UT SOUTHWESTERN MEDICAL CENTER

RNA Binding Proteins and Neurodegenerative Diseases

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Frontotemporal Dementia (FTD)

"Pick's" Disease

Politician: Ralf Klein

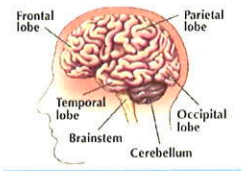
How are FTD and ALS Related?

- #1 Loss of cognition and language
- Some types of FTD also have loss of motor function

- #1 Loss of motor function
- Some ALS forms have a loss of cognition

Pathological Features

Frontotemporal Dementia (FTD)	Amyotrophic Lateral Sclerosis (ALS)
• Loss of neurons in the frontal and temporal lobes	



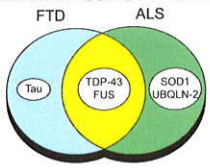
Honig *et al. Sci. Aging Knowl. Environ* 2003

Pathological Features Cont.

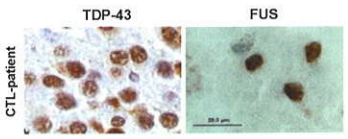
Frontotemporal Dementia (FTD)	Amyotrophic Lateral Sclerosis (ALS)

• Protein aggregation
  • Frontal and temporal lobes
	• Protein aggregation
	  • Upper and lower motor neurons

Common aggregated proteins



Pathological Protein Aggregation



- TDP-43 and FUS aggregate in both sporadic and familial FTD and ALS cases

Etiology

Frontotemporal Dementia (FTD)	Amyotrophic Lateral Sclerosis (ALS)
• Sporadic	• Sporadic

How are Subtypes of FTD and ALS Related?

FTD → Clinical Pathological Genetic ← ALS

Dementia and loss of motor function	TDP-43 and FUS aggregates	TDP-43 and FUS mutations

Do TDP-43 and FUS cause FTD and ALS?

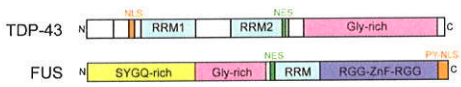
- Biological functions
- Consequences of genetic mutations
- Animal models

Can we use this information to develop targeted therapeutics?

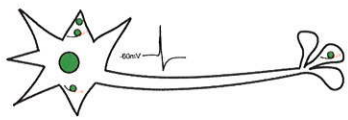
1. Biological Functions of TDP-43 and FUS

Features of TDP-43 and FUS

- RNA binding proteins

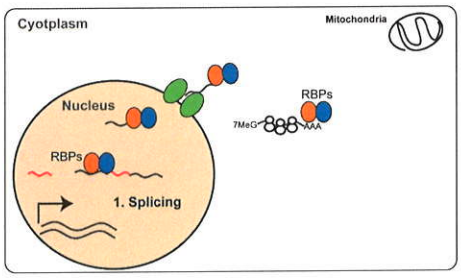


- RNA Recognition Binding motifs (RRM)
- Prion-like domains
- Nuclear-cytoplasmic shuttling proteins

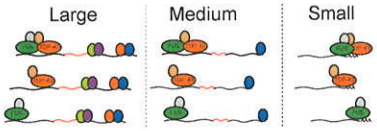


What are RNA Binding Proteins?

- Regulators of post-transcription (a.k.a. RNA metabolism)



TDP-43 and FUS Exist in Ribonucleoprotein Complexes



Sephton C.F. *et al.* JBC, 2011

TDP-43 and FUS Exist in Ribonucleoprotein Complexes

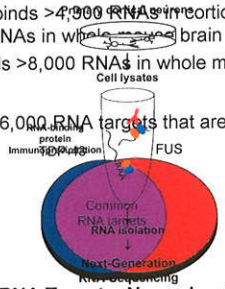
Sephton C.F. *et al.* JBC, 2011

Identification of TDP-43 and FUS RNA Targets

What are TDP-43 and FUS RNA targets?

- TDP-43 binds >4,900 RNAs in cortical neurons and >7,000 RNAs in whole mouse brain
- FUS binds >8,000 RNAs in whole mouse brain

Over 6,000 RNA targets that are the SAME!



#1 RNA Targets: Neurodevelopment

Sephton *et al.* JBC, 2011, Lagier-Tourenne *et al.* Nat. Neuro., 2012

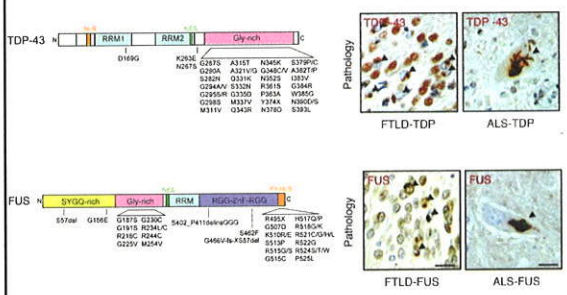
TDP-43 and FUS RNA Targets Associated with Neurodegenerative Diseases

Symbol	Gene Name	Associated Disease
App	Amyloid beta (A4) precursor protein	Alzheimer
Snca &b	α- & β-Synuclein	Parkinson
Chmp2B	Chromatin modifying protein 2B	FTLD-UPS
Fus	Fused in sarcoma	FTLD-FUS, ALS
Mapt	Microtubule-associated protein tau	Pick's, FTLD-tau
Psen1	Presenilin 1	Alzheimer 's
Prnp	Prion protein	Prion
Tdp-43	TAR DNA binding protein	AD, FTLD, PD, H, PP, ALS
Vcp	Valosin-containing protein	FTLD-TDP, myopathy

Sephton *et al.* JBC, 2011, Lagier-Tourenne *et al.* Nat. Neuro., 2012

2. Consequences of genetic mutations

Genetic Mutations of TDP-43 and FUS



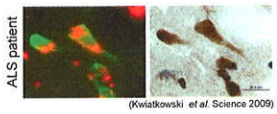
What are the consequences of TDP-43 and FUS mutations?

Consequences of Genetic Mutations:

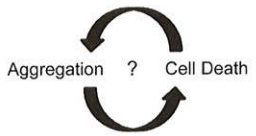
- ✓ Changes in RNA regulation
- ✓ Increased protein stability
- ✓ Protein interactions
- ✓ Aggregate prone

How do Protein Aggregates Form in FTD and ALS?

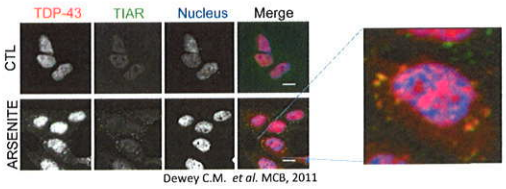
confabulatorcafe.com



(Kwiatkowski *et al.* Science 2009)

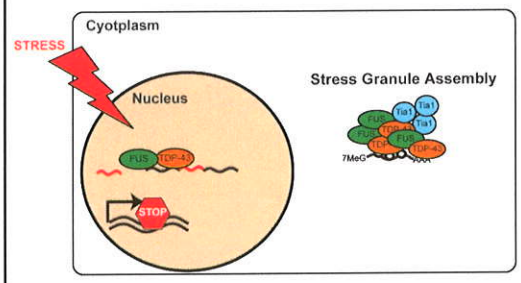


TDP-43 and FUS Stress Granule Formation



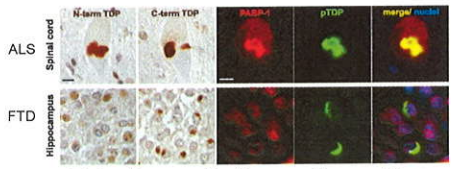
Dewey C.M. *et al.* MCB, 2011

Stress Granule Formation and Protein Aggregates



Stress Granule Markers in TDP-43 and FUS Aggregates

- TDP-43 and FUS aggregate with stress granule markers in ALS patient tissue

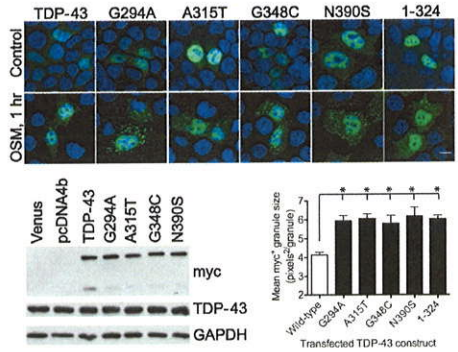


Spinal cord (*upper panels*) or hippocampus (*lower panels*) from FTD-TDP and ALS-TDP

- FUS aggregates with stress granule markers in FTD, but not TDP-43

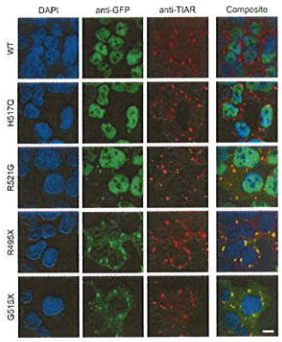
Bentmann E. *et al.* JBC, 2012

TDP-43 Familial Mutations



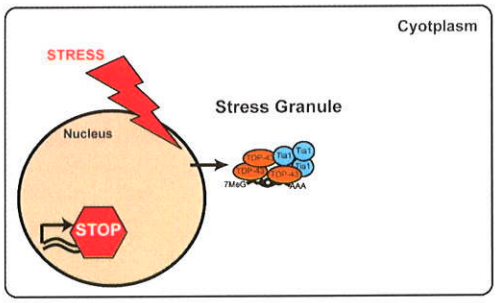
Dewey C.M. *et al.* MCB, 2011

FUS Familial Mutations



Bosco D.A. *et al.* Hum. Mol. Gen. 2010

Model for Protein Aggregation



Potential Drug Targets?

3. Animal models of TDP-43 and FUS

Generation of Animal Models

Knockout: Removal of a gene

TDP-43 gene X = ?

FUS gene X = ?

Transgenic: Overexpression of a gene

TDP-43 mutant gene ↑ = ?

FUS mutant gene ↑ = ?

Generation of Animal Models

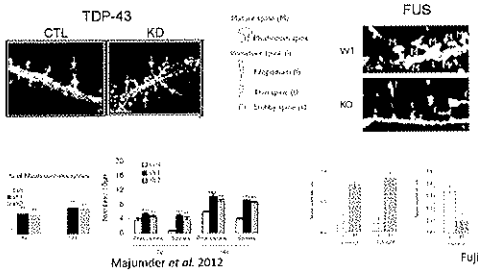
Knockout: Removal of a gene

TDP-43 gene X = embryonic lethal (Sephton *et al.* JBC, 2010)

FUS gene X = die after birth (Hicks *et al.* Nat Gen., 2000)

TDP-43 and FUS Knockout Mice

- Highly expressed in the CNS during development
- **#1 RNA Targets: Neurodevelopment**



Majumder *et al.* 2012

Fujii *et al.* 2009

Summary of TDP-43 and FUS Transgenic Models

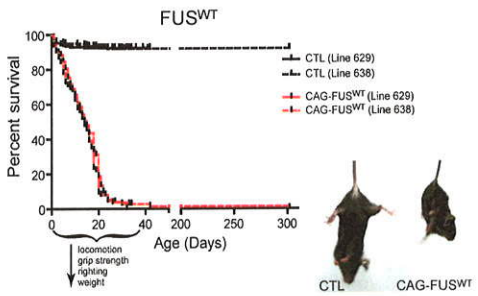
Transgenic: Overexpression of a gene

TDP-43 gene ↑ =

FUS gene ↑ =

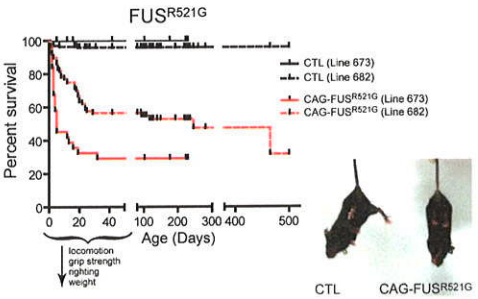
Sephton *et al.* unpublished., Swarup V. *et al.* Brain, 2011

FUS Transgenic Mice Develop ALS Phenotypes



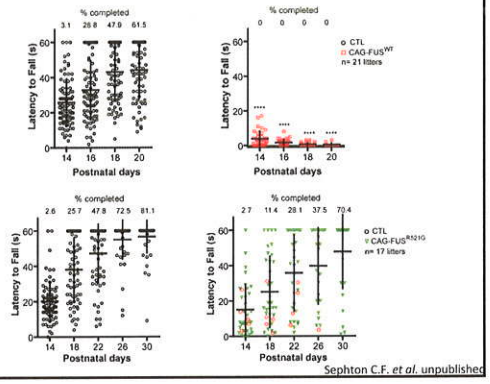
Sephton C.F. *et al.* unpublished

FUS Transgenic Mice Develop ALS Phenotypes



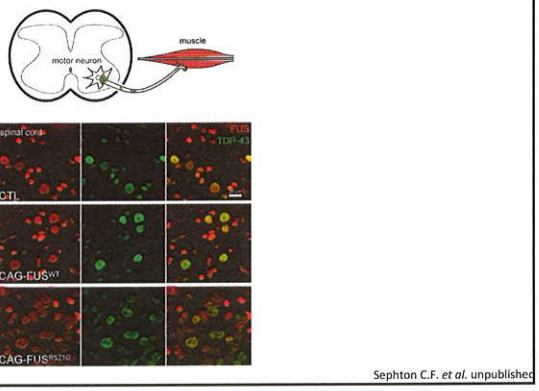
Sephton C.F. *et al.* unpublished

Behavior of FUS Transgenic Mice



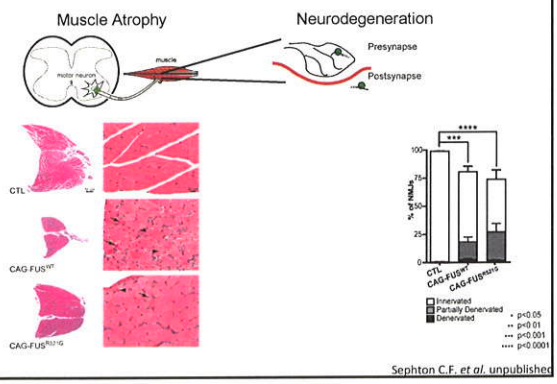
Sephton C.F. *et al.* unpublished

No Aggregation in FUS Transgenic Mice



Sephton C.F. *et al.* unpublished

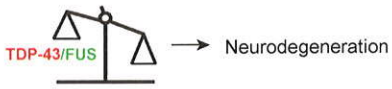
FUS Transgenic Mice Pathology



Sephton C.F. *et al.* unpublished

Summary

- ✓ TDP-43 and FUS are essential RNA binding proteins
- ✓ Altering levels of TDP-43 and FUS in the cell leads to toxicity
- ✓ Mutations in TDP-43 and FUS affect their biology



Future Work:

FTD "Pick's" Disease

Politician: Ralf Klein

ALS "Lou Gehrig's" Disease

Football Player: Steven Gleason

- ❑ How do TDP-43 and FUS mutations affect RNA metabolism?
- ❑ How to TDP-43 and FUS become mislocalized in the cell?
- ❑ Therapeutic approaches?
  - Drug screens to prevent misslocalization
  - Drugs to prevent aggregation

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SOUTHWESTERN MEDICAL CENTER

RNA Binding Proteins and Neurodegenerative Diseases

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Contact: Chantelle.Sephton@utsouthwestern.edu

1. What are Frontotemporal dementia (FTD) and Amyotrophic lateral sclerosis (ALS)?
2. What is the cause of these diseases?
3. Who is affected by these diseases?
4. How are these diseases similar?
5. What are RNA binding proteins?
6. What RNA binding proteins are involved in contributing to some types of FTD and ALS?
7. How do scientists think TDP-43 and FUS contribute to FTD and ALS?
8. Based on the information given, what research needs to be done to find out more about factors that cause FTD and ALS?
9. How can we treat/cure FTD and ALS?

Resources: http://www.theaftd.org/ ALSForums http://www.alsforums.com/ ALSTDI http://www.als.net/ http://www.bluefieldproject.org/ http://www.teamgleason.org/