RNA Binding Proteins and Neurodegenerative Diseases

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STARS Symposium
October 13th, 2012

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

<table>
<thead>
<tr>
<th>Frontotemporal Dementia (FTD)</th>
<th>Amyotrophic Lateral Sclerosis (ALS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Loss of neurons in the frontal and temporal lobes</td>
<td>- Protein aggregation</td>
</tr>
<tr>
<td></td>
<td>- Upper and lower motor neurons</td>
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</tbody>
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![Brain diagram](image-url)

### Pathological Features Cont.

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**Common aggregated proteins**

- TDP-43
- FUS
- BSGR-2

### 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)
Identification of TDP-43 and FUS RNA Targets

What are TDP-43 and FUS RNA targets?
- TDP-43 binds >4,000 RNAs in cortical neurons and >7,000 RNAs in whole mouse brain
- FUS binds >8,000 RNAs in whole mouse brain

Over 8,000 RNA targets that are the SAME!

#1 RNA Targets: Neurodevelopment
TDP-43 and FUS RNA Targets Associated with Neurodegenerative Diseases

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Gene Name</th>
<th>Associated Disease</th>
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<tbody>
<tr>
<td>App</td>
<td>Amyloid beta (Aβ) precursor protein</td>
<td>Alzheimer</td>
</tr>
<tr>
<td>Syn 1/4</td>
<td>α-β-Synuclein</td>
<td>Parkinson</td>
</tr>
<tr>
<td>Chrom2B</td>
<td>Chromatin-modifying protein 2B</td>
<td>FTLD, ALS</td>
</tr>
<tr>
<td>FUS</td>
<td>Fused in sarcoma</td>
<td>FTLD, FUS, ALS</td>
</tr>
<tr>
<td>Map1L</td>
<td>Microtubule-associated protein tau</td>
<td>Polyglutamine, FTLD</td>
</tr>
<tr>
<td>Prp1</td>
<td>Prepronin 1</td>
<td>Alzheimer’s</td>
</tr>
<tr>
<td>Prp19</td>
<td>Prion protein</td>
<td>Prion</td>
</tr>
<tr>
<td>Top-43</td>
<td>TAR DNA binding protein</td>
<td>AD, FTLD, PD, FTLD, ALS</td>
</tr>
<tr>
<td>Yop</td>
<td>Valosin-containing protein</td>
<td>FTLD, TOP, myopathy</td>
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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?

TDP-43 and FUS Stress Granule Formation

Dawson C.M. et al. NCI, 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
- FUS aggregates with stress granule markers in FTD, but not TDP-43

TDP-43 Familial Mutations

Bentivoglio E. et al, JBC 2012

Devos C.M. et al, MGL 2012
FUS Familial Mutations

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 \( \uparrow = ? \)
- FUS mutant gene \( \uparrow = ? \)

TDP-43 and FUS Knockout Mice

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

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Magriso et al. 2012
Tal et al. 2009
Summary of TDP-43 and FUS Transgenic Models

Transgenic: Overexpression of a gene

\[ \text{TDP-43 gene} \uparrow = \text{FUS gene} \uparrow \]

FUS Transgenic Mice Develop ALS Phenotypes

FUS\textsuperscript{WT}

\[
\begin{array}{c}
\text{Survival} \\
0 \quad 20 \quad 40 \quad 60 \quad 80 \quad 100
\end{array}
\]

\[
\begin{array}{c}
\text{Age (Days)}
0 \quad 20 \quad 40 \quad 60 \quad 80 \quad 100 \quad 120 \quad 140 \quad 160 \quad 180 \quad 200
\end{array}
\]

FUS Transgenic Mice Develop ALS Phenotypes

FUS\textsuperscript{R152G}

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\begin{array}{c}
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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
ALS "Lou Gehrig's" Disease

Politician: Ralf Klein
Football Player: Steven Gleason

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

There is Hope!

AFTD
http://www.aftd.org

ALSDIN
http://www.alsdini.org

The ALS Forum
http://www.alsforum.org

ALSDI
http://www.alsdi.org
Acknowledgments:

Yu Lab-UTSW
Gang Yu
Mieu Brooks
Amanda Ray
Chris Liu
James West
Cong Yu
Basar Cenk
Daniel Dries
Joachim Herz-UTSW

Lin Lab-UTSW
Weichun Lin
Yun Liu

Pathology Core-UTSW
Jim Richardson
John Shelton

Zhou Lab, T. Jefferson University
Hongxia Zhou
Xugang Xia

Funding:
Friend's of the Alzheimer's Disease Center
Consortium for Frontotemporal Dementia Research
National Institutes of Health

R.NA Binding Protein and Neurodegenerative Diseases
Presenter: Charlotte P. Ingelmo, Ph.D.
Contact: Charlotte.Ingelmo@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 various types of FTD and ALS?
7. How do we understand that 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 FTD and ALS?