Posttranscriptional regulation of neurofilament proteins and tau in health and disease

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Abstract

Neurofilament and tau proteins are neuron-specific cytoskeletal proteins that are enriched in axons, regulated by many of the same protein kinases, interact physically, and are the principal constituents of neurofibrillary lesions in major adult-onset dementias. Both proteins share functions related to the modulation of stability and functions of the microtubule network in axons, axonal transport and scaffolding of organelles, long-term synaptic potentiation, and learning and memory. Expression of these proteins is regulated not only at the transcriptional level but also through posttranscriptional control of pre-mRNA splicing, mRNA stability, transport, localization, local translation and degradation. Current evidence suggests that posttranscriptional determinants of their levels are usually regulated by RNA-binding proteins and microRNAs primarily through 3'-untranslated regions of neurofilament and tau mRNAs. Dysregulations of neurofilament and tau expression caused by mutations or pathologies of RNA-binding proteins such as TDP43, FUS and microRNAs are increasingly recognized in association with varied neurological disorders. In this review, we summarize the current understanding of posttranscriptional control of neurofilament and tau by examining the posttranscriptional regulation of neurofilament and tau by RNA-binding proteins and microRNAs implicated in health and diseases.

Keywords

Neurofilament; Tau; mRNA; RNA-binding protein; miRNA; Posttranscriptional control

1. Introduction

Neurofilament (Nf) and tau proteins are not only abundant integral components of neurofibrillary tangles and but also hyperphosphorylated in Alzheimer disease (AD)

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(Grundke-Iqbal et al., 1986; Rudrabhatla et al., 2010, 2011). Tau protein may also be a constituent of Lewy bodies (Ishizawa et al., 2003) composed of alpha-synuclein and Nf proteins (Goldman et al., 1983; Kanazawa et al., 2008) commonly found in Parkinson disease (PD) and the Lewy body dementias. Previous studies also showed that neurofilament proteins colocalized with tau aggregates in transgenic mice overexpressing human tau protein (Ishihara et al., 1999). Moreover, deletion of neurofilament proteins resulted in a dramatic decrease in the total number of tau-positive spheroids and attenuated neurodegenerative disease phenotype in these mice, suggesting a role for neurofilament proteins in the pathogenesis of neurofibrillary tau lesions in neurodegenerative disorders (Ishihara et al., 2001). Recently, neurofilament (Yuan and Nixon, 2021) and tau proteins (Holper et al., 2022) have been used together as biomarkers of neuronal integrity reflecting the magnitude of neuronal injury and neurodegeneration.

Neurofilaments (Nfs) are almost exclusively expressed in neurons. Nfs are obligate 10 nm heteropolymers composed of four different subunits, each composed of a central alpha-helical rod region, a short variable amino-terminal head domain, and a highly variable length tail at the C-terminal end. CNS neurofilaments are composed of Nf heavy (NfH), Nf medium (NfM), Nf light (NfL) and alpha-internexin (INA) subunits exhibiting apparent molecular masses of 200 kDa, 145–160 kDa, 70 kDa, and 59–65 kDa respectively (Yuan et al., 2006). In the PNS, the 57–58 kDa intermediate filament protein peripherin (PRPH) replaces INA (Yuan et al., 2012). In mature neurons, these polymers, often many micrometers in length, bundle and extensively cross-link within a cytoskeletal protein network of exceptional stability (many months) and provide structural support to maintain the large calibers of myelinated axons crucial for nerve conduction velocity (Ohara et al., 1993). Nf proteins (NfPs) have also recently found to play unique roles in synapse function (Yuan et al., 2015). Specifically, Nf subunits can be transported from soma to synaptic terminals in oligomeric form, including heterodimers (Yuan et al., 2003) or portions of them could be synthesized locally (Yuan and Nixon, 2016). The Nf network comprising heterodimers, oligomers and short filaments could function as a regulatory scaffold for reversible organelle and protein complex docking (Rao et al., 2011; Yuan et al., 2015). Notably, NfL subunits were found to modulate the turnover, levels, and synaptic activity of the NMDA receptor and thereby influence LTP and NMDA-mediated behaviors (Yuan et al., 2018). By contrast, NfM selectively binds D1R and regulates sensitization / desensitization at the post-synaptic membrane by anchoring internalized D1 dopamine receptors on endosomes and modulating their recycling back to the membrane surface to increase D1-mediated activities (Yuan et al., 2015). Loss of NfPs reduces conduction velocity and cause neuropathy in quails (Ohara et al., 1993), mice (Zhu et al., 1997), and humans (Abe et al., 2009; Fu and Yuan, 2018; Yum et al., 2009). Mutations of NfPs can cause neurological diseases and the abnormal accumulation of NfPs in soma and axons is a common feature of many neurological conditions (Table 1). NfPs therefore play prominent roles in both physiology and pathology of the neuron, especially axons.

The tau proteins are a group of six highly abundant and soluble microtubule-associated protein isoforms produced by alternative splicing from the gene MAPT (Weingarten et al., 1975). They are believed to function primarily to facilitate assembly and stabilization of microtubules mainly in axons (Wang and Mandelkow, 2016). Although generally regarded

as neuron-specific cytoskeleton proteins, tau isoforms are also expressed at very low levels in CNS astrocytes and oligodendrocytes. The presence of normal tau proteins in brains seems to be important for the physiological function of the nervous system since their deletion leads to muscle weakness, hyperactivity and impaired fear conditioning in mice (Ikegami et al., 2000). MAPT mutations can cause frontotemporal dementia and several other "tauopathies" (Table 1). Paired helical filaments of tau proteins are the main component of neurofibrillary tangles that are hallmark intraneuronal lesions in the brain in Alzheimer's disease (AD) and several other neurodegenerative "tauopathies". In summary, tau, like NfPs, plays multiple roles in the function and dysfunction of the nervous system, especially axons.

Both tau and NfPs undergo posttranslational modifications such as phosphorylation, glycosylation, nitration, oxidation and ubiquitination. Hyper-phosphorylation of tau (Karikari et al., 2020), NfH, and NfM (Rudrabhatla et al., 2010) are particularly implicated in neurodegenerative disorders including Alzheimer disease. It is also relevant that many of the kinases/phosphatases regulating these two classes of proteins are shared in common. Although posttranslational modifications of NfPs and tau are implicated in the pathogenesis of varied neurodegenerative diseases, new evidence has emerged for involvement of Nf / tau RNA-mediated mechanisms in a number of degenerative pathologies of the CNS (Chen et al., 2014; Kumar et al., 2021; Robertson et al., 2003; Santa-Maria et al., 2015). These RNA-mediated mechanisms include alternative splicing, a general phenomenon in eukaryotic genomes, which in humans impacts about 95% of multi-exonic genes (Pan et al., 2008; Wang et al., 2008). Given that alternative splicing is more common in the brain than in other tissues (Yeo et al., 2004), the posttranscriptional control of NfP and tau expression through RNA-binding proteins (RBPs) and microRNAs (miRNAs) is particularly active (Table 2). By transporting repressed mRNAs to distant compartments within the cell, posttranscriptional regulation of NfPs and tau in neurons is able to regulate local protein synthesis for immediate needs in synaptic terminals, thereby avoiding the delays in transporting new protein from the perikaryon. Moreover, RBPs play multiple roles in posttranscriptional control of RNAs, such as RNA biogenesis, alternative splicing, polyadenylation, maturation, stability, localization, transport and translation efficiency in neurons (Gebauer et al., 2021). Not surprisingly, mutations in RBPs are increasingly recognized to cause varied neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) (Table 3). Additional post-transcriptional control is exerted by miRNA, which is a small single-stranded non-coding RNA molecule (18–23 nucleotides long) that binds to and silences target mRNA at the posttranscriptional level (Gebert and MacRae, 2019). Each miRNA binds many target transcripts, providing additional broad control that complements canonical transcriptional pathways and posttranscriptional regulation by RBPs. Recently, miRNA defects have also been linked to neurodegeneration (Cheng et al., 2014; Hebert et al., 2010; Juzwik et al., 2019; Kim et al., 2007; Schaefer et al., 2007). Although posttranslational regulation of Nf and tau proteins have been previously extensively described, the importance of their posttranscriptional regulation has been under-appreciated. In this review, we discuss our current understanding of posttranscriptional control of Nf and tau proteins through RBPs and miRNAs and its influences on the brain in health and neurological diseases.

2.   Posttranscriptional regulation of NfL

2.1.   NfL mRNA dynamics

Each NfP has a distinct structure that potentially could have differential functions. Among the five Nf subunits, NfL is the most abundant and forms the core of neurofilaments in both PNS and CNS. The stoichiometries of NfPs in neurons are temporally and spatially controlled. The levels of expression of NfL are tightly coupled with those of other Nf subunits and can influence their levels. When NfL is absent in mice, NfH levels decline most, followed by NfM and PRPH (Yuan et al., 2012) although INA levels are only marginally affected (Yuan et al., 2003). While transcriptional control determines the restriction of Nf expression to neurons, the abundance of Nf gene products in different neurons at different developmental stages is also regulated post-transcriptionally (Schwartz et al., 1995). Although there is additional evidence for translational control (Antic et al., 1999), a major degree of posttranscriptional control is exerted at the level of Nf mRNA stability (Schwartz et al., 1992). Transcription of the NfL gene yields NfL mRNA (Fig. 1A), which was originally believed to be translated exclusively in the perikaryon and proximal dendrites, has gradually been appreciated to occur in all compartments of neurons (Alami et al., 2014; Holt et al., 2019; Lee and Hollenbeck, 2003; Sotelo-Silveira et al., 2000). The impact of this regulation on NfPs is exemplified by studies in zebrafish. In contrast to the single mammalian Nfl gene, zebrafish have two NfL genes, called nefla and neflb (Wang et al., 2019). Both gene knockdown and rescue experiments show that neflb rather than nefla plays an indispensable role in nervous system development. Two isoforms of the latter gene, neflE3 and neflE4, are generated by alternative splicing of neflb mRNA (Fig. 1B) (Demy et al., 2020). Alternative use of two polyadenylation sites in exon 4 in the mouse NfL gene also generates 2.3-and 3.5-kb mRNAs (Nakahira et al., 1990). These two NfL mRNAs are much more stable in mature neurons than in cultured PC12 cells (Nakahira et al., 1990; Schwartz et al., 1992). When adult DRG neurons are placed in tissue culture, NfL mRNAs are rapidly destabilized. Therefore, NfL mRNA half-lives in the presence of actinomycin in dorsal root ganglion (DRG) neurons of adult rat are estimated to be at least 5 days (Moskowitz and Oblinger, 1994) whereas those in PC12 cells are only a few hours (Nakahira et al., 1990). Blockade of either transcription or protein synthesis using inhibitors in cultured adult DRG neurons prevents the destabilization of NfL mRNAs (Schwartz et al., 1992). NfL mRNAs in cultured neuronal cells can also be stabilized by nerve growth factors (Ikenaka et al., 1990) and destabilized by okadaic acid, which inhibits protein phosphatase 2 A (Sasahara et al., 1996). The stability of NfL mRNAs *in vivo* is also highly regulated. The levels of NfL mRNAs are dependent upon axonal- or target cell-derived signals (Schwartz et al., 1990). NfL mRNAs can also be stabilized during postnatal development (Schwartz et al., 1994). The observations that NfL showed maximal rates of gene transcription at postnatal day 5 followed by a decline at later times whereas the steady-state levels of NfL mRNAs changed in manner opposite to that of transcription and increased progressively during the postnatal intervals suggests mRNA stabilization is the main factor regulating the steady-state levels of NfL mRNAs *in vivo* (Moskowitz and Oblinger, 1995). Due to this posttranscriptional regulation, overexpression in transgenic mice of NfL mRNA from 3- to 5-fold in different regions of CNS resulted only in a mild increase of 10–50% in the levels of NfL proteins (Beaudet et al., 1993). Stability of NfL mRNA may also relate to other developmental

phenomena that are characteristic of mature neurons such as the axotomy-induced 2- to 3-fold downregulation of NfL mRNA (Goldstein et al., 1988; Hoffman et al., 1987). In summary, stability of NfL mRNA may contribute to the high level of expression of NfL protein both *In vitro and in vivo.*

2.2. 3'-UTR of NfL mRNA and regulation by RBPs

The involvement of 3'-untranslated region (3'-UTR) in mRNA stability (Hentze, 1991; Sachs, 1993) and the conservation of 3'-UTR in Nf mRNAs (Schwartz et al., 1994) suggest that the 3'-UTR in Nf genes may harbor determinants of Nf expression. In fact, deletion of 3'-UTR from mouse NfL leads to a 3-fold aberrant up-regulation of NfL mRNA between embryonic days 15 and 18, and loss of its susceptibility to axotomy-induced down-regulation, supporting this hypothesis (Schwartz et al., 1995). 3'-UTR in NfL mRNAs can also trigger aggregation of NfL protein in neuronal cells (Lin et al., 2004). Interestingly, overexpression of 3'-UTR of NfL mRNA or expression of an NfL transgene with a 36-base pair c-myc mutant mRNA stability determinants could also reproduce selective degeneration of motor neurons with aggregates of RNA-binding proteins in primary motor neurons in culture (Lin et al., 2003) or degenerating motor neurons of transgenic mice (Canete-Soler et al., 1999; Nie et al., 2002). Later studies demonstrated that a major stability determinant is located to a 68-nucleotide (nt) sequence that forms the junction between 3'-coding region and 3'-UTR of NfL mRNAs (Canete-Soler et al., 1998b), and also is the binding site of a unique ribonucleoprotein complex (Canete-Soler et al., 1998a). Further investigations showed that p190RhoGEF, a RhoA-specific guanine nucleotide exchange factor, can bind to this 68-nt sequence in mouse (Canete-Soler et al., 2001) and human (Volkening et al., 2010) and increases NfL mRNA stability by nearly 2-fold. This factor is also involved in aggregation of NfL protein (Lin et al., 2005) and co-aggregation of p190RhoGEF and NfL protein is associated with loss of NfL mRNAs in degenerating spinal cord motor neurons in ALS (Droppelmann et al., 2013a; Menzies et al., 2002; Wong et al., 2000). Correspondingly, p190RhoGEF gene mutation is also linked to familial ALS (Droppelmann et al., 2013b). Intriguingly, binding of p190RhoGEF to NfL mRNA is directly competed by BC1 RNA (Ge et al., 2002), a 152 nucleotide RNA polymerase III transcript that is highly expressed postnatally in neurons (Cao et al., 2006), indicating possible co-regulation of NfL mRNA by RBPs and non-coding RNAs. In addition to p190RhoGEF, aldolases A and C also bind to this sequence and negatively regulate the stability of NfL mRNAs (Canete-Soler et al., 2005) whereas poly (A)-binding protein positively regulates their stability (Stefanizzi and Canete-Soler, 2007). Still other proteins, such as wild-type and mutant superoxide dismutase 1 (SOD1) (Ge et al., 2005), TAR DNA-binding protein of 43 kDa (TDP43) (Strong et al., 2007), fused in sarcoma (FUS) (Lagier-Tourenne et al., 2012), 14–3–3 proteins (Ge et al., 2007), hnRNP K, E1 and E2 (Thyagarajan and Szaro, 2008), have also been identified as RNA-binding proteins that bind NfL mRNAs. It is also reported that mRNP granules containing TDP43 and NfL mRNA show predominantly anterograde movements and net anterograde displacement, whereas those that contain NfL mRNA without TDP43 show predominantly retrograde movements and net retrograde displacement (Alami et al., 2014). The functional significance of this observation is not yet understood. Recent studies showed that disruption of the balance of the two isoforms of NfL mRNAs through partial deletion of TDP43 affects Nf assembly and motor axon growth with resultant motor deficits in zebrafish

(Demy et al., 2020). More recent studies demonstrated that TDP43 proteinopathy can cause translational suppression of Nf mRNAs resulting in 3-4-fold decrease in the levels of NfPs in mouse brain (Kumar et al., 2021). Thus, 3'-UTR of NfL mRNA may serve as a hub for posttranscriptional control as the target of many RBPs.

2.3. Regulation by miRNAs and interaction between miRNAs and RBPs

Beyond the interaction of RBPS with the 3'UTR of NfL mRNAs, miRNAs could also participate in NfL mRNA stability and translational regulation through mRNA decay or translational silencing (Du and Zamore, 2005; Gebert and MacRae, 2019). In fact, miRNA expression profile was shown to be broadly altered in the spinal cord of sporadic ALS and miRNAs including miR-146a, miR-424-5p and miR-582-3p (Campos-Melo et al., 2013), miR-b1336 and miR-b2403 (Ishtiaq et al., 2014) are capable of interacting with NfL mRNA 3'UTR and could play a role in the regulation of its mRNA levels. Notably, RNA is not surrounded by a lipid membrane, instead their fate is generally controlled by binding with many RBPs that form ribonucleoprotein (RNP) complexes. These membraneless compartments are called RNA granules, a category that includes transport granules, stress granules, storage granules, P-bodies and activity-dependent granules in the neuronal cytoplasm (Kiebler and Bassell, 2006; Wolozin and Ivanov, 2019). RNA granules form via liquid-liquid phase separation, which is driven by a dynamic network of multivalent interactions of protein containing intrinsically disordered regions and low complex domains such as TDP43 and FUS. On the one hand, both stress granules and P-bodies exist in a constant state of dynamic flux mediated by the nature of associated miRNAs (Anderson and Kedersha, 2006, 2008; Stoecklin and Kedersha, 2013). On the other hand, miRNAs biogenesis and metabolism are regulated by RBPs (Loffreda et al., 2015; Stroynowska-Czerwinska et al., 2014) and dysfunction of both miRNAs and RBPs is often observed in neurodegenerative diseases (Kinoshita et al., 2021). For example, TDP43 and FUS are involved in the regulation of miR-183/96/182 biogenesis and memory suppressor protein phosphatase 1, and their alterations results in age-related memory decline in the pathogenesis of ALS and FTD (Jawaid et al., 2019). Therefore, these miRNAs could interact with those RBPs binding NfL mRNAs and coordinate the posttranscription of NfL gene expression under physiological conditions and become dysfunctional in disease states (Jiang and Coller, 2012).

3. Posttranscriptional regulation of NfH

Although NfH expression is low, when compared to NfL, in developing neurons and only increases postnatally (Pachter and Liem, 1984; Shaw and Weber, 1982), the dissociation between rates of NfH gene transcription and the steady-state levels of NfH mRNAs during postnatal development are similar to those of the NfL gene, with maximal transcription at early times followed by a decline at later times whereas NfH mRNA levels increase substantially during the same interval (Moskowitz and Oblinger, 1995). Like NfL and NfM genes, NfH mRNA levels also decline following nerve transection (Goldstein et al., 1988). However, unlike NfL transgenic mice, the CNS of transgenic mice bearing multiple copies of the human NfH gene showed about 3-fold increase in the levels of both NfH mRNA and protein compared to wild-type mice, indicating NfH and NfL genes are still subject

to different posttranscriptional regulation in the CNS (Beaudet et al., 1993). Although NfL mRNA is inhibited in degenerating spinal cord motor neurons in ALS, NfH mRNA seems to be not suppressed (Chen et al., 2014; Menzies et al., 2002). Poly (C)-sensitive complexes regulate the stability of NfH mRNA through binding a 36-nt sequence in the mid-distal region of the NfH 3'UTR (Canete-Soler and Schlaepfer, 2000). Other RNA-binding proteins like hnRNP K, E1 and E2 also bind NfH mRNAs for posttranscriptional regulation (Thyagarajan and Szaro, 2008). TDP43 was also shown to interact with human NfH mRNA from spinal cord homogenates but was not co-immunoprecipitated from HEK293T cells that had been transiently transfected with a partial sequence of hNfH lacking a component of the 5' coding region of the hNfH construct (Strong et al., 2007), indicating that the 5'UTR or 5' coding region of NfH has the potential to interact with TDP43. Like in NfL mRNAs, a small group of ALS-linked miRNAs that are expressed in human motor neurons also directly regulate NfH transcript levels (Campos-Melo et al., 2018).

4. Posttranscriptional regulation of NfM

During postnatal development, some differences exist in the regulatory mechanisms that control NfM compared to NfL and NfH mRNA levels. Unlike NfL and NfH, NfM transcription rates were largely dissociated from steady-state mRNA level changes between postnatal days 2 and 10 (Moskowitz and Oblinger, 1995). However, the transcriptional activity of the NfM gene and the steady-state levels of NfM mRNA increased in a coordinate manner between postnatal days 2 and 10. Like NfL and NfH genes, NfM mRNA levels also decline following nerve transection (Goldstein et al., 1988). In addition to NfL mRNA involvement in neurodegeneration, NfM mRNA could also be associated with ALS since NSC34 cells expressing G37R or G93A SOD1 showed selective reductions of both NfM and NfL mRNA and proteins (Menzies et al., 2002). Similar to NfL and NfH, RNA-binding proteins hnRNP K, E1 and E2 can also bind 3'UTR of NfM mRNA and could regulate its stability (Thyagarajan and Szaro, 2004, 2008). Further studies showed that hnRNP K knockdown can compromise NfM mRNA nucleocytoplasmic export and disrupt their loading onto polysomes for translation in *Xenopus laevis* (Liu et al., 2008, 2012). This interaction of hnRNP K and NfM mRNA could be modulated through the phosphorylation by extracellular signal-regulated kinase (Hutchins et al., 2015). Other RBPs like ELAV-like RNA binding protein 2 also binds to 3'UTR of NfM mRNA and can cause an increase in translation initiation of NfM mRNA in transfected cells (Antic et al., 1999). Besides 3'UTR, its introns may also be involved in the posttranscriptional regulation of NfM expression in neurons (Wang and Szaro, 2016). Like in NfL and NfH mRNAs, a small group of ALS-linked miRNAs that are expressed in human motor neurons also directly regulate NfM transcript levels (Campos-Melo et al., 2018).

5. Posttranscriptional regulation of INA

Unlike NfL, MfM and NfH found in both the CNS and PNS, INA is expressed predominantly in the CNS in the adult (Pachter and Liem, 1985), indicating its special role in the normal functioning of neurons in the brain and spinal cord. In contrast to the downregulation of NfL, NfM and NfH mRNAs after peripheral nerve injury, INA mRNA increases after facial nerve lesions, suggesting its role is in the early stage of

neuronal regeneration (McGraw et al., 2002). Interestingly, the level of INA must be tightly regulated since overexpression of INA at 2–3 times the normal level produces mice with motor coordination deficiencies and neurodegeneration in aged animals (Ching et al., 1999). Remarkably, more prominent aggregation of INA than other NfPs are the neuropathological hallmark of Nf inclusion disease, a form of FTD (Cairns et al., 2004). Like NfL mRNA, INA mRNA is also reduced in motor neurons in ALS (Wong et al., 2000). INA expression is also regulated post-transcriptionally by hnRNP K since hnRNP K knockdown yields defects in its nuclear export and translation but not transcription (Liu and Szaro, 2011).

6. Posttranscriptional regulation of PRPH

PRPH is the first NfP expressed by PC12 cells stimulated by nerve growth factors (Leonard et al., 1988; Portier et al., 1983a; Thompson et al., 1992) followed by expression of NfL, NfM and NfH (Lindenbaum et al., 1988). Unlike NfL, NfM and NfH, which are found in both the CNS and PNS, PRPH is expressed predominantly in the PNS and in neurons of the CNS that have projections to the periphery, including spinal motor neurons in the adult, indicating its special role in the normal functioning of neurons in peripheral nerves (Parysek and Goldman, 1988; Portier et al., 1983b). In contrast to the downregulation of NfL, NfM and NfH mRNAs after peripheral nerve injury, PRPH mRNA increases following peripheral axotomy in motor neurons and dorsal root ganglia (Oblinger et al., 1989; Troy et al., 1990; Wong and Oblinger, 1990) or some CNS neurons after stab lesion or cerebral ischemia (Beaulieu et al., 2002), implying its role in the early stage of neuronal regeneration. The proinflammatory cytokines, interleukin-6 and leukemia inhibitory factor, can also induce PRPH expression through the JAK-STAT signaling pathway (Djabali et al., 1993; Lecomte et al., 1998; Sterneck et al., 1996). In addition to the main species of 58 kDA PRPH (Per 58), two other forms have been identified in the mouse (Fig. 1 C). Per 56 is made by a receptor on exon 9 of the PRPH gene transcript which induces a frame shift and replacement of a 21 amino acid in the C-terminus found on the dominant Per 58 form with a new 8 amino acid sequence. Per 61 is generated by the in-frame retention of intron 4 leading to a 32 amino acid insertion within coil 2b of the alpha-helical domain of PRPH (Landon et al., 1989, 2000). Per 58 and Per 56 are normally co-expressed whereas Per 61 is unable to assemble properly and is not found in the normal PRPH expressed adult motor neurons but it is expressed in motor neurons of mutant SOD1 transgenic mice, suggesting that mutant SOD1 induces differential splicing of the PRPH pre-mRNA (Robertson et al., 2003). Per 61 is also toxic to primary motor neurons in culture and induces PRPH and Nf aggregate formation, indicating alternatively spliced variants of PRPH may contribute to neurodegeneration in ALS. In fact, the pathologies of PRPH along with other NfPs have been found in spheroids in patients with ALS and overexpression of PRPH causes late onset death of motor neurons in mice (Beaulieu et al., 1999). In addition to PRPH pathology, mutations of PRPH gene have also been linked to ALS (Gros-Louis et al., 2004; Leung et al., 2004). Like NfL and INA mRNAs, PRPH mRNA is also reduced in motor neurons in ALS (Wong et al., 2000). After nucleocytoplasmic export, PRPH mRNA form particles with RNPs (Chang et al., 2006). The messenger RNPs (mRNPs) of PRPH are translationally silent while moving along microtubules and initiate translation when they cease moving. Unlike NfM mRNA which binds hnRNP K, PRPH mRNA does not bind hnRNP K and

knockdown of hnRNP K has no effect on PRPH mRNA nucleocytoplasmic export and translation (Liu et al., 2008).

Since current evidences suggest significant differences in the transcriptional regulation of different Nf proteins, these Nf subunits may show not only coordinate mRNA expression but also independent regulation. These findings are consistent with the different roles of NfPs in different neuronal compartments (Kriz et al., 2000; Yuan et al., 2015, 2018).

7. Posttranscriptional regulation of tau

7.1. tau mRNA dynamics

Human tau protein is encoded by a single gene located on chromosome 17q21 (Andreadis, 2005). By alternative splicing, six isoforms are produced in CNS whereas with apparent molecular masses between 48 and 67 kDa and additional isoforms of 110 kDa that include exons 4a and exon 6 are expressed in PNS (Fischer and Baas, 2020). The expression of tau mRNAs in the spinal cord appeared to precede that in the brain, and the expression in the brainstem appeared to precede that in cerebral cortex and cerebellum (Takemura et al., 1991). Interestingly, tau pre-mRNA is alternatively spliced to produce exon 10^+ and exon 10^- tau isoforms that are expressed in approximately equal amounts in adult human brain (Fig. 1D)(Avila et al., 2004). Some tau disease-causing mutations alter the expression levels of tau isoform in FTD (Hutton et al., 1998) and a recent study identified a new non-aggregative splicing form of human tau and showed that its level is decreased in AD brains (Garcia-Escudero et al., 2021). Like Nf mRNAs, transport, stability and local translation of tau mRNA may also be dependent on RBPs and miRNAs. Interestingly, it was suggested that motor protein KIF3 could anchor RBP HuD and transport the HuD-tau mRNA complex along axons (Aronov et al., 2002). Dysfunction of these process could lead to neurodegeneration. Unlike other mRNA targets, tau mRNA is a relatively stable molecule (Sadot et al., 1995) with a half-life of 16 h in neuronal cells. Its stability is likely determined by interaction of 3'UTR of tau mRNA, RBPs and miRNAs (Aronov et al., 1999).

7.2. 3'-UTR of tau mRNA and regulation by RBPs

Two RBPs of 43 and 38 kDa were first identified to bind a minimal sequence of 91 nucleotides within the 3'UTR of tau mRNA (Behar et al., 1995). These RBPs were later characterized as embryonic lethal abnormal vision (ELAV)-like RNA-binding proteins (HuD) (Aranda-Abreu et al., 1999). More RBPs, including the insulin-like growth factor mRNA binding-protein 1 (IMP-1) and RAS-GAP SH3 domain binding protein (G3BP), were later also found to bind tau mRNA and interact with HuD (Atlas et al., 2004). The posttranscriptional regulation of tau expression by thyroid hormone (T3) is also mediated by RBP called musashi-1 (Cuadrado et al., 2002). Splicing factor SC35 can also stabilize tau mRNA through binding to the SC35-like element of exon 10 and thus promotes 4-repeat tau expression (Qian et al., 2011). Other tau exon 10 regulators include suppressor-of white-apricot (SWAP) and hnRNP G (Wang et al., 2004). FUS also directly binds to tau pre-mRNA and loss of FUS promotes pathological tau splicing (Orozco et al., 2012), indicating a possible link between FUS and tau pathologies in FTD. Similarly, TDP43 can bind to the UG repeats of tau 3'UTR, promoting its mRNA instability and leading to suppressed tau

protein expression (Gu et al., 2017). In fact, the presence of TDP43 pathologies in about 97% of ALS and 50% FTD and significant tau pathologies in about 50% of ALS-FTD spectrum also supports the intracellular interaction of TDP43 and tau (Behrouzi et al., 2016; Moszczynski et al., 2019). Like INA, tau is also regulated post-transcriptionally by hnRNP K as hnRNP K knockdown yielded defect in its nuclear export and translation but not transcription (Liu and Szaro, 2011). G3BP1and IMP1 have also been identified to bind to the 3'UTR of the tau mRNA (Atlas et al., 2007). Induction of RNA protein granules by G3BP1 or IMP1 could lead to more than 30-fold increase in the ratio of high molecular weight to low molecular weight tau mRNA and about a 12-fold increased ratio of high molecular weight to low molecular weight tau protein (Moschner et al., 2014). Serine and arginine rich splicing factor 2 (SRSF2) is another RBP that plays important roles in splicing of mRNA precursors and its levels are elevated in the brains of patients with progressive supranuclear palsy characterized by intracellular aggregation of 4 R tau isoforms (Bruch et al., 2014). SRSF2 upregulation through inhibition of mitochondrial complex I could also promote 4 R tau in human neurons. Tau mRNA is also a component of granules containing fragile X mental retardation protein (FMRP)-and Staufen 1-positive RNA granules within the dendritic component of primary hippocampal neurons where AMPA and NMDA receptor stimulation potentially enhance local translation of tau proteins (Kobayashi et al., 2017). On the one hand, posttranscriptional regulation of tau is controlled by RBPs. On the other hand, tau itself negatively regulates protein synthesis and alters synaptic function by interacting with ribosomal proteins (Koren et al., 2019; Meier et al., 2016; Papanikolopoulou et al., 2019).

7.3. Regulation of tau by miRNAs

Dicer is a key enzyme in the biogenesis of miRNAs, small non-coding RNAs that function as part of the RNA-induced silencing complex (RISC) to repress gene expression at the posttranscriptional level. Mice lacking dicer in the forebrain displayed progressive neurodegeneration accompanied by tau hyperphosphorylation (Hebert et al., 2010), suggesting miRNAs may contribute to tau pathologies in tauopathy. Later studies found that miR-132, which is downregulated in PSP, inhibits 4 R tau expression in neuronal cells (Smith et al., 2011). Further investigations also demonstrated decrease of miR132-3p levels in neurons enriched with hyperphosphorylated tau in AD brains (Lau et al., 2013). Another non-coding miRNA miR-219 is not only downregulated in AD and primary age-related tauopathy but also can bind directly to the 3'UTR of the tau mRNA and therefore represses tau synthesis at the posttranscriptional level (Santa-Maria et al., 2015).

8. Distinctions and inter-related functions of Nf and tau in neurons

Nf and tau proteins clearly belong to two distinct class of protein family with different structures and different, and in various contexts inter-related, functions in the neuron. The former is classified as highly insoluble proteins of intermediate filaments found in the cytoplasm of neurons whereas the latter is a highly soluble microtubule-associated protein. Their newly synthesized proteins are also transported at different rates along mouse optic axons (Mercken et al., 1995; Yuan et al., 2006). However, they are directly linked physically both under physiological and pathological conditions (Miyata et al., 1986; Rudrabhatla et

al., 2011). Both Nf and tau proteins are especially enriched in axons and share functions related to microtubule polymerization and stability (Bocquet et al., 2009; Yadav et al., 2016), axonal transport and scaffolding of organelles in axons (Mueller et al., 2021; Perrot and Julien, 2009; Rao et al., 2011). Recent evidence also demonstrates their presence at the synapse (Ittner et al., 2010; Kimura et al., 2014; Yuan et al., 2015) and roles in long-term synaptic potentiation, learning and memory (Ahmed et al., 2014; Biundo et al., 2018; Yuan et al., 2015). Both NfPs and tau undergo posttranslational modifications such as phosphorylation, and hyperphosphorylation of tau (Karikari et al., 2020), NfH, and NfM (Rudrabhatla et al., 2010) are particularly implicated in Alzheimer disease. Both proteins also share many of the kinases / phosphatases for their regulation and are used as biomarkers of neurodegeneration often associated with their hyperphosphorylation or abnormal degradation. Deletion of NfP can also diminish tau pathological lesions and attenuate disease phenotype caused by tau abnormality (Ishihara et al., 2001).

9.   Potential common mechanisms of posttranscriptional dysregulation in both Nf-associated diseases of the CNS and tauopathies

Both the mRNAs and proteins of Nf and tau can be transported into axons (Alami et al., 2014; Morita and Sobue, 2009), dendrite (Balaji et al., 2018) and synapses (Crispino et al., 1993; Kobayashi et al., 2017) (Fig. 2). Since Nf and tau proteins are especially enriched in axons, any damage to neuronal cytoskeleton in this domain could potentially lead to pathologies of both proteins. In fact, tau and Nf proteins are both components of neurofibrillary tangles in AD (Rudrabhatla et al., 2011). In addition to these tangles, approximately 57% of AD cases also have TDP43 deposits in the brain (Meneses et al., 2021). It is also known that Nf aggregates and TDP43 pathology are hallmarks of ALS (Hardiman et al., 2017). Moreover, a 17 kDa neurotoxic tau fragment (tau$^{45-230}$) has been recently observed in extracts of both brain and ventral spinal cord of ALS patients, but not in controls (Vintilescu et al., 2016). More recently, elevated levels of tau and a phosphorylated form of the tau protein were reported in the brain of ALS cases who carried a mutation in the C9orf72 gene (Petrozziello et al., 2022). Similarly, PD was not initially considered to be a typical tauopathy. However, a genome-wide association study indicated a potential association between tauopathy and sporadic PD (Nalls et al., 2014). The aggregation and deposition of tau were also observed in about 50% of PD brains (Zhang et al., 2018). Since TDP43 has opposite effects on the stability of NfL (Strong et al., 2007) and tau mRNAs (Gu et al., 2017) through direct interaction with their 3'-UTR, this RBP could be involved in the posttranscriptional dysregulation of both Nf and tau proteins in these neurodegenerative diseases. Intriguingly, TDP43 may also modulate anterograde transport of messenger ribonucleoprotein granules (Chu et al., 2019) that could contain mRNAs of NfL (Alami et al., 2014) and tau (Aronov et al., 2002; Villace et al., 2004). In addition to TDP43, two other RBPs, FUS and Pabpc1, could also be involved in the dysregulation of Nf and tau mRNAs in diseases since the former can modulate mRNAs of Nefl, Nefm, Nefh and Mapt while the latter shields the NfL mRNA from aldolase attack (Stefanizzi and Canete-Soler, 2007) and co-localizes with small tau inclusions in tauopathy (Maziuk et al., 2018). Besides RBPs, some miRNAs may also have common targets involving both Nf and tau proteins since these two classes of proteins are both involved in disease pathologies of AD and PD

(Goldman et al., 1983; Rudrabhatla et al., 2011; Zhang et al., 2018). However, the specific miRNAs targeting both Nf and tau have not been reported. Nevertheless, miRNA125b was shown to be involved in the modulation of NfM and NfH mRNAs (Campos-Melo et al., 2018) and this same miRNA also induces tau hyperphosphorylation and cognitive deficits in AD (Banzhaf--Strathmann et al., 2014). Therefore, regulation of tau protein by miRNA 125b needs to be further investigated. Another miRNA, miRNA 30b was also shown to suppress NfL expression through interaction with its 3'-UTR. This miRNA is also upregulated in the brains of both AD patients and APP transgenic mice (Song et al., 2019). Future studies will be needed to examine the posttranscriptional regulation of tau protein by this miRNA.

10.   Summary and future research

Protein synthesis is an essential mechanism to ensure proper function of neurons. For years, it was assumed that protein synthesis of Nf and tau occurs exclusively in the neuronal cell body (Fig. 3A–3B), from where the synthesized proteins are then transported through kinesins or dynein associated with microtubules (Fig. 3 C) to local compartments where they carry out their functions (Fig. 3D). In recent years, however, evidence has accumulated that transport of Nf and tau proteins from the soma to peripheral sub-compartments is only one way to supply them to distal neuronal processes. Another way to provide the proteins for immediate need in peripheral subcellular domains is the transport of their mRNAs in the form of transport granules associated with molecular motors or vesicles (Cioni et al., 2019) from the soma to axons, dendrites and their synaptic terminals for subsequent translation into proteins (Fig. 3E–3 F). During their transport, these transcripts are usually translationally repressed and once they reach their target, these mRNAs are translated into proteins to fulfill rapid local demand for new proteins and to provide subcellular functions such as survival of axons, synaptogenesis and experience-dependent plasticity. Despite the importance of posttranscriptional regulation of Nf and tau proteins, our current knowledge of trans-acting factors and cis-acting elements that affect Nf and tau pre-mRNA splicing, mature mRNA stability, transport, localization, and local translation in health and disease remains rather limited. Nevertheless, available evidence suggests that RBPs, including TDP43 and FUS, and miRNAs play crucial roles in posttranscriptional control of Nf and tau expression in both physiological and pathophysiological contexts. Control of Nf and tau mRNA stability, transport and local translation facilitates the temporal and spatial expression of varied NfP assemblies and tau variants in different neuronal compartments. Dysfunction or altered abundance of RBPs, such as TDP43, FUS and also miRNAs, and consequently changes in the relative levels of NfPs and tau may be involved in pathogenesis of neurodegenerative disorders. It will be of interest in the future to directly assess the half-lives of Nf and tau mRNAs and to identify additional RNA-binding proteins and miRNAs that stabilize or destabilize these mRNAs and their impact on aging and aging-related disease. It is also important to know if different Nf mRNAs are transported alone or together along axons and dendrites and how different RBPs and miRNA work together to co-ordinate the dynamic co-translation of NfPs and their assembly and interaction with tau proteins in different neuronal compartments.

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Data Availability

No data was used for the research described in the article.

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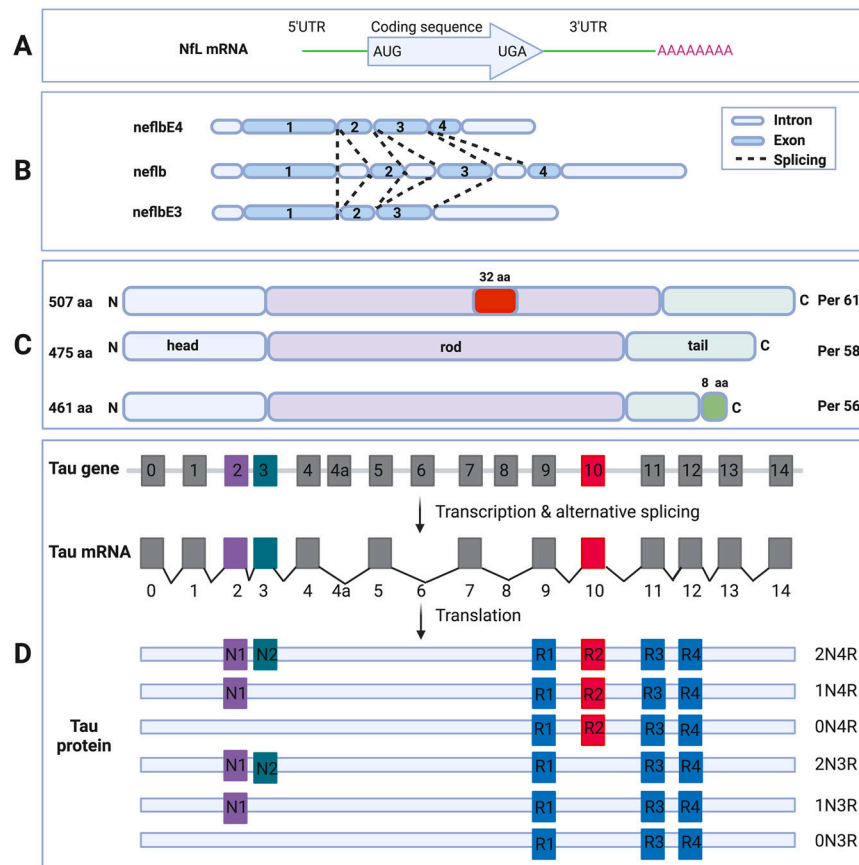
Fig. 1.

Schematic diagram of NfL mRNA (A). 5'UTR, protein coding region, 3'UTR and the poly-A tail are shown (upper box). Schematic diagram of the neflb isoforms, generated by alternative splicing of the same mRNA in zebrafish (B). neflb is expressed at all embryonic and larval stages in zebrafish, which a splicing shift from neflbE3 to neflbE4 occurring during CNS development. Schematic diagram of the PRPH isoforms, generated by alternative splicing of the same mRNA (C). Per 58 is the major constitutive form; Per 61 results from the insertion of 32 aa in the rod domain; Per 56 results from the replacing the C-terminal 21 aa with a different 8 aa sequence. Schematic diagram of MAPT gene, mRNA and splice isoforms of tau in the human brain (D). Human MAPT gene contains 16 exons. E1, E4, E5, E7, E9, E11, E12 and E13 are constitutive, whereas others are subject to alternative splicing. E0 and E1 encode the 5'UTR, whereas E14 is part of the 3'UTR. E4a, E6 and E8 are transcribed only in peripheral tissues. The alternative splicing of E2, E3 and E10 give rise to 6 different mRNAs, which are translated to 6 isoforms. These isoforms differ by the presence of 1 or 2 N-terminal inserts encoded by E2 (purple box) and E3 (green box), in combination with the presence of either 3 or 4 repeat regions coded by E9 (blue box), E10 (red box), E11 (blue box) and E12 (blue box) in the C-terminus.
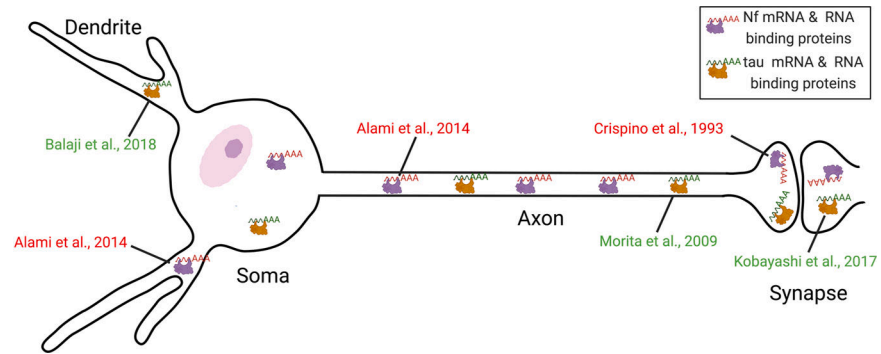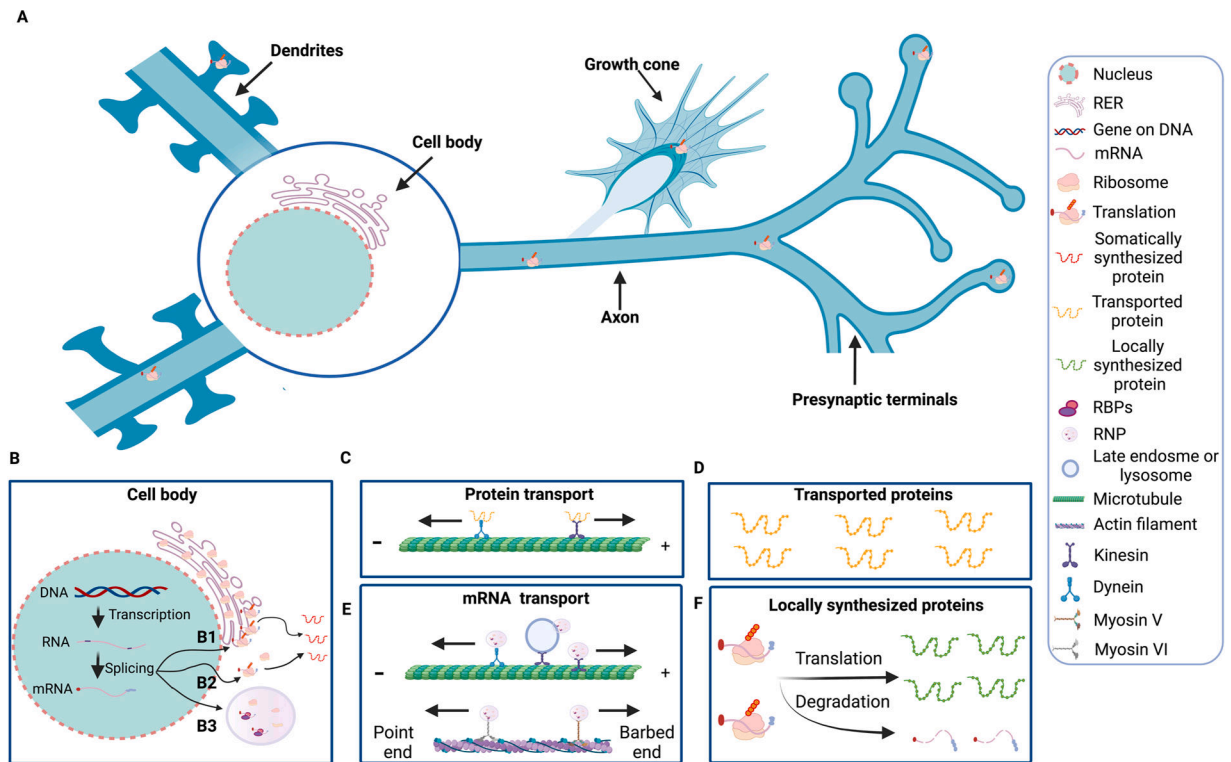
Fig. 2.
Distribution of the mRNA pools of Nf and tau in the different subcellular compartments of a neuron with references to the respective studies. mRNAs of Nf and tau can be transported into axons, dendrites and synapses in the form of transport granules composed of RNA binding proteins and RNAs.

Fig. 3.

Control points of gene expression in neurons. Genes encoded in chromosomal DNA are transcribed into heterogeneous pre-mRNA, which undergo splicing, capping and addition of a poly-A tail to an RNA molecule (A). The nuclear mRNA forms complexes with ribonucleoproteins (RNPs), some of which exit from the nucleus (B). Once in the cytosol, mRNA can be translated by ribosomes associated to rough endoplasmic reticulum (RER) (B1) and free cytosolic ribosomes (B2). The lifetime of an mRNA molecule in the cytosol affects how many proteins can be made from it. Small regulatory RNAs called miRNAs can bind to target mRNAs and cause them to be cleaved. Translation starts with the binding of 40 S ribosomal subunit to cap, scanning of the 40 S subunit for start codon recognition, and then binding of the 60 S ribosomal subunit to 40 S subunit. Following these events, translation elongation, co-initiation of new rounds of translation, translation termination of each active ribosome, and lastly complete translation termination, which releases the mRNA to degradation. Synthesized proteins are transported through kinesins or dynein associated with microtubules (C) to local compartments where they carry out their functions (D). Alternatively, mRNA transcripts are associated to RNA-binding proteins (RBPs) and assembled as RNP granules (**B3**), which can be transported with kinesins and dynein or myosin linked to actin filaments. Late endosome or lysosomes can also act as vesicular transporters for RNA granules (**E**). During their transport, these transcripts are usually translationally repressed and once reach their target, these mRNAs are translated into proteins for immediate local needs (**F**).

Table 1

Mutations or pathologies of Nf & Tau proteins linked to neurological diseases.

Genes	Mutations or pathologies of Nf or Tau	Linked diseases	References
NEFL	Both	Charcot-Marie-Tooth disease type 1 F	(Jordanova et al., 2003)
		Charcot-Marie-Tooth disease type 2E	(Mersiyanova et al., 2000)
		Charcot-Marie-Tooth disease, Dominant intermediate G	(Berciano et al., 2016)
		Congenital myopathy	(Agrawal et al., 2014)
		Hereditary spastic paraplegia	(Mul et al., 2020)
NEFH	Both	Charcot-Marie-Tooth disease, Axonal, Type 2CC	(Rebelo et al., 2016)
		Amyotrophic lateral sclerosis	(Al-Chalabi et al., 1999)
PRPH	Both	Amyotrophic lateral sclerosis	(Leung et al., 2004)
		Peripheral neuropathy	(Bjornsdottir et al., 2019)
INA	Pathology	Neuronal intermediate filament inclusion disease	(Cairns et al., 2004)
NEFM	Both	Parkinson disease	(Lavedan et al., 2002)
MAPT	Both	Frontotemporal dementia with or without	(Hutton et al., 1998)
		parkinsonism Pick disease	(Murrell et al., 1999)
		Progressive supranuclear palsy 1	(Poorkaj et al., 2002)
		Atypical progressive supranuclear palsy 1	(Pastor et al., 2001)
		Parkinson disease	(Martin et al., 2001)

Table 2

Functions of Nf & Tau mRNA binding proteins and miRNAs.

Function	RNA binding proteins & miRNAs	Binding to Nf or Tau	Cis-acting RNA element	References
mRNA stabilizers	TDP43	NEFL	$(UG)_{6-9}$	(Strong et al., 2007)
	ARHGEF28	NEFL	68 nucleotides spanning the end of the open reading frame & beginning of the 3'-UTR	(Canete-Soler et al., 2001)
	PABP	NEFL	Full-length instability determinant	(Stefanizzi and Canete-Soler, 2007)
	NGF	NEFL	Undetermined	(Ikenaka et al., 1990)
	miR-b1336 & miR-b2403	NEFL	3'-UTR	(Ishtiaq et al., 2014)
	ELAV4	MAPT	U-rich segment of 3'-UTR	(Aranda-Abreu et al., 1999)
	SRSF2	MAPT	Exon 10	(Qian et al., 2011)
mRNA destabilizers	SOD1	NEFL	Undetermined	(Ge et al., 2005)
	14-3-3 proteins	NEFL	GCTTGC motif MI	(Ge et al., 2007)
	Aldolase A	NEFL	UG sites	(Canete-Soler et al., 2005)
	Aldolase C	NEFL	UG sites	(Canete-Soler et al., 2005)
	NF-RBP1	NEFL & NEFH	45 nt at the proximal edge of the NfL 3'-UTR & 36 nt in the mid-distal region of the NfH 3'-UTR	(Canete-Soler and Schlaepfer, 2000)
	miR-219	MAPT	3'-UTR	(Santa-Maria et al., 2015)
	TDP43	MAPT	2 UG repeats of its 3'-UTR	(Gu et al., 2017)
mRNA modulation	FUS	NEFL, NEFM, NEFH & MAPT	3'-UTR	(Lagier-Tourenne et al., 2012)
	miR-146a, miR624–5p & miR-582–3p	NEFL	3'-UTR	(Campos-Melo et al., 2013)
	MiR-9–5p, miR-20b-5p, miR-92a-3p, miR-125b-5b & miR-233–3p	NEFM & NEFH	3'-UTR	(Campos-Melo et al., 2018)
Enhancer of mRNA transport	hnRNP K	NEFL, NEFM & NEFH	Prefer CU-rich elements	(Liu et al., 2008; Thyagarajan and Szaro, 2008)
Enhancer of mRNA translation	hnRNP K	NEFM, INA & MAPT	Prefer CU-rich elements	(Liu et al., 2008; Liu and Szaro, 2011)
Translation inhibition	ELAVL2	NEFM	Non-canonical AREs in the 3'-UTR	(Antic et al., 1999)
	ELAV4, IGF2BP1 & G3BP1	MAPT	3'-UTR	(Atlas et al., 2007)
Structural effects on mRNA	14-3-3 proteins	NEFL	GCTTGC motif M2	(Ge et al., 2007)
Pre-mRNA splicing	Musashi-1	MAPT	Exon 10	(Cuadrado et al., 2002)

Function	RNA binding proteins & miRNAs	Binding to Nf or Tau	Cis-acting RNA element	References
	SWAP, hnRNP G	MAPT	Exon 10	(Wang et al., 2004)
	miR-16, miR-132	MAPT	Exon 10	(Hebert et al., 2012)
	FUS	MAPT	Exons 3 & 10	(Orozco et al., 2012)
	FMRP	MAPT	Exon 10	(Zhou et al., 2017)
Undetermined	hnRNP E1/E2	NEFL, NEFM & NEFH	3'-UTR	(Thyagarajan and Szaro, 2004, 2008)

Table 3

Mutations of RNA-binding proteins linked to ALS/FTD spectrum.

Genes	RNA-binding proteins	Mutations	References
TARDBP	Yes	Missense	(Benajiba et al., 2009; Borroni et al., 2009)
FUS	Yes	Missense	(Broustal et al., 2010; Van Langenhove et al., 2010)
HNRNPA1	Yes	Missense	(Kim et al., 2013)
HNRNPA2/B1	Yes	Missense	(Kim et al., 2013)
TIA1	Yes	Missense	(Mackenzie et al., 2017)
MATR3	Yes	Missense	(Johnson et al., 2014)
TAF15	Yes	Missense	(Ticozzi et al., 2011)
EWSR1	Yes	Missense	(Couthouis et al., 2012)
ANG	Yes	Missense	(van Es et al., 2009)
GLE1	Yes	Multiple	(Kaneb et al., 2015)
SETX	Yes	Missense	(Chen et al., 2004)
ARHGEF28	Yes	Frameshift	(Droppelmann et al., 2013b)
SOD1	Yes	Missense	(Katz et al., 2012)
ATXN2	Yes	PolyQ expansions	(Elden et al., 2010)
C9orf72	RNA toxicity	G4C2 repeat expansion	(DeJesus-Hernandez et al., 2011)