THE ROLE OF PRION-LIKE PROTEINS IN HUMAN DISEASES: TAF15 AND HNRPDL
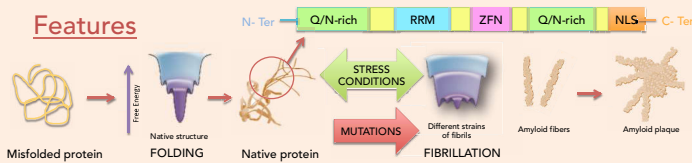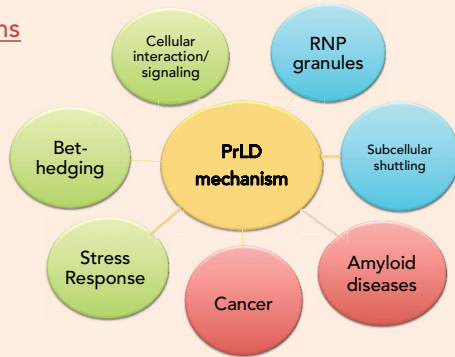
JÚLIA VENTURA MOLINA
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UAB

Introduction:
Prions are proteins that induce a variety of infectious self-templating amyloid forms. Able to confer phenotypic changes between individuals and even between species, promoting survival by generating diverse and heritable phenotypic traits in response to specific environmental stress. Priogenicity is not due to the protein structure but to the amino acid composition sequence. Strikingly, approximately 1% of human proteins harbour a Prion-Like domain (PrLD) of similar low complexity sequence and amino acid composition to priogenic domains of yeast proteins. The low complexity sequence is enriched in glycine as well as the uncharged polar amino acids (asparagine, glutamine, tyrosine and serine). The 20% of PrLD-containing proteins are RNA-binding proteins, transcription factors and granule assembly RNP mediators. The PrLD is required for optimal RNA-binding proteins functionality, that's the reason of why are so common in this kind of proteins: are necessary for alternative splicing activity, stable RNA binding and for optimal RNA annealing activity and also mediate protein-protein interactions.

1 Prion-like domains (PrLD)

Features

N-Ter — Q/N-rich — RRM — ZFN — Q/N-rich — NLS — C-Ter

Misfolded protein → Native structure FOLDING → Native protein → STRESS CONDITIONS / MUTATIONS → Different strains of fibrils FIBRILLATION → Amyloid fibers → Amyloid plaque

Mechanisms

- Cellular interaction/signaling
- RNP granules
- Bet-hedging
- PrLD mechanism
- Subcellular shuttling
- Stress Response
- Cancer
- Amyloid diseases

2 Algorithms

Basis of the algorithms for prion-like domains prediction

Unlike traditional algorithms designed to identify aggregation-prone amyloidogenic regions, these algorithms are based on the amino acid propensy from a set of yeast protein sequences. Those sequences do not share sequential characteristics common to β-sheet-amyloid forming regions.

Algorithm	Window-size	Basis	Rank of values
PAPA	41 amino acids	• According to FoldIndex • Q/N-rich domains	From 0.5 to -1
PrionScan	60 amino acids	29 yeast protein sequences	From 100 to threshold (-50).
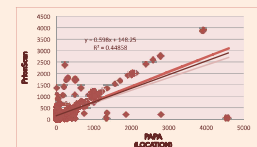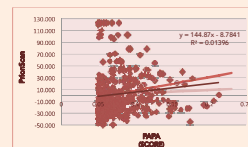
Due to algorithms are based on different criteria, to obtain significant results we make a position and score correlation. It seems (as shown in the graphs above) that using a higher threshold, then discarding the proteins lower valued, the position correlation would be linear.

Putative Prion-like containing proteins

3 FET family proteins: TAF15

TAF15 domains organization

- TAF15 RNAP II gene encodes a member of the FET family of RNA-binding proteins.
- Have been recently a focus of study due to its similarity to other RNA-binding proteins involved in severe diseases and for the evidence of prion-like behaviour.

RRM	Plays an essential role in TAF15 subcellular localization: It's controled by Post-transcriptional modifications that regulate RNA binding or protein-protein interactions. It's a common domain among proteins involved in post-transcription regulation.
Q/N-rich	Involved in DNA-binding, leads chromosomal translocations: functioning like a transcription activation domain. These events are considered cancer-driving forces.
ZFN	A single-stranded RNA recognitioon domain.
NLS	TAF15 PY-motif within the C-Ter, responsible for nuclear retention. Most mutation disease-linked were found to affect the NLS.

Transcription and splicing coupling

Roles in transcription

- TET family proteins function in RNAP II transcription by interacting with TFIID and subunits of RNAP II itself (Rbp3,5,7). This association affects:

1) Promoters choice
2) Recruitment of RNA processing factors

- N-Ter acts as a transcriptional activator when fused to DNA-binding domains.

Roles in splicing

- The C-Ter of the TET family proteins is able to interact with splicing factors affecting the patters of alternative splicing.

It's possible that connect transcription and splicing, since the **N-Ter** mediates interactions with RNAP II and the **C-Ter** binds to specific splicing factors. So may recruit splicing factors to the RNAP II, which **coordinates pre-mRNA processing events.**

Related diseases

| Associated diseases	TAF15 in disease development
Cancer (Acute Leukemia, Extraskeletal myxoid chondrosarcoma)	• Involved in differentiation, stress response and cell spreading. • **Chromosomal translocations**: The fusion joins the N-Ter domain to various DNA-binding proteins, functioning like a transcriptional activation domain.
Amyloid diseases (Familial Amyotrophic Lateral Sclerosis, Frontotemporal lobular dementia)	• Have been shown that numerous RNA-binding proteins, harbouring a prion-like domain, are involved in several amyloid diseases forming part of insoluble aggregates. Mutations in these proteins alter **RNA metabolism homeostasis**.

Associated mutations

Some recent studies are paying attention on identifying TAF15 variants related with pathological amyloid inclusions.
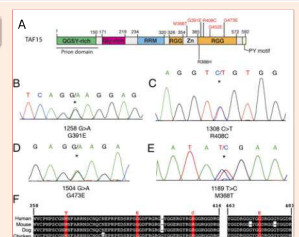
4 PAPA prediction: HNRPDL

HNRPDL predicted by PAPA algorithm (shown in the following figure) is a putative PrLD protein since when analyzing structure and interaction partners we find out many features overlapping with those observed in FET-family proteins.

PAPA Score / Fold Index
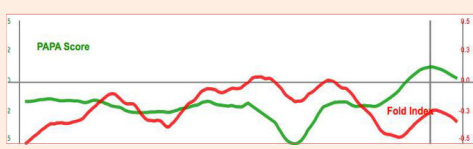
Domains
ds/ssDNA binding
HuR nucleocytoplasmic shuttling
RRM
NLS
poliA/G binding protein
Gly/Tyr-rich

5 Conclusions

- The **multifunctionality** of prion-like containing proteins makes them vulnerable targets for **cancer-causing** as such events could affect several cellular control systems simultaneously. Because are on the top of the regulation network, and are essential to maintain **RNA metabolism homeostasis**.

- The development of **bioinformatics tools** is essential to identify new putative candidates. Hopefully, further studies of RNA-binding proteins containing PrLD and sharing similar structure would provide a conceptual framework for testing hypotheses about the role of RNA-binding proteins in pathogenesis.

- Although there are many more questions to be answered about prion-mechanisms, these studies have opened up new avenues for therapeutic interventions in **neurodegenerative disorders**.

References:
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[2] Vladimir Espinosa et al. PrionScan: an online database of predicted prion domains in complete proteomes. BMC Genomics, 2014; 15:102
[3] Jenny Blechingberg et al. FET-proteins in Stress and Transcription. Gene Expression Responses to FUS, EWS, and TAF15 Reduction and Stress Granule Sequestration Analyses Identifies FET- Protein non-Redundant Functions. PLOS ONE, September 2012; Vol. 7, Issue 9.
[4] Adelene Y. Tan and James L. Manley. The TET family proteins: Functions and Roles in disease. Journal of cell biology, September 24, 2009; doi: 10.1093, Vol. 1, Nº 82-92.