Basic Biology of TDP-43

Spring 2024 ADRC Meeting
Austin, TX

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Conflicts of Interest

I have no relevant financial disclosures.

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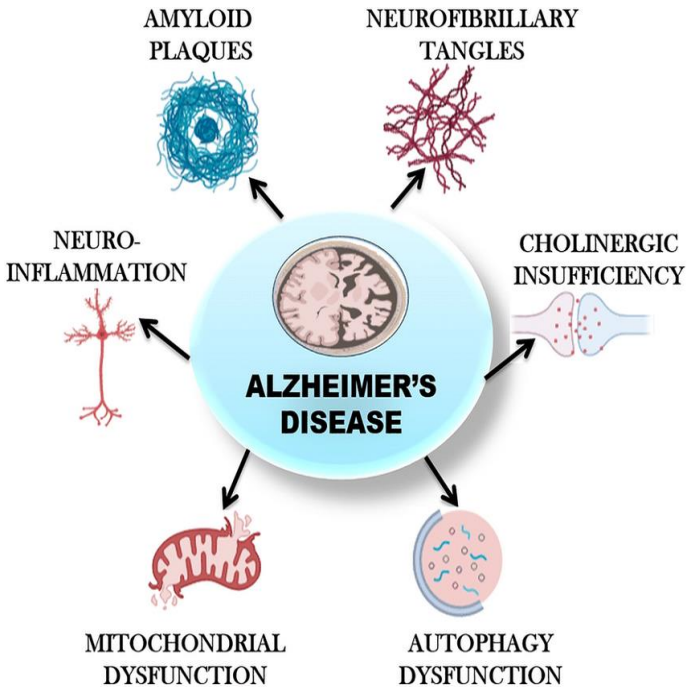
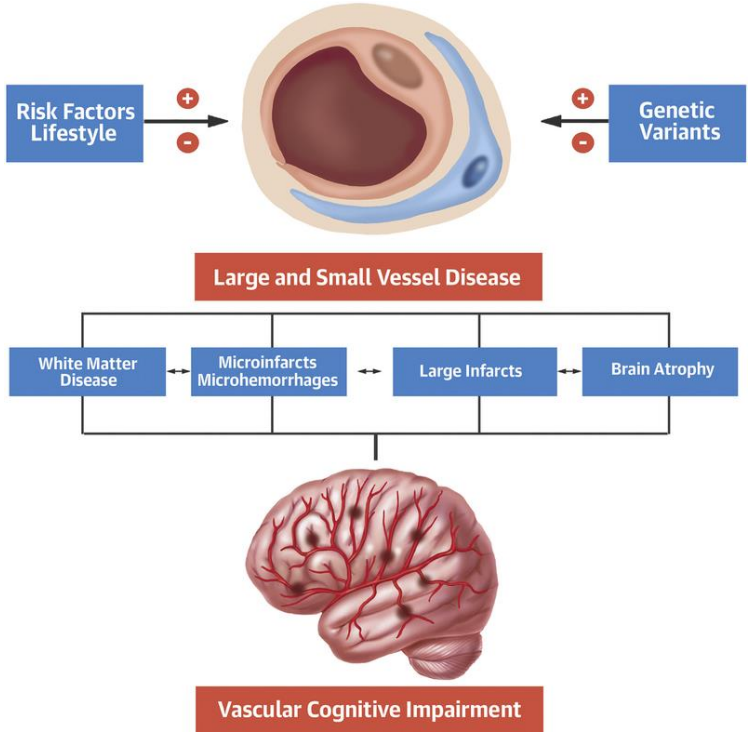
Dementia

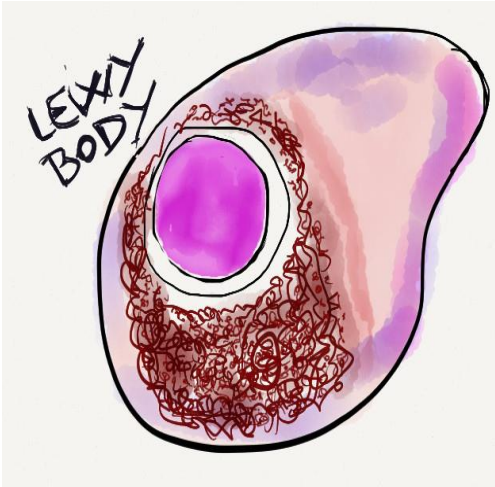
★ Alzheimer's Disease



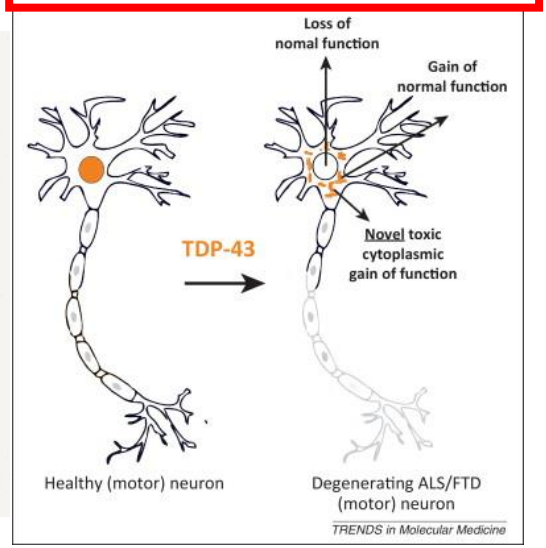
Vascular Contributions



Lewy body disease



TDP43 Proteinopathies



FTLD-TDP43 & LATE

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TDP-43 Clinical Relevance?

Higher likelihood of dementia when beyond amygdala stage

Associations with HS, tangle density & Aβ burden

Independently increases trajectory of cognitive decline

With HS and/or ADNC → increases odds of developing dementia

~ALS, FTLD TDP43 A-E etc…

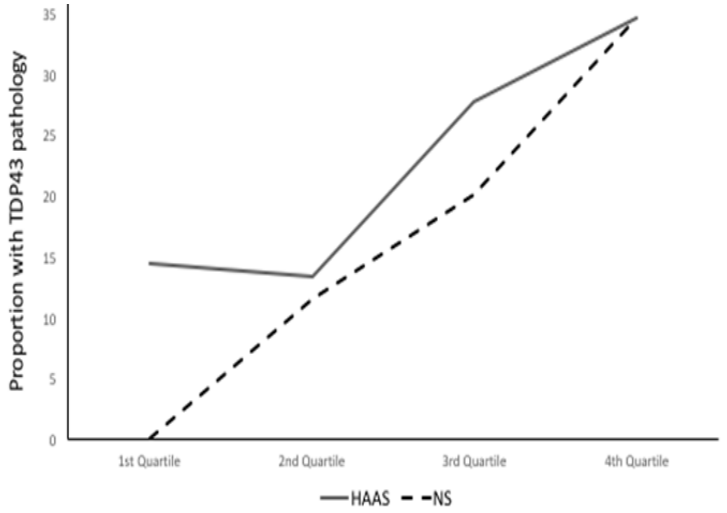
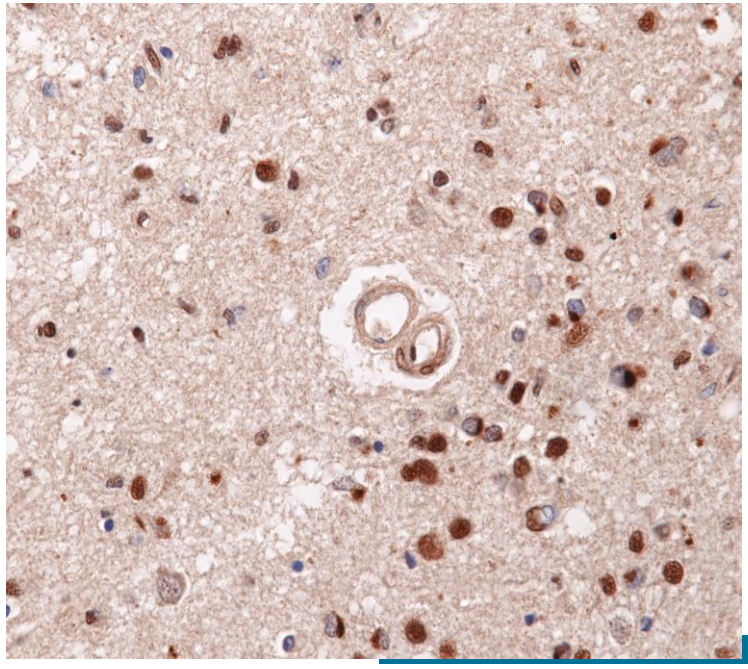


Figure 1: Proportion of subjects with pathologic TDP43 staining by cognitive performance (quartiles), HAAS and NS. CERAD/CASI quartiles: 1=highest performance quartile, 4=lowest performance



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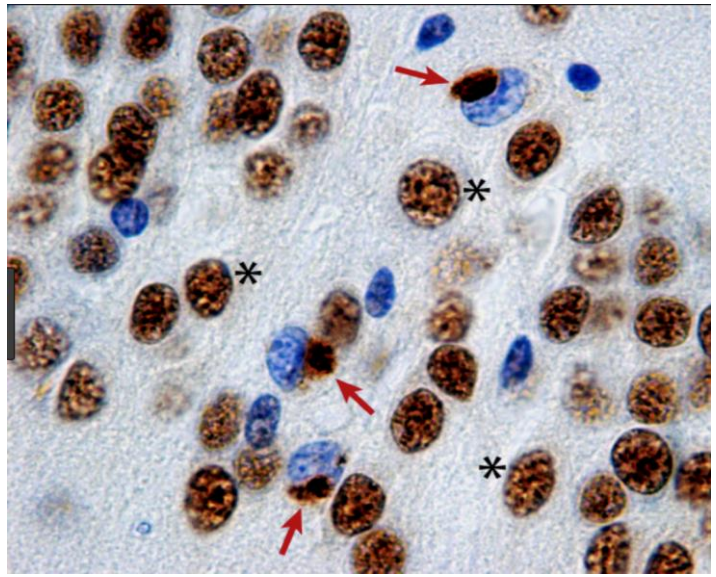
TDP43

Highly conserved heterogeneous nuclear ribonucleoprotein

Located on Chromosome 1→encodes TDP43 protein (414aas)



TDP43→essential gene in mammals, zebrafish, & flies

*Not essential in C. Elegans**

Broadly expressed but expression is very tightly regulated

- Directly regulates its own expression: binds to 3'UTR of its own mRNA
  - *promoting its degradation*

Understanding TDP43's normal structure, function & pathologic aberrations→crucial for delineating mechanisms of disease!

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TDP-43 Structure & Function

Specificity for UG-rich RNA & TG-rich DNA

N-terminal structural domain (1-78)

Ubiquitin like fold & canonical **nuclear localization sequence** (82-98)

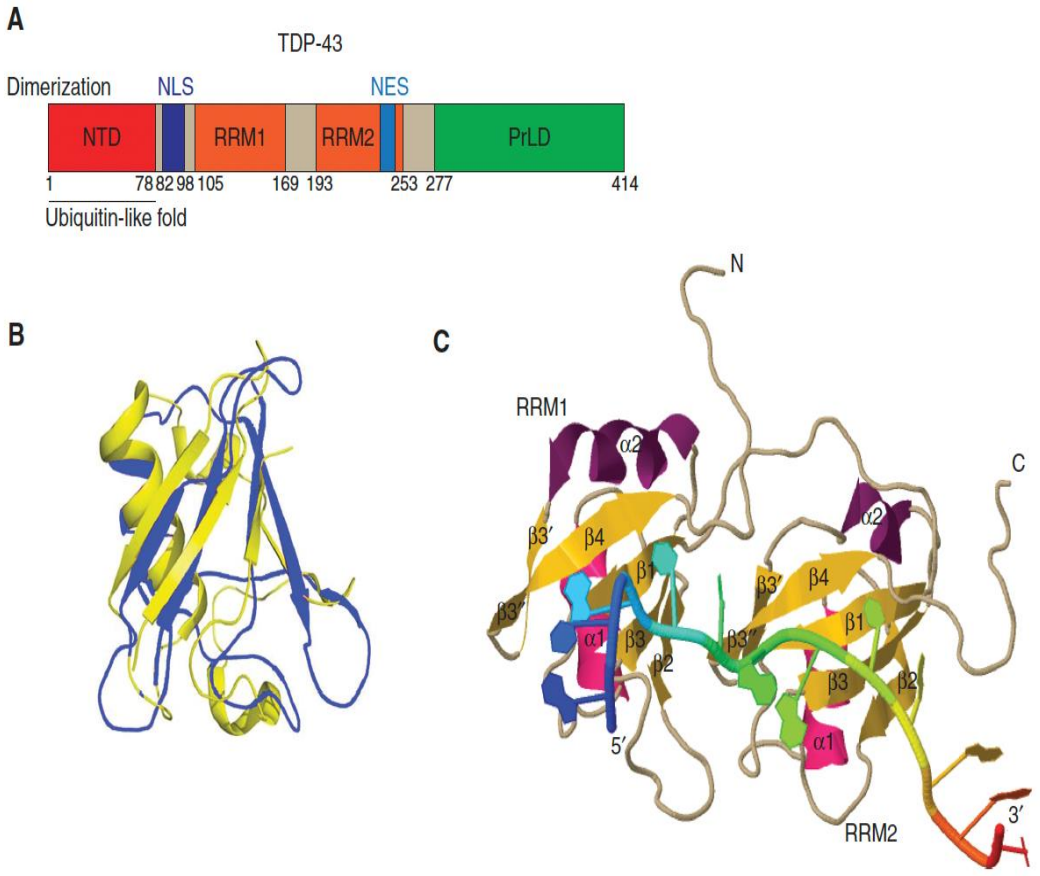
Regulates TDP homodimerization to ensure appropriate folding & mRNA splicing

2 RNA recognition motifs

- RRM1: aas 105-169
- RRM2: aas 193-253→Contains nuclear export sequence (239-250)

C-terminal domain (aas 244-414)

- *"Prion-like domain"*: low complexity, prone to aggregate/form inclusions
- Important for mRNA splicing & hnRNP interactions
- Site of >50 sporadic & ALS-associated mutations



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- de Boer EMJ et al. TDP-43 proteinopathies: a new wave of neurodegenerative diseases. J Neurol Neurosurg Psychiatry. 2020;92(1):86–95.

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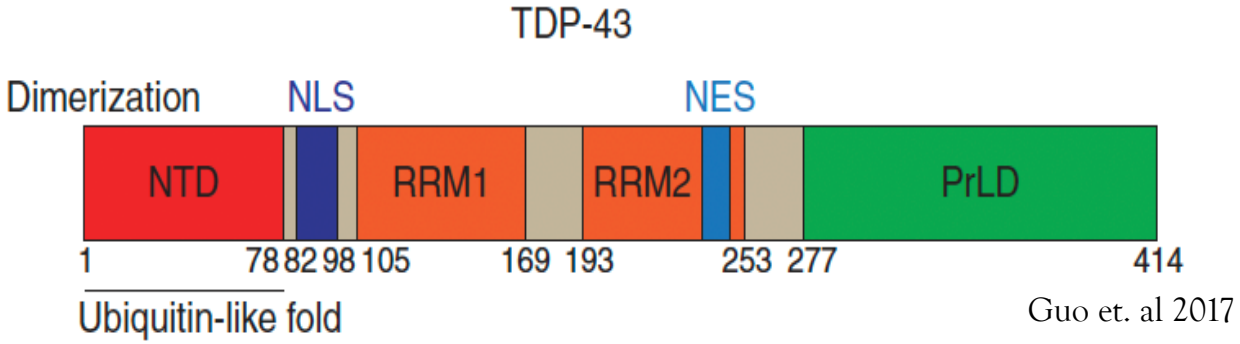
TDP43 Structure & Function

Amyloidogenic core region (residues 311-360)

- 2 alpha-helices that convert into β sheets in TDP43 aggregates

Canonical NLS (82-98) → Critical for TDP43's physiological function

- Mutations or deletions of NLS result in TDP43 mislocalization & aggregation
- Importin-α facilitates TDP43 transport inside nucleus by binding to NLS
- Characteristic of disease models



Guo et. al 2017

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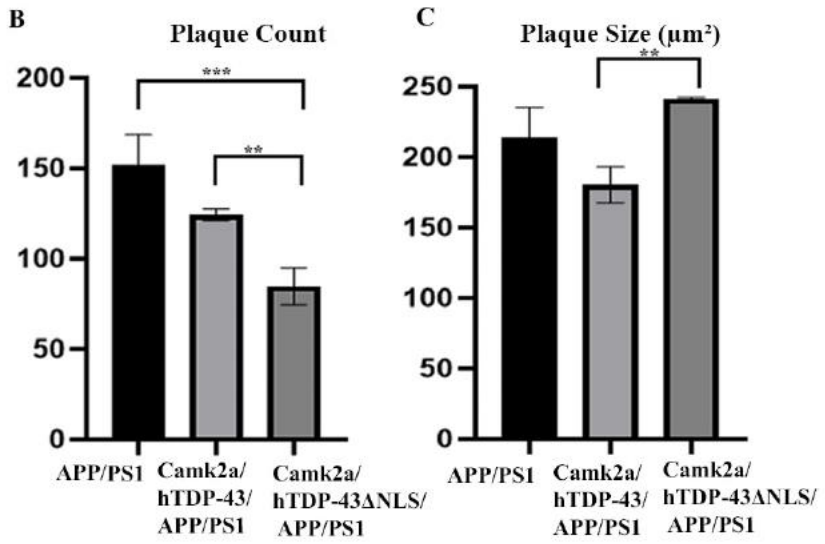
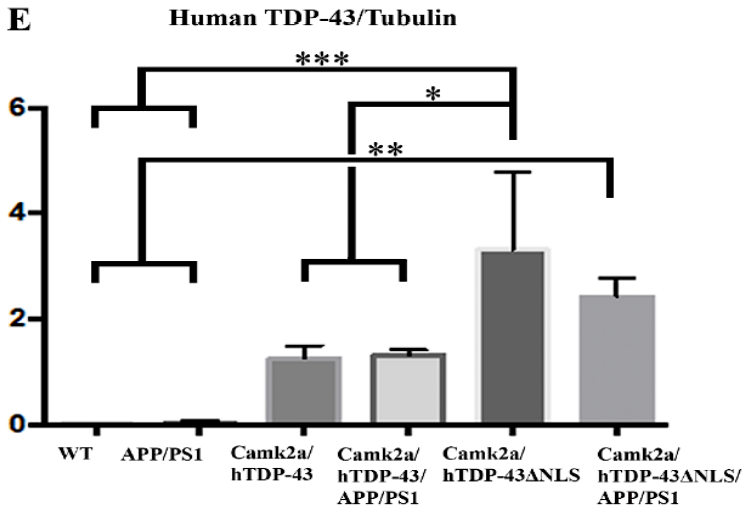
New AD/TDP43 LATE Mouse Model

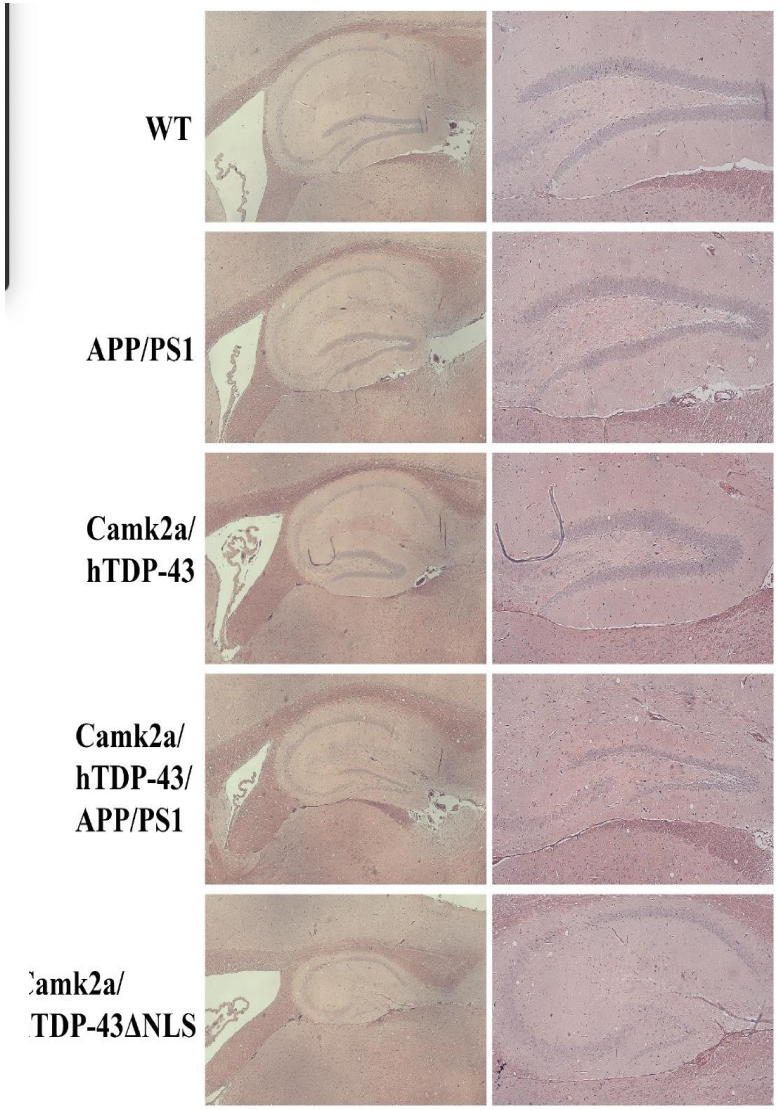
Selectively express human TDP43 & TDP43 with a defective nuclear localization signal (ΔNLS) in hippocampus in APP/PSEN1 background

24- month-old mice display severe neuronal loss in the hippocampus, change in Aβ deposition, changes in neuroinflammation & decrease in survival

Our new HS like model may provide a greater understanding of the pathogenesis of neurodegeneration seen in TDP43 proteinopathies.







Collaboration w/ Dr. Michael Gitcho (manuscript under review)*

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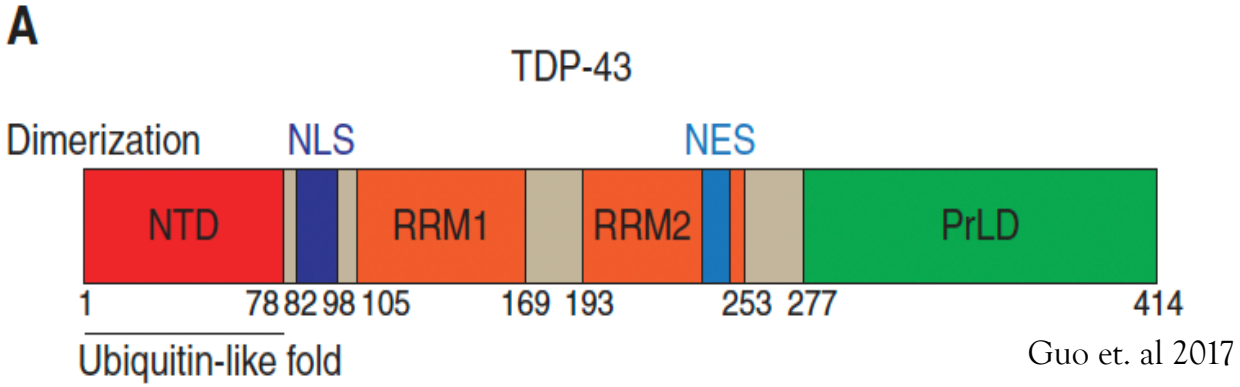
Nuclear Export Sequence (NES)

Remains controversial

TDP43's export from nucleus→cytoplasm

- Thought to be mediated by exportin XPO1 binding to NES in RRM2
- Recent data suggests that export from nucleus to cytoplasm goes not require XPO1 or NES
  - Potentially actually exported via passive diffusion



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TDP43 Function?

Normally mostly located in nucleus: regulates gene expression & other aspects of RNA processing

- Targets >4000 different mRNA transcripts→*ranging from disease-associated transcripts to its own mRNA transcript*

Downregulates Tau expression by destabilizing its mRNA transcripts & might regulate ratio of 4R/3R Tau via alternative splicing of Tau exon 10 (Gu J et. al)

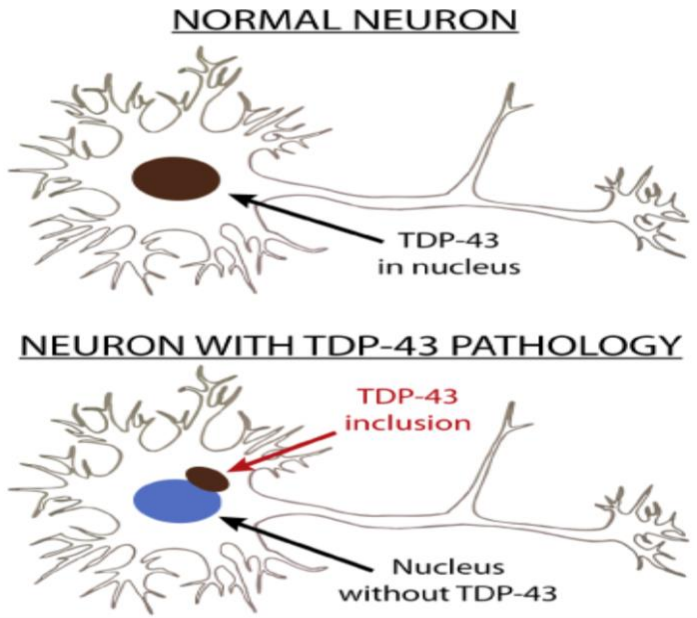
However not replicated in another independent study of AD (Niblock et al)

TDP43 shuttles between the cytoplasm & nucleus

- Dependent on transcriptional needs (Ayala YM et al)

Low TDP43 levels in mitochondria of human neurons

- Age-matched neurons from individuals w/ALS & FTLD?
- Expressed significantly higher amount of mitochondrial TDP-43
  - Altering their morphology and impairing mitochondrial function (Wang W et al).



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TDP43 Function: Pivotal Roles?

Alternative splicing

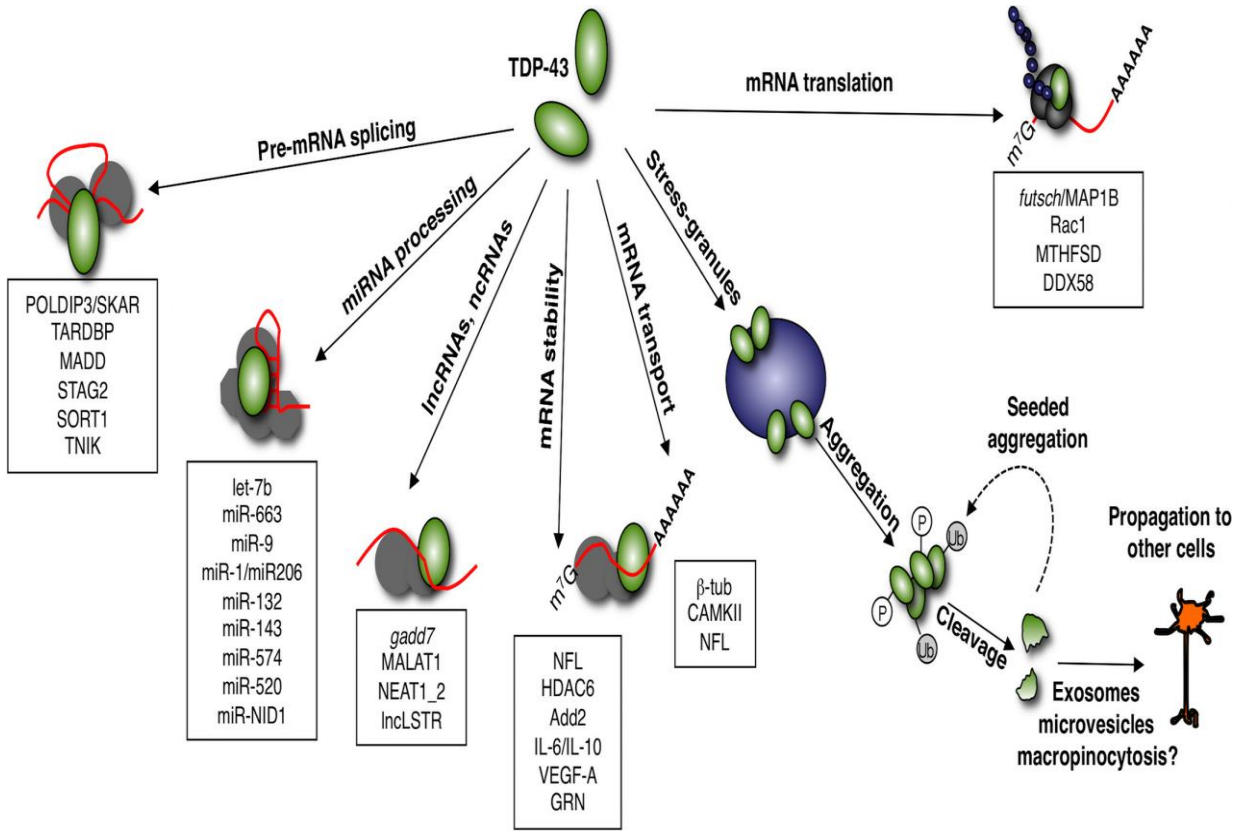
Transcriptional regulation

mRNA stabilization

Cellular stress response

- When cell exposed to stressors→regulates mRNA levels to conserve energy & prioritize survival

- TDP-43 associates w/ribosomes in stress granules
  - temporarily stop translation
  - promote cytoprotective protein synthesis



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Stress granules are cytoplasmic foci in response to cellular stress that contain non-essential RNA

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TDP43's Relationship with Tau?

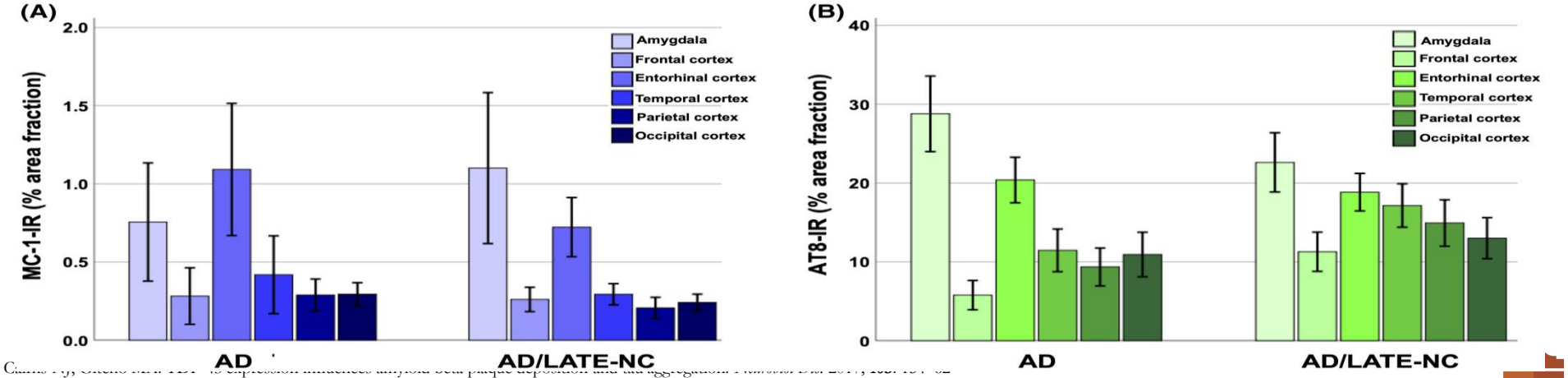
Overexpression of phospho-TDP43 in *APP/PSEN1* mutation transgenic AD mouse model?

- *increased* hyperphosphorylated tau immunoreactivity (Davis SA et al)

Physiologic TDP43 may have suppressive role in regulation of tau mRNA (Gu J et al)

- TDP43 function lost→increases tau mRNA production & subsequent translocation of tau proteins available for hyperphosphorylation

TDP type β inclusions associated w/NFTs in same neuron (Josephs et al, Tome et al, McAleese et al)



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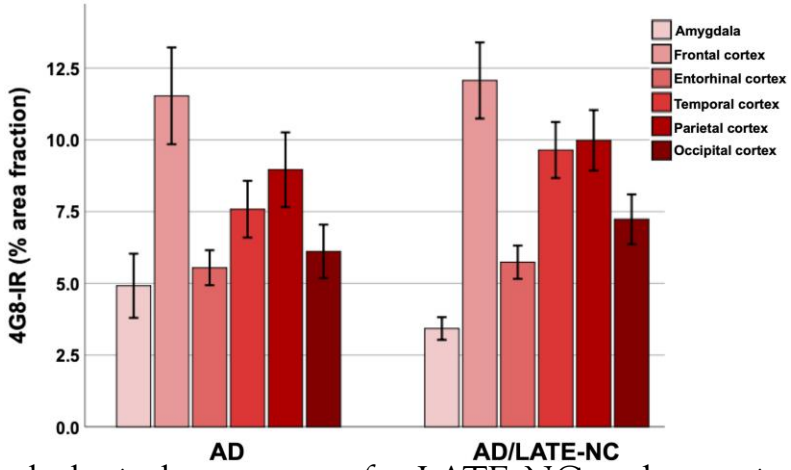
TDP43's Relationship with Aβ?

Knocking out TDP43 in hippocampus & cortex of APP background mouse ***reduced Aβ plaques***, accelerated neurodegeneration & lead to cognitive deficits (LaClair et al)

- Loss of nuclear TDP43 compromises repression of cryptic exons
- Incorporation of cryptic exons that usually induce nonsense mediated decay of associated mRNAs, thereby altering proteome of affected cells.

TDP43 nuclear depletion in forebrain neurons of AD mouse model exacerbated degeneration & correlated ***w/increased prefibrillar oligomeric Aβ & decreased Aβ plaque burden*** (LaClair et al)



61 AD cases underwent neuropathological assessment for LATE-NC and quantitative assessment [area covered by immunoreactivity (IR)] for amyloid-β in the amygdala and five neocortical regions (McAleese et al)

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Table 2. Genes linked to LATE-NC/hippocampal sclerosis (HS) neuropathologic phenotypes

Main finding replicated?	Gene (protein)	Disease-related phenotype(s)	Notes	Selected Refs.
Replicated	*TMEM106B*	LATE-NC, FTLD-TDP, pediatric leukodystrophy, viral pathogenesis	TMEM106B C-terminal amyloidogenic fragments form disease-associated "inclusion bodies"	(129, 171, 173, 188, 242, 243)
	GRN (Progranulin)	LATE-NC, HS, FTLD-TDP, neuronal ceroid lipofuscinosis	GRN is an inflammation-regulating growth factor also implicated in cancers	(167, 170, 244, 245)
	APOE	LATE-NC, ADNC, Lewy body diseases, hypercholesterolemia	*APOE* is prime driver of late-onset AD neuropathologic changes	(111, 129, 171, 205, 236, 246)
	SORL1	LATE-NC+ADNC, clinical AD, clinical FTLD	*SORL1* variants are associated with ADNC+LATE-NC pathologic phenotype	(211, 213, 214, 228)
	ABCC9 (SUR2)	HS, Cantu syndrome, *ABCC9*-related intellectual disability and myopathy syndrome, cardiomyopathy and cardiac arrhythmias	*ABCC9* variants are also associated with vascular malformations and white matter hyperintensities	(129, 169, 170, 217, 247)
Not yet replicated	*KCNMB2*	HS, possibly ALS, Epilepsy	*KCNMB2* encodes a potassium channel expressed in hippocampus	(129, 166, 230, 231, 248)
	WWOX	LATE-NC, HS, arteriolosclerosis, clinical AD, spinocerebellar ataxia, epilepsy	*WWOX* was a GWAS "hit" for clinical AD and pathological LATE/HS	(169, 225, 226, 229, 249)
	AHRGEF28 (RGNEF)	LATE-NC (suggestive), Cri-du-Chat syndrome	ALS lesions have been shown to stain for RGNEF	(233), in press
	TPCN1	LATE-NC (suggestive), clinical AD	TPCN1 is a lysosomal protein linked by GWAS to clinical AD	(213, 228)

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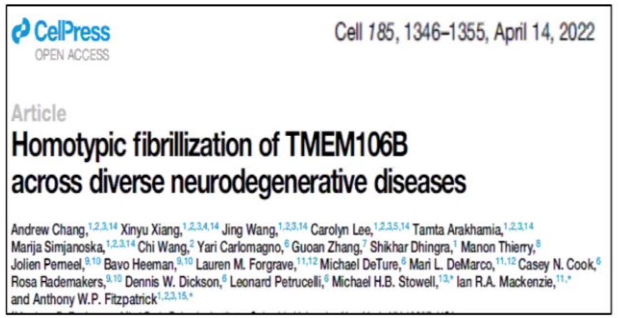
TMEM106b Filaments

Variants in *TMEM106b* affect the risk & severity of FTD

Protective variant: inhibits filament formation, delays disease progression

Risk variant: promotes filament formation, accelerating disease progression


CellPress
OPEN ACCESS

Cell *185*, 1346–1355, April 14, 2022

Article

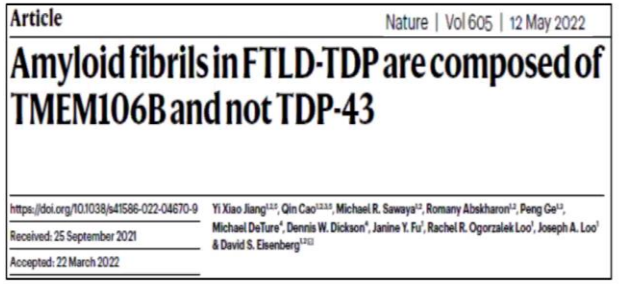
Homotypic fibrillization of TMEM106B across diverse neurodegenerative diseases

Andrew Chang, Xinyu Xiang, Jing Wang, Carolyn Lee, Tamta Arakhamia, Marija Simjanoska, Chi Wang, Yari Carlomagno, Guoan Zhang, Shikhar Dhingra, Manon Thierry, Jolien Perneel, Bavo Heeman, Lauren M. Forgrave, Michael DeTure, Mari L. DeMarco, Casey N. Cook, Rosa Rademakers, Dennis W. Dickson, Leonard Petrucelli, Michael H.B. Stowell, Ian R.A. Mackenzie, and Anthony W.P. Fitzpatrick

Recent Studies Highlighting TMEM106b Filaments?

Chang et al., 2022: Found TMEM106b filaments consistently in all 4 FTLD-*GRN* & older PSP samples

- *age-related presence in various conditions?*


Article

Nature | Vol 605 | 12 May 2022

Amyloid fibrils in FTLD-TDP are composed of TMEM106B and not TDP-43

https://doi.org/10.1038/s41586-022-04670-9

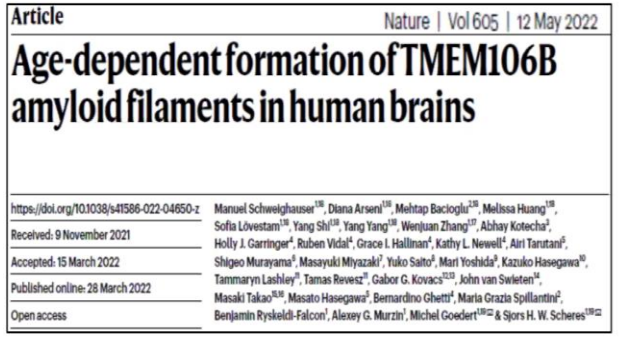
Received: 25 September 2021

Accepted: 22 March 2022

Yi Xiao Jiang, Qin Cao, Michael R. Sawaya, Romany Abskharon, Peng Ge, Michael DeTure, Dennis W. Dickson, Janine Y. Fu, Rachel R. Ogorzalek Loo, Joseph A. Loo & David S. Eisenberg

Jiang et al., 2022: Identified TMEM106b as filamentous protein in other types of FTLD-TDP (vs. TDP43)

- *challenges the exclusive focus on TDP-43?*


Article

Nature | Vol 605 | 12 May 2022

Age-dependent formation of TMEM106B amyloid filaments in human brains

https://doi.org/10.1038/s41586-022-04650-z

Received: 9 November 2021

Accepted: 15 March 2022

Published online: 28 March 2022

Open access

Manuel Schweighauser, Diana Arseni, Mehtap Bacioglu, Melissa Huang, Sofia Lövestam, Yang Shi, Yang Yang, Wenjuan Zhang, Abhay Kotecha, Holly J. Garringer, Ruben Vidal, Grace I. Hallinan, Kathy L. Newell, Airi Tarutani, Shigeo Murayama, Masayuki Miyazaki, Yuko Saito, Mari Yoshida, Kazuko Hasegawa, Tammaryn Lashley, Tamas Revesz, Gabor G. Kovacs, John van Swieten, Masaki Takao, Masato Hasegawa, Bernardino Ghetti, Maria Grazia Spillantini, Benjamin Ryskeldi-Falcon, Alexey G. Murzin, Michel Goedert & Sjors H. W. Scheres

Schweighauser et al., 2022: 25 brain samples across various diseases & ages

- *findings sugegest that TMEM106b filaments may be an age-related feature*
- *potentially independent of specific diseases?*

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TMEM106b Summary?

- **Accumulation of TMEM106b CTFs & filaments is a common age-related process**
- **TMEM106b: subcellular in lysosomal membranes**
  - Maintains lysosomal function
  - Biomarker potential?
- **Consistent features→ FTD-GRN and LATE-NC**
- **Potential therapeutic target?**
- **Perhaps only certain species of TMEM106b CTFs may be related to disease states?**

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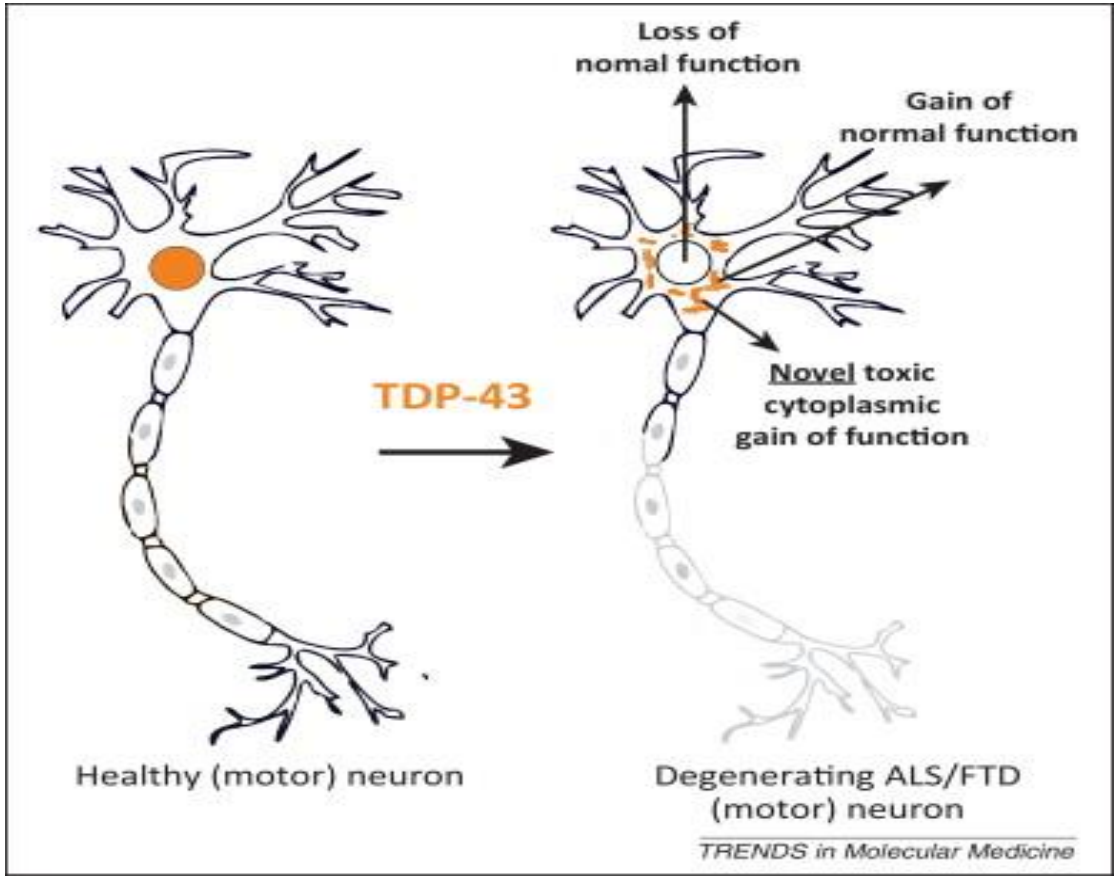
Pathologic TDP43?

Loss of normal nuclear localization

Cytoplasmic protein aggregation



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Loss of normal nuclear TDP43 function?

When TDP-43 aggregates in the cytoplasm→nuclear concentration decreases

Nuclear depletion leads to loss of its normal RNA-regulatory functions

- Disrupts multiple cellular processes & contributes to neurodegeneration
- Disrupts RNA metabolism: Leads to widespread dysregulation of RNA species that TDP43 regulates
  - Alters gene expression: *Errors in splicing: inclusion of cryptic exons/alterations in RNA stability & transport*

May also impair the neuron's ability to cope with stress & repair mechanisms

- Neurons become more vulnerable to other toxic processes
  - *including those triggered by the accumulation of TDP43 inclusions themselves*

Therapeutic strategies to enhance TDP43 nuclear localization are crucial!

- **TDP43 nuclear depletion is a key feature of its pathology**
  - modulating nuclear transport receptors
  - inhibiting nuclear export signals to retain TDP43 within the nucleus

- Suk TR et al. The role of TDP-43 mislocalization in amyotrophic lateral sclerosis. Mol Neurodegener. 2020;15:45.
- Jo M et al. The role of TDP-43 propagation in neurodegenerative diseases: integrating insights from clinical and experimental studies. Exp Mol Med. 2020;52:1652–62.
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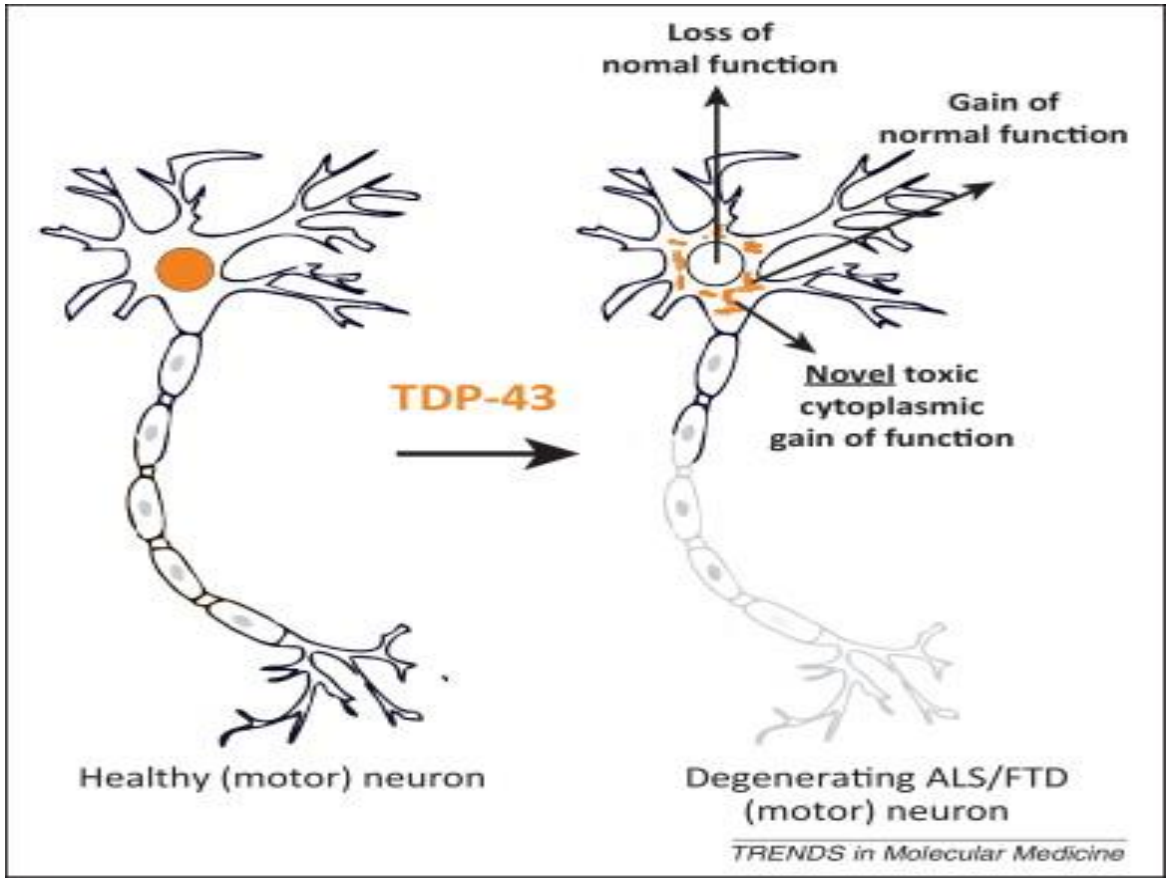

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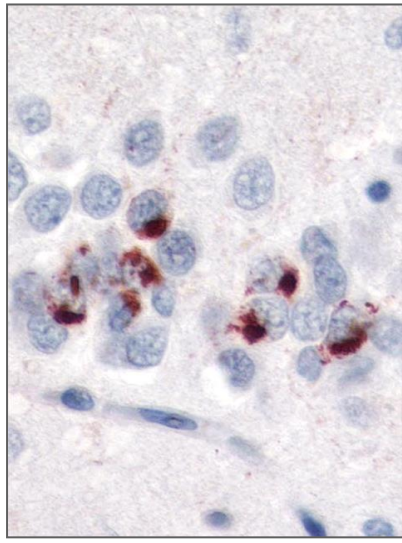
Cytoplasmic TDP43 protein aggregation?

Prion-like Domain plays critical role in TDP43 aggregation
-Promotes TDP43 misfolding into toxic oligomers & fibrillar aggregates

Post-translational modifications impair TDP43's RNA binding & splicing functions
-Phosphorylation, Acetylation

TDP43 is recruited to stress granules under cellular stress
-Hypothesized to influence its aggregation and pathological seeding



Therapeutic strategies?

1) **Inhibit aggregation**: Small molecules to stabilize TDP43's native conformation

2) **Disaggregate existing inclusions:** potentiated variants of Hsp104

3) **Gene therapy:** reduce mutant TDP43 or modify post-translational processing

4) **RNA interference:** knock down specific genetic contributors to pTDP43

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- Conicella AE et al. ALS Mutations Disrupt Phase Separation Mediated by alpha-Helical Structure in the TDP-43 Low- Complexity C-Terminal Domain. Structure. 2016;24:1537–49.

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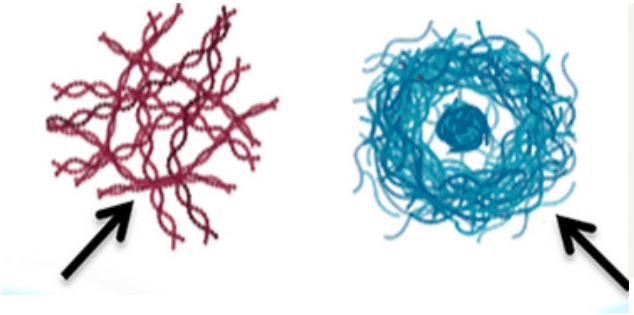
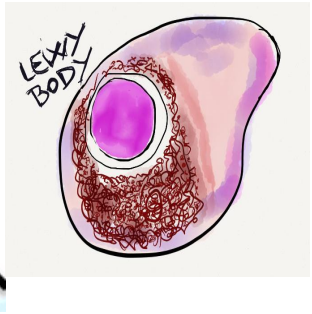
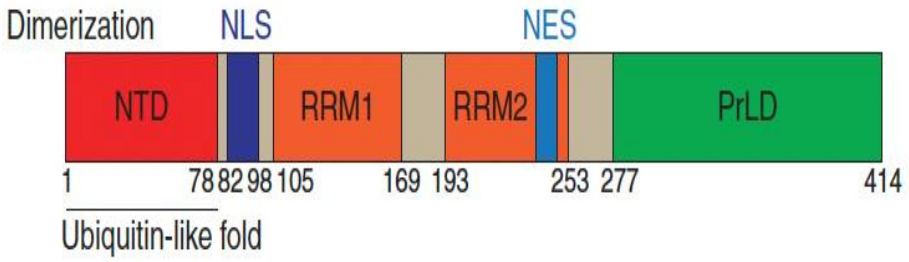
Conclusions

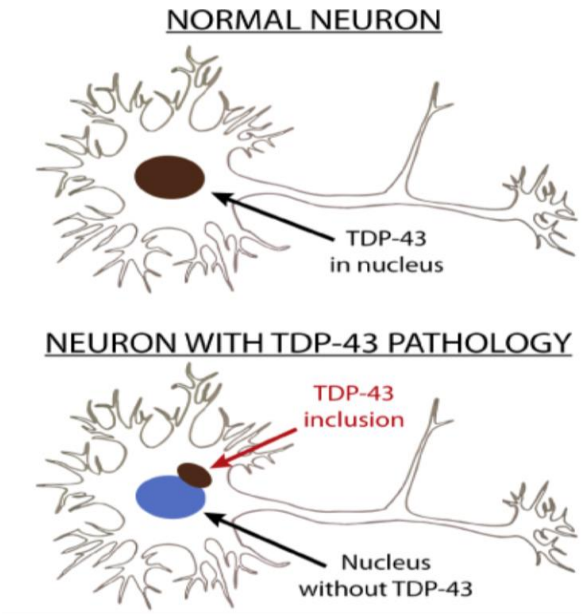
Basic biology of TDP43 is complex & multifaceted

Even more complicated when you consider co-existing Aβ, Tau, LBs TMEM106b….









Loss of function? particularly insidious → less visible than the gain of toxic function

- *But potentially just as harmful!*

Therapeutic Strategies

Aim not only to prevent the toxic gain of function (e.g., aggregation & mislocalization)

Also aim to restore or compensate for loss of TDP43's normal functions in the nucleus

* ***Dual approach*** **(?+ even more simultaneous targeted approaches): ESSENTIAL for effectively addressing the multifaceted nature of TDP43's pathobiology in neurodegenerative diseases!**

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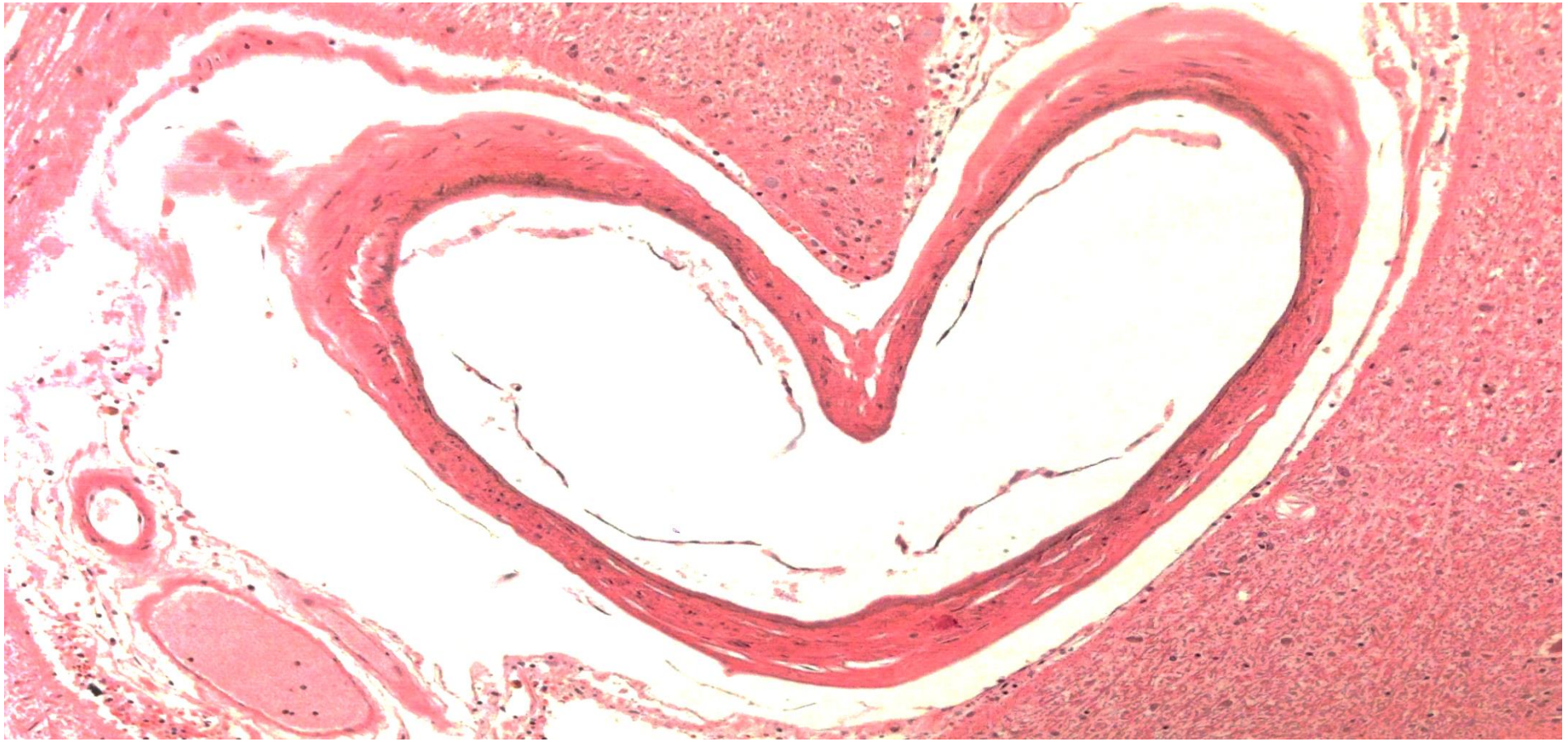

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