Is it possible reversible and irreversible aggregation of proteins?

The discovery of protein chain regions responsible for protein aggregation is an important result of studying of the molecular mechanisms of prion diseases, and different proteinopathies associated with the formation of pathological aggregations through the prion mechanism. Prion network reflects the reality of the proteome in a cell when protein changes affect the structure and function of other proteins. The ability to control aggregation of proteins could be an important tool in the arsenal of the drug development. It is not surprising that a large number of diseases are accompanied with amyloid fibril depositing in different organs. So it is required to understand the process of transformation of native proteins to amyloid fibrils in order to clarify what key elements of this process determine the pathway of protein misfolding. Much attention has been paid lately to the investigation of mechanism of formation of reversible cross-b structures which have the properties of liquids but can also develop gel-like forms, thus facilitating the retention of both RNAs and RNA-binding proteins (Fig. 1).

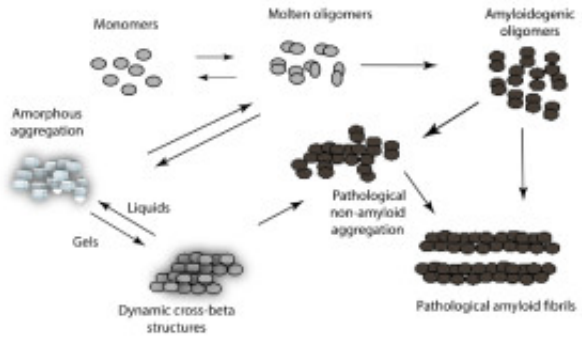

Fig. 1. Schematic representation of different conformational states of self-assembly and disintegration of prion-like domains, and a possible transition to irreversible pathological aggregation.

Many RNA-binding proteins required for the formation of stress granules contain prion-like domains that, because of the protein-protein interaction, develop dynamic cross-b structures capable of the rapid aggregation and dissociation that are so important for the correct functioning of stress granules. To understand the mechanism of assembly and disassembly of stress granules, it is necessary to know what regions in the chain of RNA-binding proteins can perform the function of a prime and what the role of disordered regions of a low complexity is. It is supposed that RNA-binding proteins could contribute to the arrangement of stress granules due to self-assembly by prion-like domains. Proteins of the FET family (FUS, EWS and TAF15) containing the prion-like domains are the perfect models for studying the processes involved in the formation of protein

aggregates by the prion mechanism. They can function by the mechanism of assembly and disassembly under favorable conditions by the principle of stress granules formation.

In any case, it has been established that specifically the disordered part of RNA-binding proteins is responsible for the formation of a hydrogel and the binding to it (see Fig. 1). Thus, protein FUS retained its ability to gel formation even when the C-terminal region, corresponding to the RNA-binding domain, was removed, but lost that ability when the N-terminal disordered region, corresponding to the prion-like domain, was removed. The presence of a large number of repeats in the disordered regions in the proteins of the FET-family could both modulate and accelerate the formation of reversible dynamic cross-beta structure in stress granules, and pathological aggregates.

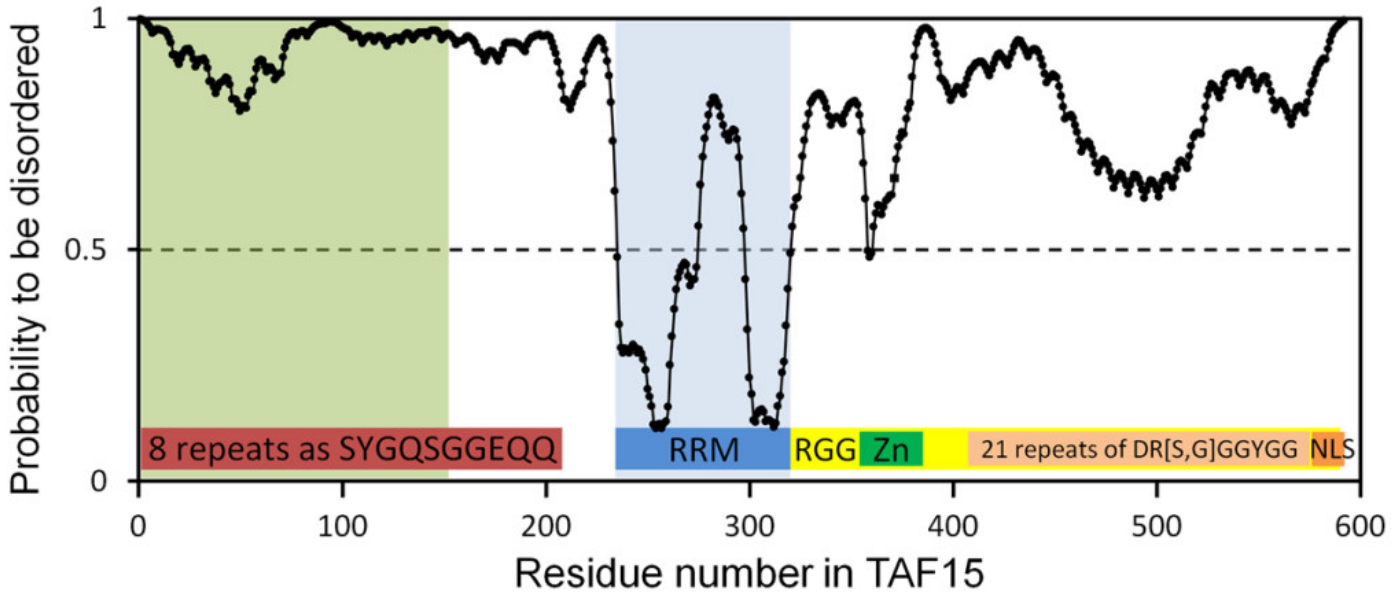

Fig. 2. Predictions of the residue status to be ordered or disordered with the IsUnstruct program for RNA-binding protein with prion-like domain (TAF15). The continuous line at 0.5 of the Y-axis is the threshold line for residues to be disordered. Prion-like domain is indicated by light green color. RRM is the RNA recognition motif. RGG corresponds region rich in arginine and glycine. Zn is the Zinc finger motif.

Predicted disordered regions in proteins of the FET family correspond both to prion-like domains and to additional regions in which tandem imperfect repeats were revealed. More than that, these proteins are characterized by the presence of homo-repeats when one amino acid is repeated many times. TAF15 includes 8 imperfect tandem repeats in the prion-like domain and 21-23 tandem repeats in the C-terminal part (see Fig. 2). These repeats one can see on the profile as saw teeth. The number of repeats increases for more complex organisms: for mouse protein there

are 19 repeats in the C-terminal part, for chicken 4, for fish 5.

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Publication

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