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Exploring cellular toxicity mechanisms and immunotherapeutic potential of TDP-43 in ALS/FTD

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Henrick Riemenschneider

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Betreuer:	Prof. Dr. rer. nat. Dr. h.c. Christian Haass
Zweitgutachterin:	PD Dr. rer. nat. Florence Bareyre
Dekan:	Prof. Dr. med. Thomas Gudermann
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Meinen Großeltern –

in unendlicher Dankbarkeit und Liebe

Don't ever let somebody tell you… you can't do something.
Not even me.
You got a dream… you gotta protect it. People can't do somethin' themselves, they wanna tell you you can't do it.
If you want somethin', go get it. Period.

- Chris Gardner in "The Pursuit of Happyness"

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List of abbreviations

Aa	Amino acids
Aβ	Amyloid β
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
ALS-TDP	Amyotrophic lateral sclerosis with underlying TDP-43 pathology
APC	Antigen-presenting cell
ASO	Antisense oligonucleotide
ATG	Autophagy-related protein
ATP	Adenosine triphosphate
BBB	Blood-brain barrier
bvFTD	Behavioral variant frontotemporal dementia
C9orf72	Chromosome 9 open reading frame 72 (C9 for short)
CCNF	Cyclin F
CDC7	Cell division cycle kinase 7
CE	Cryptic exon
CFTR	CF transmembrane conductance regulator
CHMP2B	Charged multivesicular body protein 2B
CK1δ / ε or 2	Casein kinase 1δ / ε or 2
CMA	Chaperone-mediated autophagy
CNS	Central nervous system
CpG ODN	CpG oligodeoxynucleotide
CR	Conserved region (within in the C-terminal domain of TDP-43)
cryo-EM	Cryo(genic)-electron microscopy
cryo-ET	Cryo(genic)-electron tomography
CSF	Cerebrospinal fluid
CTD	C-terminal domain
CTF	C-terminal fragment (of TDP-43)
DN	Dystrophic neurite
DPR protein	Dipeptide repeat protein
DUB	Deubiquitinating enzyme
EIF4G1	Eukaryotic translation initiation factor 4 gamma 1
ER	Endoplasmic reticulum

Fab	Antigen-binding fragment
fALS/fFTD	Familial amyotrophic lateral sclerosis / familial frontotemporal dementia
Fc	Crystallizable fragment
FcR (FcγR / FcRn)	Fc receptor (class γ / neonatal)
FDA	Food and Drug Administration
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
FTLD-TDP	Frontotemporal lobar degeneration with underlying TDP-43 pathology
FUS	Fused in sarcoma
G3BP1	G3BP stress granule assembly factor 1
GCI	Glial cytoplasmic inclusion
GOF	Gain-of-function
GRN	Progranulin
HDAC6	Histone deacetylase 6
hnRNP	Heterogeneous nuclear ribonucleoprotein
hnRNPA1 / A2B1	Heterogeneous nuclear ribonucleoprotein A1 / A2B1
HSF-1	Heat-shock transcription factor-1
HSP	Heat-shock protein
IDR	Intrinsically disordered region
IgG	Immunoglobulin G
LARKS	Low-complexity, aromatic-rich, kinked segments
LATE	Limbic-predominant age-related TDP-43 encephalopathy
LCD	Low-complexity domain
LLPS	Liquid-liquid phase separation
LMN	Lower motor neuron
LOF	Loss-of-function
lvPPA	Logopenic variant primary progressive aphasia
MAb	Monoclonal antibody
MAPT	Microtubule-associated protein tau
MATR3	Matrin 3
MHC	Major histocompatibility complex

MLO	Membraneless organelle
MND	Motor neuron disease
NCI	Neuronal cytoplasmic inclusions
NES	Nuclear export signal
NfL	Neurofilament light chain
NFT	Neurofibrillary tangle
nfvPPA	Non-fluent variant primary progressive aphasia
NLS	Nuclear localization signal
NMD	Nonsense-mediated decay
NNI	Neuronal nuclear inclusions
NTD	N-terminal domain
OPTN	Optineurin
p38α MAPK	P38α mitogen-activated protein kinase
PABP-1	Poly-A binding protein-1
PAR	Poly(ADP-ribose)
PET	Positron emission tomography
PP1	Protein phosphatase 1
PPA	Primary progressive aphasia
PQC	Protein quality control
PrLD	Prion-like domain
PrP	Prion protein
pTDP-43	Phosphorylated TDP-43
PTM	Post-translational modification
RBP	RNA-binding protein
rNLS8	Regulatable NLS8 (or NEFH-tTA/tetO-hTDP-43ΔNLS bigenic mice)
RNP	Ribonucleoprotein
RRM	RNA recognition motif
sALS / sFTD	Sporadic amyotrophic lateral sclerosis / sporadic frontotemporal dementia
scFv	Single-chain variable fragment
SG	Stress granule
SOD1	Superoxide dismutase 1

SQSTM1	Sequestosome 1 / p62
SUMO	Small ubiquitin-related modifier
svPPA	Semantic variant primary progressive aphasia
TARDBP	Transactive response (TAR) DNA-binding protein
TBK1	TANK binding kinase 1
TDP-43	Transactive response (TAR) DNA-binding protein of 43 kDa
TfR	Transferrin receptor
TIA1	T-cell-restricted intracellular antigen 1
TLR	Toll-like receptor
TMEM106B	Transmembrane protein 106B
TRIM21	Tripartite motif-containing protein 21
TTBK1 / 2	Tau tubulin kinase 1 / 2
UBE2E3	Ubiquitin conjugating enzyme E2 E3
UBQLN2	Ubiquilin 2
UMN	Upper motor neuron
UPS	Ubiquitin-proteasome system
VCP	Valosin containing protein

Publications of this thesis

I. Gel-like inclusions of C-terminal fragments of TDP-43 sequester stalled proteasomes in neurons

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II. Targeting the glycine-rich domain of TDP-43 with antibodies prevents its aggregation *in vitro* and reduces neurofilament levels *in vivo*

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Zusammenfassung

Die Amyotrophe Lateralsklerose (ALS) und die Frontotemporale Demenz (FTD) sind zwei tödlich verlaufende neurodegenerative Erkrankungen, die aufgrund ihrer sich stark überschneidenden klinischen, genetischen und pathologischen Merkmale heute als Endpunkte eines kontinuierlichen Krankheitsspektrums angesehen werden. Eine der auffälligsten Gemeinsamkeiten ist das Vorhandensein von charakteristischen neuronalen, zytoplasmatischen Einschlüssen, die TDP-43 enthalten und bei fast allen ALS-Fällen sowie bei etwa der Hälfte der FTD-Patienten nachgewiesen werden können.

TDP-43 ist ein vorwiegend nukleäres RNA-bindendes Protein, das entscheidend an Spleißvorgängen beteiligt ist und aus einer gefalteten N-terminalen und einer weitgehend unstrukturierten C-terminalen Domäne besteht, die durch zwei RNA-bindende Domänen (*engl.* RRM1 & RRM2) voneinander getrennt sind. Bei ALS und FTD verlagert sich TDP-43 allerdings aus dem Zellkern und aggregiert im Zytoplasma von Neuronen und Gliazellen, was zu einer dualen Schädigung durch Funktionsverlust im Zellkern und toxischen Funktionsgewinn im Zytoplasma führt. In Einschlüssen liegt TDP-43 hyperphosphoryliert, ubiquitiniert und häufig in C-terminale Fragmente (CTFs) gespalten vor. Da TDP-43-positive Ablagerungen stark mit der Neurodegeneration bei ALS/FTD korrelieren, ist die Untersuchung ihrer Bildung, Struktur und neurotoxischen Mechanismen von großer Bedeutung für ein tieferes Verständnis der Pathogenese und könnte neue therapeutische Optionen eröffnen.

Immer mehr Hinweise legen nahe, dass sich TDP-43 in flüssigkeitsähnliche zelluläre Kompartimente aufteilen kann, die durch einen als Phasentrennung bekannten Prozess entstehen. Unter pathologischen Bedingungen kann phasenseparierten TDP-43, vermutlich über Zwischenzustände, in feste Einschlüsse übergehen. Die Ultrastruktur von aggregiertem TDP-43 ist seit Langem umstritten. Neuere Daten haben jedoch gezeigt, dass es zumindest im Endstadium der Krankheit eine amyloidähnliche Konformation annimmt, die typischerweise auch bei Proteinen anderer neurodegenerativer Erkrankungen beobachtet wird.

Aufgrund der Bedeutung von TDP-43-Einschlüssen für ALS und FTD habe ich im ersten Projekt dieser Arbeit die **Aggregations- und Toxizitätsmechanismen des am häufigsten nachgewiesenen und zur Aggregation neigenden CTF "TDP-25"** (ein 25 kDa großes TDP-43-Fragment) analysiert. Zu diesem Zweck etablierte ich Zellkulturmodelle aus primären Neuronen, die Wildtyp-TDP-25 oder eine TDP-25-Variante mit mehreren unabhängig voneinander pathogenen ALS-Mutationen exprimieren. Die Eigenschaften der resultierenden Einschlüsse habe ich mit denen bekannter flüssigkeits- und festkörperähnlicher zellulärer Kompartimente verglichen. Während die **TDP-25-Aggregate gelartige biophysikalische Eigenschaften** aufwiesen, ergab eine

kollaborative Untersuchung ihrer Ultrastruktur *in situ* mittels Kryo-Elektronentomographie, dass sie amorph sind. Erstaunlicherweise **sequestrieren TDP-25-Einschlüsse 26S-Proteasomen**, die praktisch alle in einem Substrat-verarbeitenden Übergangszustand „blockiert" vorliegen, was auf ihre **proteolytische Inaktivität** hindeutet. In Übereinstimmung mit der Anhäufung von funktionell beeinträchtigten Proteasomen konnte ich zeigen, dass die **zelluläre Proteostase in TDP-25-exprimierenden Zellen beeinträchtigt** war, was durch **ALS-Mutationen weiter verstärkt** wurde (Publikation I).

Wie für die meisten anderen neurodegenerativen Erkrankungen gibt es auch für ALS/FTD kaum wirksame, geschweige denn kurative Therapien. Ein vielversprechender therapeutischer Ansatz ist jedoch die Bekämpfung der zur Aggregation neigenden Proteine durch aktive oder passive Immunisierung. Dies wurde kürzlich durch die deutliche Reduktion von Amyloid-β (Aβ)-Plaques und die klinische Verbesserung bei Alzheimer-Patienten nach Behandlung mit potenten monoklonalen Antikörpern (*engl.* mAbs) gegen Aβ gezeigt. Auf Grundlage dieser Erkenntnisse und einzelner vielversprechender Ergebnisse von TDP-43-Antikörpertherapien in Mausmodellen habe ich eine **systematische Suche nach sicheren und wirksamen Epitopen mittels aktiver Immunisierung** durchgeführt. Dazu habe ich 15 Peptidantigene mit hoher prognostizierter Immunogenität ausgewählt, die zusammen das gesamte TDP-43-Protein abbilden. Bei der Immunisierung von Wildtyp-Mäusen wurden die Ovalbumin-konjugierten Peptide gut vertragen und die meisten von ihnen riefen deutliche Antikörperantworten hervor, sodass wir ein **Panel neuer mAbs für künftige passive Immunisierungsstudien** erstellen konnten. Anschließend kombinierte ich die zwei immunogensten Peptide aus jeder der vier Hauptdomänen von TDP-43, um ein induzierbares, aggressives ALS-Mausmodell (rNLS8) in einem präventiven Ansatz aktiv zu immunisieren. In Übereinstimmung mit den initialen Ergebnissen konnte ich **für alle Peptidkombinationen antigenspezifische Antikörperantworten** nachweisen. Unerwarteterweise verursachten die beiden hoch immunogenen N-terminalen Peptide eine Mausstamm-spezifische, akute Letalität, was ihre weitere Verwendung verhinderte. Innerhalb weniger Wochen nach Transgeninduktion entwickeln rNLS8-Mäuse ALS/FTD-ähnliche Merkmale wie Körpergewichtsverlust, phosphorylierte TDP-43-Aggregate, Neuroinflammation, transkriptomische Veränderungen sowie neuroaxonale Schäden (gemessen an erhöhten Konzentrationen der leichten Kette des Neurofilaments, *engl.* NfL). Während die meisten Peptidkonjugate keine Wirkung zeigten, **reduzierten Epitope in der C-terminalen Domäne von TDP-43 die NfL-Spiegel oder verbesserten die transkriptomischen Veränderungen leicht**.

Darüber hinaus habe ich verschiedene *In-vitro*-Assays verwendet, um die Wirkungen der neuen mAbs auf krankheitsrelevante Prozesse zu untersuchen. **Nur solche mAbs, die gegen die C-terminale Domäne gerichtet sind, unterdrückten signifikant die**

Phasentrennung, Aggregation sowie Aggregataufnahme in neuronenähnliche Zellen. Dies steht im Einklang mit den positiven *In-vivo*-Effekten, wenn die C-terminale Region durch aktive Immunisierung adressiert wird (Publikation II).

Insgesamt unterstreicht meine hier vorgestellte Arbeit die Beeinträchtigung des Proteasoms als einen zentralen Pathomechanismus bei ALS/FTD und hebt bisher ungenutzte aktive sowie potentiell passive Immunisierungen, die auf die C-terminale Domäne von TDP-43 abzielen, als vielversprechende therapeutische Möglichkeiten zur Bekämpfung dieser Erkrankungen hervor.

Summary

The two fatal neurodegenerative diseases, amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), are considered to be at the extreme ends of a continuous disease spectrum due to their highly overlapping clinical, genetic, and pathological features. One of the most striking commonalities is the presence of characteristic neuronal cytoplasmic inclusions containing TDP-43, which are detected in almost all ALS cases as well as in about half of FTD patients.

TDP-43 is a predominantly nuclear RNA-binding protein that is critically involved in splicing and consists of a folded N-terminal and a largely unstructured C-terminal domain separated by two RNA recognition motifs (RRM1 & RRM2). However, in ALS and FTD, TDP-43 is mislocalized from the nucleus and aggregates in the cytoplasm of neurons and glia, suggesting a dual loss of nuclear function and cytoplasmic gain-of-function toxicity. TDP-43 within inclusions is hyperphosphorylated, ubiquitinated, and often cleaved into C-terminal fragments (CTFs). As TDP-43-positive deposits correlate strongly with neurodegeneration in ALS/FTD, the study of their formation, structure, and neurotoxic mechanisms is of great importance for a deeper understanding of disease pathogenesis and may open up new therapeutic options.

A growing body of evidence indicates that TDP-43 can partition into liquid-like cellular compartments that form through a process known as phase separation. Under pathological conditions, phase-separated TDP-43 may transition into solid inclusions, presumably through intermediate states. The ultrastructure of aggregated TDP-43 has long been debated, but recent data have revealed that, at least in end-stage disease, it adopts an amyloid-like conformation typical of proteins involved in neurodegenerative diseases.

Given the importance of TDP-43 inclusions in ALS and FTD, in the first project of this thesis, I analyzed the **aggregation and toxicity mechanisms of the most frequently detected CTF, the aggregation-prone "TDP-25"** (a TDP-43 fragment with a size of 25 kDa). To this end, I established primary neuron culture models expressing wild-type TDP-25 or a TDP-25 variant containing multiple independently pathogenic ALS mutations, and compared the properties of the resulting inclusions with those of known liquid- and solid-like cellular compartments. While I found the **TDP-25 aggregates to have gel-like biophysical properties**, a collaborative investigation of their *in situ* ultrastructure by cryo-electron tomography revealed that they are amorphous. Importantly, **TDP-25 inclusions sequester 26S proteasomes**, virtually all of which are locked in a substrate processing state, implying their **proteolytic inactivity**.

Consistent with the sequestration of functionally compromised proteasomes, I observed that **cellular proteostasis was impaired in TDP-25 expressing cells**, which was **exacerbated by ALS-causing mutations** (publication I).

As with most other neurodegenerative diseases, effective, let alone curative, therapies for ALS/FTD are sorely lacking. However, targeting aggregation-prone proteins via active or passive vaccination represents a promising therapeutic approach, as recently evidenced by the striking clearance of amyloid β (Aβ) plaques and clinical improvement in Alzheimer's disease patients following treatment with potent Aβ monoclonal antibodies (mAbs).

Based on these findings and the encouraging results of single TDP-43 antibody therapies in mouse models, I conducted a **systematic search for safe and effective epitopes in TDP-43 using active vaccination**. For this purpose, I selected 15 peptide antigens with high predicted antigenicity scores that collectively map the entire TDP-43 protein. When used to immunize wild-type mice, the ovalbumin-conjugated peptides were well tolerated and most induced detectable antibody responses, allowing us to generate a **panel of novel mAbs for future passive vaccination studies**. Next, I combined the two most immunogenic peptides from each of the four major domains of TDP-43 to actively immunize an inducible, aggressive ALS mouse model (rNLS8) in a preventive approach. In line with the initial findings, I detected **antigen-specific antibody responses for all peptide combinations**. Unexpectedly, the two highly antigenic N-terminal peptides caused acute lethality in a strain-specific manner, thus precluding their further use. Within weeks after transgene induction, rNLS8 mice develop ALS/FTD-like features such as body weight loss, phosphorylated TDP-43 aggregates, neuroinflammation, transcriptomic changes, and neuroaxonal damage (as assessed by elevated levels of neurofilament light chain, NfL). While most peptide conjugates were ineffective, **targeting epitopes in the C-terminal domain of TDP-43 reduced NfL levels or slightly ameliorated transcriptomic alterations**.

Furthermore, I used different *in vitro* assays to study the impact of novel mAbs on disease-relevant processes. Only **mAbs directed against the C-terminal domain markedly suppressed phase separation, aggregation, and aggregate uptake in neuron-like cells**, resonating with the beneficial *in vivo* effects when addressing this region via active immunization (publication II).

In conclusion, my work presented here emphasizes proteasome impairment as a cardinal pathomechanism in ALS/FTD and highlights previously unexploited active and potentially passive vaccination targeting the C-terminal domain of TDP-43 as promising therapeutic avenues to combat these diseases.

I. Introduction

1. The ALS/FTD disease spectrum

1.1. Clinical manifestations

1.1.1. ALS

Amyotrophic lateral sclerosis (ALS), more commonly referred to as Lou Gehrig's disease in the United States, is a multisystemic and currently incurable neurological disorder marked by progredient loss of upper and lower motor neurons (UMNs, LMNs) in the central nervous system (CNS). While the cell bodies of motor neurons are localized in the motor cortex (UMNs), brainstem and spinal cord (LMNs), their long axons project either directly or indirectly to peripheral muscles to innervate them. This neuro-muscular connection forms the basis of all (in)voluntary movement in humans, and the progressive degeneration of motor neurons in patients with ALS consequentially results in spasticity, hyperreflexia (due to UMN loss), as well as fasciculations, muscle weakness and atrophy (due to LMN loss) (van Es *et al.*, 2017).

The first symptoms typically appear in the fifth decade of life (van Es *et al.*, 2017). However, the heterogeneous age of onset, clinical manifestations, and progression rates of ALS complicate and often delay clinical diagnosis by approximately one year (Richards *et al.*, 2020). More than half of ALS patients have pure motor involvement (classical ALS). Depending on whether the degeneration begins in the cervical and lumbar regions of the spinal cord or in the brainstem, the initial symptoms may vary: while 2/3 of cases present with spinal-onset disease, usually manifesting as unilateral weakness of the upper or lower limb muscles, the remaining 1/3 of bulbar-onset cases suffer from spastic dysarthria and dysphagia due to weakness of the pharyngeal, tongue, and facial muscles (van Es *et al.*, 2017; Feldman *et al.*, 2022). Bulbar-onset patients generally have a worse prognosis, as do the very few cases that present with respiratory onset (Chiò *et al.*, 2011; van Es *et al.*, 2017). Rarer variants of ALS with exclusive upper or lower motor neuron involvement include primary lateral sclerosis or flail arm, flail leg, and progressive muscular atrophy, respectively (Feldman *et al.*, 2022). After focal onset, the disease gradually spreads to other regions of the body (Ravits & La Spada, 2009), eventually affecting the diaphragm and causing death from respiratory failure 3-4 years after the onset of symptoms (van Es *et al.*, 2017). In ventilated patients, pneumonia is a life-threatening complication (Burkhardt *et al.*, 2017). Overall, ALS is the most common motor neuron disease (MND) in adults, with an average global prevalence of ~4.4 per 100,000 individuals (Xu *et al.*, 2020) and a lifetime risk of ~1/350 for men and ~1/440 for women (Ryan *et al.*, 2019). As with other

neurodegenerative diseases (Dorsey *et al.*, 2007; Hebert *et al.*, 2013), the number of ALS cases is predicted to increase in the upcoming years (Arthur *et al.*, 2016).

1.1.2. FTD

The umbrella term frontotemporal dementia (FTD) encompasses several clinically diverse syndromes that primarily affect patients' behavior or language functions. FTD accounts for 5-15% of all cases of dementia and, unlike the far more prevalent Alzheimer's disease (AD), mostly develops in the presenium (age <65 years) (Rademakers *et al.*, 2012). The estimated lifetime risk is ~1/750, whereas the overall population prevalence of 11 per 100,000 individuals slightly exceeds that of ALS (Coyle-Gilchrist *et al.*, 2016). Depending on which region of the frontal and temporal lobes degenerates predominantly, FTD is clinically divided into behavioral variant FTD (bvFTD) and primary progressive aphasia (PPA), with the latter including a semantic variant (svPPA) and a non-fluent variant (nfvPPA) (Sivasathiaseelan *et al.*, 2019).

Among these subtypes, bvFTD is the most common and hereditary form (Rohrer *et al.*, 2009). It regularly manifests with profound personality changes and progredient executive dysfunction, such as apathy, compulsive routines, reduced empathy, altered eating behavior, or loss of social/emotional awareness, while visuospatial functions and episodic memory are usually preserved (Rascovsky *et al.*, 2011; Sivasathiaseelan *et al.*, 2019).

Beyond bvFTD, asymmetric (usually left hemispheric) atrophy in specific frontal or temporal areas of the language network represents the neuroanatomical correlate of PPA. It causes patients to suffer from advancing deterioration of language abilities and verbal expression (Sivasathiaseelan *et al.*, 2019). The semantic variant (also known as semantic dementia) is primarily characterized by a loss of vocabulary, which results in difficulty naming familiar objects and comprehending individual words. In the non-fluent or agrammatic variant, speech production and sentence formation are impaired, leading to slurred speech and progressive grammar deficits. A third subtype of PPA, the logopenic variant (lvPPA), is most commonly associated with AD neuropathology (Mesulam *et al.*, 2008; Rabinovici *et al.*, 2008) and exhibits word-finding pauses as well as problems recalling sentences and phrases owing to defects in the verbal working memory (Gorno-Tempini *et al.*, 2008). Although often distinct at onset, clinical variants of FTD may converge during disease progression as larger, initially uninvolved CNS areas become affected (Kertesz *et al.*, 2005).

On average, people with FTD have a life expectancy of 6-11 years from symptom onset (Bang *et al.*, 2015), with semantic dementia sometimes reported to have a longer survival time (Roberson *et al.*, 2005).

1.1.3. ALS/FTD

A growing body of evidence indicates that, in addition to the classical and isolated presentations of ALS and FTD, a substantial proportion of affected individuals exhibit clinical features of both disorders. In fact, up to 50% of patients diagnosed with ALS show signs of FTD and have cognitive (ALSci, ALS with cognitive impairment), behavioral (ALSbi, ALS with behavioral impairment), or combined (ALScbi) symptoms (Strong *et al.*, 2009; van Es *et al.*, 2017). Moreover, 10-15% of patients even meet the full diagnostic criteria for FTD (ALS-FTD), most of whom develop bvFTD (Phukan *et al.*, 2012). Conversely, mild motor symptoms are observed in ~30% of FTD patients, while one in eight FTD cases develops manifest ALS (Lomen-Hoerth *et al.*, 2002; Burrell *et al.*, 2011). The co-occurrence of motor deficits with behavioral and cognitive symptoms not only requires additional care management, but is also associated with a more aggressive disease course and shorter survival (Hodges *et al.*, 2003; Olney *et al.*, 2005).

The evident clinical overlap between ALS and FTD has led to the concept that these disorders should not be regarded as two separate, unrelated entities, but rather as opposite ends of a broad disease continuum along which diverse clinical presentations exist. This notion is strongly supported by the genetic and neuropathological characteristics of both diseases, as discussed in the following two sections.

1.2. Genetics

Based on the familial occurrence of the disease, patients of the ALS/FTD spectrum are categorized as either sporadic (sALS or sFTD, without a clear family history) or familial (fALS or fFTD). While up to 95% of ALS cases are considered sporadic and only 5-10% are of the familial form (Byrne *et al.*, 2011), 30-40% of FTD patients have a family history of dementia (Rohrer *et al.*, 2009; Greaves & Rohrer, 2019).

With advances in genomic sequencing technologies, familial clusters of ALS and FTD have been attributed to monogenic mutations, most of which are inherited in an autosomal dominant manner. Importantly, pathogenic gene variants are also detected in ~10% of seemingly sporadic ALS and FTD cases (Turner *et al.*, 2017). The first ALS gene identified was *SOD1*, whose mutations are highly penetrant and account for ~20% of fALS (Rosen *et al.*, 1993; Zou *et al.*, 2017). While *SOD1* (superoxide dismutase 1) normally encodes an antioxidant enzyme (Fridovich, 1995; Zelko *et al.*, 2002), its ALS-associated missense mutations result in a misfolded and aggregation-prone protein that is thought to exert toxic gain-of-function effects (Gurney *et al.*, 1994; Shibata *et al.*, 1996; Bruijn *et al.*, 1998). Whereas *SOD1* variants are almost exclusively linked to pure ALS, the two most commonly affected genes in FTD but not ALS are *MAPT* (microtubule-associated protein tau) and *GRN* (progranulin) (Bennion Callister & Pickering-Brown, 2014), each responsible for 5-20% of all fFTD cases (Rademakers *et al.*, 2004; Gijselinck *et al.*, 2008).

FTD-causing mutations in the *MAPT* gene (Hutton *et al.*, 1998; Poorkaj *et al.*, 1998; Spillantini *et al.*, 1998) lead to neuronal aggregation of the encoded protein, tau, and heterozygous loss-of-function (LOF) mutations in *GRN* result in null alleles, causing FTD via haploinsufficiency (Baker *et al.*, 2006; Cruts *et al.*, 2006). Although certain genetic mutations are found exclusively in ALS or FTD, many other genes have been causally linked to both, with the same mutations sometimes leading to strikingly different clinical presentations within affected pedigrees. This observation reinforces the notion that ALS and FTD represent two extreme poles of a continuous disease spectrum.

Among such gene variants, a first intronic hexanucleotide repeat expansion of GGGGCC (G_4C_2), located between two alternative start exons of the *C9orf72* (chromosome 9 open reading frame 72) gene, has emerged as the most frequent genetic cause of both familial and sporadic forms of pure and mixed ALS/FTD (C9-ALS/FTD). In people of European descent, the *C9orf72* mutation affects 10% of all patients, including 40% of fALS, 25% of fFTD, and 80% of fALS-FTD cases (DeJesus-Hernandez *et al.*, 2011; Renton *et al.*, 2011; Smeyers *et al.*, 2021), but is uncommon in Asian populations (Majounie *et al.*, 2012). While the G_4C_2 repeat size is generally below 30 in healthy individuals, it increases to several hundred or even thousands in heterozygous mutation carriers (DeJesus-Hernandez *et al.*, 2011). Apart from the previously discussed variants responsible for the majority of genetic ALS and FTD cases, several other disease-associated genes have been uncovered, each of which is affected in no more than 5% of familial cases and even fewer sporadic cases. For example, *FUS* (fused in sarcoma) mutations underlie an aggressive, juvenile form of ALS (Kwiatkowski *et al.*, 2009; Vance *et al.*, 2009; Bäumer *et al.*, 2010), but appear to be absent in isolated FTD, even though the FUS protein aggregates in both diseases (Kwiatkowski *et al.*, 2009; Neumann, Rademakers*, et al.*, 2009; Vance *et al.*, 2009).

A seminal discovery was the identification of rare ALS/FTD-causing missense mutations in *TARDBP* (TAR DNA binding protein; Kabashi *et al.*, 2008; Sreedharan *et al.*, 2008). Since the *TARDBP* gene encodes TDP-43, the protein found aggregated in a large number of ALS and FTD patients (*see next section*), the existence of disease-causing gene variants implies a pivotal role for TDP-43 in the pathogenesis of these diseases. Following an autosomal dominant inheritance pattern (Rutherford *et al.*, 2008), *TARDBP* mutations are most prevalent in fALS (~3% of cases), but are also found in sALS (~1.5%), ALS/FTD, and, although extremely uncommon, in pure FTD (Buratti, 2015). Importantly, the >50 identified point mutations are predominantly located in the C-terminal region of TDP-43 and their effects have been extensively studied *in vitro* and *in vivo*. While no consensus pathomechanism can be delineated, several functional consequences of these variants are discussed, including an increased tendency to aggregate as well as altered protein stability, subcellular localization, and protein-protein interactions (Buratti, 2015). Many of the more than 40 genes causally linked to the ALS/FTD spectrum to date cluster

into key molecular pathways known to be affected in disease (Nguyen *et al.*, 2018). For instance, disease-associated variants in *TARDBP* and *FUS*, but also in *TIA1* (T-cell-restricted intracellular antigen 1; Mackenzie *et al.*, 2017), *MATR3* (matrin 3; Johnson *et al.*, 2014), *hnRNPA1*, and *hnRNPA2B1* (heterogeneous nuclear ribonucleoprotein A1/A2B1; Kim *et al.*, 2013) perturb different steps of cellular RNA metabolism.

Moreover, pathogenic mutations in *C9orf72*, *TBK1* (TANK binding kinase 1; Cirulli *et al.*, 2015; Freischmidt *et al.*, 2015), *OPTN* (optineurin; Maruyama *et al.*, 2010), *UBQLN2* (ubiquilin 2; Deng *et al.*, 2011), *VCP* (valosin containing protein; Watts *et al.*, 2004; Johnson *et al.*, 2010), *SQSTM1* (sequestosome 1/p62; Fecto *et al.*, 2011), *CHMP2B* (charged multivesicular body protein 2B; Skibinski *et al.*, 2005), and *CCNF* (cyclin F; Williams *et al.*, 2016) impair protein clearance by interfering with autophagy and the ubiquitin-proteasome system (UPS). Genetic variants in other pathways result in mitochondrial dysfunction or impaired cytoskeletal dynamics and axonal transport.

In addition to the causative mutations, several genes modify the risk of developing ALS or FTD, of which *TMEM106B* (transmembrane protein 106B) is an important example. Single nucleotide polymorphisms (SNPs) in the coding and, more commonly, non-coding regions of *TMEM106B* greatly influence the risk of FTD, especially in heterozygous *GRN* mutation carriers (Van Deerlin *et al.*, 2010), but the underlying molecular mechanisms remain unclear.

Over the past 30 years, the discovery of genes associated with ALS and FTD has not only revealed common pathophysiological pathways, but has also paved the way for novel therapeutic interventions, some of which are currently entering the clinic. The list of established ALS/FTD genes continues to grow, accelerated by more accessible, cost-effective, and sophisticated sequencing methods. The ever-increasing use of artificial intelligence will further help to deepen the analysis of massive datasets, as recently exemplified by the use of machine learning algorithms to identify structural variants in risk genes for Lewy body dementia and FTD/ALS (Kaivola *et al.*, 2023).

1.3. Neuropathology

Proteinaceous deposits detected in post-mortem CNS tissue are the molecular pathological signatures of various neurodegenerative disorders, including ALS and FTD, and explain why such diseases are termed “proteinopathies”. These proteinopathies are categorized according to the principal protein constituents that accumulate in detergent-resistant, extra-, or intracellular inclusions. In a landmark discovery in 2006, ALS and FTD, whose neuropathological correlate is called frontotemporal lobar degeneration (FTLD), were both found to be associated with inclusions that are immunopositive for the ubiquitously expressed DNA/RNA-binding protein TDP-43 (Arai *et al.*, 2006; Neumann *et al.*, 2006). Over the years, TDP-43 has been found aggregated within neuronal and glial

inclusions in almost all ALS cases (~97%, ALS-TDP) and in about half of all FTD patients (FTLD-TDP), classifying these diseases as TDP-43 proteinopathies (Ling *et al.*, 2013). In addition to the profound clinical and genetic overlap between ALS and FTD, the presence of TDP-43 pathology represents another crucial piece of the puzzle in completing the full picture of a disease continuum.

The affected CNS areas, these are first and foremost the motor cortex, brainstem, and anterior horn of the spinal cord in ALS as well as the frontotemporal cortex and dentate granule cells of the hippocampus in FTD, show p62-positive inclusions of ubiquitinated and hyperphosphorylated TDP-43 (Arai *et al.*, 2006; Neumann *et al.*, 2006; Hasegawa *et al.*, 2008; Neumann, Kwong*, et al.*, 2009; Mackenzie & Neumann, 2016). These deposits can appear as cytoplasmic or neuritic, less frequently nuclear, inclusions with compact round, skein-like, or granular morphology (Neumann *et al.*, 2006; Davidson *et al.*, 2007; Mori *et al.*, 2008; Mackenzie *et al.*, 2010). Phosphorylation in the C-terminal region of TDP-43, particularly at serines 403/404 and 409/410, is a highly disease-specific signature and allows sensitive detection of TDP-43 inclusions in post-mortem tissue (Neumann *et al.*, 2006; Hasegawa *et al.*, 2008; Neumann, Kwong*, et al.*, 2009; Neumann *et al.*, 2020). Moreover, C-terminal fragments (CTFs) derived from the full-length TDP-43 protein, among which TDP of ~25 kDa size (TDP-25) is the most prevalent, are detected mainly in cortical brain areas of FTD and ALS patients, but to a much lesser degree in the spinal cord of the latter (Neumann *et al.*, 2006; Igaz *et al.*, 2008; Arai *et al.*, 2010; Tsuji, Nonaka*, et al.*, 2012). Cytoplasmic accumulation and aggregation of TDP-43 is associated with clearance from the nuclear compartment where it predominantly resides under physiological conditions (Ayala, Zago*, et al.*, 2008). This nuclear-to-cytoplasmic mislocalization is thought to be a central element in the pathogenesis of TDP-43 proteinopathies (Suk & Rousseaux, 2020).

Aberrant TDP-43 immunoreactivity in FTLD can be further subdivided into types A to E, depending on the morphological appearance, extent, and regional pattern of neuronal inclusions (Neumann *et al.*, 2021): FTLD-TDP type A is marked by abundant neuronal cytoplasmic inclusions (NCIs) as well as short, thick dystrophic neurites (DNs) in the upper cortical layers and manifests clinically as bvFTD or nfvPPA. FTD-causing mutations in *GRN* always lead to FTLD-TDP type A (Mackenzie *et al.*, 2006; Cairns *et al.*, 2007; Mackenzie & Neumann, 2017). A medium to large number of NCIs extending into deep cortical layers (mostly with a diffuse granular appearance) and a sparse amount of DNs characterize FTLD-TDP type B. Variants in *C9orf72* and *TBK1* can result in either FTLD-TDP type A or B (Snowden *et al.*, 2012; Koriath *et al.*, 2017). Long, thick DNs with scarce NCIs define FTLD-TDP type C, the most prevalent pathology in svPPA patients, whereas FTLD-TDP type D, so far exclusively linked to *VCP* mutations (Forman *et al.*, 2006; Neumann, Mackenzie*, et al.*, 2007), shows numerous neuronal nuclear inclusions (NNIs),

short DNs, and few NCIs. More recently, type E has been described with granulofilamentous NCIs and multiple fine-grained deposits in all layers of the neocortex (Lee *et al.*, 2017). Additionally, glial cytoplasmic inclusions (GCIs), predominantly in oligodendrocytes, are found in both FTLD-TDP and ALS-TDP (Mackenzie *et al.*, 2007; Neumann, Kwong*, et al.*, 2007).

TDP-43-negative FTLD cases mostly have tau-positive inclusions (FTLD-tau, ~45% of all FTD cases), while a minority show deposits that contain the RNA-binding protein FUS (termed FTLD-FET because other members of the FET protein family co-aggregate, ~9%) or that are solely positive for markers of the ubiquitin-proteasome system (FTLD-UPS, ~1%) (Neumann, Rademakers*, et al.*, 2009; Neumann *et al.*, 2011; Ling *et al.*, 2013).

As for ALS, those patients with pathogenic familial *SOD1* and *FUS* variants do not display TDP-43 pathology, but instead develop intracellular ubiquitinated SOD1- and FUS-positive inclusions, respectively (ALS-SOD1, 2% and ALS-FUS, <1%) (Mackenzie *et al.*, 2007; Tan *et al.*, 2007; Kwiatkowski *et al.*, 2009; Vance *et al.*, 2009).

Beyond ALS and FTD, TDP-43 pathology is also evident in several other neurodegenerative conditions. In 20-50% of AD cases, TDP-43 inclusions are detected in the limbic system (Amador-Ortiz *et al.*, 2007; Higashi *et al.*, 2007; Uryu *et al.*, 2008; Arai *et al.*, 2009), in addition to typical extracellular amyloid β (Aβ) plaques (Masters *et al.*, 1985) and intracellular tau-reactive neurofibrillary tangles (NFTs) (Grundke-Iqbal *et al.*, 1986; Kosik *et al.*, 1986; Goedert *et al.*, 1988; Wischik *et al.*, 1988). Importantly, the co-occurrence of TDP-43 pathology positively correlates with clinical severity and regional degeneration in AD (Josephs *et al.*, 2008; Tremblay *et al.*, 2011; Josephs *et al.*, 2014). Another recently described TDP-43 proteinopathy, named "limbic-predominant age-related TDP-43 encephalopathy" (LATE), occurs primarily in adults over the age of 80 and manifests with amnestic symptoms resembling AD (Nelson *et al.*, 2019). LATE neuropathology is dominated by TDP-43 inclusions in the amygdala and other limbic regions, along with reduced cortical atrophy compared to FTD and only modest Aβ and NFT burden, although AD pathology may coexist. It has been estimated that up to 20% of clinically diagnosed AD patients aged ≥ 80 years may suffer from LATE and that LATE may be 100 times more common than FTD (Nelson *et al.*, 2019), rendering it a potentially relevant topic for future TDP-43 research. Furthermore, pathological TDP-43 has also been described in Parkinson's disease ± dementia (Nakashima-Yasuda *et al.*, 2007), dementia with Lewy bodies (Higashi *et al.*, 2007; Arai *et al.*, 2009), Huntington's disease (Schwab *et al.*, 2008), and Guam Parkinson dementia complex (Hasegawa *et al.*, 2007; Geser *et al.*, 2008).

It should be noted, however, that even apparently neurologically unaffected individuals often develop some degree of neuropathological alteration with aging (Davis *et al.*, 1999; Elobeid *et al.*, 2016). Consistent with this notion, cytoplasmic inclusions of phosphorylated

TDP-43 have been reported in up to 30% of apparently healthy individuals aged 65 years or older (Geser *et al.*, 2010; Arnold *et al.*, 2013).

Finally, besides abnormal TDP-43 immunoreactivity, C9-ALS/FTD patients share additional unique neuropathological features. The massively expanded intronic hexanucleotide repeat in the *C9orf72* gene is bidirectionally transcribed into sense and antisense transcripts which accumulate as mostly nuclear RNA foci in neurons (DeJesus-Hernandez *et al.*, 2011; Gendron *et al.*, 2013; Lagier-Tourenne *et al.*, 2013; Mizielinska *et al.*, 2013; Mori, Weng*, et al.*, 2013). Moreover, through the unconventional process of repeat-associated non-AUG (RAN) translation (Zu *et al.*, 2011), these repetitive RNA transcripts give rise to five distinct dipeptide repeat (DPR) proteins – poly-GA (glycine-alanine), poly-GP (glycine-proline), poly-GR (glycine-arginine), poly-PR (proline-arginine), and poly-PA (proline-alanine) – that aggregate into cytoplasmic inclusions (Ash *et al.*, 2013; Gendron *et al.*, 2013; Mori, Arzberger*, et al.*, 2013; Mori, Weng*, et al.*, 2013; Zu *et al.*, 2013). Both RNA foci and DPR proteins have been demonstrated to exert toxic gain-of-functions, such as sequestration of critical cellular proteins, which may consequently promote TDP-43 pathology (Gitler & Tsuiji, 2016).

1.4. Current treatment options

To date, treatment options for ALS remain scarce, with only three, at best moderately effective, drugs approved since the disease was first described more than 150 years ago. Riluzole, an anti-glutamatergic compound thought to reduce excitotoxicity (Malgouris *et al.*, 1989; Kretschmer *et al.*, 1998; S. J. Wang *et al.*, 2004), is currently the only drug approved in the European Union and has been reported to extend median survival by 2-3 months (Bensimon *et al.*, 1994; Lacomblez *et al.*, 1996; Bensimon *et al.*, 2002; Miller *et al.*, 2012). However, the clinical potential of riluzole may have been underestimated, as recent data suggest a survival benefit of up to 19 months upon treatment (Andrews *et al.*, 2020). Edaravone, a free-radical scavenger that counteracts oxidative stress in cerebral ischemia (Abe *et al.*, 1988), has not yet been shown to extend survival, but to reduce functional decline in a well-defined subset of ALS patients (Koji *et al.*, 2017). This has allowed market access in several countries, including Japan and the United States, but not in the European Union. Nevertheless, the clinical utility of edaravone in broader populations remains questionable (Lunetta *et al.*, 2020; Witzel *et al.*, 2022). The most recent drug approved by the Food and Drug Administration (FDA) is AMX0035, a combination of the two small molecules taurursodiol and sodium phenylbutyrate, which is thought to alleviate mitochondrial dysfunction and endoplasmic reticulum (ER) stress (Paganoni *et al.*, 2020). Initial clinical trials indicated a slowing of disease progression and a 6.5-month increase in survival (Paganoni *et al.*, 2020; Paganoni *et al.*, 2021). In addition to pharmacotherapy, progressive body weight loss due to chewing and swallowing

difficulties often requires nutritional support (e.g., via percutaneous endoscopic gastrostomy), while respiratory insufficiency demands (non-invasive) ventilation. Both interventions have been reported to prolong survival in ALS patients (Spataro *et al.*, 2011; Andersen *et al.*, 2012).

For FTD, no disease-modifying medication is currently available, making the situation as unsatisfactory as for ALS. Symptomatic treatment of the diverse clinical presentations relies on the off-label use of drugs approved for other neurological disorders. Supported by reports of serotoninergic deficiency in FTD (Murley & Rowe, 2018), selective serotonin reuptake inhibitors, a widely used class of antidepressants, appear to improve behavioral symptoms, while being well tolerated (Hughes *et al.*, 2015). Trazodone, an antidepressant with agonistic and antagonistic effects on different serotonin receptors, has likewise been shown to alleviate behavioral, but not cognitive symptoms in FTD patients (Lebert *et al.*, 2004). Although antipsychotics can improve agitation and psychosis (Moretti *et al.*, 2003), they should be prescribed with caution due to increased mortality and extrapyramidal side effects to which FTD patients are especially susceptible (Pijnenburg *et al.*, 2003). The therapeutic benefit of dopaminergic drugs such as bromocriptine for the language variant of FTD (Reed *et al.*, 2004) or carbidopa/levodopa to treat Parkinsonian symptoms (Chow & Mendez, 2002) remains controversial. Acetylcholinesterase inhibitors and the NMDA receptor inhibitor memantine, all routinely used to treat mild cognitive impairment or AD, failed to slow cognitive decline in FTD and even had adverse effects (Mendez *et al.*, 2007). Overall, evidence for off-label medications is limited, and nonpharmacologic interventions such as speech and occupational therapy add to the sparse treatment options for FTD.

Meanwhile, some genetic forms of ALS/FTD have been therapeutically targeted using antisense oligonucleotides (ASOs). ASOs are short, synthetic DNA sequences that selectively bind to (pre-)mRNAs to induce their degradation via the endonuclease RNAse H or to modulate alternative splicing by steric blockade (Bennett, 2019). Through these mechanisms, they can both suppress the expression of unwanted or toxic proteins and correct splicing defects to restore normal gene expression. In a Phase III study, tofersen, an ASO directed against both wild-type and mutant *SOD1* mRNA, demonstrated safety and reduced cerebrospinal fluid (CSF) levels of SOD1 and neurofilament light chain (NfL), the latter being a component of the axonal cytoskeleton and now routinely used as a biomarker showing elevated levels in ALS/FTD biofluids (Verde *et al.*, 2021). Based on these findings, tofersen received accelerated FDA approval for the treatment of ALS, even though the trial did not statistically meet the primary clinical endpoints (Miller *et al.*, 2022; Blair, 2023). Equally promising is the development of ulefnersen, formerly known as jacifusen, which targets the P525L mutant *FUS* associated with aggressive early-onset ALS and has shown improvements in clinical and pathological parameters in compassionate use cases (Korobeynikov *et al.*, 2022). Ulefnersen is currently being

evaluated in a Phase III clinical trial. In contrast, further development of two independent ASOs directed against the sense-strand mediated RNA and DPR protein toxicity in *C9orf72* ALS/FTD was discontinued after Phase I/II trials revealed no improvement or even worsening of clinical outcomes (Wave Life Sciences, 23 May 2023; Biogen & Ionis Pharmaceuticals, 28 March 2022). However, antisense-targeting oligonucleotides, which have not yet been clinically tested, may perform better (Rothstein *et al.*, 2023).
While the efficacy of some of these ASO therapies is encouraging and demonstrates that the disease course of ALS/FTD can be significantly improved, these interventions are relevant for only a small proportion of patients. The vast majority of cases do not have a causative gene variant, so there remains an urgent need for adequate treatments. Given the success of lowering disease-causing proteins with ASO therapy, strategies to modify pathological TDP-43 appear to be an attractive approach for patients with underlying TDP-43 proteinopathy.

2. TDP-43 as the central protein in ALS/FTD

2.1. TDP-43 structure

As outlined in the previous sections, TDP-43 plays a central role in the pathogenesis of ALS and FTD. Transactive response (TAR) DNA-binding protein of 43 kDa, or TDP-43 for short, is an essential 414 amino acid long protein with strong evolutionary conservation regarding sequence, structure, and function (H. Y. Wang *et al.*, 2004; Ayala *et al.*, 2005; Romano *et al.*, 2014). In humans, the TDP-43 protein is encoded by *TARDBP*, a six-exon gene located on chromosome 1 (H. Y. Wang *et al.*, 2004).
Structurally, TDP-43 consists of four major functional domains: a well-folded N-terminal domain (NTD), two highly conserved RNA recognition motifs (RRM1 and RRM2), and an unstructured glycine-rich C-terminal domain (CTD) (François-Moutal *et al.*, 2019) (**Figure 1**).
Multiple independent studies have reported that the N-terminal region (amino acids, aa 1-100) reversibly homo-dimerizes or -oligomerizes, which appears to be crucial for proper physiological functions of TDP-43, such as splicing regulation (Shiina *et al.*, 2010; Chang *et al.*, 2012; Wang *et al.*, 2013; Y. J. Zhang *et al.*, 2013; Afroz *et al.*, 2017; Jiang *et al.*, 2017; Mompeán *et al.*, 2017; Wang *et al.*, 2018). While the NTD has been shown to be required for the toxic aggregation of TDP-43 *in vitro* and *in vivo* (Y. J. Zhang *et al.*, 2013; Sasaguri *et al.*, 2016), it remains disputed whether its self-assembly promotes or inhibits the pathological aggregation of the full-length protein (Y. J. Zhang *et al.*, 2013; Afroz *et al.*, 2017; Jiang *et al.*, 2017). However, monomeric TDP-43 that is unable to N-terminally multimerize due to the insertion of mutations has recently been demonstrated to induce

TDP-43 insolubility and further pathology (Afroz *et al.*, 2017; Oiwa *et al.*, 2023). These findings resonate with an aggregation-preventing effect of the multimerized (presumably tetrameric) NTD (Afroz *et al.*, 2017; Jiang *et al.*, 2017). Notably, the NTD is involved in sequestration of full-length TDP-43 into inclusions (Budini *et al.*, 2015; Romano *et al.*, 2015). Cellular studies have shown that the first ten N-terminal residues of TDP-43 are crucial for its functions, as their loss disrupts the proper folding, dimerization, and exon-skipping activity of TDP-43 (Y. J. Zhang *et al.*, 2013).

The N-terminal region also contains a conventional bipartite nuclear localization signal (NLS, aa 82-98) that mediates active nuclear import of TDP-43 through interaction with importin-α/β and whose disruption leads to cytoplasmic mislocalization and aggregation of TDP-43 (Winton *et al.*, 2008; Barmada *et al.*, 2010; Nishimura *et al.*, 2010).

As a member of the large family of heterogeneous nuclear ribonucleoproteins (hnRNPs), TDP-43 interacts with nucleic acids primarily through its tandem RRM domains (RRM1: aa 106-176 and RRM2: aa 191-262) (Buratti & Baralle, 2001; Ayala *et al.*, 2005; Lukavsky *et al.*, 2013; Kuo *et al.*, 2014). Both RRM domains cooperatively mediate the preferential binding of TDP-43 to (TG)/(UG)-rich sequences within DNA/RNA molecules (Ayala *et al.*, 2005; Kuo *et al.*, 2009; Buratti *et al.*, 2010; Sephton *et al.*, 2011; Lukavsky *et al.*, 2013; Kuo *et al.*, 2014). A previously proposed nuclear export signal (NES, aa 239-249) within RRM2 (Ayala, Zago*, et al.*, 2008; Winton *et al.*, 2008) could not be validated to have an effect on TDP-43 localization (Archbold *et al.*, 2018; Ederle *et al.*, 2018; Pinarbasi *et al.*, 2018). Instead, passive diffusion controlled by RNA binding likely governs TDP-43 nuclear export (Ederle *et al.*, 2018; Pinarbasi *et al.*, 2018; Duan *et al.*, 2022; Dos Passos *et al.*, 2023).

Of the four functional domains within the TDP-43 protein, the approximately 140-residue spanning CTD (aa 274-414) has probably received the most attention to date as it harbors the majority of disease-causing mutations and many disease-specific post-translational modification (PTM) sites (Buratti, 2015; Sternburg *et al.*, 2022). Unlike the well-structured NTD and RRM domains, the C-terminal region is characterized by high intrinsic disorder and low sequence complexity (relative overrepresentation of glycine (G), serine (S), glutamine (Q), and asparagine (N) residues), which is why it is also referred to as a low-complexity domain (LCD) or glycine-rich domain (Santamaria *et al.*, 2017). At the subdomain level, the core segment of the CTD (aa 318-369) is flanked by two intrinsically disordered regions (IDRs) (aa 274-317 and 370-414), also termed GaroS1/2 due to the abundance of glycines, serines, and aromatic residues (Mompean *et al.*, 2016). The core segment itself consists of a hydrophobic patch (aa 318-340) and a Q/N-rich region (aa 341-369) (Fuentealba *et al.*, 2010), which can adopt either helical or amyloid-like conformations (Jiang *et al.*, 2013; Mompeán *et al.*, 2014; Conicella *et al.*, 2016; Lim *et al.*, 2016; Guenther, Cao*, et al.*, 2018; Cao *et al.*, 2019).

The CTD is reminiscent of a prion-like domain (PrLD) (Alberti *et al.*, 2009), regions that confer self-templating properties involved in protein spreading and that are commonly found in RNA-binding proteins (RBPs) associated with neurodegenerative diseases (King *et al.*, 2012).The CTD is engaged in protein-protein interactions (Buratti *et al.*, 2005; D'Ambrogio *et al.*, 2009; Cassel & Reitz, 2013; Majumder *et al.*, 2016), is relevant for splicing function (Ayala *et al.*, 2005; D'Ambrogio *et al.*, 2009; Ayala *et al.*, 2011), and triggers phase separation and aggregation, both disease-linked processes that will be discussed in the next sections.

The disordered, unfolded CTD, along with the flexible linkers bridging the different domains, poses a challenge to the experimental determination of the still unresolved structure of the entire TDP-43 protein (François-Moutal *et al.*, 2019).

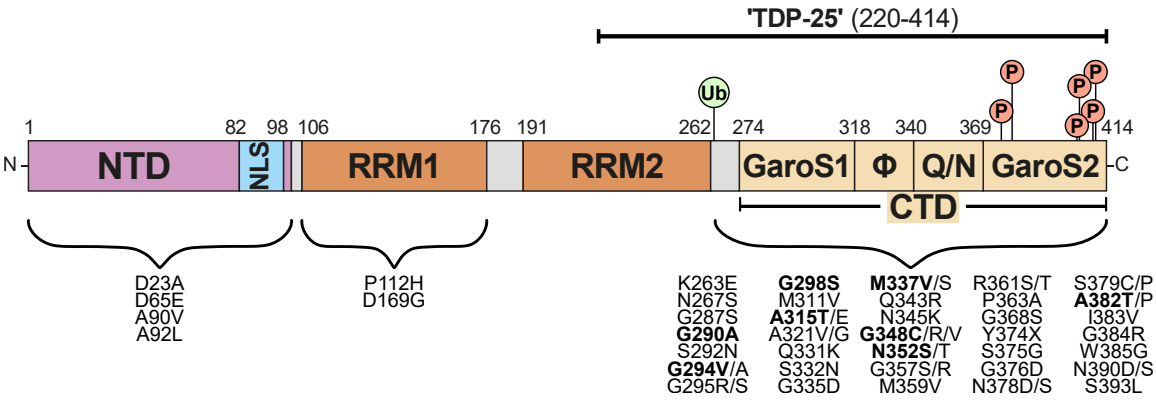

Figure 1: TDP-43 is a multi-domain hnRNP protein with a folded N-terminal region, nucleic acid binding domains, and a largely unstructured C-terminal domain (CTD) driving self-assembly. The most prominent post-translational modifications (*discussed in detail in the following sections*) include proteolytic cleavage into C-terminal fragments of ~25 kDa size ('TDP-25'), disease-specific phosphorylation (P) of serines 375, 379, 403/404, 409/410, and ubiquitination (Ub), which has been experimentally confirmed at lysine 263 in the CTD, among other sites. Most of the ALS/FTD-associated *TARDBP* mutations are concentrated in the CTD, with those relevant to this work highlighted in bold. *NTD*, N-terminal domain; *NLS*, nuclear localization signal; *RRM1/2*, RNA recognitions motifs; *GaroS1/2*, intrinsically disordered regions enriched in glycines, aromatic residues, and serines; *Φ*, hydrophobic patch; *Q/N*, glutamine- and asparagine-rich domain.

2.2. Physiological TDP-43 functions

TDP-43 is a ubiquitously expressed and abundant protein (Huang *et al.*, 2010). It has a predominant nuclear localization, but due to its ability to shuttle between the nucleus and the cytoplasm, TDP-43 is also found at 30% in the cytoplasmic compartment and to a minor extent in mitochondria (Wang *et al.*, 2002; Ayala, Zago*, et al.*, 2008; Wang *et al.*, 2016; Huang *et al.*, 2020).

Initially, TDP-43 was reported to bind to the transactive response (TAR) DNA sequence of the HIV-1 genome, thereby regulating viral gene expression (Ou *et al.*, 1995). A few years later, Buratti and colleagues demonstrated that TDP-43 also associates with UG-rich RNA and modulates pre-mRNA alternative splicing of human *CFTR* exon 9 (Buratti *et al.*, 2001). Using more global approaches, TDP-43 has been found to interact with more than 6,000 mRNA targets, many of which are critically involved in neuronal development, synaptic integrity, and neurological diseases (Polymenidou *et al.*, 2011; Sephton *et al.*, 2011; Tollervey *et al.*, 2011; Xiao *et al.*, 2011). TDP-43 preferably binds to GU/UG tandem repeats within intronic regions, 3'-untranslated regions (3'-UTRs), splice sites, or non-coding RNAs, and thus controls alternative splicing.

An important interaction of TDP-43 is with its own pre-mRNA. Through alternative splicing of an intron in the 3'-UTR, leading to nonsense-mediated decay (NMD), this negative feedback loop autoregulates and tightly maintains physiological TDP-43 levels (Ayala *et al.*, 2011; Polymenidou *et al.*, 2011; Avendano-Vazquez *et al.*, 2012). Nuclear loss of TDP-43 in model systems and disease causes abnormalities in mRNA splicing, which in turn leads to misregulation of up to thousands of genes and consequently disruption of cellular integrity (Polymenidou *et al.*, 2011; Tollervey *et al.*, 2011; Highley *et al.*, 2014; C. Yang *et al.*, 2014). A central mechanism of how TDP-43 regulates splicing events is by constitutively suppressing so-called "cryptic exons" (CEs) from being integrated into mRNA transcripts (Ling *et al.*, 2015): CEs are exon-like intronic sequences that are normally spliced out during RNA maturation. TDP-43 binds to UG dinucleotide repeats near and within CEs, preventing their incorporation into final transcripts and thus acting as a splicing repressor. However, upon nuclear loss or malfunction of TDP-43, CEs are no longer repressed from insertion into mRNA, resulting in erroneous transcripts containing in-frame or frameshift mutations, premature stop codons (leading to NMD), alternative transcription start sites, or alternative polyadenylation sites (Mehta *et al.*, 2023).

For example, the expression of *STMN2*, one of the most abundant transcripts in human motor neurons and fundamental to axonal regeneration (Mason *et al.*, 2002), is dramatically reduced upon loss of nuclear TDP-43 by incorporation of a cryptic exon containing a premature polyadenylation site and an in-frame stop codon (Klim *et al.*, 2019; Melamed *et al.*, 2019). The resulting shortened, though highly expressed transcript is predicted to yield a truncated stathmin-2 protein variant at the expense of full-length, functional stathmin-2 (Melamed *et al.*, 2019; Baughn *et al.*, 2023). In post-mortem frontal cortices, expression of the mis-spliced *STMN2* transcript is associated with FTLD-TDP, but not with other FTLD subtypes (Prudencio *et al.*, 2020). Importantly, since loss of stathmin-2 from the adult mammalian CNS induces progressive ALS-resembling motor symptoms (López-Erauskin *et al.*, 2023), restoration of stathmin-2 levels, e.g., via ASO-mediated correction of its aberrant splicing (Baughn *et al.*, 2023), provides a novel

therapeutic strategy for targeting TDP-43 proteinopathies. Another cryptic exon of strong interest is found in the *UNC13A* gene, a known major genetic risk factor for ALS (van Es *et al.*, 2009), and the TDP-43-dependent loss of the encoded protein, a critical factor for synaptic functionality (Augustin *et al.*, 1999), is likely of pathological relevance (Brown *et al.*, 2022; X. R. Ma *et al.*, 2022).

Importantly, the role of TDP-43 as a key neuronal RNA-binding protein extends far beyond the regulation of mRNA transcription and splicing, encompassing essentially all facets of RNA metabolism. This includes the regulation of mRNA stability in the cytoplasm via interaction with the 3'-UTRs of different transcripts such as *NFL* (Strong *et al.*, 2007), *HDAC6* (Fiesel *et al.*, 2010; Kim *et al.*, 2010) and *G3BP1* (McDonald *et al.*, 2011; Sidibé *et al.*, 2021). By forming ribonucleoprotein (RNP) granules through assembly with RNA and other RBPs, TDP-43 ferries synaptic transcripts along microtubules to axon terminals and dendrites for local translation. The latter is also controlled by TDP-43 (Wang *et al.*, 2008; Fallini *et al.*, 2012; Alami *et al.*, 2014; Coyne *et al.*, 2014; Nagano *et al.*, 2020).

Furthermore, TDP-43 modulates the production and maturation of non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). Regulation of miRNAs by TDP-43 can occur through direct binding to (precursor) miRNAs or through modulation of Drosha and Dicer levels, thereby affecting the miRNA pool globally (Gregory *et al.*, 2004; Kawahara & Mieda-Sato, 2012; Di Carlo *et al.*, 2013; Colombrita *et al.*, 2015). As a result, several miRNAs have been shown to be misregulated upon loss of TDP-43 (Buratti *et al.*, 2010; Z. Zhang *et al.*, 2013; Fan *et al.*, 2014; King *et al.*, 2014). Association of TDP-43 with the abundant lncRNAs *MALAT1* and *NEAT1*, both of which are involved in RNA processing steps (Clemson *et al.*, 2009; Tripathi *et al.*, 2010; Tollervey *et al.*, 2011), was found to reduce TDP-43 toxicity (Liu *et al.*, 2020; Wang *et al.*, 2020; Matsukawa *et al.*, 2021).

TDP-43 also regulates transposable elements (mainly by repressing them), and its depletion from the nucleus is accompanied by enhanced chromatin accessibility of genomic regions containing transposable elements (W. Li *et al.*, 2012; Krug *et al.*, 2017; Liu *et al.*, 2019; Romano *et al.*, 2020). Taken together, TDP-43 acts as a central regulator of RNA metabolism, and its disease-associated perturbations consequently disrupt RNA homeostasis with detrimental effects on neuronal health.

2.3. Types of TDP-43 self-assembly and their implications in disease

2.3.1. TDP-43 aggregation

Extra- and intracellular protein deposits hallmark nearly all neurodegenerative diseases and result from the accumulation of misfolded polypeptides that associate irregularly into

large assemblies known as aggregates. Aggregates are characterized by insolubility in aqueous solutions or detergents and a non-native secondary structure (Kopito, 2000).
Regarding TDP-43, early work in yeast models demonstrated that this protein is prone to aggregation, a feature that is enhanced upon the introduction of ALS-linked mutations (Johnson *et al.*, 2008; Johnson *et al.*, 2009). Ever since, numerous efforts have been made to identify the regions that drive TDP-43 aggregation, and most reports have concluded that the CTD plays a vital role in this process. While several data indicated that the C-terminal region or subdomains therein are essential and on their own sufficient to mediate aggregation and, in some cases, pathology (Guo *et al.*, 2011; Budini *et al.*, 2012; Jiang *et al.*, 2013; Mompeán *et al.*, 2014; Jiang *et al.*, 2016), others reported that the CTD in combination with the RRM2 domain is capable of forming aggregates (Johnson *et al.*, 2008; Yang *et al.*, 2010; Fallini *et al.*, 2012; Wang *et al.*, 2013). However, additional aggregation cores outside the CTD have been identified as well, including such within the RRM1 (Shodai *et al.*, 2013; Chiang *et al.*, 2016; Zacco *et al.*, 2018) and the RRM2 domains (Saini & Chauhan, 2011; Shodai *et al.*, 2012; Guenther, Ge*, et al.*, 2018; Tavella *et al.*, 2018), which may likewise contribute to TDP-43 aggregation in disease. Notably, specific binding of TDP-43 to RNA sequences has been shown to maintain its solubility and decrease its aggregation propensity (Ishiguro *et al.*, 2017; French *et al.*, 2019; Mann *et al.*, 2019; Zacco *et al.*, 2019; Rengifo-Gonzalez *et al.*, 2021). As mentioned previously, the N-terminus was demonstrated to be crucial for aggregation of full-length TDP-43 and associated toxicity (Y. J. Zhang *et al.*, 2013; Sasaguri *et al.*, 2016), but several lines of evidence indicate that N-terminal dimerization, which is known to be stabilized by RNA binding (Y. Sun *et al.*, 2014), prevents toxic TDP-43 aggregation (Afroz *et al.*, 2017; Jiang *et al.*, 2017; Miura *et al.*, 2023; Oiwa *et al.*, 2023). The aggregation behavior of TDP-43 CTFs found in disease is of particular relevance for this work and will be discussed separately below (*see section 2.3.4.*).

2.3.2. The amyloidogenic nature of TDP-43

Unraveling the (ultra)structures of misfolded, aggregated proteins in disease-characteristic inclusions is a major area of research, as it provides insights into the molecular events underlying neurodegeneration and potentially enables the (rational) design of novel therapies.
In most neurodegenerative disorders, the major protein components accumulated within the deposits adopt a conformational state termed amyloid. Amyloids consist of unbranched fibrils characterized by cross-β sheet structures: peptide β-strands, which run perpendicular to the fibril axis, stack flat on top of each other by the thousands to form β-sheets. These β-sheets are stabilized by interstrand hydrogen bonding and typically orientate parallel to each other (Sunde *et al.*, 1997; Sawaya *et al.*, 2021). The massively

layered β-sheets build up elongated protofilaments that bundle together and give rise to a (mature) fibril.

The opposing β-sheet layers frequently build adherent contacts via their side chains, so-called “steric zippers”, thereby releasing solvent molecules and increasing entropy (Sawaya *et al.*, 2021). The resulting ladder of side chains often reinforces the fibrillar structure by participating in non-covalent interactions such as van der Waals contacts, π-π stacking, or hydrogen bonding. “Steric zipper” motifs have also been described for short segments in TDP-43 RRM2 (Guenther, Ge*, et al.*, 2018). The cross-β sheet architecture confers enormous stability to the amyloids, which is reflected in their resilience to proteolysis, detergents, and chemical denaturation (Balbirnie *et al.*, 2001). Structural analysis has revealed that the amyloid core of fibril-forming protein sequences consists of comparatively short segments (ranging from a dozen to more than 100 residues) (Sawaya *et al.*, 2021), with flanking regions often forming a “fuzzy coat” surrounding it (Ulamec *et al.*, 2020).

Key methods for studying amyloids include cryo-electron microscopy (cryo-EM) and cryo-electron tomography (cryo-ET), whose technical advances have revolutionized the field by yielding the first atomic-/near-atomic-resolution structures. Since then, not only fibrils generated from recombinant or synthetic peptides have been investigated, but also those isolated from patient brain tissue. For instance, tau fibrils extracted from various tauopathies, including AD (Fitzpatrick *et al.*, 2017; Falcon, Zhang, Schweighauser*, et al.*, 2018), chronic traumatic encephalopathy (Falcon *et al.*, 2019), Pick’s disease (Falcon, Zhang, Murzin*, et al.*, 2018), and corticobasal degeneration (Zhang *et al.*, 2020) adopt distinct amyloid conformations (or polymorphs) (Shi *et al.*, 2021), which may imply the need for different therapies.

The question of whether TDP-43 in pathological deposits is of amyloid nature has led to conflicting answers. Utilizing well-established organic amyloid-binding dyes such as Congo red, fluorescent thioflavin T or S, as well as electron microscopic imaging of immunolabeled TDP-43 inclusions from ALS/FTD brain and spinal cord tissue, some studies found no evidence of amyloid properties (Cairns *et al.*, 2007; Kwong *et al.*, 2008; Johnson *et al.*, 2009). However, other groups in fact reported filaments of 10-20 nm diameter and positivity for thioflavin staining, albeit with some heterogeneity of results (Hasegawa *et al.*, 2008; Lin & Dickson, 2008; Mori *et al.*, 2008; Bigio *et al.*, 2013; Nonaka *et al.*, 2013; Robinson *et al.*, 2013).

Compelling evidence suggests that the amyloidogenic properties stem mainly from the C-terminal prion-like, low-complexity domain (**Figure 2**). Collectively, data from *in vitro* experiments indicate that (I) not only the entire CTD, but also several shorter fragments thereof can form amyloids and self-aggregate, (II) TDP-43 fibrils display structural polymorphism, (III) the sparse amyloidogenic cores outside the CTD are located in the

RRM domains and not in the NTD, (IV) essentially any subdomain of the CTD may be capable of driving fibrillization, but the double-helical hydrophobic patch and the Q/N-rich region are thought to be of particular importance, (V) no clear consensus sequence can be deduced as the minimal amyloid core.

A major breakthrough was the recent solution of the atomic structure of TDP-43 filaments isolated from post-mortem cortical brain tissue of ALS/FTLD patients (Arseni *et al.*, 2022; Arseni *et al.*, 2023). The amyloid-atypical, double spiral-shaped fold in cases with ALS/FTLD-TDP type B pathology encompasses residues 282-360 and is composed of several small β-sheets and β-turns, reminiscent of *in vitro* structures of other hnRNPs (Arseni *et al.*, 2022). The lack of deeper grooves on the surface may explain why amyloid dyes or positron emission tomography (PET) tracers have often failed in staining pathological TDP-43. In contrast, the conformation in FTLD-TDP type A is distinctly different, resembling a chevron-like shape (Arseni *et al.*, 2023). The fold, which spans ten additional residues (272-360), presumably engages a cofactor and is stabilized by a citrullinated arginine residue, underscoring the importance of PTMs for protein conformation. While both fibril types are composed of a single protofilament and do not resemble any of the TDP-43 *in vitro* structures, the disease-dependent structural polymorphism may underlie the clinical and neuropathological variability of FTLD-TDP, as has been speculated for tauopathies and synucleinopathies (Schweighauser *et al.*, 2020; Shi *et al.*, 2021).

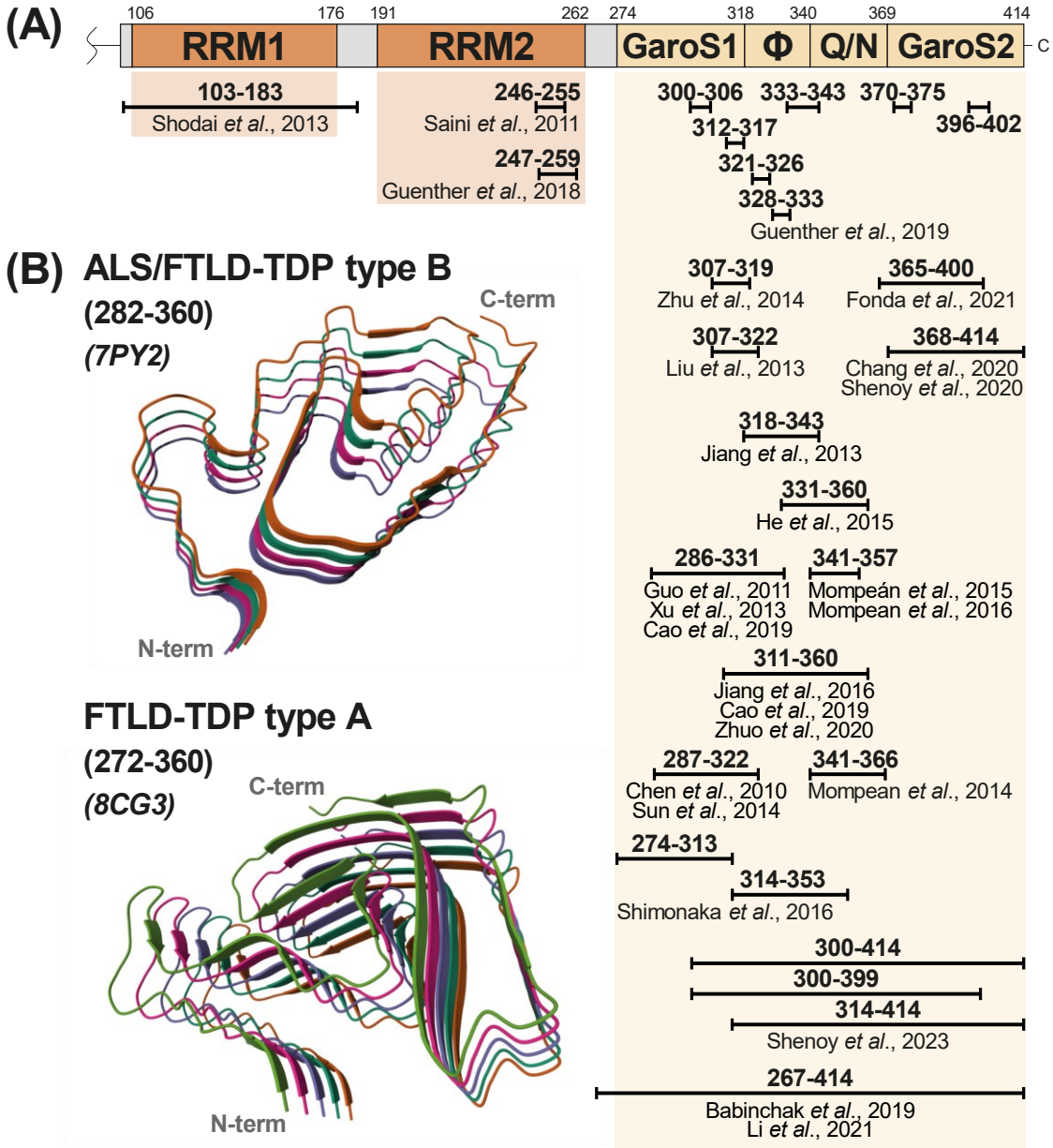

Figure 2: (A) Most of the reported amyloidogenic regions of TDP-43 are located in its CTD. *In vitro* amyloid fibrils have been derived from extremely short peptides (as few as six amino acids), but also from the entire CTD. (B) Recent structures of pathological TDP-43 amyloid filaments from ALS with type B FTLD-TDP (image from the RCSB PDB (RCSB.org) of PDB ID 7PY2, https://doi.org/10.2210/pdb7py2/pdb) (Arseni *et al.*, 2022) and type A FTLD-TDP (variant 1, image from the RCSB PDB of PDB ID 8CG3, https://doi.org/10.2210/pdb8cg3/pdb) (Arseni *et al.*, 2023) differ significantly from *in vitro* structures, but confirm the filament core resides in the TDP-43 CTD.

2.3.3. The toxic potential of TDP-43 aggregates

Aggregation of TDP-43 is generally thought to contribute to the toxicity in ALS/FTD. Consistent with this paradigm, TDP-43-positive inclusions correlate well with key clinical features and the extent of neurodegeneration in disease-affected brain regions (Geser *et*

al., 2009; Mackenzie *et al.*, 2013; Brettschneider, Arai*, et al.*, 2014), and sporadic ALS cases with an exceptionally long disease duration show only mild TDP-43 pathology (Nishihira *et al.*, 2009). Many *in vitro* and *in vivo* models support a toxic role for TDP-43 aggregates in disease. For example, delivery of purified TDP-43-positive inclusion bodies into neuron-like cells causes toxicity (Capitini *et al.*, 2014). Intracellular TDP-43 aggregation is often induced by overexpression of either wild-type, disease-mutated, or cytoplasmically mislocalized TDP-43 and is associated with profound toxicity and reduced viability (Winton *et al.*, 2008; Johnson *et al.*, 2009; Wegorzewska *et al.*, 2009; Barmada *et al.*, 2010; Wils *et al.*, 2010; Igaz *et al.*, 2011; Walker, Spiller*, et al.*, 2015). Mechanistically, aggregated proteins may acquire novel and toxic functions, e.g., by sequestering and thus reducing the functional pool of cellular components (Olzscha *et al.*, 2011; Yang & Hu, 2016). These findings suggest a toxic gain-of-function (GOF) of TDP-43 as a cardinal disease mechanism.

However, despite the high toxicity observed in mammalian overexpression models, TDP-43 inclusions are only occasionally detected (Barmada *et al.*, 2010; Walker, Spiller*, et al.*, 2015). In fact, abnormally elevated nuclear and/or cytoplasmic TDP-43 levels alone – in the absence of aggregate formation – are highly cytotoxic (Barmada *et al.*, 2010; Igaz *et al.*, 2011; R. Liu *et al.*, 2013; Yamashita *et al.*, 2014). These observations challenge the relevance of TDP-43 aggregates, while a toxic GOF due to excessive quantities and/or altered subcellular localization of TDP-43 may still be at play.

A common strategy to mimic the cytoplasmic aggregation of TDP-43 observed in ALS/FTD patients is its overexpression with a dysfunctional NLS ("ΔNLS") (Winton *et al.*, 2008). As elucidated above, this causes toxicity *in vitro* and *in vivo* (Winton *et al.*, 2008; Barmada *et al.*, 2010; Igaz *et al.*, 2011). During disease, increased redistribution of TDP-43 to the cytoplasm may result from ALS-linked gene variants (Barmada *et al.*, 2010; Kabashi *et al.*, 2010; De Marco *et al.*, 2011), elevated cellular stress (Colombrita *et al.*, 2009; Liu-Yesucevitz *et al.*, 2010; Dewey *et al.*, 2011) or impaired degradation (van Eersel *et al.*, 2011), and such abnormal cytoplasmic enrichment may eventually lead to pre-inclusions and subsequently to mature aggregates (Giordana *et al.*, 2010). In line with the general lack of nuclear immunoreactivity in inclusion-harboring cells in ALS/FTD post-mortem tissue, cytoplasmic TDP-43 aggregates have been reported to recruit endogenous, nuclear TDP-43 ('sink mechanism'), resulting in a loss of function (LOF) (Winton *et al.*, 2008; Budini *et al.*, 2012). Interestingly, sequestration of nuclear TDP-43 appears to be relevant for the toxicity of cytoplasmic TDP-43 (Y. J. Zhang *et al.*, 2013). Given the multitude of functions of TDP-43 in the nuclear compartment, such loss of TDP-43 is thought to be another fundamental disease mechanism in the pathogenesis of TDP-43 proteinopathies, in addition to the proposed GOF toxicity (Lee *et al.*, 2011). Knockdown of the TDP-43 encoding gene decreases neurite outgrowth and viability in different cell

culture models (Ayala, Misteli*, et al.*, 2008; Iguchi *et al.*, 2009; Fiesel *et al.*, 2011). Similarly, global loss of TDP-43 during embryogenesis or postnatally results in enhanced lethality (Feiguin *et al.*, 2009; Chiang *et al.*, 2010; Kraemer *et al.*, 2010; Sephton *et al.*, 2010; Wu *et al.*, 2010; Schmid *et al.*, 2013), and partial loss as well as conditional knockout in relevant tissues induces disease-resembling motor and degenerative phenotypes (Kabashi *et al.*, 2010; Wu *et al.*, 2012; Iguchi *et al.*, 2013; C. Yang *et al.*, 2014). Taken together, both abnormally high and low levels of TDP-43 are detrimental to cells, a situation that is physiologically prevented by the conserved autoregulatory feedback loop. Accumulating evidence suggests that a loss of regular TDP-43 function occurs early in the disease course (Irwin *et al.*, 2023), likely preceding inclusion formation, although gain- and loss-of-function toxicity do not necessarily develop as sequential events.

The effects of cytoplasmic TDP-43 aggregation can be studied *in vivo* using transgenic mouse models. Among the most widely used models is the “rNLS8” (regulatable NLS8) line generated by Walker and colleagues (Walker, Spiller*, et al.*, 2015). It overexpresses human TDP-43 with a disrupted NLS (hTDP-43ΔNLS) pan-neuronally in a doxycycline-controlled fashion using the neurofilament heavy chain (*NEFH*) promoter. Doxycycline supplementation in the diet enables transgene repression during critical stages of neurodevelopment. Upon removal of doxycycline, mice develop cytoplasmic ubiquitinated and phosphorylated TDP-43 inclusions in the brain and spinal cord, as well as nuclear clearance of endogenous mouse TDP-43. Thus, this model mimics both TDP-43 gain- and loss-of-function mechanisms of neurotoxicity. The rNLS8 mice exhibit progredient neuronal degeneration, muscle denervation, severe motor dysfunction, body weight loss, and premature death (Walker, Spiller*, et al.*, 2015). Remarkably, re-suppression of the *hTDP-43ΔNLS* transgene a few weeks after induction largely eliminates TDP-43 pathology and improves the phenotype even at advanced stages of the disease, implying that deposited TDP-43 can be cleared from neurons in this model.
Furthermore, rNLS8 mice recapitulate additional hallmarks of ALS/FTD, namely astrogliosis and microgliosis (Walker, Spiller*, et al.*, 2015; Spiller *et al.*, 2018; Hunter *et al.*, 2021; Swanson *et al.*, 2023). As CNS-resident glial cells, astrocytes and microglia have diverse roles in maintaining homeostasis and preserving neuronal integrity, but are also fundamentally involved in the pathogenesis of several neurodegenerative diseases, including ALS and FTD, where they can have both protective and detrimental effects (Kwon & Koh, 2020). Activated microglia have been detected in autopsy cases as well as in living ALS and FTD patients by brain PET scans (Cagnin *et al.*, 2004; Henkel *et al.*, 2004; Turner *et al.*, 2004; Corcia *et al.*, 2012), and both wild-type and pathological TDP-43 can cause a proinflammatory microglial activation (Swarup, Phaneuf, Dupre*, et al.*, 2011; Zhao *et al.*, 2015). In addition, global loss as well as aggregation or disease-specific

mutation of TDP-43 has been implicated in the reactive transformation of astrocytes (Tong *et al.*, 2013; C. Yang *et al.*, 2014; Peng *et al.*, 2020; Velebit *et al.*, 2020), and astrogliosis is evident in ALS post-mortem tissue (Schiffer *et al.*, 1996). Sustained, excessive activation of glial cells is thought to drive inflammation through multiple pathways, such as secretion of proinflammatory cytokines, ultimately leading to neuronal damage (Kempuraj *et al.*, 2016). At the same time, inflammation triggers cytoplasmic TDP-43 mislocalization in microglia and astrocytes (Correia *et al.*, 2015), which in turn may potentiate the abovementioned effects. Altogether, astro- and microgliosis are considered critical factors in TDP-43-mediated toxicity in disease.

It should be noted that in addition to macroaggregates, small misfolded or oligomerized protein species may also confer toxicity. Several lines of evidence acquired over the years, particularly from studies on Aβ, suggest that soluble oligomers may be the primary toxic species (Sengupta *et al.*, 2016) and that mature fibrillar aggregates, rather than acting as the pathogenic form, may represent a protective “junkyard” for misfolded proteins to prevent toxicity of aggregate precursors (Treusch *et al.*, 2009). For TDP-43, disease-associated oligomeric species have been detected in FTLD-TDP, and these oligomers have indeed demonstrated neurotoxic properties (Fang *et al.*, 2014; Kao *et al.*, 2015).
The role of TDP-43 aggregates, including oligomeric species, in neuronal and glial degeneration remains debatable and experimentally difficult to dissect because of the typically concomitant toxic effects of nuclear and cytoplasmic overexpression as well as nuclear clearance of endogenous TDP-43 leading to a loss of function. From the data collected so far, it seems plausible that TDP-43 aggregates are neither innocent bystanders nor the sole cause of TDP-43 proteinopathies, but are likely to fuel the degenerative processes observed in ALS and FTD, not least by entrapping endogenous TDP-43, which in turn generates a viscous cycle of GOF and LOF toxicity. Further research is needed to discern toxic and protective TDP-43 species, with the goal of developing effective therapeutic interventions for these protein misfolding diseases.

2.3.4. TDP-43 C-terminal fragments

In addition to a high-molecular-weight smear and a band at ~45 kDa corresponding to polyubiquitinated and hyperphosphorylated TDP-43, immunoblotting of detergent-insoluble fractions of ALS/FTD brain homogenates typically reveals one or more truncated forms of TDP-43 (Neumann *et al.*, 2006; Hasegawa *et al.*, 2008; Igaz *et al.*, 2008; Tsuji, Arai*, et al.*, 2012). Irrespective of ALS or FTD, these low-molecular-weight species are found almost exclusively in aggregates of disease-affected brain regions (mainly frontal and temporal cortices), but rarely in the spinal cord, and are detected solely with C-terminal but not N-terminal antibodies, indicating that they represent TDP-43 C-terminal

fragments (CTFs) (Neumann *et al.*, 2006; Hasegawa *et al.*, 2008; Igaz *et al.*, 2008; Tsuji, Arai*, et al.*, 2012; Tsuji, Nonaka*, et al.*, 2012). N-terminally truncated fragments in the range of ~22-27 kDa with a predominant band at ~25 kDa (TDP-25) are most reliably and abundantly detected, but shorter (~15-19 kDa) and longer (~35 kDa, TDP-35) variants have also been reported (Neumann *et al.*, 2006; Zhang *et al.*, 2007; Hasegawa *et al.*, 2008; Igaz *et al.*, 2008; Neumann, Kwong*, et al.*, 2009; Tsuji, Arai*, et al.*, 2012; Tsuji, Nonaka*, et al.*, 2012). TDP-25 fragments exhibit a disease-specific phosphorylation pattern and in some cases may even exceed the amount of the full-length protein. Despite being a hallmark of various TDP-43 proteinopathies, CTFs have not been found to correlate with disease subtype or neurodegeneration (Lee *et al.*, 2011; Berning & Walker, 2019).

TDP-35 and TDP-25 are thought to originate from proteolytic cleavage of the full-length protein by activated caspases 3, 4, and 7 (Zhang *et al.*, 2007; Dormann *et al.*, 2009; Zhang *et al.*, 2009; Nishimoto *et al.*, 2010; Suzuki *et al.*, 2011; De Marco *et al.*, 2014; Li *et al.*, 2015), Ca^{2+}-dependent calpains (Yamashita *et al.*, 2012; Z. Yang *et al.*, 2014), or asparaginyl endopeptidase (Herskowitz *et al.*, 2012). Apart from enzymatic cleavage by cysteine proteases, TDP-25 and TDP-35 may also result from translation of truncated alternative transcripts (Nishimoto *et al.*, 2010; Xiao *et al.*, 2015).

In cultured neurons, overexpressed CTFs, first and foremost TDP-25, are substantially more aggregation-prone than full-length TDP-43 and form insoluble, ubiquitinated, and hyperphosphorylated inclusions in the cytoplasm due to the absence of an intact NLS (Igaz *et al.*, 2009; Nonaka *et al.*, 2009; Zhang *et al.*, 2009; Che *et al.*, 2011; Fallini *et al.*, 2012; Wang *et al.*, 2013). However, the cytotoxic potential of TDP-43 CTFs in *in vitro* systems remains controversial: several studies attributed a certain toxicity to TDP-25 CTFs (Yang *et al.*, 2010; Chou *et al.*, 2015), with some reports suggesting that it exceeds the toxicity of TDP-43 or TDP-35 (Zhang *et al.*, 2009; X. Wang *et al.*, 2015), while others showed the opposite effect (Suzuki *et al.*, 2011; Yamashita *et al.*, 2014). Interestingly, the harmful effects of TDP-25 seem to depend on its cytoplasmic localization (Kitamura *et al.*, 2016).

CTFs have been shown to interfere with RNA processing when overexpressed in cells, as exemplified by altered *CFTR* exon skipping (Igaz *et al.*, 2009; Yang *et al.*, 2010; Che *et al.*, 2011). This may be due in part to the recruitment of endogenous TDP-43, which has been convincingly demonstrated for TDP-35 through cooperation with RNA (Nonaka *et al.*, 2009; Che *et al.*, 2015; Jiang *et al.*, 2022), but is less clear for TDP-25 (Nonaka *et al.*, 2009; Zhang *et al.*, 2009; Kitamura *et al.*, 2016). Furthermore, TDP-35 sequesters other RBPs into cytoplasmic aggregates (Jiang *et al.*, 2022), whereas cytosolic TDP-25 co-aggregates with nucleoporins and nucleocytoplasmic transport factors, consequently perturbing nuclear core complexes and overall protein and RNA trafficking between the nuclear and cytoplasmic compartments (Woerner *et al.*, 2016; Chou *et al.*, 2018). Nuclear

pore pathology has been extensively described in the context of cytoplasmic aggregation of full-length TDP-43 (Gasset-Rosa *et al.*, 2019), *C9orf72* pathology (Freibaum *et al.*, 2015; Jovicic *et al.*, 2015; Zhang *et al.*, 2015; Zhang *et al.*, 2016; Zhang *et al.*, 2018; Coyne *et al.*, 2020) and sporadic ALS cases (Kinoshita *et al.*, 2009; Shang *et al.*, 2017; Aizawa *et al.*, 2019; Coyne *et al.*, 2021), highlighting dysfunctional nucleocytoplasmic transport as a prevailing pathogenic mechanism in ALS/FTD.

In contrast to rapid inclusion formation in cell culture, TDP-25 barely aggregates when overexpressed either pan-neuronally or regionally in forebrain neurons in transgenic rodent models, although it is found to be disease-specifically phosphorylated (Caccamo *et al.*, 2012; Dayton *et al.*, 2013; Walker, Tripathy*, et al.*, 2015; Tsuiji *et al.*, 2017). This is accompanied by a moderate cognitive or motor phenotype and subtle signs of neurodegeneration, indicating that CTFs alone are insufficient to fully recapitulate the human diseases, at least in these models. Furthermore, despite the strong phenotype of some mouse lines expressing wild-type or mutant TDP-43, CTFs are detected inconsistently and generally at low levels, at later stages of the disease, and with a predominance of TDP-35 (Stallings *et al.*, 2010; Wils *et al.*, 2010; Igaz *et al.*, 2011; Swarup, Phaneuf, Bareil*, et al.*, 2011; Walker, Spiller*, et al.*, 2015). However, an early study reported that TDP-25 was present before symptoms were observed, suggesting that CTFs may contribute to disease onset (Wegorzewska *et al.*, 2009). Interestingly, TDP-43(M337V) mutant pigs (G. Wang *et al.*, 2015) and macaques (Yin *et al.*, 2019) resemble the human fragmentation pattern comparatively better than mice. Indeed, while primate caspase 4 generates TDP-43 CTFs, its mouse homolog, caspase 11, does not (Yin *et al.*, 2019), implying that mice may not be the ideal organism to study the pathobiology of TDP-43 CTFs.

Overall, aggregation-prone TDP-43 CTFs, especially TDP-25, hallmark ALS/FTD with regional heterogeneity, possibly due to cell type-specific abundance of cleaving proteases, alternative splice transcripts, or differences in degradation pathways (Berning & Walker, 2019), but current *in vitro* and *in vivo* models argue that they are not the main culprits in TDP-43 proteinopathies. Nonetheless, cytosolic CTF aggregates may exert gain-of-function toxicity, for example by recruiting nuclear pore proteins (Chou *et al.*, 2018), and thus contribute to disease.

2.3.5. Liquid-Liquid Phase Separation of TDP-43

Just like vinegar in oil, intracellular macromolecules like proteins and nucleic acids can (self-)assemble and compartmentalize into structures called biomolecular condensates (Banani *et al.*, 2017; Shin & Brangwynne, 2017). These condensates typically arise from the process of liquid-liquid phase separation (LLPS), in which macromolecular components segregate (“demix”) into two separate, coexisting phases: a dilute phase

depleted of macromolecules and a dense phase enriched with these components. The dense phase often forms droplets with “liquid” properties, i.e., they display rapid fusion, fission, and exchange of components with the surrounding milieu (Mathieu *et al.*, 2020). LLPS is often a reversible process and highly dependent on physical-chemical conditions (e.g., temperature, pH, salt concentration) as well as the concentrations of the macromolecules involved (Alberti & Dormann, 2019). Inside cells, phase separation (or biomolecular condensation) gives rise to diverse membraneless organelles (MLOs), such as nucleoli and stress granules (SGs) (Alberti & Dormann, 2019). MLOs are typically composed of a variety of different RNAs as well as RBPs and are referred to as RNP granules. Many disease-associated RBPs that partition into phase-separated RNP granules contain intrinsically disordered regions (IDRs). These are regions that lack a stable, well-folded three-dimensional structure and that often represent low-complexity domains (LCDs) (King *et al.*, 2012; Banani *et al.*, 2017). Intrinsically disordered, prion-like LCDs, in cooperation with RRMs, allow RBPs to engage in multiple weak and temporary RNA-RNA, protein-RNA, and protein-protein interactions (e.g., dipole–dipole, π-stacking, cation–π interactions) (Nedelsky & Taylor, 2019). This results in a molecular network and provides the basis for the phase separation behavior of RBPs. Indeed, multivalency, i.e., the number of interactions a macromolecule can have with other biomolecules to create a non-covalent, transient network of contact sites, is a key determinant of LLPS (P. Li *et al.*, 2012; Alberti & Dormann, 2019).

In keeping with this concept, the prion-like LCD in the C-terminal region of TDP-43 has been shown to be critical and sufficient by itself to drive self-assembly via LLPS *in vitro* and in living mammalian cells (Conicella *et al.*, 2016; Schmidt & Rohatgi, 2016; Li, Chen*, et al.*, 2018; Li, Chiang*, et al.*, 2018; Babinchak *et al.*, 2019; Hallegger *et al.*, 2021). In particular, an evolutionarily highly conserved region (CR) of ~20 amino acids (319-341) within the mostly unstructured CTD can adopt a transient α-helical conformation at high TDP-43 concentrations, which, with the support of the adjacent IDRs (GaroS1/2), allows weak, homotypic contacts that promote TDP-43 condensation (Conicella *et al.*, 2016; Hallegger *et al.*, 2021). Consequently, deletion of the CR, introduction of ALS-causing mutations (e.g., Q331K, G335D, M337V), or mutations in other critical residues (e.g., W334G) in this region significantly impair TDP-43 phase separation (Conicella *et al.*, 2016; Li, Chen*, et al.*, 2018; Li, Chiang*, et al.*, 2018; Conicella *et al.*, 2020; Hallegger *et al.*, 2021; Mohanty *et al.*, 2023). However, the CR may instead drive self-assembly and phase separation through the formation of labile cross β-structures formed via mainchain hydrogen bonding (Lin *et al.*, 2020; Zhou *et al.*, 2022). Another short, structured motif in the CTD that is relevant to its self-assembly is called LARKS (low-complexity, aromatic-rich, kinked segments) (Guenther, Cao*, et al.*, 2018; Hughes *et al.*, 2018). These special β-sheet segments, frequently found in phase-separating proteins, allow for weak, transient

amyloid-like adhesion between LCDs, while ALS-related TDP-43 mutations switch LARKS into irreversibly aggregated assemblies (Guenther, Cao*, et al.*, 2018).

Moreover, multivalent association with RNA modulates biomolecular condensation of TDP-43. At high concentrations in the nucleoplasm, RNA solubilizes prion-like RBPs such as TDP-43, whereas a lower abundance of RNA in the cytosol allows their demixing (Maharana *et al.*, 2018). Total RNA and, to a greater extent, short RNA stretches with high affinity for TDP-43 can impede the phase separation and aggregation of TDP-43 (Mann *et al.*, 2019; Rengifo-Gonzalez *et al.*, 2021). In contrast, other studies suggest that specific TDP-43 target RNAs can trigger the formation of condensates with liquid-like properties (Wang *et al.*, 2020; Grese *et al.*, 2021). This discrepancy may be due to differences in RNA sequence, length, or concentration.

Several lines of evidence indicate that phase separation of TDP-43 is relevant for at least some of its main functions, namely binding and regulation of specific RNA transcripts (Hallegger *et al.*, 2021), autoregulation (Hallegger *et al.*, 2021; Koehler *et al.*, 2022) and splicing activity (Wang *et al.*, 2018; Conicella *et al.*, 2020), although the latter was not found to be affected by some condensation-deficient variants (Schmidt *et al.*, 2019; Gruijs da Silva *et al.*, 2022). The fact that TDP-43 LLPS deficiency causes neuronal and behavioral deficits as well as perturbations in global protein synthesis (Gao *et al.*, 2021) argues for a biological relevance of TDP-43 biomolecular condensation. Nonetheless, more rigorous and holistic approaches are needed to determine exactly how TDP-43 functionality is modulated by its phase separation behavior.

2.3.6. Aberrant phase transitions within stress granules may drive TDP-43 proteinopathy

Although biomolecular condensation is essential for many intracellular processes, it is also associated with disease, particularly neurodegeneration. *In vitro,* several ALS/FTD-associated, LCD-harboring RBPs can undergo LLPS to form liquid droplets that slowly convert into gel-like states and eventually into solid-like, fibrillar assemblies (Kato *et al.*, 2012; Lin *et al.*, 2015; Alberti & Hyman, 2016; Boeynaems *et al.*, 2018). Such a liquid-to-solid phase transition (also referred to as “maturation” or “molecular aging”) has been observed for FUS (Murakami *et al.*, 2015; Patel *et al.*, 2015), hnRNPA1/hnRNPA2 (Kim *et al.*, 2013; Molliex *et al.*, 2015) as well as TDP-43 LCD (Babinchak *et al.*, 2019; Zhuo *et al.*, 2020; Shuster & Lee, 2022) and is typically promoted by disease-causing mutations. Based on stronger intermolecular interactions, the resulting structures exhibit diverse material properties and can represent (disordered) hydrogels, glass-like assemblies and, ultimately and irreversibly, high-order crystal-like amyloid fibers reminiscent of pathological aggregates (Alberti & Hyman, 2016). With respect to TDP-43, it is important to note that droplets do not necessarily develop into fibrils (Conicella *et al.*, 2016; Li, Chen,

et al., 2018; Li, Chiang*, et al.*, 2018; Conicella *et al.*, 2020) and that fibrils can form independently of droplets (Lim *et al.*, 2016; Shenoy *et al.*, 2020).

In cells, a membraneless compartment thought to be involved in disease-promoting aberrant phase transitions of RBPs is the cytoplasmic SG. These large, complex RNP granules represent a rapid pro-survival response to various types of stress (e.g., heat shock, oxidative and osmotic stress) and are readily disassembled after the insult is removed and the cell recovers (Anderson & Kedersha, 2008).

Notably, multiple ALS/FTD-linked RBPs, including FUS, hnRNPA1/A2, TIA1, ataxin-2, and TDP-43, are constituents of SGs to which they are recruited upon cellular stress, while disease-associated mutations in these proteins enhance their recruitment to SGs or alter key SG features (Li *et al.*, 2013). For example, TDP-43, whose association with SGs depends on its cytoplasmic localization as well as its RRM1 and CTD domains (Bentmann *et al.*, 2012), is not critical for SG formation but is relevant for SG assembly, dynamics, and maintenance, in part by controlling the key SG components G3BP1 and TIA1 (Colombrita *et al.*, 2009; Liu-Yesucevitz *et al.*, 2010; McDonald *et al.*, 2011; Aulas *et al.*, 2012; Aulas *et al.*, 2015; Khalfallah *et al.*, 2018). However, several disease-associated mutations within TDP-43 have been reported to increase the size and number of SGs (Dewey *et al.*, 2011; Liu-Yesucevitz *et al.*, 2014) and disrupt their dynamics (Q. Ding *et al.*, 2021).

Importantly, several SG marker proteins such as TIA1, EIF4G1, and PABP-1 are found within pathological FUS and TDP-43 inclusions in post-mortem tissue from ALS/FTD cases (Fujita *et al.*, 2008; Volkening *et al.*, 2009; Bäumer *et al.*, 2010; Dormann *et al.*, 2010; Liu-Yesucevitz *et al.*, 2010; Bentmann *et al.*, 2012; McGurk *et al.*, 2014).

Together, these findings have led to the paradigm that in disease, initially dynamic, reversible, and cytoprotective SGs may convert into pathological, insoluble, and presumably neurotoxic aggregates (Dewey *et al.*, 2012; Wolozin, 2012; Bentmann *et al.*, 2013; Li *et al.*, 2013; Aulas & Vande Velde, 2015; Molliex *et al.*, 2015). Such an abnormal phase transition may be attributed to the irregular persistence and perturbed dynamics of SGs caused by increased cytoplasmic localization of recruited RBPs (Dormann & Haass, 2011), RBP mutations that promote solidification, decreased clearance mechanisms (Buchan *et al.*, 2013), or prolonged cellular stress (Bowden & Dormann, 2016).

Although experimental data from living cells argue for a direct transition of SGs into pathogenic, cytotoxic inclusions (Zhang *et al.*, 2019), stress-induced insoluble aggregates may also evolve independently of SGs, and indeed SGs may even protect RBPs from being trapped in cytoplasmic inclusions (McGurk *et al.*, 2018; Gasset-Rosa *et al.*, 2019; Mann *et al.*, 2019; Lu *et al.*, 2022). Apart from LLPS, aggresomes may alternatively mediate the self-assembly of TDP-43 into aggregates (Watanabe *et al.*, 2020; Pérez-Berlanga *et al.*, 2023).

In summary, while several data suggest that initially dynamic SGs can transform into pathological TDP-43 deposits, the role of SGs in the context of ALS/FTD is likely more nuanced and alternative aggregation pathways may (also) trigger inclusion formation.

2.3.7. Post-translational modifications beyond C-terminal fragmentation: phosphorylation and ubiquitination

The repertoire of post-translational modifications (PTMs) associated with pathological TDP-43 is not limited to irreversible proteolysis resulting in C-terminal fragments. Other modifications include the reversible covalent addition of chemical groups through enzymes, causing altered conformation, functionality, localization, or stability of a protein after its synthesis (de Hoog & Mann, 2004; Buratti, 2018). Among the first and most extensively studied PTMs of TDP-43 is its phosphorylation, which has been identified so far mainly at serines 409/410, 403/404 and 379 in the C-terminal region and has emerged as a hallmark of TDP-43 proteinopathies (Arai *et al.*, 2006; Neumann *et al.*, 2006; Hasegawa *et al.*, 2008; Inukai *et al.*, 2008; Neumann, Kwong*, et al.*, 2009). Phospho-specific antibodies against serines 409/410 have proven to be sensitive immunohistological tools for assessing TDP-43 pathology in post-mortem tissue (Hasegawa *et al.*, 2008; Neumann, Kwong*, et al.*, 2009). The importance of TDP-43 phosphorylation in ALS/FTD is further highlighted by the fact that approximately half of the known disease-causing variants within *TARDBP* insert or remove putative phosphorylation sites on serines/threonines or generate the phosphomimetic residues glutamate and aspartate (Buratti, 2015). As with the vast majority of ALS/FTD-linked *TARDBP* mutations, essentially all disease-specific phosphorylation sites discovered to date in ALS samples are located in the LCD of TDP-43 (Kametani *et al.*, 2016), although other phosphorylated residues outside the CTD have recently been identified (Cracco *et al.*, 2022) and may come into focus in the future. Several kinases have been demonstrated to directly phosphorylate TDP-43 *in vitro* or *in vivo*, including CK1 (Hasegawa *et al.*, 2008; Kametani *et al.*, 2009) - more specifically CK1δ (Nonaka *et al.*, 2016) and CK1ε (Choksi *et al.*, 2014; Gu *et al.*, 2020) -, CK2 (Carlomagno *et al.*, 2014), TTBK1/2 (Liachko *et al.*, 2014; Taylor *et al.*, 2018), CDC7 (Liachko *et al.*, 2013), and p38α MAPK (Aikio *et al.*, 2021). By contrast, TDP-43 has been shown to be dephosphorylated by the cellular phosphatases calcineurin (Liachko *et al.*, 2016) and PP1 (Gu *et al.*, 2018).

Importantly, as reported by several independent groups, phosphorylation of TDP-43 and its CTFs is associated with their aberrant accumulation, mislocalization to the cytoplasm, reduced solubility, increased oligomerization/aggregation propensity, and enhanced cytotoxicity, collectively indicating a pathological role of this PTM (Liachko *et al.*, 2010; Liachko *et al.*, 2013; Choksi *et al.*, 2014; Liachko *et al.*, 2014; Liachko *et al.*, 2016; Nonaka *et al.*, 2016). According to these data, inhibition of TDP-43 phosphorylating protein kinases

appears to be an attractive treatment option and, in agreement with this hypothesis, has revealed beneficial effects both *in vitro* and *in vivo* (Liachko *et al.*, 2013; Salado *et al.*, 2014; Martínez-González *et al.*, 2020). In stark contrast to these findings, C-terminal hyperphosphorylation, as mimicked by introducing glutamate/aspartate residues at known phosphorylation sites, was found to increase TDP-43 solubility and decrease its propensity to self-associate into condensates or aggregates (Brady *et al.*, 2011; Li *et al.*, 2011; Gruijs da Silva *et al.*, 2022). The enhanced liquid character of TDP-43 was accompanied by reduced toxicity in cells and *in vivo* (Brady *et al.*, 2011; Li *et al.*, 2011) and may therefore reflect a defensive cellular reaction to combat aberrant TDP-43 self-assembly (Gruijs da Silva *et al.*, 2022). It is widely assumed that phosphorylation in the CTD occurs rather late in the disease course, only after TDP-43 has become insoluble and aggregated (Dormann *et al.*, 2009; Brady *et al.*, 2011; Li *et al.*, 2011; Zhang *et al.*, 2019), which could be interpreted as an effort to induce its clearance (François-Moutal *et al.*, 2019).

Many additional PTMs of TDP-43 have been discovered in the past years, including oxidation, acetylation, SUMOylation as well as non-covalent attachment of poly(ADP-ribose) (PAR) units (PARylation), and their effects have begun to be studied in more detail (Cohen *et al.*, 2012; Cohen *et al.*, 2015; McGurk *et al.*, 2018; Sternburg *et al.*, 2022).

The last TDP-43 modification to be mentioned here is ubiquitination, which represents the signature by which TDP-43 was initially identified in tau-negative FTLD cases (Neumann *et al.*, 2006). The process of (poly)ubiquitination involves the covalent attachment of the small regulatory protein ubiquitin to specific lysine (or N-terminal methionine) residues of a substrate, thereby influencing its fate (Pickart & Eddins, 2004). The modification can occur in several fashions, that is, by conjugation of a single ubiquitin molecule to either a single lysine (K) residue (monoubiquitination) or to multiple lysines (multi-monoubiquitination) (Komander & Rape, 2012). Moreover, the extension of a substrate-bound ubiquitin with additional ubiquitin molecules results in various types of polyubiquitin chains, of which the K48 and K63 chains are most relevant as degradation signals in the context of neurodegeneration (Le Guerroué & Youle, 2021). (Poly)ubiquitination is mediated by an ATP-dependent multi-step cascade involving the consecutive activity of E1 (ubiquitin-activating), E2 (ubiquitin-conjugating), and E3 (ubiquitin ligase) enzymes (Komander & Rape, 2012), which typically route their substrates for degradation via the proteasome (*see section 2.4.2.*)

With respect to TDP-43, the E3 ubiquitin ligase parkin as well as the ubiquitin-conjugating enzyme UBE2E3 were found to (poly)ubiquitinate TDP-43, increasing its cytoplasmic accumulation and insolubility (Hebron *et al.*, 2013; Hans *et al.*, 2014). These findings are somewhat surprising, since (poly)ubiquitination of aggregation-prone proteins is generally regarded as a stimulus for their proteolysis. However, polymeric ubiquitin chains have indeed been reported to promote protein aggregation (Morimoto *et al.*, 2015), suggesting

that the consequences of this PTM may be more complex. Of the 20 lysine residues in TDP-43, predominantly located in the NTD and RRM1 domains, multiple have been identified as ubiquitination sites, including K84 in the NLS, with relevance for the nuclear import of TDP-43, and several others in the RRM1 domain (K102, K114, K145, K181), which affect TDP-43's aggregation (Dammer *et al.*, 2012; Hans *et al.*, 2018). Additionally, K263 of the C-terminal region was found to be ubiquitinated in both full-length and fragmented TDP-43 (Hans *et al.*, 2018).

In conclusion, the rapidly growing understanding of TDP-43 PTMs reveals that they affect a variety of physiological as well as pathophysiological aspects of TDP-43 biology (e.g., splicing activity, LLPS, and aggregation behavior). Importantly, the identification of truly disease-specific and -relevant PTMs of TDP-43 may pave the way for attractive therapeutic strategies, as these would target the main culprit in ALS/FTD without interfering with normal TDP-43 functions.

2.3.8. Prion-like spreading of TDP-43

Although protein aggregates were originally thought to arise autonomously in affected cells (Goedert *et al.*, 2010), compelling evidence has accumulated over the past decades that seeding and spreading of pathological protein species, reminiscent of prion diseases, are key features of several neurodegenerative disorders. Prion diseases are rare transmissible neurodegenerative conditions characterized by aggregation of the endogenous prion protein (PrP) and comprise (variant) Creutzfeldt-Jakob disease or kuru. In these "protein-only" diseases, normal intracellular PrP (PrP^{C}) conformationally changes to a β-sheet-enriched structure (PrP^{Sc}) that confers protease resistance. Importantly, even small amounts of PrP^{Sc} can induce pathological misfolding and aggregation of the native soluble protein ("seeding" activity), resulting in recurrent self-templating of the aberrant protein. Seeding-competent PrP^{Sc} species, whose levels increase as aggregates fragment, are released into the extracellular space and taken up by surrounding cells or otherwise transferred intercellularly, allowing pathology to spread throughout the brain (Prusiner, 1982, 2013). Similar to prions, seeded aggregation and spreading have been reported for proteins involved in other neurodegenerative diseases such as Aβ, tau, or α-synuclein (Brundin *et al.*, 2010). Recent clinical, neuropathological, biochemical, and structural data imply a similar pathogenic mechanism driving TDP-43 proteinopathies.

For example, the onset of symptoms in ALS is typically focal and asymmetric, but as the disease progresses, additional sites become affected and clinical signs spread throughout the body (Ravits *et al.*, 2007; Ravits & La Spada, 2009). Consistently, neuropathologists classify ALS and FTD into stages based on regional staining patterns of phosphorylated TDP-43 (pTDP-43) in the CNS, all of which suggest that the pathology propagates from a focal site as the disease advances. In ALS, TDP-43 deposits first appear in the UMNs in

the motor cortex, as well as in the LMNs in the lower brainstem and spinal cord, before the pathology reaches the prefrontal neocortical area and eventually the temporal lobe and hippocampus (Braak *et al.*, 2013; Brettschneider *et al.*, 2013). Conversely, TDP-43 pathology in FTD, particularly in the behavioral variant, begins focally in the prefrontal neocortex or amygdala before expanding to other areas of the frontal cortex and hippocampus and ultimately invading cortical and spinal cord regions as well as the occipital neocortex (Brettschneider, Del Tredici*, et al.*, 2014).

Another key feature of prions and prion-like proteins is the occurrence of distinct molecular conformers or “strains”, that underlie different clinical presentations, progression rates, and disease severity. The existence of separate pathogenic TDP-43 strains is suggested by (I) varying distribution patterns and morphologies of TDP-43 inclusions in different FTLD subtypes, (II) specific immunoblot profiles of disease-associated TDP-43 isolated from these subtypes (Hasegawa *et al.*, 2008; Tsuji, Arai*, et al.*, 2012), and (III) distinct amyloid-like filament structures of TDP-43 in FTLD-TDP types A and B (Arseni *et al.*, 2022; Arseni *et al.*, 2023). Importantly, within the same FTLD subtype, TDP-43 ultrastructures and banding patterns are identical between brain regions, fueling the concept of intercellular transmission in TDP-43 proteinopathies (Tsuji, Arai*, et al.*, 2012; Arseni *et al.*, 2022; Arseni *et al.*, 2023).

During the last few years, a series of experiments have investigated the cell-to-cell transmission and seeding potential of TDP-43 in both *in vitro* and *in vivo* models. Recombinant fibrillar TDP-43 or fragments thereof, but also insoluble TDP-43 extracted from ALS/FTD brains, have been shown to seed aggregation of endogenous TDP-43 into disease-resembling inclusions in various human cell lines (Furukawa *et al.*, 2011; Nonaka *et al.*, 2013; Feiler *et al.*, 2015; Shimonaka *et al.*, 2016; Laferrière *et al.*, 2019). In addition, multiple studies indicate cell-to-cell propagation of pathological TDP-43 in cellular (Nonaka *et al.*, 2013; Feiler *et al.*, 2015; Sackmann *et al.*, 2020) and animal models (Iguchi *et al.*, 2016; Porta *et al.*, 2018). Injection of synthetic TDP-43 fibrils or patient brain extracts into mouse brains induced ALS-like symptoms by temporal spread of TDP-43 pathology along axonal connections of the pyramidal tract (Porta *et al.*, 2018; X. Ding *et al.*, 2021; Zhang *et al.*, 2021), consistent with an assumed propagation along neural projections in humans (Brettschneider *et al.*, 2013; Brettschneider, Del Tredici*, et al.*, 2014). There is evidence that TDP-43, like other prion-like proteins, is transferred between cells via exosomes (Nonaka *et al.*, 2013; Feiler *et al.*, 2015; Iguchi *et al.*, 2016), which are endocytosed by nearby cells or transmitted via synapses or tunneling nanotubes (Ding *et al.*, 2015). However, the exact mechanisms of TDP-43 transmission remain elusive. An amyloid-like conformation of TDP-43 has been shown to be indispensable for its prion-like behavior. Loss of a detergent-, heat-, and proteinase-resistant but formic acid-sensitive β-sheet conformation abolished templated aggregation of patient material (Nonaka *et al.*, 2013).

In particular, an amyloid core (residues 279-360) in the prion-like C-terminal domain, which highly overlaps with the sequence of pathological TDP-43 filaments isolated from ALS/FTD brains (Arseni *et al.*, 2022; Arseni *et al.*, 2023), appears to be essential for seeding activity and is presumably exposed in disease after proteolytic cleavage of full-length TDP-43 (Kumar *et al.*, 2023).

Overall, numerous studies, ranging from human post-mortem analyses to *in vivo* models, have provided substantial support for a prion-like spreading of pathological TDP-43 in neurodegenerative diseases. This has not only advanced the mechanistic understanding of TDP-43 proteinopathies, but also opens the door to novel therapeutic concepts for these disorders.

2.4. The protein quality control system and its relevance to TDP-43 proteinopathies

The accumulation of ubiquitinated TDP-43 aggregates suggests degradation efforts by the principal protein clearance pathways, autophagy and the ubiquitin-proteasome system (UPS), which together with molecular chaperones establish an intricate network that acts as a protein quality control (PQC) system to ensure cellular protein homeostasis (proteostasis). The control mechanisms range from mediating proper protein (re)folding upon translation to eliminating misfolded and dysfunctional proteins, and are especially relevant in post-mitotic cells such as neurons (Ciechanover & Kwon, 2017). Genetically encoded defects in the PQC machinery have long been associated with ALS/FTD. In line with this notion, an age-related decline in the functionality of the proteostasis network, including reduced protein turnover, coincides well with an increased risk of neurodegenerative diseases in the elderly, suggesting a causal relationship (Vilchez *et al.*, 2014; Sabath *et al.*, 2020; Kluever *et al.*, 2022). These observations, together with the fact that neurodegenerative disorders are generally associated with protein misfolding and aggregation, argue that the PCQ system takes on special significance in the pathogenesis of these diseases.

2.4.1. Molecular chaperones

Molecular chaperones, most of which are classified as heat-shock proteins (HSPs) based on their induction by stressors such as heat shock (Garrido *et al.*, 2001), account for nearly 10% of the cellular proteome (Finka & Goloubinoff, 2013) and are grouped into different families according to their size (HSP100, HSP90, HSP70, HSP60, HSP40, and small HSPs) (Kästle & Grune, 2012). The main function of molecular chaperones is to guide the correct folding of newly synthesized proteins as well as the unfolding/refolding of damaged or conformationally aberrant protein species, thus guaranteeing structural (and functional) integrity of client proteins (Hartl *et al.*, 2011). This is achieved by sensing and transiently

interacting with abnormally exposed hydrophobic residues in non-natively folded proteins, thereby preventing aberrant contacts that potentially lead to aggregation (Buchner, 1996). However, if proteins remain misfolded, chaperones can route them for degradation via either the UPS or autophagy (Ciechanover & Kwon, 2017). As chaperones diminish the pool of misfolded protein species, they prevent aggregate formation. Furthermore, by consuming ATP, chaperones can act as “disaggregases” for pre-existing aggregates (Doyle & Wickner, 2009; Shorter, 2011). Molecular chaperones are functionally supported by co-chaperones such as the large family of HSP40 (DnaJ) proteins that regulate ATP hydrolysis of HSP70 (Liberek *et al.*, 1991; Fan *et al.*, 2003).

Owing to their potential to counteract protein misfolding and aggregation, chaperones have been associated with beneficial effects on neurodegeneration-related proteins, including TDP-43. For example, upregulation of the small heat-shock protein B8 (HSPB8) has been shown to reduce the accumulation and aggregation of TDP-43, TDP-35, and especially TDP-25 through autophagic clearance and to attenuate the associated neurotoxicity in cells and *in vivo* (Crippa, Carra*, et al.*, 2010; Crippa, Sau*, et al.*, 2010; Gregory *et al.*, 2012; Crippa, Cicardi*, et al.*, 2016; Crippa, D'Agostino*, et al.*, 2016). A closely related small HSP, HSPB1, localizes to cytoplasmic TDP-43 droplets and inhibits their transition into fibrils, while depletion of HSPB1, as observed in ALS spinal cords, promotes abnormal TDP-43 phase separation and mislocalization (Lu *et al.*, 2022). Moreover, an HSP90 ATPase inhibitor, which also modulates the activity of other HSPs, was reported to reduce TDP-43 levels (Jinwal *et al.*, 2012) and inhibit reactive oxygen species (ROS)-stimulated TDP-43 aggregation (Chang *et al.*, 2013). HSP70 is another molecular chaperone involved in TDP-43 self-assembly: it stabilizes RNA-deficient TDP-43 as the core component of liquid-like “anisosomes”, but loss of its ATP activity transforms TDP-43 into gels, which presumably precede intracellular aggregates (Yu *et al.*, 2021; Lu *et al.*, 2022). Indeed, the interaction of HSP40/HSP70 chaperones with TDP-43 has previously been shown to maintain its solubility and diminish its stress-induced aggregation (Gregory *et al.*, 2012; Udan-Johns *et al.*, 2014; Chen *et al.*, 2016).

The heat-shock transcription factor-1 (HSF-1), a key transcription factor that upregulates levels of cellular chaperones (Trinklein *et al.*, 2004), including those of HSP40/HSP70, mitigates TDP-43 pathology (Chen *et al.*, 2016; Wang *et al.*, 2017). Lastly, an engineered variant of the yeast-derived disaggregase HSP104 has been demonstrated to dissolve not only TDP-43, but also α-synuclein and FUS aggregates and mitigate associated toxicities (Jackrel *et al.*, 2014; Tariq *et al.*, 2019). Taken together, these data emphasize that enhancing chaperone activity offers an attractive therapeutic concept for the treatment of TDP-43-associated diseases. However, since chaperones have also been implicated in cancer promotion (Calderwood & Murshid, 2017), caution must be exercised in the development of such therapies.

2.4.2. The ubiquitin-proteasome system and autophagy as the principal cellular clearance pathways

If refolding attempts by chaperones fail, misfolded and damaged soluble proteins, but also short-lived regulatory proteins, are typically ubiquitinated by a cascade involving E1, E2, and E3 enzymes described earlier (*see section 2.3.7.*). Such polyubiquitinated substrates are typically degraded by one of the proteolytic "workhorses" in eukaryotic cells, the 26S proteasome. The 26S proteasome is a 2.5 MDa multi-subunit complex consisting of a barrel-shaped 20S core particle capped on one or both sides by a 19S regulatory particle (Bard *et al.*, 2018). Subunits of the regulatory particle recognize the polyubiquitin chains of substrates, which are removed by deubiquitinating enzymes (DUBs) prior to degradation. Utilizing the energy from ATP hydrolysis, the 19S particle unfolds the bound substrates and translocates them through a narrow pore into the 20S core particle, which functions as a catalytic chamber for the actual proteolytic cleavage, leaving behind small peptides in the range of 8-12 amino acids that are further degraded by carboxy- or aminopeptidases or used for antigen presentation (Ciechanover & Kwon, 2015, 2017; Rousseau & Bertolotti, 2018).

The second highly conserved and vital cellular degradation pathway is autophagy, which either non-selectively (bulk autophagy) or selectively (using receptors to recognize only specific substrates such as organelles or aggregates) targets cytosolic material for digestion within lysosomes (Glick *et al.*, 2010). Depending on how cargo is directed to lysosomes, autophagy can be subdivided into macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). The best characterized variant, macroautophagy (hereafter simply referred to as autophagy), encompasses a multi-step process: upon initiation, a phagophore is formed at dysfunctional proteins, pathogens, or organelles, which expands into a closed double-membrane vesicle called an autophagosome. The autophagosome then fuses with the lysosome to produce an autolysosome, in which hydrolases digest the engulfed cargo before releasing the end products back into the cytosol (Feng *et al.*, 2014). Autophagy is viewed as a pro-survival cellular response to a wide range of stresses, including nutritional, ER, and oxidative stress (Murrow & Debnath, 2013). While the proteasome can efficiently break down soluble misfolded and short-lived proteins, the autophagic machinery primarily deals with long-lived and larger, aggregated protein species ("aggrephagy") (Lamark & Johansen, 2012; Kocaturk & Gozuacik, 2018; X. Ma *et al.*, 2022). Autophagy and the UPS are not completely independent proteolytic systems, but interplay in a delicate and complex fashion, resulting in both mutual compensatory and inhibitory effects. In fact, several proteins function at the crossroad of both clearance pathways, such as the multi-functional p62/SQSTM1, which is not only a classical autophagy receptor, but also directs ubiquitinated proteins to 26S proteasomes (Cohen-Kaplan *et al.*, 2016; Liu *et al.*, 2016). Moreover, the linkage pattern of polyubiquitin

chains is thought to determine the proteolytic route, with the K48 and K63 chains representing the prime signal for proteasomal and autophagic clearance, respectively (Tan *et al.*, 2008; Ciechanover & Stanhill, 2014).

The importance of the UPS and autophagy in the ALS/FTD disease spectrum has been strongly evidenced at multiple levels. As mentioned above, mutations in genes linked to the proteostasis network increase the risk of developing ALS and/or FTD, disrupt protein clearance pathways, and lead to the accumulation of TDP-43 (Filimonenko *et al.*, 2007; Gitcho *et al.*, 2009; Ju *et al.*, 2009; Deng *et al.*, 2011; Goode *et al.*, 2016). Autophagy and the UPS have also been implicated in the pathophysiology of sporadic ALS/FTD: ubiquitin homeostasis and proteasomal activity are compromised in sALS (Kabashi *et al.*, 2012; Farrawell *et al.*, 2020), and autophagosomes are enriched in the spinal cord of such cases (Sasaki, 2011). Moreover, in mice, knockout of the essential proteasome subunit *Rpt3* specifically in motor neurons results in ALS-like motor dysfunction, neuronal loss, as well as TDP-43 mislocalization and accumulation (Tashiro *et al.*, 2012), whereas loss of the key autophagy inducers *Atg5* or *Atg7* in the CNS leads to a neurodegenerative phenotype accompanied by the accumulation of ubiquitin-positive inclusions (Hara *et al.*, 2006; Komatsu *et al.*, 2006). The presence of p62- and ubiquitin-positive inclusions containing misfolded and aggregated ALS/FTD-linked proteins indicates that degradation by the UPS, autophagy, or both is dysfunctional and/or overwhelmed.

Both the proteasomal and autophagic machinery are involved in the turnover of TDP-43 and its CTFs, and consequently their blockade results in the accumulation and aggregation of TDP-43 protein species (Urushitani *et al.*, 2010; Wang *et al.*, 2010; Brady *et al.*, 2011; Scotter *et al.*, 2014; Cascella *et al.*, 2017; Cicardi *et al.*, 2018). Following the consensus of protein clearance pathways, soluble TDP-43 is thought to be mainly eliminated by the UPS, whereas oligomeric/microaggregated TDP-43 species are preferentially removed by autophagy, and large macroaggregates are unlikely to be efficiently degraded (Scotter *et al.*, 2014; Cascella *et al.*, 2017). Interestingly, TDP-43 aggregates contain both K48- and K63-linked polyubiquitin chains, presumably because non-degradable K48-labeled substrates are tagged with K63 ubiquitin for autophagic processing (Seyfried *et al.*, 2010; Scotter *et al.*, 2014). Inhibition of the proteasome in cells causes nuclear or cytoplasmic TDP-43 demixing (Yu *et al.*, 2021; Lu *et al.*, 2022) and mislocalization to the cytoplasm, accompanied by the formation of phosphorylated and ubiquitinated aggregates (van Eersel *et al.*, 2011), all features linked to TDP-43-driven neurodegeneration. Of note, the proteasome inhibitor bortezomib may similarly induce TDP-43 dysfunction, which could underlie the peripheral neuropathy observed in multiple myeloma patients treated with this drug (Argyriou *et al.*, 2008; Klim *et al.*, 2021). TDP-25 has been reported to be mainly proteolyzed by the UPS pathway (Liu *et al.*, 2014), while its disease-specific C-terminal hyperphosphorylation confers stability towards

proteasomal breakdown (Zhang *et al.*, 2010). However, TDP-43 also impacts the UPS functionality: aggregation of disease-mutated TDP-43 results in UPS malfunction, sequesters ubiquitin, and thus reduces the cellular ubiquitin pool (Farrawell *et al.*, 2020). Impairment of proteasome activity by (aggregated) protein species may in turn prevent their own clearance, exacerbating the dysfunction in a vicious cycle.

Likewise, the relationship between TDP-43 and the autophagic system is not one-sided. On the one hand, small-molecule activators of autophagy have been convincingly demonstrated to booster TDP-43 turnover and/or to mitigate associated pathology, toxicity, and phenotypic abnormalities *in vitro* and *in vivo* (Caccamo *et al.*, 2009; Wang *et al.*, 2012; Barmada *et al.*, 2014; X. Wang *et al.*, 2015; Imamura *et al.*, 2017; Zhou *et al.*, 2018; Kumar *et al.*, 2021; Lee *et al.*, 2021; Chu *et al.*, 2023). On the other hand, loss of TDP-43 leads to (I) depletion of the crucial autophagy gene *ATG7*, whose upregulation attenuates motor dysfunction in TDP-43-deficient flies (Bose *et al.*, 2011; Donde *et al.*, 2020), (II) a decrease in dynactin 1 and HDAC6, two proteins relevant for proper autophagic function (Fiesel *et al.*, 2010; Xia *et al.*, 2016), and (III) a downregulation of parkin, which is involved in mitophagy (Polymenidou *et al.*, 2011; Lagier-Tourenne *et al.*, 2012), altogether suggesting that TDP-43 dysfunction negatively affects autophagy. Furthermore, TDP-43 has also been shown to be cleared by CMA (Ormeño *et al.*, 2020) and the endo-lysosomal system (Liu *et al.*, 2017; Leibiger *et al.*, 2018).

Collectively, these data establish a strong, mutual link between TDP-43 pathology and cellular degradation pathways. Enhancing their functionality to remove aberrantly accumulated TDP-43 is considered a promising target for intervention in ALS and FTD.

3. Active and passive vaccination targeting pathological proteins in neurodegenerative diseases

The invention of vaccination (hereafter used synonymously with "immunization" for simplicity) is undoubtedly one of the greatest achievements in medicine, and its worldwide use, primarily against infectious diseases, saves millions of lives every year (Pollard & Bijker, 2021). By targeting inclusion-forming proteins, immunization strategies can also be applied to neurodegenerative disorders, and many of these approaches have shown promising preclinical effects. The following sections summarize the immunological basis, relevant examples, and commonly proposed mechanisms by which antibody-based approaches can be directed against pathological proteins in neurodegenerative diseases, including TDP-43 in ALS/FTD.

3.1. Immunological basics of active and passive immunization

In general, immunization can be divided into an active and a passive variant, both of which equip the body with antibodies. Conventional antibodies are Y-shaped, modular macromolecules consisting of antigen-binding regions (antigen-binding fragment, Fab) that confer high epitope specificity and constant regions (crystallizable fragment, Fc) as the tail that mediate effector functions through interactions with Fc receptors (FcRs) or complement proteins (Chiu *et al.*, 2019). Passive vaccination refers to the administration of (nowadays mostly) human or humanized therapeutic monoclonal antibodies (mAbs), mainly delivered systemically by intravenous injection (Lu *et al.*, 2020). Active vaccination involves the application, mostly intramuscularly, of an antigen (in the case of neurodegenerative diseases, typically a synthetic peptide fragment of an aggregation-prone protein) that is recognized by the immune system and stimulates a specific immune response (Pollard & Bijker, 2021). In brief, antigen-presenting cells (APCs), such as dendritic cells, engulf the peptide antigen and subsequently degrade it into smaller peptide fragments that are presented on the cell surface via two types of major histocompatibility complex molecules (MHC I and II). In the lymph nodes, activated APCs can initiate two cascades of adaptive immunity: (a) peptide-loaded MHC class II molecules interact with naïve $CD4^+$ T cells, which in turn become activated and differentiate into Th1 or Th2 cells. Th2-driven proliferation of soluble antigen-primed B lymphocytes generates antibody-secreting plasma cells, some of which reside long-term in the bone marrow and spleen, and memory B cells that can respond rapidly and efficiently to the antigen upon re-exposure (humoral immune response). This T cell-dependent B cell reaction results in high-affinity antibodies of different isotypes. (b) The second pathway, the cellular immune response, eliminates infected cells by cytotoxic $CD8^+$ effector and memory T cells that develop from naïve $CD8^+$ T cells upon recognition of MHC I molecules on APCs and additional stimuli. The cell-mediated immune response can also be initiated by Th1 cells (Akkaya *et al.*, 2020; Pollard & Bijker, 2021).

For active immunization in neurodegenerative diseases, a Th2-mediated humoral immune response is usually the preferred effect (Vassilakopoulou *et al.*, 2021). This requires the presence of both B and T cell epitopes in the administered active vaccine. However, the induction of cytotoxic T cells targeting epitopes within endogenous proteins is a potential safety concern. The careful selection of shorter peptides within native, aggregation-prone proteins minimizes the risk of a detrimental cellular immune response (Axelsen *et al.*, 2011), as does the conjugation of *per se* weakly immunogenic peptides to carrier proteins such as tetanus or diphtheria toxoids (Vassilakopoulou *et al.*, 2021). Carrier molecules provide T cell epitopes to elicit a robust immune response, but have no sequence homology in humans. Moreover, active vaccine formulations typically contain adjuvants, components that additionally stimulate the immune system towards an antigen. Examples

of adjuvants commonly used in vaccines include the well-established aluminum salts (which primarily promote Th2 immune responses), emulsions such as MF59, and immune potentiators like CpG oligodeoxynucleotides (CpG ODNs), which act as Toll-like receptor (TLR) 9 agonists (Facciolà *et al.*, 2022). The antigen-enhancing effects of vaccine adjuvants have been attributed to complex and not fully understood mechanisms, including depot effects resulting from antigen absorption and continuous release, increased antigen uptake by APCs, promotion of a local proinflammatory milieu that recruits immune cells, or direct activation of immune cells (Shi *et al.*, 2019).

The fundamental importance of epitope and adjuvant selection for active vaccines is highlighted by early work on Aβ vaccines: 6% of patients immunized with the preclinically promising full-length $A\beta_{1-42}$ peptide (*see next section*) developed meningoencephalitis, leading to the termination of a clinical trial and attributed to T cell epitopes in Aβ and/or the strong Th1-inducing adjuvant used (Orgogozo *et al.*, 2003; Lemere & Masliah, 2010). Today, active and passive immunotherapies target specific epitopes within neurodegeneration-related proteins, some of which are implicated in aggregation, spreading, or harmful cellular interactions. Alternatively, they may recognize disease-specific conformations (monomers, oligomers, fibrils, …) or PTMs, thus minimizing cross-reaction with the functional native protein (Congdon *et al.*, 2022).

Specific characteristics of active and passive vaccination can be advantageous or disadvantageous depending on the therapeutic need. Active immunization is usually cost-effective, requires only a few injections, and produces a long-lasting immune response (Lemere, 2013). While active vaccines induce a polyclonal antibody response (different B cells produce antibodies against multiple epitopes of the antigen), mAbs for passive immunization selectively target a single epitope. Therefore, active immunotherapy may result in broader coverage of the antigen, whereas mAbs are characterized by high specificity, both of which may be desirable but are mutually exclusive. In addition, due to immunosenescence, elderly individuals often do not respond efficiently to active vaccination, as do immunocompromised patients, and hence passive immunization is preferred (Lannfelt *et al.*, 2014). Therapeutic mAbs offer tight dosage control and immediate, reversible effects, but are expensive and require frequent administration.

3.2. Vaccination approaches in preclinical and clinical studies

Tremendous efforts have been made in recent decades to explore the therapeutic potential of both active and passive vaccination in neurodegenerative diseases, with research on AD leading the way. In 1999, Schenk *et al.* showed that active vaccination using full-length $A\beta_{1-42}$ greatly reduced plaque pathology in an AD mouse model (Schenk *et al.*, 1999). Shortly thereafter, a mAb directed against the N-terminus of Aβ was reported to induce microglial clearance of Aβ deposits in transgenic AD mice (Bard *et al.*, 2000).

These experiments were the starting point for numerous clinical trials testing synthetic peptides and mAbs for active and passive immunization, respectively, in AD and other neurodegenerative diseases (Mortada *et al.*, 2021). Although many of the drug candidates along the way failed to show clinical improvement (presumably in part because they were administered too late in the disease course) or caused adverse effects, the two Aβ-specific mAbs aducanumab and lecanemab reduced amyloid burden, slowed cognitive decline in AD patients, and were recently approved by the FDA (Sevigny *et al.*, 2016; Budd Haeberlein *et al.*, 2022; van Dyck *et al.*, 2023). Their entry into the market can be considered historic, not only because the observed clinical benefits support a long debated pathogenic role for Aβ, but also because these antibodies are the first ever disease-modifying therapeutics for AD (Cummings, 2023).

Active and passive immunotherapeutic approaches have also been developed to target tau in tauopathies and α-synuclein in synucleinopathies, and several candidates are in ongoing clinical trials. The active vaccine AADvac1, for example, is a carrier-conjugated synthetic peptide derived from the tau microtubule-binding region and is currently being investigated for the treatment of AD and nfvPPA. So far, it has been well tolerated, robustly induced a strong antigen-specific antibody response, reduced the increase in plasma NfL and, although only in a subset of patients, slowed clinical decline (Novak *et al.*, 2017; Novak *et al.*, 2021).

Immunotherapies directed against other aggregating proteins involved in the ALS/FTD spectrum are still in the preclinical stage. In this context, the abundant DPR protein poly-GA in C9-ALS/FTD is a promising target. High-affinity poly-GA antibodies, interestingly originally derived from healthy individuals, reduced levels of multiple DPR proteins, prolonged survival, and improved phenotypic abnormalities when systemically administered to a *C9orf72* mouse model (Nguyen *et al.*, 2020). Similarly, an active vaccination approach using $(GA)_{10}$ conjugated to the carrier protein ovalbumin resulted in a pronounced anti-GA response, lowered poly-GA accumulation, decreased aberrant microglial activation, and ameliorated the motor phenotype of transgenic poly-GA mice (Zhou *et al.*, 2020).

For TDP-43, only strategies involving the application or expression of mAbs (or fragments thereof) have been pursued to date. A full-length mAb targeting TDP-43 RRM1 was shown to reduce cytoplasmic TDP-43 as well as p65-driven NFκB activation both *in vitro* and in motor neurons of a TDP-43 mouse model after intrathecal administration (Pozzi *et al.*, 2020). A single-chain variable fragment (scFv) of this antibody ameliorated TDP-43 proteinopathy, neuroinflammation as well as cognitive and motor function when AAV-delivered in the brains of mice expressing ALS-associated *TARDBP* mutations (Pozzi *et al.*, 2019). In addition, another scFv targeting an RRM2 epitope and carrying two proteolytic signals enhanced the clearance of aggregated TDP-43 in cells and in mice that

were *in utero* electroporated with plasmids encoding the scFv and aggregation-prone TDP-43 (Tamaki *et al.*, 2018). Recently, the CTD of TDP-43 has been identified as another potential target domain for antibody-based therapy: following systemic application, a CTD-directed mAb was found to reduce levels of pTDP-43 and microglial inflammation in rNLS8 mice, as well as neuronal loss in an *in vivo* seeding model of TDP-43 proteinopathy (Afroz *et al.*, 2023).

3.3. Proposed mechanisms of antibody therapy

To combat CNS diseases, the biggest obstacle for antibodies, whether from active or passive immunization, is crossing the tight blood-brain barrier (BBB). The BBB represents a physical barrier at the interface of blood vessels and the brain interstitium and is formed by tight junction-connected endothelial cells, pericytes, and astrocyte endfeet. It plays a protective role for the CNS by selectively regulating the bidirectional shuttling of substances between the brain and the external milieu (Daneman & Prat, 2015). Because antibodies are large (~150 kDa for immunoglobulin G, IgG) and show non-specific uptake, their CNS penetrance is generally very low, estimated at 0.01-0.4% (Pepinsky *et al.*, 2011; St-Amour *et al.*, 2013; Zhao *et al.*, 2022). While this limited uptake may be sufficient for the treatment of certain diseases, various (bioengineering) strategies have been explored to increase the delivery of antibodies into the CNS, e.g., by harnessing endogenous transport systems. The endothelial transferrin receptor (TfR), for instance, mediates transcellular delivery of transferrin-bound iron to the brain, but is also utilized when different types of TfR binders are introduced into macromolecular cargoes (Gosselet *et al.*, 2021). As a result, brain concentrations of macromolecules can be substantially increased, as recently demonstrated for two mAbs that promote clearance of Aβ deposits (Weber *et al.*, 2018; Kariolis *et al.*, 2020; Schlepckow *et al.*, 2020; van Lengerich *et al.*, 2023).

Once taken up into the CNS, antibodies can exert multiple, mutually non-exclusive beneficial effects (**Figure 3**), either inside or outside the cell. Regardless of their intra- or extracellular localization, antibodies can prevent or reverse the formation of pathological protein assemblies such as oligomers or aggregates. The resulting smaller protein species are generally more amenable to clearance (Congdon *et al.*, 2022). In the extracellular space, antibodies can bind to proteins and block their uptake into neighboring cells through reduced interaction with surface receptors. This prevents cell-to-cell transmission and reduces seeding potency (“neutralizing effect”) (Katsinelos *et al.*, 2019), thereby inhibiting disease propagation throughout the CNS in a prion-like fashion, as has been suggested for several neurodegeneration-related proteins, including TDP-43 (*see section 2.3.8.*). Treatment with mAbs has been shown to reduce cellular uptake and/or transmission of tau (Evans *et al.*, 2018), α-synuclein (Tran *et al.*, 2014), and poly-GA (Zhou *et al.*, 2017),

and such a mechanism is also likely to underlie the neuroprotective effect of TDP-43 mAb injection in a mouse model of TDP-43 spreading (Afroz *et al.*, 2023). In addition, antibodies can enhance protein internalization and degradation by microglia (opsonization), which has been reported for Aβ (Bard *et al.*, 2000), tau (Funk *et al.*, 2015), α-synuclein (Bae *et al.*, 2012), and TDP-43 (Afroz *et al.*, 2023). Importantly, protein clearance relies on Fcγ receptors (FcγRs), which are predominantly expressed on microglia and mediate the uptake of protein:antibody complexes via interaction with the Fc region of IgGs (Katsinelos *et al.*, 2019). In general, the effector functions conferred by Fc regions depend on the IgG isotype, with some of these functions being undesirable, such as inducing the release of pro-inflammatory cytokines. For the latter reason, certain mAbs rely on the less potent IgG4 instead of the effective IgG1 backbone, or on mAb fragments that lack Fc regions entirely (Vidarsson *et al.*, 2014; Katsinelos *et al.*, 2019; Congdon *et al.*, 2023). Although the absence of effector functions does not generally preclude beneficial effects (Lee *et al.*, 2016), FcγR-dependent microglial phagocytosis of pathological proteins is widely considered an important mode of action for antibody therapy (Novak *et al.*, 2018).

The neonatal Fc receptor (FcRn) is highly expressed on the BBB endothelium (Schlachetzki *et al.*, 2002) and putatively responsible for reverse transcytosis of pathological proteins from the brain, as suggested by work on Aβ (Deane *et al.*, 2005), although the therapeutic relevance remains elusive. Peripheral Aβ is bound by mAbs in the blood, which – assuming an equilibrium between the CNS and the periphery – would promote the efflux of free Aβ from the brain, thereby lowering the CNS Aβ burden (DeMattos *et al.*, 2001). This highly controversial “peripheral sink” mechanism has been proposed for Aβ, but so far not for other amyloid-like proteins.

In contrast to the largely extracellular Aβ deposited in plaques, pathological inclusions of other neurodegeneration-associated proteins, including those of TDP-43, are predominantly found within neuronal cells. Indeed, antibodies against tau (Congdon *et al.*, 2013), poly-GA (Jambeau *et al.*, 2022), and TDP-43 (Pozzi *et al.*, 2020) have been reported to be internalized into neurons, either alone or in complexes with their target protein (Evans *et al.*, 2018). The efficacy of neuronal uptake is influenced by antibody charge, glycosylation, and isotype, among other parameters, and occurs via endocytosis (Congdon *et al.*, 2023). Inside neurons (and likely other relevant brain cells), antibodies bind to target proteins and exert their protective functions at several stages: antibodies have been detected within endosomal-lysosomal vesicles (Pozzi *et al.*, 2020), where they can promote the disassembly and enhanced lysosomal degradation of pathological proteins, as well as block their escape into the cytoplasm to induce seeding (Katsinelos *et al.*, 2019; Congdon *et al.*, 2022). Outside the vesicles, in the cytoplasmic compartment, antibodies can prevent the interaction of toxic protein species with cellular structures (e.g., membranes) as well as their release from neuronal cells.

An important role has recently been attributed to tripartite motif-containing protein 21 (TRIM21), a cytosolic Fc receptor and ubiquitin ligase expressed in neurons and microglia. IgG antibodies bind to protein targets with their variable regions and recruit the highly affine TRIM21 through Fc regions, and due to the E3 ubiquitin ligase activity of TRIM21, the complex is targeted for proteasomal degradation (Mallery *et al.*, 2010). TRIM21-dependent, antibody-mediated clearance has been shown to reduce not only seeded aggregation of tau *in vitro* and *in vivo* (McEwan *et al.*, 2017; Mukadam *et al.*, 2023), but also cellular poly-GA (Nguyen *et al.*, 2020) and TDP-43 (Pozzi *et al.*, 2020) levels, highlighting it as a broad and critical pathway activated by antibody therapy.

Overall, after years of failed clinical trials, immunotherapeutic strategies targeting aggregating proteins in neurodegenerative diseases now appear to have reached a level of safety and efficacy that allows for market access, as demonstrated by Aβ mAbs. The growing understanding of disease mechanisms and the modes of action of antibodies in the CNS (e.g., increasing clearance, preventing the propagation and aggregation of neurotoxic proteins) makes active and passive immunization a promising therapeutic approach to combat aggregating proteins involved in disease. Emerging technologies such as the bioengineering of antibodies to confer multispecificity and multivalency, or the use of small antibody fragments such as scFvs or nanobodies, offer several advantages over classic IgGs and thus represent additional powerful tools in the future fight against neurodegenerative diseases.

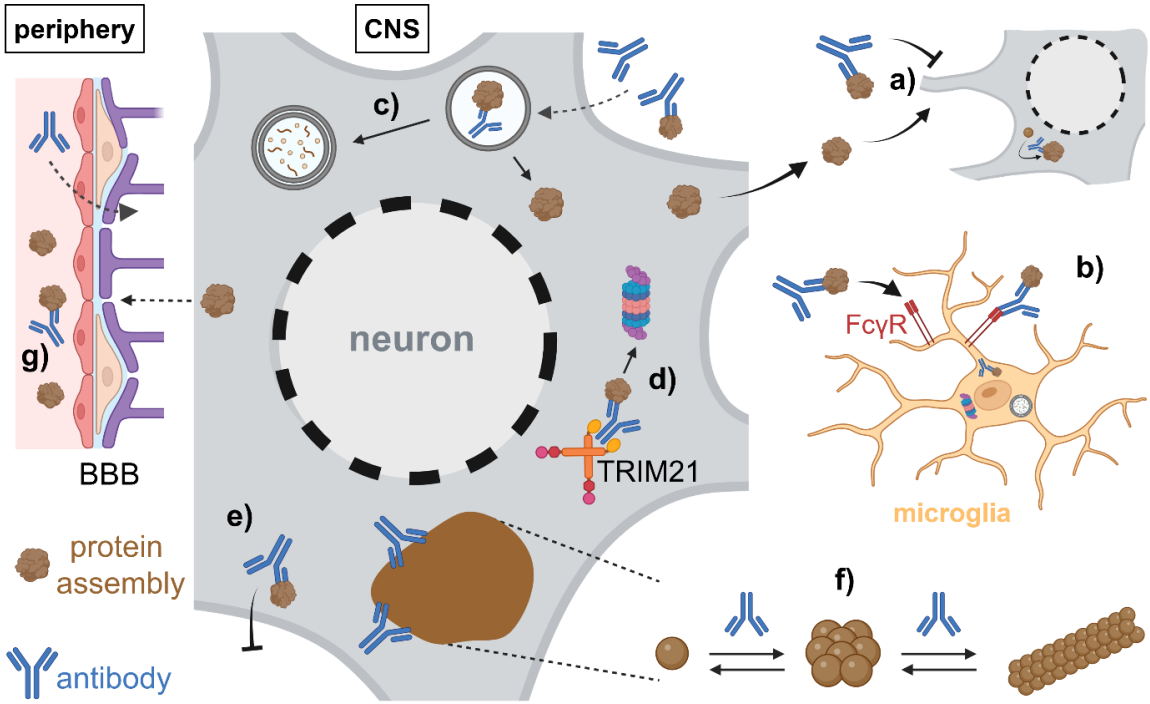

Figure 3: Postulated modes of action of antibodies derived from active or passive vaccination. Peripherally administered monoclonal antibodies (mAbs; passive vaccination) as well as polyclonal antibodies induced by active vaccines cross the blood-brain barrier (BBB) to a minor extent. Within the central nervous system (CNS), antibodies can act extracellularly by (**a**) inhibiting cellular uptake and seeding activity of proteins with prion-like transmission or (**b**) promoting microglial clearance of protein aggregates after uptake through Fcγ receptors (FcγR). Once internalized into neurons, antibodies can enhance antigen degradation by (**c**) lysosomes or (**d**) the proteasome, the latter in cooperation with the cytosolic Fc receptor TRIM21. Antibodies can also block toxic cellular interactions or (**e**) the release of protein aggregates. Either inside or outside neurons, antibodies are thought to (**f**) inhibit or reverse the formation of toxic higher-order assemblies such as oligomers or amyloids. In the periphery, (**g**) antibodies may sequester circulating protein species and thus “pull” pathological protein out of the brain (highly debated “peripheral sink” mechanism). Together, these non-exclusive mechanisms counteract the deleterious effects of neurodegeneration-related proteins at multiple levels. Note that this figure was created using BioRender.com.

4. Aims of this work

Despite the central role of TDP-43 aggregates in ALS and FTD, their native conformations within cells and their downstream toxicity mechanisms remain poorly understood. So far, structural analysis of TDP-43 has focused on purified recombinant or synthetic protein fragments and *ex vivo* patient material enriched for insoluble TDP-43 (Guenther, Cao*, et al.*, 2018; Arseni *et al.*, 2022). However, these methods have inherent limitations because the structures obtained are either derived from purely *in vitro* experiments or, in the case of patient-derived samples, can be affected by harsh extraction methods (Zielinski *et al.*, 2021), making both approaches unlikely to yield true structures in living ALS/FTD patients. In addition, these reductionist approaches completely lack information about the native cellular interactions of the aggregates, preventing deeper insight into disease mechanisms.

Therefore, in the **first project** of my doctoral studies, I aimed to decipher the structure and toxic mechanisms of the inclusion-forming "TDP-25" fragment in primary neurons. In a collaborative effort combining cryo-electron tomography (cryo-ET), proteomics, and functional assays, I intended to

- elucidate the structural architecture and material properties of TDP-25 *in situ*,
- identify proteins that interact with TDP-25 in neurons and,
- use these insights to uncover novel mechanisms of how TDP-25 contributes to ALS/FTD pathogenesis.

Despite much progress in understanding the role of TDP-43 in disease, targeting TDP-43 pathomechanisms therapeutically has proven difficult. This is largely explained by the fact that an excess or deficiency of TDP-43 is detrimental to neuronal health (Lee *et al.*, 2011). Encouraged by the recent success of antibody therapy against Aβ in AD (Cummings, 2023), in the **second project**, I explored the therapeutic potential of active immunization targeting TDP-43. My specific aims included:

- identify safe and immunogenic epitopes within TDP-43 by actively immunizing mice with multiple peptide antigens that collectively cover the entire TDP-43 protein,
- test the therapeutic efficacy of these peptide antigens for active immunization in an ALS mouse model,
- generate a panel of monoclonal antibodies (mAbs) and examine their effects on disease pathways *in vitro*, with the goal of identifying mAbs for future passive vaccination.

In summary, these projects aim to deepen the understanding of TDP-43's role in ALS/FTD and to explore novel therapeutic concepts for these incurable neurodegenerative diseases.

II. Publications and contributions

1. Publication I

Gel-like inclusions of C-terminal fragments of TDP-43 sequester stalled proteasomes in neurons

Published as:

Riemenschneider, H.*, Guo, Q.*, Bader, J., Frottin, F., Farny, D., Kleinberger, G., Haass, C., Mann, M., Hartl, F. U., Baumeister, W., Hipp, M. S., Meissner, F., Fernández-Busnadiego, R., & Edbauer, D. (2022). Gel-like inclusions of C-terminal fragments of TDP-43 sequester stalled proteasomes in neurons.

EMBO Rep, 23(6), e53890. doi: 10.15252/embr.202153890

(* co-first authorship)

Contribution:

As co-first author of this publication, I have been critically involved in the design, execution, analysis, and visualization of all the experiments presented. I cultured and infected primary neuronal cells for all experiments. I also performed immunostainings (Fig. 1A, 3E, EV3B), biochemical fractionation (Fig. 1B), FRAP experiments (Fig. 2, EV2) and, with minor assistance, flow cytometry reporter assays (Fig. 3F, EV3C). I analyzed and visualized the collected data from these experiments. For the cryo-ET experiments (Fig. 1C-F, EV1), I provided TDP-25-expressing neuronal cells. For the interactome studies (Fig. 3A-D, EV3A and D), I conducted the co-immunoprecipitation experiments, analyzed parts of the data, and prepared the figures. The shared first authorship is explained by the combination of expertise in primary neuron cultures (including biochemical and functional assays) (myself) and cryo-electron tomography (Q. Guo). Only the synergy of these techniques allowed for the deep insights revealed by this work.

2. Publication II

Targeting the glycine-rich domain of TDP-43 with antibodies prevents its aggregation *in vitro* and reduces neurofilament levels *in vivo*

Published as:

Riemenschneider, H., Simonetti, F., Sheth, U., Katona, E., Roth, S., Hutten, S., Farny, D., Michaelsen, M., Nuscher, B., Schmidt, M. K., Flatley, A., Schepers, A., Gruijs da Silva, L. A., Zhou, Q., Klopstock, T., Liesz, A., Arzberger, T., Herms, J., Feederle, R., Gendron, T. F., Dormann, D., & Edbauer, D. (2023). Targeting the glycine-rich domain of TDP-43 with antibodies prevents its aggregation in vitro and reduces neurofilament levels in vivo.

Acta Neuropathol Commun, 11(1), 112. doi: 10.1186/s40478-023-01592-z

Contribution:

As the first author of this publication, I performed all *in vivo* experiments, analyzed most of the tissue samples, and conducted all *in vitro* assays. Only the generation and initial affinity testing of novel mAbs as well as the pTDP-43(S409/410) immunoassay, immunostaining (Fig. 3A and B) and RNA-seq data analysis (Fig. 6A-D, S4A, B and D) of my samples were done by collaborators. I also contributed to the immunoassay for the inflammatory markers (Fig. 6E, S4C) and the time-lapse recordings of TDP-43 droplets (Fig. S5A). I prepared all figures.

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