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Mechanisms of protein misfolding: Novel therapeutic approaches to protein-misfolding diseases

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ABSTRACT

In protein misfolding, protein molecule acquires wrong tertiary structure, thereby induces protein misfolding diseases. Protein misfolding can occur through various mechanisms. For instance, changes in environmental conditions, oxidative stress, dominant negative mutations, error in post-translational modifications, increase in degradation rate and trafficking error. All of these factors cause protein misfolding thereby leading to diseases conditions. Both *in vitro* and *in vivo* observations suggest that partially unfolded or misfolded intermediates are particularly prone to aggregation. These partially misfolded intermediates aggregate *via* the interaction with the complementary intermediates and consequently enhance oligomers formation that grows into fibrils and proto-fibrils. The amyloid fibrils for example, accumulate in the brain and central nervous system (CNS) as amyloid deposits in the Parkinson's disease (PD), Alzheimer's disease (AD), Prion disease and Amylo lateral Sclerosis (ALS). Furthermore, tau protein shows intrinsically disorder conformation; therefore its interaction with microtubule is impaired and this protein undergoes aggregation. This is also underlying cause of Alzheimers and other neurodegenerative diseases. Treatment of such misfolding maladies is considered as one of the most important challenges of the 21st century. Currently, several treatments strategies have been and are being discovered. These therapeutic interventions partly reversed or prevented the pathological state. More recently, a new approach was discovered, which employs nanobodies that targets multisteps in fibril formation pathway that may possibly completely cure these misfolding diseases. Keeping the above views in mind in the current review, we have comprehensively discussed the different mechanisms underlying protein misfolding thereby leading to diseases conditions and their therapeutic interventions.

1. Introduction

Protein misfolding occurs because of several factors including, dominant-negative mutations, changes in environmental conditions (pH, ionic strength, temperature, and protein concentrations), error in post-translational modifications, increase degradation rate, oxidative stress and error in trafficking. Such factors may act either independently or simultaneously [1]. Various experiments (*in vitro* and *in vivo*) suggest that misfolded or partially unfolded intermediates are particularly liable to aggregation, especially at high peptide concentrations [2–6]. These partially unfolded or misfolded intermediates are enhanced under equilibrium conditions. The partially unfolded intermediates contain large patches of adjoining surface hydrophobicity, hence they can aggregate more easily than native and unfolded proteins, which possess hydrophobic amino acid situated at the interior core of protein and lie scattered in the polypeptide chain, respectively. These partially unfolded intermediates tend to aggregate by interacting with complementary intermediate and consequently enhance oligomers formation which grows into proto-fibrils and fibrils (Fig. 1). The amyloid fibrils are important origins of toxicities that led to diseases conditions such as amyloidosis. The amyloid fibrils characteristically composed of 2–6 unbranched protofilaments with a diameter of 2–5 nm which is linked laterally or twisted together forming fibrils with diameters of 4–13 nm [7–9]. The fibrillar

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Abbreviations

Aβ	Amyloid beta peptide
APP	Amyloid Precursor Protein
AD	Alzheimer's disease
AGEs	Advanced Glycation End Products
ALS	AmyloLateral Sclerosis
CNS	Central nervous system
DM	Diabetes Mellitus
DBD	DNA-binding Domain
ER	Endoplasmic Reticulum
ERAD	Endoplasmic-Reticulum-Associated protein Degradation
ECMs	Extracellular Membranes
FDAP	Fluorescence Decay After Photoconversion
GAGs	Glycosaminoglycans
GSK-3	Glycogen Synthase Kinase-3
HA	Hyaluronic Acid
HS	HeparanSulfate
JNK	c-Jun N-terminal Kinase
LB	Lewy bodies
NFTs	Neurofibrillary Tangles
PD	Parkinson's Disease
PDI	Protein Disulfide Isomerase
PGs	Proteoglycans
PrP	Prion protein
PTMs	Post Translational Modifications
RAGE	Receptor for AGE
ROS	Reactive Oxygen Species

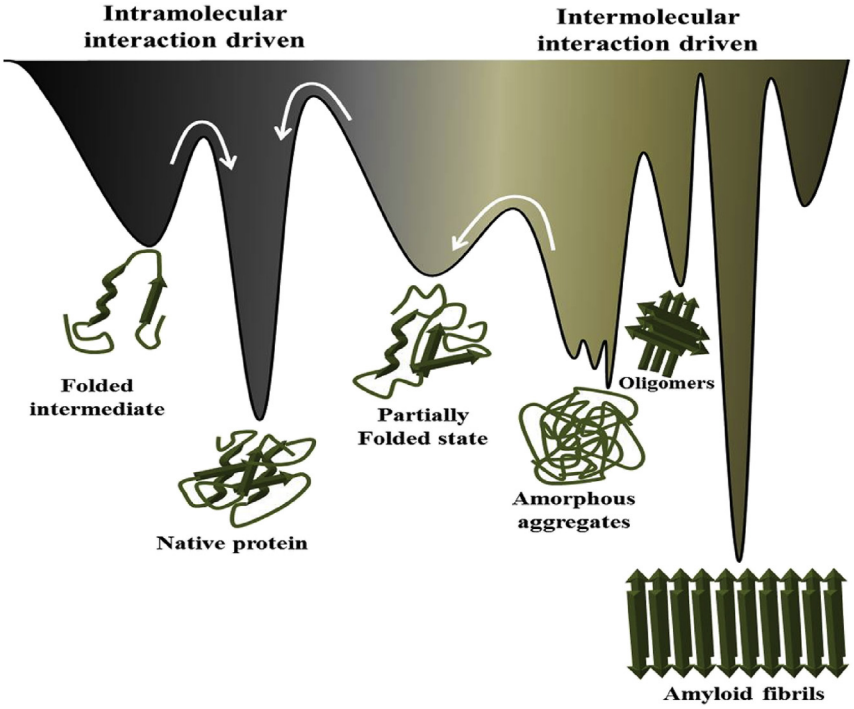

Fig. 1. Energy landscape scheme of protein folding and aggregation. The landscape scheme shows the different types of aggregates including amorphous aggregates, oligomers, and fibrils.

aggregates can interact with dyes such as Congo red leading to birefringence as well as thioflavin-T resulting in fluorescence.

Initial studies have shown that amyloid fibrils were the main culprit behind toxicity that led to neurodegenerative diseases. However, currently attention shifted to the cytotoxicity of amyloid fibril precursors, notably amyloid oligomers, which are the major reason of toxicity. Molecular mechanisms that induce the formation or stabilization of oligomers of the wild-type Aβ remain unclear. In our earlier review [10] we have discussed that there are several mechanisms of toxicities caused by oligomers. Later on, in our review we have hypothesized two major possible mechanisms of toxicities instigated by oligomers of Aβ (amyloid beta), PrP (prion protein) (106–126), and α-Syn (alpha-synuclein) including direct formation of ion channels and neuron membrane disruption by the increase in membrane conductance or leakage in the presence of small globulomers to large prefibrillar assemblies This is also validated by most recent findings that showed oligomer-related toxicities including: nonspecific perturbance of cellular and intracellular membranes and amyloid pore channel formation [11].

Intrinsically disorder conformation of tau is also important origin of different neurodegenerative diseases. Since tau protein adopts intrinsically disorder conformation therefore its interaction with microtubule is impaired and it undergoes aggregation leading to Alzheimer's diseases and several other neurodegenerative diseases Using predictive atomic resolution descriptions of intrinsically disordered hTau40 and α-synuclein in solution from NMR and small angle scattering, enhanced polyproline II sampling occurred in aggregation-nucleation sites, supporting the suggestions that