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# Review Article

## TDP-43: A COMMON THREAD IN NEURODEGENERATION AND CANCER

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**ABSTRACT**

TDP-43, a multifunctional RNA-binding protein encoded by the TARDBP gene, plays critical roles in RNA metabolism, including splicing, transport, and stability. Dysregulation of TDP-43 is implicated in a range of neurodegenerative diseases, most notably Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Lobar Degeneration (FTLD). Recent evidence also identifies TDP-43 as a significant contributor to oncogenesis, with aberrant expression linked to various cancers, including breast, lung, and colorectal cancer. This review explores the dual role of TDP-43 in neurodegeneration and cancer, highlighting its structural domains, pathological aggregation mechanisms, and regulatory functions in cellular processes. We provide a detailed analysis of TDP-43's involvement in neurodegenerative disorders through mechanisms such as mis localization, gain- and loss-of-function mutations, and interactions with stress granules, as well as its contribution to cancer progression via regulation of oncogenes and tumor suppressors. Furthermore, we discuss therapeutic strategies targeting TDP-43 in both disease contexts, including RNA-based therapies, molecular chaperones, and modulation of autophagy and cell signalling pathways. By integrating current research on TDP-43's molecular interactions and pathogenic roles, this review underscores the need for further investigation into its dual functions and therapeutic potential in treating both neurodegenerative diseases and cancer.

***Keywords:*** TDP-43, Neurodegenerative Disorders, Cancer, Protienopathy, Future therapies, RNA Metabolism, Dysregulation.

## INTRODUCTION

TAR DNA-binding protein 43 (TDP-43) is a nuclear protein encoded by the *TARDBP* gene, primarily known for its role in RNA processing, including splicing, transport, and stability. Initially identified in the context of neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Lobar Degeneration (FTLD), TDP-43 has gained attention for its role in pathological protein aggregation (Prasad *et al.,* 2019). Mis localization and aggregation of TDP-43 in the cytoplasm have been hallmarks of neurodegenerative conditions, implicating it as a key player in disease pathogenesis (Arnold *et al.,* 2013).

However, research into TDP-43's involvement in cancer remains relatively underexplored. Recent studies suggest that TDP-43 may contribute to tumorigenesis by regulating oncogenes and tumor suppressors, highlighting its dual role in neurodegeneration and cancer (H.-R. Li *et al.,* 2018). Despite these findings, significant research gaps exist. There is limited understanding of the exact molecular mechanisms through which TDP-43 transitions between its physiological roles and pathological states (Scotter *et al.,* 2015). Additionally, there is a need for innovative therapeutic approaches targeting TDP-43's involvement in both neurodegeneration and cancer, as current therapies fail to address its dual functionality (Francois-Moutal *et al.,* 2021).

This review addresses these gaps by analysing TDP-43's structural domains, its interactions in pathological states, and its potential as a therapeutic target. We aim to shed light on how studying TDP-43 can lead to novel therapeutic innovations, particularly in developing RNA-based therapies and targeting aggregation pathways in ALS and cancer.

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### *Structural pathology*

Understanding the structure of this protein is important for exploring the mechanisms and the role it plays in the body. TDP-43 is a 414 amino acids long sequence, that has been divided into four regions namely, N-terminal (82-98 aa) with a nuclear localization signal (NLS, aa 82–98), RNA Recognition motifs 1(104-176 aa) and 2 (192-262 aa), a nuclear export signal (NES, aa 239–250), C-terminal (274-414 aa) which encompasses a prion-like glutamine/asparagine-rich (Q/N) domain (aa 345–366) and a glycine-rich region (aa 366–414) (Cohen *et al.,* 2011; Jiang *et al.,* 2017; Kuo *et al.,* 2009; Lukavsky *et al.,* 2013; Qin *et al.,* 2014; Shenoy *rgefc* 2023). The protein is predominantly present in the nucleus but due to its structure it can shuttle between nucleus and cytoplasm for its functions such as RNA metabolism. Mitochondrial localization of TDP-43 depends on internal motifs M1 (aa 35–41), M3 (aa 146–150), and M5 (aa 294–300), which consists of continuous stretch of hydrophobic amino acids (Reddi, 2017).

TDP-43, a key protein involved in various cellular processes, primarily exists as a dimer. This dimerization, primarily mediated by interactions within the protein's N-terminal domain, is crucial for its normal function and may help prevent harmful aggregation(Ling et al., 2013). However, the N-terminal domain also has a propensity to aggregate, especially under certain conditions. The balance between dimerization and aggregation can be influenced by factors such as the protein's oligomerization state and interactions with other molecules. Mutations in the N-terminal domain, particularly in the nuclear localization signal, can disrupt this balance and lead to the formation of cytoplasmic aggregates, which are associated with neurodegenerative diseases like ALS (Arnold *et al.,* 2013).

TDP-43, a multifunctional RNA binding protein, contains two highly conserved RNA recognition motifs (RRMs) that are essential for its interactions with nucleic acids(Romano & Buratti, 2013). These RRM domains, characterized by their β1-α1-β2-β3-α2-β4-β5 structural arrangement, exhibit a high affinity for UG/TG-rich sequences within RNA and DNA molecules(Sun & Chakrabartty, 2017). Mutations

within the RRM domains, including the ALS-associated P112H and D169G variants, have been shown to disrupt RNA binding and increase the protein's aggregation propensity (Chiang *et al.,* 2016). Furthermore, TDP-43's ability to bind to its own mRNA, a process known as autoregulation, plays a crucial role in controlling its cellular concentration and potentially its aggregation state. Notably, interactions with single-stranded nucleic acids, such as DNA or RNA, have been found to enhance TDP-43's solubility, suggesting a potential protective mechanism against aggregation (Ayala *et al.,* 2011).

The highly disordered C-terminal region of TDP-43 shares similarities with prion-like domains found in yeast proteins, such as Sup35 and Rnq1 (B. K. Patel *et al.,* 2009). This region is enriched in glycine and glutamine/asparagine residues, which contribute to its aggregation-prone nature. Notably, the C-terminal region harbours most ALS-associated mutations and phosphorylation sites, suggesting its critical role in disease pathogenesis. Furthermore, C-terminal fragments of TDP-43, generated through aberrant caspase activity, are highly cytotoxic and form inclusion bodies in ALS-affected brains (Zhang *et al.,* 2007). The C-terminal region also contains a helix-turn-helix motif that can form amyloid-like fibrils with prion-like seeding properties. Additionally, the C-terminal region can undergo liquid-liquid phase separation (LLPS), forming dynamic protein droplets. However, under pathological conditions, these droplets may undergo liquid-to-solid phase separation, leading to the formation of irreversible aggregates (Conicella *et al.,* 2016; A. Patel *et al.,* 2015).

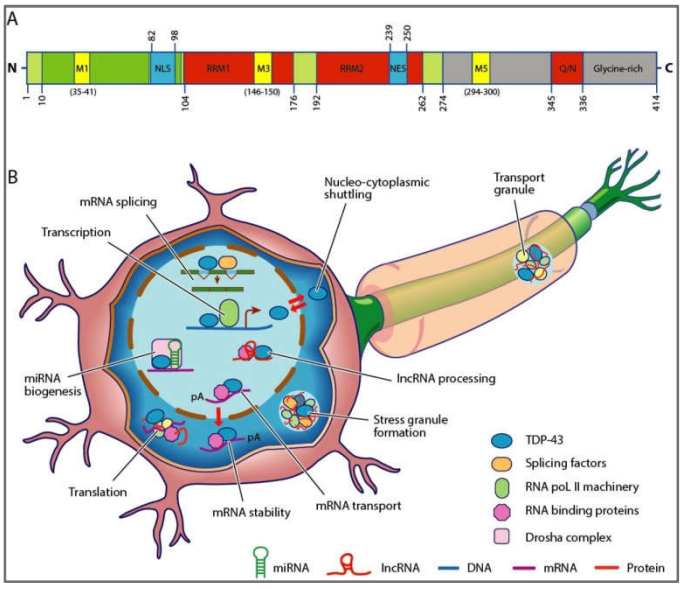


**Figure 1:** It has a modular structure with regions responsible for nuclear localization, RNA binding, and protein-protein interactions. Mutations in the C-terminal region is often associated with neurodegenerative diseases. TDP-43 plays a crucial role in various cellular processes, including transcription, splicing, mRNA stability, transport, and stress granule formation, both in the nucleus and cytoplasm (de Boer *et al.,* 2020).

## TDP-43 IN NEURODEGENERATION

### *Role of TDP-43*

**Table 1: Role of TDP-43 in RNA metabolism**

| Function | Description | Reference |
|---|---|---|
| Transcription and Splicing | Regulates splicing patterns of transcripts for various genes. Nuclear depletion of TDP-43 leads to splicing aberrations. | (Bright et al., 2021; Buratti & Baralle, 2001, p. 9; Heyburn & Moussa, 2017; Janssens et al., 2013) |
| mRNA Maturation and Stability | Binds to mRNA transcripts, regulating their stability. Can positively or negatively affect mRNA half-life. | (Ayala et al., 2011; Buratti, 2021) |
| mRNA Transport | Forms ribonucleoprotein (RNP) granules with RNA molecules for transport to distant locations. ALS-associated mutations can impair RNP transport. | (Alami et al., 2014; M. Strong et al., 2020) |
| mRNA Translation | May regulate localization and translation of specific mRNAs. Interacts with proteins involved in translation machinery. | (Aulas & Vande Velde, 2015; Coyne et al., 2015; Prasad et al., 2019) |
| Stress Granule Formation | Assembles into stress granules, structures that store RNA during cellular stress. Regulates expression of key stress granule proteins. ALS-linked mutations can influence stress granule dynamics. | (Aulas & Vande Velde, 2015; Colombrita et al., 2009; Dewey et al., 2011; McDonald et al., 2011) |
| miRNA Processing | Promotes biogenesis and processing of microRNAs (miRNAs) by interacting with Drosha and Dicer complexes.lncRNA Processing | (Kawahara & Mieda-Sato, 2012; Ling et al., 2013) |
| lncRNA Processing | Binds to long non-coding RNAs (lncRNAs), suggesting a potential role in their regulation. | (Tollervey et al., 2011) |

### *Pathological significance of TDP-43 in Neurodegeneration*

**Table 2: Pathological significance and characteristics of TDP-43**

| Feature | Pathological Significance | Therapeutic Implications | References |
|---|---|---|---|
| Cytoplasmic Mislocalization | Associated with ALS and FTD, caused by mutations, stress, or impaired degradation | Develop strategies to prevent mislocalization or target factors involved. | (Buratti, 2021; Liu-Yesucevitz et al., 2014; McDonald et al., 2011; Neumann et al., 2006; Polymenidou et al., 2011; van Eersel et al., 2011) |
| Fragmentation | Generates aggregation-prone CTFs | Targeting fragmentation may not be beneficial. | (Hasegawa et al., 2008; Xiao et al., 2011; Zhang et al., 2007) |
| Misfolding and Aggregation | Linked to disease progression, but role of aggregates is controversial | Prevent misfolding, target early aggregation stages, and consider chaperones or protein degradation pathways. | (Fuentealba et al., 2010; Igaz et al., 2008; Johnson et al., 2008; M. J. Strong et al., 2007; van Eersel et al., 2011; W. Wang et al., 2016; X. Wang et al., 2008; Zhang et al., 2009) |
| Post-Translational Modifications (Phosphorylation and | Linked to disease progression, but role of aggregates is | Target specific modifications or pathways involved in phosphorylation | (Hasegawa et al., 2008; Scotter et al., 2015; Sreedharan et |

| | | | |
|---|---|---|---|
| Ubiquitination) | controversial | or ubiquitination. | al., 2008; X. Wang et al., 2008) |

TDP-43 proteinopathy has several pathogenic characteristics, each with possible treatment implications. While more study is needed to completely understand the mechanisms driving these characteristics, targeting early misfolding events, chaperones, protein degradation pathways, and specific post-translational alterations may open new paths for creating effective therapeutics for ALS and FTD (Lehmkuhl *et al.,* 2021).

***Molecular mechanisms of TDP-43 underlying mediated-toxicity***

Loss-of-Function vs. Gain-of-Function: The pathological mechanisms of TDP-43 remain under debate. Traditionally, the loss of nuclear TDP-43 function due to cytoplasmic mis localization has been a central hypothesis (Polymenidou *et al.,* 2011). Studies have shown that TDP-43 deficiency can lead to aberrant splicing and reduced protein production. However, recent findings suggest a more complex scenario. ALS-associated mutations in TDP-43 can alter its splicing activity, leading to both loss and gain of function. Mutant TDP-43 may also disrupt the splicing of specific mRNAs critical for neuronal function (de Boer *et al.,* 2020).

***Cytoplasmic TDP-43 and its Pathological Effects:***

TDP-43, a protein linked to neurodegenerative disorders, has multiple activities within cells. It interacts with stress granules, which are cytoplasmic organelles generated during stressful conditions (Fernandes *et al.,* 2020). This interaction could alter the dynamics of stress granules as well as other RNA granule pathways including processing bodies and RNA transport granules. These granules are involved in several aspects of RNA metabolism, such as mRNA translation, stability, and destruction.TDP-43 can also be detected in dendrites, where it may control local translation (Dewey *et al.,* 2012). This shows that TDP-43 is involved in the transport of mRNAs to certain cellular compartments for protein production. Localized protein synthesis is critical for neuronal function and survival. Furthermore, TDP-43 has been found within mitochondria, where it can disrupt mitochondrial activity. This can cause decreased ATP synthesis, increased oxidative stress, and, eventually, neuronal cell death. TDP-43 can bind to a variety of mitochondrial proteins, including those involved in mitochondrial dynamics, respiratory chain complexes, and calcium signalling (Mackenzie *et al.,* 2010).

TDP-43 can also be released by exosomes, which are extracellular vesicles that promote molecular transfer between cells. This shows that TDP-43 could move from cell to cell, perhaps contributing to the advancement of neurodegenerative disorders. TDP-43 aggregates in exosomes may be transferred to distant parts of the brain or perhaps other organs, spreading TDP-43's detrimental consequences (Cohen *et al.,* 2011). Finally, TDP-43's varied actions inside cells emphasize its relevance in cellular health. Dysregulation of these processes, which include interactions with stress granules, localized translation, mitochondrial function, and exosome-mediated dissemination, may contribute to the onset of neurodegenerative disorders. Understanding these pathways is critical to establishing effective therapy solutions (Sackmann *et al.,* 2020).

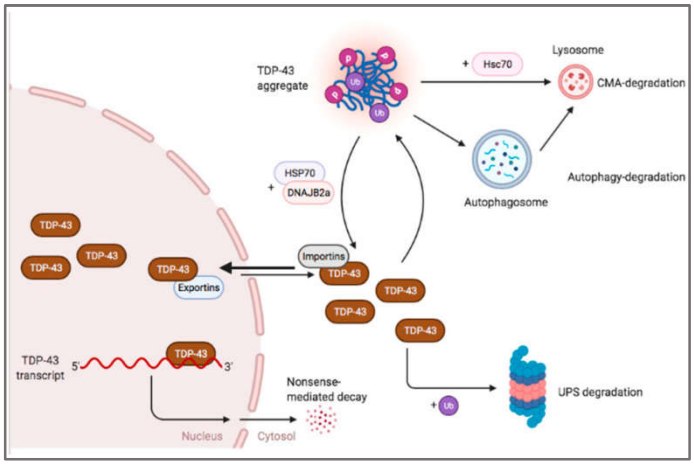


**Figure 2:** (H.-J. Chen & Mitchell, 2021)

## HOW A NEURO-PROTEIN IS EMERGING IN CANCER

TDP-43, primarily studied in the context of neurodegenerative diseases, has recently emerged as a significant player in cancer development and progression. The multifaceted roles of TDP-43 in neurobiology, including its functions in RNA metabolism, stress granule formation, and mitochondrial dynamics, may also be relevant to its involvement in cancer. For instance, TDP-43's ability to regulate gene expression through RNA splicing and microRNA processing could influence the expression of oncogenes and tumour suppressors. Additionally, its role in stress granule formation and mitochondrial function may impact cellular survival and proliferation, processes that are critical for cancer development. Understanding the connections between TDP-43's neurobiological functions and its role in cancer could provide valuable insights into the molecular mechanisms underlying tumorigenesis and potentially identify novel therapeutic targets.

## TDP-43 IN CANCER: A MULTIFACETED ROLE

Studies have made a strong connection between common polymorphism that showed TDP:43's role in cancer. In the past five year, more research has explained an understanding between how a neuro protein is also involved in different types of cancer such as breast cancer, lung cancer, hepatocellular carcinoma and more (Mackenzie *et al.,* 2010). Emerging evidence suggests that TDP-43 plays a pivotal role in regulating various aspects of tumorigenesis, including cell proliferation, invasion, and metastasis (Kumar & Rai, 2020).

***TDP-43's RNA Metabolism Functions and Cancer***

Since TDP-43 has been identified in cancer, several mechanisms have been identified through which TDP-43 can promote tumorigenesis. TDP-43 can directly bind to and stabilize oncogenes, such as c-Myc. This interaction prevents the degradation of oncogenes, leading to their over expression and uncontrolled cell growth. In breast cancer, TDP-43 over expression has been shown to activate c-Myc, promoting tumor cell proliferation and invasion (Chen & Mitchell, 2021). Regulating the expression of tumor suppressors, such as p53, through various mechanisms, including alternative splicing and microRNA processing.TDP-43 can also directly bind to and inhibit the function of tumor suppressors, preventing their ability to suppress cell growth and tumorigenesis. In lung cancer, TDP-43 has been shown to down regulate p53 expression, leading to increased cell proliferation and invasion(H.-J. Chen & Mitchell, 2021). TDP-43 can promote the expression of cyclin D1 and CDK4/6, key

proteins involved in cell cycle progression. Overexpression of cyclin D1 and CDK4/6 can drive cells through the cell cycle, leading to uncontrolled proliferation (W. Wang *et al.,* 2016). TDP-43 can induce EMT, a process that allows epithelial cells to acquire mesenchymal characteristics, such as increased motility and invasion (Guo *et al.,* 2020).

**Table 3: Types of Cancer Associated with TDP-43 Protein Dysregulation**

| Cancer Type | Evidence of TDP-43 Dysregulation | Specific Mechanisms | Methodology | Reference |
|---|---|---|---|---|
| Breast Cancer | Elevated TDP-43 levels have been associated with poor prognosis in triple-negative breast cancer (TNBC). TDP-43 overexpression promotes tumorigenesis and metastasis by regulating multiple pathways, including the PI3K/AKT/mTOR pathway and the Wnt/β-catenin pathway. | Overexpression of TDP-43 activates oncogenes (e.g., c-Myc), inactivates tumor suppressors (e.g., p53), and regulates cell cycle progression. | Immunohistochemistry, Western blotting, qPCR, cell proliferation assays, migration assays | (Guo et al., 2020) |
| Lung Cancer | Dysregulated TDP-43 expression has been linked to tumor stage and prognosis in lung cancer. TDP-43 can promote tumor growth and invasion by regulating various signalling pathways and microRNAs. | TDP-43 can promote tumor growth and invasion by regulating various signalling pathways and microRNAs. | Immunohistochemistry, Western blotting, qPCR, RNA sequencing, survival analysis | (H.-J. Chen & Mitchell, 2021) |
| Colorectal Cancer | Altered TDP-43 expression has been associated with tumor progression and metastasis in colorectal cancer. TDP-43 can regulate the expression of oncogenes and tumor suppressors, affecting cell proliferation. | TDP-43 can regulate the expression of oncogenes and tumor suppressors, affecting cell proliferation and invasion. | Immunohistochemistry, Western blotting, qPCR, RNA sequencing, in vivo xenograft models | (W. Wang et al., 2016) |

***Mechanism of tumorigenesis***

Tumorigenesis is defined as the process by which normal cells are transformed into cancerous cells, it is a complex multi-step process that involves series of genetic and epigenetic changes. The exact mechanism depends on the type of cancer by the key pathways and process are common such as genetic altercations, tumour suppression gene inactivation, epigenetic changes, cell signalling pathways, angiogenesis and metastasis (Hanahan & Weinberg, 2011). Understanding these mechanisms is important in terms of targeting TDP-43 as a potential target of cancer.

**Table 4: Mechanism of tumorigenesis**

| Mechanism | Description | Example | Reference |
|---|---|---|---|
| Genetic Alterations | Mutations in oncogenes or tumor suppressor genes | KRAS mutations in lung cancer, TP53 mutations in various cancers | (Bos, 1989) |
| Epigenetic Changes | Abnormal DNA methylation or histone modifications | Hypermethylation of p16INK4A promoter, histone deacetylase inhibitor therapy | (Virani et al., 2012) |
| Cell Signaling Pathways | Deregulation of signalling pathways, such as RAS-RAF-MEK-ERK and PI3K-AKT-mTOR | EGFR mutations in lung cancer, PI3K-AKT pathway activation | (Jo et al., 2014) |
| Angiogenesis | Stimulation of new blood vessel growth | VEGF signalling | (Folkman, 1971) |
| Metastasis | Invasion and spread of cancer cells to distant organs | EMT, cell motility | (Thiery et al., 2009) |

## Interconnected Pathologies: A Comparative Analysis of Neurodegeneration and Cancer

***Interaction of Neuro protein with Cancer protein***

TDP-43, a multifunctional RNA-binding protein, has emerged as a complex player in cancer development. While research suggests context-dependent effects, its role in promoting tumorigenesis seems more prevalent

**Table 5: Interaction of TDP-43 with various cancer-causing proteins**

| Proteins | TDP-43 Interaction | Effect on Cancer Cells | References |
|---|---|---|---|
| | | **Oncogene Activation** | |
| c-Myc | Directly binds and stabilizes | Increased proliferation, inhibited apoptosis, EMT induction | (Zhang et al., 2009) |
| EGFR | Regulates expression and activation | Overactivation leads to uncontrolled growth and invasion | (H.-R. Li et al., 2018) |
| Ras | Indirect regulation via cell signalling pathways | Activation promotes proliferation and survival | (W. Wang et al., 2016) |

| | | | |
|---|---|---|---|
| **Tumour Suppressor Inactivation** | | | |
| p53 | Directly binds and regulates expression | Inactivation leads to uncontrolled proliferation, genomic instability, and apoptosis resistance | (Levine, 1997) |
| PTEN | Indirect regulation | Loss of function activates PI3K-AKT pathway, promoting proliferation and survival | (G. Li et al., 2018) |
| RB | May regulate expression or function | Inactivation leads to uncontrolled proliferation and tumorigenesis | (L. Chen et al., 2015) |
| **Cell Cycle Regulation** | | | |
| Cyclin D1 | Promotes expression | Increased cell cycle progression | (Liu et al., 2014) |
| CDK4/6 | Promotes expression | Increased cell cycle progression | (P. Chen et al., 2016) |
| **Epithelial-Mesenchymal Transition (EMT)** | | | |
| Snail | Promotes expression | Induces EMT | (Liu et al., 2014) |
| Twist | Promotes expression | Induces EMT | (P. Chen et al., 2016) |

## THERAPEUTIC ADVANCEMENTS

### *TDP-43 and neurodegeneration*

TDP-43 is a protein known for its protein aggregation, (Arrasate *et al.,* 2004) in its study suggested Chaperone Therapy which aims to reduce the aggregation by enhancing protein folding and degradation. The method used in this paper was by using the molecular chaperons to assist in proper protein folding and help in the degradation of misfolded proteins. Since the protein is an RNA based, RNA-based therapies were developed by (Guo *et al.,* 2020), that reduced TDP-43 expression or improve its functioning by using antisense oligonucleotides to target TDP-43 mRNA thus reducing the levels. By understanding the underlying mechanisms involved in TDP-43 related disorders, targeting those specific pathways or the proteins that were up or down regulated in TDP-43 associated diseases by Chen et al., 2016 showed about Targeted Therapies. Studies have shown that TDP-43 promotes autophagy in motor neurons through the AMPK/mTOR pathway. Hence Targeting autophagy pathways could be a potential therapeutic strategy(W. Wang *et al.,* 2016).

### *TDP-43 and cancer*

TDP-43 promotes tumorigenesis and metastasis of breast cancer by regulating glycolysis. Wang *et al.,* 2019. While specific therapies targeting TDP-43 with respect to cancer are still under development, there are several approaches that have been understood. Modulating TDP-43 expression through approaches like RNA interference (Guo *et al.,* 2020) or antisense oligonucleotides can be effective. Targeting downstream pathways, such as the PI3K/AKT/mTOR pathway (W. Wang *et al.,* 2016), can inhibit cancer cell growth. Immunotherapy techniques, including checkpoint inhibitors and adoptive cell therapy, offer potential benefits. Combination therapies, as explored by (Zhang *et al.,* 2007), may enhance treatment outcomes. While significant progress has been made, further research is essential to fully understand the complex role of TDP-43 in cancer and develop effective therapeutic interventions.

**Table 6: Therapeutic Advancements**

| Therapeutic Approach | Potential Benefits | Limitations | References |
|---|---|---|---|
| Chaperone Therapy | Reduces TDP-43 aggregation, prevents toxic effects | May not be sufficient for complete aggregation prevention | (Arrasate et al., 2004) |
| RNA-Based Therapies | Reduces TDP-43 expression, mitigates toxic effects | Delivery challenges, off-target effects | (Guo et al., 2020) |
| Targeted Therapies | Addresses specific pathways involved in TDP-43-related diseases | Identifying targets can be complex, limited efficacy | (P. Chen et al., 2016) |
| Autophagy Targeting | Promotes aggregate clearance, reduces toxicity | Unintended consequences on other cellular processes | (W. Wang et al., 2016) |
| TDP-43 Expression Modulation | Reduces TDP-43 expression, mitigates toxic effects | Off-target effects, incomplete suppression | (Guo et al., 2020) |
| Downstream Pathway Targeting | Inhibits cancer cell growth, improves disease outcomes | May not directly address underlying cause of TDP-43 aggregation | (W. Wang et al., 2016) |
| Immunotherapy | Stimulates immune system to target cancer cells, improves outcomes | Not effective in all patients, immune-related adverse events | (Folkman, 1971) |
| Combination Therapies | Enhances treatment outcomes, addresses multiple aspects | Increased complexity, potential for adverse interactions | (Zhang et al., 2009) |

## FUTURE DIRECTIONS

To advance our understanding of TDP-43's role in cancer and develop effective treatments, future research should focus on identifying specific TDP-43 mutations, investigating its involvement in a wider variety of cancer types, and exploring innovative therapeutic approaches such as drug development or gene editing. By addressing these areas, researchers can gain valuable insights into the molecular mechanisms underlying TDP-43-mediated tumorigenesis and design more targeted and effective interventions. How can molecular modelling and dynamic studies of full-length protein might help in understanding the pharmacodynamic and pharmacokinetic nature of the protein structure.

## CONCLUSION

TDP-43, encoded by the TARDBP gene, plays crucial roles in both neurodegenerative diseases and cancer. Dysregulation of TDP-43 leads to protein misfolding, aggregation, and cellular dysfunction, which are implicated in the pathology of diseases like ALS and FTLD, as well as various cancers. While considerable progress has been made in understanding TDP-43's molecular mechanisms, therapeutic interventions remain limited.

Future research should prioritize the development of targeted therapies that modulate TDP-43 aggregation and restore its normal function. Key research questions include: What specific mutations or post-translational modifications lead to TDP-43 aggregation, and can

these processes be reversed? How does TDP-43 interact with other proteins or RNA molecules in neurodegenerative diseases versus cancer, and what therapeutic windows exist for these interactions? Can TDP-43's involvement in RNA metabolism be selectively modulated without affecting its broader cellular roles? What role does autophagy play in clearing TDP-43 aggregates, and how can autophagy pathways be harnessed for treatment? Addressing these questions through experimental studies, such as high-resolution structural analysis and advanced RNA-based therapies, will be essential in developing novel, effective treatments for TDP-43-related diseases.

## REFERENCES


Alami, N. H., Smith, R. B., Carrasco, M. A., Williams, L. A., Winborn, C. S., Han, S. S. W., Kiskinis, E., Winborn, B., Freibaum, B. D., Kanagaraj, A., Clare, A. J., Badders, N. M., Bilican, B., Chaum, E., Chandran, S., Shaw, C. E., Eggan, K. C., Maniatis, T., & Taylor, J. P. (2014). Axonal transport of TDP-43 mRNA granules is impaired by ALS-causing mutations. *Neuron*, *81*(3), 536–543. https://doi.org/10.1016/j.neuron.2013.12.018

Arnold, E. S., Ling, S.-C., Huelga, S. C., Lagier-Tourenne, C., Polymenidou, M., Ditsworth, D., Kordasiewicz, H. B., McAlonis-Downes, M., Platoshyn, O., Parone, P. A., Da Cruz, S., Clutario, K. M., Swing, D., Tessarollo, L., Marsala, M., Shaw, C. E., Yeo, G. W., & Cleveland, D. W. (2013). ALS-linked TDP-43 mutations produce aberrant RNA splicing and adult-onset motor neuron disease without aggregation or loss of nuclear TDP-43. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(8), E736-745. https://doi.org/10.1073/pnas.1222809110

Arrasate, M., Mitra, S., Schweitzer, E. S., Segal, M. R., & Finkbeiner, S. (2004). Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. *Nature*, *431*(7010), 805–810. https://doi.org/10.1038/nature02998

Aulas, A., & Vande Velde, C. (2015). Alterations in stress granule dynamics driven by TDP-43 and FUS: A link to pathological inclusions in ALS? *Frontiers in Cellular Neuroscience*, *9*, 423. https://doi.org/10.3389/fncel.2015.00423

Ayala, Y. M., De Conti, L., Avendaño-Vázquez, S. E., Dhir, A., Romano, M., D'Ambrogio, A., Tollervey, J., Ule, J., Baralle, M., Buratti, E., & Baralle, F. E. (2011). TDP-43 regulates its mRNA levels through a negative feedback loop. *The EMBO Journal*, *30*(2), 277–288. https://doi.org/10.1038/emboj.2010.310

Bos, J. L. (1989). ras oncogenes in human cancer: A review. *Cancer Research*, *49*(17), 4682–4689.

Bright, F., Chan, G., van Hummel, A., Ittner, L. M., & Ke, Y. D. (2021). TDP-43 and Inflammation: Implications for Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. *International Journal of Molecular Sciences*, *22*(15), 7781. https://doi.org/10.3390/ijms22157781

Buratti, E. (2021). Targeting TDP-43 proteinopathy with drugs and drug-like small molecules. *British Journal of Pharmacology*, *178*(6), 1298–1315. https://doi.org/10.1111/bph.15148

Buratti, E., & Baralle, F. E. (2001). Characterization and functional implications of the RNA binding properties of nuclear factor TDP-43, a novel splicing regulator of CFTR exon 9. *The Journal of Biological Chemistry*, *276*(39), 36337–36343. https://doi.org/10.1074/jbc.M104236200

Chen, H.-J., & Mitchell, J. C. (2021). Mechanisms of TDP-43 Proteinopathy Onset and Propagation. *International Journal of Molecular Sciences*, *22*(11), Article 11. https://doi.org/10.3390/ijms22116004

Chen, L., Chu, C., Lu, J., Kong, X., Huang, T., & Cai, Y.-D. (2015). Gene Ontology and KEGG Pathway Enrichment Analysis of a Drug Target-Based Classification System. *PLOS ONE*, *10*(5), e0126492. https://doi.org/10.1371/journal.pone.0126492

Chen, P., Lee, N. V., Hu, W., Xu, M., Ferre, R. A., Lam, H., Bergqvist, S., Solowiej, J., Diehl, W., He, Y.-A., Yu, X., Nagata, A., VanArsdale, T., & Murray, B. W. (2016). Spectrum and Degree of CDK Drug Interactions Predicts Clinical Performance. *Molecular Cancer Therapeutics*, *15*(10), 2273–2281. https://doi.org/10.1158/1535-7163.MCT-16-0300

Chiang, C.-H., Grauffel, C., Wu, L.-S., Kuo, P.-H., Doudeva, L. G., Lim, C., Shen, C.-K. J., & Yuan, H. S. (2016). Structural analysis of disease-related TDP-43 D169G mutation: Linking enhanced stability and caspase cleavage efficiency to protein accumulation. *Scientific Reports*, *6*, 21581. https://doi.org/10.1038/srep21581

Cohen, T. J., Lee, V. M. Y., & Trojanowski, J. Q. (2011). TDP-43 functions and pathogenic mechanisms implicated in TDP-43 proteinopathies. *Trends in Molecular Medicine*, *17*(11), 659–667. https://doi.org/10.1016/j.molmed.2011.06.004

Colombrita, C., Zennaro, E., Fallini, C., Weber, M., Sommacal, A., Buratti, E., Silani, V., & Ratti, A. (2009). TDP-43 is recruited to stress granules in conditions of oxidative insult. *Journal of Neurochemistry*, *111*(4), 1051–1061. https://doi.org/10.1111/j.1471-4159.2009.06383.x

Conicella, A. E., Zerze, G. H., Mittal, J., & Fawzi, N. L. (2016). ALS mutations disrupt phase separation mediated by -helical structure in the TDP-43 low complexity C-terminal domain. *Structure (London, England : 1993)*, *24*(9), 1537–1549. https://doi.org/10.1016/j.str.2016.07.007

Coyne, A. N., Yamada, S. B., Siddegowda, B. B., Estes, P. S., Zaepfel, B. L., Johannesmeyer, J. S., Lockwood, D. B., Pham, L. T., Hart, M. P., Cassel, J. A., Freibaum, B., Boehringer, A. V., Taylor, J. P., Reitz, A. B., Gitler, A. D., & Zarnescu, D. C. (2015). Fragile X protein mitigates TDP-43 toxicity by remodeling RNA granules and restoring translation. *Human Molecular Genetics*, *24*(24), 6886–6898. https://doi.org/10.1093/hmg/ddv389

de Boer, E. M. J., Orie, V. K., Williams, T., Baker, M. R., De Oliveira, H. M., Polvikoski, T., Silsby, M., Menon, P., van den Bos, M., Halliday, G. M., van den Berg, L. H., Van Den Bosch, L., van Damme, P., Kiernan, M. C., van Es, M. A., & Vucic, S. (2020). TDP-43 proteinopathies: A new wave of neurodegenerative diseases. *Journal of Neurology, Neurosurgery, and Psychiatry*, *92*(1), 86–95. https://doi.org/10.1136/jnnp-2020-322983

Dewey, C. M., Cenik, B., Sephton, C. F., Dries, D. R., Mayer, P., Good, S. K., Johnson, B. A., Herz, J., & Yu, G. (2011). TDP-43 Is Directed to Stress Granules by Sorbitol, a Novel Physiological Osmotic and Oxidative Stressor. *Molecular and Cellular Biology*, *31*(5), 1098–1108. https://doi.org/10.1128/MCB.01279-10

Dewey, C. M., Cenik, B., Sephton, C. F., Johnson, B. A., Herz, J., & Yu, G. (2012). TDP-43 aggregation in neurodegeneration: Are stress granules the key? *Brain Research*, *1462*, 16–25. https://doi.org/10.1016/j.brainres.2012.02.032

Fernandes, N., Nero, L., Lyons, S. M., Ivanov, P., Mittelmeier, T. M., Bolger, T. A., & Buchan, J. R. (2020). Stress Granule Assembly Can Facilitate but Is Not Required for TDP-43 Cytoplasmic Aggregation. *Biomolecules*, *10*(10), Article 10. https://doi.org/10.3390/biom10101367

Folkman, J. (1971). Tumor angiogenesis: Therapeutic implications. *The New England Journal of Medicine*, *285*(21), 1182–1186. https://doi.org/10.1056/NEJM197111182852108

Francois-Moutal, L., Scott, D. D., & Khanna, M. (2021). Direct targeting of TDP-43, from small molecules to biologics: The therapeutic landscape. *RSC Chemical Biology*, *2*(4), 1158–1166. https://doi.org/10.1039/D1CB00110H

Fuentealba, R. A., Udan, M., Bell, S., Wegorzewska, I., Shao, J., Diamond, M. I., Weihl, C. C., & Baloh, R. H. (2010). Interaction with Polyglutamine Aggregates Reveals a Q/N-rich Domain in TDP-43. *The Journal of Biological Chemistry*, *285*(34), 26304–26314. https://doi.org/10.1074/jbc.M110.125039

Guo, F., Wang, H., Jiang, M., Yang, Q., Xiang, Q., Zhou, H., Hu, X., Hao, K., Yang, J., Cao, H., & Shen, Z. (2020). TDP-43 induces EMT and promotes hepatocellular carcinoma metastasis via activating Wnt/β-catenin signaling pathway. *American Journal of Cancer Research*, *10*(10), 3285–3301.

Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. *Cell*, *144*(5), 646–674. https://doi.org/10.1016/j.cell.2011.02.013

Hasegawa, M., Arai, T., Nonaka, T., Kametani, F., Yoshida, M., Hashizume, Y., Beach, T. G., Buratti, E., Baralle, F., Morita, M., Nakano, I., Oda, T., Tsuchiya, K., & Akiyama, H. (2008). Phosphorylated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Annals of Neurology*, *64*(1), 60–70. https://doi.org/10.1002/ana.21425

Heyburn, L., & Moussa, C. E.-H. (2017). TDP-43 in the spectrum of MND-FTLD pathologies. *Molecular and Cellular Neurosciences*, *83*, 46–54. https://doi.org/10.1016/j.mcn.2017.07.001

Igaz, L. M., Kwong, L. K., Xu, Y., Truax, A. C., Uryu, K., Neumann, M., Clark, C. M., Elman, L. B., Miller, B. L., Grossman, M., McCluskey, L. F., Trojanowski, J. Q., & Lee, V. M.-Y. (2008). Enrichment of C-terminal fragments in TAR DNA-binding protein-43 cytoplasmic inclusions in brain but not in spinal cord of frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *The American Journal of Pathology*, *173*(1), 182–194. https://doi.org/10.2353/ajpath.2008.080003

Janssens, J., Wils, H., Kleinberger, G., Joris, G., Cuijt, I., Ceuterick-de Groote, C., Van Broeckhoven, C., & Kumar-Singh, S. (2013). Overexpression of ALS-Associated p.M337V Human TDP-43 in Mice Worsens Disease Features Compared to Wild-type Human TDP-43 Mice. *Molecular Neurobiology*, *48*(1), 22–35. https://doi.org/10.1007/s12035-013-8427-5

Jiang, L.-L., Xue, W., Hong, J.-Y., Zhang, J.-T., Li, M.-J., Yu, S.-N., He, J.-H., & Hu, H.-Y. (2017). The N-terminal dimerization is required for TDP-43 splicing activity. *Scientific Reports*, *7*(1), 6196. https://doi.org/10.1038/s41598-017-06263-3

Jo, U., Park, K. H., Whang, Y. M., Sung, J. S., Won, N. H., Park, J. K., & Kim, Y. H. (2014). EGFR endocytosis is a novel therapeutic target in lung cancer with wild-type EGFR. *Oncotarget*, *5*(5), 1265–1278.

Johnson, B. S., McCaffery, J. M., Lindquist, S., & Gitler, A. D. (2008). A yeast TDP-43 proteinopathy model: Exploring the molecular determinants of TDP-43 aggregation and cellular toxicity. *Proceedings of the National Academy of Sciences*, *105*(17), 6439–6444. https://doi.org/10.1073/pnas.0802082105

Kawahara, Y., & Mieda-Sato, A. (2012). TDP-43 promotes microRNA biogenesis as a component of the Drosha and Dicer complexes. *Proceedings of the National Academy of Sciences*, *109*(9), 3347–3352. https://doi.org/10.1073/pnas.1112427109

Kumar, P., & Rai, V. (2020). Catechol-O-methyltransferase gene Val158Met polymorphism and obsessive compulsive disorder susceptibility: A meta-analysis. *Metabolic Brain Disease*, *35*(2), 241–251. https://doi.org/10.1007/s11011-019-00495-0

Kuo, P.-H., Doudeva, L. G., Wang, Y.-T., Shen, C.-K. J., & Yuan, H. S. (2009). Structural insights into TDP-43 in nucleic-acid binding and domain interactions. *Nucleic Acids Research*, *37*(6), 1799–1808. https://doi.org/10.1093/nar/gkp013

Lehmkuhl, E. M., Loganathan, S., Alsop, E., Blythe, A. D., Kovalik, T., Mortimore, N. P., Barrameda, D., Kueth, C., Eck, R. J., Siddegowda, B. B., Joardar, A., Ball, H., Macias, M. E., Bowser, R., Van Keuren-Jensen, K., & Zarnescu, D. C. (2021). TDP-43 proteinopathy alters the ribosome association of multiple mRNAs including the glypican Dally-like protein (Dlp)/GPC6. *Acta Neuropathologica Communications*, *9*(1), 52. https://doi.org/10.1186/s40478-021-01148-z

Li, G., Guo, X., Chen, M., Tang, L., Jiang, H., Day, J. X., Xie, Y., Peng, L., Xu, X., Li, J., Wang, S., Xiao, Z., Dai, L., & Wang, J. (2018). Prevalence and spectrum of AKT1, PIK3CA, PTEN and TP53 somatic mutations in Chinese breast cancer patients. *PLoS ONE*, *13*(9), e0203495. https://doi.org/10.1371/journal.pone.0203495

Li, H.-R., Chiang, W.-C., Chou, P.-C., Wang, W.-J., & Huang, J.-R. (2018). TAR DNA-binding protein 43 (TDP-43) liquid-liquid phase separation is mediated by just a few aromatic residues. *The Journal of Biological Chemistry*, *293*(16), 6090–6098. https://doi.org/10.1074/jbc.AC117.001037

Ling, S.-C., Polymenidou, M., & Cleveland, D. W. (2013). Converging mechanisms in ALS and FTD: Disrupted RNA and protein homeostasis. *Neuron*, *79*(3), 416–438. https://doi.org/10.1016/j.neuron.2013.07.033

Liu, Z., Chen, X., Song, H., Wang, H., Zhang, G., Wang, H., Chen, D., Fang, R., Liu, H., Cai, S., & Du, J. (2014). Snail regulated by PKC/GSK-3β pathway is crucial for EGF-induced epithelial-mesenchymal transition (EMT) of cancer cells. *Cell and Tissue Research*, *358*(2), 491–502. https://doi.org/10.1007/s00441-014-1953-2

Liu-Yesucevitz, L., Lin, A. Y., Ebata, A., Boon, J. Y., Reid, W., Xu, Y.-F., Kobrin, K., Murphy, G. J., Petrucelli, L., & Wolozin, B. (2014). ALS-linked mutations enlarge TDP-43-enriched neuronal RNA granules in the dendritic arbor. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *34*(12), 4167–4174. https://doi.org/10.1523/JNEUROSCI.2350-13.2014

Lukavsky, P. J., Daujotyte, D., Tollervey, J. R., Ule, J., Stuani, C., Buratti, E., Baralle, F. E., Damberger, F. F., & Allain, F. H.-T. (2013). Molecular basis of UG-rich RNA recognition by the human splicing factor TDP-43. *Nature Structural & Molecular Biology*, *20*(12), 1443–1449. https://doi.org/10.1038/nsmb.2698

Mackenzie, I. R., Rademakers, R., & Neumann, M. (2010). TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. *The Lancet. Neurology*, *9*(10), 995–1007. https://doi.org/10.1016/S1474-4422(10)70195-2

McDonald, K. K., Aulas, A., Destroismaisons, L., Pickles, S., Beleac, E., Camu, W., Rouleau, G. A., & Vande Velde, C. (2011). TAR DNA-binding protein 43 (TDP-43) regulates stress granule dynamics via differential regulation of G3BP and TIA-1. *Human Molecular Genetics*, *20*(7), 1400–1410. https://doi.org/10.1093/hmg/ddr021

Neumann, M., Sampathu, D. M., Kwong, L. K., Truax, A. C., Micsenyi, M. C., Chou, T. T., Bruce, J., Schuck, T., Grossman, M., Clark, C. M., McCluskey, L. F., Miller, B. L., Masliah, E., Mackenzie, I. R., Feldman, H., Feiden, W., Kretzschmar, H. A., Trojanowski, J. Q., & Lee, V. M.-Y. (2006). Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science (New York, N.Y.)*, *314*(5796), 130–133. https://doi.org/10.1126/science.1134108

Patel, A., Lee, H. O., Jawerth, L., Maharana, S., Jahnel, M., Hein, M. Y., Stoynov, S., Mahamid, J., Saha, S., Franzmann, T. M., Pozniakovski, A., Poser, I., Maghelli, N., Royer, L. A., Weigert, M., Myers, E. W., Grill, S., Drechsel, D., Hyman, A. A., & Alberti, S. (2015). A Liquid-to-Solid Phase Transition of the ALS Protein FUS Accelerated by Disease Mutation. *Cell*, *162*(5), 1066–1077. https://doi.org/10.1016/j.cell.2015.07.047

Patel, B. K., Gavin-Smyth, J., & Liebman, S. W. (2009). The yeast global transcriptional co-repressor protein Cyc8 can propagate as a prion. *Nature Cell Biology*, *11*(3), 344–349. https://doi.org/10.1038/ncb1843

Polymenidou, M., Lagier-Tourenne, C., Hutt, K. R., Huelga, S. C., Moran, J., Liang, T. Y., Ling, S.-C., Sun, E., Wancewicz, E., Mazur, C., Kordasiewicz, H., Sedaghat, Y., Donohue, J. P., Shiue, L., Bennett, C. F., Yeo, G. W., & Cleveland, D. W. (2011). Long pre-mRNA depletion and RNA missplicing contribute to neuronal vulnerability from loss of TDP-43. *Nature Neuroscience*, *14*(4), 459–468. https://doi.org/10.1038/nn.2779

Prasad, A., Bharathi, V., Sivalingam, V., Girdhar, A., & Patel, B. K. (2019). Molecular Mechanisms of TDP-43 Misfolding and Pathology in Amyotrophic Lateral Sclerosis. *Frontiers in Molecular Neuroscience*, *12*, 25. https://doi.org/10.3389/fnmol.2019.00025

Qin, H., Lim, L.-Z., Wei, Y., & Song, J. (2014). TDP-43 N terminus encodes a novel ubiquitin-like fold and its unfolded form in equilibrium that can be shifted by binding to ssDNA. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(52), 18619–18624. https://doi.org/10.1073/pnas.1413994112

Reddi, P. P. (2017). Transcription and Splicing Factor TDP-43: Role in Regulation of Gene Expression in Testis. *Seminars in Reproductive Medicine*, *35*(2), 167–172. https://doi.org/10.1055/s-0037-1599088

Romano, M., & Buratti, E. (2013). Targeting RNA binding proteins involved in neurodegeneration. *Journal of Biomolecular Screening*, *18*(9), 967–983. https://doi.org/10.1177/1087057113497256

Sackmann, C., Sackmann, V., & Hallbeck, M. (2020). TDP-43 Is Efficiently Transferred Between Neuron-Like Cells in a Manner Enhanced by Preservation of Its N-Terminus but Independent of Extracellular Vesicles. *Frontiers in Neuroscience*, *14*, 540. https://doi.org/10.3389/fnins.2020.00540

Scotter, E. L., Chen, H.-J., & Shaw, C. E. (2015). TDP-43 Proteinopathy and ALS: Insights into Disease Mechanisms and Therapeutic Targets. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics*, *12*(2), 352–363. https://doi.org/10.1007/s13311-015-0338-x

Shenoy, J., Lends, A., Berbon, M., Bilal, M., El Mammeri, N., Bertoni, M., Saad, A., Morvan, E., Grélard, A., Lecomte, S., Theillet, F.-X., Buell, A. K., Kauffmann, B., Habenstein, B., & Loquet, A. (2023). Structural polymorphism of the low-complexity C-terminal domain of TDP-43 amyloid aggregates revealed by solid-state NMR. *Frontiers in Molecular Biosciences*, *10*. https://doi.org/10.3389/fmolb.2023.1148302

Sreedharan, J., Blair, I. P., Tripathi, V. B., Hu, X., Vance, C., Rogelj, B., Ackerley, S., Durnall, J. C., Williams, K. L., Buratti, E., Baralle, F., de Belleroche, J., Mitchell, J. D., Leigh, P. N., Al-Chalabi, A., Miller, C. C., Nicholson, G., & Shaw, C. E. (2008). TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. *Science (New York, N.Y.)*, *319*(5870), 1668–1672. https://doi.org/10.1126/science.1154584

Strong, M., Donison, N., & Volkening, K. (2020). Alterations in Tau Metabolism in ALS and ALS-FTSD. *Frontiers in Neurology*, *11*, 598907. https://doi.org/10.3389/fneur.2020.598907

Strong, M. J., Volkening, K., Hammond, R., Yang, W., Strong, W., Leystra-Lantz, C., & Shoesmith, C. (2007). TDP43 is a human low molecular weight neurofilament (hNFL) mRNA-binding protein. *Molecular and Cellular Neurosciences*, *35*(2), 320–327. https://doi.org/10.1016/j.mcn.2007.03.007

Sun, Y., & Chakrabartty, A. (2017). Phase to Phase with TDP-43. *Biochemistry*, *56*(6), 809–823. https://doi.org/10.1021/acs.biochem.6b01088

Thiery, J. P., Acloque, H., Huang, R. Y. J., & Nieto, M. A. (2009). Epithelial-mesenchymal transitions in development and disease. *Cell*, *139*(5), 871–890. https://doi.org/10.1016/j.cell.2009.11.007

Tollervey, J. R., Curk, T., Rogelj, B., Briese, M., Cereda, M., Kayikci, M., König, J., Hortobágyi, T., Nishimura, A. L., Zupunski, V., Patani, R., Chandran, S., Rot, G., Zupan, B., Shaw, C. E., & Ule, J. (2011). Characterizing the RNA targets and position-dependent splicing regulation by TDP-43. *Nature Neuroscience*, *14*(4), 452–458. https://doi.org/10.1038/nn.2778

van Eersel, J., Ke, Y. D., Gladbach, A., Bi, M., Götz, J., Kril, J. J., & Ittner, L. M. (2011). Cytoplasmic accumulation and aggregation of TDP-43 upon proteasome inhibition in cultured neurons. *PloS One*, *6*(7), e22850. https://doi.org/10.1371/journal.pone.0022850

Virani, S., Colacino, J. A., Kim, J. H., & Rozek, L. S. (2012). Cancer Epigenetics: A Brief Review. *ILAR Journal*, *53*(3–4), 359–369. https://doi.org/10.1093/ilar.53.3-4.359

Wang, W., Wang, L., Lu, J., Siedlak, S. L., Fujioka, H., Liang, J., Jiang, S., Ma, X., Jiang, Z., da Rocha, E. L., Sheng, M., Choi, H., Lerou, P. H., Li, H., & Wang, X. (2016). The inhibition of TDP-43 mitochondrial localization blocks its neuronal toxicity. *Nature Medicine*, *22*(8), 869–878. https://doi.org/10.1038/nm.4130

Wang, X., Arai, S., Song, X., Reichart, D., Du, K., Pascual, G., Tempst, P., Rosenfeld, M. G., Glass, C. K., & Kurokawa, R. (2008). Induced ncRNAs allosterically modify RNA-binding proteins in cis to inhibit transcription. *Nature*, *454*(7200), 126–130. https://doi.org/10.1038/nature06992

Xiao, S., Sanelli, T., Dib, S., Sheps, D., Findlater, J., Bilbao, J., Keith, J., Zinman, L., Rogaeva, E., & Robertson, J. (2011). RNA targets of TDP-43 identified by UV-CLIP are deregulated in ALS. *Molecular and Cellular Neurosciences*, *47*(3), 167–180. https://doi.org/10.1016/j.mcn.2011.02.013

Zhang, Y.-J., Xu, Y., Dickey, C. A., Buratti, E., Baralle, F., Bailey, R., Pickering-Brown, S., Dickson, D., & Petrucelli, L. (2007). Progranulin Mediates Caspase-Dependent Cleavage of TAR DNA Binding Protein-43. *The Journal of Neuroscience*, *27*(39), 10530–10534. https://doi.org/10.1523/JNEUROSCI.3421-07.2007

Zhang, Y.-J., Xu, Y.-F., Cook, C., Gendron, T. F., Roettges, P., Link, C. D., Lin, W.-L., Tong, J., Castanedes-Casey, M., Ash, P., Gass, J., Rangachari, V., Buratti, E., Baralle, F., Golde, T. E., Dickson, D. W., & Petrucelli, L. (2009). Aberrant cleavage of TDP-43 enhances aggregation and cellular toxicity. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(18), 7607–7612. https://doi.org/10.1073/pnas.0900688106

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