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Pathomechanisms of TDP-43 in neurodegeneration

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Abstract

Neurodegeneration, a term that refers to the progressive loss of structure and function of neurons, is a feature of many neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). There is no cure or treatment available that can prevent or reverse neurodegenerative conditions. The causes of neurodegeneration in these diseases remain largely unknown; yet, an extremely small proportion of these devastating diseases are associated with genetic mutations in proteins involved in a wide range of cellular pathways and processes. Over the past decade, it has become increasingly clear that the most notable neurodegenerative diseases, such as ALS, FTLD, and AD, share a common prominent pathological feature known as TAR DNA-binding protein 43 (TDP-43) proteinopathy, which is usually characterized by the presence of aberrant phosphorylation, ubiquitination, cleavage and/or nuclear depletion of TDP-43 in neurons and glial cells. The role of TDP-43 as a neurotoxicity trigger has been well documented in different *in vitro* and *in vivo* experimental models. As such, the investigation of TDP-43 pathomechanisms in various major neurodegenerative diseases is on the rise. Here, after a discussion of stages of TDP-43 proteinopathy during disease progression in various major neurodegenerative diseases, we review previous and most recent studies about the potential pathomechanisms with a particular emphasis on ALS, FTLD, and AD, and discuss the possibility of targeting TDP-43 as a common therapeutic approach to treat neurodegenerative diseases.

Keywords

Alzheimer's disease; amyotrophic lateral sclerosis; frontotemporal lobar degeneration; neurodegeneration; Neurodegenerative diseases; TDP-43

Neurodegenerative diseases encompass a large number of disorders characterized by progressive loss or dysfunction of neurons in the central nervous system (CNS) or peripheral nervous system (PNS) during aging. Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and frontotemporal lobar degeneration (FTLD) are all widely known neurodegenerative diseases. Although progressive neuronal impairment is the common hallmark of all neurodegenerative diseases, specific neurodegenerative disorders demonstrate distinct pathological and clinical features

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and can be distinguished by their characteristic neuronal loss occurring in specific brain regions or spinal cord. The prevalence of neurodegenerative diseases has increased rapidly in the past decades. However, effective treatments for these devastating diseases remain very limited.

TAR DNA-binding protein 43 (TDP-43, encoded by the *TARDBP* gene and also referred to as ALS10) was first identified as a host cell protein that binds specifically to pyrimidine-rich DNA motifs in a long terminal repeat, known as TAR of human immunodeficiency virus type 1 and represses virus type 1 gene transcription (Ou *et al.* 1995). However, subsequent studies have demonstrated that TDP-43 more frequently binds RNA and regulates messenger ribonucleic acid (mRNA) splicing, translation, transportation, and even degradation (Buratti and Baralle 2001; Buratti *et al.* 2001, 2005; Hefferon *et al.* 2004; Ayala *et al.* 2005; Mercado *et al.* 2005). The link between TDP-43 and neurodegenerative diseases was established by the initial identification of TDP-43 as the major component of the pathological hallmark, ubiqui-tin-positive protein inclusions, in patients with ALS and FTLD (Arai *et al.* 2006; Neumann *et al.* 2006). The discovery of genetic mutations in TDP-43 associated with both ALS and FTLD soon followed (Kabashi *et al.* 2008; Kwiatkowski *et al.* 2009; Vance *et al.* 2009). Since then, TDP-43 has become a novel rising star in the field of neurodegenerative diseases.

Despite different etiologies, clinical symptoms, and pathological hallmarks, various major neurodegenerative diseases demonstrate similar TDP-43 pathological manifestations in neurons and even glia including the accumulation of detergent-resistant, ubiquitinated or hyperphosphorylated TDP-43 inclusions in the cytoplasm, usually accompanied by the depletion of TDP-43 from the nucleus. These characteristic TDP-43-related pathological features are usually referred to as TDP-43 proteinopathy. Interest in understanding the path-omechanisms underlying TDP-43 proteinopathy has increased substantially in the past decade, largely because of the presence of TDP-43 proteinopathy as a common key pathological feature in a wide range of different neurodegenerative diseases including ALS (Kabashi *et al.* 2008; Sreedharan *et al.* 2008), FTLD (Kabashi *et al.* 2008; Sreedharan *et al.* 2008), AD (Amador-Ortiz *et al.* 2007; Josephs *et al.* 2014), PD (Chanson *et al.* 2010), and HD (Schwab *et al.* 2008; Davidson *et al.* 2009). In this review, we first describe the stages and progression of TDP-43 proteinopathy in various major neurodegenerative diseases with a particular emphasis on ALS, FTLD, and AD, extensively discuss the potential pathomechanisms of TDP-43, and finally provide insight into the possibility of targeting TDP-43 as a common therapeutic approach to treat neurodegenerative diseases.

Stages of TDP-43 proteinopathy in ALS, FTLD, and AD

Amyotrophic lateral sclerosis

ALS, also known as Lou Gehrig's disease, is the most common motor neuron disease characterized by progressive and fatal degeneration of both upper and lower motor neurons, causing progressive muscle denervation, weakness, atrophy, spasticity, paralysis, and eventually death (Pasinelli and Brown 2006). The vast majorities of ALS cases have no family history and are usually referred to as sporadic ALS (sALS). Less than 10% of ALS cases are familial (fALS), of which approximately 40% are caused by repeat expansions of

the C9ORF72 gene, 20% by mutations in the gene encoding copper–zinc super-oxide dismutase (SOD1), 4% each by mutations in TDP-43 or fused in sarcoma (FUS), and less than 1% each by mutations in many other genes encoding p62 (SQSTM1), optineurin, TANK-binding kinase 1, ubiliquin-2 (UBQLN2), vesicle-associated membrane protein-associated protein B, senataxin (SETX), angiogenin (ANG), valosin-containing protein (VCP), SIGMAR1, or dynactin (DCTN1) (Chen *et al.* 2013; Picher-Martel *et al.* 2016).

Although a very small subset of sALS and fALS patients are associated with TDP-43 mutations, TDP-43 proteinopathy can be present in up to 97% of ALS patients (Arai *et al.* 2006; Neumann *et al.* 2006; Mackenzie *et al.* 2007), suggesting the likely critical role of TDP-43 in the pathogenesis of this devastating disease. Based on TDP-43 proteinopathy in neurons, ALS can be effectively divided into different stages with the first stage characterized by the appearance of lesions in the motor cortex, brainstem, and spinal cord; the second stage by increased lesions in the prefrontal neocortex, brainstem, precerebellar nuclei, and the red nucleus; the third stage by the spreading of pathology to the prefrontal and postcentral neocortex and striatum, and the advanced stage by the greatest burden of lesions in anteromedial portions of the temporal lobe (Brettschneider *et al.* 2013, 2014), further highlighting the role of TDP-43 in disease progression. Although TDP-43 proteinopathy is unlikely epiphenomena in ALS, its role in the degeneration of motor neurons remains debatable. Notably, TDP-43 proteinopathy was also seen in non-neural cells such as astrocytes and microglia in patients with ALS (Brettschnei-der *et al.* 2012; Sloan and Barres 2013), providing the possibility that TDP-43 proteinopathy may trigger motor neuron death in both cell-autonomous and non-cell-autonomous models.

Frontotemporal lobar degeneration

FTLD, characterized by the progressive decline in behavior or language associated with degeneration of the frontal and anterior temporal lobes of the brain, is the second most frequent form of dementia in people under the age of 65 years after AD (Ratnavalli *et al.* 2002). The most common clinical presentations of FTLD typically include behavioral variant frontotemporal dementia, semantic variant primary progressive aphasia, and nonfluent variant primary progressive aphasia, with behavioral variant frontotemporal dementia as the most common form accounting for nearly 60% of FTLD patients (Onyike and Diehl-Schmid 2013; Pan and Chen 2013). As a group of clinically heterogeneous disorders, FTLD may also comprise progressive supranuclear palsy and corticobasal syndrome (CBS), and clinically and neuropathologically overlap with ALS and other motor neuron diseases (MND) (Tsai and Boxer 2014). Approximately 30–50% of FTLD cases are familial and associated commonly with genetic mutations in C9ORF72, progranulin (GRN), and microtubule-associated protein tau, and rarely with VCP and Chromatin-modifying protein 2B, TDP-43, FUS, p62/SQSTM1, and ubiquilin 2 (UBQLN2) (Galimberti *et al.* 2015). The non-coding G4C2 hexanucleotide repeat expansion in C9orf72 has been identified as the most common causal mutation in patients with concomitant FTLD and ALS (FTLD-ALS) (Mori *et al.* 2013). Of note, unlike C9ORF72, mutations in other ALS-associated proteins such as TDP-43 and FUS have only been linked to FTLD-ALS but not FTLD lacking MND (Mackenzie *et al.* 2010).

Historically, FTLD patients largely show cytoplasmic aggregates of proteins, often referred to as inclusion bodies, in neurons and glial cells. From a neuropathological perspective, FTLD can be classified into different pathological FTLD subtypes such as FTLD with tau-positive inclusions (FTLD-tau), FTLD with tau and alpha-synu-clein-negative but TDP-43 and ubiquitin-positive inclusions (FTLD-TDP, previously called FTLD with ubiquitin-positive inclusions, FTLD-U), FTLD with FUS-positive inclusions (FTLD-FUS) and rare FTLD with no inclusion (FTLD-ni or previously known dementia lacking distinctive histopathology) (Arai *et al.* 2006; Bigio 2011; Dickson *et al.* 2011). Despite the very rare prevalence of TDP-43 mutations in FTLD, FTLD-TDP represents the most frequent FTLD subtype and TDP-43 proteinopathy (largely TDP-43-positive cytoplasmic inclusions and neurites and occasionally TDP-43-positive neuronal intranuclear inclusions) can be noted in up to 50% of FTLD cases (Cairns *et al.* 2007; Mackenzie 2007; Hasegawa *et al.* 2008; Weihl *et al.* 2008). In FTLD patients, TDP-43-positive inclusions are primarily noted in the frontotemporal cortex as well as the dentate gyrus of the hippocampus, and may also be found in the cranial nerve nuclei of the brainstem and anterior horn of the spinal cord (Davidson *et al.* 2007).

Alzheimer's disease

AD is the most prevalent form of dementia in the elderly characterized by the progressive loss of neurons in brain regions critical for memory, learning, conscious thought, and language and is usually accompanied by two pathologic hallmarks, neurofibrillary tangles (NFTs) and senile plaques (SPs), and other prominent pathological changes such as neuronal loss, granulovacuolar degeneration, and dystrophic neurites (Smith 1998). NFTs are intracellular lesions composed of hyperphosphorylated tau, while SPs are made up of bundles of amyloid-β(Aβ) peptide fibrils (Smith 1998). Recently, cytoplasmic TDP-43-positive inclusions have been identified as the third predominant proteinopathy in the brains of individuals diagnosed with AD (Amador-Ortiz *et al.* 2007; Higashi *et al.* 2007; Arai *et al.* 2009). About 90% of AD cases are referred to as sporadic AD and are not genetically transmitted (Zhu *et al.* 2005). Less than 10% of AD cases are familial AD, involving a mutation in β-amyloid precursor protein (APP), presenilin 1 (PS1), or presenilin 2 (PS2), with PS1/2 associated with the majority of early-onset familial AD (Czech *et al.* 2000; Fraser *et al.* 2000; Tanahashi and Tabira 2000).

TDP-43-positive inclusions detected using a C-terminal TDP-43 antibody occur in a stereotypic manner over the latest six distinctive stages in AD (Josephs *et al.* 2014, 2016). The cytoplasmic accumulation of TDP-43 in neurons begins in the amygdala in stage 1 and then moves to the entorhinal cortex and subiculum in stage 2, to the dentate gyrus of the hippocampus and occipitotemporal cortex in stage 3, to the insular cortex, ventral striatum, basal forebrain, and inferior temporal cortex in stage 4, to the substantia nigra, inferior olive, and midbrain tectum in stage 5 and finally to the basal ganglia and middle frontal cortex in stage 6. It is also worth noting that the recent report that cytoplasmic TDP-43 inclusions are associated with AD-type dementia independent of pathologic hallmarks NFTs and SPs, and that patients with mixed TDP-43, Aβ, and tau proteinopathies show more severe AD-type dementia than patients with Aβand tau proteinopathies alone (James *et al.* 2016).

Pathomechanisms of TDP-43

RNA alternate splicing

As an ubiquitously expressed 414-amino acid (aa) protein structurally resembling the members of RNA-binding protein heterogeneous nuclear ribonucleoprotein (hnRNPs) (Buratti and Baralle 2008; Buratti and Baralle 2012; Lee *et al.* 2011), TDP-43 is composed of an N-terminal domain (NTD, 1-102aa), two RNA recognition motifs (RRM1, 106-177aa and RRM2, 192-259aa) and a carboxy-terminal glycine-rich domain (CTD, 274-414aa). RRM1 and RRM2 belong to a widely existing eukaryotic RNA recognition motif family (RRM is also referred to as RNA-binding domain or ribonucleoprotein domain (RNP)) (Clery *et al.* 2008) (Fig. 1a). Like hnRNPs, as a primarily nuclear RNA-binding protein, TDP-43 has been consistently reported to bind UG-rich domains within proximal intron regions or 3′-untranslated regions of mRNAs encoding proteins such as cystic fibrosis transmembrane conductance regulator (Buratti *et al.* 2001), POLDIP3 (Fiesel *et al.* 2012; Shiga *et al.* 2012; Colombrita *et al.* 2015), SORT1 (Prudencio *et al.* 2012; Mohagheghi *et al.* 2016), MADD/STAG2/FNIP1/BRD8 (De Conti *et al.* 2015), SEPT6/SULT4A1/TNIK/DICER/ELAVL3 (Colombrita *et al.* 2015), or even *TARDBP's* own transcripts (Ayala *et al.* 2011) to regulate mRNA alternative splicing. Previous studies found that TDP-43 deficiency could facilitate the use of cryptic splice sites to reduce correctly spliced protein-encoding mRNAs (Mercado *et al.* 2005; Ayala *et al.* 2006). Although the global functional consequence(s) of the binding of TDP-43 to a variety of RNAs remains largely unknown, exciting recent findings of TDP-43 acting as a repressor of non-conserved cryptic exon splicing may lead to the identification of major functional RNA targets of TDP-43 (Ling *et al.* 2015; Tan *et al.* 2016; Humphrey *et al.* 2017).

A prominent feature of TDP-43 proteinopathy, the redistribution of TDP-43 from the nucleus to the cytoplasm is generally believed to cause a considerable loss of TDP-43 nuclear function and subsequent neuronal dysfunction (Buratti and Baralle 2009). In support of the loss of function hypothesis, the significantly enhanced TDP-43-associated cryptic exon splicing was reported in ALS patients with TDP-43-positive inclusions (Ling *et al.* 2015). And, unlike wild-type TDP-43, exogenously expressed ALS-associated mutant TDP-43 increases exon exclusion of mRNA targets involved in neuronal transmission and function (Polymenidou *et al.* 2011), further indicating that mutant TDP-43 proteins may lose their mRNA splicing abilities. Along this line, TDP-43 directly binds and regulates the splicing of pre-mRNAs of FTLD-associated FUS, progranulin, or tau (Polymenidou *et al.* 2011; Gu *et al.* 2017a, b). Accordingly, FTLD-ALS patients show significantly reduced expression of FUS or increased expression of progranulin at the mRNA and protein levels (Polymenidou *et al.* 2011). Even though a very recent study showed that TDP-43 suppresses tau expression by binding to its 3′-UTR, and the protein level of tau is increased in ALS patients and animal models expressing ALS-associated mutant TDP-43 (Gu *et al.* 2017b), reduced tau protein expression has been reported to be associated with at least a subset of FTLD patients, especially FTLD patient bearing progranulin mutations (Adamec *et al.* 2001; Zhukareva *et al.* 2001; Papegaey *et al.* 2016). Noteworthily, despite a previous study reporting the lack of association between TDP-43 proteinopathy and tau expression and mis-splicing in AD patients (Niblock *et al.* 2016), two very recent studies have shown the

regulation of tau mRNA stability and exon 10 alternative splicing by TDP-43 in cell and animal models (Gu *et al.* 2017a,b). In addition, it has been found that the cryptic exon incorporation can occur in AD cases showing TDP-43 nuclear depletion but lacking cytoplasmic TDP-43-positive inclusions (Sun *et al.* 2017).

Although these evidence support the possible involvement of TDP-43-related RNA splicing in neurodegeneration, the loss-of-function hypothesis is challenged by the absence of altered alternative splicing of exon 9 of cystic fibrosis transmembrane conductance regulator, one of the earliest and best-characterized targets of TDP-43 (Buratti and Baralle 2001), and other reported mRNA targets in ALS, FTLD, or AD patients or transgenic animal models. And, it still remains to be determined how the general pre-mRNA splicing activity of TDP-43 contributes to disease progression and how TDP-43 may interfere with the alternative splicing of diverse mRNAs to disrupt convergent molecular pathways.

Stress granules

TDP-43 contains both nuclear localization sequence and nuclear export sequence (NES), which are localized in the NTD and RRM2 domain, respectively (Ou *et al.* 1995; Lee *et al.* 2011) (Fig. 1a). Under physiological conditions, the majority of TDP-43 resides in the nucleus. However, likely due to the presence of NES, up to 30% of TDP-43 is also noted in the cytoplasm (Barmada *et al.* 2010) (Fig. 1b). Accompanying nuclear depletion, TDP-43 also shows characteristic cytoplasmic accumulation in neurons of ALS, FTLD, and AD patients. Previous studies have revealed that nuclear depletion is not required for neuronal toxicity induced by ALS-associated mutant TDP-43 (Arnold *et al.* 2013; Austin *et al.* 2014), and cytoplasmic mutant TDP-43 is sufficient to cause neurodegeneration (Barmada *et al.* 2010), therefore this suggests that, in addition to the loss of nuclear function, TDP-43 may also contribute to disease progression by the gain of neuronal toxicity function in the cytoplasm.

Stress granules (SGs) are cytoplasmic foci formed to suppress the translation of non-essential proteins to favor protective protein expression in response to stress. As non-membrane-bound RNA granules, SGs contain non-translating mRNA, translation initiation factors (eIF2α, eIF3 and eIF4A/B/G), and characteristic markers such as T-cell-restricted intracellular antigen-1 (TIA-1), TIA-like-1 (TIAR), Tristetraprolin, poly(A)-binding protein (PABP), and Ras-GTPase-activating protein SH3 domain-binding protein 1 (Decker and Parker 2012). In addition to SGs, mRNAs not engaged in translation can co-assemble with RNA-binding proteins to form other cytoplasmic mRNP granules such as processing bodies (P-bodies) and RNA transport granules. P-bodies consist of decapping enzymes and decapping activators to regulate RNA silencing and degradation, while RNA transport granules are responsible for the delivery of translationally repressed mRNAs (Decker and Parker 2012).

In ALS or FTLD patients, TDP-43 or phosphorylated TDP-43 has been reported to co-localize with SG makers TIA-1/PABP-1/eIF3 (Volkening *et al.* 2009; Liu-Yesucevitz *et al.* 2010; Bentmann *et al.* 2012; McGurk *et al.* 2014) (Fig. 1b), leading to one prevalent hypothesis that SG play an important role in the formation of TDP-43 inclusions. In support of this notion, TDP-43 inclusion formation can be suppressed by the inhibition of SG

formation using translational inhibitors (Liu-Yesucevitz *et al.* 2010). Along this line, the ablation of ataxin-2, a polyglutamine protein necessary for SG assembly (Nonhoff *et al.* 2007; Nihei *et al.* 2012), reduces TDP-43 proteinopathy and neurotoxi-city (Elden *et al.* 2010; Becker *et al.* 2017). In addition, ALS-associated mutant TIA-1 has recently reported to slow down SG disassembly and enhance the accumulation of non-dynamic SGs containing TDP-43 (Mackenzie *et al.* 2017). Meanwhile, TDP-43 may also contribute to SG formation and maintenance in response to stress, even though it is not an essential SG component (Colombrita *et al.* 2009; Liu-Yesucevitz *et al.* 2010; McDonald *et al.* 2011; Aulas *et al.* 2012). Noteworthily, although one previous study reported enhanced SG formation by disease association mutant TDP-43 (Liu-Yesucevitz *et al.* 2010), other studies showed either reduced or unchanged SG formation in cells or primary human fibroblasts bearing TDP-43 mutations (McDonald *et al.* 2011; Bentmann *et al.* 2012; Orru *et al.* 2016). And, surprisingly, a most recent study has reported that despite the presence of widespread TDP-43 pathology in ALS/FTD with TIA1 mutations, TDP-43 inclusions do not co-localize with TIA1 (Hirsch-Reinshagen *et al.* 2017). While these discrepancies remain to be resolved, the functional roles of TDP-43 in translational control in stress response have been increasingly recognized. Further studies will be important to investigate the detailed mechanisms by which mislocalized cytoplasmic TDP-43 influences the dynamics of SGs and possibly other RNA granule pathways.

Axonal transport

Axonal transport is essential for neuronal function and survival (Maday *et al.* 2014). Abnormal vesicles or mitochondrial transport along axon has been extensively reported in ALS patients (Collard *et al.* 1995; Williamson and Cleveland 1999; Chevalier-Larsen and Holzbaur 2006) and AD patients (Stokin *et al.* 2005; Wang *et al.* 2009). Like another ALS causing protein FUS, ALS-associated mutations in TDP-43 suppress the microtubule-dependent axonal transport of TDP-43 granules containing mRNAs (Alami *et al.* 2014). In neuronal cells, TDP-43 has been reported to be enriched in dendrites to regulate localized translation (Wang *et al.* 2008). And, TDP-43 has also been found to form granules containing mRNAs encoding proteins such as VEGFA/GRN (Colombrita *et al.* 2012), survival motor neuron (SMN) protein/fragile X mental retardation protein (FMRP) (Fallini *et al.* 2012), neurofilament light chain (NFL) (Alami *et al.* 2014), actin/CAMKII (Wang *et al.* 2008), and MTHFSD/DDX58 (MacNair *et al.* 2016) to mediate mRNA degradation, transport, and translation (Fig. 1d). As the over-expression of either wild-type or mutant TDP-43 also impairs mitochondrial transport (Wang *et al.* 2013b; Magrane *et al.* 2014), another possible mechanism by which cytoplasmic TDP-43 causes neuronal dysfunction may involve the regulation of axonal transport of mRNA, mitochondria, and other cargos for localized protein translation or metabolism.

Mitochondrial dysfunction

In addition to its endoplasmic reticulum (ER) localization (Wang *et al.* 2017), we and at least other four groups have independently reported the localization of TDP-43 inside of mitochondria by immuno-electron microscopy and different biochemical and genetic approaches (Mori *et al.* 2008; Wang *et al.* 2016, 2017; Izumikawa *et al.* 2017; Ruan *et al.* 2017; Woo *et al.* 2017) (Fig. 1b). Although these data are contradictory to one study

reporting the association of ALS-mutant TDP-43 with the outer mitochondrial membrane (Hibiki Kawamata *et al.* 2017), a number of studies have consistently indicated mitochondria as targets of either wild-type or mutant TDP-43 (Mori *et al.* 2008; Xu *et al.* 2010, 2011; Braun *et al.* 2011; Lu *et al.* 2012; Wang *et al.* 2013b, 2016b, 2017; Magrane *et al.* 2014; Stribl *et al.* 2014; Izumikawa *et al.* 2017; Ruan *et al.* 2017; Woo *et al.* 2017). It is worth noting that the study from Kawamata *et al.* used a high concentration of KCl at 6M for mitochondrial isolation, which has been reported to greatly disrupt mitochondrial integrity and proteome by breaching the electrostatic force between the lipids and proteins (Mishra 2015).

Abundant evidence has revealed a prominent role for mitochondrial dysfunction in the pathogenesis of ALS (Cozzolino and Carri 2012). Multiple laboratories reported mitochondrial dysfunction as well as accumulation of SOD1 in mitochondria in various cell and animal models expressing ALS-associated mutant SOD1 (Mattiazzi *et al.* 2002; Liu *et al.* 2004; Bergemalm *et al.* 2006; Deng *et al.* 2006; Israelson *et al.* 2010). Mitochondrial dysfunction has also been implicated in widely studied transgenic mice expressing FTLD-associated tau (David *et al.* 2005). Interestingly, our recent study has revealed that TDP-43 can accumulate inside of mitochondria in neurons of ALS or FTLD patients (Wang *et al.* 2016). TDP-43 could be imported into mitochondria *in vitro* and either the loss of nuclear localization sequence signal or ALS-associated mutations in TDP-43 enhance its localization in mitochondria (Wang *et al.* 2013b, 2016), indicating mitochondrial localization as an intrinsic property of cytoplasmic TDP-43 (Wang *et al.* 2016). Noteworthily, the deletion of several TDP-43 motifs was able to suppress but not completely abolish its mitochondrial localization (Wang *et al.* 2016), indicating that the targeting of TDP-43 into mitochondria may need multiple sequences. Within mitochondria, TDP-43 binds a subset of mitochondria-transcribed mRNAs or transfer RNA (tRNA) to specifically impair the function of oxidative phosphorylation complex 1 (Wang *et al.* 2016; Izumikawa *et al.* 2017). The suppression of TDP-43 mitochondrial localization was sufficient to abolish TDP-43-induced mitochondrial dysfunction in TDP-43 transgenic mouse model showing ALS or FTLD-like phenotypes (Wang *et al.* 2016, 2017). Thus, cytoplasmic TDP-43 inclusions may target mitochondria to cause neurotoxicity in both ALS and FTLD. Nevertheless, the same discrepant study from Kawamata *et al.* reported unchanged mitochondrial function in mutant TDP-43 transgenic mice (Hibiki Kawamata *et al.* 2017), even though these mice exhibit remarkable neuronal death, mitochondrial cristae loss, and mitochondrial transport deficits (Xu *et al.* 2011; Wang *et al.* 2013b, 2017; Magrane *et al.* 2014). No study of TDP-43 mitochondrial localization and its relationship with mitochondrial function in AD has been reported so far. However, like ALS, mitochondrial dysfunction is a prominent and early feature of AD (Castellani *et al.* 2002) and complex I dysfunction has long been reported in AD (Chen and Yan 2006). Interestingly, TDP-43 can bind mitochondria-transcribed RNA and regulate the activity of oxidative phosphorylation complex 1 (Wang *et al.* 2016; Izumikawa *et al.* 2017). Mitochondria have been increasingly indicated as targets of Aβ and tau (Gao *et al.* 2017), therefore implicating the possible convergence of Aβ, tau, and TDP-43 pathogenic pathways at the point of impairing mitochondrial function.

Overall, while some apparent discrepancies need to be addressed, mitochondrial dysfunction has been consistently reported in cells or neurons expressing wild-type or mutant TDP-43 (Braun *et al.* 2011; Lu *et al.* 2012; Wang *et al.* 2013b, 2016b, 2017; Stribl *et al.* 2014; Izumikawa *et al.* 2017; Ruan *et al.* 2017; Woo *et al.* 2017), indicating that in addition to axonal transport, accumulated cytoplasmic TDP-43 may also directly interfere with mitochondrial bioenergetics to produce neuronal dysfunction and loss, and further detailed investigation of Aβ, tau, and TDP-43 functional interaction in mitochondrial bioenergetics may be warranted.

Protein quality control

Many ALS or FTLD-associated proteins such as UBQLN2, p62, VCP, and optineurin are involved in the protein quality control system (Chen *et al.* 2012) and the familial cases associated with genetic mutations in these proteins consistently show TDP-43-positive inclusions (Cairns *et al.* 2007; Mackenzie 2007; Hasegawa *et al.* 2008; Weihl *et al.* 2008). p62 has been proposed to link the ubiquitin proteasome system (UPS) and autophagy (Cohen-Kaplan *et al.* 2016). In addition, the disrupted physical interaction between TDP-43 and p62 has been reported in the cerebral cortex from patients with FTLD-TDP (Tanji *et al.* 2012). Therefore, these findings suggest that TDP-43 proteinopathy and related neurodegeneration may be consequences of systematic impaired protein quality control. To support this notion, it has indeed been shown that the suppression of either the ubiquitin proteasome system (UPS) or autophagy pathways was sufficient to cause TDP-43 cytoplasmic accumulation and neurotoxicity (Wang *et al.* 2010; van Eersel *et al.* 2011), while over-expression of p62 reduced TDP-43 cytoplasmic accumulation in both an UPS- and autophagy- dependent manner (Brady *et al.* 2011). In brain neurons, over-expression of mutant TDP-43 induces the unfolded protein response (response to unfolded or misfolded protein and accumulation in the lumen of the endoplasmic reticulum (ER)), ubiquitin aggregation and Golgi fragmentation preceding neuronal loss (Tong *et al.* 2012), further indicting the interplay between TDP-43 and the protein quality control system. However, it is worth mentioning here that, in motor neurons, only the ablation of proteasome subunit Rpt3 but not autophagy inducer Atg7 causes TDP-43 cytoplasmic accumulation and occasional nuclear inclusions in mice (Tashiro *et al.* 2012), suggesting that the role of both UPS and autophagy in mediating TDP-43 proteinopathy in neurons in the brain needs further detailed investigation.

Post-translational modifications

Abnormal post-translational modifications including ubiquitination, hyper-phosphorylation, and aberrant cleavage are known to be the characteristics for TDP-43 inclusions (Sreedharan *et al.* 2008). Although the ubiquitination sites in TDP-43 remain largely elusive, many phosphorylation sites at serine, threonine, or tyrosine residues have been identified within TDP-43, among which the phosphorylation at serine 403, 404, 409, and 410 sites have been extensively studied (Gendron *et al.* 2010) (Fig. 1c). Although *in vitro* experiments have identified casein kinase as one likely kinase responsible for TDP-43 phosphorylation at serine 379, 403/S404, and 409/S410 and suggested the potential role of TDP-43 phosphorylation in regulating its oligomerization or aggregation (Hasegawa *et al.* 2008), the impact of TDP-43 phosphorylation on its physiological and pathological function needs to

be explored by future studies. TDP-43 N-terminal fragments (NTFs) or CTD fragments with the molecular weight of 20–25 kDa or 35 kDa have been consistently reported in either patients with ALS or FTLD (Zhang *et al.* 2007; Hasegawa *et al.* 2008; Xiao *et al.* 2015) as well as cell and animal models expressing wild-type or mutant TDP-43 (Rutherford *et al.* 2008; Dormann *et al.* 2009; D'Alton *et al.* 2014; Li *et al.* 2015) (Fig. 1c). Previous studies have identified several proteases such as calpain, caspase 3, and caspase 7 that mediate TDP-43 cleavage (Zhang *et al.* 2007, 2009; Suzuki *et al.* 2011; Yamashita *et al.* 2012). Nearly all ALS/FTLD-associated mutations are found in the low-complexity CTD of TDP-43. NTFs are required for its splicing activities (Jiang *et al.* 2017). The CTD region is essential for hnRNP interactions and mRNA splicing activity and is generally believed to be involved in the formation of cytoplasmic TDP-43 inclusions (Conicella *et al.* 2016). In support of this notion, the QN-rich region of 331-369aa in CTD has been consistently reported to form amyloid-like β-sheet structures (Igaz *et al.* 2009; Johnson *et al.* 2009; Zhang *et al.* 2009; Fuentealba *et al.* 2010). The definitive pathological role for TDP-43 aggregates in triggering neurotoxicity remains elusive, though it was suggested that pathologic TDP-43 species form insoluble aggregates to exert toxicity on neurons (Lee *et al.* 2011). The molecular basis of cytoplasmic TDP-43 accumulation is not completely understood either, but aberrant post-translational modifications, or the presence of prion-like or amyloid-prone domains have long been implicated to mediate the mislocalization and aggregation of TDP-43 (Zhang *et al.* 2009; Dewey *et al.* 2012; Nonaka *et al.* 2013; Robinson *et al.* 2013).

Exosomes

Insoluble TDP-43 aggregates extracted from brains or cerebrospinal fluid (CSF) of patients with ALS and FTLD have been reported to induce TDP-43 phosphorylation and ubiquitination, and nucleate the aggregation of phosphorylated and ubiquitinated TDP-43 (Nonaka *et al.* 2013; Ding *et al.* 2015). Moreover, some recent studies have demonstrated that TDP-43 could be released from the cell via secreted vesicles known as exosomes to facilitate the spreading of prion-like TDP-43 aggregates from one cell to another (Feiler *et al.* 2015; Iguchi *et al.* 2016; Zondler *et al.* 2017) (Fig. 1b). Along this line, inhibition of exosome secretion by inactivation of neutral sphingomyelinase 2 with GW4869 exacerbated the disease phenotypes of transgenic mice expressing human TDP-43 A315T mutant (Iguchi *et al.* 2016). Therefore, in future studies it will be interesting to test whether and how cytoplasmic TDP-43 inclusions may use the prion-like spreading model via exosomes to affect different brain areas during the disease progression.

TDP-43 in other neurodegenerative diseases

TDP-43 proteinopathy has also been reported as a prominent pathological feature in many other neurodegenerative diseases including but not limited to PD and HD. PD is a neurodegenerative disorder that affects predominately dopaminergic neurons in the substantia nigra. TDP-43-positive cytoplasmic inclusions were found in the spinal cord and bulbar nuclei but not in the dentate gyrus and neocortex of PD patients with MND, accompanied by SPs and topographically limited NFTs (Nakashima-Yasuda *et al.* 2007). TDP-43-positive inclusions have also been reported to be associated with neuronal loss in the CA1 of familial PD patients bearing a Parkin mutant (Markopoulou *et al.* 2008),

suggesting that there is likely a link between Parkin and TDP-43. Parkin over-expression has been reported to alleviate TDP-43-induced cell death in cell (Hebron *et al.* 2013, 2014) and animal models (Wenqiang *et al.* 2014). It is noteworthy that the co-expression of TDP-43 exacerbates dopaminergic neuron loss in transgenic mice expressing mutant α-synuclein, further suggesting the possible synergistic role of TDP-43 in PD (Tian *et al.* 2011).

TDP-43-positive inclusions have also been reported to coexist with huntingtin (Htt)-positive inclusions in many CNS regions of patients with HD (Schwab *et al.* 2008; Doi *et al.* 2010; DeJesus-Hernandez *et al.* 2011), a hereditary polyglutamine disorder caused by extension of the triplet repeat region of the Htt gene. Although it remains controversial whether TDP-43 indeed co-localizes with Htt with inclusions (Tada *et al.* 2012), in a transgenic worm model, the ablation of nematode orthologue of TDP-43 has been shown to reduce mutant Htt-induced neurodegeneration and behavioral defects (Tauffenberger *et al.* 2013), thus suggesting a possible function for TDP-43 in promoting mutant Htt toxicity that is worth further investigation.

TDP-43 as a common therapeutic target for multiple neurodegenerative diseases

The presence of TDP-43 proteinopathy in a wide variety of neurodegenerative diseases suggest that targeting the TDP-43 pathomechanism may provide a common therapeutic approach to treat these devastating diseases. Stress granule formation has been implicated as the early stage of protein aggregation (Wolozin 2012). It has been reported that ataxin-2 is important for the assembly of stress granules through the recruiting of TDP-43 (Nonhoff *et al.* 2007; Hart and Gitler 2012). Genetic mutations in TDP-43 only represent a very small portion of all ALS/FTLD patients. Unlike antisense oligonucleotide (ASO)-based therapy targeting mutant SOD1 (Miller *et al.* 2013), ASO targeting mutant TDP-43 may not have broad translational significance. However, ASO-based therapy targeting ataxin-2 has recently been reported to block the TDP-43 and ataxin-2 interaction, alleviate TDP-43-induced neurotoxicity, improve motor function, and extend survival in transgenic animal models expressing ALS-associated mutant TDP-43 (Elden *et al.* 2010; Becker *et al.* 2017), suggesting the prevention of TDP-43 inclusion formation may be a promising common therapeutic approach for TDP-43-related neurodegenerative diseases.

Our recent studies have consistently shown that the suppression of TDP-43 mitochondrial localization by a TDP-43-derived inhibitory peptide (PM1) is sufficient to abolish motor and cortical neuron loss, and prevent and even reverse behavior deficits in two mutant TDP-43 transgenic mouse models demonstrating ALS and FTLD-like phenotypes (Wang *et al.* 2016, 2017), further supporting the targeting of TDP-43 mitochondrial localization as another possible promising therapeutic approach. Moreover, autophagy activators such as rapamycin, fluphenazine dihydrochloride (FPZ), methotrimeprazine (MTM) and 10-(4′-(N-diethylamino)butyl)-2-chlorophenoxazine (NCP), have been consistently reported to protect neurons and improve cognitive function in TDP-43 experimental models (Caccamo *et al.* 2009; Wang *et al.* 2012, 2013; Barmada *et al.* 2014). Similarly, the inhibition of eIF2a signaling transduction pathway by GSK2606414, a small molecule inhibitor of protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK) and eIF2α phosphorylation, has been reported to alleviate TDP-43 induced climbing dysfunction in flies (Kim *et al.* 2014).

As we discussed above, TDP-43 has been linked to the protein quality control system. Therefore, TDP-43-associated neurodegeneration may also be alleviated by therapeutic approaches targeting either enhanced protein clearance or reduced protein translation.

Conclusions and perspectives

TDP-43 proteinopathy has been reported as a prominent pathological feature in a wide range of neurodegenerative diseases including ALS, FTLD, AD, PD, HD, hippocampal sclerosis (Amador-Ortiz *et al.* 2007; Nelson *et al.* 2011; Pao *et al.* 2011), spinocerebellar ataxia type 2 (Toyoshima *et al.* 2011), and Alexander disease (Walker *et al.* 2014). An increasing body of pathological and mechanistic evidence indicates that TDP-43 proteinopathy is likely a convergent pathological mechanism underlying neuronal loss among various neurodegenerative diseases. While it still remains controversial whether TDP-43 proteinopathy behaves through ‘gain of toxicity’ or ‘loss of function’, the pathomechanisms of TDP-43 or mutant TDP-43 in diseases seem to be more complex than originally proposed. TDP-43 nuclear depletion and cytoplasmic accumulation are two apparently unrelated conditions that appear to be associated with distinct pathomechanisms involving RNA biogenesis, protein aggregation, axonal transport, UPS, autophagy, and even mitochondrial bioenergetics. Future studies will be important to evaluate and compare these TDP-43-regulated biological and pathological processes in various major neurodegenerative diseases. Notably, it is still possible that TDP-43 proteinopathy alone is not sufficient to induce neurodegeneration. Considering the coexistence of TDP-43 proteinopathy with many other pathological hallmarks, TDP-43 likely cooperates with other factors to trigger neurodegeneration. In this respect, the investigation of TDP-43 pathomechanisms in the context of other pathological conditions may be of particular importance. Along this line, it is also important to consider if any reported or newly discovered pathomechanisms for Aβ, tau, and many other neurodegeneration-related factors also apply to TDP-43.

In the past decade, our increasing understanding of TDP-43 pathomechanisms in neurodegeneration highlights the urgent need to advance our TDP-43 translational research efforts. The consistently reported TDP-43-mediated RNA splicing may be coherent enough for the use of specific RNA targets of TDP-43 as prognostic biomarkers. Encouraging TDP-43 translational studies targeting stress granules, mitochondria, autophagy, and protein synthesis warrant further investigation of the feasibility of moving these ASO, peptides, and small molecules into phase I clinical trials. TDP-43 proteinopathy is found in an increasing number of various neurodegenerative diseases, suggesting that the cause of TDP-43 proteinopathy could be multifactorial. However, emerging studies suggest that the targeting of TDP-43 may be a common therapeutic approach to prevent neurodegeneration. Further strong efforts are needed to translate any discovered knowledge about TDP-43 pathomechanisms into clinical practice.

Acknowledgments

Conflict of interest disclosure

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Abbreviations used

AD	Alzheimer's disease (AD)
ALS	amyotrophic lateral sclerosis
APP	β-amyloid precursor protein
ASO	antisense oligonucleotide
bvFTD	behavioral variant frontotemporal dementia
CBS	corticobasal syndrome
CFTR	cystic fibrosis transmembrane conductance regulator
CHMP2B	chromatin-modifying protein 2B
CNS	central nervous system
CSFs	cerebrospinal fluids
DLDH	dementia lacking distinctive histopathology
DNs	dystrophic neurites
ER	endoplasmic reticulum
fALS	familial amyotrophic lateral sclerosis
FTLD	frontotemporal lobar degeneration
FUS	fused in sarcoma
G3BP	Ras-GTPase-activating protein SH3 domain-binding protein 1
GVD	granulovacuolar degeneration
HD	Huntington's disease
hnRNP	heterogeneous nuclear ribonucleoprotein
MND	motor neuron diseases
ncRNAs	non-coding RNAs (ncRNAs)
mRNA	messenger ribonucleic acid (mRNA)
NES	nuclear export sequence
NFTs	neurofibrillary tangles
nfvPPA	nonfluent variant primary progressive aphasia

NLS	nuclear localization sequence
OXPHOS	oxidative phosphorylation
PABP	poly(A)-binding protein
P-bodies	processing bodies
PD	Parkinson's disease
PNS	peripheral nervous system
PS1	presenilin 1
PS2	presenilin 2
PSP	progressive supranuclear palsy
RRM	RNA recognition motif
sALS	sporadic amyotrophic lateral sclerosis
SCA2	spinocerebellar ataxia type 2
SGs	stress granules (SGs)
SOD1	superoxide dismutase 1
SPs	senile plaques
svPPA	semantic variant primary progressive aphasia
TBK1	TANK-binding kinase 1
TDP-43	TAR DNA-binding protein 43
TIA	T-cell-restricted intracellular antigen-1
UPR	unfolded protein response
UPS	ubiquitin proteasome system
VAPB	vesicle-associated membrane protein-associated protein B (VAPB)
VCP	valosincontaining protein

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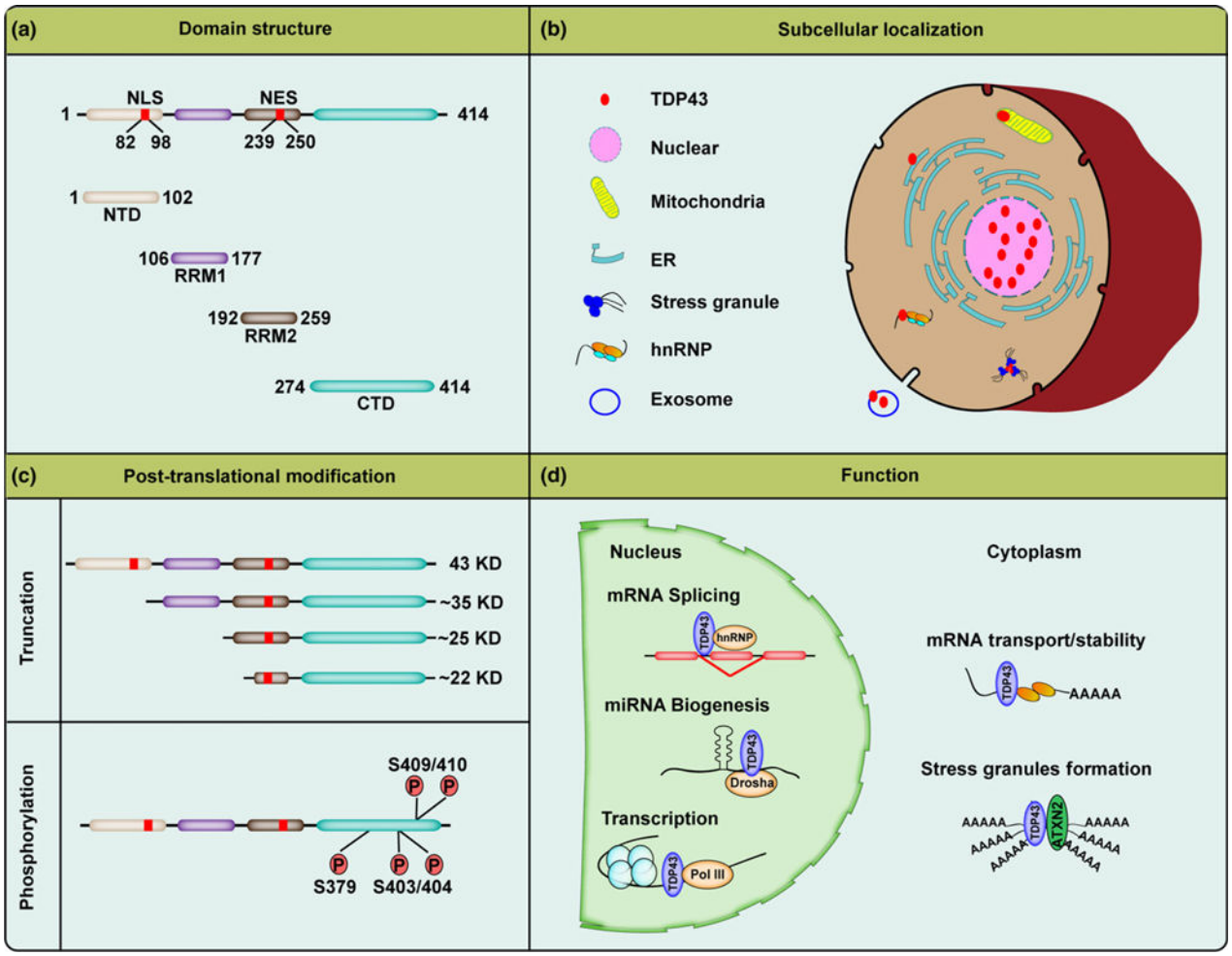

Fig. 1.

Domain structure, subcellular localization, post-translational modification, and function of TDP-43. (a) TDP-43 is a 414 amino acid protein, including an N-terminal domain (NTD, 1-102aa), two RNA recognition motifs (RRM1, 106-177aa and RRM2, 192-259aa) and a carboxy-terminal glycine-rich domain (CTD, 274-414aa). TDP-43 contains both a nuclear localization sequence (NLS, 82-98aa) and a nuclear export sequence (NES, 239-250aa). (b) The majority of TDP-43 resides in the nucleus under physiological conditions, while the remaining TDP-43 has been found to be present in other organelles, such as mitochondria, endoplasmic reticulum (ER), and exosomes. During stressful conditions, TDP-43 can be recruited to stress granules and hnRNPs. (c) The full-length 43 kDa TDP-43 is cleaved by caspases or calpain to generate ~35 kDa and 20-25 kDa fragments under disease conditions. The fragments and the full-length protein become aberrantly phosphorylated at serine residues 379, 403/404, and 409/410 in neurodegenerative disease affected brains. (d) TDP-43 exhibits multiple normal biological functions, predominantly those that regulate RNA pathways, including mRNA splicing, miRNA biogenesis, and transcription in nucleus, while it is also thought to play a role in mRNA transport, mRNA stability, and stress granule formation in the cytoplasm.