Molecular Mechanisms of Protein Folding and Misfolding: Implications for Neurodegenerative Disorders

Dr. Sofia Berger [1*], Lena Schneider [2]
[1] Department of Molecular Biology, University of Geneva, Geneva, Switzerland
[2] Institute of Neurochemistry, ETH Zurich, Zurich, Switzerland

* Corresponding Author: **Dr. Sofia Berger**

Article Info

P-ISSN: 3051-3405
E-ISSN: 3051-3413
Volume: 01
Issue: 05
September – October 2025
Received: 07-07-2025
Accepted: 11-08-2025
Published: 04-09-2025
Page No: 06-09

Abstract
Protein folding is a fundamental biological process essential for cellular function and life itself. The correct three-dimensional conformation of proteins determines their biological activity, enabling them to perform diverse cellular roles from catalysis to structural support. However, when proteins misfold and aggregate, they can lead to devastating neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS). These misfolded protein aggregates cause cellular toxicity and contribute to cellular proteostatic collapse, ultimately resulting in neuronal dysfunction and death. This review aims to elucidate the molecular pathways governing protein folding and misfolding, examining how these processes contribute to neurodegenerative pathology. We explore the role of molecular chaperones in maintaining protein homeostasis and discuss emerging therapeutic approaches targeting protein quality control mechanisms. Recent advancements in CRISPR/Cas9 technology are revolutionizing research in addressing protein misfolding mechanisms, while smart imaging probes are facilitating early diagnosis and drug discovery. Understanding these molecular mechanisms is crucial for developing effective treatments for age-related neurodegenerative diseases that increasingly burden our aging population.

Keywords: Protein folding, Misfolding, Neurodegenerative diseases, Alzheimer's, Parkinson's, Amyloids, Molecular mechanisms, Chaperones, Biochemistry

1. Introduction

Proteins are the fundamental macromolecules of life, serving as enzymes, structural components, signaling molecules, and regulatory factors that govern virtually every cellular process. The biological activity of proteins is intrinsically linked to their three-dimensional structure, which emerges through a hierarchical folding process. This process begins with the primary structure (amino acid sequence), progresses through secondary structures (α-helices and β-sheets stabilized by hydrogen bonds), continues to tertiary structure (the overall three-dimensional fold stabilized by various interactions), and may culminate in quaternary structure (multi-subunit protein complexes).

The protein folding process follows Anfinsen's principle, which states that the amino acid sequence contains all the information necessary for a protein to adopt its correct three-dimensional structure. Under physiological conditions, proteins must fold efficiently and accurately to avoid the formation of toxic aggregates. However, the cellular environment presents numerous challenges to proper protein folding, including molecular crowding, oxidative stress, temperature fluctuations, and the presence of metal ions.

The problem of protein misfolding represents one of the most significant challenges in cell biology and medicine. When proteins fail to achieve or maintain their native conformation, they can form aberrant structures that aggregate into toxic species. These misfolded proteins not only lose their normal biological function but also gain harmful properties that can disrupt cellular homeostasis and trigger cell death. The accumulation of misfolded protein aggregates is a hallmark of numerous neurodegenerative disorders, collectively known as proteinopathies.

The objective of this review is to establish clear connections between the fundamental biochemical mechanisms of protein folding and misfolding and their pathological consequences in neurodegenerative disorders. By understanding these molecular processes, we can identify potential therapeutic targets and develop strategies to prevent or treat these devastating diseases.

2. Literature Review

The foundation of our understanding of protein folding was established by Christian Anfinsen in the 1960s through his ground breaking work on ribonuclease. Anfinsen's dogma demonstrated that proteins could spontaneously refold to their native state after denaturation, proving that the amino acid sequence contains all the necessary information for proper folding. This discovery earned him the Nobel Prize in Chemistry in 1972 and established the thermodynamic principle that native protein structures represent the global energy minimum under physiological conditions.

The connection between protein misfolding and human disease emerged in the 1980s and 1990s through several key discoveries. The amyloid hypothesis of Alzheimer's disease was proposed following the identification of β-amyloid peptides as the major component of senile plaques. Simultaneously, researchers discovered that tau protein dysfunction contributed to neurofibrillary tangles, establishing the dual pathology model of Alzheimer's disease. In Parkinson's disease, the identification of α-synuclein as the primary component of Lewy bodies revealed another protein misfolding mechanism underlying neurodegeneration.

The prion diseases provided crucial insights into how misfolded proteins could propagate their aberrant conformation to normal proteins, introducing the concept of template-directed misfolding. This mechanism has since been recognized in other neurodegenerative diseases, with misfolded proteins exhibiting striking similarities to prions in terms of seeding capacity.

Current research has expanded our understanding of the molecular mechanisms underlying protein misfolding, yet significant gaps remain in our knowledge. Key areas of ongoing investigation include the precise molecular events that trigger the transition from soluble, functional proteins to toxic aggregates, the role of cellular stress responses in modulating protein homeostasis, and the development of therapeutic strategies that can effectively target misfolding processes without disrupting normal cellular function.

3. Molecular Mechanisms of Protein Folding

The process of protein folding is governed by the fundamental principle established by Anfinsen, which states that the amino acid sequence determines the final three-dimensional structure of a protein. This process occurs through a complex energy landscape where proteins navigate through various conformational states to reach their thermodynamically stable native conformation.

Molecular chaperones play a crucial role in facilitating proper protein folding by preventing aggregation and assisting in the folding process. The major chaperone families include the heat shock proteins (Hsps), with Hsp70 and Hsp90 being particularly important for protein folding in eukaryotic cells. Hsp70 chaperones bind to hydrophobic regions of nascent and misfolded proteins, preventing aggregation and providing multiple opportunities for correct folding. The GroEL/GroES chaperonin system in bacteria provides an enclosed folding chamber that allows proteins to fold in isolation from potential aggregation partners.

The energy landscape theory of protein folding describes how proteins navigate through conformational space to reach their native state. This landscape is characterized by a funnel-like topology where the native state represents the global energy minimum. However, proteins can become trapped in local energy minima, forming kinetic traps that may lead to misfolding. The presence of molecular chaperones helps proteins escape these traps and continue toward their native conformation.

Co-chaperones and chaperone cofactors further modulate the folding process by regulating chaperone activity and substrate specificity. The interplay between different chaperone systems creates a sophisticated protein quality control network that ensures proper protein folding under various cellular conditions. When this system fails or becomes overwhelmed, proteins may misfold and aggregate, leading to cellular dysfunction and disease.

4. Molecular Mechanisms of Protein Misfolding

Protein misfolding occurs when proteins adopt non-native conformations that often expose hydrophobic regions normally buried in the protein core. This exposure promotes intermolecular interactions that can lead to the formation of toxic oligomers and insoluble aggregates. The pathways of misfolding are complex and can involve multiple intermediates, each with different toxic properties.

The formation of β-sheet-rich structures is a common feature of protein misfolding in neurodegenerative diseases. These β-sheet structures can stack together to form amyloid fibrils, which are highly ordered, insoluble protein aggregates. The cross-β structure of amyloid fibrils is stabilized by extensive hydrogen bonding networks and represents a thermodynamically stable alternative to the native protein fold.

Several factors can influence protein misfolding, including oxidative stress, mutations that destabilize the native structure, metal ion imbalances that disrupt protein stability, and cellular aging processes that compromise protein quality control mechanisms. Environmental factors such as pH changes, temperature fluctuations, and the presence of other misfolded proteins can also promote misfolding events.

Disease-specific misfolding patterns have been identified in various neurodegenerative disorders. In Alzheimer's disease, the amyloid precursor protein is processed to generate β-amyloid peptides that aggregate into plaques, while tau protein becomes hyperphosphorylated and forms neurofibrillary tangles. Parkinson's disease is characterized by α-synuclein aggregation into Lewy bodies, which disrupt normal cellular function. Huntington's disease results from polyglutamine (PolyQ) expansion in the huntingtin protein, leading to the formation of intracellular inclusions that interfere with cellular processes.

The formation of toxic entities that contribute to neuronal degeneration involves aberrant folding, aggregation, and accumulation of key proteins such as β-amyloid (Aβ), tau, and α-synuclein. Understanding these specific misfolding pathways is essential for developing targeted therapeutic interventions.

5. Implications for Neurodegenerative Disorders

The connection between protein misfolding and neurodegenerative disorders involves complex biochemical pathways that ultimately lead to neuronal dysfunction and death. Misfolded protein aggregates can disrupt cellular function through multiple mechanisms, including interference with normal protein function, sequestration of essential cellular components, disruption of membrane integrity, and activation of inflammatory responses.

Neurotoxicity arises from both the loss of normal protein function and the gain of toxic properties by misfolded proteins. Toxic oligomers, which are intermediate species in the aggregation pathway, are often more harmful than mature fibrils and can disrupt synaptic function, alter membrane permeability, and interfere with cellular signaling pathways. These effects lead to synaptic dysfunction, which is often the earliest manifestation of neurodegeneration, preceding cell death by years or decades.

Animal model studies have provided crucial insights into the mechanisms of protein misfolding diseases. Transgenic mouse models expressing human disease proteins have demonstrated that the accumulation of misfolded proteins leads to progressive neurodegeneration, cognitive decline, and motor dysfunction that recapitulates key features of human disease. These models have also revealed that different misfolded proteins can interact and influence each other's aggregation, suggesting common pathways in neurodegeneration.

Comparative analysis across different neurodegenerative disorders reveals both shared and distinct mechanisms. While the specific proteins involved differ, common themes include disruption of protein homeostasis, mitochondrial dysfunction, oxidative stress, inflammation, and impaired cellular clearance mechanisms. Similar abnormal protein aggregation phenomena occur in common neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), with misfolded proteins exhibiting striking similarities to prions in terms of seeding capacity.

The progressive nature of these diseases suggests that initial protein misfolding events trigger cascading pathological processes that eventually overwhelm cellular protective mechanisms. Understanding these progression mechanisms is crucial for identifying intervention points where therapeutic strategies might be most effective.

6. Therapeutic Strategies and Future Directions

The development of therapeutic strategies for protein misfolding diseases requires a multi-faceted approach targeting different aspects of protein homeostasis and disease progression. Targeting molecular chaperones represents a promising therapeutic approach for neurodegenerative diseases, with chaperones serving as potential targets to interfere with disease progression.

Chaperone-based therapies focus on enhancing the cellular protein quality control system. Small molecule compounds that target molecular chaperones such as Hsp90 have been successfully demonstrated to be effective in various neurodegenerative diseases. These approaches include pharmacological chaperones that stabilize native protein conformations, compounds that upregulate endogenous chaperone expression, and direct administration of recombinant chaperone proteins.

Regulation of proteasome and autophagy pathways represents another therapeutic avenue. The ubiquitin-proteasome system and autophagy are the two major cellular mechanisms for protein degradation. Enhancing these pathways can promote the clearance of misfolded proteins before they aggregate into toxic species. Therapeutic options are currently being explored that target different steps in the production and processing of proteins.

Molecular inhibitors of amyloid aggregation directly target the misfolding process by preventing the formation of toxic aggregates. These compounds can work by stabilizing native protein conformations, disrupting protein-protein interactions involved in aggregation, or redirecting misfolding pathways toward less toxic species.

CRISPR/Cas9 technology is revolutionizing research, particularly in the context of human neurodegenerative disorders, with potential to address the protein misfolding mechanisms underlying these diseases. Gene editing approaches can correct disease-causing mutations at their source, potentially preventing the production of misfolding-prone proteins.

Personalized medicine approaches recognize that neurodegenerative diseases are heterogeneous conditions with varying genetic, environmental, and lifestyle factors contributing to disease development. Tailoring treatments based on individual patient characteristics, genetic profiles, and disease stages may improve therapeutic outcomes and reduce adverse effects.

7. Discussion

The study of protein folding and misfolding mechanisms has provided fundamental insights into the molecular basis of neurodegenerative disorders. The recognition that diverse diseases share common pathways involving protein homeostasis disruption has opened new avenues for therapeutic development and revealed potential targets for intervention.

The clinical relevance of this research is profound, as neurodegenerative diseases represent one of the greatest medical challenges of our aging society. The ability to detect, prevent, or treat protein misfolding could dramatically impact millions of patients worldwide. Visualizing the misfolding process with smart imaging probes would greatly facilitate early diagnosis, etiology elucidation, disease progression monitoring, and drug discovery.

However, significant challenges remain in translating this knowledge into effective treatments. Early detection of protein misfolding before irreversible neuronal damage occurs requires sensitive biomarkers and imaging techniques. Drug delivery to the central nervous system presents substantial barriers, particularly for large molecules such as therapeutic proteins. Achieving therapeutic specificity while avoiding disruption of normal cellular processes requires careful target selection and drug design.

The integration of biochemistry with clinical neuroscience has accelerated progress in understanding disease mechanisms and identifying therapeutic targets. Molecular chaperones have become potential therapy targets concerning with the prevention and therapeutic approach, representing a convergence of basic science discoveries with clinical applications.

Future research directions should focus on developing combination therapies that target multiple aspects of protein misfolding diseases simultaneously, improving methods for early detection and intervention, and personalizing treatments based on individual patient characteristics and disease subtypes.

8. Conclusion

The molecular mechanisms of protein folding and misfolding represent a fundamental aspect of cellular biology with profound implications for human health. Normal protein folding requires precise coordination of amino acid sequence information, cellular chaperone systems, and environmental conditions to achieve functional three-dimensional structures. When this process fails, the resulting misfolded proteins can trigger cascading pathological events that lead to neurodegeneration.

The connection between protein misfolding and neurodegenerative disorders has been firmly established through decades of research revealing common themes across different diseases. While specific proteins and pathways may differ between Alzheimer's disease, Parkinson's disease, Huntington's disease, and ALS, the underlying principle of protein homeostasis disruption provides a unifying framework for understanding these conditions.

Therapeutic opportunities arising from this understanding are promising and diverse. Chaperones are a promising therapeutic target to interfere with the progression of neurodegenerative diseases, while advances in gene editing, drug delivery, and personalized medicine offer additional avenues for intervention. The development of sensitive detection methods and imaging technologies will enable earlier diagnosis and monitoring of treatment responses.

Future research should continue to explore the detailed molecular mechanisms of protein quality control, the role of cellular stress responses in disease progression, and the development of combination therapies that target multiple pathways simultaneously. The integration of basic science discoveries with clinical applications will be essential for translating this knowledge into effective treatments for patients suffering from these devastating diseases.

References

1. Prusiner SB. Prions. Proc Natl Acad Sci USA. 1998;95(23):13363-13383.
2. Dobson CM. Protein folding and misfolding. Nature. 2003;426(6968):884-890.
3. Chiti F, Dobson CM. Protein misfolding, amyloid formation, and human disease: a summary of progress over the last decade. Annu Rev Biochem. 2017;86:27-68.
4. Hartl FU, Bracher A, Hayer-Hartl M. Molecular chaperones in protein folding and proteostasis. Nature. 2011;475(7356):324-332.
5. Ross CA, Poirier MA. Protein aggregation and neurodegenerative disease. Nat Med. 2004;10 Suppl:S10-17.
6. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med. 2016;8(6):595-608.
7. Spillantini MG, Goedert M. Tau pathology and neurodegeneration. Lancet Neurol. 2013;12(6):609-622.
8. Lashuel HA, Overk CR, Oueslati A, Masliah E. The many faces of α-synuclein: from structure and toxicity to therapeutic target. Nat Rev Neurosci. 2013;14(1):38-48.
9. Walker LC, Jucker M. Neurodegenerative diseases: expanding the prion concept. Annu Rev Neurosci. 2015;38:87-103.
10. Balch WE, Morimoto RI, Dillin A, Kelly JW. Adapting proteostasis for disease intervention. Science. 2008;319(5865):916-919.
11. Powers ET, Morimoto RI, Dillin A, Kelly JW, Balch WE. Biological and chemical approaches to diseases of proteostasis deficiency. Annu Rev Biochem. 2009;78:959-991.
12. Hetz C, Saxena S. ER stress and the unfolded protein response in neurodegeneration. Nat Rev Neurol. 2017;13(8):477-491.
13. Muchowski PJ, Wacker JL. Modulation of neurodegeneration by molecular chaperones. Nat Rev Neurosci. 2005;6(1):11-22.
14. Ciechanover A, Brundin P. The ubiquitin proteasome system in neurodegenerative diseases: sometimes the chicken, sometimes the egg. Neuron. 2003;40(2):427-446.
15. Nixon RA. The role of autophagy in neurodegenerative disease. Nat Med. 2013;19(8):983-997.
16. Kayed R, Head E, Thompson JL, McIntire TM, Milton SC, Cotman CW, Glabe CG. Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science. 2003;300(5618):486-489.
17. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β-peptide. Nat Rev Mol Cell Biol. 2007;8(2):101-112.
18. Gitler AD, Dhillon P, Shorter J. Neurodegenerative disease: models, mechanisms, and a new hope. Dis Model Mech. 2017;10(5):499-502.
19. Polymenidou M, Cleveland DW. Prion-like propagation of protein aggregates in neurodegeneration. J Exp Med. 2012;209(5):889-893.
20. Brettschneider J, Del Tredici K, Lee VM, Trojanowski JQ. Spreading of pathology in neurodegenerative diseases: a focus on human studies. Nat Rev Neurosci. 2015;16(2):109-120.
21. Aguzzi A, O'Connor T. Protein aggregation diseases: pathogenicity and therapeutic perspectives. Nat Rev Drug Discov. 2010;9(3):237-248.
22. Taylor JP, Hardy J, Fischbeck KH. Toxic proteins in neurodegenerative disease. Science. 2002;296(5575):1991-1995.
23. Soto C. Unfolding the role of protein misfolding in neurodegenerative diseases. Nat Rev Neurosci. 2003;4(1):49-60.
24. Brunden KR, Trojanowski JQ, Lee VM. Advances in tau-focused drug discovery for Alzheimer's disease and related tauopathies. Nat Rev Drug Discov. 2009;8(10):783-793.
25. Cookson MR. α-Synuclein and neuronal cell death. Mol Neurodegener. 2009;4:9.