# PRION-LIKE PROTEINS, PHASE SEPARATION AND NEURODEGENERATIVE DISORDERS


**Marcos Gil García**

Tutored by Prof. **Salvador Ventura Zamora**

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## INTRODUCTION

Proteins are molecules implied in a myriad of tasks in the cell. To perform biological functions, proteins need to fold into defined three-dimensional structures. Mistakes in this complex process produce unfolded states, ultimately leading to the formation of stable **aggregates.**

The role played by intrinsically disordered proteins in cell processes is receiving increasing attention. These proteins promote phase separation states in cytoplasm and punctual mutations in their sequences are behind **neurodegenerative disorders.**

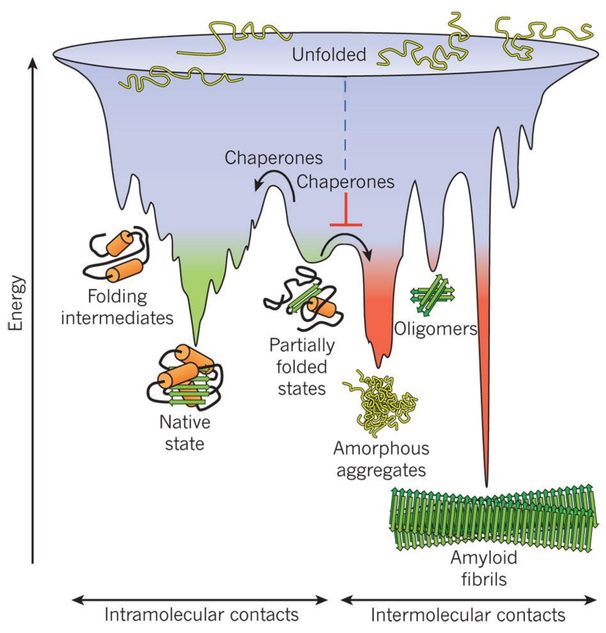



Figure 1: Folding funnel hypothesis [1].

## WHAT IS A PRION-LIKE PROTEIN?

Prion-Like proteins are a group of proteins sharing long disordered domains rich in Gly, Tyr and polar amino acids, known as **Low Complexity Domains** (LC domain). Most of these polypeptides are **DNA or RNA binding proteins** and they are important components of **non-membrane functional structures.**

Fused in Sarcoma (FUS) protein as an example of Prion-Like protein

- ❖ Predominantly nuclear protein
- ❖ Involved in RNA homeostasis
- ❖Related with Amyotrophic Lateral Sclerosis (ALS)

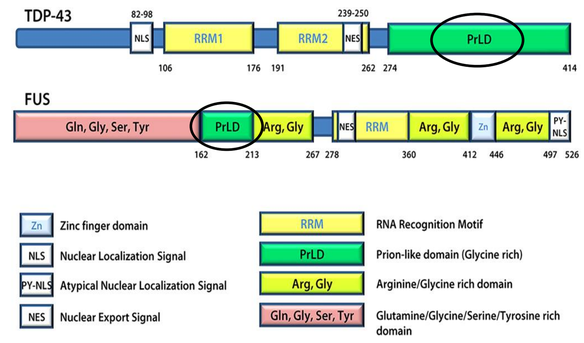



Figure 2: TDP-43 and FUS sequences representation [2].

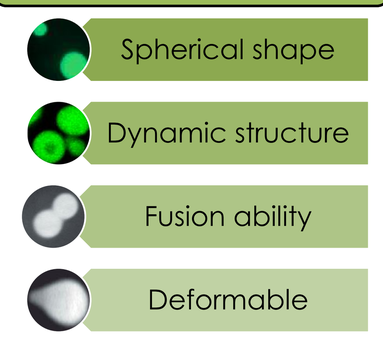
## LIQUID-LIQUID PHASE SEPARATION

**Dynamic** macromolecular assemblies maintained by specific protein-protein and protein-nucleic acids **weak interactions**.

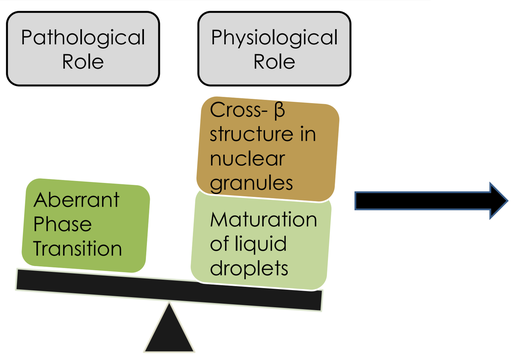
What is needed for a liquid phase separation?

- ❖ Interactions among Low Complexity Domains
- ❖ A defined protein concentration that does not compromise dynamism

Hallmarks




Controversy about the role of cross- β structure



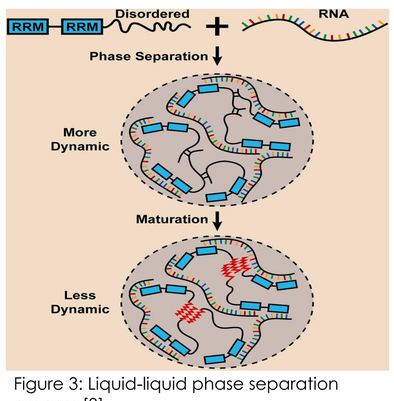




Figure 3: Liquid-liquid phase separation process [3].

## ABERRANT PHASE TRANSITION

Mistakes in phase separation equilibrium produce an **aberrant transition** to a fibrous and **pathological** state.

Which is the main source promoting an aberrant phase transition?

- ❖Mutations in Prion-like proteins
- ❖ High concentration of Prion-like proteins inside phase separation

Low Complexity Domains of Prion-Like proteins are essential to promote phase transition

- ❖Low Complexity Domain of TIA1 mediates aggregation reactions in the presence of b-isox compound

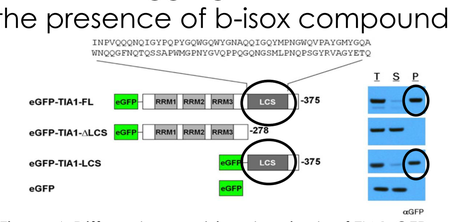



Figure 4: Different recombinant variants of TIA1-GFP localize in different fractions depending on the presence of b-isox [4].

Punctual mutations in Low Complexity Domains promote an aberrant phase transition

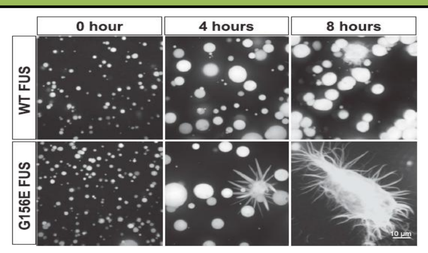



Figure 5: The aberrant phase transition is clear in G156E FUS sample at 8h [5].

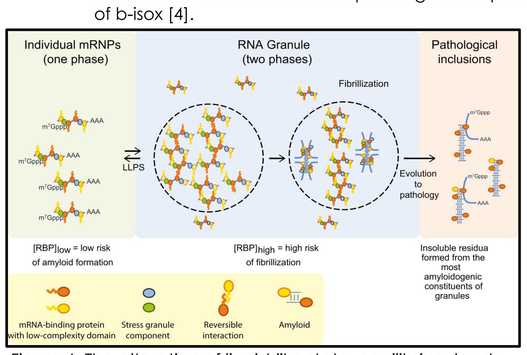



Figure 6: The alteration of liquid-like state equilibrium leads to pathological conformations [6].

## NEUROPATHOLOGY OF PRION-LIKE PROTEINS

Mutations in Prion-like proteins are involved in the onset of **neurodegenerative disorders**.

❖ Punctual mutations in FUS protein are related with the onset of ALS

FUS-R521C mutant decreases dendrite growth

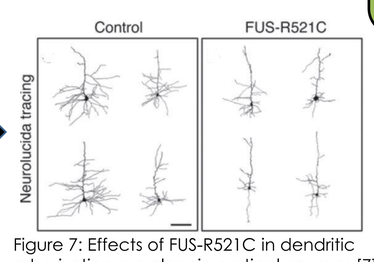



Figure 7: Effects of FUS-R521C in dendritic arborization are clear in cortical neurons [7].

Failure in FUS-dependent DNA repair causes neurodegeneration

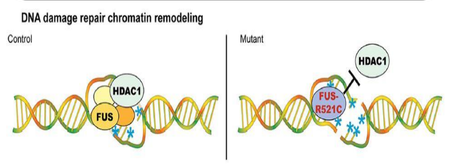



Figure 8: Mechanisms of FUS and HDAC1 in DNA repair [7].

## CONCLUSION

In contrast to what is usually assumed, the neurotoxic mechanism behind the aberrant phase transition of prion-like proteins **is not caused by the intrinsic toxicity of the amyloid-like aggregates,** but rather results from the role of RNA-binding proteins in transcriptional and DNA repair processes. **Amyloid-like deposits inhibit the correct function of RNA-binding proteins**, decreasing cell fitness and viability.

This novel mechanism **will change the way we look at neurodegenerative disorders,** likely opening **novel therapeutic opportunities.**

## REFERENCES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