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TDP-43 in CNS development and function: clues to TDP-43-associated neurodegeneration

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Abstract

From the earliest stages of embryogenesis and throughout life, transcriptional regulation is carefully orchestrated in order to generate, shape, and reshape the central nervous system (CNS). TAR DNA-binding protein 43 (TDP-43), is identified as a regulator of essential transcriptional events in the CNS. Evidence for its importance comes from the identification of TDP-43 protein aggregates and genetic mutations in patients with amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). Efforts are being made to learn more about the biological function of TDP-43 and gain a better understanding of its role in neurodegeneration. TDP-43 RNA targets and protein interactions have now been identified and *in vivo* evidence shows that TDP-43 is essential in CNS development and function. This review will highlight aspects of these findings.

Keywords

TDP-43; neural development; RNA binding protein; amyotrophic lateral sclerosis (ALS); PTPB2; RIP-seq

Neurodegenerative diseases include a spectrum of chronic neurological disorders that are associated with deficits in behavior and cognition as well as the progressive loss of sensory, motor and perceptual functions. These changes occur due to the degeneration and death of neurons. The biological cause of some of the most prevalent neurodegenerative diseases, such as, ALS and FTLD remain unclear.

TDP-43 is identified as the major protein component of inclusions that are characteristic of most forms of ALS and FTLD (Neumann et al., 2006), now referred to as FTLD-TDP. TDP-43 accumulates abnormally in cytoplasmic, ubiquitinated inclusions in glia and degenerating neurons of ALS and FTLD-TDP patients. Since this discovery, over 30 different mutations in the *TDP-43* gene in familial and sporadic ALS patients and more rarely in FTLD-TDP cases have been reported (Dormann and Haass, 2011). Pathological TDP-43 inclusions are also present in other neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's disease (Baloh, 2011). The prevalence of TDP-43

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dysregulation in multiple neurodegenerative diseases has made it an attractive target for understanding mechanisms of neurodegeneration.

TDP-43 gene, protein structure and function

TDP-43 is found in all higher eukaryotes including *Drosophila melanogaster*, *Xenopus laevis*, and *Caenorhabditis elegans* (Wang et al., 2004). In humans, the gene encoding TDP-43, *TARDBP*, is located at the chromosomal locus 1p36.22 and is comprised of six exons, five of which encode the predominant 43 kDa protein, TDP-43. However, *TARDBP* can undergo alternative splicing to generate up to 11 protein isoforms (Wang et al., 2004). In addition to full-length TDP-43, three protein isoforms of TDP-43 are identified in human brain and spinal cord, but the biological significance of these isoforms is not known and their presence in other species has not been identified (Strong et al., 2007).

TDP-43 is a member of the heterogeneous nuclear ribonucleoproteins (hnRNPs) family, a group of proteins that bind RNAs (Krecic and Swanson, 1999). TDP-43 is ubiquitously expressed and localizes primarily to the nucleus of cells. At the N-terminus, there are two highly conserved RNA recognition motifs, which are involved in RNA/DNA binding (Buratti and Baralle, 2001; Kuo et al., 2009; Ou et al., 1995). Additionally, the N-terminus of TDP-43 can mediate the formation of homodimers (Kuo et al., 2009). TDP-43 contains a bipartite nuclear localization signal sequence and a nuclear export signal which allows nucleocytoplasmic shuttling (Winton et al., 2008). The C-terminal glycine-rich region of TDP-43 is less conserved among species (Wang et al., 2004). The C-terminus of TDP-43 is involved in protein-protein interactions and influences it's solubility and cellular localization (Ayala et al., 2008b). TDP-43 was first characterized for its roles in DNA binding and transcriptional regulation of human immunodeficiency virus 1 (HIV) and the spermatid-specific gene SP-10 (Acharya et al., 2006; Ou et al., 1995). Little effort has been made to identify more genes that are transcriptionally regulated by TDP-43. Instead, studies have focused on characterizing roles of TDP-43 in RNA metabolism.

TDP-43 ribonucleoprotein complexes and RNA targets

In neural cells, TDP-43 exists in high molecular mass ribonucleoprotein complexes that are dependent on the presence of nucleic acids (Kim et al., 2010; Sephton et al., 2011). Many of the proteins associated with TDP-43 in these complexes are involved in pre-mRNA splicing, RNA stability and transport (Kim et al., 2010; Sephton et al., 2011). In rodent brain nuclear extracts, TDP-43 forms a stable protein complex with several RNA binding proteins as well as two neuron-enriched proteins, methyl CpG-binding protein 2 (MECP2) and polypyrimidine tract-binding protein 2 (PTBP2) (Sephton et al., 2011). In cell culture, overexpressed TDP-43 also forms ribonucleoprotein complexes in HELA and HEK293 cells (Freibaum et al., 2010; Kim et al., 2010). TDP-43 associates with the microRNA microprocessor complexes in MEFs and HEK293 cells (Fukuda et al., 2007; Gregory et al., 2004). However, these interactions have not been shown with endogenously expressed proteins, nor have they been shown in neuronal cells.

TDP-43 RNA targets identified in cortical neurons using RNA immunoprecipitation followed by deep sequencing (RIP-seq) reveal that TDP-43 binds to thousands of cellular transcripts (Sephton et al., 2011). TDP-43 has enriched binding to over 4,500 RNA species, preferentially localizing to introns, 3' and 5' untranslated regions (UTRs), and non-coding RNAs (Sephton et al., 2011). Moreover, TDP-43 binds RNAs in regions that contain the previously identified consensus motif, (UG)*n* (Buratti et al., 2001) as well as the novel consensus motif, (UG)*n*UA(UG)*m*, where adenine is frequently in the middle of a UG repeat sequence (Sephton et al., 2011). Moreover, the RNA consensus motif for PTBP2, $(CU)_6$ is enriched in the TDP-43 RIP-seq library, suggesting that PTBP2 may co-regulate TDP-43

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RNA targets (Sephton et al., 2011). The identification of the numerous RNA targets of TDP-43 has highlighted the multiple cellular processes that TDP-43 is involved in regulating.

Several studies show that TDP-43 binds to the 3'UTR of its own RNA transcript and in part controls its own expression (Ayala et al., 2011; Polymenidou et al., 2011; Sephton et al., 2011; Tollervey et al., 2011). Early observations in TDP-43 knockout mice alluded to self-regulation, wherein heterozygous mice had TDP-43 protein levels equal to that of wild type mice (Kraemer et al., 2010; Sephton et al., 2010; Wu et al., 2010). Similarly, in TDP-43 transgenic mice, expression of the transgene without the regulatory 3′UTR caused reduction of endogenous TDP-43 mRNA and protein (Igaz et al., 2011; Wegorzewska et al., 2009; Xu et al., 2010). The mechanism underlying auto-regulation is proposed to occur through binding to its own 3′UTR and promoting RNA stability (Ayala et al., 2011; Polymenidou et al., 2011). Self-regulation of TDP-43 expression may be an important factor in understanding TDP-43-associated pathogenesis as TDP-43 inclusions could disrupt its ability to self-regulate, thus contributing to neurodegeneration.

Functional classification of TDP-43 RNA targets from cortical neurons reveals a number of essential cellular processes (Sephton et al., 2011). Notably, a significant number of TDP-43 RNA targets encode proteins that have functions in neural development, such as the transcripts of Notch homolog 1 (*Notch1*), microtubule-associated protein (*Mapt*), disks large homolog 4 (*Dlg*4 also known as *PSD-95*), and dual specificity tyrosine-phosphorylation-regulated kinase 1A (*Dyrk1a*) (Fig. 1) (Sephton et al., 2011). Other TDP-43 RNA targets encode proteins that have functions in axon guidance, including netrins (*Ntn2*), semaphorins (*Sema3f, 4d, 6b*), and ephrin receptors (*Ephb1-3*) (Fig. 1). Several of the TDP-43 RNA targets encode proteins involved in neural function are also associated with neurodegenerative diseases, such as, itself, *Tardbp*, fused in sarcoma (*Fus*) (Fig. 1), progranulin (*Grn*), α-synuclein (*Scna*), and ataxin 1 and -2 (*Atxn 1,2*) (Sephton et al., 2011). Other studies using murine and human tissues have identified additional RNA targets (Polymenidou et al., 2011; Tollervey et al., 2011), which could reflect mixed cell populations found in the brain or non-specific interactions inherent to cross-linking methods.

TDP-43 RNA regulation in the CNS

TDP-43 regulation of RNA in the CNS occurs at sites of highly specialized bodies in both the nucleus and cytoplasm of the cell. In the nucleus of neurons, splicing activities of TDP-43 occur in the perichromatin fibrils of euchromatin domains, which are nuclear sites of transcription and cotranscriptional splicing (Casafont et al., 2009). TDP-43 is also present in nuclear speckles (Casafont et al., 2009), which act as splicing factor reservoirs and sites of post-transcriptional processing of pre-mRNAs (Melcak et al., 2000). TDP-43 can function as a scaffold for nuclear bodies through interaction with the RNA binding protein, survival of motor neuron (SMN) (Wang et al., 2002). Wang *et. al.* demonstrate that TDP-43 is localized to multiple discrete subnuclear structures including a new category of nuclear body referred to as the TDP-43 body (TB). TBs co-localize with several different types of nuclear bodies: Cajal bodies, promyelocytic leukemia protein (PML) bodies, splicing speckles and gems (Wang et al., 2002). TBs could act as a bridge between nuclear bodies, for example TBs would couple small nuclear ribonucleoprotein particles (snRNPs) in Cajal bodies with RNA splicing in splicing speckles.

TDP-43 regulation of RNA in the cytoplasm occurs through its association transport granules, processing bodies and stress granules (Dewey et al., 2011; Dewey et al., 2012; Moisse et al., 2009; Nishimoto et al., 2010; Volkening et al., 2009; Wang et al., 2008). Transport of RNAs by TDP-43 can occur *via* transport granules. In rat hippocampal neurons,

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TDP-43 is colocalized with PSD-95 in the postsynapse, in transport granules (Wang et al., 2008). Depolarization of neurons results in TDP-43 localization to dendrites and repetitive depolarization increases the colocalization of TDP-43 with fragile X mental retardation protein and Staufen (Wang et al., 2008), two RNA-binding proteins that regulate mRNA transport and local translation in neurons. Additionally, TDP-43 associates with RNA stress granules (Dewey et al., 2011; Nishimoto et al., 2010; Volkening et al., 2009). Stress granules form as protein-RNA aggregates in the cytoplasm in response to cellular stressors and function to protect RNAs from harmful conditions (Dewey et al., 2012). In an injury model using sciatic axotomies of mice, TDP-43 protein and mRNA levels are upregulated in motor neurons and colocalized with Staufen and TIA-1 to cytosolic stress granules (Moisse et al., 2009). TDP-43 protein and mRNA levels return to baseline post-injury, suggesting that TDP-43 is involved in neural function and responding to and recovery from stressful stimuli (Moisse et al., 2009).

The way in which TDP-43 coordinates regulation of its RNA targets in the nucleus and cytoplasm is not well understood and the answers could lie with the numerous TDP-43 protein isoforms and/or its protein-protein interactions. Loss of TDP-43 association with both nuclear and cytoplasmic bodies TDP-43 would be predicted to have an effect on any of the specialized processes occurring within.

TDP-43 expression in the embryo and adult CNS

TDP-43 is expressed throughout CNS development into adulthood (Huang et al., 2010; Sephton et al., 2010), which is consistent with the discovery that TDP-43 regulates RNAs involved in neuronal development and neural function (Polymenidou et al., 2011; Sephton et al., 2011; Tollervey et al., 2011). TDP-43 is detected as early as the two cell stage and is present through all undifferentiated stages of the mouse embryo (Fig. 1) (Sephton et al., 2010). In the blastocyst stage, TDP-43 is expressed in the nucleus in every single cell including cells of the inner cell mass which gives rise to all progenitor cells (Sephton et al., 2010; Wu et al., 2010). In later stages of embryonic development, TDP-43 expression pattern is ubiquitous, mostly nuclear, with prominent expression in neural stem cells of the neuroepithelium (Sephton et al., 2010). The neuroepithelium will eventually differentiate into multiple cell types, including neurons, astrocytes and other glial cells and give rise to the adult CNS. In later stages of embryonic development, E10.5–12.5, TDP-43 is expressed in both differentiated neural cells and their progenitors (Sephton et al., 2010).

As the CNS matures, TDP-43 protein expression is significantly reduced in the brain and spinal cord without a reduction in mRNA levels (Huang et al., 2010; Sephton et al., 2010). Temporal reduction in TDP-43 expression in the brain correlates with the presence of PSD-95, a synaptic protein and marker for synapse maturation and a RNA target of TDP-43 (Sephton et al., 2010). In adult mice, TDP-43 is ubiquitously expressed in the brain and spinal cord with prominent levels in various regions afflicted in neurodegenerative diseases (Baloh, 2011; Neumann et al., 2006; Sephton et al., 2010). TDP-43 is prominently expressed in the hippocampus, cortex, and Purkinje cells of the cerebellum and the glomerular layer of the olfactory bulb in the brain (Sephton et al., 2010). In the spinal cord, TDP-43 is expressed in the grey and white matter with prominent expression in the dorsal and ventral horn which contain sensory and motor neurons, respectively (Sephton et al., 2010).

ALS patients experience loss of motor function and have TDP-43 inclusions in the gray matter of the spinal cord, whereas FTLD-TDP patients have TDP-43 inclusions in the cortex (Baloh, 2011; Neumann et al., 2006). Considering TDP-43 expression is localized to the neuroepithelium during development, which gives rise to interneuron subtypes and motor neurons, it is possible that mutations or alterations in TDP-43 regulation may alter normal

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CNS function, making individuals more sensitive to developing TDP-43-related neurodegenerative diseases later in life.

TDP-43 and CNS function

Evidence for the role of TDP-43 in the CNS has been demonstrated by *in vivo* manipulation of the protein. These studies demonstrate that TDP-43 is necessary for viability of the cell and the organism. In cell culture, knockdown of TDP-43 in Neuro 2A cells impairs neurite outgrowth, through miRNA production (Kawahara and Mieda-Sato, 2012) and possibly through inactivation of Rho family GTPases (Iguchi et al., 2009). RNAi of TDP-43 in HEK293 cells causes abnormal nuclear morphology, missregulated cell cycle and apoptosis, due to increased CDK6 and phosphorylation of retinoblastoma protein (Ayala et al., 2008a). Although Ayala *et. al.* (2008a) did not perform their study in neuronal cells (Ayala et al., 2008a), elevated CDK6 activity and phosphorylation of retinoblastoma protein are linked to neuronal death (Nguyen et al., 2002). Moreover, induced knockdown of TDP-43 in mouse embryonic stem cells (ESCs), which leads to loss of proliferation and cell death, results in reduced mRNA levels for proteins involved in processes such as RNA metabolism, cell signaling, cell cycle regulation, axon guidance, and long-term potentiation (Chiang et al., 2010). These findings are consistent with TDP-43 RNA targets and their cellular functions (described above). Given that TDP-43 has numerous RNA targets, the exact mechanism by which TDP-43 controls neurite outgrowth or other phenotypes caused by TDP-43 knockdown is difficult to determine.

Depletion of TDP-43 in *Drosophila melanogaster* has produced conflicting results with one model having early lethality (Fiesel et al., 2010) and the other model having a semi-lethal phenotype with reduced lifespan, locomotor defects, defects at the neuromuscular junctions and reduced dendritic branching (Feiguin et al., 2009; Lin et al., 2011; Lu et al., 2009). Lin *et al.* show that both depletion and overexpression of TDP-43 in *Drosophila melanogaster* motor neurons affect locomotion (Lin et al., 2011). However depletion of TDP-43 increased the number of boutons at the neuromuscular junctions and overexpression of TDP-43 has the opposite effect (Lin et al., 2011). In *Danio rerio*, both overexpression of human TDP-43 and knockdown of *TARDBP* resulted in swimming behavior defects caused by short motor neuron axons that have premature and excessive branching (Kabashi et al., 2010).

TDP-43 knockout and transgenic mouse models show that disruption of cellular TDP-43 levels is toxic to the CNS (Dormann and Haass, 2011; Igaz et al., 2011; Wegorzewska et al., 2009; Xu et al., 2010). TDP-43 knockout mice die at early stages of embryonic development between E3.5 and E6.5 (Kraemer et al., 2010; Sephton et al., 2010; Wu et al., 2010). Moreover, global conditional knockout of TDP-43 in adult mice resulted in rapid lethality (Chiang et al., 2010). The most recent transgenic rat model is tissue specific in motor neurons and expression of the transgene can be turned on and off (Huang et al., 2012). Rats expressing mutant TDP-43^{M337V} in motor neurons alone develop denervation of the neuromuscular junctions and atrophy of the skeletal muscles (Huang et al., 2012). Interestingly, progression of the disease is prevented after the transgene expression is switched off; with dramatic recovery of motor function (Huang et al., 2012), suggesting that mutant TDP-43 in motor neurons is sufficient to promote the onset and progression of ALS-like degeneration. Taken together, these studies demonstrate that TDP-43 regulates a wide range of cellular processes and both the loss of normal TDP-43 function and gain of new toxic function are damaging.

Summary and Perspective

TDP-43 is an essential RNA binding protein in both the developing and mature CNS. However, we must further define the mechanism by which loss and/or gain of TDP-43

function during development and in adult contributes to neurodegenerative disorders and determine how the selective vulnerability of neurons in different neurodegenerative disorders is induced by the differential expression of RNA targets, protein partners, or post-translational modifications of TDP-43 in different neurons/cells. Outstanding questions regarding TDP-43 biology in the CNS include: 1) how is TDP-43 transcriptionally regulated?, 2) what post-translational modifications does TDP-43 undergo and how do they influence function, protein-protein interactions, localization and degradation?, 3) how does TDP-43 regulate neural development and function pre- and post-transcriptionally?, and 4) how do TDP-43 mutations affect neural development and function? It is clear that TDP-43 is an essential RNA binding protein and alterations in its ability to carry out its cellular roles are toxic. The identification of TDP-43 ribonucleoprotein complexes and RNA targets has laid the foundation for more detailed studies into its cellular functions. These studies may in turn lead to the development of targeted therapies for neurodegenerative diseases.

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References

Acharya KK, Govind CK, Shore AN, Stoler MH, Reddi PP. cis-requirement for the maintenance of round spermatid-specific transcription. Dev Biol. 2006; 295:781–790. [PubMed: 16730344]

Ayala YM, De Conti L, Avendano-Vazquez SE, Dhir A, Romano M, D'Ambrogio A, Tollervey J, Ule J, Baralle M, Buratti E, et al. TDP-43 regulates its mRNA levels through a negative feedback loop. EMBO J. 2011; 30:277–288. [PubMed: 21131904]

Ayala YM, Misteli T, Baralle FE. TDP-43 regulates retinoblastoma protein phosphorylation through the repression of cyclin-dependent kinase 6 expression. Proc Natl Acad Sci U S A. 2008a; 105:3785–3789. [PubMed: 18305152]

Ayala YM, Zago P, D'Ambrogio A, Xu YF, Petrucelli L, Buratti E, Baralle FE. Structural determinants of the cellular localization and shuttling of TDP-43. J Cell Sci. 2008b; 121:3778–3785. [PubMed: 18957508]

Baloh RH. TDP-43: the relationship between protein aggregation and neurodegeneration in amyotrophic lateral sclerosis and frontotemporal lobar degeneration. FEBS J. 2011; 278:3539–3549. [PubMed: 21777387]

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]

Buratti E, Dork T, Zuccato E, Pagani F, Romano M, Baralle FE. 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]

Casafont I, Bengoechea R, Tapia O, Berciano MT, Lafarga M. TDP-43 localizes in mRNA transcription and processing sites in mammalian neurons. J Struct Biol. 2009; 167:235–241. [PubMed: 19539030]

Chiang PM, Ling J, Jeong YH, Price DL, Aja SM, Wong PC. 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]

Dewey CM, Cenik B, Sephton CF, Dries DR, Mayer P 3rd, Good SK, Johnson BA, Herz J, Yu G. 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]

Dewey CM, Cenik B, Sephton CF, Johnson BA, Herz J, Yu G. TDP-43 aggregation in neurodegeneration: Are stress granules the key? Brain Res. 2012

Dormann D, Haass C. TDP-43 and FUS: a nuclear affair. Trends Neurosci. 2011

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Feiguin F, Godena VK, Romano G, D'Ambrogio A, Klima R, Baralle FE. Depletion of TDP-43 affects Drosophila motoneurons terminal synapsis and locomotive behavior. FEBS Lett. 2009; 583:1586–1592. [PubMed: 19379745]

Fiesel FC, Voigt A, Weber SS, Van den Haute C, Waldenmaier A, Gorner K, Walter M, Anderson ML, Kern JV, Rasse TM, et al. Knockdown of transactive response DNA-binding protein (TDP-43) downregulates histone deacetylase 6. EMBO J. 2010; 29:209–221. [PubMed: 19910924]

Freibaum BD, Chitta RK, High AA, Taylor JP. 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]

Fukuda T, Yamagata K, Fujiyama S, Matsumoto T, Koshida I, Yoshimura K, Mihara M, Naitou M, Endoh H, Nakamura T, et al. DEAD-box RNA helicase subunits of the Drosha complex are required for processing of rRNA and a subset of microRNAs. Nat Cell Biol. 2007; 9:604–611. [PubMed: 17435748]

Gregory RI, Yan KP, Amuthan G, Chendrimada T, Doratotaj B, Cooch N, Shiekhattar R. The Microprocessor complex mediates the genesis of microRNAs. Nature. 2004; 432:235–240. [PubMed: 15531877]

Huang C, Tong J, Bi F, Zhou H, Xia XG. Mutant TDP-43 in motor neurons promotes the onset and progression of ALS in rats. J Clin Invest. 2012; 122:107–118. [PubMed: 22156203]

Huang C, Xia PY, Zhou H. Sustained expression of TDP-43 and FUS in motor neurons in rodent's lifetime. Int J Biol Sci. 2010; 6:396–406. [PubMed: 20616880]

Igaz LM, Kwong LK, Lee EB, Chen-Plotkin A, Swanson E, Unger T, Malunda J, Xu Y, Winton MJ, Trojanowski JQ, et al. Dysregulation of the ALS-associated gene TDP-43 leads to neuronal death and degeneration in mice. J Clin Invest. 2011; 121:726–738. [PubMed: 21206091]

Iguchi Y, Katsuno M, Niwa J, Yamada S, Sone J, Waza M, Adachi H, Tanaka F, Nagata K, Arimura N, et al. TDP-43 depletion induces neuronal cell damage through dysregulation of Rho family GTPases. J Biol Chem. 2009; 284:22059–22066. [PubMed: 19535326]

Kabashi E, Lin L, Tradewell ML, Dion PA, Bercier V, Bourgouin P, Rochefort D, Bel Hadj S, Durham HD, Vande Velde C, et al. Gain and loss of function of ALS-related mutations of TARDBP (TDP-43) cause motor deficits in vivo. Hum Mol Genet. 2010; 19:671–683. [PubMed: 19959528]

Kawahara Y, Mieda-Sato A. TDP-43 promotes microRNA biogenesis as a component of the Drosha and Dicer complexes. Proc Natl Acad Sci U S A. 2012; 109:3347–3352. [PubMed: 22323604]

Kim SH, Shanware NP, Bowler MJ, Tibbetts RS. 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]

Kraemer BC, Schuck T, Wheeler JM, Robinson LC, Trojanowski JQ, Lee VM, Schellenberg GD. Loss of murine TDP-43 disrupts motor function and plays an essential role in embryogenesis. Acta Neuropathol. 2010; 119:409–419. [PubMed: 20198480]

Krecic AM, Swanson MS. hnRNP complexes: composition, structure, and function. Curr Opin Cell Biol. 1999; 11:363–371. [PubMed: 10395553]

Kuo PH, Doudeva LG, Wang YT, Shen CK, Yuan HS. Structural insights into TDP-43 in nucleic-acid binding and domain interactions. Nucleic Acids Res. 2009; 37:1799–1808. [PubMed: 19174564]

Lin MJ, Cheng CW, Shen CK. Neuronal function and dysfunction of Drosophila dTDP. PLoS One. 2011; 6:e20371. [PubMed: 21673800]

Lu Y, Ferris J, Gao FB. Frontotemporal dementia and amyotrophic lateral sclerosis-associated disease protein TDP-43 promotes dendritic branching. Mol Brain. 2009; 2:30. [PubMed: 19781077]

Melcak I, Cermanova S, Jirsova K, Koberna K, Malinsky J, Raska I. Nuclear pre-mRNA compartmentalization: trafficking of released transcripts to splicing factor reservoirs. Mol Biol Cell. 2000; 11:497–510. [PubMed: 10679009]

Moisse K, Volkening K, Leystra-Lantz C, Welch I, Hill T, Strong MJ. Divergent patterns of cytosolic TDP-43 and neuronal progranulin expression following axotomy: implications for TDP-43 in the physiological response to neuronal injury. Brain Res. 2009; 1249:202–211. [PubMed: 19046946]

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Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM, et al. Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis. Science. 2006; 314:130–133. [PubMed: 17023659]

Nguyen MD, Mushynski WE, Julien JP. Cycling at the interface between neurodevelopment and neurodegeneration. Cell Death Differ. 2002; 9:1294–1306. [PubMed: 12478466]

Nishimoto Y, Ito D, Yagi T, Nihei Y, Tsunoda Y, Suzuki N. Characterization of alternative isoforms and inclusion body of the TAR DNA-binding protein-43. J Biol Chem. 2010; 285:608–619. [PubMed: 19887443]

Ou SH, Wu F, Harrich D, Garcia-Martinez LF, Gaynor RB. Cloning and characterization of a novel cellular protein, TDP-43, that binds to human immunodeficiency virus type 1 TAR DNA sequence motifs. J Virol. 1995; 69:3584–3596. [PubMed: 7745706]

Polymenidou M, Lagier-Tourenne C, Hutt KR, Huelga SC, Moran J, Liang TY, Ling SC, Sun E, Wancewicz E, Mazur C, et al. Long pre-mRNA depletion and RNA missplicing contribute to neuronal vulnerability from loss of TDP-43. Nat Neurosci. 2011; 14:459–468. [PubMed: 21358643]

Sephton CF, Cenik C, Kucukural A, Dammer EB, Cenik B, Han Y, Dewey CM, Roth FP, Herz J, Peng J, et al. Identification of neuronal RNA targets of TDP-43-containing ribonucleoprotein complexes. J Biol Chem. 2011; 286:1204–1215. [PubMed: 21051541]

Sephton CF, Good SK, Atkin S, Dewey CM, Mayer P 3rd, Herz J, Yu G. TDP-43 is a developmentally regulated protein essential for early embryonic development. J Biol Chem. 2010; 285:6826–6834. [PubMed: 20040602]

Strong MJ, Volkening K, Hammond R, Yang W, Strong W, Leystra-Lantz C, Shoesmith C. TDP43 is a human low molecular weight neurofilament (hNFL) mRNA-binding protein. Mol Cell Neurosci. 2007; 35:320–327. [PubMed: 17481916]

Tollervey JR, Curk T, Rogelj B, Briese M, Cereda M, Kayikci M, Konig J, Hortobagyi T, Nishimura AL, Zupunski V, et al. Characterizing the RNA targets and position-dependent splicing regulation by TDP-43. Nat Neurosci. 2011; 14:452–458. [PubMed: 21358640]

Volkening K, Leystra-Lantz C, Yang W, Jaffee H, Strong MJ. 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]

Wang HY, Wang IF, Bose J, Shen CK. Structural diversity and functional implications of the eukaryotic TDP gene family. Genomics. 2004; 83:130–139. [PubMed: 14667816]

Wang IF, Reddy NM, Shen CK. Higher order arrangement of the eukaryotic nuclear bodies. Proc Natl Acad Sci U S A. 2002; 99:13583–13588. [PubMed: 12361981]

Wang IF, Wu LS, Chang HY, Shen CK. TDP-43, the signature protein of FTLD-U, is a neuronal activity-responsive factor. J Neurochem. 2008; 105:797–806. [PubMed: 18088371]

Wegorzewska I, Bell S, Cairns NJ, Miller TM, Baloh RH. 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]

Winton MJ, Igaz LM, Wong MM, Kwong LK, Trojanowski JQ, Lee VM. 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]

Wu LS, Cheng WC, Hou SC, Yan YT, Jiang ST, Shen CK. TDP-43, a neuro-pathosignature factor, is essential for early mouse embryogenesis. Genesis. 2010; 48:56–62. [PubMed: 20014337]

Xu YF, Gendron TF, Zhang YJ, Lin WL, D'Alton S, Sheng H, Casey MC, Tong J, Knight J, Yu X, 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]

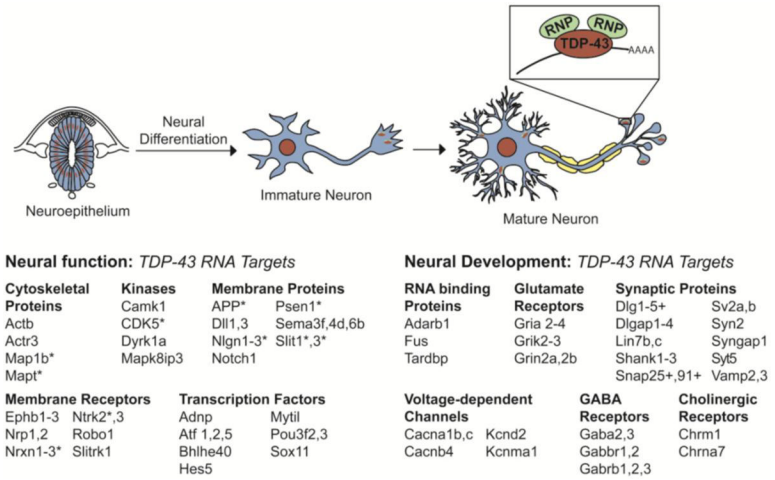

Figure 1. TDP-43 involvement in neural development and function

TDP-43 is expressed (depicted in red) throughout embryonic development from the blastocyst stage through to differentiated tissues. TDP-43 is highly expressed in the neuroepithelium, which contains all the CNS progenitors for neurons and glia. TDP-43 is involved in neural development and function through its interactions with other RNA binding proteins (RNP) and its regulation of specific RNA targets. The RNA targets marked with (*) or (+) are also involved in neural function or neural development, respectively. For the complete listing of TDP-43 RNA targets in cortical neurons see Sephton *et. al.* 2011.

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