DECODING THE KEY INSIDE THE PATHOGENESIS OF TDP-43 IN ALS DISEASE

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INTRODUCTION

Liquid-liquid phase separation (LLPS) is a relevant physical process in which membraneless organelles are formed and is essential for cell survival. In this context, **mutations in TDP-43**, which is a LLPS-forming protein, dysregulate LLPS causing **protein aggregation** in ALS disease. Therefore, the study of TDP-43 pathogenesis can reveal clues to unravel ALS disease and sparks hope for **future therapies**.

Objective

To study the mechanism of LLPS in TDP-43 and its relationship with ALS disease.

Metodology

Literature review via PubMed.

LIQUID-LIQUID PHASE SEPARATION (LLPS)

What LLPS is?

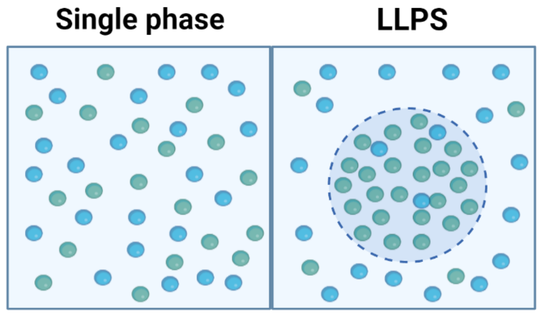


Fig1. Schematic representation of LLPS.

LLPS is a cellular process that generates **two phases**: one highly concentrated in macromolecules and one dilute with low concentration. Due to its **liquid and solid features,** it can exchange molecules with the solution, and create different microenvironments according to cellular needs.

What factors modulate and drive LLPS?

1. Scaffolds and clients
2. Salt concentration and Temperature
3. Posttranslational Modifications (PTMs)
4. Protein structure and IDRs

Fig2. Protein with both folded and disoder regions.

IDRs allow the interaction with other proteins or RNAs making possible the LLPS and **influencing the phase behaviour**

How IDR mutations affect LLPS?

Mutations in IDR can **dysregulate LLPS** causing an aberrant phase transition. Protein aggregates are observed in several **neurogenerative diseases.**

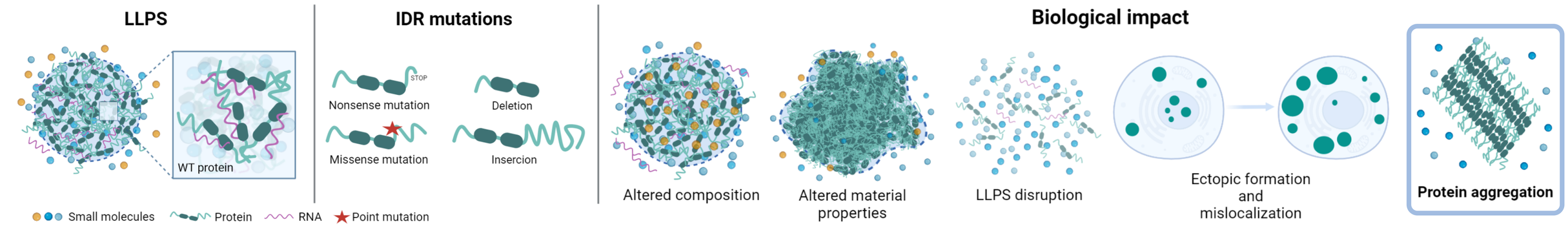


Fig3. Schematic representation of different IDR mutations and their biological impact in LLPS.

RNA BINDING PROTEIN: TPD-43

TDP-43 aggregates have been found in aprox. 97% of ALS patients.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that affects upper and lower **motor neurons**, causing progressive muscle weakness and dystarthia, among others. The incidence is low and there are unknown, **sporadic and familiar cases**. Genes such as *C9orf72, SOD1* and *TARDBP* are associated with ALS.

TDP-43 contains 3 regions. NTD of TDP-43 promotes CTD interactions necesarry for LLPS

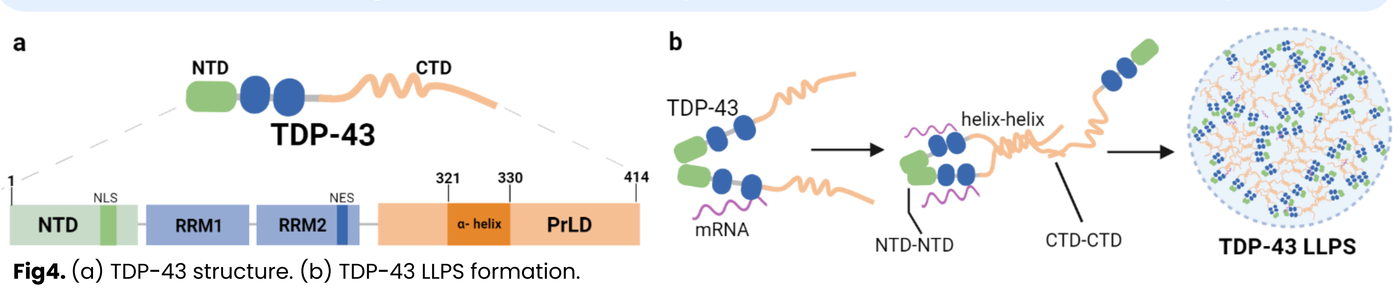
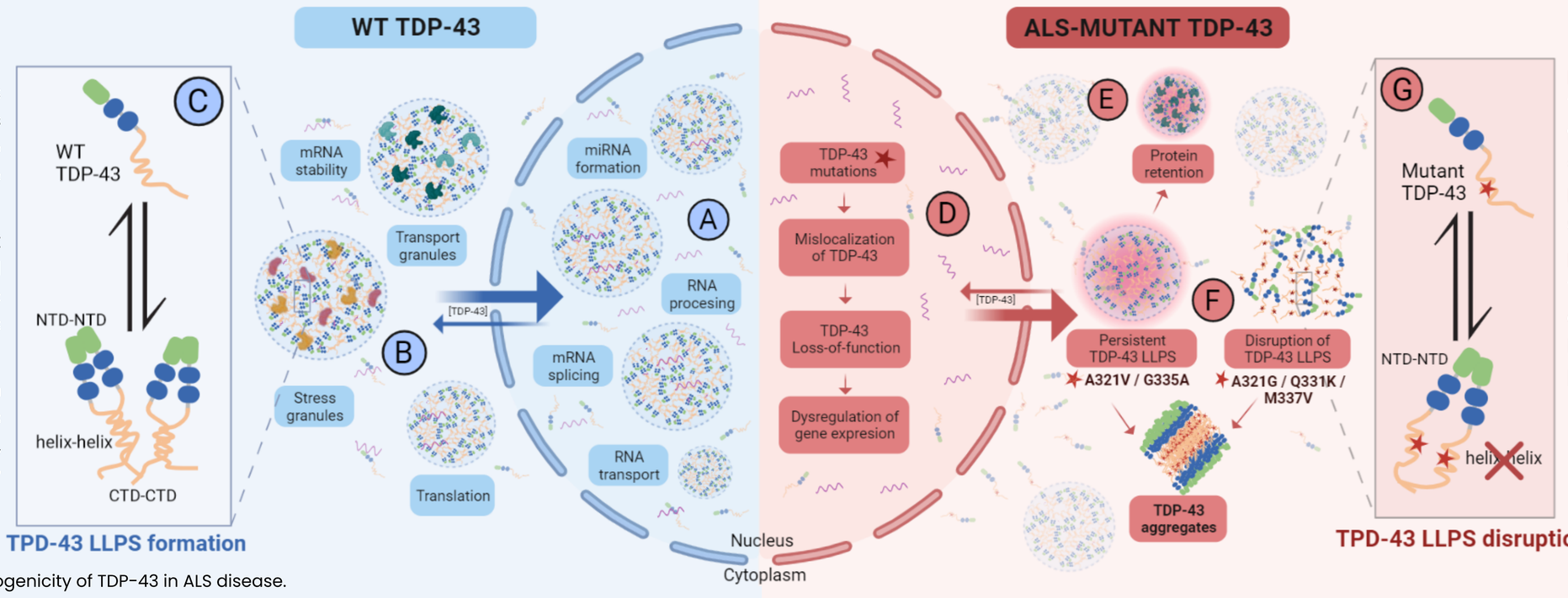


Fig4. (a) TDP-43 structure. (b) TDP-43 LLPS formation.

ABERRANT PHASE TRANSITION OF TDP -43 IN ALS DISEASE



A. WT TDP-43 forms **nuclear condensates** that are essencial to regulate and module RNA.

B. TDP-43 takes part in **SGs formation** and other cytoplasmatic proceses. However, its concentration is low.

C. LLPS formation requires interactions between NTD - NTD, **CTD - CTD and helix-helix** of TDP-43.

D. TDP-43 mututations in TDP-43 cause **loss-of function** in the nucleus afecting gene expresion

E. Persistent LLPS may **sequester other proteins.**

F. Mutacions in CTD of TDP-43 can keep a **chronic LLPS or disrupt it**. Both cases can produce protein aggregation.

G. Mutacions in CTD of TDP-43 prevent helix-helix interactions **reducing the condensates.**

Fig5. Mechanism of pathogenicity of TDP-43 in ALS disease.

THERAPEUTICS STRATEGIES

bait RNA

regulate LLPS by binding to the protein

1,6-hexanediol / ATP

Reduce LLPS formation

Mitoxantrone / MPTs

Modulate the behaviour of LLPS

CONCLUSIONS

- LLPS is important for essential cellular processes to occur.
- CTD mutations in TDP-43 can cause persistent LLPS or disrupt it. Both cases can result in protein aggregation.
- Protein aggregation does not produce cell toxicity but reduces it.
- **Personalised medicine** is needed to establish patient-specific therapies.

Future studies: Better disease models to study the relationship between TDP-43-mediated LLPS and ALS. It is also important to identify the mechanisms of TDP-43 mislocalisation to better understand the disease and how mutations can produce protein aggregation.

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