REVIEW ARTICLE

Motor Neuron Disease: The Contribution of TAR-43 Gene in Amyotrophic Lateral Sclerosis

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Received on: 08 June 2023; *Accepted on*: 08 July 2023; *Published on*: 04 August 2023

Abstract

Motor neuron diseases are a spectrum of neurodegenerative disorders, characterized by their physicochemical propinquity for the voluntary motor systems. The most notorious of these neurodegenerative disorders is amyotrophic lateral sclerosis (ALS), which is a multifocal disorder affecting both lower and upper motor neurons. Amyotrophic lateral sclerosis has been defined as a progressive nervous system disease that affects nerve cells in the brain and spinal cord, causing loss of muscle control. Transactive response element (TAR) DNA binding protein 43 (TDP-43) is an ribonucleic acid (RNA)/DNA binding protein contributing to RNA-related metabolism. Hyperphosphorylated and ubiquitinated TDP-43 deposits function as inclusion bodies in the brain and spinal cord which causes ALS. Majority of the ALS cases are sporadic amyotrophic lateral sclerosis's (SALS's) and 5–10% of cases are familial amyotrophic lateral sclerosis (FALS), where mutations of the TDP-43 DNA binding protein (TARDBP) gene occur and the rest (90–95%) are due to mutations in other genes like C9ORF72, SOD1, etc. Whether the ALS is familial or sporadic it has been seen that there is a significant contribution of TDP43 protein in the ALS pathology. Thus, the modality of TDP43-based proteinopathies and its involvement in ALS has been the focal point in the study of ALS-mediated neurodegeneration.

Keywords: Amyotrophic lateral sclerosis, Familial amyotrophic lateral sclerosis, Sporadic amyotrophic lateral sclerosis, TAR DNA-binding protein 43.

Bengal Physician Journal (2023): 10.5005/jp-journals-10070-8009

Introduction

Lack of motor neurons is a hallmark of amyotrophic lateral sclerosis (ALS), a devastating neurodegenerative contamination. In 1869, Jean-Martin Charcot supplied the primary comprehensive description of ALS, noting the disorder's function amyotrophy (muscle losing) and sclerosis (gliotic hardening) of the anterior and posterior corticospinal tracts, which impacts each higher and decreased motor neurons. "Lou Gehrig disease" is a common name for ALS because of its affiliation with the terrific baseball player Lou Gehrig, who changed into recognized with ALS in 1939. Amyotrophic lateral sclerosis is especially of 2 types; firstly, sporadic ALS or (SALS) is the most common shape of ALS. Nearly 95% of ALS is sporadic in incidence. Secondly, familial ALS (FALS), that is five to ten percentage of the ALS spectrum and the inheritance pattern of this subtype is autosomal dominant. Various cell pathways were proven to play a critical position in the starting place of ALS after the identification of the familial cases. Expertise in the commonplace pathogenic motifs in ALS has been greatly aided with the aid of the locating of mutations in TDP43 and other uncommon genetic instances. The general common prevalence charge of ALS international is around one in 50,000 humans each year which estimates to be about five, 760–6, four hundred new diagnoses in step with year. The average age of the onset of the ailment is ready 60 years, where men have a higher rate of prevalence than girls (a male-to-girl ratio of 1. five to at least one), but with advancing age, the gender hole narrows down.[1]

Inadvertent reactions mutations inside the TARDBP gene, which codes for DNA binding protein (TDP forty-three) in people, are related to each sporadic and familial ALS. As a result, TDP43 connects SALS and FALS and is still a dominant protein of hobby in the study of the ailment's pathophysiology. Patients with ALS have been shown to have TDP 43 cytosolic aggregates, and this locating serves as a characteristic of ALS due to the fact it is visible in nearly 97% of ALS sufferers. More than 50 TARDP mutations have been related to ALS because 2008, indicating that TDP43 malfunction is an important part of the sickness. As a result, TDP43 malfunction offers a shared framework for expertise an exceptionally heterogeneous disease like ALS. TAR DNA-binding protein 43 (TDP43) pathology is found in forty-five percent of instances with frontotemporal lobar dementia (FTLD), which has a few similarities to ALS.[2] This assessment intends to provide an overview of TDP43's shape and characteristics, in addition to its affiliation with ALS and different neurodegenerative ailments. It additionally sheds light onto the records of the contemporary and possibilities of ALS medicines underneath development.

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How to cite this article: Guha G. Motor Neuron Disease: The Contribution of TAR-43 Gene in Amyotrophic Lateral Sclerosis. Bengal Physician Journal 2023;10(2):50–54.

Source of support: Nil

Conflict of interest: None

Structural Analysis of TDP43

In relation to HIV transcription, TDP 43, a nuclear RNA-binding protein, functions as a repressor protein. TDP43, an RNA or DNA binding protein that is widely expressed and a member of the hnRNP family, is highly conserved. It mostly recognizes UG-rich motifs in RNA and TG-rich motifs in DNA.

The 414-amino acid TDP43 protein is encoded by the TARDP gene, which is located on chromosome 1 in humans. The TDP43

protein has a well-folded N-terminal region (NTD), which spans up to 76 residues, two relatively conserved RNA reputation motifs, which span residues 106–176 (RRM1) and 191–259 (RRM2), and a glycine-rich C-terminal region (CTD), which takes up residues 217–414.

The polymerization of the TDP 43 protein involves the NTD, which has roughly 76 residues. The protein dimerization is aided by the head-to-head contacts between NTD. As a result, a dimerized structure is created that aids in pre-mRNA splicing. However, this protein will become hazardous if it continues to oligomerize. The conformational equilibrium of TDP 43 monomers, homodimers, and oligomers determines whether this mode of polymerization results in dimers, bigger forms or simply stabilizes monomers. TDP-43 is consequently overexpressed in sick cells, which causes the N terminal domain to have a higher propensity for aggregation. However, folding NTD is permitted by normal amounts of TDP-43 in normal cells, preventing polymerization and consequently aggregation.

The nuclear localization signal (NLS), which is present in TDP 43 protein and is situated between residues 82 and 98, is important in ALS. The nucleus loses function and aggregates as a result of mutations like A90V that occur in this area. As a result, NLS is crucial in controlling ALS's typical physiological processes. Between residues 239 and 251, there is a signal called the nuclear export signal (NES). The TDP43 protein, also known as a nucleocytoplasmic protein, is capable of moving back and forth between the nucleus and cytoplasm since NLS and NES are present. However, the nucleus is where it is found most frequently.

The glycine-rich CTD has a Q/N-rich domain similar to the yeast prion sequence, which is known as a prion-like domain (PLD). Prion-like domains are low-complexity sequences that have been shown to regulate gene regulation via liquid-liquid phase transition (LLP), resulting in the construction of ribonucleoprotein (RNP) granules. These microscopically apparent RNP granules have the potential to initiate an effective gene regulation process. Ribonucleoprotein granules may also have a role in stress response and therefore aging, or persistent stress, which might cause LLPs to undergo irreversible liquid solid phase separation and form pathogenic aggregates, as seen in ALS neurons. As a result, CTDs frequently play a key role in TDP-43 pathogenicity.

TAR DNA-binding protein 43 also possesses six mitochondrial localization markers that aid in its movement into the mitochondria, association with mtDNA, and contribution to the respiratory chain route.

Due to the very hydrophobic nature of TDP43, it is challenging to fully understand many aspects of the protein and many of its structural details. It is still difficult to pinpoint exact phosphorylation, methylation, or even binding sites Figure 1.[3,4]

TDP 43 Associated Proteinopathies

Numerous neurodegenerative illnesses, some of which have a hereditary or spontaneous pattern, are included in TDP43 proteinopathies. The C9Orf72 hexanucleotide repeats have been found in patients with SALS and FTLD, AD, and other TDP-43 proteinopathies where the TAR43 protein has translocated from its usual nuclear site to form cytoplasmic aggregates. Although it has been noted that many TDP43 proteinopathies involve the nuclear depletion of TDP43 protein, which is evident nearly at the terminal stage of the disease, the exact mechanism underlying these pleiotropic effects remains unknown. The loss of TDP43 from the nucleus will result in the decrease and degradation of RNAs as well as altered splicing events since it shuttles between the nucleus and cytoplasm.

These transcriptional and splicing events will thus contribute to neuronal dysfunction in TDP 43 proteinopathies.

The nucleocytoplasmic shuttle of TDP-43 is regulated by nuclear localization signal (NES) and NES, and deletion of these segments will result in a decrease in TDP-43 nuclear pool, which will affect the control of chromatin assembly and histone processing, two processes that result in nuclear aggregation. It has been demonstrated that an accumulation of mutant the TDP-43 causes nucleoporins and other transport factors to be sequestered and mis-localized, affecting the movement of proteins and RNA through the nucleo-cytoplasm. Patients with sporadic and familial (TARDBP) ALS have brain tissue with nuclear pore abnormalities. Surprisingly, there are fewer reports of NLS mutations in ALS; nonetheless, C-terminal mutations may also cause cytoplasmic localization. Through its interactions with the ribosomal proteins, TDP-43 aggregation may function as a translational repressor in the cytoplasm. It will be necessary to conduct more studies on substances that monitor nucleocytoplasmic transport since they might possess therapeutic potential. Nuclear depletion of the TDP-43 protein, which is primarily shown in the terminal stage of the disease, is a key pathogenic characteristic of all TDP-43 proteinopathies. TAR DNA-binding protein 43 (TDP-43) performs a variety of tasks in both compartments as it moves back and forth between the nucleus and cytoplasm.

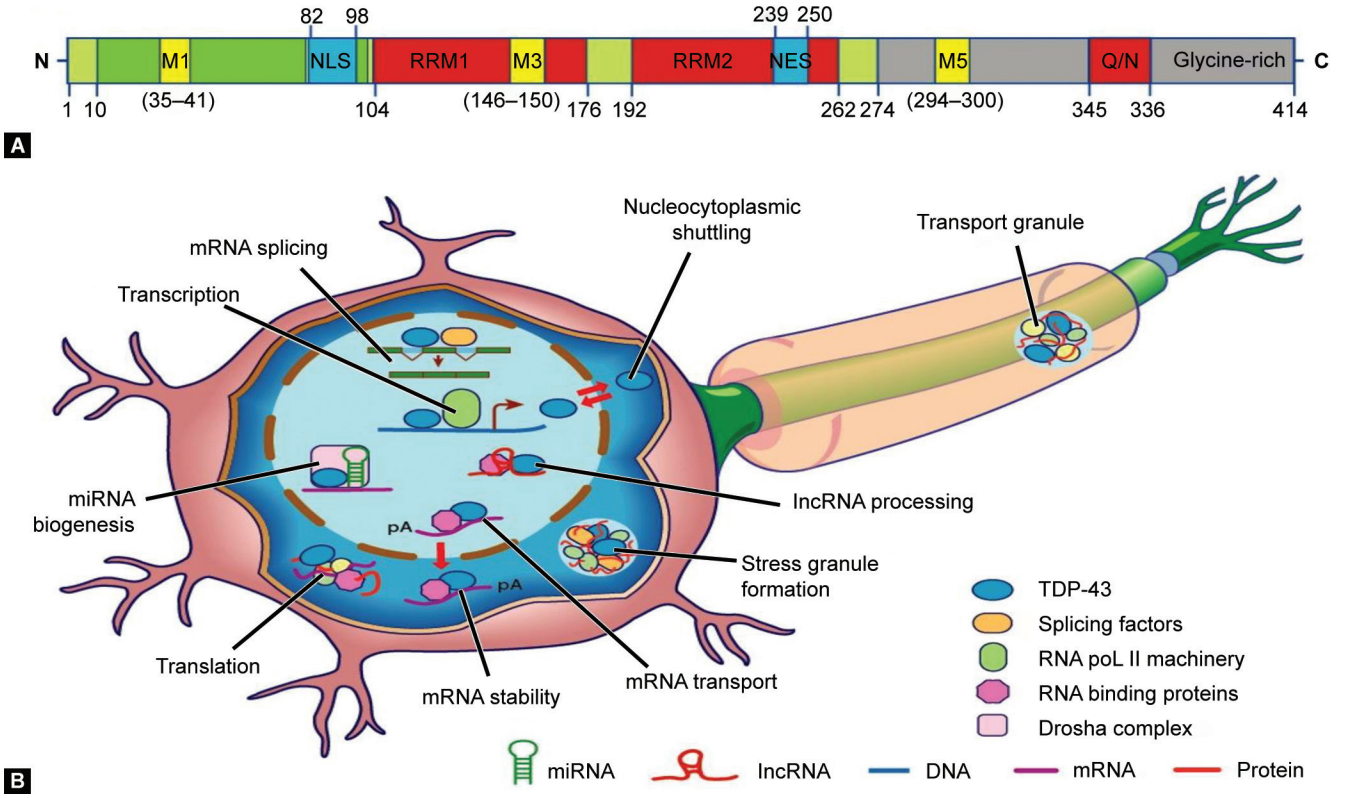
In both the cortex and the spinal cord, phosphorylation of TDP-43 is a pronounced pathogenic feature of ALS and FTLD. The enhanced oligomerization, fibrillization, cytoplasmic mislocalization, and aggregation in neuronal cells as a result of TDP-43 phosphorylation contributed to the disease. Other alterations that can cause TDP-43 to aggregate and lose its ability to interact with DNA/RNA and protein-protein interactions include ubiquitination, acetylation, poly ADP-ribosylation, and cysteine oxidation.

TDP-43 toxicity in cells and its negative effects on mitochondrial function have been shown to increase as a result of the interplay between TDP-43 aggregation and oxidation. Additionally, it has been demonstrated that inhibiting TDP-43's mitochondrial location reduces its cellular toxicity and enhances the clinical phenotype in animal models. The mitochondrial dysfunction seen in patients with ALS is demonstrated by the recent discovery that TDP-43 and its disease-associated mutations dramatically exacerbate the mitochondrial abnormalities in numerous models. As a result, a key mechanism for inducing toxicity in TDP-43 proteinopathies is the interaction between pathogenic TDP-43 and mitochondria.

In TDP43 neuropathies, other neurotoxic mechanisms, including endocytic dysfunction, an imbalance in metal-ion homeostasis, and interference with chromatin remodeling, have been researched. Future research will need to provide an in-depth explanation of the significance of these events in the etiology of TDP 43 proteinopathy.[5]

TDP-43 in ALS

ALS has a variety of clinical manifestations, and because of this, it is categorized as a primary brain neurodegenerative condition. Even though TARDP genetic mutations are exceedingly rare (1–5%) in ALS patients, TDP 43 protein aggregation is nonetheless noticeable in the majority of these cases. A prototype of TDP 43 pathology specific to the ALS 3 predominating cell type has been identified.



Figs 1A and B: (A) Structure of TAR DNA-binding protein 43 (TDP-43) protein. The TDP-43 protein contains 414 amino acids and comprises an N-terminal region with a nuclear localization signal (NLS). In addition, the protein consists of two RNA recognition motifs (RRM1 and RRM2), a nuclear export signal (NES), and a C- terminal domain with a glutamine/asparagine-rich (Q/N) and glycine-rich regions. Mitochondrial localization motifs (M1; M3; M5) are also evident. Pathogenic mutations are predominantly located within the C-terminal region which can exhibit prion-like properties. The numbers represent amino acid lengths; (B) The TDP-43 protein is critical for mediating RNA metabolism. In the nucleus, TDP-43 is important for transcription and splicing of messenger RNA (mRNA), as well as maintaining RNA stability (pA) and transport to the nucleus. In addition, TDP-43 regulates the biogenesis of microRNA (miRNA) and the processing of long non-coding RNA (lncRNA). Although predominantly located within the nucleus, TDP-43 shuttles between the nucleus and the cytoplasm. In the cytoplasm, TDP-43 participates in mRNA stability, translation, formation of stress, and RNP transport granules

Source: Eva Maria Johanna de Boer et al. from https://jnnp.bmj.com/content/92/1/86.full with UploadWizard

(A) Glial (22%)
(B) Neuronal (7%)
(C) Mixed neuronal and glial (59%)

(A) TDP43 is expressed constitutively in the glial cells of the central nervous system along the glial route. Astrocytes or microglial cells have been seen to become activated in ALS patients with TDP 43 proteinopathy, which contributes to the disease's neurodegeneration. The neuroinflammation caused by microglia is correlated with protein tyrosine phosphatase 1B (PTP1B). Recent studies demonstrate that the overexpression of TDP 43 upregulates the expression of PTP1B in astrocytes and that PTP1B inhibition reduces the proinflammatory responses to TDP 43 that are induced in astrocytes, indicating that PTP1B is a crucial modulator of TDP43-induced inflammation. Although TDP43's malfunction in glial cells is not trivial, it has been discovered that TDP43 prefers to impact neuronal cells using the glial-mediated pathway as opposed to glial cells.[6]

(B) Inclusions are seen in the motor nuclei of the brainstems and anterior horn cells of the spinal cord in the majority of instances of SALS and a subtype of FALS. The most widely recognized theory regarding the inclusion formation route is that there will be a change in how these neuronal cells' stress granules—which contain TDP 43—function, which will cause a buildup of TDP43 inclusions. The development of stress granules (SG) in neuronal cells can result from exposure to a variety of stimuli, including oxidative stress, thermal shock, viral infections, etc. The process of SG production is momentary and reversible. When the tension is passed, the SGs disappear. Because they are sensitive to stress, neuronal cells will transform SGs into pathogenic inclusion bodies if their stress response is compromised. TAR DNA-binding protein has over 40 mutations, mostly in SLAS and FALS patients. Among them, it has been demonstrated that the A315T mutation significantly increases TDP43 inclusions and aggregation, which would result in neurotoxicity. TDP43 is mostly found in mitochondrial membranes and SGs, outside of the nucleus, and it is crucial for mitochondrial protein translation, mRNA transport, and other processes The fundamental functions of the nervous system, such as energy and intermediate metabolism, Ca +2 homeostasis, and apoptosis, are heavily influenced by mitochondria. Mutant TDP 43 can impair mitochondrial function, and aberrant mitochondrial aggregation and a loss

of mitochondrial function can result in gradual neuronal death. TDP43 aggregates in the mitochondria will interfere with mtDNA transcription, lower ATP synthesis, interfere with Ca +2 homeostasis, disrupt axonal transport, and other processes that result in the development of mitochondrial stress and, in a sense, also help to generate SG.[7]

(C) A mixture of both, neuronal and glial pathology is predominant in most ALS patients.

The Elusive Cure

Creating medications that specifically target TDP43 has received very little research attention. Numerous neurodegenerative diseases, including FLTD, AD, CTE, CARTS, and others have been linked to TDP 43 proteinopathies, which are not just associated with ALS. TDP43 is expressed at varying levels in all of the cells in our body. For instance, TDP43 is expressed at low levels throughout CNS development in the brain and spinal cord, indicating that TDP 43's expression is regulated in a time-dependent manner. It has been observed that drugs like Anacardic acid (a histone acetyltransferase inhibitor) can significantly lower the TDP 43 mRNA expression levels and thus reduce the insoluble fraction of TDP 43 protein but not the soluble fraction in induced pluripotent stem cells (iPSCs) derived motor neurons showing ALS pathology. Regulation of TDP43's nucleocytoplasmic balance is a good way to lengthen cell life because TDP43's nucleocytoplasmic transport, along with that of other proteins, is disrupted in ALS.[8] In HEK293E cells, N-acetyl cysteine (NAC), a well-known invitro and in vivo antioxidant has been observed to reduce TDP43 insolubility and ubiquitination, reducing the likelihood of TDP43 aggregation among all the compounds.

An additional feature of TDP 43 aggregates is its characteristic phosphorylation. Initially, it was believed that the CTD of the protein was the only part of the protein that underwent phosphorylation, but evidence now suggests that disease-specific mutations can alter or add possible amino acids in this area of the TDP 43 protein.[9]

Although the functional importance is still not fully understood, some data suggests that phosphorylation may modify TDP 43's aggregation characteristics. As a result, kinase targeting has emerged as a very promising field of study for ALS therapies like cell division cycle 7-protein. Although the role of TDP 43 aggregation in neurodegenerative disease is still hotly contested, only a small number of substances have been examined to determine whether they could modulate the process; TDP 43 has also been discovered as an aggregation-prone protein; Riluzole, one of the few medications licensed for the treatment of ALS, only aims to moderately extend life expectancy by three months.

Without generating cell toxicity or altering the level of TDP 43 expression, riluzole has demonstrated a strong suppression of TDP43 self-interaction.[10] Riluzole, however, did not extend the lives of A315T-TDP43 mutant mice or FUS mutant rats, nor did it alleviate behavioral impairments and neuropathology in a rat model with M337V-TDP 43 mutations.[11] however, it has been suggested that Riluzole may be an ATP-competitive creatine kinase 16 (CK 16) inhibitor and may connect TDP-43 and glutamate excitotoxicity.[12]

Discussion

Although extensive study has been done to identify the clinical signs of ALS, the precise cause of neurodegeneration and a treatment for it are still unknown. Several studies have suggested that protein aggregation and mitochondrial dysfunction are two of the main causes of ALS and other neurodegenerative disorders. It is very likely that these ostensibly unrelated disorders are connected. One knowledge gap at the moment is a better understanding of why particular injuries are vulnerable to particular neuronal subtypes. Even though it has been demonstrated that neurotoxic proteins expressed only by glia are sufficient for degeneration, it is still unclear why the motor neurons selectively degenerate in ALS. Protein products, interactions, and known mutation analysis has been used to identify functional pathways which get affected in ALS. Additionally, no recent research has been conducted that specifically examines the part that SGs play in ALS. Numerous investigations have identified SG elements as having effects on the pathophysiology of ALS. More research has been done to demonstrate that protein aggregation is a defining feature of many neurodegenerative disorders, not just ALS. These facts from SG Pathology may pave the way for beneficial research in the future.

Future Prospects

Despite 20 years of research, there is still no known treatment for ALS. Some recent studies offer novel methodologies and targets which have the potential for new treatment targets, albeit additional research is required. The FDA has approved medications like riluzole and edaravone to treat ALS; the former may extend life by a few months. Potential targets for ALS include the tight relationship between stress-induced mitochondrial damage and the disease. The progression of the disease may be slowed or prevented by therapeutic medicines that stop the release of harmful defective mitochondria while yet allowing the intact mitochondria to extend their neuroprotective impact. Although the pathogenic relevance of these aggregates is unclear, there are a few putative pathways with supportive data. Cytoplasmic aggregates of TDP 43 are particularly prevalent in ALS. This suggests that therapeutic targeting of TDP 43 inclusions for disaggregation may be a successful therapeutic approach.[13]

Conclusion

Though the molecular and cellular mechanisms underlying these disorders are not obvious, multiple routes based on genetic and clinical data are developing. Significant progress has been achieved in expanding the biology of TDP 43 proteinopathy-linked neurodegenerative problems like ALS and FTLD. These include abnormal protein homeostasis, faulty RNA processing, TDP 43 autoregulation, and more. Hence the majority of ALS and FTLD disease etiologies involve many pathways with a common characteristic known as TDP 43 misprocessing. The wide range of physiological TDP 43's functions slows down the discovery of disease-related anomalies and, as a result, the creation of possible treatments. For these degenerative conditions, there are now very few licensed drugs, but regrettably, no such effective therapy has been identified that might cure or halt the course of both FTLD and ALS.

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