

Therapeutic approaches for the treatment of Frontotemporal Lobar Degeneration

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TABLE OF CONTENTS

Abstract -----	85
1. Introduction -----	86
2. Clinical approaches for the treatment of FTLD symptomatology -----	87
2.1. Behavioral symptoms -----	87
2.2. Cognitive symptoms -----	87
2.3. Dietary changes -----	87
2.4. Motor symptoms -----	87
3. Disease-modifying therapies -----	88
3.1. Tau-related approaches -----	88
3.2. Progranulin-based approaches -----	89
3.3. TDP-43-related approaches -----	91
4. Conclusion -----	93
Acknowledgments -----	93
Conflict of Interest Statement -----	93
References -----	93

Abstract

Frontotemporal Lobar Degeneration (FTLD) is nowadays considered the second cause of dementia, accounting for 20% of all the cases under the age of 65 years. The earliest signs of frontotemporal dementia are a fundamental change in personality, social behavior, and communication abilities. The pathological and clinical heterogeneity of FTLD has made the application of effective therapies a difficult task.

No treatments for FTLD are available yet, and off-label medications are commonly used as symptomatic drugs to counteract behavioral, cognitive and motor disturbances. In general, two different approaches to treat FTLD have been considered. First, treatments to improve clinical symptoms and second, disease-modifying therapies aimed at slowing disease progression by acting on molecular mechanisms, thought to be involved in FTLD pathogenesis. This brief review aims to highlight recent advances in the treatment of FTLD.

Keywords: Frontotemporal Lobar Degeneration, tau, progranulin, TDP-43, therapies

Abbreviations

AD	-	Alzheimer's Disease
ALS	-	Amyotrophic Lateral Sclerosis
bv-FTD	-	behavioral variant Frontotemporal Dementia
CHMP2B	-	Chromatin-Modifying 2B Protein
CNS	-	Central Nervous System
C9ORF72	-	Chromosome 9 Open Reading Frame 72
ERK	-	Extracellular Regulated Kinase
FTD	-	Frontotemporal Dementia
FTLD	-	Frontotemporal Lobar Degeneration
FUS	-	Protein Fused in Sarcoma
GABA	-	γ -Aminobutyric Acid
GRN	-	Granulin gene

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GWAS	-	Genome Wide Association Study
HDAC	-	Histone Deacetylase
hnRNP	-	heterogeneous nuclear Ribonucleoprotein
hnRNPA2B1	-	heterogeneous nuclear Ribonucleoprotein A2B1
iPS cells	-	induced Pluripotent Stem cells
MAPT	-	Microtubule Associated protein tau
miRNA	-	MicroRNA
NMDA	-	N-methyl-D-aspartate
NPI	-	Neuropsychiatric Inventory
PD	-	Parkinson's Disease
PI3K	-	Phosphatidyl Inositol-3 Kinase
PGRN	-	Progranulin
PPA	-	Primary Progressive Aphasia
SAHA	-	Suberoylanilide Hydroxamic Acid
SORT1	-	Sortilin 1
SQSTM1	-	Sequestome 1
SNP	-	Single Nucleotide Polymorphism
SSRIs	-	Selective Serotonin Reuptake Inhibitors (SSRIs)
TDP-43	-	Transactive response DNA-binding protein-43
TNF	-	Tumor Necrosis Factor
TNFR	-	Tumor Necrosis Receptor
UBQLN2	-	Ubiquilin-2
VCP	-	Valosin-Containing Protein
Vsp10	-	Vacuolar Sorting Protein 10

1. Introduction

Frontotemporal lobar degeneration (FTLD) is the second most common cause of early-onset dementia after Alzheimer's Disease (AD) [1, 2] in which degeneration of the frontal and temporal lobes of the brain results in progressive changes in personality, behavior, and language with relative preservation of perception and memory [3]. FTLD affects men and women equally with onset commonly in the fifth or sixth decade, but can be earlier or later than this, especially in familial forms of the disease. A positive family history of FTLD is present in 25-50% of cases [4] and the transmission is usually autosomal dominant [5]. A few genes have been associated with familial FTLD: *microtubule associated protein tau (MAPT)*

[6, 7] *progranulin (GRN)* [8, 9], *transactive response (TAR) DNA-binding protein-43 (TDP-43)* [10, 11], *chromatin-modifying 2B protein (CHMP2B)* [12], *Valosin-containing protein (VCP)* [13], and *chromosome 9 open reading frame 72 (C9ORF72)* [14]. More recently mutations in *Sequestome1/p62 (SQSTM1)* [15], *heterogeneous nuclear ribonucleoprotein A2B1 (hnRNPA2B1)* [16] and *Ubiquilin-2 (UBQLN2)* [17, 18] were identified in families presenting FTLD, myopathy and amyotrophic lateral sclerosis (ALS). Even in the case of a genetic defect being found, post-mortem neuropathological brain examination is essential to identify the entity underlying FTLD. Pathologically, these diseases share deposits of abnormal proteins in neuroectodermic cells and severe cell loss with atrophy of vulnerable cortical and subcortical structures [19]. The most common pathology in FTLD, accounting for 40%-65% of cases, has been found to be neuritis, neuronal cytoplasmic inclusions, and lentiform intranuclear inclusions, containing the TAR-DNA binding protein 43 (TDP-43) as the major component [11, 20], and thus named FTLD-TDP [21, 22]. Four different patterns of TDP-43 pathology are recognized in FTLD-TDP, based on the anatomical distribution, morphology, and relative proportion of distinct types of inclusions [23]. This heterogeneity is also supported by different clinical and genetic features. The FTLD-TDP includes the behavioral variant of frontotemporal dementia (bv-FTD), PPA (primary progressive aphasia), and FTD with motor neuron disease (FTD-MND) [24]. The next largest group of FTLD cases comprises FTLD with tau-positive pathology (FTLD-tau) [25], and these patients can present atypical parkinsonism in addition to bv-FTD and PPA. More recently another small group of cases has been described to present inclusions of the DNA/RNA binding protein Fused in Sarcoma (FUS), and thus named (FTLD-FUS) [26, 27]. Mutations in the *FUS* gene cause familial ALS (ALS-FUS) [28]. The overlap between ALS and FTD, as well as the homology of FUS and TDP-43 prompted a number of studies that demonstrated that inclusions of the several tau/TDP-43 negative FTLDs were immunoreactive for FUS [29, 30].

At present there are no effective treatments for FTLD, and treatment choices are often selected

from those used for AD and psychiatric disorders. Disease-modifying therapies based on the increasing knowledge of FTLD biology have begun to emerge. The American and European registers of clinical trials are summarized in www.clinicaltrial.gov and www.clinicaltrialsregister.eu, respectively.

This review aims to briefly summarize therapeutic options to alleviate FTLD symptomatology and to highlight recent advances in disease-modifying therapies based on molecular targets.

2. Clinical approaches for the treatment of FTLD symptomatology

Evidence suggests that several neurotransmitter pathways, i.e. the cholinergic, serotonergic, dopaminergic, glutamatergic, noradrenergic and γ -aminobutyric acid (GABA)-ergic, may be defective in FTLD [31-36]. In this direction, pharmacological strategies have focused on neurotransmitter replacement and modulation for the treatment of behavioral, motor and cognitive symptoms of FTLD. Different classes of drugs like selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics, acetylcholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists are commonly used in other neurodegenerative disorders [37-40]. At present, adequate management of FTLD symptoms involves a combination of pharmacological therapy with behavioral, physical and environmental modification techniques. Although these treatments do not prevent disease progression, they alleviate the symptoms, and improve the quality of life of patients and their caregivers.

2.1. Behavioral symptoms

Behavioral symptoms in FTLD patients are often very embarrassing for caregivers. Some of them, mainly personality changes and loss of interpersonal skills are difficult to treat, but others like sexual disinhibition, obsessive-compulsive tendencies are amenable by pharmacotherapy. Deficit in the serotonergic, noradrenergic, and dopaminergic systems have been reported in FTLD patients [41, 42]. For this reason serotonin SSRIs such as fluoxetine, fluvoxamine, sertraline, and paroxetine have been used, showing benefits in reducing Neuropsychiatric Inventory (NPI) [43].

Other antidepressants as moclobemide or atypical antipsychotics had also been used [44-46] (See Table 1). On the other hand, an antagonist of glutamate receptor (NMDA), memantine has also been used, based on the experience gained in the treatment of AD patients. Although it was not effective in improving cognitive skills it was reported to lower NPI scores in two different studies [47, 48]. Recently, the hormone oxytocin has been shown to improve social interactions and NPI scores over 1 week of administration in FTD patients [49].

2.2. Cognitive symptoms

Frontal and lobar degeneration in FTLD can give rise to cognitive symptoms, the most important being language disturbance, involving either fluency or semantic knowledge [50]. Disturbances in the cholinergic and glutaminergic systems have been documented in FTLD, and therefore, it was assumed that agents targeting these neurotransmitter systems might prove beneficial in FTLD. Experimental evidence suggests that cholinesterase inhibitors may stabilize loss of language and executive functions in some of the clinical presentations [51], although other studies have reported behavioral worsening in FTLD patients treated with Donepezil [52]. There are evidences that bromocriptine, a dopamine agonist used in the treatment of Parkinson Disease (PD), could be of benefit in the treatment of PPA [53].

2.3. Dietary changes

Depending on the clinical course, FTLD patients may present lack of satiety, craving for sweets and weight gain, although other patients may experience more peculiar dietary preferences that eventually let them to lose weight. These symptoms are difficult to manage, however, they respond in a limited degree to treatment with SSRIs [54].

2.4. Motor symptoms

Rigidity, bradykinesia, muscle atrophy, fasciculations, bulbar motor involvement including swallowing difficulties, extraocular movement abnormalities and falls can all be signs of extra-pyramidal, brainstem or MND involvement in FTD with parkinsonism [55], and thus could be treated with carbidopa/levodopa and dopaminergic

Table 1. Symptomatic therapy in Frontotemporal Lobar Degeneration.

Symptom	Therapy	Candidate molecules	Refs
	Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine Fluvoxamine Sertraline Paroxetine Tradozone	[44, 46, 54, 131-133]
Behavioural and psychiatric symptoms	Dopaminergic agents	Selegiline	[46]
	MAO-A inhibitors	Moclobemide	[45]
	Atypical antipsychotics	Aripiprazole	[134]
	Antagonist of glutamate receptor (NMDA)	Memantine	[47]
	Others	Oxytocin hormone	[49]
Cognitive symptoms (language disturbances)	Dopaminergic agents	Bromocriptine	[53]
	Cholinesterase inhibitors	Donepezil Venlafaxine Rivastigmine	[52, 135, 136]
		Levodopa Carbidopa Pramipexole	[137, 138]
Motor symptoms (Parkinsonism)	Dopaminergic agents	Levodopa Carbidopa Pramipexole	[137, 138]
Motor symptoms (FTD-MND)	Sodium channel blockers	Riluzole	[56]

agonist therapy such as pramipexole or ropinirole (See Table 1). For the treatment of FTD-MND the pharmacological management remains poor, but since riluzole has been shown to slow the progression of disability in ALS-MND, the use of this drug is an option for FTD-MND treatment [56, 57]. Urinary incontinence is common in FTLD because patients lose their voluntary sphincter control due to degeneration of medial frontal cortex, and both upper and lower motor neuron bladder dysfunction. This symptom is treated with anti-cholinergic medications.

3. Disease-modifying therapies

The recent progress in the understanding of genetic and neuropathological causes of FTLD has allowed the development of disease-modifying treatments that target molecular mechanisms involved in the disease pathogenesis. It is now known that mutations in *tau* and *GRN* genes account for most of the familial cases of FTLD (<http://www.molgen.ua.ac.be/FTDMutations>).

These two genes are located in the chromosome 17, but despite their physical proximity, the pathogenic consequences of mutations in one or the other gene are different. The pathological inclusions in the brain associated with mutation in *tau* are aggregates of hyperphosphorylated tau protein [6, 58, 59], while mutations in *GRN* lead to ubiquitinated inclusions containing mainly TDP-43 [8, 9]. The discovery that *TDP-43* mutations themselves are sufficient to cause neurodegeneration within the FTLD-TDP spectrum of disease [60] supported a pathogenic role for this protein. Below we discuss ongoing strategies based on the current knowledge of the biology of tau, PGRN and TDP-43 proteins.

3.1. Tau-related approaches

Microtubule-associated protein (MAPT) tau is a highly soluble protein, mostly expressed in neurons. The protein is involved in microtubule polymerization [61]. There are six tau isoforms as the consequence of alternative splicing of exons-2-3 and 10 of the *MAPT* gene. These isoforms

differ in the presence of three or four microtubule-binding domains, so called 3R and 4R tau. Preferential deposits of 3R or 4R are observed in different tauopathies [62], thus providing a biochemical classification. Tau mutations shift the ratio of tau isoforms 3R/4R. For this reason shifting the tau isoform ratio from 4R to 3R isoforms by alternative splicing has been proposed as a therapeutic option in tauopathies. To this end, modifying-splicing drugs are of great interest, either acting at the splice donor site of exon 10, like Neomycin or Mitoxantrone [63, 64] or by direct binding to mRNA [65, 66]. On the other hand, pathogenic *tau* mutations induce microtubule disruption and accumulation of hyperphosphorylated tau filaments within neurons and glia cells [67]. Both toxic gain of function and loss of normal function have been proposed in tau pathogenesis, although a combination of mechanisms is likely [68, 69]. Strategies for the treatment of FTLD-tauopathy include inhibiting tau phosphorylation [70-72], reversing tau aggregation [73], and enhancing misfolded or conformationally altered tau degradation by interfering in the ubiquitin-proteasome and autophagy systems [72, 74] among others. Table 2 provides some potential tau-based therapies for the treatment of FTLD. For a more comprehensive description of tau-related therapeutic approaches, the reader is referred to Lee *et al.* and Borroni reviews [72, 74]. Clinical trials for some of these drugs are currently underway for AD. Considering the pathological heterogeneity of FTLD patients, clinical trials for this disease should focus on patients with known *tau* mutations or clinical presentation clearly associated with tau pathology.

3.2. Progranulin-based approaches

Since the discovery of *GRN* mutations linked to FTLD in 2006, more than 60 different mutations in *GRN* have been described that are associated with the etiology of the disease (www.molgen.ua.ac.be/FTDmutations/) (Gijselinck *et al.*, 2008). Most of pathogenic *GRN* mutations identified so far cause disease through haploinsufficiency. Identification of molecular targets to slow or hopefully prevent the PGRN-related FTLD relays in a better understanding of both the biological functions of PGRN, and the role of protein insufficiency in the development of dementia. PGRN is expressed in

neurons and microglia [75]. Some data suggest that PGRN may function as an autocrine neuronal growth factor. For instance, the addition of low concentrations of PGRN can promote mitogenesis in PC12 cells [76]. In addition, a possible role for PGRN in CNS (central nervous system) inflammation has been proposed [75, 77]. On these grounds, it seems plausible that neurodegeneration may result from reduced neuronal growth support or protection [78]. PGRN has also been described to increase neurite outgrowth, branching, and survival in primary neuronal cultures and neuron-like cell lines [79-81]. Nevertheless, the mechanism by which PGRN may be protective to neurons remains to be defined.

Due to the pathogenic consequences of PGRN deficit, this gene has been considered a suitable drug target to restore PGRN levels either by interfering with gene expression or with the protein turnover. The challenge is to find out how much PGRN expression levels need to be raised to have a significant clinical effect, avoiding potential adverse effects like tumorigenesis [82] or insulin resistance [83]. For this purpose the development of cellular and animal models of PGRN deficiency to test novel therapeutic drugs are very valuable.

Two landmark studies, published in 2011, hold promise in regulating PGRN levels. First, Capell *et al.* [84] found that alkalizing reagents, some of them already used in humans for other applications including chloroquine, bepridil, and amiodarone, stimulate PGRN production. Moreover four different vacuolar ATPase inhibitors (bafilomycin A1, concanamycin A, archazolid B, and apicularen A) significantly increased the levels of PGRN. This study was designed to search for compounds able to inhibit the proteolytic degradation of PGRN. To this end cells were treated with a variety of protease inhibitors, and subsequently cell lysates, as well as conditioned media were analyzed for an elevation in PGRN levels. The increase in PGRN content occurs via a translational mechanism independent of lysosomal degradation, autophagy, or endocytosis, but seems to be related to the prevention of vesicular acidification. Interestingly, these authors could confirm that alkalizing reagents rescue PGRN deficiency in organotypic

Table 2. Proposed targets and candidate molecules in tau-associated FTLD therapy.

Target	Mechanisms	Candidate molecules	Refs.
Tau	<i>MAPT</i> splicing modulators	Neomycine	[63]
		Mitoxantrone	[139, 140]
	Microtubuli-stabilizing drugs	Paclitaxel	[141-143]
		Davunetide	[144-146]
	Tau phosphorylation inhibitors	Lithium	[147, 148]
		Valproic acid	[149, 150]
		Thiamet-G	[151, 152]
	Tau aggregation inhibitors	Phenothiazine methylene blue	[153]
		Anthraquinones	[154]
		N-phenylamines	[155]
		Phenylthiazolhydrazides	[156]
		Rhodanines	[157]
	Tau-degradation enhancers (UPS)	Chaperones HSP90 and HSP70	[158, 159]
		Co-chaperones	[160]
Tau-degradation enhancers (cellular autophagy)	Rapamycin	[161]	
	NH ₄ Cl o chloroquina	[162]	
Mitochondrial energy production	Coenzyme Q10 (CoQ10)	[163]	
Immunosuppression of tau	Tau antibodies	[164]	
	Vaccines		
Tau expression modulators	Rotenone	[165]	

cortical slice cultures from a mouse model for PGRN deficiency and in lymphoblastoid cells derived from human patients carrying a *GRN* loss-of-function mutation. Second, Cenick *et al.* [85] used a high-throughput screening (HTS) of chemical libraries to identify small molecule enhancers of *GRN* expression. The rationale for this was the assumption that, therapeutic drugs, in addition to modulating *GRN* expression by acting through signaling pathways, could also change gene transcription by chromatin remodeling. They reported that suberoylanilide hydroxamic acid (SAHA), a histone deacetylase (HDAC) inhibitor, currently in clinical use for T-cell lymphoma [86] increases *GRN* expression in a number of cultured cells, including human fibroblasts and lymphoblasts derived from an individual carrier of a nonsense *GRN* R493X mutation. SAHA has demonstrated therapeutic potential in other neurodegenerative diseases [87]. Therefore, this drug may be useful for the prevention and treatment of FTLD associated to PGRN haploinsufficiency. In addition, the fact that SAHA was shown to induce

changes in inflammatory markers in a mouse model of septic shock [88] suggests that SAHA may have secondary beneficial effects in FTLD-TDP besides normalizing PGRN deficiency.

On the other hand, increasing *GRN* expression could be achieved by ribosomal read-through compounds that might circumvent nonsense-mediated mRNA decay, resulting in enhanced expression of functional protein. One of these compounds, PTC124, orally available, is in clinical trials for other genetic deficiency syndromes like Duchenne muscular dystrophy and cystic fibrosis [89, 90]. Other genetic modifiers of *GRN* levels are microRNAs (miRNAs), for example mi-29b and miR-107 have been described to negatively regulate *GRN* levels [91, 92]. A single nucleotide polymorphism (SNP) rs5848, located in a predicted miRNA-binding site for miR-659 in the 3' UTR of *GRN*, is shown to be a risk factor for FTLD-TDP [93]. The fact that *GRN* mutation carriers usually have circulating levels of PGRN below the expected 50%, reduction by loss of one allele [94] indicates

additional regulation of *GRN* expression. In this regard it has been suggested that epigenetic modifications of *GRN* mRNA may occur [95, 96]. Therefore a better understanding of these mechanisms might be useful for designing therapies aimed at raising PGRN levels.

Finally, the recent discovery of PGRN receptors, mainly Sortilin 1 and TNFR, has provided other avenues to develop new therapies to regulate PGRN levels. Sortilin 1 (*SORT1*) was identified as the first known receptor for PGRN [97]. Using an alkaline phosphatase tagged PGRN binding assay, it was found that *SORT1* was the only high affinity-binding partner of PGRN in neurons. *SORT1* belongs to a class of receptors known as vacuolar sorting protein 10 (*Vsp10*) domain gene family [98]. After binding to *SORT1*, PGRN is endocytosed and delivered to the lysosome leading to a considerable decrease in extracellular levels of PGRN. A genome wide association study (GWAS) reported *SORT1* variants capable of regulating PGRN levels in human plasma [99]. The opposing effects of *SORT1* knockdown and overexpression in cultured cells regulating PGRN levels add further support to the role of *SORT1* as receptor for PGRN. Furthermore, PGRN deficit of *GRN*^{-/-} mice can be normalized by blocking *SORT1* expression [100]. Taken together, these results open new avenues for designing therapeutic strategies.

A global genetic screen performed in [101] led to the identification of tumor necrosis factor receptor 2 (TNFR2) as the PGRN-associated receptor. Analytical surface plasmon resonance revealed that PGRN exhibited higher affinity for TNF receptors, especially TNFR2 when compared with TNF α . In contrast to TNF α , which demonstrated higher affinity for TNFR1 than TNFR2, PGRN exhibited comparable binding affinity for TNFR1 and TNFR2. The possibility that PGRN acts as antagonist of TNF α provided the basis of PGRN-related therapies to decrease inflammation in arthritis, and suggest that they may also be beneficial for improving neuroinflammation in FTLT. The knowledge of specific binding domains for PGRN to TNFR allowed the design of a mimetic PGRN peptide, Asttrin, that showed greater efficiency in preventing inflammation than PGRN [101], suggesting that development of

specific compounds could be important to treat PGRN deficient FTLT patients. However a recent report shows no evidence for PGRN binding to TNFRs and impaired TNF α signaling in both immune and neuronal cells [102]. Further work is needed to clarify the potential PGRN-TNFRs interactions in the CNS.

It is known that PGRN interacts, outside and inside the cell, with signaling transduction pathways to regulate a wide number of cellular functions. For example, PGRN can activate various growth factor signaling pathways involved in cell growth/survival, including extracellular regulated kinase (ERK), phosphatidylinositol-3 kinase (PI3K)/Akt and p70S6 [103-105]. More recently, it has been reported that PGRN may be involved in Wnt signaling [106]. The Wnt signaling pathway is upregulated in progranulin-deficient human cells, mice and worms [106, 107]. Aberrant activation of Wnt signaling is associated with several neurodegenerative disorders including AD, ALS and PD [108-111]. Therefore targeting Wnt signaling pathway may prove beneficial for PGRN associated FTLT [112] and other neurodegenerative disorders. More likely, unknown PGRN receptors (or other signaling pathways inside the cell) mediating the pleiotropic functions of PGRN will be discovered in the near future.

In Table 3 we have summarized potential PGRN-based therapies.

3.3. TDP-43-related approaches

One of the pathologic hallmarks of FTLT-TDP is the accumulation of TDP-43 within the cytoplasm of diseased neurons [113]. Distinct patterns of FTLT-TDP correlate with genetic abnormalities, including mutations in *GRN*, *VCP* and *COR9F72* genes [13, 77, 114]. The normal function of TDP-43 in the brain is not fully understood, but it actively regulates the expression of numerous genes involved in neuronal development and functioning, and regulates alternative splicing of several pre mRNA transcripts [115, 116]. TDP-43 pathology is characterized by hyperphosphorylation, ubiquitination, and nucleus-to-cytoplasm translocation [11] and pathogenesis may involve both loss of normal function in the nucleus and toxic gain of function in the cytoplasm [117]. Null mutations in *TARDBP* are lethal in embryogenesis [118, 119],

Table 3. Proposed targets and candidate molecules for PGRN-associated FTLD therapy.

Target	Mechanisms	Candidate molecules	Refs.
Progranulin	Vacuolar-ATPase inhibition	Bafilomicina A1 (BafA1) Concanamycin A Archazolid Apicularen A Cloroquine Bepredil Amiodarone	[84]
	Histone deacetylase inhibition	Suberoylanilide hydroxamic acid (SAHA) Resveratrol	[85] [85, 87]
	Modulation of Sortilin expression	-	[99]
	Increasing <i>GRN</i> expression	PTC124	[89, 90]
	microRNA knockdown	miR-29b miR-107	[91] [92]
	Block Sortilin receptor	Progranuline C-terminal peptide	[97, 166]
	Increasing secreted progranulin	PDI4 (protein Disulfide isomerasa 4) overexpression	[167]
	Block Wnt upregulation	Wnt antagonists	[106]

and the conditional knockout or overexpression of TDP-43 in adult animals results in cell death and toxicity. Mutations in *TARDBP* have been identified in patients with familial ALS, a neurodegenerative disease that primarily affects motor neurons, as well as in patients with familial FTLD-ALS, characterized by loss of both motor and cortical neurons [120, 121]. FTLD-TDP and ALS share similar mechanisms of pathogenesis involving TDP-43, and both diseases lack efficacious medicine to slow disease progression [11]. Therapeutic strategies based on TDP-43 biology should be directed to prevent protein ubiquitination and hyperphosphorylation, to enhance protein aggregates clearance, and to block the translocation of the protein towards the cytosolic compartment, as these are the most likely causative mechanisms of the disease. Animal models based on TDP-43 will allow addressing the relationships between TDP-43 expression levels, pathology, neuronal loss, muscle atrophy, and motor function. Consequently, new targets that modify TDP-43 function could be tested in these animal models. A recent report, for example, has shown beneficial

effects of activating autophagy by rapamycin administration in a mouse model of FTLD-TDP [122]. These authors found improved motor functions and decreased TDP-43-containing aggregates. Therefore, compounds that increase cellular protein turnover via autophagy or the proteasome pathway might also be candidate therapies. In addition, immunotherapies (vaccines or neutralizing antibodies) targeted towards TDP-43 would be attractive therapies.

In the past few years, increasing evidence point to an unprecedented convergence of molecular pathways in ALS and FTLD involving RNA metabolism [123]. In addition to the implication of TDP-43, *FUS* mutations have been reported in ALS and familial FTLD, characterized by pathological cytoplasmic aggregates of FUS with nuclear to cytoplasmic translocation [27]. FUS is a ribonucleoprotein (hnRNP) low expressed in cytoplasm with a conserved C-terminal region, strikingly similar to TDP-43 [26]. FUS is involved in transcription, RNA processing and RNA transport [124, 125]. It has been suggested that the pathogenic hexanucleotide repetition within chromosome 9 open reading frame 72

(*C9ORF72*) gene in familial FTLN-ALS may alter RNA metabolism leading to mRNA accumulation and toxicity [126]. The identification of selective genetic or pharmacological modifiers of TDP-43, FUS and *C9ORF72* toxicity [127, 128] will likely be key to accelerate efforts to develop better therapies for these disorders.

Finally it is worthy to comment that TDP-43 and FUS, like other RNA-binding proteins contain a putative prion domain [129], suggesting a cell-to-cell, prion-like, spread of FTLN and ALS [130].

4. Conclusion

The field of FTLN pathobiology is experiencing a rapid growth, uncovering novel genetic and proteins involved in FTLN pathology. Virtually all cases of FTLN can now be assigned to one of the three major molecular subgroups (FTLN-tau, FTLN-TDP, or FTLN-FUS), but other not yet known proteins are likely to emerge in the near future. Moreover, familial FTLN only accounts for around 20% of all cases, so there are clearly more autosomal dominant genes and genetic risk factors to be found. The specific role of the pathologic proteins, and their relationship to causal gene defects have only been partially elucidated. However the recent discoveries have already provided new avenues for the development of disease-modifying drugs. The availability of cellular and animal models of FTLN, including patient-derived iPS cells and their derivatives, together with high-throughput genotyping technologies will accelerate efforts to develop better therapies for these disorders.

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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