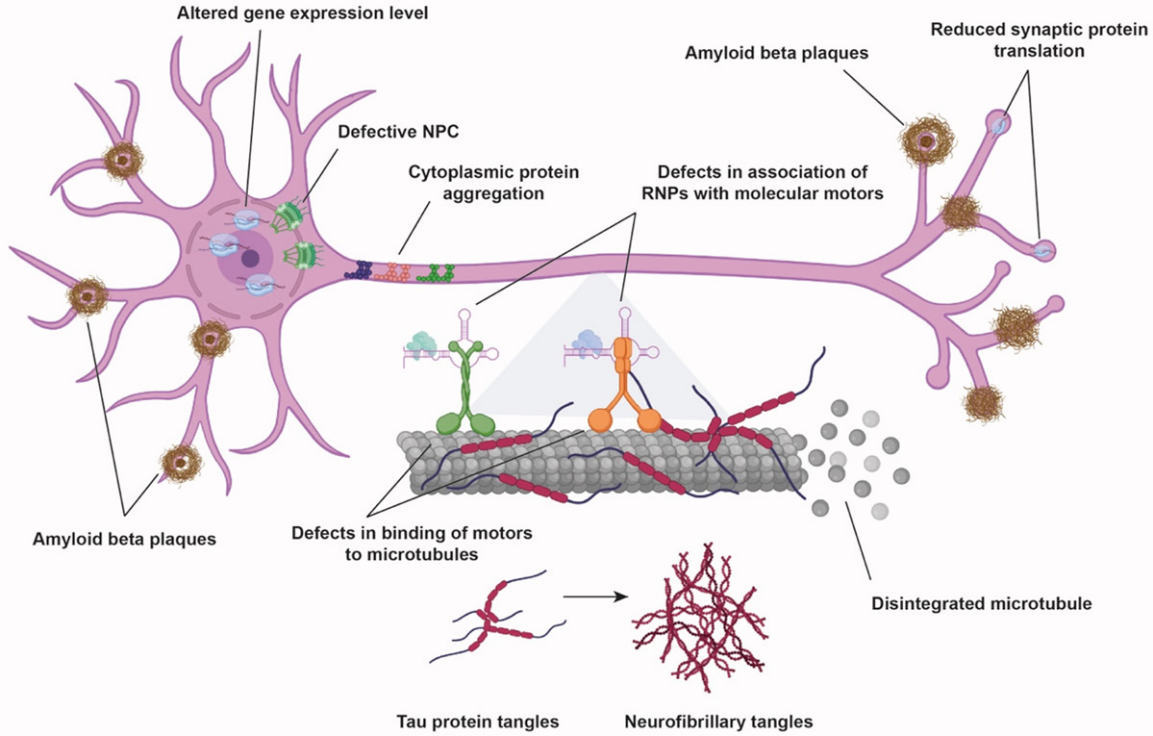

Figure 1. An overview of events during the mRNA lifecycle that can be disrupted in neurodegenerative diseases. Defects in nuclear events, such as altered gene expression level and nuclear export through the nuclear pore complex (NPC) can reduce the availability of localizing mRNAs. Protein aggregation in the cytoplasm can block the assembly of RNPs with adaptor proteins and disruption in subsequent loading of cargo on the molecular motors. Disintegration of microtubules can impede the delivery of RNPs to the axon terminal. Aggregation of amyloid beta particles can also cause a reduction in the synaptic translation of mRNAs.

(α-Syn) aggregates are present in PD and dementia with Lewy bodies patients [8].

NDD involves a progressive and irreversible loss of neurons resulting in the atrophy of various brain regions. As highly polarized cells with extensions reaching up to meters in vertebrates, neurons rely on an intricate mechanism of active transportation for delivery of various cargoes such as proteins, messenger ribonucleic acids (mRNAs), organelle and lipids to axon terminals. While anterograde transport provides axon terminals with a fresh supply of cargoes required for establishment and maintenance of synaptic plasticity, retrograde transport is responsible for degrading and recycling aged proteins and organelles in the cell body to maintain a homeostatic condition [9].

Development and maintenance of a functional nervous system require precise spatial and temporal control of gene expression. Localization of translationally silenced mRNAs in the axons and subsequent protein synthesis *in situ* enable neurons to fulfil their task of transmitting information in the correct spatial and temporal order by devolving protein synthesis machinery to local territories in neuronal extensions [10]. mRNA localization and local translation is an evolutionarily conserved mechanism which is present from yeast to human [11]. While most previous studies concentrated on studying the localization of single mRNA species, recent transcriptomic studies suggest distinct families of mRNAs are compartmentalized in dendrites, axons and cell bodies, many of which contain predicted and actual localization motifs required for their transportation [12-15]. Therefore, mRNA localization coupled to the local synthesis of proteins is more of a rule in neurons than an exception. While many neurodevelopmental and neurodegenerative diseases arise from dysfunctional processes in axonal transport machinery, different aspects of mRNA lifecycle such as transcription, alternative splicing and polyadenylation, nuclear export, axonal localization and synaptic translation can be disrupted in NDD (**Figure 1**). It is worth emphasizing that in this review, I focus on the localization aspect of mRNA lifecycle

Table 1. An overview of localizing mRNAs and proteins involved in neurodegeneration

Disease	Proteins and mRNAs involved	Mechanism of mRNA localization and protein synthesis disruption	Reference
Alzheimer's disease	*Atf4* mRNA *NF-200* mRNA FMRP	Dysregulation of axonal trafficking and retrograde mRNA trafficking after exposure of axons to Aβ peptide. mRNA which localize to axons in healthy neurons where mislocalized to senile plaques in dendrites.	[49, 51, 57]
ALS	TDP-43	TDP-43 forms cytoplasmic mRNP granules for bidirectional axonal transport of cargoes along microtubule in *vitro* and *in vivo.* Mutations in TDP-43 blocks mRNA transport *in vivo* and *in vitro and* in stem cell-derived motor neurons from ALS patients. TDP-43 knockdown reduces transportation of mRNAs encoding ribosomal components.	[65, 71]
SMA	*β-actin* mRNA $Ca_v2.2$ mRNA *GAP43* mRNA	A reduction in the level of mRNA associated with SMN in the axon.	[81, 82, 97]

and other defective events in NDD, such as nuclear and synaptic translation, ribonucleoprotein particles (RNPs) assembly, and degradation are briefly mentioned but not covered extensively here; readers can refer to other reviews for more information [16-19].

The journey of mRNA localization in neurons begins in the nucleus and cell body. Upon transcription of mRNA in the nucleus, transcripts earmarked for transportation are exported from the cell body in granules containing mRNAs bound to protein. These RNPs and trafficked to their final destination in the axon or dendrites via different mechanisms such as diffusion of transcripts followed by entrapment with the help of pre-localized factors or cytoskeleton, degradation of non-localizing mRNAs, and motor-dependent active transportation of mRNAs along the polarized microtubule [10, 20]. Localizing mRNAs contain specific zipcodes *cis* sequences, usually in the form of secondary RNA structures where they are recognized and bound to *trans*-acting RNA binding proteins (RBPs) [20, 21].

RBPs interacting with localization signals play a major role in sorting mRNAs designated for localization by recruiting adaptor molecules, repressing translation and forming mRNA granules for loading on molecular motors. For example, the zip-code binding protein 1 (ZBP-1) is a well-established RBP, which mediates localization and subsequent translation of *β-actin* mRNA to distal regions of axons [22]. RBPs can bind with different affinities to microtubule-associated molecular proteins kinesin and dynein and move along the microtubule tracks towards their destinations [23]. Anterograde and retrograde transport of mRNA is further fine-tuned by the ability of cargoes to bind to both motors simultaneously and move bidirectionally [24].

mRNA translation can occur in response to internal and external stimuli. For example, synaptic firing can induce translation of mRNAs localized in dendrites, and guidance cues can trigger the translation of mRNAs localized in growing axons [20]. In addition to their roles in mediating localization of transcripts, RBPs can have different functions such as processing of pre-mRNAs to mature mRNAs, alternative splicing and polyadenylation, mRNAs stability and degradation [11, 21, 25], making brain tissues sensitive to pathological consequences as the result of impairments in RBPs. Interestingly, multiple RNAs can bind to the same RBP and co-transported synchronously to their destination. For example, multiple mRNAs required for axon survival are transported to the axons of dorsal root ganglion neurons via the action of splicing factor proline-glutamine rich (SPFQ) protein [26].

While many biopsychosocial factors can affect the onset and progress of NDD, age remains as the greatest risk factor [27]. As neurons age, their requirement for protein synthesis alters accordingly [28]. To maintain a homeostatic response, it has been shown that the cohort of localizing mRNAs change in neurons during aging [4, 29, 30]. Developing neurons form synapses; therefore, they localize and synthesise proteins required in axonal guidance, synaptic formation and remodelling, whereas mature neurons need proteins to maintain their synapses and cytoskeleton [20]. Also, it has been shown that the number and expression level of transcripts can change in response to injury [20, 30], indicating the presence of a homeostatic mechanism to regulate mRNA localization and local translation. Recent evidence shows that disruption of mRNA transport and translation can cause pathological symptoms which will be discussed below (**Table 1**).

Alzheimer's disease and mRNA localization

AD is the most common type of dementia worldwide, which is associated with progressive loss of memory and other cognitive and behavioural functions such as speech difficulties, motor system abnormalities as a result of irreversible neuronal loss among elderly. It is estimated that AD affects more than 47 million people worldwide with over $1 trillion annual financial burden [31]. It is also estimated that 10% of above 65 years old population and 40% of above 80 years old individuals have AD [32, 33]. While amyloid-β (Aβ) plaques and hyperphosphorylated tau aggregates are pathological hallmark features of AD patients [34-36], a long asymptomatic preclinical phase exists, which can affect the prognosis of AD patients if remained undiagnosed [36].

Several studies have established a link between mRNA localization and AD. Excessive amyloidogenic processing of the amyloid precursor protein (APP) can result in synaptic degeneration through the production of soluble Aβ peptide [37, 38]. Aβ peptide triggers the synthesis of APP at synapses, via an mRNA translation-dependent mechanism that involving the RBP fragile X mental retardation protein (FMRP) [39]. FMRP interacts with numerous mRNAs in the neuron to regulate translation and trafficking of proteins [40-43]. FMRP interacts with highly conserved cytoplasmic FMRP-interacting proteins 1 and 2 (CYFIP1 and CYFIP2) in both excitatory and inhibitory neurons [44-46]. The expression level of CYFIP2 protein is diminished in post-mortem histological studies of AD brain and in AD mouse models [47], indicating a connection between AD and regulation of mRNA localization and protein synthesis. By interacting with the eukaryotic initiation factor 4E (eIF4E), CYFIP proteins inhibit cap-dependent translation of specific mRNAs [47, 48]. Additionally, exposure of neurons to small amounts of Aβ proteins enhances FMRP-regulated protein synthesis [49].

As β-amyloid pathology plays a central role in AD [50], exposure of neurons to Aβ peptide can trigger the synthesis of proteins such as the transcription factor ATF4 in axons [51]. Additionally, ATF4 protein and transcripts were found at a greater frequency in post-mortem axons in different regions of AD patients' brains, such as the hippocampus, the subiculum, and the entorhinal cortex [51].

On the other hand, post-mortem examinations of AD patients' brain tissue have shown increased concentrations of iron, indicating dysfunction of iron metabolism, such as excessive iron deposition leading to oxidative stress [52-54]. Mitochondria play a significant role in iron metabolism [55]. Expression and localization of mitochondrial ferritin (*Mtf*) mRNA were increased in the cerebral cortex of AD patients [52]. Similar observations were reported after exposure of neurons to *Aβ peptide* [52], indicating alternative routes connecting *Aβ* pathology to mRNA localization and local translation.

The ability of Aβ plaques to localize several mRNAs was investigated previously [56]. It was shown that immature senile plaques containing Aβ peptides were able to localize specific mRNAs, including mRNAs encoding neurofilaments, which were mislocalized to dendrites in human brain temporal lobe cortex [57]. Furthermore, mutations in 3' untranslated region (UTR) of tau showed that its 3'UTR sequence mediates localization of mRNA into axons [58].

ALS and mRNA localization

ALS is a neurodegenerative disease which primarily affects upper and lower motor neurons of the brain and spinal cord, resulting in muscle weakness, paralysis and eventually death within 2-5 years of clinical diagnosis [59, 60]. While the main clinical presentation of ALS is associated with motor neuron dysfunction, some patients can develop cognitive and behavioural impairments [61]. Familial ALS accounts for about 10% of cases worldwide [62]. The exact aetiology of ALS remains unknown; however, some gene mutations have been involved in the pathology of the disease.

Various studies have established a connection between RNA abnormalities, including impairment of axonal mRNA trafficking and ALS. Abnormal localization, as well as mutations of TAR DNA-binding protein (TDP-43) in the cytoplasm, is extensively seen in ALS neurons, frontotemporal lobar degeneration (FTLD), and inclusion body myopathy [63, 64]. TDP-43 is a highly conserved DNA/RNA binding protein which binds to 5' and 3'UTR regions of various transcripts, and it is responsible for major

events such as RNA splicing, stability, as well as localization of different mRNAs *in vivo* and *in vitro* [65-68]. TDP-43 is normally present in the nucleus, but it can shuttle between the nucleus and cytoplasm [69]. In neurons affected in ALS, TDP-43 disappears from the nucleus, and it is deposited in the cytoplasm, which is termed TDP-43 proteinopathy [70]. Cytoplasmic aggregations of TDP-43 causes a gain of toxicity, and its nuclear disappearance results in a loss of function [66]. It has been discovered recently that knock-down of TDP-43 in neurites resulted in a reduction of mRNAs encoding proteins involved in translation, such as ribosomal proteins [71]. By binding to their 5'UTR, TDP-43 mediates transportation of mRNAs encoding ribosomal proteins, which upon translation, form functionally active ribosomes responsible for axonal protein synthesis [71], indicating a global protein reduction in axons with defects in TDP-43.

In addition to its role in transporting transcripts, TDP-43 stabilizes neurofilament light chain (*NFL)* mRNA by interacting with its 3'UTR sequence [72]. ALS patients have an abnormal level of *NFL* β-actin, and similarly, altering *NFL* mRNA levels in mice models caused ALS-like symptoms [73, 74].

Furthermore, recent studies showed that the level of mRNAs encoding ribosomal proteins were diminished in the pyramidal tract of sporadic ALS cases with TDP-43 mutations [71]. Data from RNA sequencing studies showed that loss of TDP-43 altered expression of more than 600 transcripts, many of which were required for synaptogenesis and neurotransmitter release [67], indicating the crucial role of TDP-43 in the activity of neurons.

These findings demonstrate that impairment of RBPs responsible for providing a supply of crucial mRNAs to neurites can result in perturbation of neuronal trafficking and results in neuronal dysfunction.

SMA and mRNA localization

SMA is the most common type of inherited motor neuron disease in children and adolescents due to the homozygous deletion or mutation in the survival motor neuron 1 (SMN1) gene [75, 76]. SMA results in disrupted spontaneous excitation [77], disrupted axonal outgrowth [78], defective neuromuscular junction, and synaptopathy [79, 80]. Since their axons navigate large distances from the spinal cord to the target muscle tissue, motor neurons can be extensively dependent on local protein synthesis. Impairment and subsequent degeneration of motor neurons followed by muscle paralysis is seen in SMA and ALS. Therefore, disruption of axonal transport and mRNA processing has been seen in SMA [81].

In addition to the role of dysfunctional TDP-43 RBP in giving rise to ALS, SMN is another RBP involved in mRNA localization. While knockdown of SMN protein resulted in an axonal downregulation of mRNAs associated with axon formation and synaptic activity, the somatodendritic level of mRNAs involved in splicing was upregulated, indicating an imbalance in mRNA localization [81]. Furthermore, a lack of SMN in primary motoneurons resulted in a reduction of axonal poly(A)-mRNA level in general, which can indicate a common defect in RNA transport [82]. Other studies showed that, more specifically, *GAP43* mRNA level was downregulated and miscolocalized, and this phenotype was restored upon increasing the expression of mRBPs, Hu-antigen D (HuD) and insulin-like growth factor 2 mRNA-binding protein 1 (IMP1) proteins [82].

Therefore, motor neurons rely heavily on local protein synthesis and any dysregulation in the level of mRNA expression, packaging and transportation can severely disrupt the normal physiology of neurons.

Mitochondria mRNA localization and neurodegeneration

Localization of mRNAs in axons and subsequent local translation require energy in the form of ATP derived from mitochondria. Neurons are particularly susceptible to mitochondrial abnormalities. Mitochondria biogenesis occurs in axons and its dysregulation can result in PD [83, 84]. In addition to their roles in providing energy, emerging evidence suggests the loss of local translation of nuclear-encoded mitochondrial mRNA in axons disrupts mitochondria function [85]. For example, a reduction in the axonal level of *ATP5G1* mRNA resulted in a significant reduction of ATP level and an increase in the level of reactive oxygen species (ROS) followed by diminishing axon elongation

rate [86]. Additionally, disruption of *Cytochrome C oxidase IV (COXIV)* mRNA trafficking to the axon of superior cervical ganglion neurons (SCG) resulted in an increase in the ROS levels with subsequent "anxiety-like" behavior in mice models [87], indicating importance of axonal mRNA localization in neuropsychiatric disorders. Interestingly, mitochondrial dysfunction, disrupted ATP and ROS levels and can be related to many psychiatric disorders [88-90].

Therefore, disruption of mitochondria biogenesis as the result of defects in mitochondrial mRNA localization can have severe adverse consequences on the normal physiology of neurons.

Conclusion and outlook

It is well-established that mRNA transportation and translation in axons plays a significant role in maintaining homeostasis during the lifetime of neurons. Most of the mRNA studies in axons have focused on the role of RBPs and local translation in synapses. To fulfil local translation, mRNAs should first be trafficked into the synapse. Mutations and deletion of proteins involved in mRNA localization and local translation can lead to the formation of NDD.

Despite advances in our understanding of local protein synthesis in axons, multiple questions remain unanswered. How do neurons distinguish between axonal and dendritic mRNA transport? For example, SPFQ and FMRP proteins mediate localization of multiple mRNAs into axons and dendrites [40-43], and it remains to be understood how they can distinguish localizing from non-localizing transcripts. I speculate various adaptor proteins should exist to bind specific axonal and dendritic cargos for transportation. This begs the next question: what are RBPs mediating mRNA localization in axons? While some RBPs involved in mRNA trafficking are discovered, further genome wide screenings are required to identify a broader range of RBPs which mediate mRNA transportation into axons.

While accumulating evidence has demonstrated that mRNA localization and RNP remodelling can be regulated by external and internal signalling [91], it remains to be explored whether mRNA trafficking can be fulfilled autonomously in the absence of internal and external cues? Neurons generally do not have the ability to divide. Recent data has shown that autonomous clocks can regulate the biogenesis of organelles in embryos [92]. Extension of such studies to mRNA localization and biogenesis of other organelles in neurons can shed light on autonomous localization of mRNAs as well as neuronal biogenesis, independent of internal and external cues.

Another open question is the regarding the "chicken and egg" problem of neuronal cargo trafficking with regards to the onset of neurodegeneration: which one occurs first? Does disruption of mRNA localization and a reduced protein abundance in axon terminals lead to protein aggregation, or does protein aggregation cause a blockage mRNA localization? Furthermore, can restoring mRNA localization have a potentially therapeutic effect on neurodegeneration?

Many of the localizing mRNAs in axons encode secretory and membrane proteins which require organelles such as endoplasmic reticulum and the Golgi apparatus [18]. While it has been shown that smooth endoplasmic reticulum exists in axons [93], there has not been a piece of conclusive ultrastructure evidence demonstrating the presence of such organelles. This raises the long-lasting question of how membrane and secretory proteins are locally synthesized and modified despite the absence of such organelles? One possibility is that axons do not have canonical ER and Golgi apparatus, instead, they rely on "functional equivalent" organelles to fulfil the job [94]. Future studies are required to address the absence of canonical protein expression and modification machinery in axons. Another organelle which is crucial for the mRNA localization is mitochondria. Neurons require energy to mediate mRNA localization and mitochondria disruption can halt this process. Future studies are required to establish the importance of mRNA localization in rare genetic disorders involved neurons, such as mitochondrial neurogastroinstestinal encephalomyopathy and its connection to NDD [95]. Neurodegenerative diseases are the main challenge of global health in the future [96]. More research is required to address fundamental questions in NDD, which can pave the way for better diagnostic and therapeutic approaches.

Disclosure of conflict of interest

None.

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