Published in final edited form as:

Trends Mol Med. 2011 November ; 17(11): 659–667. doi:10.1016/j.molmed.2011.06.004.

TDP-43 functions and pathogenic mechanisms implicated in TDP-43 proteinopathies

Todd J. Cohen, Virginia M.Y. Lee, and John Q. Trojanowski*

Department of Pathology and Laboratory Medicine, Institute on Aging and Center for Neurodegenerative Disease Research, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA

Abstract

Given the critical role for TDP-43 in diverse neurodegenerative diseases including amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD-TDP), there has been a recent surge in efforts to understand the normal functions of TDP-43 and the molecular basis of dysregulation that occurs in TDP-43 proteinopathies. Here, we highlight recent findings examining TDP-43 molecular functions with particular emphasis on stress-mediated regulation of TDP-43 localization, putative downstream TDP-43 target genes and RNAs, as well as TDP-43 interacting proteins, all of which represent viable points of therapeutic intervention for ALS, FTLD-TDP, and related proteinopathies. Finally, we review current mouse models of TDP-43 and discuss their similarities and potential relevance to human TDP-43 proteinopathies including ALS and FTLD-TDP.

TDP-43 and neurodegeneration

Trans-activation response DNA-binding protein of 43 kDa (TDP-43), encoded by the *TARDBP* gene on chromosome 1, is a major component of tau-negative and ubiquitin-positive inclusions that characterize amyotrophic lateral sclerosis (ALS; see Glossary) and frontotemporal lobar degeneration (FTLD) linked to TDP-43 pathology (FTLD-TDP) [1]. TDP-43 aggregation and neuropathology have been observed in a spectrum of distinct neurodegenerative disorders collectively known as the TDP-43 proteinopathies, suggesting a central role for TDP-43 in neurodegenerative disease pathogenesis [2, 3]. Indeed, the identification of more than 35 missense mutations in the *TARDBP* gene has further implicated abnormal TDP-43 function as a cause, rather than a consequence, of neurodegeneration in ALS and FTLD-TDP [3–5]. Thus, a more detailed understanding of TDP-43 functions will be necessary to devise therapeutic strategies aimed at increasing TDP-43 activity or preventing the potential toxic effects of TDP-43 aggregates to alleviate disease onset or progression.

TDP-43 regulates mRNA expression and gene transcription

TDP-43 is abundantly expressed in nearly all tissues and is well conserved among mammals and invertebrates [6]. Structural analysis has identified two RNA-recognition motifs (RRMs)

© 2011 Elsevier Ltd. All rights reserved

*To whom correspondence should be addressed: Trojanowski, J. Q. (trojanow@mail.med.upenn.edu).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

termed RRM1 and RRM2 that are capable of binding nucleic acids [7], and a glycine-rich region harboring the majority of ALS-associated mutations (Figure 1). TDP-43 binds both mRNA and DNA, thereby regulating mRNA splicing, stability and translation as well as gene transcription. Although early *in vitro* studies showed that TDP-43 preferentially bound RNAs via a GU dinucleotide repeat element [7], a clear consensus TDP-43 binding site *in vivo* has not been firmly established. However, in agreement with GU element binding specificity recent analyses of global TDP-43 binding sites showed that the most significant RNA binding occurred at either uninterrupted GU repeats, or a GU-rich motif interrupted by a single adenine [8, 9]. In an attempt to identify putative TDP-43 targets, initial studies showed that TDP-43 bound and stabilized human neurofilament (*hNFL*) mRNA [10], promoted exon skipping of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene [7, 11], and promoted exon 7 inclusion of the *SMN2* gene [12]; however, the significance of these TDP-43 targets with regard to disease pathogenesis is currently unclear.

The fused in sarcoma protein, or FUS/TLS, possesses a similar domain structure to TDP-43, consisting of RRM and glycine-rich domains. *FUS/TLS* mutations have been identified in both familial and sporadic ALS cases, and evidence indicates that FUS/TLS aggregates accumulate in a subset of tau and TDP-43-negative ALS and frontotemporal lobar degeneration, or FTL-D-FUS [13]. The possibility that these two RNA-associated proteins could physically and/or functionally interact was supported by studies showing that both TDP-43 and FUS/TLS bind and stabilize the mRNA encoding histone deacetylase 6 (*HDAC6*) [14, 15], a previously described microtubule deacetylase [16]. Although not fully characterized, TDP-43 and/or FUS/TLS could promote neuron survival or neuroprotection via increased HDAC6 expression, as HDAC6 has recently been implicated in mitophagy and the clearance of misfolded protein aggregates [17, 18]. Although it is conceivable that TDP-43 aggregation could directly cause mitochondrial defects similar to those observed with mutant Huntingtin and A β fragments [19, 20], the improper regulation of HDAC6 and other TDP-43 regulated targets could additionally compromise mitochondrial integrity. Supporting an indirect role for TDP-43 in mitochondria function, abnormal expression of the mitochondria fission/fusion proteins MFN1 and Fis1 was observed in transgenic (Tg) mice that constitutively express a human wild-type TDP-43 transgene driven by the mouse prion promoter [21]. These results support the notion that TDP-43 is either directly or indirectly linked to mitochondrial function.

A recent study performed transcriptional profiling of embryonic stem (ES) cells lacking TDP-43 and identified the RAB GTPase Tbc1d1 as a putative target, suggesting TDP-43 is critical for cellular metabolism and obesity [22], a phenotype previously linked to Tbc1d1 expression [23]. Given that Tbc1d1 is expressed in most tissues, its regulation by TDP-43 could be extended to highly metabolic non-CNS tissues, including skeletal muscle, in which TDP-43 pathology has been observed in patients with Inclusion Body Myositis (IBM) [24–27]. Thus, TDP-43 regulation of metabolic gene expression could have distinct tissue-specific effects and may explain the exquisite sensitivity of affected neurons in TDP-43 proteinopathies. Similarly, TDP-43 could uniquely regulate gene expression in other non-CNS tissues such as germ cells; TDP-43 was recently shown to repress testis specific expression of the *ACRV1* gene, thereby regulating spermatogenesis [28, 29].

TDP-43 Tg mice expressing a TDP-43 mutant that is localized to the cytoplasm by virtue of a defective nuclear localization sequence (TDP-43- Δ NLS) were recently generated, and it was shown that endogenous mouse TDP-43 was depleted, providing a putative TDP-43 loss of function mouse model [30]. Surprisingly, mRNA expression of histones and histone regulatory factors, typically expressed in mitotic cells, were among a subset of genes whose mRNA expression profile was significantly altered in the brain tissue of TDP-43- Δ NLS

mice. Although the significance of histone gene expression in neurons remains unclear, altered cell cycle profiles have been observed in neurodegenerative diseases [31], including the abnormal expression of mitotic cyclins and cyclin-dependent kinases (CDKs) [32] as well as cell cycle regulatory proteins such as Pin1 [33] and cdc25 [34]. Increased expression of cell cycle genes in post-mitotic neurons, in contrast to rapidly dividing cells, may promote apoptosis and neurodegeneration. If true, this suggests an exciting link between TDP-43, neuronal cell cycle gene expression, and the neuronal cell death observed during disease pathogenesis. This possibility is supported by TDP-43-mediated regulation of cyclin-dependent kinase 6 (cdk6) [35]. A more detailed analysis of TDP-43 target genes including cell-cycle regulated gene expression, particularly in diseased brains, is an ongoing area of investigation.

Two recent studies have demonstrated a more global role for TDP-43 in the regulation of RNA expression and splicing. Polymenidou *et al.* showed that TDP-43 is crucial for sustaining mRNA levels of synaptic proteins, choline acetyltransferase, the disease-related proteins FUS/TLS and progranulin as well others implicated in various neurologic diseases [8]. Tollervey *et al.* showed that TDP-43 bound RNAs that encode proteins which regulate neuronal development and survival, and identified the noncoding RNAs MALAT1 and NEAT1 as disease relevant TDP-43 targets in FTLT [36]. Future studies may further clarify the splicing regulatory role of this exciting class of non-coding RNAs in both normal and pathological states. The direct binding of TDP-43 to a wide range of critical target RNAs presented in these studies suggests that TDP-43 activity promotes and/or sustains proper neuronal function and integrity. As such, the factors that alter TDP-43 function or expression levels, including environmental stress and genetic mutations, could have profound indirect consequences on global neuronal protein expression and splicing patterns.

Finally, several reports have indicated that cells are exquisitely sensitive to TDP-43 levels and thus tightly regulate TDP-43 expression. For example, increased TDP-43 expression in Tg mouse models or cultured cells led to a prominent reduction in endogenous TDP-43 levels [30, 37]. Two recent studies have provided evidence that TDP-43 auto-regulation occurs via direct binding of the TDP-43 protein to its own 3'UTR sequence, and contributes to TDP-43 mRNA instability and degradation [8, 38]. Such a negative auto-regulatory feedback loop could be critical to maintain proper levels of functional TDP-43 protein. Indeed, ALS-associated mutations or environmental stressors that perturb such auto-regulation could promote abnormal TDP-43 expression and initiate aberrant expression of TDP-43 targets. In this regard, it was recently shown that TDP-43 regulates expression of a subset of miRNAs, including let-7b and miR-663 [39], which could feedback to regulate TDP-43 expression levels, suggesting that a complex signaling network exists to fine-tune TDP-43 expression levels, which, if de-regulated, could contribute to neuronal cell death. Thus, genetic and environmental factors that perturb the TDP-43 auto-regulatory network may contribute to neuronal dysfunction and disease pathogenesis.

TDP-43, stress granules, and pathological aggregates

Although TDP-43 regulates mRNA levels under normal physiological conditions, accumulating evidence indicates that TDP-43 is a stress-responsive RNA-associated factor. Exposure to a variety of stressors including zinc [40] or the lipid mediator 15d-PGJ(2) [41], both of which promote oxidative stress, led to accumulation of insoluble TDP-43 aggregates similar to those observed under pathological conditions [1]. However, any definitive role for TDP-43 in initiating or executing an oxidative stress response had not been characterized. More recent studies using a variety of cultured cells have demonstrated that exposure to stress causes TDP-43 re-localization to stress granules (SGs) [42–47], cytoplasmic foci that represent both sites of translationally stalled RNAs as well as active sites of RNA regulation

and sorting [48, 49]. SG assembly involves a physiological protein aggregation mechanism whereby polyglutamine-rich regions of the SG initiator T-cell intracellular antigen-1 (TIA-1) promotes prion-like TIA-1 aggregation [50], providing a scaffold that drives SG formation. Moreover, SG formation is a reversible process, in which TIA-1 aggregation is inhibited by chaperone-mediated refolding via heat shock protein 70 (HSP70) [50]. In fact, the mechanism of TIA-1 protein aggregation resembles that of pathological prion protein or huntingtin, highlighting the similarity between SG protein assembly dynamics and pathological protein aggregation that occurs in neurodegenerative diseases.

Using HEK293 cells, HeLa cells, human neuroblastoma cells, NSC-34 cells (a motor neuron-like cell line), or cultured primary glia, recent studies have shown re-localization of endogenous or ectopically expressed TDP-43 to SGs in response to a variety of stresses including arsenite and sorbitol [43, 45]. Although the descriptive nature of SG localization reveals a physical incorporation of TDP-43 within SGs, whether TDP-43 has an active role within SGs or a causal role in SG assembly remains uncertain. Initial evidence in cell-based studies indicated that loss of TDP-43 function had no effect on SG assembly [42, 45]; however, Macdonald *et al.* suggest the kinetics of SG assembly in response to oxidative stress are significantly delayed in the absence of functional TDP-43 [46]. In addition, indirect evidence showing TDP-43 interacts with TIA-1 and regulates the expression of SG components including GTPase activating protein binding protein 1 (G3BP), which also localizes to SGs, further supports a potential role in SG assembly [45, 46]. These conflicting views as to whether TDP-43 is implicated in SG formation could reflect the dynamic and transient nature of SG formation, in which the particular cell type and stress paradigm are critical variables to be considered.

The specific type of oxidative insult analyzed introduces additional complexity underlying SG regulation, which could lead to the formation of distinct types of SGs that incorporate a unique set of RNA-binding proteins including TDP-43. For example, TDP-43 was prominently observed in sorbitol-induced SGs but showed less pronounced re-localization to arsenite-induced SGs, suggesting TDP-43 controls a subset of RNAs in response to specific types of stressors [43]. The enigmatic role of TDP-43 in SG dynamics may be further clarified with the identification of TDP-43 target RNAs that are recruited into SGs. Novel genomic approaches using RNA sequencing methods have generated potential TDP-43 target RNAs whose active regulation within SGs may be critical for neuron survival during exposure to stress [8, 9, 36]. One tantalizing TDP-43 target mentioned above is the mRNA encoding HDAC6, whose protein product itself is required for SG formation, potentially through the reversible deacetylation of tubulin [51–53]. Thus, whether TDP-43 directly or indirectly regulates SG dynamics awaits further investigation.

Similar to TIA-1 aggregation, incorporation of TDP-43 into SGs could occur via an identified poly-glutamine/asparagine (Q/N)- rich region that is potentially critical for TDP-43 self-aggregation [50, 54]. The abnormal or aberrant localization of TDP-43 to SGs could initiate pathological TDP-43 aggregation or pathogenic interactions with other SG-localized proteins, and a similar phenomenon could underlie aggregation of the related RNA-binding protein FUS/TLS [55, 56]. This suggests a potential link between SG assembly and the formation and/or emergence of pathological aggregates or inclusions in neurons and glia of ALS and FTLTDP CNS tissues. However, until recently, biochemical or immunohistological analysis of SGs in the brain had not been well characterized, although SGs were proposed to have overlapping functions with reported neuronal RNA granules, which are storage compartments for mRNAs composed of Staufen and Fragile-X mental retardation protein (FMRP) [57]. Using cultured neurons, Wang *et al.* have shown that TDP-43 incorporates into neuronal granules that co-localize with FMRP in response to

repetitive stimuli [58], suggesting that significant accumulation of TDP-43-containing granules occur in the brain.

The detection of putative pathological SGs in ALS spinal cord and FTLTDP brain tissues was recently observed [45], characterized by phosphorylated and aggregated TDP-43 protein. Indeed, it was suggested that these structures are in fact SGs, and this was supported by co-localization studies of pathological TDP-43 aggregates with the SG markers TIA-1 and eIF3 [45]. These studies suggest that recruitment of misfolded TDP-43 into SG aggregates could be linked to disease pathogenesis. Supporting this possibility, several ALS-associated missense mutations in TDP-43 alter SG dynamics, both increasing (Gly 294Ala, Gln331Lys, Gly348Cys) and decreasing (Arg361Ser) the propensity to form SGs in cell culture models [43, 45], providing a potential pathogenic mechanism for a subset of ALS mutations. Domain mapping from several studies has indicated that the glycine-rich region harboring the majority of pathogenic mutants is required for TDP-43 association with SGs [42, 43, 45]. Indeed, expression of an insoluble, aggregated TDP-43 C-terminal fragment (a.a. 216–414) is sufficient for recruitment to SGs [45], suggesting that pathological TDP-43 species alter SG dynamics. Thus, SGs could represent a functional intersection of normal TDP-43 function and the pathological accumulation of TDP-43 inclusions, reflecting the potential for both loss and gain of function toxicity associated with TDP-43 aggregation in ALS and FTLTDP (Figure 2).

Physiological and pathological TDP-43 interacting proteins

The identification of TDP-43 interacting proteins could provide critical insight into the functions described above for TDP-43 in gene transcription, RNA binding, and SG formation. Buratti *et al.* showed that the C-terminal region of TDP-43 is capable of binding directly to several proteins of the heterogeneous nuclear ribonucleoprotein (hnRNP) family including hnRNP A1/A2/B1 [59]. Recent proteomics analyses verified and extended these TDP-43 interactions to include several hnRNP family members and splicing factors [9, 44, 60]. Functional analysis determined that TDP-43 residues 321–366 are critical for TDP-43/hnRNP A2 interaction and demonstrated that a TDP-43/hnRNP complex regulates splicing activity [61]. Although the ALS-linked mutations within this region (Gln331Lys, Met337Val, and Gly348Cys) did not affect formation of a TDP-43/hnRNP complex, more subtle TDP-43 complex perturbations could result from these pathogenic mutations. For example, a slightly reduced TDP-43/hnRNP interaction occurring throughout a lifetime could progressively manifest an ALS phenotype in individuals with these mutations. Although TDP-43 physically and functionally associates with hnRNP complexes, pathological incorporation into protein aggregates is a unique aspect of TDP-43, as accumulation of hnRNPs was not observed in TDP-43 positive inclusions in FTLTDP brain tissue [62].

While studies have shown that *hNFL* mRNA is bound and stabilized by a complex of proteins that includes TDP-43, SOD1, and 14-3-3 proteins [10], the intervening RNA scaffold accounts for the observed binding between several of these components. However, immunoprecipitation analysis showed that the TDP-43 and SOD1 interaction was direct and independent of RNA. The exact SOD-1 species bound by TDP-43 is unclear, as Higashi *et al.* showed that mutant SOD-1 preferentially interacts with TDP-43 via a unique SOD-1 dimer interface that is exposed specifically in ALS spinal motor neurons [63]. The unique and specific binding of mutant SOD-1 to TDP-43 correlates with reduced TDP-43 solubility, suggesting that mutant SOD-1 could alter TDP-43 conformation and promote the accumulation of TDP-43 aggregates. However, given that spinal cord pathology in SOD1-positive fALS cases were demonstrated to be TDP-43-negative [64], it is currently unclear whether mutant SOD1 would in fact functionally interact with TDP-43 in pathological human brain tissue.

In addition to *hNFL* expression, a TDP-43 complex likely binds and regulates a large subset of mRNAs with diverse cellular functions [8, 9, 36]. Recent evidence indicates that TDP-43 associates with FUS/TLS in a 300–400 kDa complex, which regulates expression of the *HDAC6* mRNA [14, 60]. It is conceivable that disruption of a TDP-43/FUS complex and abnormal mRNA expression could be linked to an ALS phenotype. Supporting this possibility, the pathogenic TDP-43 mutants Q331K and M337V showed dramatically elevated binding to FUS/TLS, potentially causing misregulation of *HDAC6* expression as well as other TDP-43 targets [60]. These observations suggest that the shared association of TDP-43 and FUS/TLS with the ALS phenotype may reflect a common function in the regulation of a subset of critical target RNAs, including *HDAC6*.

Using a yeast screen to identify proteins that modify TDP-43-induced toxicity, Elden *et al.* demonstrated that TDP-43 interacts with the cytoplasmic localized Ataxin-2 protein in an RNA-dependent manner, and this interaction occurs in the cytoplasm where TDP-43 abnormally accumulates into misfolded aggregates [65]. Moreover, mutant polyglutamine (polyQ) expansions present within Ataxin-2 enhanced binding to TDP-43, suggesting a pathological interaction in which expanded polyQ repeats may facilitate accumulation of TDP-43 inclusions in ALS brain tissue [65]. Supporting a more global role for polyQ containing proteins in modifying TDP-43 function, TDP-43 co-localizes with expanded mutant Huntingtin in cell-based studies, and this recruitment required at least part of the TDP-43 C-terminal Q/N rich region [54]. TDP-43 binding to polyQ aggregates appears to be specific, as prominent co-localization or binding to other types of misfolded protein aggregates has not been observed. Extending these observations to humans, TDP-43 was detected within polyQ aggregates in Huntington's disease patients [66]. These findings raise the possibility that physical interactions specifically between TDP-43 and pathological polyQ-containing species could trigger abnormal TDP-43 conformational changes, altered solubility, and/or aberrant TDP-43 aggregation.

In addition to interactions with splicing factors and RNA regulatory proteins, TDP-43 readily self-associates to form dimers *in vitro* and in cell-based studies, and these findings are supported by structural analysis of TDP-43 RRM2 dimers [67]. Shiina *et al.* confirmed these observations demonstrating that ectopically expressed TDP-43 could associate with endogenous TDP-43, and importantly, that TDP-43 self-interaction occurs in the cytoplasm where TDP-43 inclusions are prominently detected in TDP-43 proteinopathies [68]. Protein analyses in this study using human brain indicated that dimerized TDP-43 could be detected in ALS brain lysates, suggesting multimeric species may occur pathologically in the diseased brain, although the authors suggest that more detailed analysis of control and diseased brains is required. Thus, protein self-association, commonly observed with other neurodegenerative disease-associated proteins including tau and alpha-synuclein, could underlie the pathological changes observed with TDP-43 in ALS and FTLTDP.

Mouse models of TDP-43 proteinopathies

TDP-43 protein levels are abundantly and widely expressed in most human tissues, including cells that comprise central nervous system (CNS) tissues such as neurons and glia. Genetic and biochemical studies suggest that the abnormal sequestration of TDP-43 within neuronal and glial inclusions observed in diseased brains could reflect loss of TDP-43 functions resulting in disease onset or progression. To address the physiological role for TDP-43, several laboratories have generated *Tardbp* null mice and in all instances TDP-43 was essential for embryonic development, with lethality occurring between embryonic day 3.5 and 8.5 [69–71]. Interestingly, heterozygous *Tardbp* mutant mice showed deficits in motor function, including decreased grip strength, without any apparent degeneration of motor neurons, suggesting that mild reductions in TDP-43 levels are sufficient to cause a

motor weakness phenotype [69]. However, a more recent study using conditional *Tardbp* knock-out mice demonstrated that postnatal deletion led to whole body deficits including loss of body fat and a transcriptional profile linked to metabolic dysfunction and obesity in which one critical target of TDP-43 was identified as *Tbc1d1* [22]. Given the lack of clear pathological changes in motor neurons in the mouse models described above, *Tardbp* null mice are likely insufficient models to recapitulate the pathogenesis of ALS. This insufficiency necessitated the subsequent generation of transgenic animal models of TDP-43 toxicity. The section below highlights TDP-43 transgenic mouse models (see Table 1), however, we reference a recent review for a more detailed summary of other animal models of TDP-43 [72].

Tg mice expressing a wild-type human *TARDBP* transgene directed TDP-43 protein expression to neurons using a Thy-1 promoter, which caused prominent degeneration of cortical and spinal motor neurons giving rise to impaired motor function and neuronal cell death, phenotypes reminiscent of ALS and FTLTDP [73]. Neuropathological analysis of cortical layers and spinal cord detected a small number of cytoplasmic and nuclear TDP-43 inclusions (NCIs and NIIs, respectively), which were ubiquitinated and phosphorylated on serines 409 and 410 (P409/410), both of which are indicators of pathological TDP-43 found in ALS and FTLTDP. Interestingly, these pathological changes were accompanied by increased caspase-3 activation and accumulation of distinct 25 kDa C-terminal TDP-43 cleavage products within the nucleus, a prominent species detected in human FTLTDP brain that may promote neuronal toxicity [74, 75]. However, the exact role for these fragments in driving disease pathogenesis of TDP-43 proteinopathies is unclear given that they are present in FTLTDP but reduced in ALS spinal cord, in which TDP-43 pathology comprises predominantly full-length TDP-43 protein [76].

A separate study directed wild-type TDP-43 expression to the forebrain using a CAMKII-promoter driven transgene [77]. Analysis of these mice indicated impaired learning and memory, attenuated long-term potentiation (LTP), and progressive motor abnormalities. Interestingly, the levels of several proteins required for synaptic signaling including phospho-ERK (pERK) and phospho-CREB (pCREB) were reduced in these Tg mice, providing a potential pathogenic mechanism associated with the observed deficits. Similar to Wils *et al.* [73], Tg mice expressing wild-type TDP-43 from a CAMKII-promoter driven transgene showed prominent hippocampal atrophy and neurodegeneration accompanied by activation of apoptosis and accumulation of ubiquitin-positive TDP-43 inclusions, similar to that observed in FTLTDP. Moreover, neurons containing NCIs in these mice showed depletion of normal nuclear TDP-43, consistent with a nuclear clearing mechanism and potential loss-of-function previously suggested [1]. Indeed, using a mouse-specific TDP-43 antibody, Igaz *et al.* demonstrated endogenous mouse TDP-43 clearing in either wild-type TDP-43 or TDP-43-ΔNLS expressing mice, which was accompanied by neurodegeneration [30], suggesting that perturbations of endogenous TDP-43 levels via autoregulation (see above) could represent a TDP-43 loss-of-function mechanism leading to neuronal cell death.

Tg mice expressing wild-type TDP-43 generated by Shan *et al.* [78] and Xu *et al.* [21] caused prominent motor phenotypes characterized by loss of body weight and hindlimb clasping. Xu *et al.* observed nuclear and cytoplasmic TDP-43 aggregates that were phosphorylated on serines 403/404, which correlated with elevated levels of ubiquitination in the nucleus and cytoplasm of spinal cord neurons. Surprisingly, although TDP-43 itself was not ubiquitinated, TDP-43 physically associated with ubiquitinated proteins. Further analysis indicated that the eosinophilic aggregates present in motor neurons were composed of abnormal clusters of mitochondria present within swollen axons of spinal cord motor neurons, suggesting Tg expression of TDP-43 causes mitochondria damage and dysfunction. Supporting this possibility, abnormal expression of mitochondria fission/fusion machinery

including mitofusin 1 (MFN1) and Fis1 was observed in TDP-43 expressing homozygous mice [21], suggesting either direct or indirect alterations of mitochondrial dynamics. In accordance with mitochondrial abnormalities, Shan *et al.* observed cytoplasmic inclusions within motor neurons composed of accumulated mitochondria, and this phenomenon was attributed to impaired mitochondrial trafficking reflected by a marked reduction of mitochondria at nerve terminals [78].

Although mitochondria dysfunction has been linked to ALS pathogenesis, the role of TDP-43 in mediating these deleterious effects is not yet clear. In addition to the fusion/fission machinery described above, TDP-43 regulates components of mitochondria quality control including HDAC6, which could be critical for the clearance of damaged mitochondria, as evidenced in cell-based studies [14, 15]. Similarly, components of the trafficking machinery including kinesin-associated proteins such as Kif3a and KAP3, previously implicated in ALS disease progression, could be regulated by TDP-43 [78]. The future identification of the full scope of TDP-43 targets could shed light on putative TDP-43 targets involved in mitochondria dynamics and quality control mechanisms.

Given the identification of ALS-associated mutations linked to *TARDBP* [3], two recent mouse models were generated in which the prion promoter directed expression of TDP-43 containing the Ala315Thr or Met337Val mutations, previously identified in a small number of familial ALS (fALS) kindreds [79, 80]. In both studies, TDP-43 mutant expressing mice developed a progressive and severe motor phenotype with reduced survival. Wegorzewska *et al.* observed ubiquitin-positive aggregates selectively in cortical layer V and spinal cord motor neurons, but in all cases these structures were TDP-43 negative [80]. In contrast, Stallings *et al.* observed phosphorylated TDP-43 (P409/410) within ubiquitin-positive inclusions in spinal cord motor neurons especially from late stage mice, suggesting the TDP-43 pathology in these mice is due to accumulation of abnormal mutant TDP-43 proteins [79]. Thus, the mechanisms underlying TDP-43 mediated neurodegeneration in ALS and FTLTDP are currently unclear. However, future studies may clarify whether mutant TDP-43 itself is abnormally sequestered within inclusions, thereby suggesting that disease is mediated by a loss of nuclear TDP-43 function, or whether mutant TDP-43 undergoes a gain of toxic function that might have a number of deleterious consequences, such as impairments in the protein degradation machinery causing neurodegeneration (see Table 1 for a summary of mouse models)

Concluding remarks

Biochemical, neuropathological, and genetic studies have shown that TDP-43 is a major component of ubiquitinated inclusions in ALS and FTLTDP and has sparked intense efforts to elucidate the role of RNA-binding proteins in neurodegenerative diseases [81]. Although it is emerging that TDP-43 nuclear functions, including gene transcription and mRNA regulation, are critical for cell survival, the exact mechanisms by which TDP-43 regulates these processes remains uncertain. A detailed understanding of TDP-43 function in normal and pathological contexts is required to identify future therapeutic avenues to pursue for these devastating diseases. Figure 2 integrates the putative functions of TDP-43 with the deleterious consequences of TDP-43 pathology in neurodegenerative TDP-43 proteinopathies. The generation of TDP-43 mouse models that faithfully recapitulate key aspects of the pathogenesis of ALS and FTLTDP has proved challenging. However, significant progress has been made in understanding TDP-43 molecular functions including its role as a stress responsive RNA-associated factor, the identification of TDP-43-associated proteins and RNAs, and illuminating the pathological processes that post-translationally alter TDP-43 properties in the disease state (e.g., phosphorylation, C-terminal cleavage, and aggregation). Proteomic and genomic methods have spurred novel approaches

to further understand TDP-43 function, and will undoubtedly provide a platform to identify mechanisms associated with TDP-43 function and dysregulation in disease. Ultimately, diverse approaches and methodologies will hopefully foster the identification of TDP-43 targeted therapeutics that could both increase TDP-43 protein activity and/or prevent the potential toxic effects associated with TDP-43 aggregation.

Glossary

ALS	Amyotrophic Lateral Sclerosis, characterized by progressive degeneration of motor neurons
dinucleotide repeat element	repetitive nucleic acid sequences consisting of two nucleotides present in DNA or RNA that provide specificity for protein binding
Eosinophilic	cytoplasmic structures staining positive with the acidic dye eosin, which can be used to characterize cytoplasmic protein aggregates in ALS and other neurodegenerative diseases
FTLD-FUS: Frontotemporal Lobar Degeneration linked to FUS pathology	a clinical syndrome characterized by progressive changes in behaviour, personality and/or language with the common feature being relatively selective degeneration of the frontal and temporal lobes. FTLD-FUS neuropathology represents a distinct subset of tau and TDP-43 negative FTLD containing pathological FUS protein aggregates
FTLD-TDP	Frontotemporal Lobar Degeneration linked to TDP-43 pathology: clinically similar to FTLD-FUS, however neuropathological analysis has shown that TDP-43 represents the pathological aggregated species
FUS/TLS	Fused in Sarcoma (FUS) protein, RRM and glycine-rich domain containing protein found in protein aggregates of a specific subtype of TDP-43-negative ALS
HDAC6	histone deacetylase 6, a microtubule deacetylase implicated in protein quality control mechanisms including removal of misfolded protein aggregates and damaged mitochondria
Hindlimb clasping	an indicator of neurological impairment in which hindlimbs are retracted towards the abdomen
Inclusion Body Myositis	an inflammatory muscle disease characterized by progressive muscle weakness and wasting
RAB GTPase Tbc1d1	a member of the TBC1 Rab-GTPase family of proteins that regulates glucose transport. Tbc1d1 has been linked to severe obesity in humans.
RRM	RNA recognition motif present in TDP-43 and FUS, which facilitates protein binding to RNA
Stress Granules (SGs)	cytoplasmic structures that recruit stalled protein-RNA complexes as a cellular response to environmental stressors
TDP-43 proteinopathies	spectrum of neurodegenerative diseases including ALS and FTLD-TDP characterized by hallmark TDP-43 inclusions in affected brain regions

References

1. Neumann M, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science*. 2006; 314:130–133. [PubMed: 17023659]
2. Lagier-Tourenne C, et al. TDP-43 and FUS/TLS: emerging roles in RNA processing and neurodegeneration. *Hum Mol Genet*. 2010; 19:R46–64. [PubMed: 20400460]
3. Pesiridis GS, et al. Mutations in TDP-43 link glycine-rich domain functions to amyotrophic lateral sclerosis. *Hum Mol Genet*. 2009; 18:R156–162. [PubMed: 19808791]
4. Barmada SJ, Finkbeiner S. Pathogenic TARDBP mutations in amyotrophic lateral sclerosis and frontotemporal dementia: disease-associated pathways. *Rev Neurosci*. 2010; 21:251–272. [PubMed: 21086759]
5. Lagier-Tourenne C, Cleveland DW. Rethinking ALS: the FUS about TDP-43. *Cell*. 2009; 136:1001–1004. [PubMed: 19303844]
6. Ayala YM, et al. Human, Drosophila, and C.elegans TDP43: nucleic acid binding properties and splicing regulatory function. *J Mol Biol*. 2005; 348:575–588. [PubMed: 15826655]
7. Buratti E, Baralle FE. Characterization and functional implications of the RNA binding properties of nuclear factor TDP-43, a novel splicing regulator of CFTR exon 9. *J Biol Chem*. 2001; 276:36337–36343. [PubMed: 11470789]
8. Polymenidou M, et al. Long pre-mRNA depletion and RNA missplicing contribute to neuronal vulnerability from loss of TDP-43. *Nat Neurosci*. 2011
9. Sephton CF, et al. Identification of neuronal RNA targets of TDP-43-containing ribonucleoprotein complexes. *J Biol Chem*. 2011; 286:1204–1215. [PubMed: 21051541]
10. Volkening K, et al. Tar DNA binding protein of 43 kDa (TDP-43), 14-3-3 proteins and copper/zinc superoxide dismutase (SOD1) interact to modulate NFL mRNA stability. Implications for altered RNA processing in amyotrophic lateral sclerosis (ALS). *Brain Res*. 2009; 1305:168–182. [PubMed: 19815002]
11. Buratti E, et al. Nuclear factor TDP-43 and SR proteins promote in vitro and in vivo CFTR exon 9 skipping. *Embo J*. 2001; 20:1774–1784. [PubMed: 11285240]
12. Bose JK, et al. TDP-43 overexpression enhances exon 7 inclusion during the survival of motor neuron pre-mRNA splicing. *J Biol Chem*. 2008; 283:28852–28859. [PubMed: 18703504]
13. Mackenzie IR, et al. TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. *Lancet Neurol*. 2010; 9:995–1007. [PubMed: 20864052]
14. Kim SH, et al. Amyotrophic lateral sclerosis-associated proteins TDP-43 and FUS/TLS function in a common biochemical complex to co-regulate HDAC6 mRNA. *J Biol Chem*. 2010; 285:34097–34105. [PubMed: 20720006]
15. Fiesel FC, et al. Knockdown of transactive response DNA-binding protein (TDP-43) downregulates histone deacetylase 6. *Embo J*. 2010; 29:209–221. [PubMed: 19910924]
16. Hubbert C, et al. HDAC6 is a microtubule-associated deacetylase. *Nature*. 2002; 417:455–458. [PubMed: 12024216]
17. Lee JY, et al. Disease-causing mutations in parkin impair mitochondrial ubiquitination, aggregation, and HDAC6-dependent mitophagy. *J Cell Biol*. 2010; 189:671–679. [PubMed: 20457763]
18. Kawaguchi Y, et al. The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. *Cell*. 2003; 115:727–738. [PubMed: 14675537]
19. Damiano M, et al. Mitochondria in Huntington's disease. *Biochim Biophys Acta*. 2010; 1802:52–61. [PubMed: 19682570]
20. Pavlov PF, et al. Mitochondrial accumulation of APP and Aβeta: significance for Alzheimer disease pathogenesis. *J Cell Mol Med*. 2009; 13:4137–4145. [PubMed: 19725915]
21. Xu YF, et al. Wild-type human TDP-43 expression causes TDP-43 phosphorylation, mitochondrial aggregation, motor deficits, and early mortality in transgenic mice. *J Neurosci*. 2010; 30:10851–10859. [PubMed: 20702714]
22. Chiang PM, et al. Deletion of TDP-43 down-regulates Tbc1d1, a gene linked to obesity, and alters body fat metabolism. *Proc Natl Acad Sci U S A*. 2010; 107:16320–16324. [PubMed: 20660762]

23. Stone S, et al. TBC1D1 is a candidate for a severe obesity gene and evidence for a gene/gene interaction in obesity predisposition. *Hum Mol Genet.* 2006; 15:2709–2720. [PubMed: 16893906]
24. Greenberg SA. Inflammatory myopathies: disease mechanisms. *Curr Opin Neurol.* 2009; 22:516–523. [PubMed: 19680126]
25. Olive M, et al. TAR DNA-Binding protein 43 accumulation in protein aggregate myopathies. *J Neuropathol Exp Neurol.* 2009; 68:262–273. [PubMed: 19225410]
26. Salajegheh M, et al. Sarcoplasmic redistribution of nuclear TDP-43 in inclusion body myositis. *Muscle Nerve.* 2009; 40:19–31. [PubMed: 19533646]
27. Weihl CC, et al. TDP-43 accumulation in inclusion body myopathy muscle suggests a common pathogenic mechanism with frontotemporal dementia. *J Neurol Neurosurg Psychiatry.* 2008; 79:1186–1189. [PubMed: 18796596]
28. Abhyankar MM, et al. A novel CpG-free vertebrate insulator silences the testis-specific SP-10 gene in somatic tissues: role for TDP-43 in insulator function. *J Biol Chem.* 2007; 282:36143–36154. [PubMed: 17932037]
29. Lalmansingh AS, et al. TDP-43 is a transcriptional repressor; the testis-specific mouse ACRV1 gene is a TDP-43 target in vivo. *J Biol Chem.* 2010
30. Igaz LM, et al. Dysregulation of the ALS-associated gene TDP-43 leads to neuronal death and degeneration in mice. *J Clin Invest.* 2010; 121:726–738. [PubMed: 21206091]
31. Currais A, et al. The neuronal cell cycle as a mechanism of pathogenesis in Alzheimer's disease. *Aging (Albany NY).* 2009; 1:363–371. [PubMed: 20157524]
32. Ueberham U, Arendt T. The expression of cell cycle proteins in neurons and its relevance for Alzheimer's disease. *Curr Drug Targets CNS Neurol Disord.* 2005; 4:293–306. [PubMed: 15975031]
33. Butterfield DA, et al. Pin1 in Alzheimer's disease. *J Neurochem.* 2006; 98:1697–1706. [PubMed: 16945100]
34. Ding XL, et al. The cell cycle Cdc25A tyrosine phosphatase is activated in degenerating postmitotic neurons in Alzheimer's disease. *Am J Pathol.* 2000; 157:1983–1990. [PubMed: 11106571]
35. Ayala YM, et al. TDP-43 regulates retinoblastoma protein phosphorylation through the repression of cyclin-dependent kinase 6 expression. *Proc Natl Acad Sci U S A.* 2008; 105:3785–3789. [PubMed: 18305152]
36. Tollervy JR, et al. Characterizing the RNA targets and position-dependent splicing regulation by TDP-43. *Nat Neurosci.* 2011
37. Winton MJ, et al. Disturbance of nuclear and cytoplasmic TAR DNA-binding protein (TDP-43) induces disease-like redistribution, sequestration, and aggregate formation. *J Biol Chem.* 2008; 283:13302–13309. [PubMed: 18305110]
38. Ayala YM, et al. TDP-43 regulates its mRNA levels through a negative feedback loop. *Embo J.* 2010
39. Buratti E, et al. Nuclear factor TDP-43 can affect selected microRNA levels. *Febs J.* 2010; 277:2268–2281. [PubMed: 20423455]
40. Caragounis A, et al. Zinc induces depletion and aggregation of endogenous TDP-43. *Free Radic Biol Med.* 2010; 48:1152–1161. [PubMed: 20138212]
41. Zhang HX, et al. Alteration of biochemical and pathological properties of TDP-43 protein by a lipid mediator, 15-deoxy-Delta(12,14)-prostaglandin J(2). *Exp Neurol.* 2010; 222:296–303. [PubMed: 20083106]
42. Colombrita C, et al. TDP-43 is recruited to stress granules in conditions of oxidative insult. *J Neurochem.* 2009; 111:1051–1061. [PubMed: 19765185]
43. Dewey CM, et al. TDP-43 is directed to stress granules by sorbitol, a novel physiological osmotic and oxidative stressor. *Mol Cell Biol.* 2011; 31:1098–1108. [PubMed: 21173160]
44. Freibaum BD, et al. Global analysis of TDP-43 interacting proteins reveals strong association with RNA splicing and translation machinery. *J Proteome Res.* 2010; 9:1104–1120. [PubMed: 20020773]

45. Liu-Yesucevitz L, et al. Tar DNA binding protein-43 (TDP-43) associates with stress granules: analysis of cultured cells and pathological brain tissue. *PLoS One*. 2010; 5:e13250. [PubMed: 20948999]
46. McDonald KK, et al. TAR DNA-binding protein 43 (TDP-43) regulates stress granule dynamics via differential regulation of G3BP and TIA-1. *Hum Mol Genet*. 2011; 20:1400–1410. [PubMed: 21257637]
47. Nishimoto Y, et al. Characterization of alternative isoforms and inclusion body of the TAR DNA-binding protein-43. *J Biol Chem*. 2010; 285:608–619. [PubMed: 19887443]
48. Anderson P, Kedersha N. Stress granules: the Tao of RNA triage. *Trends Biochem Sci*. 2008; 33:141–150. [PubMed: 18291657]
49. Anderson P, Kedersha N. RNA granules: post-transcriptional and epigenetic modulators of gene expression. *Nat Rev Mol Cell Biol*. 2009; 10:430–436. [PubMed: 19461665]
50. Gilks N, et al. Stress granule assembly is mediated by prion-like aggregation of TIA-1. *Mol Biol Cell*. 2004; 15:5383–5398. [PubMed: 15371533]
51. Nadezhkina ES, et al. Microtubules govern stress granule mobility and dynamics. *Biochim Biophys Acta*. 2010; 1803:361–371. [PubMed: 20036288]
52. Kwon S, et al. The deacetylase HDAC6 is a novel critical component of stress granules involved in the stress response. *Genes Dev*. 2007; 21:3381–3394. [PubMed: 18079183]
53. Chernov KG, et al. Role of microtubules in stress granule assembly: microtubule dynamical instability favors the formation of micrometric stress granules in cells. *J Biol Chem*. 2009; 284:36569–36580. [PubMed: 19843517]
54. Fuentealba RA, et al. Interaction with polyglutamine aggregates reveals a Q/N-rich domain in TDP-43. *J Biol Chem*. 2010; 285:26304–26314. [PubMed: 20554523]
55. Bosco DA, et al. Mutant FUS proteins that cause amyotrophic lateral sclerosis incorporate into stress granules. *Hum Mol Genet*. 2010; 19:4160–4175. [PubMed: 20699327]
56. Dormann D, et al. ALS-associated fused in sarcoma (FUS) mutations disrupt Transportin-mediated nuclear import. *Embo J*. 2010; 29:2841–2857. [PubMed: 20606625]
57. Krichevsky AM, Kosik KS. Neuronal RNA granules: a link between RNA localization and stimulation-dependent translation. *Neuron*. 2001; 32:683–696. [PubMed: 11719208]
58. Wang IF, et al. TDP-43, the signature protein of FTL-D, is a neuronal activity-responsive factor. *J Neurochem*. 2008; 105:797–806. [PubMed: 18088371]
59. Buratti E, et al. TDP-43 binds heterogeneous nuclear ribonucleoprotein A/B through its C-terminal tail: an important region for the inhibition of cystic fibrosis transmembrane conductance regulator exon 9 splicing. *J Biol Chem*. 2005; 280:37572–37584. [PubMed: 16157593]
60. Ling SC, et al. ALS-associated mutations in TDP-43 increase its stability and promote TDP-43 complexes with FUS/TLS. *Proc Natl Acad Sci U S A*. 2010; 107:13318–13323. [PubMed: 20624952]
61. D'Ambrogio A, et al. Functional mapping of the interaction between TDP-43 and hnRNP A2 in vivo. *Nucleic Acids Res*. 2009; 37:4116–4126. [PubMed: 19429692]
62. Neumann M, et al. Absence of heterogeneous nuclear ribonucleoproteins and survival motor neuron protein in TDP-43 positive inclusions in frontotemporal lobar degeneration. *Acta Neuropathol*. 2007; 113:543–548. [PubMed: 17415574]
63. Higashi S, et al. TDP-43 physically interacts with amyotrophic lateral sclerosis-linked mutant CuZn superoxide dismutase. *Neurochem Int*. 2010; 57:906–913. [PubMed: 20933032]
64. Mackenzie IR, et al. Pathological TDP-43 distinguishes sporadic amyotrophic lateral sclerosis from amyotrophic lateral sclerosis with SOD1 mutations. *Ann Neurol*. 2007; 61:427–434. [PubMed: 17469116]
65. Elden AC, et al. Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS. *Nature*. 2010; 466:1069–1075. [PubMed: 20740007]
66. Schwab C, et al. Colocalization of transactivation-responsive DNA-binding protein 43 and huntingtin in inclusions of Huntington disease. *J Neuropathol Exp Neurol*. 2008; 67:1159–1165. [PubMed: 19018245]

67. Kuo PH, et al. Structural insights into TDP-43 in nucleic-acid binding and domain interactions. *Nucleic Acids Res.* 2009; 37:1799–1808. [PubMed: 19174564]
68. Shiina Y, et al. TDP-43 dimerizes in human cells in culture. *Cell Mol Neurobiol.* 2010; 30:641–652. [PubMed: 20043239]
69. Kraemer BC, et al. Loss of murine TDP-43 disrupts motor function and plays an essential role in embryogenesis. *Acta Neuropathol.* 2010; 119:409–419. [PubMed: 20198480]
70. Sephton CF, et al. TDP-43 is a developmentally regulated protein essential for early embryonic development. *J Biol Chem.* 2010; 285:6826–6834. [PubMed: 20040602]
71. Wu LS, et al. TDP-43, a neuro-pathosignature factor, is essential for early mouse embryogenesis. *Genesis.* 2010; 48:56–62. [PubMed: 20014337]
72. Węgorzewska I, Baloh RH. TDP-43-Based Animal Models of Neurodegeneration: New Insights into ALS Pathology and Pathophysiology. *Neurodegener Dis.* 2011; 8:262–274. [PubMed: 21124004]
73. Wils H, et al. TDP-43 transgenic mice develop spastic paralysis and neuronal inclusions characteristic of ALS and frontotemporal lobar degeneration. *Proc Natl Acad Sci U S A.* 2010; 107:3858–3863. [PubMed: 20133711]
74. Dormann D, et al. Proteolytic processing of TAR DNA binding protein-43 by caspases produces C-terminal fragments with disease defining properties independent of progranulin. *J Neurochem.* 2009; 110:1082–1094. [PubMed: 19522733]
75. Zhang YJ, et al. Aberrant cleavage of TDP-43 enhances aggregation and cellular toxicity. *Proc Natl Acad Sci U S A.* 2009; 106:7607–7612. [PubMed: 19383787]
76. Igaz LM, et al. Enrichment of C-terminal fragments in TAR DNA-binding protein-43 cytoplasmic inclusions in brain but not in spinal cord of frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Am J Pathol.* 2008; 173:182–194. [PubMed: 18535185]
77. Tsai KJ, et al. Elevated expression of TDP-43 in the forebrain of mice is sufficient to cause neurological and pathological phenotypes mimicking FTL-D. *J Exp Med.* 2010; 207:1661–1673. [PubMed: 20660618]
78. Shan X, et al. Altered distributions of Gemini of coiled bodies and mitochondria in motor neurons of TDP-43 transgenic mice. *Proc Natl Acad Sci U S A.* 2010; 107:16325–16330. [PubMed: 20736350]
79. Stallings NR, et al. Progressive motor weakness in transgenic mice expressing human TDP-43. *Neurobiol Dis.* 2010; 40:404–414. [PubMed: 20621187]
80. Węgorzewska I, et al. TDP-43 mutant transgenic mice develop features of ALS and frontotemporal lobar degeneration. *Proc Natl Acad Sci U S A.* 2009; 106:18809–18814. [PubMed: 19833869]
81. Ule J. Ribonucleoprotein complexes in neurologic diseases. *Curr Opin Neurobiol.* 2008; 18:516–523. [PubMed: 18929657]

Figure 1. Schematic of TDP-43 domain structure, ALS-associated mutations, and C-terminal fragments

TDP-43 protein contains a nuclear localization sequence (NLS), two RNA recognition motifs (RRMs), a nuclear export sequence (NES), and a glycine-rich domain that harbors the majority of ALS-associated genetic mutations. More than 35 ALS mutations have been identified, with the majority of mutations found within the glycine-rich region. Those mutations mentioned in the text are highlighted in the expanded view above. TDP-43 C-terminal truncated protein was identified within insoluble aggregates from FTLTDP brain tissue, and the precise fragment lengths identified are indicated.

Figure 2. Stress-granule mediated regulation of TDP-43 and its target RNAs

RNA bound TDP-43 complexes regulate global expression of genes required for diverse functions including auto-regulation of TDP-43 mRNA itself. Such regulation could potentially occur in the context of other RNA-binding proteins including FUS and RNA-associated factors (represented by X). Pathogenic ALS-associated mutations or conditions of oxidative insult promote recruitment of TDP-43 containing RNA complexes into stress granules via a TDP-43 Q/N rich C-terminal domain. TDP-43 is selectively recruited into specific stress granules (SGs) depending on the type of stress condition. Once recruited to SGs, TDP-43 may have a physiological role in the regulation of TDP-43-dependent RNAs during acute stress. However, pathological factors including prolonged stress or ageing, for example, could induce the formation of 'pathological stress granules', representing persistent accumulation of coalesced SGs that form TDP-43 positive inclusions, characterized pathologically as TDP-43 aggregates in ALS and FTLT-TDP. The formation of pathological SGs could inhibit TDP-43 function via cytoplasmic sequestration of normal TDP-43 and/or initiate a toxic gain of function leading to mitochondrial damage and other neuronal dysfunctions.

Table 1

Comparison of transgenic mouse models of TDP-43

	TDP-43 Transgene	Promoter ^a	TDP-43 Pathology (C=cytoplasmic, N=nuclear)	Phospho-TDP-43 Positive ^b	Neurodegeneration	Nuclear TDP-43 Clearing ^c	Phenotype	Refs.
Wegorzewska et al. 2009	A315T	mouse PrP	no	no	yes	yes	motor impairments, axonal degeneration, denervation	80
Wils et al. 2010	WT	mouse Thy-1	yes (C/N)	yes	yes	yes	motor impairments, paralysis, reduced survival	73
Tsai et al. 2010	WT	CAMKII	yes (C/N)	not reported	yes	yes	reduced learning/memory, reduced LTP, motor impairments	77
Shan et al. 2010	WT	Thy1.2	intracellular granules	no	no	no	growth retardation, decreased large-caliber axon length, muscle atrophy	78
Xu et al. 2010	WT	mouse PrP	yes (C/N)	yes	yes	no	axonal degeneration, gait abnormalities, early lethality	21
Stallings et al. 2010	WT, A315T, M337V	mouse PrP	yes (C/ rare N)	yes	no	no	motor impairments, denervation, myopathy (in WT TDP-43 mice)	79
Igaz et al. 2011	WT, ΔNLS	CAMKII	yes (C) (ΔNLS)	yes	yes (WT and ΔNLS)	yes	motor impairments, more severe in ΔNLS mice	30

^a Cell-type specific promoter driving TDP-43 transgene expression

^b As indicated by immunoreactivity using antibodies against serines 409/410 or 403/404

^c Nuclear TDP-43 clearing due to the presence of a TDP-43 transgene