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Rodent Models of TDP-43 Proteinopathy: Investigating the Mechanisms of TDP-43-Mediated Neurodegeneration

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Abstract Since the identification of phosphorylated and truncated transactive response DNA-binding protein 43 (TDP-43) as a primary component of ubiquitinated inclusions in amyotrophic lateral sclerosis and frontotemporal lobar degeneration with ubiquitin-positive inclusions, much effort has been directed towards ascertaining how TDP-43 contributes to the pathogenesis of disease. As with other protein misfolding disorders, TDP-43-mediated neuronal death is likely caused by both a toxic gain and loss of TDP-43 function. Indeed, the presence of cytoplasmic TDP-43 inclusions is associated with loss of nuclear TDP-43. Moreover, post-translational modifications of TDP-43, including phosphorylation, ubiquitination, and cleavage into C-terminal fragments, may bestow toxic properties upon TDP-43 and cause TDP-43 dysfunction. However, the exact neurotoxic TDP-43 species remain unclear, as do the mechanism(s) by which they cause neurotoxicity. Additionally, given our incomplete understanding of the roles of TDP-43, both in the nucleus and the cytoplasm, it is difficult to truly appreciate the detrimental consequences of aberrant TDP-43 function. The development of TDP-43 transgenic animal models is expected to narrow these gaps in our knowledge. The aim of this review is to highlight the key findings emerging from TDP-43 transgenic animal models and the insight they provide into the mechanisms driving TDP-43-mediated neurodegeneration.

Keywords TDP-43 · Neurodegeneration · Amyotrophic lateral sclerosis · Frontotemporal lobar degeneration · Transgenic animal models

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Introduction

Many neurodegenerative diseases are characterized by the misfolding and aggregation of proteins into intracellular inclusions. The transactive response DNA-binding protein 43 (TDP-43) was recognized as one such protein when, in 2006, it was identified as a primary component of ubiquitinated inclusions in the most frequent form of frontotemporal lobar degeneration (FTLD) and in most cases of amyotrophic lateral sclerosis (ALS; Arai et al. 2006; Neumann et al. 2006).

Frontotemporal dementia (FTD), the third most common cause of dementia in industrialized countries after Alzheimer's disease (AD) and dementia with Lewy bodies (Neary et al. 1998; Snowden et al. 2002), encompasses a heterogeneous group of neurodegenerative disorders distinguished clinically by abnormalities in behavior, language, and personality (Seelaar et al. 2011). The most common clinical syndrome, behavioral-variant FTD, is associated with disinhibition and social inappropriateness. Other clinical syndromes include progressive non-fluent aphasia and semantic dementia. In some instances, FTD patients display movement abnormalities with clinical features of motor neuron disease (MND) resembling ALS. FTLD is the neuropathologic substrate of FTD being characterized by the predominant atrophy of the frontal and temporal lobes and the presence of proteinaceous inclusions in neurons and glia. It is broadly divided into cases with tau-positive inclusions (FTLD-tau) and those with tau-negative, ubiquitin-positive inclusions (FTLD-U). The ubiquitinated protein in most FTLD-U cases is TDP-43, and these are consequently classified as FTLD–TDP.

ALS is characterized by the progressive degeneration of motor neurons in the cerebral cortex (upper motor neurons), brain stem, and spinal cord (lower motor neurons), resulting

in muscle weakness, atrophy, and spasticity. Additionally, ALS can involve several non-motor systems and subcortical structures, and there is evidence of cognitive deficits in a considerable number of ALS patients (Lowe 1994; Abe et al. 1997; Frank et al. 1997; Lomen-Hoerth et al. 2003; Ringholz et al. 2005; Murphy et al. 2007). Cytoplasmic ubiquitin-positive inclusions are present in lower motor neurons and, less frequently, upper motor neurons (Leigh et al. 1991; Ince et al. 1998). In cases of ALS with dementia, and in some patients with minor cognitive changes, ubiquitin-positive inclusions are also present in other brain regions including the extramotor neocortex and hippocampus (Okamoto et al. 1991; Wightman et al. 1992; Mackenzie and Feldman 2005; Geser et al. 2008a). It is now well established that TDP-43 is the primary component in glial and neuronal inclusions present in most ALS patients, with the exception of those with familial ALS caused by mutations in *Cu/Zn superoxide dismutase (SOD1)* (Arai et al. 2006; Neumann et al. 2006; Cairns et al. 2007; Davidson et al. 2007; Grossman et al. 2007; Higashi et al. 2007a; Mackenzie et al. 2007; Neumann et al. 2007; Seelaar et al. 2007; Tan et al. 2007; Hatanpaa et al. 2008; Pikkarainen et al. 2008; Josephs et al. 2009). Based on the significant overlap of clinical and pathological features among FTLD-TDP with or without MND and ALS-TDP with or without dementia, it has been suggested that these TDP-43 proteinopathies are situated at points along one continuous clinicopathological spectrum of multi-system neurodegenerative diseases (Geser et al. 2010).

In addition to ALS-TDP and FTLD-TDP, TDP-43 pathology has been observed, to a variable extent, in other neurodegenerative disorders including Lewy body disease (Higashi et al. 2007b; Nakashima-Yasuda et al. 2007), parkinsonism–dementia complex of Guam (Hasegawa et al. 2007; Geser et al. 2008b), corticobasal degeneration (Arai et al. 2006; Uryu et al. 2008), Pick's disease (Arai et al. 2006), AD (Arai et al. 2006; Amador-Ortiz et al. 2007; Higashi et al. 2007b; Uryu et al. 2008), Perry syndrome (Wider et al. 2009), and hippocampal sclerosis (Amador-Ortiz et al. 2007; Cairns et al. 2007). Whether the presence of TDP-43 pathology in these diseases indicates that TDP-43 contributes to their development or progression has yet to be determined. It is interesting to note, however, that the presence of TDP-43 pathology in AD is associated with greater brain atrophy and more severe clinical deficits (Josephs et al. 2008). Studies also suggest that amyloid-β triggers TDP-43 pathology (i.e., TDP-43 phosphorylation, cleavage, and accumulation in the cytosol) in mouse models of AD (Caccamo et al. 2010; Herman et al. 2011), while TDP-43 overexpression heightens α-synuclein toxicity to dopaminergic neurons in transgenic mice (Tian et al. 2011).

The identification of numerous missense mutations in *TARDBP*, the gene encoding TDP-43, in sporadic and familial ALS, as well as in patients with FTD, provides evidence of a direct link between TDP-43 abnormalities and neurodegeneration (Gitcho et al. 2008; Kabashi et al. 2008; Kuhnlein et al. 2008; Rutherford et al. 2008; Sreedharan et al. 2008; Van Deerlin et al. 2008; Yokoseki et al. 2008; Benajiba et al. 2009; Borroni et al. 2009; Corrado et al. 2009; Daoud et al. 2009; Del Bo et al. 2009; Gitcho et al. 2009; Kovacs et al. 2009; Lemmens et al. 2009). As with other protein misfolding diseases, TDP-43-mediated neuronal death in ALS-TDP and FTLD-TDP is likely caused by multiple pathways involving a combination of toxic gain and loss of TDP-43 function. The sequestration of TDP-43 from the nucleus to cytoplasmic inclusions is expected to result in loss of TDP-43 function. The inclusions themselves may be neurotoxic, merely inert by-products, or a protective mechanism used by cells to sequester harmful TDP-43 species. Additionally, phosphorylation, ubiquitination, and cleavage of TDP-43 into C-terminal TDP-43 fragments, post-translational modifications observed only in disease, may both bestow toxic properties upon TDP-43 and cause TDP-43 dysfunction.

As our knowledge of the normal function of TDP-43 continues to grow, so too shall our understanding of the mechanisms that drive TDP-43-mediated neurodegeneration. TDP-43, an RNA/DNA binding protein, is among the class of heteregeneous riobonucleoproteins and is believed to regulate multiple steps of RNA metabolism, including transcription, splicing, mRNA transport, and microRNA biosynthesis (Buratti and Baralle 2010). Although TDP-43 is largely a nuclear protein, it does shuttle between the nucleus and cytoplasm in a transcription-dependent manner, and a small proportion of TDP-43 is present in the cytoplasm under physiological conditions (Ayala et al. 2008; Winton et al. 2008). This suggests that, in addition to its nuclear functions, TDP-43 may play an important role in the cytoplasm, a hypothesis that is strengthened by the findings that the post-synaptic localization of TDP-43, in the form of RNA granules, is enhanced following depolarization of primary hippocampal neurons (Wang et al. 2008a) and that TDP-43 relocates to cytoplasmic stress granules in response to harmful stimuli in cell and animal models (Colombrita et al. 2009; Moisse et al. 2009a, b; Freibaum et al. 2010; Liu-Yesucevitz et al. 2010; Dewey et al. 2011; McDonald et al. 2011). Together, these findings suggest that TDP-43 regulates synaptic plasticity by controlling the transport and splicing of synaptic mRNAs and assists in the physiological response to neuronal injury.

Recently developed rodent TDP-43 transgenic models are expected to serve as valuable tools to better understand the role of TDP-43 within the central nervous system, as well as provide insight on the mechanisms by which TDP-43 contributes to the development and progression of neurodegeneration (Wegorzewska et al. 2009; Shan et al.

2010; Stallings et al. 2010; Tsai et al. 2010; Wils et al. 2010; Xu et al. 2010; Zhou et al. 2010; Igaz et al. 2011; Tian et al. 2011). The aim of this review is to highlight key findings emerging from TDP-43 transgenic animals, as well as some of the many questions in need of further investigation.

Rodent Models of TDP-43 Overexpression

Several TDP-43 transgenic animal models have now been generated (Table 1). Despite variations in the design of these models, which include differences in the selection of promoter driving transgene expression and, consequently, the regional expression of exogenous TDP-43, in the form of TDP-43 being expressed (i.e., mouse vs. human or wild-type vs. mutant TDP-43), and even in the species chosen for the model (mouse vs. rat), many commonalities exist among them. For instance, ubiquitin accumulation, TDP-43 fragmentation, astrogliosis, microgliosis, axonal degeneration, neuronal loss, motor function impairments, and shortened lifespan are observed in many of the transgenic animals (Table 1). Conspicuously lacking, however, is the presence of overt TDP-43 cytoplasmic inclusions. Summarized below are the findings that have emerged from the primary characterization of the currently available TDP-43 transgenic mice and rats.

Behavioral Phenotypes in TDP-43 Transgenic Rodents

In four of the TDP-43 transgenic models discussed herein, the TDP-43 transgene is under the control of the mouse prion protein (PrP) promoter which drives high expression in the brain and spinal cord, regions relevant to ALS. Wegorzewska and colleagues (2009) generated a transgenic mouse line that overexpresses flag-tagged human TDP-43 with the ALS-linked mutation, A315T. These mice develop progressive gait abnormalities, weight loss, and finally become unable to right or feed themselves by ~5 months of age. Notably, although transgene expression occurs throughout the nervous system and other tissues, selective toxicity is observed in layer V cortical neurons and in spinal motor neurons (Wegorzewska et al. 2009). These results indicate that PrP-TDP-43_{A315T} mice develop motor neuron disease with involvement of both cortical and spinal motor neurons, reminiscent of human ALS.

Xu and colleagues (2010) observe a similar phenotype in transgenic mice engineered to overexpress wild-type human TDP-43. Homozygous PrP-TDP-43_{WT} mice show reduced body and brain weights, develop body tremors and gait abnormalities, exhibit degenerating neurites, axons and neurons in the spinal cord, and finally become unable to right themselves between 1 and 2 months of age. Unlike homozygous PrP-TDP-43_{WT} mice, hemizygous mice are virtually indistinguishable from non-transgenic controls, indicating that TDP-43 expression must meet a certain threshold for toxicity to ensue.

The findings generated from PrP-TDP-43_{A315T} (Wegorzewska et al. 2009) and PrP-TDP-43_{WT} (Xu et al. 2010) mice indicate that both wild-type and mutant TDP-43 overexpression is toxic. This is consistent with the findings of Stallings and colleagues, who report that founder mice expressing high levels of mutant TDP-43 (A315T or M337V) or wild-type TDP-43 develop early-onset and progressive motor deficits, the severity of which correlates with level of transgene expression in the spinal cord. However, when comparing lines that express intermediate levels of mutant or wild-type TDP-43, only PrP-TDP-43_{A315T} mice develop a progressive motor phenotype and early lethality, with PrP-TDP-43_{WT} mice showing no obvious phenotype up to 11 months of age. While these results suggest that mutant TDP-43 may be more toxic than wild-type TDP-43, it must be kept in mind that transgene expression in PrP-TDP-43_{WT} mice is lower than that in PrP-TDP-43_{A315T} mice (Stallings et al. 2010). Nonetheless, additional evidence of differential toxicity between wild-type and mutant TDP-43 is provided by rat transgenic models. The Xia group generated transgenic rats that overexpress wild-type or mutant (M337V) human TDP-43 utilizing a human TDP-43 "minigene" extracted from a BAC clone. Founder miniTDP-43_{M337V} rats developed weakness, became paralyzed, and died at postnatal ages. In contrast, miniTDP-43_{WT} rats, which expressed human wild-type TDP-43 protein at comparable levels, did not develop paralysis by the age of 200 days, suggesting that TDP-43_{M337V} is indeed more toxic than wild-type TDP-43 (Zhou et al. 2010). To overcome the toxicity associated with the constitutive expression of TDP-43_{M337V} during development, rats conditionally expressing TDP-43_{M337V} were generated. iTDP-43_{M337V} expression in post-natal rats induces limb weakness and paralysis, with axonal degeneration of motor neurons occurring at disease onset. Progressive degeneration of motor neurons and denervation atrophy of skeletal muscles are subsequently observed. Moreover, neurodegeneration of cortical, hippocampal, and cerebellar neurons occurs but at later time-points and less severely than for motor neurons (Zhou et al. 2010). Using the CAG promoter to drive robust and ubiquitous transgene expression, the Xia group next generated mice that overexpress wild-type or mutant (M337V) human TDP-43 (Tian et al. 2011). Similar to their findings in rat, mice constitutively expressing TDP-43_{M337V} rapidly become immobile and die soon after birth, thus preventing CAG-TDP-43_{M337V} lines from being established. In contrast, transgenic founders overexpressing wild-type TDP-43 are healthy

Table 1 TDP-43 transgenic animal models generated

	Wegorzewska et al. 2009; Wegorzewska and Baloh 2011	Stallings et al. 2010	Stallings et al. 2010	Xu et al. 2010	Wils et al. 2010	Shan et al. 2010
Promoter	PrP	PrP	PrP	PrP	Thy1.2	Thy1.2
Transgene	Flag-tagged human TDP-43_{A315T}	Human TDP-43_{WT}	Human TDP-43_{A315T}	Human TDP-43_{WT}	Human TDP-43_{WT}	Human TDP-43_{WT}
Species	Mouse	Mouse	Mouse	Mouse	Mouse	Mouse
Abbreviation used in text	PrP-TDP-43_{A315T}	Prp-TDP-43_{WT}	PrP-TDP-43_{A315T}	Prp-TDP-43_{WT}	Thy1-TDP-43	Thy1-TDP-43
Expression	Constitutive	Constitutive	Constitutive	Constitutive	Constitutive	Constitutive
Motor impairment	Y	N	Y	Y	Y	Y
Increased ubiquitin staining or inclusions	Y	Y	Y	Y	Y	Y
Loss of nuclear TDP-43	Y	None reported	None reported	None reported	Y	None reported
TDP-43 NII	N	N	Y	Y	Y	Y
Cytoplasmic TDP-43 (diffuse staining or presence in cytoplasmic fraction)	N	Y	Y	Y	Y	None reported
TDP-43 NCI	Y	N	Y	Y	Y	N
Mitochondrial clusters	Y	None reported	None reported	Y	None reported	Y
Astrogliosis and/or microgliosis	Y	Y	Y	Y	Y	None reported
TDP-43 cleavage products	Y	Y	Y	Y	Y	None reported
Neurodegeneration	Selective degeneration of layer V cortical neurons and motor neurons.	None reported for Prp-TDP-43_{WT} line 21	None reported for PrP-TDP-43_{A315T} line 23	Degeneration of neurites, axons and neurons in the spinal cord	Degeneration of cortical and spinal motor neurons. Loss of CA3 hippocampal neurons and degeneration of Purkinje cells.	Decreased number of large-caliber axons in lumbar region of spinal cords.
Survival	154+/−19 days	Normal	75 days (line 23)	30–60 days	~30–200 days depending on level of transgene expression in a given line	Normal

	Tsai et al. 2010	Igaz et al. 2011	Igaz et al. 2011	Zhou et al. 2010	Zhou et al. 2010	Tian et al. 2011
Promoter	CaMKII	TRE (CaMKII-tTA)	TRE (CaMKII-tTA)	Endogenous	TRE (CAG-tTA)	CAG
Transgene	Mouse TDP-43_{WT}	Human TDP-43_{WT}	Human TDP-43 with mutated NLS	Human TDP-43_{WT} mini-gene	Human TDP-43_{M337V}	Human TDP-43_{WT}
Species	Mouse	Mouse	Mouse	Rat	Rat	Mouse
Abbreviation used in text	CaMKII-mTDP-43	iTDP-43	iTDP-43ΔNLS	miniTDP-43_{WT}	iTDP-43_{M337V}	CAG-TDP-43
Expression	Constitutive	Conditional (P28+)	Conditional (P28+)	Constitutive	Conditional (P10+)	Constitutive
Motor impairment	Y	Y	Y	N	Y	N
Increased ubiquitin staining or inclusions	Y	Y	Y	Y	Y	N

Table 1 (continued)

	Tsai et al. 2010	Igaz et al. 2011	Igaz et al. 2011	Zhou et al. 2010	Zhou et al. 2010	Tian et al. 2011
Loss of nuclear TDP-43	Y	Y	Y	None reported	None reported	None reported
TDP-43 NII	N	N	N	N	N	N
Cytoplasmic TDP-43 (diffuse staining or presence in cytoplasmic fraction)	Y	N	Y	Y	Y	N
TDP-43 NCI	Y	Y	Y	N	Y	N
Mitochondrial clusters	None reported	None reported	None reported	None reported	None reported	None reported
Astrogliosis and/or microgliosis	Y	Y	Y	N	Y	None reported
TDP-43 cleavage products	Y	N	N	N	Y	None reported
Neurodegeneration	Loss of cortical neurons and decreased hippocampal volume.	Progressive neuron loss in hippocampal dentate gyrus and neocortex.	Progressive neuron loss in hippocampal dentate gyrus. Deep neocortical layers also affected. Select loss of corticospinal axons in cervical spinal cord.	No neurodegeneration	Reduction in spinal cord motor neurons. Degenerating axons in ventral and dorsal roots, as well as in corticospinal track. At end stages of disease, neurodegeneration occurs in cortex, hippocampus and cerebellum.	Significant loss of neurons in the frontal cortex, but not in the dentate gyrus, at 10–12 months of age.
Survival	495 days	Not reported	Not reported	Normal	35–55 days depending on level of transgene expression and sex of rats	Not reported

Y presence of a given phenotype regardless of how rare or abundant it may be, *N* absence of a given phenotype, *NCI* neuronal cytoplasmic inclusions, *NII* neuronal intranuclear inclusions, *P* post-natal, *WT* wild-type

and fertile. Other than a moderate loss of cortical neurons at 10–12 months of age, homozygous CAG-TDP-43 mice show no obvious abnormalities compared with non-transgenic controls (Tian et al. 2011).

Transgenic mice that express wild-type TDP-43 under control of the mouse Thy1 promoter, which drives expression in post-natal neurons of the central nervous system, including motor neurons, develop a similar phenotype as mice in which transgene expression is regulated by the mouse PrP promoter (Shan et al. 2010; Wils et al. 2010). For instance, dose-dependent degeneration of cortical and spinal motor neurons is observed in the Thy1-TDP-43 mice generated by the Kumar-Singh group. These mice develop abnormal hindlimb reflex, reduced motor performance, and early lethality. Upon comparing hemizygous and homozygous mice produced from different founder lines, it was determined that human TDP-43 expression dose-dependently influences the onset and rate of disease progression (Wils et al. 2010). Similarly, the severity of the phenotype observed in Thy1-TDP-43 mice developed by Shan and colleagues correlates with the copy number of the transgene: mice with the highest transgene copy number are markedly smaller than non-transgenic littermates and die within 3 weeks of age, whereas mice derived form lines expressing lower levels of transgene exhibit less growth retardation and most live to adulthood. Of note, transgenic males, which express human TDP-43 at two- to threefold higher levels than transgenic females, develop a more severe phenotype (Shan et al. 2010).

As in the above-mentioned models, transgenic mice in which exogenous TDP-43 expression is controlled by the Ca^{2+}/calmodulin-dependent kinase II (CaMKII) promoter, which drives neuronal expression predominantly in the forebrain but not in the spinal cord, develop progressive motor deficits (Tsai et al. 2010). Tsai et al. (2010) observed that their transgenic mice, which overexpress wild-type mouse TDP-43 (mTDP-43), become impaired in motor coordination, balance, and grip strength at 6 months of age. CaMKII-mTDP-43 mice also develop abnormal limb-clasping reflexes when suspended by their tails, a phenotype observed, albeit to a lesser extent, in iTDP-43 mice that inducibly overexpress wild-type human TDP-43 under the control of a CaMKII tetracycline transactivator (Igaz et al. 2011). The motor deficits in these two models are likely caused by the degeneration of upper motor neurons, which express exogenous TDP-43 and not due to the degeneration of lower motor neurons in the brainstem and spinal cord, which do not express the transgene. Consistent with this, no difference in the size and number of spinal cord motor neurons is present in CaMKII-mTDP-43 mice, but a reduction in the number of cortical neurons, as well as a decrease in hippocampal volume, are observed (Tsai et al. 2010). In a similar fashion, iTDP-43 mice that conditionally express high levels of human TDP-43, but not low-expressing mice, show selective and progressive neuron loss in the neocortex and hippocampal dentate gyrus (Igaz et al. 2011). In addition to motor deficits, Tsai and colleagues observe that their CaMKII-mTDP-43 mice exhibit impaired learning and memory, as assessed by the Morris water maze and fear-conditioning tasks. The cognitive impairment in these transgenic mice is accompanied by abnormalities in hippocampal long-term potentiation, a form of synaptic plasticity believed to be required for the molecular mechanisms of learning and memory. It is worth noting that many TDP-43 RNA targets involved in the long-term potentiation pathway are misregulated following depletion of TDP-43 from mouse adult brain (Polymenidou et al. 2011).

Overall, axonal and/or neuronal degeneration, motor deficits, and early lethality are relatively consistent features among TDP-43 transgenic models. The mechanisms responsible for initiating these events, however, have yet to be fully elucidated. Given that TDP-43 aggregation, phosphorylation, and truncation are now considered hallmark features of ALS-TDP and FTLD-TDP, most groups have investigated whether these abnormalities are present in their transgenic models and whether they may contribute to TDP-43-induced neurotoxicity.

TDP-43 Cytoplasmic Inclusions

Cytoplasmic ubiquitin- and TDP-43-immunopositive inclusions are a defining feature in ALS-TDP and FTLD-TDP (Arai et al. 2006; Neumann et al. 2006). An accumulation of ubiquitin is observed in the nucleus and/or cytoplasm of neurons of most TDP-43 transgenic rodent models, in the form of multiple small aggregates, large aggregates, or present diffusely (Wegorzewska et al. 2009; Shan et al. 2010; Stallings et al. 2010; Tsai et al. 2010; Wils et al. 2010; Xu et al. 2010; Zhou et al. 2010; Igaz et al. 2011). Of interest, Wegorzewska and colleagues noted that the cytoplasmic accumulation of ubiquitin, like neurodegeneration, occurs in cortical layer V and large neurons of the ventral horn of the spinal cord in their Prp-TDP-43_{A315T} mice despite widespread transgene expression (Wegorzewska et al. 2009). Similarly, although the Thy1 promoter drives wild-type human TDP-43 expression in virtually all neurons of the brain, dense large neuronal cytoplasmic and intranuclear inclusions composed of ubiquitin are present only in cortical layer V of Thy1-TDP-43 mice (Wils et al. 2010).

Immunoprecipitation studies have revealed that the accumulation of ubiquitin observed in TDP-43 transgenic models is not necessarily indicative of increased levels of ubiquitinated TDP-43 per se; ubiquitinated TDP-43 is detected in miniTDP-43_{M337V} rats (Zhou et al. 2010), but is not observed in PrP-TDP-43_{WT} mice despite a marked

increase in ubiquitin levels (Xu et al. 2010). Moreover, while Tsai and colleagues do detect TDP-43-positive cytoplasmic inclusions in ~15–20% of cortical neurons of their CaMKII-mTDP-43 mice, in most other models, TDP-43-immunopositive cytoplasmic inclusions are seldom or never observed when immunostaining of brain or spinal cord sections is carried out using phosphorylation-independent TDP-43 antibodies (Wegorzewska et al. 2009; Shan et al. 2010; Stallings et al. 2010; Wils et al. 2010; Xu et al. 2010; Zhou et al. 2010; Igaz et al. 2011; Tian et al. 2011). Somewhat surprisingly, when using antibodies that detect TDP-43 phosphorylated at S403/S404 or S409/S410, sites abnormally phosphorylated in ALS-TDP and FTLD-TDP (Hasegawa et al. 2008), TDP-43-positive intranuclear inclusions, and punctate cytoplasmic inclusions are detected, albeit with varying prevalence, in the spinal cord and/or brain of many models (Wegorzewska et al. 2009; Stallings et al. 2010; Wils et al. 2010; Xu et al. 2010; Zhou et al. 2010; Igaz et al. 2011). It remains unclear why phospho-TDP-43 antibodies are more sensitive at detecting TDP-43 inclusions, but a similar effect is observed in human tissue. For instance, a higher frequency of TDP-43 pathology is detected in AD patients when immunohistochemistry is performed with phosphorylation-specific TDP-43 antibodies (Arai et al. 2009) than with phosphorylation-independent TDP-43 antibodies (Amador-Ortiz et al. 2007; Uryu et al. 2008; Kadokura et al. 2009).

The general scarcity of TDP-43 cytoplasmic inclusions within neurons of the currently available TDP-43 transgenic animals argues against a primary role for such inclusions in mediating the neurotoxic effects resulting from TDP-43 overexpression. Of course, while this indicates that TDP-43 inclusions are not required for neuronal death, it does not exclude their pathogenic potential. Indeed, studies conducted in yeast have shown that only those TDP-43 species that form aggregates are toxic (Johnson et al. 2008). Furthermore, ALS-linked mutations that accelerate aggregation of human TDP-43 in vitro promote TDP-43 toxicity in yeast (Johnson et al. 2009). Evidence that TDP-43 aggregation is detrimental to mammalian cells is provided by a model in which a C-terminal TDP-43 fragment, corresponding to a caspase cleavage product of TDP-43, is overexpressed in differentiated human neuroblastoma cells (Zhang et al. 2009). The aggregation of these fragments is associated with increased cytotoxicity which likely results from a toxic gain of function since it does not alter the nuclear distribution of endogenous full-length TDP-43 (Zhang et al. 2009). Other studies, however, suggest that it is the cytosolic localization of TDP-43 and not its aggregation that causes neurotoxicity. While EGFP-TDP-43_{A315T} overexpression in primary rat cortical neurons leads to the formation of detergent-resistant inclusions, Barmada and colleagues (2010) found that neuronal toxicity resulting from EGFP-TDP-43_{A315T} expression occurs independently of inclusion formation. Rather, the amount of cytosolic EGFP-TDP-43_{A315T} was shown to be a powerful predictor of cell death, suggesting that soluble forms of cytosolic TDP-43 are neurotoxic (Barmada et al. 2010).

Cytoplasmic TDP-43 and C-Terminal TDP-43 Fragments

The diffuse redistribution of TDP-43 to the cytoplasm appears to be an early event in ALS-TDP (Giordana et al. 2010). Despite the largely nuclear localization of exogenous TDP-43 and the paucity of TDP-43 cytoplasmic inclusions in TDP-43 transgenic rodents, diffuse cytoplasmic TDP-43 staining is occasionally observed (Stallings et al. 2010; Tsai et al. 2010; Wils et al. 2010; Xu et al. 2010; Zhou et al. 2010). Additionally, C-terminal TDP-43 fragments are present in many (Wegorzewska et al. 2009; Stallings et al. 2010; Tsai et al. 2010; Wils et al. 2010; Xu et al. 2010; Zhou et al. 2010), but not all (Shan et al. 2010; Igaz et al. 2011), models. C-terminal TDP-43 fragments of ~25 and ~35 kDa are recovered in the sarkosyl-insoluble fraction of affected brain regions of ALS-TDP and FTLD-TDP patients (Neumann et al. 2006), and it is suspected that they seed the aggregation of TDP-43 into inclusions. In support of this, the overexpression of C-terminal TDP-43 fragments in various cell lines leads to the aggregation of TDP-43 into insoluble cytoplasmic inclusions (Winton et al. 2008; Igaz et al. 2009; Nonaka et al. 2009; Zhang et al. 2009). Much remains unknown regarding the processes responsible for the generation of TDP-43 cleavage products and what role they play in the pathogenesis of disease. Because C-terminal fragments lack a nuclear localization signal, their shuttling between the cytoplasm and nucleus is presumably impaired, and this would lead to a loss of TDP-43 function. Additionally, the increased presence of TDP-43 in the cytosol, either in a soluble or insoluble form, may cause a toxic gain of function. Since animals can be killed at different time-points during disease, they provide an ideal tool with which to examine the involvement of C-terminal TDP-43 fragments in TDP-43 toxicity. For example, in Prp-TDP-43_{A315T} mice, C-terminal TDP-43 fragments of approximately ~25 and ~35 kDa are observed in the brain and spinal cord at an early stage, prior to the onset of gait abnormalities and significant brain pathology (Wegorzewska et al. 2009). It is noteworthy that the TDP-43 fragments observed in these Prp-TDP-43_{A315T} mice are mostly present in a soluble form, consistent with the lack of insoluble TDP-43 inclusions. By way of subcellular fractionation studies, Stallings and colleagues also found a clear correlation between disease progression and an increase in the presence of cytoplasmic full-length TDP-43, as well as TDP-43 fragments, in Prp-TDP-43_{A315T} mice. Wils et al. (2010) observed a ~25 kDa TDP-43 fragment only in the nuclear fraction of brains from

Thy1-TDP-43 mice and found that levels of this fragment increase with disease severity, whereas levels of ~35 kDa TDP-43 fragments, present in both the nucleus and cytoplasm, decrease with increasing disease severity (Wils et al. 2010). While correlative, the findings from these studies are consistent with the hypothesis that ~25 kDa C-terminal fragments play an important role in TDP-43-mediated neurodegeneration. They suggest that TDP-43 fragments are toxic in and of themselves and not necessarily because they assemble into inclusions. Arguing against this hypothesis are findings from other TDP-43 transgenic models that suggest TDP-43 fragments are generated only after the first appearance of symptoms. For example, Tsai and colleagues found that the appearance of ~25- and 35-kDa TDP-43 fragments in the urea-soluble fractions of brain extracts from CaMKII-mTDP-43 mice coincides with motor deficits, but occurs only after signs of cognitive impairment. Likewise, Zhou et al. (2010) report that TDP-43 fragments are present only at end-stage of disease, suggesting that the formation of such fragments is a consequence, rather than a cause, of neurodegeneration in TDP-43 transgenic rats. Finally, there exist TDP-43 transgenic models with signs of neurodegeneration and/or premature death in which TDP-43 fragments are not generated (Shan et al. 2010; Igaz et al. 2011), indicating that, at least in these models, TDP-43 cleavage products are not responsible for TDP-43-mediated toxicity. Again, however, this does not rule out the potentially harmful consequence of TDP-43 fragments were they to be formed.

Nuclear TDP-43 Inclusions and Altered Distribution of Gemini of Coiled Bodies

In addition to cytoplasmic inclusions, TDP-43-positive inclusions can take the form of dystrophic neurites and intranuclear inclusions in ALS-TDP and FTLD-TDP (Gendron et al. 2010). TDP-43-immunopositive nuclear inclusions are also observed in some TDP-43 transgenic models (Shan et al. 2010; Stallings et al. 2010; Wils et al. 2010; Xu et al. 2010). Of note, the Thy1-TDP-43 mice generated by Shan and colleagues develop TDP-43-positive nuclear aggregates that also contain SC35, a marker of non-snRNP (small nuclear ribonucleoprotein), and the fused in sarcoma (FUS) protein, two proteins involved in RNA metabolism. Like TDP-43, FUS is an RNA-binding protein that forms aggregates in certain cases of ALS and FTLD. It has been shown to co-localize with TDP-43 in familial and sporadic ALS (Deng et al. 2010), although other groups report that TDP-43 and FUS pathology in ALS and FTLD are mutually exclusive (Kwiatkowski et al. 2009; Neumann et al. 2009; Vance et al. 2009; Hewitt et al. 2010; Seelaar et al. 2010).

In addition to TDP-43-containing nuclear inclusions, Thy1-TDP-43 mice have an increased number of Gemini of coiled bodies in the nucleus of motor neurons, whereas GEMs are absent altogether in mice in which TDP-43 expression is prevented (Shan et al. 2010). GEMs, small punctate nuclear structures, are enriched with survival motor neuron (SMN) protein and play a role in small nuclear ribonucleoprotein maturation and pre-RNA splicing. Using SMN minigenes, TDP-43 was previously shown to enhance exon 7 inclusion and stability of SMN2 in cultured cells (Bose et al. 2008). This function of TDP-43 may underlie the increase in GEMs observed in Thy1-TDP-43 mice. While the role of increased GEMs in TDP-43-induced toxicity remains to be determined, these findings suggest that TDP-43 overexpression impacts pathways that control RNA metabolism.

Loss of Nuclear TDP-43

In ALS-TDP and FTLD-TDP, a loss of nuclear TDP-43 staining is commonly observed in affected spinal cord and/or brain neurons (Neumann et al. 2006). Although exogenous TDP-43 in TDP-43 transgenic rodents is primarily nuclear, in some models, a loss of nuclear TDP-43 in selectively vulnerable neurons is observed prior to obvious signs of degeneration (Wegorzewska et al. 2009; Tsai et al. 2010; Wils et al. 2010; Igaz et al. 2011). To mimic the nuclear clearance of TDP-43, Igaz and colleagues generated transgenic mice that inducibly overexpress, within the forebrain, human TDP-43 with a mutated nuclear localization signal (iTDP-43ΔNLS) using the CaMKII tetracycline-off inducible system (Igaz et al. 2011). This paradigm was based on their earlier findings that expression of TDP-43ΔNLS in cultured cells accumulates into cytoplasmic aggregates and also sequesters endogenous nuclear TDP-43 (Winton et al. 2008). iTDP-43ΔNLS mice develop neuron loss in the cortex and hippocampus, as well as degeneration of the corticospinal tract (Igaz et al. 2011). However, unlike cultured cells expressing TDP-43ΔNLS, few ubiquitin- and phosphorylated-TDP-43-immunopositive cytoplasmic aggregates are present in iTDP-43ΔNLS mice. What is more, TDP-43 inclusions do not correlate with neurotoxicity in this model. Nonetheless, a dramatic loss of endogenous nuclear mTDP-43 is observed in iTDP-43ΔNLS mice, as well as in mice that inducibly express full-length TDP-43, and this phenotype does correlate with the rate and extent of neurodegeneration (Igaz et al. 2011). Double-label immunofluorescence studies using antibodies specific to either mouse or human TDP-43 revealed that neurons expressing exogenous human TDP-43 exhibit decreased staining for endogenous mTDP-43. This decrease in mTDP-43 does not result from its sequestration into cytoplasmic inclusions (Igaz et al. 2011) but is most likely

due to a decrease in endogenous mTDP-43 mRNA and protein expression. Xu and colleagues have shown that mTDP-43 mRNA levels decrease upon expression of human TDP-43 in PrP-TDP-43_{WT} mice, indicating that a compensatory mechanism exists to tightly control levels of mTDP-43 (Xu et al. 2010). Indeed, it has since been shown that TDP-43 auto-regulates its mRNA levels through a negative feedback loop; TDP-43 binds to 3′UTR sequences in its own mRNA and this promotes RNA instability (Ayala et al. 2011).

Since loss of mTDP-43 correlates with neurodegeneration in iTDP-43ΔNLS and iTDP-43 mice (Igaz et al. 2011), the authors speculate that perturbations of endogenous nuclear mTDP-43 results in loss of normal TDP-43 function, culminating in the degeneration of selectively vulnerable neurons. Certainly, there is a great deal of evidence supporting that mTDP-43 function is critical for the survival of mice. For example, knock-down of mTDP-43 expression in mice causes motor deficits (Kraemer et al. 2010), and knock-out of mTDP-43 results in embryonic lethality (Chiang et al. 2010; Kraemer et al. 2010; Sephton et al. 2010; Wu et al. 2010). Furthermore, even if embryonic lethality is overcome by knocking-out mTDP-43 expression only after the birth of mice, rapid death still ensues (Chiang et al. 2010). It remains possible, however, that loss of endogenous mTDP-43 is not the contributing factor leading to neurodegeneration in iTDP-43ΔNLS and iTDP-43 mice. TDP-43 transgenic mice overexpressing mTDP-43 display similar neurodegeneration and share many characteristics as mice overexpression human TDP-43, even though they maintain high levels of nuclear mTDP-43 (Tsai et al. 2010). Furthermore, mouse and human TDP-43 are highly homologous, especially within the RNA recognition motifs (Wang et al. 2004). Given this, the question arises as to why loss of endogenous nuclear mTDP-43 in iTDP-43 mice should be detrimental to neurons when human TDP-43 levels within the nucleus remain elevated. Of course, it must be mentioned that mTDP-43 may modulate specific and vital RNA targets that cannot be regulated by human TDP-43. Moreover, multiple TDP-43 isoforms are expressed in mice, and these may have unique functions that cannot be compensated for by full-length human TDP-43 (Wang et al. 2002; Wang et al. 2004).

With regards to iTDP-43ΔNLS mice, neurodegeneration may be caused, not only by nuclear mTDP-43 depletion, but also by enhanced hTDP-43 expression within the cytoplasm. In rat primary cortical cultures that overexpress EGFP-TDP-43_{A315T}, neuronal survival is unaffected by the total amount of exogenous TDP-43 in the nucleus, yet the amount of cytoplasmic TDP-43 is a strong predictor of neuronal death (Barmada et al. 2010). Importantly, preventing the nuclear export of EGFP-TDP-43_{A315T} by mutating its nuclear export signal significantly blunts the toxicity associated with EGFP-TDP-43_{A315T} expression, confirming that it is the cytoplasmic mislocalization of EGFP-TDP-43_{A315T} that induces neuronal toxicity in rat primary neurons (Barmada et al. 2010). Whether a similar mechanism is responsible for toxicity in vivo has yet to be determined, nor is it definitely known whether it is the loss of endogenous mTDP-43, per se, that induces toxicity, or rather the dysregulation of TDP-43 expression in general.

Mitochondrial Abnormalities

Among the notable features characterized in rodent TDP-43 transgenic models, Xu and colleagues were first to report that TDP-43 overexpression in vivo has a profound effect on mitochondria. They found that PrP-TDP-43_{WT} mice develop cytoplasmic eosinophilic aggregates in spinal motor neurons that sometimes displace the nucleus. Ultrastructural analysis revealed that these eosinophilic aggregates are composed of clusters of abnormal mitochondria, many of which have features suggestive of degeneration, such as decreased cristae and vacuoles within the mitochondrial matrix (Xu et al. 2010). The clustering of mitochondria is also present in Thy1-TDP-43 mice generated by Shan and colleagues, as well as in PrP-TDP-43_{A315T} mice developed by the Baloh group, indicating that this phenotype is not unique to one model (Shan et al. 2010; Wegorzewska and Baloh 2011).

How TDP-43 overexpression in mice causes mitochondria to cluster, and what effect it may have on mitochondrial function, is not yet known. Given the primarily nuclear localization of exogenous TDP-43 in these transgenic models, it is likely that aberrations in nuclear TDP-43 function underlie the mitochondrial abnormalities, as opposed to a direct association of TDP-43 with mitochondria. Since changes in fission or fusion have previously been shown to cause abnormal perinuclear clustering of mitochondria (Baloh et al. 2007; Huang et al. 2007; Wang et al. 2008b), one potential cause may be that TDP-43 overexpression leads to the misregulation of transcripts that encode proteins which modulate mitochondria fission or fusion. Indeed, the expression of key proteins in the regulation of mitochondrial fission and fusion were found to be abnormally expressed or regulated in PrP-TDP-43_{WT} mice (Xu et al. 2010). TDP-43-mediated mitochondrial clustering may alternatively result from aberrant splicing or transcription of crucial mediators of axonal transport. Altered mitochondrial trafficking in association with proteins linked to neurodegenerative disease is not without precedent (Vives-Bauza et al. 2010). The presence of axonal degeneration in spinal cord neurons, together with perinuclear clusters of mitochondria in PrP-TDP-43_{WT} mice, does suggest that axonal transport deficits may cause

the abnormal distribution of mitochondria. To directly evaluate the distribution of mitochondria in different compartments of motor neurons, Shan and colleagues crossed Thy1-TDP-43 mice with Thy1-mitoCFP mice, in which a subpopulation of mitochondria are fluorescently labeled with CFP in neurons. In Thy1-mitoCFP mice, CFP-labeled mitochondria are evenly distributed in the cell body of motor neurons and are also present in neuronal processes. In contrast, mitochondria cluster into inclusions within cell bodies of motor neurons in Thy1-mitoCFP/TDP-43 mice (Shan et al. 2010). The sparse distribution of mitochondria in neuronal processes suggests that trafficking of mitochondria is impaired. Consistent with this speculation, there is an obvious reduction of mitochondria at nerve terminals of neuromuscular junctions in Thy1-mitoCFP/TDP-43 mice. Moreover, Kif3a and KAP3, proteins associated with the motor protein kinesin, are localized within the mitochondrial clusters of Thy1-TDP-43 mice (Shan et al. 2010).

Taken together, these results suggest that aberrations in mitochondrial dynamics and/or trafficking may play a role in TDP-43-mediated toxicity. Of note, the expression of TDP-43 in NSC-34 cells induces mitochondrial dysfunction and oxidative stress in the absence of TDP-43 inclusion formation (Duan et al. 2010). Additionally, the expression of TDP-43 in yeast, which leads to the formation of perimitochondrial TDP-43 aggregates, causes mitochondrial-dependent oxidative stress and cytotoxicity (Braun et al. 2011). It is especially noteworthy that abnormal mitochondria accumulate in presynaptic axosomatic terminals of motor neurons in ALS (Sasaki and Iwata 1999) and that cytoplasmic granules in motor neurons contain mitochondria with TDP-43 immunoreactivity (Mori et al. 2008). Also of interest is the observation that SOD1 is associated with aberrant spinal motor neuron mitochondria in humans and rodents with ALS due to *SOD1* mutations and that mitochondrial clusters are present in motor axons of mutant SOD1 transgenic rats (Sotelo-Silveira et al. 2009). Together, these findings implicate mitochondrial abnormalities in TDP-43-induced toxicity and provide a potential convergence between TDP-43 and SOD1 in the pathogenesis of ALS.

Conclusions

Although many questions remain regarding the mechanisms underlying TDP-43-mediated neurodegeneration, the findings emerging from the above-mentioned TDP-43 transgenic animal models bring to light a number of interesting observations. For instance, TDP-43-induced toxicity is dependent on the level of transgene expression, with intermediate expression of TDP-43 producing an attenuated phenotype, if any, compared with animals expressing higher TDP-43 levels (Stallings et al. 2010; Wils et al. 2010; Xu et al. 2010; Igaz et al. 2011). Of particular interest, compared with controls, FTLD-TDP brain samples show substantially higher total amounts of TDP-43, including high and low molecular weight TDP-43 species (Guo et al. 2011). Additionally, while no copy number variation of the *TARDBP* locus have been identified in ALS-TDP or FTLD-TDP (Gijselinck et al. 2009), perhaps because of the toxicity associated with heightened TDP-43 expression, sequencing analyses has identified a variant in the 3′-UTR *TARDBP* in a FTLD-TDP patient that increases TDP-43 mRNA levels (Gitcho et al. 2009).

The comparison of TDP-43 transgenic models indicates that both wild-type and mutant TDP-43 are neurotoxic upon overexpression. However, the threshold of TDP-43 expression required to induce toxicity appears to be lower for mutant TDP-43 than for wild-type TDP-43. That mutant TDP-43 may be more toxic than wild-type TDP-43 in rodents is consistent with some studies conducted in other model organisms, including yeast (Johnson et al. 2009), chicken embryos (Sreedharan et al. 2008), *Drosophila melanogaster* (Guo et al. 2011), and mammalian cells (Guo et al. 2011).

Even though mutations in *TARDBP* have been identified in a relatively small proportion of ALS patients, understanding how these mutations confer toxicity is expected to provide insight on the role of TDP-43 in neurodegeneration. Certain mutations accelerate the aggregation of TDP-43 in vitro and in yeast (Johnson et al. 2009), as well as in cultured cells (Nonaka et al. 2009; Liu-Yesucevitz et al. 2010; Guo et al. 2011). Mutations in TDP-43 also alter TDP-43 stress granule formation, leading to increased TDP-43 inclusion formation in response to stressful stimuli (Liu-Yesucevitz et al. 2010; Dewey et al. 2011). Furthermore, mutant TDP-43 is reportedly more prone to mislocalize to the cytoplasm of primary neurons, where it induces a toxic gain-of-function and cell death (Barmada et al. 2010). Additionally, some mutations are thought to increase the propensity of TDP-43 to become cleaved into C-terminal fragments (Kabashi et al. 2008; Rutherford et al. 2008; Sreedharan et al. 2008; Yokoseki et al. 2008; Corrado et al. 2009) and to produce higher amounts of protease-resistant fragments of 10–11 and 24–25 kDa (Guo et al. 2011). With regards to TDP-43 transgenic animals, few TDP-43 inclusions are observed, indicating that TDP-43 aggregation is not the initiating neurotoxic factor in these models. However, TDP-43 mislocalization and fragmentation do arise in various models (Table 1), suggesting that these abnormalities may play a role, at least in part, in TDP-43-mediated neurodegeneration.

Not only may cytosolic TDP-43 species contribute disease pathogenesis by a toxic gain of function, but they may also lead to the dysregulation of normal TDP-43

function. Of note, altered RNA expression and splicing are likely contributors to TDP-43 toxicity in rodent TDP-43 transgenic models. Using a transcriptome-wide differential RNA expression (RNA-Seq) approach, Shan and colleagues identified 313 genes with changes in splicing pattern and 2,017 genes that are differently expressed in spinal cord of Thy1-TDP-43 mice compared with non-transgenic controls. Similarly, more than 4,700 genes were differently expressed between iTDP-43ΔNLS and non-transgenic mice, as assessed by microarray analysis (Igaz et al. 2011). Based on biological pathway analysis, the "macromolecular complex organization" pathway was among the top dysregulated pathways in iTDP-43ΔNLS mice, with genes involved in chromatin assembly accounting for a significant enrichment in this category (Igaz et al. 2011). These two studies highlight that TDP-43 overexpression, and the consequences thereof, influence the regulation of a vast number of RNA targets. Indeed, several groups have undertaken the daunting task of identifying TDP-43 RNA targets in cultured cells, mouse brain, and human brain from FTLD or ALS patients (Polymenidou et al. 2011; Tollervey et al. 2011; Xiao et al. 2011). These studies emphasize that TDP-43 interacts with a diverse spectrum of RNA targets with important functions in the brain. As such, a greater understanding of the role played by TDP-43 in regulating the splicing and expression of RNA is crucial. This information will help decipher how the characteristic traits of ALS-TDP and FTLD-TDP, such as TDP-43 mislocalization, truncation, phosphorylation, and aggregation influence TDP-43 RNA metabolism. TDP-43 transgenic rodents, which recapitulate many of these features, should prove valuable in this endeavor.

Overall, the novel transgenic animals described herein, combined with other in vivo and in vitro models, provide much needed tools with which to answer the many questions regarding TDP-43 function and dysfunction. As the gaps in our knowledge continue to narrow, the likelihood of developing successful therapeutic strategies for the treatment of ALS-TDP and FTLD-TDP will greatly improve.

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