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Review

Protein folding, misfolding and aggregation: A tale of constructive to destructive assembly

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ABSTRACT

The newly synthesized unfolded polypeptide attains its functional and unique three-dimensional conformation through the process of protein folding for which several models have been proposed. The protein misfolding diseases include Alzheimer's, Parkinson's and Cataract which are result of formation of amyloid or amorphous aggregates, respectively. The distinction in morphology shows relation with the melting temperature (T_m). The temperatures near or slightly higher than Tm induces amyloids while much higher or low temperature mediate amorphous aggregation. The aggregation is not always deleterious rather it also performs several important cellular functions essential for survival wide range of organisms called as functional amyloids. Protein gets modulated by several modulators which mediate the aggregation, acceleration, delay, transformations, inhibition and disaggregation of protein aggregates. The exclusive properties of inhibition and disaggregation displayed by various molecules can be employed to treat the life threatening disorders.

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1. Introduction

The complete information for the conduction of appropriate biological action by proteins at cellular level is encoded in the well-defined 3-dimensional structure of its native state [1]. The loss of such proper activity of protein may occur by attaining any intermediate states which could be aggregation prone and cause several human health complications [2]. The polymerization of 20 L-amino acids in linear form constitutes the protein which is translated product of mRNA. Genetic code determines the amino acid sequence of the protein. Amino acid is made up of centrally located carbon atom (C_α), covalently attached to carboxylic group, a hydrogen group and precise side-chain. The proficient packing of hydrophobic side chains as well as hydrogen bonding propensity minimization of polar groups present on the side chains and peptide backbone are prerequisite for the proper folding of proteins.

2. Protein folding

The protein folding study is mesmerizing interdisciplinary field, drawing the attention of scientists of various field especially from mathematics, chemistry, biology, physics and computer sciences background. The groundwork in the field of protein folding started more than 55 years before when Anfinsen et al. performed the thermodynamically controlled experiment. In his experiment, he demonstrated unfolding of native protein forming random coil turned back to its native state and proved the existence of reversibility of protein during folding. On the basis of this observation, he concluded that native state of the protein is unique state with lowest Gibbs free energy [3]. Fig. 1 shows that after production of nascent peptide *via* a complex mechanism of transcription and translation it is gratuity for protein to accomplish the functional native state through the proper folding.

In year 1969, milestone was laid in the field of molecular biology when Cyrus Levinthal considered every ϕ and ψ bond angles. Considering one of three possible stable conformations and only two probable conformations regarding single amino acid residue of polypeptide chain, he calculated that protein may attain 10^{30} different conformations. The mathematical calculations revealed that 10^{11} years would be require to fold the comparatively small protein made up of merely 100 amino acids, where each step was measured to be shortest as 10^{-12} S. This time is so improbable since few seconds to minutes are required by spontaneous protein folding in the cells. The contradictory correlation between two time scales required for *in vivo* and by calculation for protein folding known as Levinthal paradox and some time as protein folding paradox[4,5].

3. Different folding models explaining Levinthal paradox

3.1. Frame work model

This model assumes that in initial step, establishment of local interaction in secondary structure before tertiary structure formation govern the folding of protein [6,7].

3.2. Modular model

This model suggests that domains as well sub-domains behave as autonomous folding units in respect to folding. The structural modules which came into existence during folding of these autonomous folding units further organize to give native and functional conformation [8,9].

3.3. Hydrophobic collapse model

This model claims that hydrophobic effect is responsible for the folding as well as stabilization of proteins. According to this model generation of collapse intermediate or molten globule population occurs due to collapse of hydrophobic interactions and achievement of native conformation takes place from conformationally selected state [10].

3.4. Jigsaw puzzle model

This model denies the existence of single direction for protein molecule undergoing unfolding as was suggested by earlier models. According to this model, every single protein folds *via* multiple route to form native functional protein [11].

3.5. Stepwise sequential and hierarchical model

According to this model, a lot of structures formation and arrangements take place to attain the native conformation. This model assumes that there is an inimitable direction for native conformation. The construction of numerous structures in patch form assembled in special pattern is prerequisite to follow that direction. Firstly, the nucleation step leads to the development of super secondary conformation *via* secondary structure induction. The super secondary conformation

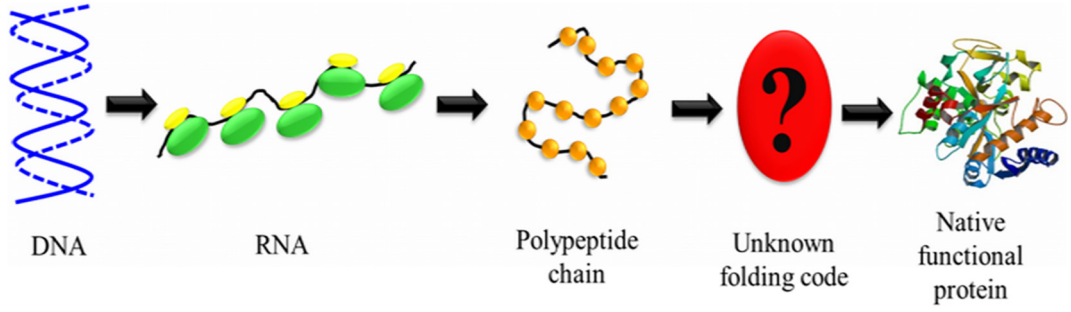

Fig. 1. Existence of key step between nascent poly-peptide chain produced by transcription, translational machinery and native functional protein. This key step governs the correct folding of protein by involving unknown folding code.