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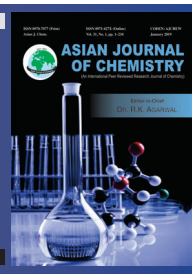

MINI REVIEW

Protein Misfolding, Associated Diseases and Potential Therapeutic Routes: A Mini Review

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Correctly folded proteins play key role in all biological reactions. Folding of protein into its native structure is the most astonishing example of biological self-assembly. Gene mutation, translational or transcriptional error, failure of chaperon mechanism results in misfolded protein structure. Misfolded proteins are responsible for a number of human diseases namely Alzheimer's disease or Parkinson's disease. Research for finding therapeutic breakthrough against these ailments has invoked different strategies.

Keywords: Misfolding, Aggregation, Neurodegenerative disease, Native protein stabilizer, β-Sheet blocker.

INTRODUCTION

Proteins are essential for life to survive in our planet since all *in vivo* chemical reactions depend on them. Human body contains nearly 1,00,000 proteins [1] with astonishing diversity in their structure and selectivity in their functional behaviour. Backbone of any protein is a polypeptide chain which is built by 20 natural α-amino acids. Three conformations are possible for every single peptide unit in the polypeptide chain. A small protein of only 101 residues thus could exist in 3^{100} possible conformations [2]. But the polypeptide chain spontaneously finds the unique native conformation from this large number of possible conformations. The necessary information to achieve the unique three dimensional structure of a protein is encoded by its amino acid sequence. Exploring the underlying mechanism of this complex folding process *in vivo* is still a major challenge.

The interior environment of the cell is extremely crowded and assistance of folding catalyst and chaperons are required for successful folding of the polypeptide chain [3]. Protein quality control mechanism of the cell monitors the folding process and also stimulate trafficking and degradation of incompletely folded protein. In spite of this finely designed system, some protein molecules cannot fold to their functional native conformation and also escape the quality control system of the cell, these are termed as misfolded proteins. These misfolded proteins are in focus of interest of chemical biologists because they are responsible for different pathological conditions namely the neurodegenerative diseases like Alzheimer's disease (AD) and Perkinson disease (PD) [4]. Investigation of the reason and underlying mechanism of protein misfolding and search for therapeutic avenue to a number of human ailments has become very relevant in last few decades. This review is aimed to shed light on protein misfolding and aggregation, consequent diseases and potential therapeutic routes.

Mechanism of protein folding: Studies on protein folding started nearly 100 years before when in 1920s Anson and Mirsky found that denaturation of many protein is reversible [5]. Protein folding began to grow as a research discipline after 1961 when Anfinsen *et al.* [6] revealed that native three dimensional conformation of a particular protein is dictated totally by its amino acid sequence and there after research work in the field of 'protein folding' were carried out at explosive rate. Each polypeptide chain, even for a very small protein, can have a large number of conformations and if folding of the polypeptide chain occurs *via* systematic search of all the conformations then it would require extremely long time to fold. But proteins fold *in vivo* in millisecond to second time scale. Based upon this observation, Levinthal [7] suggested that real protein fold by specific 'folding pathways' and not

by random search of all the conformations and this is known as 'Levinthal's paradox'. Following the Levinthal's paradox, a series of 'protein folding model' were proposed. These were the nucleation-growth model [8], the diffusion-collision-adhesion model [9], the framework model [10] and the hydrophobic collapse model [11]. Finally, the jigsaw puzzle model [12] proposed that each polypeptide can fold to the native state *via* multiple path and not through a single route. This proposal resembles the multiple ways by which a jigsaw puzzle can be solved and it is accordant with the energy landscape view of protein folding [13].

According to this model, the energy landscape of protein folding is assumed as a rough funnel surface where the native state is at bottom of the funnel *i.e.* global energy minimum and the nascent polypeptide chain at the top. Progression from top to bottom *i.e.* folding of the nascent polypeptide chain passes through an ensemble of halfway conformations *via* a number of microscopic routes. In the latter part of the process when the option is narrower, the microscopic routes may converge to one and the intermediate structure with substantial folding pattern may be trapped at the rough surface of the funnel representative of local free energy minimum [14-17].

Smaller proteins normally folds efficiently to their native state without any intermediate formation [18]. But specific folding intermediate has been detected in case of many proteins [19-22]. Sometimes folding of proteins is assisted by other proteins called molecular chaperons. Molecular chaperones 'recognize' and 'bind' nonnative protein conformations without becoming permanent components of the structures and guide them to their proper folding routes and prevent off pathway structures [3]. Two enzymes namely protein disulfide isomerase (PDI) and peptidyl-prolyl *cis-trans* isomerase (PPI) have important role in the protein folding phenomenon. PDI is involved in disulfide bond formation or dissociation between cysteine residues [23] whereas PPI usually participate in *cis-trans* isomerization of proline residues during folding [24].

Protective mechanism to avoid misfolding and its failure: Most proteins fold in post translational period in the cytoplasm or in some specific cellular compartments like mitochondria or endoplasmic reticulum. Since specific function of any protein exclusively depends on its native folded structure, incompletely folded structures have the chance to interact with some other molecule inside the cell leading to undesirable consequences [4]. In this kind of situation molecular chaperones play an important role. Chaperones are also called 'heat shock proteins' (Hsp) since it is the stress condition (*e.g.*, heat shock or oxidative stress) that stimulate their synthesis *in vivo*. Earlier the chaperones were labeled as Hsp followed by molecular weight: Hsp40s, Hsp60s, Hsp70s, Hsp90s, Hsp100s and the small Hsps. Chaperone (Hsp70s, Hsp90s), cochaperone (Hsp40s) and chaperonin (GroEL and GroES) cooperate in complex mechanistic network to facilitate de novo protein folding [25]. Some chaperone binds the nascent polypeptide chain in cotranslational period [26] whereas others sequester the partially folded protein in downstream and assist in final steps of folding [27]. Beside chaperone there exists quality control mechanism of the cell [28,29] which discriminates between correctly folded and misfolded structures by means of a number of glycosylation and deglycosylation steps. The misfolded polypeptide chains are then degraded naturally within the cell [30].

In spite of these protective mechanisms of cell, protein misfolding occurs which results in nonfunctional structure. Misfolding can have several reasons like somatic mutations in gene sequence; error involved in transcription or translation; disruption in chaperone action; wrong post-translational modifications, inappropriate trafficking of proteins; structural alteration caused by environmental factors [31-33].

Aggregation of misfolded proteins: mechanism and intermediates: Misfolded proteins are prone to undesirable interaction with solvent because the hydrophobic portions, which are otherwise buried in the core of properly folded protein structure, may come into contact of the solvent molecules. This exposure leads to high degree of stickiness between hydrophobic patches of different molecules and results in protein aggregation [34]. β-Sheet structural motif is most importantly associated with the protein aggregation and can accommodate a large number of polypeptide chain. Mutation can cause α to β switch in protein conformation and leads to aggregation [35,36]. Aggregation is often correlated with low net charge on protein [37]. Protein aggregation follows nucleation-dependent polymerization mechanism. In the initial thermodynamically unfavourable, slow phase small amount of oligomeric unit is produced which serves as the nucleus for aggregation process. Once nuclei are formed, exponential growth of the polymer takes place in elongation phase at very fast speed [38].

Based on the equilibrium of associative mechanism, different aggregation intermediates can form which are classified in the following categories:

Amorphous aggregate: This type of aggregates is devoid of any defined shape or structure because the assembled protein molecules have no specific interactions in between [38].

Oligomers: The oligomers are soluble small assembly of misfolded proteins (size < 50 nm) ranging from dimer to 24-mer. In the misfolding and aggregation pathway, probably these have the maximum toxicity [39].

Protofibrils: These represent small thin filamentous structures with diameter of 4-11 nm and length of less than 200 nm. Protofibrils which are mainly β aggregate can transform to full-length fibril [40].

Amyloid or fibrillar aggregate: They represent extracellular β-sheet rich protein deposit. They usually consist of unbranched and elongated morphology with diameter of 6-12 nm. They are visible under electron microscope. Amyloid aggregates are responsible for many diseases termed as amyloid disordres. Alzheimer's, spongiform encephalopathies and type II diabetes are common examples of this disorder [41].

Spherulite: Spherulites are spherical shaped amyloid-like superstructure. These spherical structures consist of radiating amyloid fibrils from a central core and typical feature of it is a dense core and a low-density corona [42]. Formation of the central part is based on non-specific aggregation of protein molecules [43]. Spherulites are characterized by the Maltese cross-section pattern monitored by cross-polarized light microscope [44].

Protein misfolding diseases: There are several human diseases caused due to inappropriate folding of protein mole-

cules. Now we shall briefly discuss some of the most occurring human disease with characteristic pathological symptoms. Table-1 represents some human diseases along with the respective associated proteins.

TABLE-1
REPRESENTATIVE PROTEIN MISFOLDING DISEASES

Disease	Responsible protein
Alzheimer's disease	Amyloid β peptide/tau
Parkinson's disease	α-Synuclein
Huntington's disease	Huntingtin
Cancer	p53
Hereditary systemic amyloidosis	Transthyretin/lysozyme
Prion disease	Prion protein
Sickle cell anaemia	Haemoglobin
Retinitis pigmentosa	Rhodopsin

Alzheimer's disease (AD): Alzheimer's disease (AD) is a progressive neurodegenerative dysfunction of aged persons and most common symptom of Alzheimer's disease is memory loss. Patients with Alzheimer's disease are generally diagonized with extracellular amyloid plaques, intracellular helical filamentous neurofibrillary tangles (NFTs), synaptic deterioration and neuronal death. The plaques contain β-amyloid protein (A β). A β is a peptide formed by proteolytic cleavage of amyloid precursor protein (APP) by β-site APP cleaving enzyme 1 (BACE1) and γ-secretase. Two types of peptide - A β 1-40 and A β 1-42 are formed in this process and excess of Aβ 1-42 associate to form oligomers and fibrils which finally results into amyloid plaques. NFT are generated from tau proteins which are hyper-phosphorylated and finally accumulated within neurons present in the mesial temporal lobe (especially hippocampus), lateral parieto-temporal region and the frontal association cortices [45]. Tau proteins in normal human brain contain 2-3 moles of phosphate per mole of protein and its normal function is to stimulate the polymerization of tubulin to form microtubules, one of the main components of cytoskeleton. Phosphorylation level of tau protein in Alzheimer's disease affected human exceeds about 3-4 times than normal case. It was also found that phosphorylation of Thr231, Ser396 and Ser422 triggers self-aggregation of the tau proteins forming filaments [46].

Parkinson's disease (PD): Parkinson's disease is another common progressive neurodegenerative disease. Patients with Perkinson disease suffer from tremor, stiffness, dementia and gastrointestinal problems and they are generally diagonized with selective degeneration of dopaminergic neurons and presence of microscopic marker 'Lewy bodies'. These Lewy bodies consist of mainly aggregated form of misfolded α-synuclein protein [47]. It is suggested that misfolded α-synuclein spread from one cell to another in a prion-like manner [48]. When received by another cell, that transmitted misfolded α-synuclein can promote misfolding of normal α-synuclein molecules [48,49] in that cell and the misfolded proteins assemble themselves resulting aggregation which finally leads to Lewy bodies.

Huntington's disease (HD): Huntington's disease is associated with motor dysfunction along with psychiatric and cognitive disturbance. HD normally starts at elderly age, deteriorate with time which can't be reversed. HD is associated with Huntington protein and it is a monogenic disease inherited in autosomal-dominant pattern. Expanded CAG repeats in the Huntingtin protein encoding gene on the short arm of chromosome 4 create an elongated polyglutamine (PolyQ) stretch at the N-terminal of the mutated protein. It is observed that the wild-type gene has 10-35 CAG repeats, whereas 40 or more repeats cause HD [50].

Prion disease: Another neurodegenerative disorder is Prion disease which was formerly familiar as transmissible spongiform encephalopathies. Prion disease affects the central nervous system. The neuropathological findings of this disease are spongiform appearance in the gray matter of brain along with neuronal loss, reactive gliosis and accumulation of misfolded prion protein in the brain. Misfolding of infectious prion protein is the reason behind this fatal disease. Normal prion protein (PrP^C) occurs on the cell surface and it exists in a predominantly α-helical conformation. But the abnormal misfolded protein (PrP^{Sc}) turns into amyloid assemblies which have high β-sheet content and they are resistant to protease degradation. Prion disease is highly infectious and it can be transmitted among the same species or different species. Abnormal PrP^{Sc} serves as a template for transformation of PrP^C to PrP^{Sc}. Human Prion diseases are of three types - sporadic, inherited or acquired. The most commonly encountered human prion disease is Sporadic Creutzfeldt-Jakob disease (sCJD), occurring mostly in above 60 years of age. Major symptoms of sCJD are fast progressive dementia and cerebellar ataxia eventually leading to loss of mobility and speech before death [51,52].

Hereditary systemic amyloidosis: The human lysozyme enzyme contains 130 amino acid residues and it is found in high abundance in saliva, tears, mucus and breast milk. Pepys *et al.* demonstrated that point mutation namely I56T and D67H in the human lysozyme causes hereditary systemic amyloidosis [53]. Common feature of the disease is large quantity accumulation of the lysozyme as fibrils in many internal organs like kidneys, gastrointestinal tract, lymph nodes, blood vessels, spleen and liver [54] and two fatal consequences - renal dysfunction and hepatic hemorrhage generally observed [55,56].

Potential therapeutic avenues: Advances in medical science have increased the human life expectancy. But in parallel with increased longevity, neurodegenerative diseases have become very much prevalent. Today the number of Alzheimers patients in the world is about 50 million and is likely to rise to about 152 million by 2050. A few symptomatic therapies exist which confer only limited benefit and fails to stave off the disease progression. Diverse strategies have been taken in search of major therapeutic breakthrough.

Inhibition of misfolding prone protein production: A straight forward approach to prevent the toxic effect of misfolded protein is to reduce the generation of the proteins which are prone to misfolding and subsequent aggregation. Few inhibitors of APP proteolytic enzymes were designed and synthesized to reduce the production of Aβ peptide, as a therapeutic approach to prevent Alzheimer's disease. For prevention of HD, antisense drug is intended to be synthesized which can stop translation of Huntington protein. But these therapeutic

approaches are under clinical trial and may cause unforeseen consequences because of the lack of the endogenous protein would prevent the associated cellular function [57].

Stabilizing protein structure using small molecules: Many small molecules have been found which can bind with native protein or partially unfolded protein and thus inhibit aggregation. These results have started a new era of drug development [58]. For example, transthyretin (TTR) is a 55 kDa homotetrameric protein. Aggregation of this protein leading to fibrils is known to occur because of many single point mutations. Then the TTR fibrils are deposited in different organs in our body like nerves, heart and kidneys. Thus regular function these organs are badly affected. Studies show that tetramer dissociation is the slow step in the aggregation process [59]. 2,4,6-Triiodophenol was the first discovered molecule which binds selectively with TTR tetramer and acts as a 'kinetic stabilizer' inhibiting TTR amyloid formation [60]. Till now, more than 1000 small aromatic compounds have been reported which can stop the dissociation process of the TTR tetramer [61].

Again, tumor suppressor protein (p53) is known as the cell guardian. Mutation of p53 and loss of its function is involved in most human cancer. Two small molecules known as PRIMA-1 and MIRA-3 (Fig. 1) were discovered which binds with p53 mutant and results in p53 reactivation and induction of massive apoptosis [62]. Pyridine dicarbonitriles (Fig. 2) were found to stabilize native prion protein (PrP^{C}) and inhibits formation of misfolded prion protein (PrP^{Sc}) [63] and thus reveals therapeutic route to still untreatable fatal prion disease. Gazova and coworkers identified that acridines (Fig. 3) have ability to prevent lysozyme aggregation responsible for amyloidosis disorder [64,65]. Another class of small

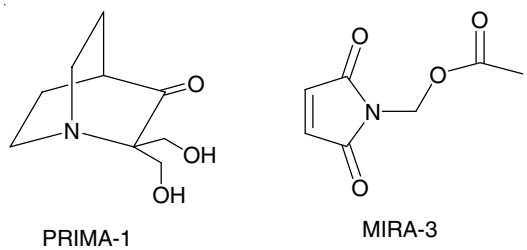

Fig. 1. Structure of small molecules reported which reactivates p53

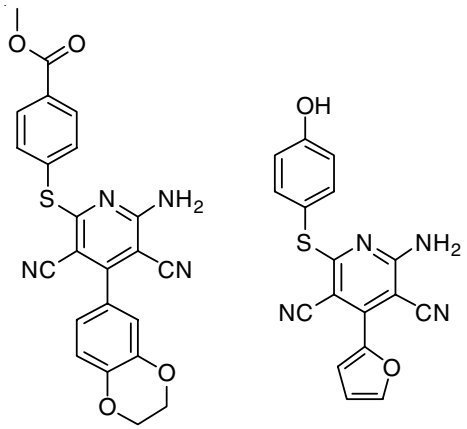

Fig. 2. Structure of pyridine dicarbonitriles reported as native prion protein stabilizers

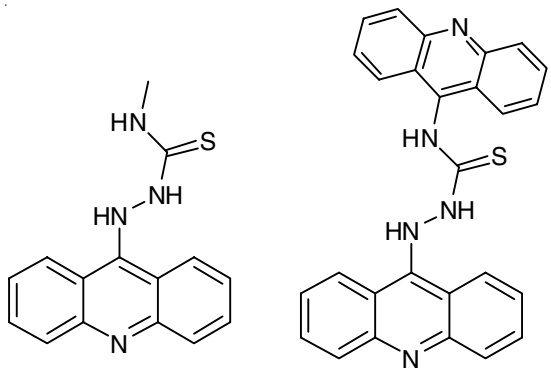

Fig. 3. Structures of acridines reported as lysozyme aggregation inhibitors

molecules which prevent aggregation is the osmolytes. These naturally occurring molecules are known as 'chemical chaperones' under condition of stress. The well known naturally occurring osmolytes are methylamines (*e.g.* TMAO, Choline -O-sulphate), polyols (*e.g.* sorbitol, glycerol, sucrose) and amino acids (*e.g.* glycine, proline, betain) [66]. These osmolytes combine with protein molecules and thereby diminishing its aggregation tendency or changing the nature of aggregate. Hence osmolytes are potential therapeutic agents for protein misfolding disorders [67].

Restraining the aggregations process using β-sheet blockers: Transition from α-helix to β-sheet conformation has often been sparked the aggregation pathway. It was found that misfolded proteins are generally rich in β-sheet structural motif. There occurs some synthetic peptides which act as 'β-sheet breaker'. These peptides destabilize the β-sheet rich abnormal structure and instead favour regaining to the normal form. These designed peptides consist of amino acid sequence similar to the part of protein sequence which was responsible for the self-association. The peptide sequence also include some amino acids residues that particularly favour or disfavour a particular structural motif [68]. For example, modified short peptides comprising α-synuclein amino acid sequences were synthesized. This synthetic peptide called α-synuclein inhibitor, restrains formation of lewy bodies by interacting with full-length α-synuclein and thus shows a route to treatment of Perkinson disease [69]. In another case, aggregation of insulin to amyloid fibril, under acidic pH and elevated temperature, results loss of insulin functions followed by adverse immune response. Gibson and Murphy [70] demonstrated that a synthetic modified small peptide comprising residues B12-17 of insulin significantly reduces insulin aggregation. Again, transformation of PrP^{C} to PrP^{Sc} was also found to be inhibited by peptides homologous to PrP and comprising β-sheet blocker residues [71]. Then a synthetic 5 residue short peptide was reported for its ability to inhibit fibrilogrnesis of amyloid β protein both *in vitro* and *in vivo* and as a result neuronal death is inhibited providing an implication for Alzheimer's disease therapy [72].

Reducing aggregate accumulation by enhancing clearance: When prevention of protein misfolding and aggregation is not possible another alternative approach is removal of aggregates by improving clearance mechanism. Schenk *et al.* [73] first reported a synthetic amyloid β aggregate which behaves as antigen and promotes our immune system to generate antibodies which clear the aggregates. Study on transgenic

animal models of Alzheimer's disease reveals that this approach leads to less amyloid formation, cerebral damage and behavioural injuries [73-75]. Another strategy is to use antibodies which are able to specifically recognize the conformational epitopes on the oligomeric species and as consequence degradation mechanism initiates [76,77]. Studies have demonstrated that autoantibodies normally exist in humans, which select different amyloidogenic proteins including Aβ and α-synuclein. Origin and function of these antibodies are not yet clearly understood but they shows new horizon in the therapeutic field of protein misfolding ailment [78-80].

Use of nanoparticle to prevent protein aggregation: Nanoparticles (NPs) are materials which have dimension in the range of 1-100 nm. NPs may be constituted of various types of organic compounds, inorganic molecules or various metals. These NPs always possess small size and a large surface/mass ratio, key factor for its extraordinary function. Protein molecules adsorped on the surface of NPs and this association of nanoparticle-protein, described as nanoparticle-protein (NP-P) corona, results in change of structure and function of proteins [81]. Experiments demonstrated that adsorped proteins generally have reduced α-helical content whereas β-sheet contents get increased sometimes or sometimes it remains unchanged [82,83]. Nps can also affect fibrilogenesis and they can cross blood brain barrier. Overall if the synthesized NPs are biocompatible and biodegradable, then they can be very useful to control amyloid-related diseases like Alzheimer's disease and Perkinson disease [84-86].

Conclusion

Prevalence of neurodegenerative diseases across the globe has inspired the scientific community to explore the inherent mechanism and best possible remedy for those ailments in last few decades. To conclude, this review concisely discussed intricate mechanism of protein folding; failure of proper folding and consequent misfolded proteins; associated disease and potential therapeutic gateways. It is well established that the protein misfolding and aggregation is underlying reason for these fatal diseases, but the mechanism of aggregation and amyloid formation at molecular level is yet to be explored. Extensive research is going on worldwide to find therapeutic breakthrough against the protein misfolding diseases. Many medicines are still at clinical trial phase. Insight into the molecular detail of misfolding and aggregation mechanism will allow design and synthesis of newer medicine to prevent and cure these human ailments.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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