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Roles of mRNA Axonal Localization and Translation in Neurodegenerative Diseases

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Abstract

Neurons are highly polarized cells with processes that extend over a meter in humans, thus requiring careful management of the structural and metabolic needs of their network. Indeed, neurons need to tightly regulate the flux of information from the periphery to the center, and transport defects of a variety of peripheral signaling complexes, including endosomes, mitochondria, and mRNP granules, have been shown to result in neuronal degeneration. Axonal local translation has emerged as a way of maintaining axonal homeostasis and achieving signaling compartmentalization in neurons. Though an established hallmark of neuronal development and injury, axonal local translation has also been implicated in neurodegeneration and may be an important regulatory mechanism. Alteration in the local synthesis of key proteins involved in the establishment of neurodegenerative diseases and axonal survival could be central to the dying back phenomenon observed in neurodegenerative disorders, whereby axons degenerate before toxicity is manifested in the corresponding cell bodies. In this book chapter, we will briefly review the history and the mechanisms behind axonal translation and its involvement in neurodegenerative diseases.

7.1 Introduction

Neurons are a highly diverse group of polarized cells with a complex morphology linked to their various functions in the nervous system (Zeng &

Sanes, 2017). Indeed, nerve cells are characterized by long cytoplasmic extensions, axons, and dendrites, with lengths ranging from millimeters to meters in large vertebrates, while still retaining the ability to appropriately and timely respond to both internal and external stimuli. Human motor neurons might be over one meter long, while basal brain cholinergic neurons might reach a combined length of a hundred meters, due to their complex arborization (Wu et al., 2014). Thus, functional compartmentalization coupled with a certain degree of subcellular autonomy is critical for neurons (Jung et al., 2014, 2012; Turner-Bridger et al., 2020; Sahoo et al., 2018).

To overcome the hurdles posed by their extreme morphology, neurons transport, localize, and translate mRNAs within specific subcellular domains at different stages of axonal development, from initial growth to maintenance and regeneration (Glock et al., 2017; Rangaraju et al., 2017). In addition, axonal biology is supported by a constant flow of organelles, such as mitochondria, lysosomes, and endosomes. These organelles require a cohort of proteins for their movement and function, which need to be constantly replenished (Vargas et al., 2022). Thus, the presence of an axonal pool of mRNAs is critical to the support of organelle maintenance and transport, with recent evidence showing a direct linkage of mRNAs to axonal organelles, allowing for fast and localized translation (Vargas et al., 2022). Indeed, the use of "on-demand" stored mRNA for axonal protein synthesis enables spatial and temporal regulation of the protein content of subcellular compartments (Jung et al., 2014), allowing for a rapid response to external and/or internal stimuli.

Several attempts have been made to define the pool of axonal mRNAs and its size has been expanding as a function of the technological progress in the sensitivity of sequencing and the development of new tools for specific labeling and retrieval of RNA, ribosomes, and newly translated proteins (Koppel & Fainzilber, 2018; Holt et al., 2019). While an in-depth discussion about these technologies is outside the scope of this chapter, a comprehensive review of the tools developed to study RNA localization and local synthesis, including fluorescence-based techniques (e.g., FISH and FRAP), modern genomic approaches (e.g., RNAseq), metabolic bio-orthogonal labeling (e.g. Puromycin), and combination of the aforementioned tools (e.g., FUNCAT, Puro-PLA, MERFISH, ExSeq), can be found in (Holt et al., 2019; Taliaferro, 2022). To date, more than 2500 mRNAs, albeit some at low levels, have been shown to localize to neuronal distal compartments (Glock et al., 2017; Vargas et al., 2022). Given the extent of the phenomena, axonal protein synthesis is involved in an increasing amount of physiological and pathological processes (Costa & Willis, 2018; Batista & Hengst, 2016; Spaulding &

Burgess, 2017). In this book chapter, we will briefly address axonal translation and its implications in neuronal pathologies

7.2 Axonal Polyribosomes as a Pre-requisite for Local Translation

Neuronal subcellular compartments need to spatially and temporally control their protein content to respond to local intercellular and extracellular cues. For proteins to be synthesized locally, mRNA needs to be transcribed in the nucleus and transported to the site of synthesis. mRNA transport and localization of the translational machinery are evolutionarily conserved mechanisms critical to the spatial regulation of protein synthesis (Martin & Ephrussi, 2009; Andreassi & Riccio, 2009). Indeed, early electron microscopy (EM) studies in the 1980s identified synapse-associated polyribosomes as well as the post-translational machinery in dendrites of the rat dentate gyrus and hippocampus (Steward & Levy, 1982; Steward & Reeves, 1988). These findings suggested a supportive role for local translation in the maintenance of synapses and their activity, possibly modulating the strength of synapses, a mechanism known to play a role in learning and memory (Steward & Levy, 1982; Steward & Reeves, 1988; Steward & Schuman, 2001). Pulse labeling of de novo proteins with 3H-leucine was performed to prove that the local protein synthesis machinery was active. The use of a compartmentalized culture system in which neurites were allowed to pass through a porous membrane, while the soma remained on either side, revealed extensive dendritic labeling after minutes of exposure to 3H-leucine (Torre & Steward, 1992). A similar study by Sherry Fieg and Peter Lipton in 1993, measured the rate of 3H-leucine incorporation into dendrites in hippocampal slices that had been afferently stimulated using electrical stimulation and exposure to the cholinergic agonist, carbachol (Feig & Lipton, 1993). The presence of the cholinergic agonist coupled with a level of stimulation similar to that of CA1 and CA3 neuronal activity was able to initiate protein synthesis in target dendrites (Feig & Lipton, 1993). Further studies provided evidence for the localization of a specific mRNA subset to synaptic sites in dendrites using RNA fluorescence in situ hybridization (RNA-FISH) (Berry & Brown, 1996; Cox & Racca, 2013; Glock et al., 2017; Steward & Reeves, 1988). For instance, calmodulin I (CaM I) mRNA (Berry & Brown, 1996) and Ca2+/calmodulin-dependent protein kinase type II (CaM-KII) mRNA (Burgin et al., 1990) were found to be localized in the dendrites of cortical neurons in postnatal and developing rat brains respectively.

In contrast to dendrites, axonal mRNA localization, and local translation has been historically subject of debate. As early as 1965, biochemical evidence hinted at the possibility of axonal protein synthesis (Koenig, 1965a, 1965b, 1967a, 1967b). These studies suggested local synthesis of acetylcholinesterase (AChE) in axotomized hypoglossal nerve and the presence of RNA in unmyelinated motor axons of the accessory nerve of adult cats. A series of contrasting observations over the next couple of decades, however, casted doubts on the presence of the translational machinery in axons. For instance, while EM studies from the 1970s provided evidence of ribosomes and smooth endoplasmic reticulum in the growth cone of dorsal root ganglion axons undergoing elongation (Yamada et al., 1971, Bunge 1973, Tennyson 1970, Koenig 1967 a and b), other studies failed to detect polysomes in mature axons of hippocampal neurons (Steward & Levy, 1982). In addition, while mRNA was found in axons of olfactory and hypothalamic neurons, neither ribosomes nor golgi apparatus could be detected in the same system (Mohr & Richter, 1992; Denis-Donini et al., 1998). Critical studies of the 80s and 90s performed in the squid giant axon showed clear evidence of intra-axonal proteins synthesis in invertebrate neurons (Giuditta et al., 1980, 1986, 1991; Sotelo et al., 1999; Crispino et al., 1997). This notion was later expanded to vertebrates, where mature axons of adult neurons were shown to contain mRNA associated with ribosomes and be capable of de novo protein synthesis even during adult life (Twiss & Minnen, 2006; Sotelo-Silveira et al., 2008; Perry & Fainzilber, 2014; Kalinski et al., 2015; Taliaferro et al., 2016; Kun et al., 2007; Bassell et al., 1998). Interestingly, a recent study showed evidence supporting local protein synthesis at axon branches by revealing the presence of microtubules, ER, compact mitochondria, and locally clustered ribosomes using in situ cellular cryo-electron tomography (Nedozralova et al., 2022).

The origin of axonal ribosomes has also been the topic of debate (Sotelo et al., 2014; Twiss & Fainzilber, 2009), with different sets of evidence pointing to a somatic or an extra-neuronal source. As early as 1970, ribosomal transfer from glia was proposed (Lasek et al., 1977; Gainer et al., 1977). Successive studies further documented the presence of glial-derived ribosomes in axons (Court et al., 2008, 2011; Sotelo et al., 2013; Shakhbazau et al., 2016). Recent studies based on genetically tagged ribosomes have shown both the neuronal origin of axonal ribosomes *in vivo* (Shigeoka et al., 2016, 2019, 2018) and in compartmental cultures, where isolated axons are devoid of glia (Perry et al., 2016), and glial origin (Müller et al., 2018). More careful investigation is required to resolve this ongoing debate.

Following technical and experimental improvements in the detection of mRNAs and newly synthetized proteins (Terenzio et al., 2018; Holt et al.,

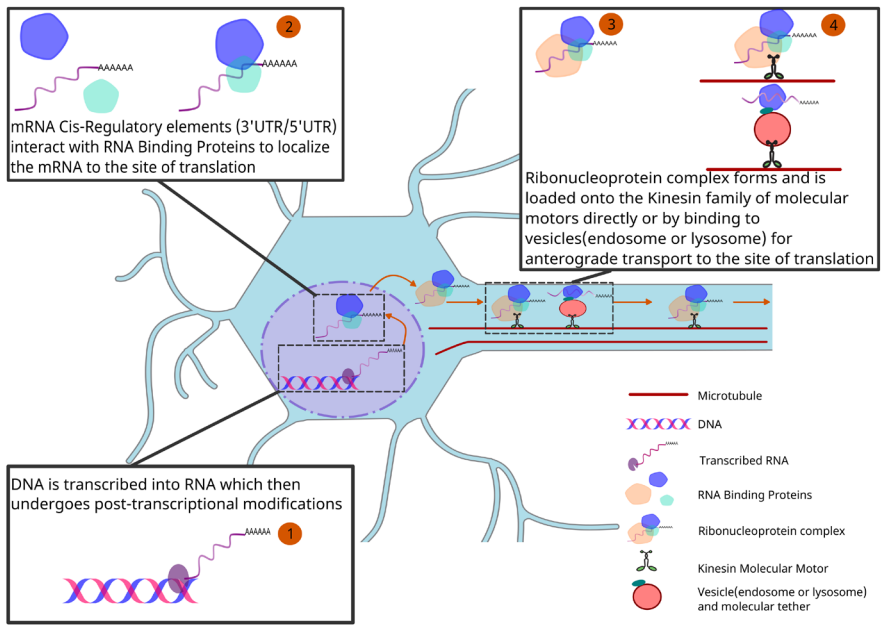

Figure 7.1 mRNA localization and trafficking. Following transcription, RNA undergoes several post-transcriptional modifications after which trans-acting factors, namely RNA binding proteins and miRNAs, interact with the Cis-regulatory elements found in the 3′UTR and/or 5′UTR to regulate mRNA stability, determine its subcellular localization and regulate its translation. mRNA targeted to the axons along with the bound RBPs will then be exported from the nucleus and form a ribonucleoprotein complex (RNP), which is subsequently transported anterogradely by the kinesin family of molecular motors to the site of local translation. Recent evidence has also shown the association of mRNA, mRNA granules and component of the translational machinery with vesicular organelles such as endosomes, lysosomes, and mitochondria.

2019), the repertoire of axonally localized mRNAs has exponentially grown and axonal local translation has been correlated to a variety of critical neuronal functions, which we will explore in the sections below.

7.3 Mechanisms of mRNA Transport and Peripheral Localization

In addition to localizing the translational machinery in axons and dendrites, mRNA needs to be transported to these subcellular compartments (Figure 7.1).

mRNAs carry information in their sequence and structure related to translational regulation, cellular localization, and splicing as well as their

own stability and turnover (Batey, 2006). Indeed, the mRNA 3′-untranslated regions (UTRs) are known to house cis-regulatory elements (CREs), that regulate mRNA stability, cellular localization, and efficiency of translation (Andreassi & Riccio, 2009; Moore, 2005; Moore & Proudfoot, 2009; Gomes et al., 2014) by interacting with one or more trans-acting factors, such as RNA-binding proteins (RBPs) and microRNAs (Martin & Ephrussi, 2009; Andreassi & Riccio, 2009; Sahoo et al., 2018). 5′UTRs have also been implicated in axonal localization of mRNAs such as Neuritin (Merianda et al., 2013). One of the most known dynamics leading to mRNA axonal transport and localization is perhaps the interaction between β-actin mRNA and the zip code binding protein 1 (ZBP1) (Sotelo-Silveira et al., 2008; Zhang et al., 1999) and 2 (ZBP2) (Pan et al., 2009). Interestingly, longer 3′UTRs are overrepresented in axonal transcripts compared to their somatodendritic counterparts, suggesting the presence of specific CREs in axonal mRNAs and the possibility of their involvement in modulating mRNA axonal localization (Tushev et al., 2018).

The interaction between RBPs and axonal localization motifs in either the 5′ or 3′ UTR results in the formation of ribonucleoprotein complexes (RNPs), which are actively transported into the axon by molecular motors (Andreassi & Riccio, 2009; Gomes et al., 2014; Sahoo et al., 2018). A differential sedimentation approach was used to isolate and characterize RNA granule composition (Krichevsky & Kosik, 2001), while in a study published in 2004, researchers isolated RNPs associated with the anterograde molecular motor Kif5 and were able to identify 42 proteins and the mRNA for CaMKIIα and Arc (Kanai et al., 2004). Importantly, these studies were looking at a mixture of RNA granules, thus the identified proteins could belong to different granules. Nucleolin is another known axonal RBP associated with axonally localized mRNAs, including importin β1 mRNA. 3′ UTR deletion of importin β1, small interfering RNA (siRNA) mediated knockdown of Kif5A and Kif5B, and treatment with AS1411, an aptamer that binds nucleolin thereby inhibiting its binding to kinesin molecular motors, reduced the levels of importin β1 mRNA from the axons of sensory neurons (Perry et al., 2016). Several other RBPs have been linked to the regulation of translation and mRNA localization in both dendrites and axons. Mutations in these RBPs or their aggregation and mislocalization have also been implicated in neurodegenerative diseases (Lagier-Tourenne et al., 2010; Sahoo et al., 2018) (Table 7.1.).

Recent evidence has also shown the association of some axonal mRNAs with organelles such as endosomes, multivesicular bodies, lysosomes, and proteins involved in the endoplasmic reticulum (ER)–golgi complex trafficking (Dalla Costa et al., 2021). Indeed, endosomes, lysosomes, and

Table 7.1 Summary of mutations and risk factors associated with neurodegenerative diseases.

Disease(s)	Gene	Protein	Function(s)	Reference(s)
ALS	*SOD1*	Superoxide dismutase [Cu-Zn]	An oxidoreductase that catalyzes the conversion of toxic superoxide species	(Rosen, Siddique et al., 1993)
ALS/FTD	*UBQLN2*	Ubiquilin 2	A shuttle protein involved in the ubiquitin-proteasome system (UPS) and implicated in macroautophagy and the degradation of protein aggregates	(Deng, Chen et al., 2011, Renaud, Picher-Martel et al., 2019)
ALS/ FTD-ALS	*OPTN*	Optineurin	An autophagy adaptor reported to be involved in parkin-mediated mitophagy targeting damaged mitochondria for degradation	(Maruyama, Morino et al., 2010, Wong Yvette and Holzbaur Erika 2014)
ALS/FTD	*SQSTM1*	Sequestosome 1	A ubiquitin-binding protein that plays a role in protein degradation via the proteasome pathway and autophagy	(Fecto, Yan et al., 2011)
ALS/FTD, HD	*VCP*	Transitional endoplasmic reticulum ATPase (also known as valosin-containing protein or p97)	Involved in UPS-mediated protein degradation	(Johnson, Mandrioli et al., 2010)
ALS/FTD	*TBK1*	TANK-binding kinase 1 (Serine/ threonine-protein kinase TBK1)	A Serine/threonine-protein kinase involved in the degradation of ubiquitinated cargo by the autophagosome	(Freischmidt, Wieland et al., 2015)
ALS	*DCTN1*	Dynactin-1	Part of the dynein-dynactin molecular motor complex	(Puls, Jonnakuty et al., 2003)

(continued)

Table 7.1 *Continued.*

Disease(s)	Gene	Protein	Function(s)	Reference(s)
ALS	*TUBA4A*	Tubulin α-4A chain	A microtubule subunit	(Smith, Ticozzi et al., 2014)
ALS	*PFN1*	Profilin 1	Binds to monomeric G-actin and regulates the growth of filamentous F-actin	(Wu, Fallini et al., 2012)
ALS/FTD	*TARDPB*	TAR DNA binding protein 43	RNA and DNA binding protein involves in multiple RNA processes including splicing, trafficking, stability, and translation	(Sreedharan, Blair Ian et al., 2008, Kapeli, Martinez et al., 2017)
ALS	*FUS/TLS*	Fused in Sarcoma/Translocated in Liposarcoma	Associated with several RNA processing events including splicing, trafficking, and transcription	(Kwiatkowski, Bosco et al., 2009, Vance, Rogelj et al., 2009, Kapeli, Martinez et al., 2017)
ALS/FTD	*C9orf72*	Human chromosome 9 open reading frame 72	Linked to RNA processes and autophagy	(Farg, Sundaramoorthy et al., 2014, Kapeli, Martinez et al., 2017, Shi, Lin et al., 2018)
ALS	*hnRNP A1*	heterogeneous nuclear ribonucleoproteins A1	RNA processing and stability including splicing and nuclear export	(Kapeli, Martinez et al., 2017)
ALS	*hnRNPA2/B1*	heterogeneous nuclear ribonucleoproteins A2/B1	RNA splicing, trafficking, and translational regulation	(Kapeli, Martinez et al., 2017)
ALS	*EWSR1*	EWS RNA-binding protein 1	Essential to various cellular processes including meiosis, mitosis, and homologous recombination during the DNA damage response. It has been also found to interact with RNA and RNA-binding proteins such as FUS and TAF15	(Kapeli, Martinez et al., 2017)

ALS	*ANG*	Angiogenin	A ribonuclease and an inducer of angiogenesis	(Taylor, Brown et al., 2016)
ALS/FTD	*MATR3*	Matrin	A nuclear matrix RNA and DNA binding protein that has been found to interact with TDP-43	(Taylor, Brown et al., 2016)
ALS/ FTD-ALS	*ATXN2*	Ataxin-2	RNA-binding protein with multiple roles in RNA metabolism	(Renton, Chiò et al., 2014, Taylor, Brown et al., 2016)
ALS	*TAF15*	TATA-box binding protein associated factor 15	An RNA-binding protein that plays a role in transcription and RNA splicing	(Kapeli, Martinez et al., 2017)
PD	*SNCA*	α-synuclein	Involved in the regulation of neurotransmitter release and synaptic vesicle trafficking	(Stefanis 2012)
PD	*LRRK2*	Leucine-rich repeat kinase 2	A multidomain protein kinase	(Imai, Gehrke et al., 2008)
PD	*PINK1/ PARK6*	Pten-induced kinase 1	A mitochondrial serine/threonine-protein kinase associated with the local translation of nuclear-encoded respiratory chain complexes (nRCC) mRNAs	(Singleton, Farrer et al., 2013, Gehrke, Wu et al., 2015)
PD	*PARK2*	Parkin	An E3 ubiquitin ligase involved in mitochondrial homeostasis, protein degradation, and implicated in the local translation of nuclear-encoded respiratory chain complexes (nRCC) mRNAs along with PINK1	(Singleton, Farrer et al., 2013, Gehrke, Wu et al., 2015)

(continued)

Table 7.1 *Continued.*

Disease(s)	Gene	Protein	Function(s)	Reference(s)
AD	*APP*	Amyloid precursor protein	A transmembrane protein involved in synaptic plasticity and synaptogenesis. It is a precursor of Aβ as a result of cleavage by β- and γ-secretases	(Thinakaran and Koo 2008, Gamarra, de la Cruz et al., 2021, Knopman, Amieva et al., 2021)
AD	*PSEN1*	Presenilin 1	Involved in γ-secretase activity responsible for proteolytic cleavage of APP	(Knopman, Amieva et al., 2021)
AD	*PSEN2*	Presenilin 2	Involved in γ-secretase activity responsible for proteolytic cleavage of APP	(Knopman, Amieva et al., 2021)
AD	*APOE ε4*	Apolipoprotein E	Involved in lipid metabolism	(Knopman, Amieva et al., 2021)
AD	*TREM2*	Triggering Receptor Expressed on Myeloid Cells 2	Microglial transmembrane receptor protein	(Bellenguez, Charbonnier et al., 2017, Knopman, Amieva et al., 2021)
AD	*SORL1*	Sortilin-Related Receptor 1	Receptors involved in the endosomal sorting of proteins	(Rogaeva, Meng et al., 2007, Bellenguez, Charbonnier et al., 2017, Knopman, Amieva et al., 2021)
AD	*ABCA7*	ATP-Binding Cassette Subfamily A Member 7	Involved in lipid metabolism and phagocytosis of apoptotic cells	(Bellenguez, Charbonnier et al., 2017, Knopman, Amieva et al., 2021)
AD	*BIN1*	Bridging Integrator 1	An adaptor protein that functions in clathrin-mediated endocytosis and endocytic recycling and has been shown to interact with Tau	(Knopman, Amieva et al., 2021)

AD	*CD2AP*	CD2 Associated Protein	An adaptor protein involved in regulating signal transduction and cytoskeletal molecules	(Knopman, Amieva et al., 2021)
AD	*FERMT2*	Kindlin-2	A protein that localizes to focal adhesions and is associated with integrin activation	(Eysert, Coulon et al., 2021, Knopman, Amieva et al., 2021)
AD	*CASS4*	Cas scaffold protein family member 4	A scaffolding protein involved in tyrosine-kinase signaling and associated with focal adhesions	(Knopman, Amieva et al., 2021)
AD	*PTK2B*	Protein tyrosine-kinase 2 beta	A Ca^{2+}-activated non-receptor tyrosine kinase	(Knopman, Amieva et al., 2021)
HD	*HTT*	Huntingtin	Proposed to have a flexible structure that alters its activity. It contains HEAT (Huntingtin, Elongator factor3, PR65/A regulatory subunit of PP2A, and Tor1) repeats which are through to mediate protein-protein interactions possible through scaffolding and is involved in mRNA transport	(Gauthier, Charrin et al., 2004, Schulte and Littleton 2011)
SMA	*SMN1*	Survival motor neuron protein	Associated with the assembly of the pre-mRNA splicing complex and plays a role in mRNA localization and regulation of RNP granules	(Fallini, Donlin-Asp et al., 2016, Khalil, Morderer et al., 2018)
FXS	*FMR1*	Fragile X mental retardation protein (FMRP)	An RNA-binding protein that is essential for local translation and synaptic plasticity	(Akins, Berk-Rauch et al., 2017)

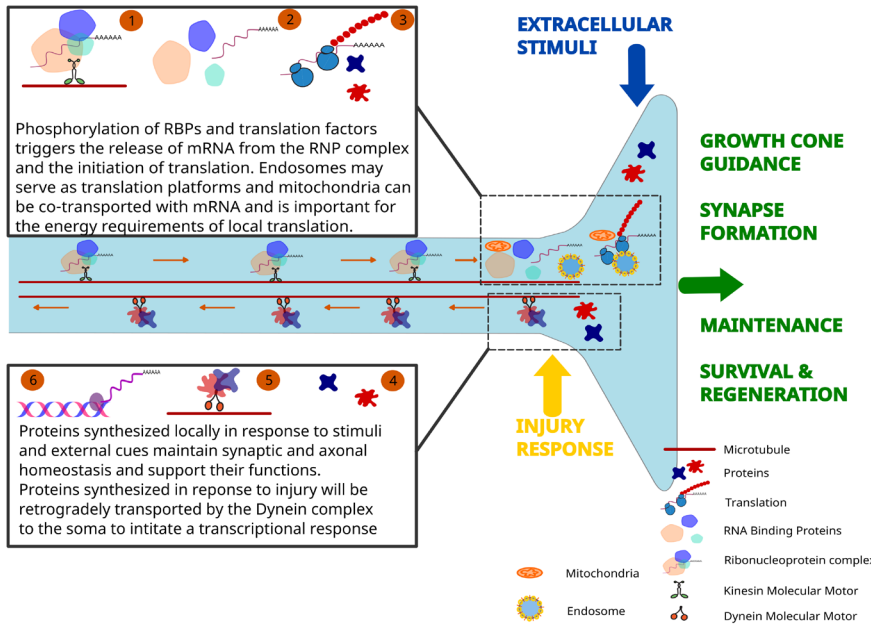

Figure 7.2 Local translation and the role of locally synthesized proteins. Upon reaching the site of local translation, RBPs will undergo modifications, such as phosphorylation, triggered by external or internal stimuli, which will then determine the release of the mRNA, the assembly of the translation complex and the initiation of translation by the phosphorylation of translation initiation factors. Locally translated proteins perform important functions in axonal maintenance, synaptogenesis, growth cone guidance and neuronal survival. In addition, local translation can be triggered by injury, upon which locally translated proteins are then retrogradely transported by the dynein-dynactin molecular motor complex to the soma, where a transcriptional cellular response is initiated.

mitochondria were shown to mediate axonal RNA transport and/or translational regulation. RNA granules were found to tether to lysosomes through Annexin 11 (ANXA11), with mutations in ANXA11 impairing their transport by disrupting their interactions with lysosomes (Liao et al., 2019). Late endosomes were also described to interact with RNA granules, translation machinery, and mitochondria (Cioni et al., 2019). Recently, the involvement of mitochondria in the axonal localization and transport of the RNAi machinery has also been described (Gershoni-Emek et al., 2018). Pink1 mRNA was shown to be co-transported with mitochondria via an RNA-binding domain in synaptojanin 2 (SYNJ2) and synaptojanin 2 binding protein (SYNJ2BP) (Harbauer, Hees et al., 2022) (Figure 7.2).

7.4 Regulation of Axonal Local Translation

Regulation of localized mRNA translation, including extracellular and chemical triggers, ribosomal heterogeneity, RBP/mRNA interaction, RNA post-transcriptional modifications, mitochondrial contribution, and non-coding RNAs, adds another layer of complexity to mRNA spatiotemporal dynamics. The coupling of receptors to ribosomes has been proposed to link extrinsic signals to the local intracellular translation machinery (Koppers et al., 2022). Receptor-ribosome coupling seems to be common to several receptors, including the Deleted in Colorectal Carcinoma (DCC) transmembrane receptor that interacts with translation components and is regulated by the extracellular cue Netrin-1 (Tcherkezian et al., 2010). Several receptors were also found to associate with distinct pools of RBPs and mRNAs (Koppers et al., 2022), which could help fine-tune the regulation of local protein synthesis in response to extracellular cues. Specific extracellular stimuli can also directly modify local mRNA levels independently of new transcription (Willis et al., 2005, 2007). Differential localization of mRNAs to specific locations in axons is yet another way to regulate the identity of the proteins synthetized locally. Furthermore, specific cues can lead to protein synthesis of subsets of mRNAs by the activation of kinases, which triggers site-specific phosphorylation of RBPs and translation factors, resulting in the local release of associated mRNAs, which are then available for translation (Hörnberg & Holt, 2013; Jung et al., 2012). Netrin-1, for instance, induces hyperphosphorylation of growth factor receptor-bound protein 7 (Grb7), decreasing its RNA-binding and translation repressive activity, and resulting in increased translation of KOR mRNA (Tsai et al., 2007). Further, BDNF signaling was shown to lead to Src-mediated phosphorylation of ZBP1, which in turn initiates axonal translation of β-actin (Sasaki et al., 2010). The mechanistic target of rapamycin (mTOR) is a kinase involved in a plethora of cellular mechanisms including axonal local translation (Laplante & Sabatini, 2012; Hörnberg & Holt, 2013). Indeed, activation of the mTOR pathway by extracellular signals can increase cap-dependent translation initiation of axonal mRNAs through the phosphorylation of eIF4E binding proteins, which leads to their dissociation from eIF4E (Sonenberg & Hinnebusch, 2009). For instance, NGF can activate mTOR, resulting in local protein synthesis of TC10 and Par3, which are involved in membrane expansion and cytoskeletal dynamics, thus triggering dorsal root ganglion (DRG) axonal outgrowth (Hengst et al., 2009; Gracias et al., 2014). Another level of spatiotemporal regulation of mTOR activity was shown to be the localization of its own mRNA, which is transported in axons by the RBP nucleolin (Terenzio et al., 2018).

Following sciatic nerve injury, resident mTOR protein was shown to amplify its signaling by triggering local protein synthesis of its own mRNA, leading to the translation of critical retrograde injury signals such as importin-β1 and STAT3 (Terenzio et al., 2018). Deletion of mTOR 3′UTR, which contains its axonal localization motif, negatively impacted axonal translation after injury, resulting in decreased survival of injured DRG neurons (Terenzio et al., 2018). In addition, axonal mTOR is required for the sequential axonal translation of several mRNAs in response to nerve injury, including axonal Casein Kinase 2α (CK2α) (Sahoo et al., 2020), and mTOR mRNA miss-localization negatively impacted the speed of axonal regeneration (Sahoo et al., 2020).

Another important mechanism of translational regulation hinges on mRNA post-transcriptional modifications. Indeed, it was shown that n6-methyladenosine (m6A) mRNA modification participates in axonal translation (Yu et al., 2018, 2021). Whether or not additional post-transcriptional modifications of mRNAs can modulate local translation is yet to be found.

Different RBPs can compete for the same mRNA, resulting in fine regulation of its local translation. For instance, HuD and KHSRP share the same target mRNAs, including GAP43 mRNA, and either stabilize or destabilize it (Yoo et al., 2013; Gardiner et al., 2015; Smith et al., 2004; Bird et al., 2013; Anderson et al., 2000). Multiple mRNAs can also compete for the binding to the same RBP. Indeed, β-actin and GAP43 mRNAs were shown to compete for ZBP1 (Donnelly et al., 2011).

Ribosomes are another key component of the translational machinery that might be subjected to regulation. Indeed, localization and translation of mRNA coding for ribosomal proteins were shown in dendrites and axons (Zivraj et al., 2010; Cajigas et al., 2012; Shigeoka et al., 2016; Hodas et al., 2012). Inhibition of axonal translation of ribosomal proteins also decreased local translation activity and negatively impacted axon branching *in vivo* (Shigeoka et al., 2019). Finally, the observation of variability in the half-life of neuronal ribosomes (Dörrbaum et al., 2022) compared to canonical stable "lifelong" assembly of nuclear ribosomes could suggest that, in specialized neuronal ribosomes, ribosomal proteins may be exchanged to repair or replace components in these complexes (Pulk et al., 2010; Xue & Barna, 2012; Jung et al., 2014; Fusco et al., 2021), possibly constituting a further level for regulation of spatiotemporal protein synthesis in axons.

Axonal non-coding RNAs, including microRNAs (miRNAs), were also found to inhibit or activate translation and/or promote mRNA degradation. As mentioned above, axonal mRNAs are generally defined by longer 3′UTRs, which contain miRNA binding sites (Bae & Miura, 2020). Indeed,

miRNAs are localized to DRG and mature peripheral axons, together with a functional miRNA silencing machinery (Hengst et al., 2006; Murashov et al., 2007). There is also evidence of modulation of gene expression by the microRNA-mediated silencing machinery in neurons (Kosik, 2006). For instance, miR-21 and miR-199a-3p modulation of expression post-injury can regulate the axonal regeneration associated with the mTOR pathway (Kar et al., 2021), while miR-338, a brain-specific miRNA, indirectly regulates mitochondrial activity through the modulation of nuclear-encoded mitochondrial transcripts COXIV and ATP5G1, and consequently affects axon growth (Aschrafi et al., 2008, 2012). More recently, a long intergenic non-coding RNA (lincRNA) called ALAE was found enriched in axons, leading to the local translation of the GAP43 transcript (Wei et al., 2021).

Finally, mitochondria have been shown to participate in driving translation in dendrites (Rangaraju et al., 2019), while synthesis of the mitochondrial proteins ATP5G1 and COXIV was found to be regulated locally (Aschrafi et al., 2008, 2012). Mitochondria are known to be recruited not only to dendrites but also to axon branching sites to provide energy supply for local protein synthesis (Spillane et al., 2013). Interestingly, local translation of the short-lived PINK1 protein in axon has been recently described to provide distal mitochondria with the required supply of PINK1 for the activation of mitophagy (Harbauer et al., 2022), suggesting a possible role for translation in mitochondrial homeostasis.

7.5 Functions of Axonally Synthetized Proteins

Excluding their role in pathology, axonally synthesized proteins have been implicated in a variety of critical biological axonal functions, including axon growth, guidance, branching, and maintenance, synapse formation and regulation, retrograde signaling, and neuronal survival and regeneration (Figure 7.2). Here we will briefly explore some of these roles.

Growth and guidance of axons are sensed by the growth cone and mediated by extracellular stimuli. Interestingly, attractant cues have been shown to increase axonal β-actin mRNA levels in growing axons (Bassell et al., 1998; Zhang et al., 1999), and activate local translation (Campbell & Holt, 2001; Pratt et al., 2012). Moreover, external attractant or repellant stimuli can modify the localization of mRNA and translational machinery within a growth cone (Leung et al., 2006; Yao et al., 2006; Piper et al., 2006; Walker et al., 2012; Wu et al., 2005). Once axons navigate to their targets, they extend branches harboring synapses (Kalil & Dent, 2014). The enrichment of the translational machinery and mitochondria at incipient branch points was

shown to result in local translation, inducing axon branching (Spillane et al., 2013; Spillane et al., 2012). Indeed, axonal β-actin mRNA and its translation drive axonal branching (Donnelly et al., 2013), while β-actin mRNA and subsequent protein localization to axonal branches were shown to predict longer-lived branching events in developing axons (Wong et al., 2017). These results suggest an essential role for local protein synthesis in axonal development.

Local translation was initially believed to be a minor contribution to synaptic protein production, activated in particular circumstances during synaptic plasticity (Kosik, 2016). The discovery of a large number of mRNAs in neurites, however, challenged this assumption (Zappulo et al., 2017; Taliaferro et al., 2016). Polyribosomes were also shown to be at the site of synapses in response to synaptic activity (Ostroff et al., 2017, 2018). Formation of the presynaptic terminal was found to require the recruitment of the SNAP25 transcript and its local translation (Batista et al., 2017). mRNAs coding for proteins involved in both presynaptic and postsynaptic zones were also shown to be present at synapses, suggesting a role for local protein production in the development, maintenance, and modulation of this structure (Shigeoka et al., 2016; Hafner et al., 2019).

Local axonal protein synthesis has also been heavily implicated in neuronal homeostasis and survival. Dynein regulators, such as Lis1 and p150glued, were shown to be axonally translated in response to survival signals, mediating the transport of vesicles presumed to contribute to axonal survival (Villarin et al., 2016). Furthermore, pro-survival transcription factors are also translated locally and delivered to the soma, resulting in retrograde signaling triggering the activation of an anti-apoptotic transcriptional response in neurons (Harrington & Ginty, 2013; Cox et al., 2008). Local synthesis of mitochondrial-related proteins might also be critical for axon viability and maintenance, given the role of axonal mitochondrial activity in regulating metabolism and energy production and the activation of apoptotic pathways (Hillefors et al., 2007). Indeed, nuclear-encoded mitochondrial mRNAs are enriched and translated in axons (Zivraj et al., 2010; Gumy et al., 2011; Shigeoka et al., 2016; Aschrafi et al., 2016).

7.6 Axonal Local Translation in Nerve Injury and Regeneration

Nerve injury triggers a catastrophic chain of molecular events in damaged axons, which leads to Wallerian degeneration and ultimately can cause loss of the neuronal cell body in absence of a robust regenerative response (Li

et al., 2013; Hetz & Saxena, 2017). After an injury, neurons must be able to convert a mature damaged axon into a new growth cone that allows for its regeneration (Sahly et al., 2006; Chierzi et al., 2005; Verma et al., 2005). An interesting feature of the nervous system is the existence of a differential capacity for responses to injury in the central nervous system (CNS) as compared to the peripheral nervous system (PNS). Regeneration and functional recovery are typically much more successful in the PNS than in the CNS (Verma & Fawcett, 2005). Since regeneration after axotomy heavily depends on the capacity to locally synthetize new proteins in injured axons, providing both the components for axonal regrowth as well as cytoskeletal elements and retrograde signals that activate the regenerative response (Ben-Yaakov et al., 2012; Cox et al., 2008; Donnelly et al., 2011; Hanz et al., 2003; Michaelevski et al., 2010; Verma et al., 2005; Willis et al., 2007; Yudin et al., 2008; Perlson et al., 2005), axonal injury in the PNS has historically been used as a model to dissect the mechanisms underpinning axonal translation and its effect on neuronal survival and regeneration.

Initial studies described the presence of over 200 mRNAs in adult sensory axons of injury-conditioned DRG (Willis et al., 2007), where mRNAs related to the ribosomal/translational machinery and mitochondrial/oxidative phosphorylation were highly represented (Gumy et al., 2010). Subsequent studies reported the presence of ribosomal proteins, translation promoters, and ribosomal RNA in axons of adult sensory neurons after injury (Gumy et al., 2011; Minis et al., 2014). An early wave of Ca^{2+} from the site of injury can trigger the translation of a variety of axonal mRNAs, including Importin-β1 and STAT3, which then form an injury signaling complex that is retrogradely transported to the soma (Hanz et al., 2003; Perry et al., 2012; Ben-Yaakov et al., 2012; Rishal & Fainzilber, 2014). The Dual Leucine-zipper 1 (DLK1) is involved in retrograde injury-response signaling by phosphorylating the Mitogen-activated Protein Kinases (MAPK) (Tedeschi & Bradke, 2013; Mahar & Cavalli, 2018) and was shown to promote mRNA stability and local translation after axon injury (Yan et al., 2009). Kinases such as ERK1/2, members of the MAPK family, are also phosphorylated upon injury, bound to a locally translated proteolytic fragment of Vimentin, and retrogradely transported (Perlson et al., 2005). mTOR, a serine-threonine-protein kinase, has also been shown to be translated and phosphorylated in axons after nerve injury (Terenzio et al., 2018). Finally another major player involved in axonal regeneration are mitochondria, which normally accumulate at the site of injury, while their absence was shown to harm the regenerative capacity of injured axons, suggesting that mitochondria might provide the energy for local translation after injury (Han et al., 2016). All results taken together,

it has become clear in recent years that axonal protein synthesis is crucial for retrograde injury signaling and axonal regeneration in sensory neurons (Rishal & Fainzilber, 2014; Terenzio et al., 2017; Sahoo , 2018; Koley et al, 2019).

7.7 Axonal mRNA Localization and Translation in Neurodegenerative Diseases

Due to lifespan increase and consequent population aging, neurodegenerative diseases are becoming a major public health concern worldwide (Heemels, 2016). Patients affected by neurodegenerative pathologies display an array of different clinical manifestations but share common features such as the progressive course of the disease and irreversible neuronal loss in different anatomical regions of the brain (Soto & Pritzkow, 2018). Current clinical approaches for these diseases are aimed at managing symptoms, which can help to slow down the progression of neurodegeneration but do not necessarily treat the cause of the disease. One of the hallmarks of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD), is an aggregation of abnormal (misfolded/insoluble) proteins in neurons (Davis et al., 2018). Genes encoding for RBPs are also often affected, like in spinal muscular atrophy (SMA) or fragile X syndrome (FXS), and a cohort of published results suggest that impaired axonal transport, localization, and translation in axon might be involved in neurodegenerative diseases. We will explore these studies in the following sections, focusing on the contribution of mRNA localization and translation to the pathophysiology of these neurodegenerative diseases. Understanding the mechanisms of neurodegeneration and the involvement of mRNA axonal transport and local protein synthesis could be useful to propose new therapeutic approaches.

7.7.1 Amyotrophic lateral sclerosis (ALS)/frontotemporal dementia (FTD)

Amyotrophic lateral sclerosis (ALS) is a fatal disease characterized by progressive degeneration of motor neurons in the motor cortex, brainstem, and spinal cord (Taylor et al., 2016; Taylor, Brown et al., 2016). ALS symptoms vary from skeletal muscular atrophy and asymmetric weakness in the limbs (Swinnen & Robberecht, 2014), weakened muscles in the neck, jaw, and tongue (Rowland & Shneider, 2001; Swinnen & Robberecht, 2014; Taylor et al., 2016), to a respiratory onset of the disease with extremely poor

prognosis (Swinnen & Robberecht, 2014). Frontotemporal dementia (FTD) is a form of dementia characterized by progressive neurodegeneration in the frontal and temporal lobes of the brain (Bang et al., 2015). Affected patients display personality and behavioral changes, and progressive impairment in language skills and executive function (Van Langenhove et al., 2012; Bang et al., 2015). Around 15–20% of patients with ALS meet the clinical criteria of FTD, the two diseases sharing some pathological and clinical features and underlying genetic mutations (Ringholz et al., 2005; Ling et al., 2013; Taylor et al., 2016). Common causes for both diseases include mutations in RBPs, disruption of proteostasis, and protein aggregation and inclusion bodies (Ling et al., 2013; Taylor et al., 2016). In the following section, we will discuss the underlying causes of both diseases with a focus on ALS to avoid redundancy.

ALS is classified into two categories, familial ALS, which accounts for about 10% of ALS cases, and sporadic ALS, accounting for 90% of cases (Renton et al., 2014; Swinnen & Robberecht, 2014; Taylor et al., 2016). In contrast, around 50% of FTD cases are familial (Ling et al., 2013; Taylor et al., 2016). Several genetic mutations have been linked to ALS, which can be roughly classified into three categories: 1) genes involved in protein homeostasis and autophagy, 2) genes related to cytoskeletal dynamics and motor protein complexes, and 3) genes associated with RNA metabolism, stability, and transport. In 1993, a study by Daniel R Rosen et al. identified the first genetic mutation associated with ALS in a gene encoding the enzyme superoxide dismutase (SOD1), an oxidoreductase that catalyzes the conversion of toxic superoxide species (Rosen et al., 1993), causing the protein to aggregate in association with mitochondria (Renton et al., 2014; Yasuda & Mili, 2016). Mutations of genes involved in the lysosomal degradation pathway were also linked to ALS, such as UBQLN2 encoding Ubiquilin 2, a shuttle protein that plays a role in the ubiquitin-proteasome system (UPS) (Rosen et al., 1993; Renaud et al., 2019), Optineurin (OPTN), an autophagy adaptor (Maruyama et al., 2010), involved in parkin-mediated mitophagy (Wong & Holzbaur, 2014), Sequestosome 1 (SQST1) (Fecto, Yan et al., 2011), the Transitional endoplasmic reticulum ATPase (VCP) (Johnson et al., 2010) and the Serine/threonine-protein kinase TBK1 (Freischmidt et al., 2015). Genes involved in cytoskeletal dynamics and motor protein complexes responsible for cargo trafficking were also found mutated in ALS, such as Dynactin-1 (DCTN1), which is part of the retrograde dynein-dynactin molecular motor complex (Puls et al., 2003); Tubulin α-4A (TUBA4A), a microtubule subunit that affects microtubule polymerization and results in the formation of ubiquitinated aggregates (Smith et al., 2014); and Profilin-1 (PFN1), which binds to monomeric G-actin and regulates the growth of filamentous F-actin

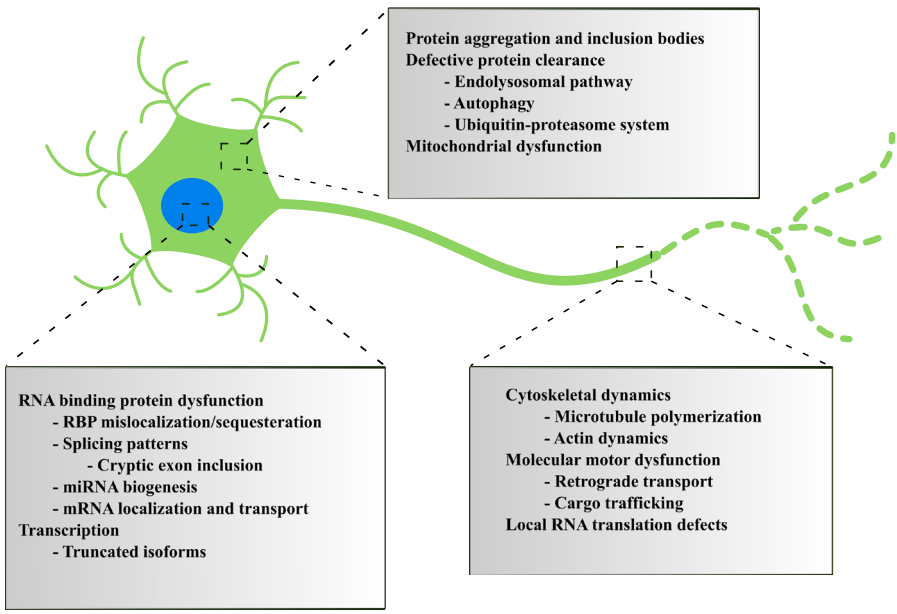

Figure 7.3 Summary of ALS pathology. ALS pathology has been linked to dysfunction in RNA binding proteins resulting in RBP sequestration, mislocalization and aggregation, which also leads to disruption of RNA processes such as transcription, splicing patterns and mRNA localization and transport. Additionally, ALS has also been linked to defects in the protein degradation pathways such as the ubiquitin-proteasome system, endo-lysosomal pathway, autophagy and mitophagy, leading to increased protein aggregation and the formation of inclusion bodies as well as mitochondrial dysfunction. Defects in the cytoskeletal dynamics such as microtubule and actin polymerization, molecular motor dysfunction and disruption of local translation have also been found to be associated with ALS pathology.

(Wu et al., 2012). Finally, genes associated with RNA metabolism, stability, and transport have also been implicated in ASL, including TARDPB (TAR DNA binding protein 43), FUS/TLS (Fused in Sarcoma/Translocated in Liposarcoma), C9orf72 (human chromosome 9 open reading frame 72), hnRNP A1 (heterogeneous nuclear ribonucleoproteins A1), hnRNPA2/B1, EWSR1 (EWS RNA-binding protein 1), ANG (Angiogenin), SETX (Senataxin), MATR3 (Matrin), ATXN2 (Ataxin-2), and TAF15 (TATA-box binding protein associated factor 15) (Kapeli et al., 2017). Indeed, a growing set of evidence suggests that defects in mRNA transport, processing, and translation caused by mutations in RBP coding genes or the impairment of RBP functions are a key factor underlying ALS and FTD pathologies (Figure 7.3).

TDP-43, a highly conserved RNA/DNA binding protein involved in multiple RNA processes, was first linked to ALS in 2008 (Sreedharan et al.,

2008). TDP-43 cytoplasmic aggregates and nuclear depletion have been reported in more than 96% of ALS and FTD cases, including both familial and sporadic ALS, except for SOD1-associated ALS, and are recognized as hallmarks of the disease (Arai et al., 2006; Neumann et al., 2006; Lagier-Tourenne et al., 2010). TDP-43 depletion in the mouse brain results in altered mRNA levels and mRNA splicing patterns in 601 and 965 mRNAs respectively (Polymenidou et al., 2011). Additionally, TDP-43 binds to the 3′UTR of Fus/Tls and Grn mRNAs, which are known to correlate with ALS (Polymenidou et al., 2011). A Drosophila study revealed an impairment in the anterograde trafficking of ALS-associated mutant TDP-43 containing RNP granules and their depletion at the neuromuscular junction (Alami et al., 2014). Additionally, two recent studies revealed how mislocalization of TDP-43 and its depletion from the nucleus result in a cryptic exon (CE) inclusion in the transcripts for UNC13A, encoding an essential neuronal protein involved in synaptic function, and STMN2, which encodes the regulator of microtubule stability stathmin-2 (Brown et al., 2022; Ma et al., 2022). The CE inclusion in STMN2 transcript results in a truncated isoform, significantly reducing stathmin-2 protein levels, a characteristic feature of ALS and FTD (Ma et al., 2022). Mutated forms of TDP-43 have been shown to reduce the movement of their associated RNP granules in the dendritic arbor of rat hippocampal neurons, likely resulting in a disruption of the transport and local translation of mRNA essential for synaptic function (Liu-Yesucevitz et al., 2014). Axonal accumulation of mutated TDP-43 RNP aggregates was also found to inhibit nuclear-encoded mitochondrial protein translation in neuromuscular junctions and distal axons (Altman et al., 2021).

Mutations of FUS/TLS, an RBP involved in several RNA processes essential for neuronal function and survival have also been linked to ALS/FTD. Like TDP-43, mutant variants of FUS were reported to mislocalize to the cytoplasm and form aggregates (Kwiatkowski et al., 2009; Vance et al., 2009). For instance, a study conducted in ALS-associated FUS-mutant motor neurons, identified increased levels of Fos-B mRNA, one of the mRNAs targeted by FUS, in correlation with irregular axonal branching (Akiyama et al., 2019). Additionally, both *in vivo*, in the mouse sciatic nerve, and *in vitro*, in primary cultured mouse hippocampal neurons, ALS/FTD-linked mutations in FUS have been reported to disrupt local axonal protein synthesis (López-Erauskin et al., 2018). Finally, the most common genetic mutation linked to both ALS and FTD is the C9orf72 hexanucleotide repeat expansion (HRE), which can lead to a decreased level of C9orf72, affecting vesicle trafficking and autophagy (Farg et al., 2014; Shi et al., 2018). C9orf72 HRE has also been linked to altered RNA processing, resulting in the formation of RNA foci due to expanding RNA repeats, which localize in the nucleus and sequester RBPs,

inhibiting their function (Barker et al., 2017). The aforementioned examples highlight how defects in mRNA localization and local translation are linked to the ALS/FTD pathology either directly through mutations in the RNA-binding proteins or indirectly, like in the case of C9orf72 expanded repeats.

Recently, a previously not described interaction between RNA, RNA granules, and components of the translational machinery with vesicular organelles such as endosomes, late endosomes, lysosomes, and mitochondria has been found (Dalla Costa et al., 2021). Interestingly, ANXA11, an RNA granule-associated phosphoinositide-binding protein was shown to tether RNA granules and lysosomes (Liao et al., 2019). Mutations of ANXA11 linked to ALS were found to disrupt RNA granules binding to lysosomes, thus impairing their transport (Liao et al., 2019). In addition, miR-124 was shown to be actively transported in axons and to be associated with mitochondria at growth cones and axonal branching points (Gershoni-Emek et al., 2018). Mitochondrial localization of this miRNA was reduced by the expression of hSOD1G93A, a gene linked to familial ALS, in motor neurons (Gershoni-Emek et al., 2018). While these observations are relatively recent, they strengthen the potential link between defects in transport observed in neurodegenerative diseases such as ALS and local translation.

7.7.2 Parkinson's disease (PD)

Parkinson's disease (PD) is a progressive neurodegenerative disease, affecting about 1% of the population aged 60 or above. The presence of protein aggregates called Lewy Bodies and the loss of dopaminergic (DA) neurons are hallmarks of PD (Goedert et al., 2013) and result in the characteristic motor and cognitive dysfunction observed in patients (Alexander, 2004). Unlike ALS and FTD, PD is mostly a sporadic disease with rare familial cases (Warner & Schapira, 2003; Alexander, 2004). α-synuclein was identified as the main constituent of LB in both sporadic and familial cases of PD. Indeed, the first genetic mutations to be linked to familial PD mapped in the gene encoding α-synuclein (SNCA) (Stefanis 2012). Amyloid β(Aβ) and Tau accumulations are also observed in PD, and Aβ aggregates are found to be linked to cognitive decline (Lim et al., 2019).

While the disruption of the unfolded protein response has been reported in PD, a direct link between impaired mRNA localization and local protein synthesis has not been established. Protein aggregation and misfolding trigger ER stress, activating the UPR signaling cascade, which controls mRNA stability and the rate of protein synthesis (Hetz & Saxena, 2017). For instance, the UPR PKR-like endoplasmic reticulum kinase (PERK) has been shown to

induce an increase in local translation via phosphorylation of the translation initiation factor eIF2α (Cagnetta et al., 2019). Semaphorin-3A (Sema3A) was suggested to induce mTOR and ERK1/2 mediated protein synthesis, which activates PERK and causes the subsequent eIF2α phosphorylation, accompanied by eIF2Bε dephosphorylation via GSK-3β inhibition and activation of PP1 by ERK-1/2, which increases eIF2B activity (Cagnetta et al., 2019). Aberrant protein translation has also been linked to genetic mutations in leucine-rich repeat kinase 2 (LRRK2), which are associated with both familial and sporadic PD (Imai et al., 2008). The eIF4E-binding protein (4E-BP) was shown to be a phosphorylation target of LRRK2, resulting in its activation and subsequent promotion of protein translation (Imai et al., 2008). The increase in protein synthesis was proposed to be detrimental to post-mitotic DA neurons, leading to an increase in aberrant proteins and/or a disruption of synapse integrity and neurodegeneration (Imai et al., 2008). Lastly, mutations in Pten-induced kinase 1 (PINK1/PARK6) and Parkin (PARK2) have also been associated with PD (Singleton et al., 2013). Interestingly, PINK1 and Parkin have been implicated in the local translation of a subset of nuclear-encoded respiratory chain complexes (nRCC) mRNAs essential for mitochondrial function (Gehrke et al., 2015). PINK1 interacts with Tom20 to localize nRCCs mRNA to the mitochondrial outer membrane and subsequently promote their translation in concert with Parkin (Gehrke et al., 2015). Recently, another study showed that Pink1 mRNA is co-transported with mitochondria and that its local translation along with the mitochondrial outer membrane proteins synaptojanin 2 binding protein (SYNJ2BP) and synaptojanin 2 (SYNJ2) are needed for its recruitment to the mitochondria (Harbauer, Hees et al., 2022). The local translation of PINK1 was described to be essential for the activation of mitophagy and the clearing of damaged mitochondria (Harbauer, Hees et al., 2022). These recent studies highlight the direct contribution of impaired proteostasis and aberrant protein synthesis and indirectly suggest the possibility of dysregulation of local translation and RNA metabolism in PD.

7.7.3 Alzheimer's disease (AD)

Alzheimer's disease (AD) is a genetic and sporadic neurodegenerative disease that causes dementia and cognitive impairment (Yang et al., 2016). The presence of Amyloid β (Aβ) and hyperphosphorylated forms of the microtubule-associated protein Tau-containing neurofibrillary tangles are hallmarks of AD (Knopman et al., 2021). Genetic mutations associated with AD such as PSEN1 (encoding presenilin 1) and PSEN2 (encoding presenilin 2) as well as

APP (encoding amyloid precursor protein (APP)) are rare and account for the inherited, generally early-onset, cases (Knopman et al., 2021). However, several genes have been identified as risk factors for the development of the disease. Those are APOE ε4, TREM2 (surface receptor required for microglial functions), SORL1 (neuronal sortilin-related receptor), and ABCA7(ATP-binding cassette, subfamily A member 7), as well as mutations in Tau-binding proteins such as BIN1, CD2AP, FERMT2, CASS4, and PTK2B, but not the gene encoding Tau (MAPT) (Knopman, Amieva et al., 2021). AD has also been found to be associated with α-synuclein and TDP-43 pathologies (Karanth et al., 2020).

APP is an Aβ precursor that undergoes cleavage by β- and γ-secretases to release Aβ peptides (Thinakaran & Koo, 2008). APP mutation or incorrect cleavage results in Aβ peptides prone to aggregation, resulting in fibril formation (Thinakaran & Koo, 2008; Gamarra et al., 2021). There are several examples of modulation of mRNA axonal translation in AD, which are mostly connected with Aβ induced toxicity. Aβ peptides, for instance, have been found to play a role in modulating the axonal local translation of the transcription factor ATF4, which is a component of the PERK signaling pathway (Baleriola et al., 2014). Indeed, pathogenic exposure to Aβ peptide was shown to elicit ATF4 axonal local translation and its subsequent retrograde transport to the nucleus, where it elicited a transcriptional response, which was suggested to not directly result in neurodegeneration and cell death, but rather in pathogenic changes that lead to degeneration further on (Baleriola et al., 2014). ATF4 siRNA knockdown was sufficient to rescue the degeneration phenotype in this context (Baleriola et al., 2014). Similarly, the protein Vimentin was found to be locally translated and retrogradely transported in response to Aβ exposure, in a way that is connected to ATF4 local translation (Walker et al., 2018). Additionally, Aβ oligomers were shown to impede retrograde trafficking of Brain-derived Neurotrophic Factor (BDNF), which is known to play a role in synaptic plasticity and memory, in response to altered ubiquitin homeostasis and the downregulation of Ubiquitin C-terminal hydrolase L1 (UCH-L1) (Poon et al., 2013). A similar study also described NMDAR dysfunction induced by Aβ oligomers to impair axonal trafficking of BDNF and mitochondria by regulating signaling cascades that result in the activation of Glycogen Synthase Kinase-3 (GSK-3β) (Decker et al., 2010). Furthermore, Aβ has been linked to the mislocalization and local translation of Mapt mRNA encoding Tau (Kobayashi et al., 2017; Li & Götz, 2017), with Aβ mediating the activation of Fyn via kinase-dependent activation of ERK/S6, resulting in the mislocalized translation and hyperphosphorylation of Tau, and leading to its accumulation

in the somatodendritic compartment (Li & Götz, 2017). Additionally, Tau hyperphosphorylation was also shown to be triggered by AMPA and NMDA receptor stimulation (Kobayashi et al., 2017)). Finally, Aβ was recently found to regulate the translation of several mRNAs bound to FMRP, resulting in the impaired synthesis of proteins that are important for synaptic function (Ghosh et al., 2020). Interestingly, using an optical reporter where the coding sequence of Venus was flanked by short stretches of the Calcium/calmodulin-dependent Kinase IIa (CAMKIIa) 5′- and 3′-UTRs, decreased translation of CAMK2a was reported adjacent to Alzheimer-related amyloid plaques *in vivo* (Meyer-Luehmann et al., 2009).

7.7.4 Huntington's disease (HD)

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by a pathogenic unstable trinucleotide CAG repeat expansion (over 36 repeats) in the Huntingtin (HTT) gene, which manifests as abnormal uncontrolled movements (chorea), psychiatric symptoms, and cognitive deficits that worsen over time (Landles & Bates, 2004; Li & Li, 2004). Mutant HTT (mHTT) protein differs from its wild-type counterpart by an elongated polyglutamine (polyQ) region near the amino terminus of the protein, with longer polyQ expansions associated with earlier onset and increased severity (Duyao et al., 1993). Aberrant aggregation, and subsequent inactivation, of mHTT are detected in the brains of patients with Huntington's disease (Davies et al., 1997; DiFiglia et al., 1997).

HTT is transported in axons and plays a role in dendritic RNA delivery (Ma et al., 2010). Indeed, HTT protein inactivation leads to defective BDNF mRNA localization in axons of cortical neurons (Ma et al., 2010). HTT was also shown to colocalize with specific RNPs, Ago2 and Staufen, in P bodies containing translationally repressed mRNA (Savas et al., 2008) and in dendritic RNA granules regulating transport and local translation (Savas et al., 2010). Moreover, HTT can bind the 3'UTRs of mRNAs targeted to the dendrites, such as Actb or Bdnf (Ma et al., 2010; Savas et al., 2010). Interestingly, BDNF is a known regulator of local translation (Swanger & Bassell, 2013). Recently HTT protein was found in a complex with its own mRNA, RNA-binding proteins, and translation factors (Culver et al., 2016). Thus, HTT may be involved in modulating its expression through post-transcriptional pathways. Similarly, to other neurodegenerative disorders, HD is yet another example of deregulation in the interaction with RBPs or in the direct binding to mRNA 3'UTRs leading to mRNA transport impairment. While we have

data regarding dendrites, it is possible that axonal translation could also be hindered in HD.

7.7.5 Spinal muscular atrophy (SMA)

Spinal muscular atrophy (SMA) is one of the most common autosomal recessive hereditary disorders, manifesting as a gradual spinal alpha motor neuron degeneration caused mostly by bi-allelic loss-of-function mutations in the SMN1 gene (Wirth, 2000; Verhaart et al., 2017; Calucho et al., 2018). Hallmarks of the disease are progressive proximal muscle weakness and atrophy, which can lead to paralysis, with the severity of the disease being modulated by the copy number variation of SMN2, a paralog of the SMN1 gene (Crawford et al., 2012). SMA patients are classified clinically into five types, from 0 to 4, according to the highest achieved motor abilities, which loosely correlate with the age of symptoms onset (Mercuri et al., 2018; Finkel et al., 2018). Currently, no cure has been found for this pathology, and symptoms management is mostly performed via mechanical supportive care, the use of disease-modifying agents, and gene therapy aimed at restoring SMN protein expression (Nicolau et al., 2021).

The SMN protein is involved in the assembly of the pre-mRNA splicing complex small-nuclear ribonucleoproteins (snRNPs) (Khalil et al., 2018) and plays a role in the modulation of mRNA localization and RNP regulation in axons (Fallini et al., 2012, 2016). Axonal SMN-RNP complexes differ from their snRNPs counterparts, suggesting an axonal function for SMN other than splicing regulation (Fallini et al., 2011). Indeed, SMN was found to control mRNA axonal transport and axonal growth in cooperation with HuD, a neuron-specific RNA binding protein (Akten et al., 2011; Hao le et al., 2017). Thus, alteration of SMN1 expression can lead to mRNA mislocalization and impairment of axonal local translation in motor neurons. For instance, β-actin (mRNA is miss-localized), and its local protein synthesis is impaired in SMN-deficient motor neurons, causing defects in axonal growth (Rossoll et al.., 2003; Rathod et al., 2012). Interestingly, GAP43 is highly expressed during neuronal growth and axonal regeneration and its axonal mRNA mislocalization leads to motor neuron axonal growth defect, and SMN was shown to control GAP43 mRNA transport and translation (Hartl & Schneider, 2019; Fallini et al., 2016). GAP43 and β-actin mRNAs can compete for their localization and translation, and, in doing so, regulate axon elongation and branching respectively (Donnelly et al., 2013). SMN deficiency also affects Annexin A2 (Anxa2) mRNA localization (Rage et al., 2013). Anxa2 is involved in actin

cytoskeleton regulation and its mRNA miss-localization and impaired axonal translation, could in part explain the observed cytoskeleton defects in SMN models (Rihan et al., 2017). Finally, Axonal localization of the transcript coding for the voltage-gated calcium channel CaV2.2 is decreased in growth cones of SMA cultured neurons, leading to a reduction of Ca^{2+} signaling (Jablonka et al., 2007). SMN also regulates local protein synthesis through miRNA expression. Indeed, miR-183, which targets mTOR, a key regulator of local translation in neurons, was shown to be increased in neurites of SMN-deficient neurons leading to decreased translation (Kye et al., 2014). Interestingly, recent evidence acquired by ultrastructural analyses of ribosomes showed a 27% decrease in axonal ribosomes in motor axons of SMA mice compared to their wild-type counterpart, suggesting an overall decreased capacity for translation in axons (Bernabò et al., 2017). Altogether, these data suggest that mRNA mislocalization and local translation impairment could be among the underlying causes of neurite growth, presynaptic functions, and cytoskeleton organization defects in SMA motor neurons.

7.7.6 Fragile X syndrome (FXS)

Fragile X syndrome (FXS) is a neurodevelopmental disorder, which has not been associated with axonal loss during adult life. The initiation of the pathology is linked to mutations in the FMR1 gene, which encodes the RNA-binding protein FMRP. The symptoms of FXS are variable on the autism spectrum and depend on gender, age, genetic background, and environmental effects (Dyer-Friedman et al., 2002; Loesch et al., 2004; Hoogeveen et al., 2002). Since the FMR1 allele is localized on the X chromosome, FMRP levels also correlate with X-inactivation in females. Consequently, the disease has a lower prevalence and is less severe in females (Hagerman et al., 2017).

Abnormal trinucleotide repeats in FMR1 5'-UTR reduce FMRP protein synthesis and manifest in behavioral features associated with the autism spectrum (Maurin et al., 2014). The triplet repeats lead to DNA methylation of FMR1, transcriptional inactivation of the gene, and finally partial or complete loss of FMRP (Pieretti et al., 1991; Verkerk et al., 1991). FMRP is enriched in the brain RNA and has an essential role in synaptic plasticity and architecture (Ashley et al., 1993; Darnell et al., 2011; Siomi et al., 1993). Several pieces of evidence point to the role of FMRP in dendrite local translation (Feuge et al., 2019; Antar et al., 2004; Banerjee et al., 2018). However, FMRP-containing granules, called Fragile X granules (FXG), have also been found in a subset

of axons, mostly during synapse formation and pruning (Akins et al., 2012; Christie et al., 2009). While FMRP is not required for the axonal transport of ribosomes (Akins et al., 2017), loss of FMRP in mice is linked to the regulation of local translation. FMRP is responsible for the transport of Map1b and Calm1 mRNAs together with the local translational regulator miR-181d. Upon NGF stimulation, FMRP and miR-181d mediate axon elongation by translational regulation of their targets (Wang et al., 2015). Thus, disruption of the local translation machinery due to FMRP loss or mutation might play a role in the developmental symptoms of this pathology.

7.8 Conclusion

mRNA localization and local translation are important mechanisms by which highly polarized cells with specialized functions such as neurons can spatially and temporally control the subcellular proteome. This spatiotemporal control is important for a variety of neuronal processes including synaptic function and plasticity, growth cone guidance, axonal maintenance, neuronal survival and homeostasis, and response to injury. The disruption of mRNA trafficking and local translation either directly, such as mutations in RNA-binding proteins involved in RNA processes, or indirectly thought the disruption of the proteasome, UPS, autophagy, and in general protein homeostasis has been implicated in many neurodegenerative pathologies such as ALS, FTD, HD, AD, PD, SMA and FXS. In this chapter, we tried to give an overview of the neurodegenerative pathologies, which involve defects in mRNA local translation and localization (Table 7.1). Further research on the subject, focused on understanding the physiological and pathological functions and mechanisms underlying this alteration for the individual pathology, is needed to propose efficient treatments. For instance, finding out how to promote the localization of specific mRNAs and/or activating the local translational machinery could preserve axonal integrity and ameliorate disease prognosis. Indeed, the range of technologies allowing for direct visualization of mRNA and proteins as well as de novo discovery of axonal mRNA and RBPs has been drastically expanded in recent years (Koppel & Fainzilber, 2018; Holt et al., 2019), with an increasing number of proximity-based approaches to transcriptomics and proteomics, which allows for the investigation of axonal organelle-based mRNA transport (Liao et al., 2019; Williams et al., 2014; Qin et al., 2021). Data generated via these novel technologies is likely to uncover the critical mechanism underlying neurodegeneration and recovery from injury.

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