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TARDBP mutation analysis in TDP-43 proteinopathies and deciphering the toxicity of mutant TDP-43

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Abstract

The identification of TAR DNA-binding protein 43 (TDP-43) as the major disease protein in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration with ubiquitin inclusions (FTLD-U) has defined a new class of neurodegenerative conditions: the TDP-43 proteinopathies. This breakthrough was quickly followed by mutation analysis of *TARDBP*, the gene encoding TDP-43. Herein, we provide a review of our previously published efforts that led to the identification of 3 *TARDBP* mutations (p.M337V, p.N345K, and p.I383V) in familial ALS patients, 2 of which were novel. With over 40 *TARDBP* mutations now discovered, there exists conclusive evidence that TDP-43 plays a direct role in neurodegeneration. The onus is now on researchers to elucidate the mechanisms by which mutant TDP-43 confers toxicity, and to exploit these findings to gain a better understanding of how TDP-43 contributes to the pathogenesis of disease. Our biochemical analysis of TDP-43 in ALS patient lymphoblastoid cell lines revealed a substantial increase in TDP-43 truncation products, including a ~25 kDa fragment, compared to control lymphoblastoid cell lines. We discuss the putative harmful consequence of abnormal TDP-43 fragmentation, as well as highlight additional mechanisms of toxicity associated with mutant TDP-43.

Keywords

TDP-43; *TARDBP*; mutation; neurodegeneration; amyotrophic lateral sclerosis; frontotemporal lobar degeneration

Introduction

In 2006, the transactive response DNA-binding protein 43 (TDP-43) was recognized as a primary component of intracellular inclusions in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration with ubiquitin-positive inclusions (FTLD-U) [1, 2]. On the heels of this landmark discovery, many groups, including our own, set out to determine whether, and how, mutations in *TARDBP*, the gene encoding TDP-43, contribute to the pathogenesis of disease. Multiple mutations in *TARDBP* have since been discovered, underscoring the pathogenic nature of TDP-43 and providing evidence of a direct link between TDP-43 abnormalities and neurodegeneration [3–33]. Indeed, TDP-43 pathology now defines a growing class of neurological diseases, collectively referred to as TDP-43 proteinopathies. For instance, TDP-43 pathology has been observed to varying degrees in Lewy body disease [34, 35], parkinsonism-dementia complex of Guam [36, 37], corticobasal degeneration [1, 38], Alzheimer's disease (AD) [1, 39, 34, 38], and hippocampal sclerosis

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[39, 40]. This review will discuss our effort to identify *TARDBP* mutations in TDP-43 proteinopathy patients, and to elucidate the mechanisms by which mutant TDP-43 confers toxicity [7].

Frontotemporal dementia (FTD), one of the major causes of dementia in adults below the age of 65 [41, 42], encompasses a heterogeneous group of disorders distinguished clinically by abnormalities in behavior, language and personality [43]. FTD patients may also display movement abnormalities with clinical features of motor neuron disease (MND) resembling ALS. FTLD, the neuropathologic substrate of FTD, is characterized by atrophy of the frontal and temporal lobes, and the presence of glial and neuronal inclusions composed either of tau, TDP-43 or fused-in-sarcoma (FUS) [44]. Now that virtually all cases of FTLD-U can be assigned to one of these three major molecular subgroups, they have been classified as FTLD-tau, FTLD-TDP and FTLD-FUS [44].

ALS, the most common adult-onset MND, is characterized by the progressive degeneration of upper and lower motor neurons, resulting in muscle weakness, atrophy and spasticity. Additionally, cognitive deficits occur in a number of ALS patients, and some meet the criteria of FTLD [45–50]. In the majority of ALS patients, affected neuronal and glial cells harbor TDP-43-positive inclusions, with the exception of familial ALS cases caused by mutations in *Cu/Zn superoxide dismutase (SOD1)* [1, 2, 40, 51–59].

While a complete understanding of the functions of TDP-43 is lacking, this ubiquitously expressed RNA-binding protein plays a variety of roles in RNA metabolism, including transcription, splicing, mRNA transport and microRNA biosynthesis [60]. TDP-43 is largely a nuclear protein, but a small portion of TDP-43 is present in the cytoplasm under physiological conditions [61, 62]. For instance, the post-synaptic localization of TDP-43, in the form of RNA granules, is enhanced following depolarization of primary hippocampal neurons [63]. Moreover, in response to harmful stimuli in cell and animal models, TDP-43 relocates to cytoplasmic stress granules, dynamic structures that consist of mixed protein-RNA complexes [64–72].

The structure of TDP-43 resembles that of members of the heterogeneous ribonucleoprotein (hnRNP) family, a group of proteins that bind heterogeneous nuclear RNAs (hnRNAs) [73]. Like hnRNP members, TDP-43 contains two highly conserved RNA recognition motifs (RRM), and a C-terminal glycine-rich domain, known to promote protein-protein interactions [74–78]. TDP-43 also contains a nuclear localization signal (NLS) sequence and a leucine-rich nuclear export signal (NES) [79, 62] for shuttling between the nucleus and cytoplasm. Several potential phosphorylation sites are present within TDP-43, including 41 serine, 15 threonine and 8 tyrosine residues. Three putative caspase-3 recognition motifs (DXXD) are also present, the cleavage of which is predicted to generate C-terminal fragments of approximately 42, 35 or 25 kDa [80].

At the biochemical level, TDP-43 exhibits a disease-specific signature; pathologically altered TDP-43 is ubiquitinated, phosphorylated and cleaved to generate C-terminal fragments of 24–26 kDa in affected brain and spinal cord regions [2]. Because of the significant overlap of clinical and pathological features between FTLD and ALS, it is believed they are situated within a continuous clinicopathological spectrum of neurodegenerative diseases [81]. Both FTLD and ALS are etiologically complex disorders with genetic, as well as environmental factors, contributing to disease. A positive family history is reported in up to 50% of FTLD patients, often with an autosomal dominant pattern of inheritance [82]. Likewise, a positive family history is reported in 5–10% of ALS patients [83, 84], and these numbers increase to 17–23% based on prospective studies that investigated genealogies [85].

TARDBP Mutations Analysis in TDP-43 Proteinopathies

Spurred by the identification of TDP-43 inclusions in ALS and FTLD-TDP [1, 2], we hypothesized that mutations in *TARDBP* contribute to the development of TDP-43 proteinopathies given that, for several neurodegenerative diseases, rare missense mutations and multiplications have been identified in genes that encode proteins known to abnormally aggregate. An extensive mutation screening of *TARDBP* in a diverse cohort of patients with neurodegenerative diseases characterized by TDP-43 pathology was thus spear-headed by Dr. Rosa Rademakers [7]. Among these patients, 176 were clinically diagnosed as having ALS (95), FTLD (60) or FTLD-ALS (21), and another 120 patients had pathologically confirmed TDP-43 proteinopathy. The latter group included 21 cases pathologically diagnosed as ALS (21), FTLD-TDP (29) or FTLD-MND (17). Also included were 46 cases of Alzheimer's disease (AD), 4 cases of Lewy-body disease (LBD) and 3 cases of hippocampal sclerosis (HpScl), all of which had TDP-43-immunopositive inclusions.

Sequencing analyses of the 5 coding and 2 non-coding exons of *TARDBP* in the 296 patients revealed 3 heterozygous missense mutations (c.1009 A>G, c.1035 C>A, and c.1147 A>G) in 3 of the 116 ALS patients (2.6%). No mutations were detected in any of the remaining patients, in 825 control individuals, nor in 652 additional sporadic ALS patients. All 3 mutation carriers were part of the clinical patient series and, since they were also index patients of autosomal dominant ALS families, the frequency of *TARDBP* mutations increased to 3.3% in the subpopulation of familial ALS patients (3/92 patients).

As are the majority of *TARDBP* mutations, the mutations identified in our study are located in exon 6, which encodes the highly conserved, glycine-rich, C-terminus of TDP-43. This region, involved in protein-protein interactions, is necessary for the splicing inhibitory activity of TDP-43 for certain RNA transcripts [86], and influences the solubility and cellular localization of TDP-43 [61]. Two of the 3 mutations that we identified had not previously been reported: c.1035 C>A, predicted to change asparagine to lysine at codon 345 (p.N345K), and c.1147 A>G, which predicts an isoleucine for a valine substitution at codon 383 (p.I383V). The third mutation identified in our series, c.1009 A>G, is predicted to substitute valine for methionine at codon 337 (p.M337V), and had been reported to segregate with disease in a large British autosomal dominant ALS kindred [8]. We identified the M337V mutation in an index patient from a US family with a strong family history of ALS. This patient showed upper limb-onset ALS at age 38, 6 years prior to the earliest age of onset in the British M337V family. Based on an allele sharing study, our US M337V mutation carrier and the UK family are not likely to be descendants of a common founder, although the set of markers analyzed would not have detected a very distant common ancestor [87, 88].

We found the N345K mutation in a 43 year old male who showed early onset of disease at 39 years of age, whereas the I383V mutation carrier showed symptom onset at 59 years, 2 decades later than the other 2 mutations identified in our study. A separate group has since identified the N345K mutation in 1 of the 208 familial ALS patients they screened; this patient had an age of onset of 41 years of age, similar to our N345K mutation carrier [30]. Also identified were 3 familial ALS patients with the I383V mutation, with ages of disease onset of 25, 57 and 66 years of age [30]. That these mutations have now been observed in additional ALS patients provides evidence to support their pathogenic nature.

Biochemical Analysis of *TARDBP* Mutations in Familial ALS Patients

To investigate the pathological significance of *TARDBP* missense mutations, Dr. Leonard Petrucelli and his team examined human lymphoblastoid cell lines derived from the 3 familial *TARDBP* mutation carriers identified in our study [7]. Kabashi and colleagues had

previously reported that, in the presence of the proteasomal inhibitor, MG-132, lymphoblastoid cells from *TARDBP* mutation carriers (G348C, R361S, N390D, N390S) have increased levels of a ~28 kDa TDP-43 fragment compared to lymphoblastoid cells derived from control individuals and sporadic ALS patients [4]. Similarly, we observed that MG-132 treatment led to a marked increase in the accumulation of detergent insoluble TDP-43 fragments of ~25 and ~35 kDa in the lymphoblastoid cell lines derived from patients with *TARDBP* mutations (M337V, N345K, and I383V), but not in those derived from control individuals. However, an increase in TDP-43 fragments was also observed in lymphoblastoid cells from sporadic ALS patients. That we did not observe enhanced fragmentation between wild-type and mutant TDP-43 suggests that this phenomenon may be mutation- or model-specific. Of interest, levels of full-length and truncated TDP-43 were recently reported to be elevated in neurons differentiated from induced pluripotent stem cells derived from lymphoblasts of an ALS patient carrying the M337V mutation [89]. It should be noted, however, that not all *TARDBP* missense mutations result in enhanced TDP-43 levels and/or fragmentation; rather, Borroni and colleagues observed a substantial drop in TDP-43 expression levels in lymphoblastoid cells derived from a behavioral variant FTD patient with an N267S mutation [13].

Given our observation that proteasomal inhibition enhanced TDP-43 cleavage, we next investigated whether proteasome-induced toxicity was associated with proteolytic processing of endogenous TDP-43 in cell culture models. To this end, H4 neuroglioma cells were treated with either vehicle (DMSO), proteasome inhibitor I (PSI) or MG132 for 24 hours. In the presence of PSI and MG132, TDP-43 was cleaved into ~35 and ~25 kDa fragments, similar to the fragments found in the above-mentioned lymphoblastoid cell lines derived from *TARDBP* mutation carriers. PSI treatment also led to a marked increase in active capase-3, which promotes apoptotic cell death. When cells where co-treated with PSI and the caspase inhibitor, Z-VAD (OMe)-FMK, caspase-3 activation was attenuated and the generation of proteolytic TDP-43 fragments was inhibited. We and others have identified TDP-43 as a caspase substrate [90, 91, 80, 92, 93], and we have shown that the proteolytic cleavage of TDP-43 by caspases leads to the redistribution of TDP-43 from the nucleus to the cytoplasm, and generates insoluble C-terminal fragments similar to those found in diseased brains [80]. Taken together, these findings suggest that proteasome inhibition is sufficient to promote proteolytic cleavage of TDP-43 and the accumulation of TDP-43 fragments, through a mechanism that implicates programmed cell death. What is more, our data indicates that TDP-43 is more prone to cleavage in ALS patients than in healthy individuals, and various studies provide evidence that certain mutant forms of TDP-43, but not all, are cleaved more readily than wild-type TDP-43 [4, 8, 10, 14, 94].

So then, what are the consequences of TDP-43 cleavage, and how may the resulting TDP-43 fragments contribute to the pathogenesis of disease? First, cleavage of full-length TDP-43 is expected to adversely affect TDP-43 function given that TDP-43 fragments lack key functional domains [75]. For example, unlike full-length TDP-43, various C-terminal TDP-43 fragments, including $TDP_{208–414}$, GFP-$TDP_{218–414}$ and GFP-$TDP_{220–414}$, do not enhance skipping of exon 9 in a *CFTR* splicing assay, indicating that the N-terminal region of TDP-43 is required for this function [95, 94, 96]. Second, proteolytic cleavage products of TDP-43 are more aggregation-prone, as evidenced by the fact that TDP-43 fragments form inclusions more readily in cultured cells than does full-length TDP-43 [95, 94, 96, 97]. Cleavage of TDP-43, and the subsequent aggregation of TDP-43 fragments, depletes the pool of functional TDP-43 and may also lead to the sequestration of remaining full-length TDP-43 to the cytoplasmic inclusions [94]. Depletion or loss of TDP-43 has been shown to have detrimental, and even lethal, consequences in a variety of models. For example, deletion of the *Drosophila* homolog of TDP-43 results in anatomical defects at the neuromuscular junctions, a paralytic phenotype, and reduced lifespan [98]. In mice, TDP-43

depletion causes changes in a great number of RNA transcripts, many of which encode proteins implicated in neurodegeneration [99], and complete loss of TDP-43 results in embryonic lethality [100–103].

In addition to loss-of-function mechanisms, TDP-43 fragments, as well as the inclusions formed by these products, may themselves be toxic entities. A connection between TDP-43 aggregation and toxicity has been established in yeast models: only TDP-43 products that form aggregates and contain an intact RRM are toxic in yeast [104]. We have provided evidence that the aggregation of truncated TDP-43 is toxic to differentiated M17 neuroblastoma cells [96]. The overexpression of a TDP-43 fragment corresponding to caspase-cleaved TDP-43 (GFP-$TDP_{220–p414}$) results in the formation of cytosolic TDP-43 inclusions and cytoxicity [96]. Toxicity associated with GFP-$TDP_{220–414}$ expression likely occurs through a gain-of-function since GFP-$TDP_{220–414}$ binds only weakly to full-length TDP-43, does not markedly sequester full-length TDP-43 from the nucleus, nor does it inhibit nuclear TDP-43 function, as assessed using a *CFTR* exon 9 skipping assay [96].

Additional Putative Mechanism Driving Mutant TDP-43 Toxicity

As does TDP-43 cleavage, TDP-43 phosphorylation distinguishes pathological TDP-43 from normal TDP-43. It is thus of interest that many TDP-43 mutations result in substitutions to threonine and serine residues [4, 5, 9, 14, 16]. This aberrant modification may influence various functions of TDP-43 and its ability to polymerize into aggregates. Indeed, we have shown that phosphorylation of the C-terminal TDP-43 fragment, GFP-$TDP_{220–414}$, renders it resistant to degradation and enhances its accumulation into insoluble inclusions [105]. Conversely, it has also been proposed that phosphorylation of TDP-43 serves as a defense-mechanism to reduce TDP-43 aggregation [97]. While the consequence of phosphorylation on the aggregation propensity of TDP-43 remains to be elucidated, it has been shown that phosphorylation of TDP-43 at serine residues 409/410 drives mutant TDP-43 toxicity in *C. elegans* models of TDP-43 proteinopathy [106].

The phosphorylation status of TDP-43 not withstanding, certain mutations (Q331K, M337V, Q343R, N345K, R361S and N390D) accelerate TDP-43 aggregation *in vitro* and enhance aggregate formation and toxicity in yeast [107]. ALS-linked mutations additionally enhance the aggregation potential of a C-terminal TDP-43 fragment, GFP-$TDP_{162–414}$, in SH-SY5Y cells, despite having no effect on full-length TDP-43 inclusion formation, suggesting that pathogenic mutations, in combination with N-terminal truncation, promote abnormal TDP-43 accumulation in mammalian cells [94]. In a similar fashion, findings from a cell model developed to test the effect of missense mutations on TDP-43 aggregation, suggest that the G348V and N352S mutations enhance TDP-43 aggregation and insolubility in U2OS cells [108]. Of particular interest, we have found that missense mutations in TDP-43 influence its assembly into stress granules [68]. Many groups have shown that TDP-43 is a component of stress granules [64–72]. These cytoplasmic RNA-protein complexes, which temporarily assemble in response to stress-induced translational arrest [109], are thought to assist cells in coping with environmental assaults by helping them reprogram mRNA metabolism and repair stress-induced damage. TDP-43 expression, and its localization to cytosolic stress granules, are transiently increased following neuronal injury [65, 66], suggesting that TDP-43 plays a role in the physiological response of neurons to stressful stimuli. We have shown that disease-linked mutations (G294A, A315T, Q331K, Q343R) in TDP-43 increase TDP-43 stress granule assembly in the presence of sodium arsenite, a treatment that induces oxidative stress [68]. Of note, mutant TDP-43 variants also showed a striking decrease in nuclear localization in response to arsenite treatment, suggesting that mutations in TDP-43 increased the degree of nuclear TDP-43 export [68]. This may have harmful consequences given that the amount of cytoplasmic TDP-43 is proposed to be a

strong predictor of neuronal death [110]. For instance, preventing the nuclear export of EGFP-TDP-43_{A315T} significantly blunts the toxicity normally associated with its expression in rat primary neurons [110]. We found that the signaling pathway that regulates cytoplasmic stress granule formation also modulates TDP-43 inclusion formation, and that the toxicity associated with arsenite treatment is enhanced upon overexpression of mutant TDP-43, compared to wild-type TDP-43 [68]. Finally, we demonstrated that TDP-43 positive-inclusions in FTLD-TDP brain tissue and ALS spinal cord tissue co-localize with protein markers of stress granules, including TIA-1 and eIF3. Taken together, these findings provide additional evidence that TDP-43 participates in stress granule formation, and suggest that mutations in TDP-43 affect the dynamics of their assembly.

Despite the body of evidence linking TDP-43 aggregation and toxicity, *in vivo* models of wild-type and mutant TDP-43 overexpression confirm that TDP-43 has toxic properties even in the absence of its aggregation (for review, see [111, 112]). To gain a better understanding of mutant TDP-43 toxicity, we generated a transgenic mouse model in which human TDP-43_{M337V} expression is driven by the mouse prion protein promoter, and compared the phenotype of these mice to our transgenic mice expressing wild-type TDP-43 [113, 114]. Features of TDP-43 proteinopathies, including TDP-43 fragmentation, increased cytoplasmic and nuclear ubiquitin levels, and nuclear and cytoplasmic inclusions immunopositive for phosphorylated TDP-43 were observed to similar degrees in both our TDP-43_{WT} and TDP-43_{M337V} mice [113, 114]. These features were accompanied by reactive gliosis, axonal and myelin degeneration, gait abnormalities, and early lethality [113, 114]. A comparison of various rodent TDP-43 transgenic models indicates that both wild-type and mutant TDP-43 are neurotoxic upon overexpression, and that toxicity is dependent on the extent of transgene expression [111, 112]. That we did not observe differential toxicity between wild-type and mutant TDP-43 may therefore stem from the fact that TDP-43 overexpression was relatively high in both of our mouse models. Nonetheless, there is evidence that TDP-43_{M337V} is indeed more harmful than wild-type TDP-43 in rats. TDP-43 fragmentation, phosphorylation and aggregation are observed in transgenic rats engineered to overexpress human TDP-43_{M337V} from a BAC clone. These mice develop progressive degeneration of motor neurons, become paralyzed and die early, in contrast to transgenic rats that express human wild-type TDP-43 at comparable levels [115]. That mutant TDP-43 may be more toxic than wild-type TDP-43 in rodents is consistent with studies conducted in other model organisms, including yeast [107], chicken embryos [8], *Drosophila melanogaster* [116], *C. elegans* [106] and zebra fish [117].

Conclusion

Since the identification of TDP-43 inclusions in ALS and FTLD-TDP [1, 2], numerous *TARDBP* mutations have been reported (http://www.molgen.ua.ac.be/FTDMutations/), and mutations in *TARDBP* are now recognized as a cause of familial ALS, having been identified in several populations of different geographic origin. *TARDBP* mutations have also been identified in sporadic ALS, familial and sporadic FTLD with or without MND, and in a subject with behavioral variant FTD (in association with supranuclear palsy and chorea) [4, 8, 9, 12–15, 118, 21, 30, 32]. In addition, the A382T mutation, causative of ALS and FTLD with MND [4, 14, 27, 33], has been found in 8 unrelated patients with a Parkinson's disease phenotype, as well as in a family with FTD with parkinsonism [119].

Despite the fact that over 40 different *TARDBP* mutations have been found, the majority of which are predicted to be pathogenic, mutations in *TARDBP* are considered rare in ALS, with an estimated frequency of ~4% in familial ALS patients, and ~1.5% in sporadic ALS patients [120]. Nevertheless, given the prevalence of TDP-43 pathology in ALS and FTLD, even in those cases caused by mutations not in *TARDBP*, but in *PGRN* and *C9ORF72*,

understanding how these mutations confer toxicity will provide insight on the role of TDP-43 in neurodegeneration [40, 51, 121, 122]. TDP-43 loss-of-function and toxic gain-of-function are thought to contribute, perhaps in concert, to the development of TDP-43 proteinopathies; while the pathogenic mechanisms of *TARDBP* mutations remain elusive, mutant TDP-43 is likely to impede the normal function of TDP-43, as well as generate TDP-43 products that are inherently more toxic than wild-type TDP-43.

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