Finding proteins with prion-like domains and their involvement in neurodegenerative diseases: FUS and HNRNPD

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Introduction: Prionoids & RNA-binding Proteins

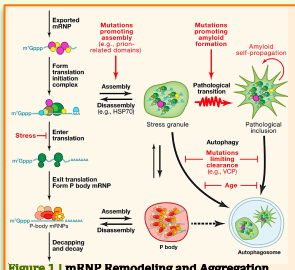


Figure 1 | mRNP Remodeling and Aggregation in the lifecycle of an mRNA [1].

A fascinating and potentially revolutionary new concept is emerging in several neurodegenerative diseases. It involves the propagation of **RNA-protein aggregates** from cell to cell during the onset and progression of diseases. It now appears that many "protein-folding" diseases, such as Alzheimer's and Parkinson's diseases, can be transmitted between cells by a **prion-like mechanism**.

RNA-binding proteins affect **pre-mRNA processing** and are **transported with the mRNA to the cytosol**, where they are removed by translation-dependent and independent mechanisms for recycling into the nucleus. Once into the cytosol, when mRNAs are not engaged in translation, they assemble into **P bodies** or **Stress Granules (SGs)**.

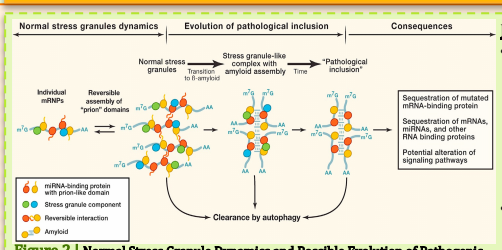


Figure 2 | Normal Stress Granule Dynamics and Possible Evolution of Pathogenic Inclusions [1].

Key points:

- RNA-binding proteins contain such **prion-like domains** or low complexity (LC) domains: mediate assembly into higher-order structures
- **Bioinformatic algorithms** detect LCs domains

Algorithms to detect prion-like domains

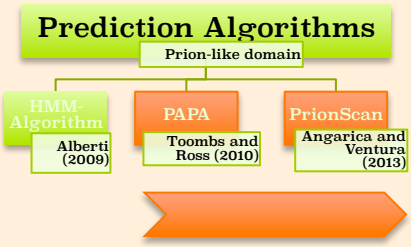


Figure 3 | Score PrionScan-PAPA correlation graphic.

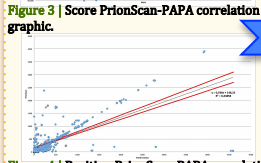


Figure 4 | Position PrionScan-PAPA correlation graphic.

Table 1 | FUS and HNRNPD Human RNA- binding proteins with prion-like domains. FUS and HNRNPD human proteins were scanned for prion-like domains using the PAPA and PrionScan algorithms. The location of the prion-like domain and a core region of highest score are provided.

Protein	Prion domain rank (whole genome)	Prion domain rank (RRM proteins)	Prion domain (core) residues	Prion domain central residues		Prion propensity Score (FoldIndex)		Yeast overexpression phenotype (toxicity & localization)
				PAPA (Toombs)	PrionScan	PAPA (Toombs)	PrionScan	
FUS	12	1	1-237 (118-177)	40-80 (39)	137-197 (137)	0.101 (-0.211)	46.168	Highly toxic, cytoplasmic aggregates
HNRNPD	29.5	5	262-355 (281-340)	292-332 (219)	280-330 (280)	0.164 (-0.291)	39.869	Mildly toxic, diffuse nuclear

FUS/TLS & HNRNPD

Domains and Mutations

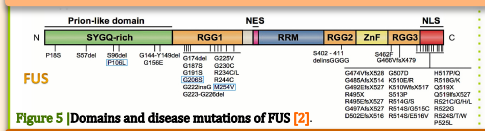


Figure 5 |Domains and disease mutations of FUS [2].

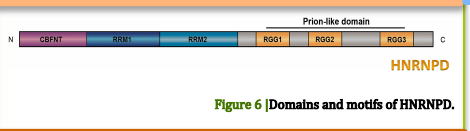


Figure 6 |Domains and motifs of HNRNPD.

Implication in disease

	Gene	Disease	Mutation	Location	Mechanism	Process
RNA-Binding Protein	**FUS**	ALS (Amyotrophic lateral sclerosis)	Missesense, nonsense, in/del, splicing	Exons. (Protein domains: NLS, NES, Prion-like)	RNA gain of function	**FUS protein aggregates**
		ETM4 (Hereditary essential tremor 4)	Missense, nonsense	Exons	RNA loss of function	Unknown
		FTLD (Frontotemporal lobar degeneration)	Missense	Exons, splice sites	Unknown	**FUS protein aggregates**
		Leukemia and Sarcoma	Translocation transcription factor	Prion-like domain	Dysfunction transcription factor	Misfolding, aberrant oligomerization
	HNRNPD (Determined by similarity with RNA-binding proteins)	ALS	Unknown			
		FTLD				
		WDM (Welander distal myopathy)				
		IBMPFD (Inclusion body myopathy with early onset paget disease with or without frontotemporal dementia)				

Cellular localization and function

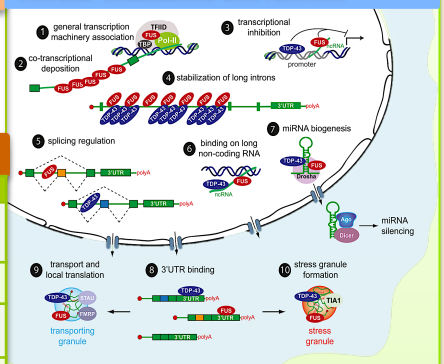


Figure 7 | Proposed functions for FUS/TLS [3].

Nucleus and **cytoplasm** are the **subcellular localization** of these two proteins. The FUS functions are represented in **Figure 7**.

HNRNPD is present in a big amount of biological processes as FUS: RNA catabolic process, RNA metabolic process, RNA processing, RNA splicing, gene expression, mRNA metabolic process, mRNA splicing (via spliceosome), regulation of mRNA stability and regulation of transcription (DNA-templated), poly(A) RNA binding and **telomeric DNA binding**.

Prion Mechanisms

Cellular stress induces **FUS/TLS** or **HNRNPD** incorporation into **stress granules**, which form through the ordered aggregation of several RNA-binding proteins complexed RNA molecules. This physiologic reaction to cellular stress may be an initial trigger for pathogenic inclusion formation, given that the increased local protein concentration and RNA scaffolding molecules may facilitate ordered aggregation of FUS/TLS or HNRNPD. In this context, the functional conformational changes of these two proteins associated with their physiological roles in stress granule formation may transform into **pathogenic,** self-perpetuating, irreversible aggregation upon **chronic cellular stress** and **defects in stress granule disassembly** occurring with aging. Possible **cell-to-cell spread** of prion-like aggregates may underline or contribute to disease spread from a focal initiation.

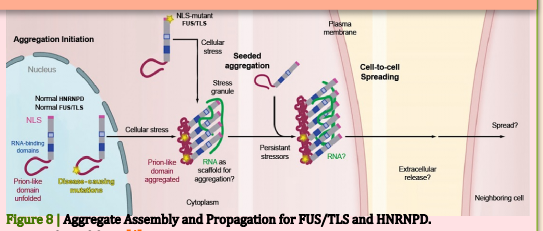


Figure 8 | Aggregate Assembly and Propagation for FUS/TLS and HNRNPD.
Figure adapted from [4].

Relevant references

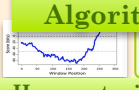
1. Ramaswami M, Taylor JP, Parker R. Altered Ribostasis: RNA-Protein Granules in Degenerative Disorders. Cell. 2013; 154: 727-736.
2. Dormann D, Bentmann E. Stress granules in neurodegeneration – lessons learn from TAR DNA binding protein of 43 kDa and fused in sarcoma. FEBS Journal. 2013; 280: 4348-4370.
3. Ling SC, Polymenidou M, Cleveland DW. Converging Mechanisms in ALS and FTD: Disrupted RNA and Protein Homeostasis. Neuron, Cell. 2013; 79: 416-438.
4. Cleveland DW, Polymenidou Magdalini. The seeds of Neurodegeneration: Prion-like spreading in ALS. Cell. 2011; 147: 498-508.

Concluding Remarks

Animals models

Identifying solutions for correcting defective RNA and protein proteostasis

New Algorithms

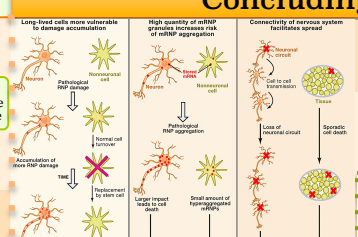


prion-domain prediction with the aggregation-prone

Improving Protein Homeostasis

Therapeutic approaches [3]

Future: investigation and treatment



Why neurodegenerative diseases?

Figure 9 | Models for the Selective Sensitivity of Neurons to Altered Ribostasis [1].

Prion mechanism as clinical strategy?

- Diseases caused by proteins with excess of activity
- Pathogens