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MECHANISMS OF PROTEIN FOLDING AND MISFOLDING: BIOPHYSICAL INSIGHTS INTO NEURODEGENERATIVE DISEASES

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Abstract: *Protein folding — the process by which polypeptide chains attain functional three-dimensional structures — is fundamental to all cellular processes. However, errors in this process, termed protein misfolding, are implicated in the pathogenesis of a wide range of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and prion diseases. These disorders share a common hallmark: the aberrant accumulation of misfolded proteins that aggregate into toxic oligomers and insoluble fibrils, disrupting neuronal integrity and leading to progressive cognitive and motor decline. Biophysical mechanisms that govern folding and misfolding involve complex energy landscapes, thermodynamic stability, and proteostasis network dysfunctions. Recent studies reveal that misfolded proteins can propagate via seeding and prion-like mechanisms, amplifying pathological aggregates throughout the nervous system. This review examines the molecular basis of protein folding and misfolding, the pathophysiological roles of protein aggregates in neurodegenerative diseases, and current and emerging therapeutic strategies aimed at mitigating misfolding and aggregation.*

Keywords: *protein folding; protein misfolding; neurodegenerative diseases; amyloid aggregation; proteostasis; biophysics*

1. Introduction

Proteins are essential molecular machines responsible for virtually all cellular functions. Their activity is intrinsically tied to their three-dimensional structure, which is determined by the sequence of amino acids in the polypeptide chain. Protein folding — often conceptualized as the process by which unfolded polypeptides traverse an energy landscape to reach the native state — is driven by intramolecular interactions such as hydrogen bonds, hydrophobic effects, and van der Waals forces. However, the sheer number of possible conformations for even moderately sized proteins makes folding a non-trivial problem, historically illustrated by Levinthal's paradox, which highlights that a protein cannot reasonably sample all conformations sequentially to find its native state. Instead, folding

occurs via directed pathways governed by thermodynamic and kinetic principles that guide proteins toward their most energetically favorable native conformations.

Yet even under normal physiological conditions, proteins may misfold due to mutations, environmental stress, or failures in cellular quality control systems. Misfolded proteins can accumulate and form aggregates with β-sheet–rich structures known as amyloids. Such aggregates are remarkably stable, often resist proteolytic degradation, and are central to the pathology of many neurodegenerative diseases.

This article reviews the biophysical underpinnings of protein folding and misfolding, explores how misfolded proteins contribute to neurodegeneration, and examines recent advances in therapeutic strategies designed to counteract misfolding, aggregation, and their toxic consequences.

2. Biophysical Principles of Protein Folding

2.1 Protein Folding Landscape

Protein folding can be conceptualized through an energy landscape framework in which numerous accessible states funnel toward the native configuration. The energy landscape is rugged, containing local minima that represent folding intermediates and kinetic traps. Successful folding depends on navigating this landscape efficiently, minimizing the risk of becoming stuck in misfolded conformations.

The driving forces of folding include hydrophobic collapse — whereby non-polar residues aggregate to minimize exposure to aqueous environments — and the formation of secondary structures such as α-helices and β-sheets. These local features then assemble into tertiary structures stabilized by a network of interactions, including hydrogen bonding, electrostatic interfaces, and disulfide bridges.

2.2 Chaperone-Mediated Folding and Quality Control

Cells deploy sophisticated proteostasis networks to manage protein folding. Molecular chaperones — such as Hsp70 and chaperonins like GroEL/GroES — bind nascent or misfolded polypeptides, preventing inappropriate interactions and facilitating correct folding pathways. Chaperone activity is crucial for maintaining cellular homeostasis, especially under stress conditions that promote misfolding.

Proteostasis mechanisms also include quality control pathways such as the ubiquitin-proteasome system (UPS) and autophagy, which degrade irreversibly misfolded proteins. Failures in these pathways can lead to the accumulation of toxic species, as seen in many neurodegenerative conditions.

3. Protein Misfolding and Aggregation

3.1 Mechanisms of Misfolding

Protein misfolding can arise from genetic mutations that destabilize the native state or from cellular stressors that overwhelm proteostasis systems. Misfolded proteins often expose hydrophobic regions normally buried in the native structure, promoting aberrant intermolecular interactions. These interactions can lead to the formation of soluble oligomers and eventually insoluble fibrillar aggregates with cross-β sheet structures — a definitive feature of amyloid.

Notably, the aggregation process often follows a nucleation-dependent mechanism. Initial formation of a small oligomer (“seed”) can catalyze further aggregation, ultimately producing large fibrils. This nucleation event is a key step in disease progression and a target for therapeutic intervention.

3.2 Aggregation Pathways and Toxicity

Aggregated proteins in neurodegenerative diseases vary by disease type: amyloid-β and tau in Alzheimer’s disease, α-synuclein in Parkinson’s disease, huntingtin with polyglutamine expansions in Huntington’s disease, and superoxide dismutase 1 (SOD1) in familial forms of amyotrophic lateral sclerosis. Despite differences in sequence and structure, these aggregates share similar β-sheet–rich amyloid architectures that confer stability but also cytotoxic properties.

Emerging evidence suggests that *soluble oligomeric intermediates* — rather than the final fibrillar aggregates — are the primary mediators of toxicity due to their ability to disrupt cellular membranes, impair synaptic functions, and perturb intracellular signaling pathways.

4. Protein Misfolding in Neurodegenerative Diseases

4.1 Alzheimer’s Disease

In Alzheimer’s disease, amyloid-β (Aβ) peptides derived from amyloid precursor protein (APP) form extracellular plaques, while tau proteins form intracellular neurofibrillary tangles. Both aggregates contribute to synaptic dysfunction, neuroinflammation, and neuronal death. Aβ aggregation follows a classic nucleation-dependent mechanism, where soluble oligomers exert potent neurotoxicity, disrupting synaptic transmission and inducing oxidative stress.

The tau protein, normally associated with microtubule stabilization, becomes abnormally phosphorylated in AD. Hyperphosphorylated tau detaches from microtubules, misfolds, and aggregates into paired helical filaments, contributing to cytoskeletal collapse and neurodegeneration.

4.2 Parkinson’s Disease

Parkinson’s disease (PD) is characterized by intraneuronal aggregates of α-synuclein called Lewy bodies. α-Synuclein is a natively unstructured protein that can misfold into

β-sheet–rich aggregates. These aggregates propagate via cell–cell transmission, exerting prion-like spreading of pathology throughout the brain.

4.3 Huntington’s Disease and ALS

Huntington’s disease results from CAG repeat expansions in the huntingtin gene, producing polyglutamine-rich proteins prone to misfolding and aggregation, particularly in striatal neurons. Familial ALS involves misfolding of SOD1 and other proteins, leading to aggregate formation that disrupts motor neuron function.

4.4 Prion Diseases

Prion diseases, such as Creutzfeldt-Jakob disease, exemplify protein misfolding disorders that can be infectious. Prion proteins (PrP) misfold into pathological conformers that catalyze the conversion of normal PrP into the misfolded state, amplifying neurotoxic aggregates in a self-propagating cycle.

5. Biophysical Characterization of Misfolded Structures

Understanding the conformational changes that lead to misfolded states has been advanced through biophysical tools such as nuclear magnetic resonance (NMR) spectroscopy, cryo-electron microscopy (cryo-EM), and X-ray crystallography. These techniques reveal intermediate states and structural motifs that define aggregation pathways.

For example, cross-β structures characteristic of amyloid fibrils are stabilized by extensive intermolecular hydrogen bonding and hydrophobic contacts, conferring resistance to proteolysis and high thermodynamic stability.

6. Therapeutic Approaches and Strategies

6.1 Enhancing Proteostasis

Since misfolded proteins overwhelm cellular quality control systems, therapeutic strategies include upregulating chaperones and enhancing degradation pathways. Small molecules that stimulate heat shock proteins and autophagy have shown promise in reducing aggregate burden in experimental models.

6.2 Inhibiting Aggregation and Seeding

Interventions targeting early aggregation steps aim to prevent oligomer formation or block seeding processes. Small-molecule inhibitors, antibodies against misfolded conformers, and peptide inhibitors that stabilize native structures are areas of active research.

6.3 Targeting Downstream Toxicity

Other strategies focus on mitigating downstream effects of aggregates, such as reducing oxidative stress, inflammation, and synaptic dysfunction. Several anti-amyloid and anti-tau therapies are in clinical development for Alzheimer’s disease, with mixed but evolving results.

7. Challenges and Future Directions

Despite extensive research, many questions remain regarding the precise mechanisms by which misfolded proteins cause neuronal death. Isolation of toxic species, understanding their propagation across neural circuits, and reconciling differences between disease models and human pathology are ongoing challenges.

Future research aims to integrate biophysical insights with systems biology and advanced imaging to map the dynamics of misfolding in living brains. Additionally, leveraging artificial intelligence and deep learning to predict misfolding propensities and screen potential therapeutics offers promising avenues for discovery.

8. Conclusion

Protein folding and misfolding lie at the heart of neurodegenerative disease biology. While native folding ensures functional proteins, misfolding and aggregation underpin the pathology of Alzheimer’s, Parkinson’s, Huntington’s, ALS, and prion diseases. Biophysical mechanisms — including energy landscape navigation, β-sheet formation, and proteostasis network failures — shape the course of disease progression. Continued research into the molecular basis of misfolding and the development of strategies to counteract it will be essential to address the growing global burden of neurodegenerative disorders.

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