Pages 9-15

Volume 1, Number 2, 2024

ADVANCES IN BIOSCIENCES RESEARCH

advbioresearch.com
editor@advbioresearch.com
ISSN: 3080-3438 (Print)
ISSN: 3080-3446 (Online)

Unraveling the Role of Protein Folding Disorders in Human Diseases: Mechanisms, Pathological Implications, and Therapeutic Strategies

Zia Ur Rehman[1]*, Hassan Yar Mahsood[2], Ammara Riaz[3], Rabia Nasir[4]

[1]*Institute of Biological Sciences, Gomal University, Dera Ismail Khan 29050, Khyber Pakhtunkhwa, Pakistan*
[2]*Gomal Medical College, MTI, Dera Ismail Khan 29050 Khyber Pakhtunkhwa, Pakistan*
[3]*Superior University, Faisalabad Campus, Faisalabad*
[4]*District Headquarter Teaching Hospital, MTI, Dera Ismail Khan-29050, Pakistan*
**Corresponding Author Email: k.zia59@yahoo.com*

Article Information

Article History

Received:	July 10, 2024
Revised:	August 05, 2024
Accepted:	September 28, 2024
Available Online:	December 31, 2024

Keywords:
Protein misfolding, Protein Folding Disorders, Conformational Diseases, protein quality control

Abstract

Protein folding represents a fundamental biological process which cells require to maintain their functionality and equilibrium. Several human diseases which are categorized as protein folding disorders or conformational diseases develop because of proteins that have improperly folded. The range of conditions covered involves neurodegenerative diseases such as Parkinson's and Alzheimer's as well as metabolic disorders like phenylketonuria. The study investigates protein misfolding mechanics and its pathological effects while exploring new treatment methods for related diseases. Our research examines how PQC systems operate alongside genetic mutations and their subsequent physiological responses to protein misfolding which results in aggregation and oxidative stress. In our final section we examine several treatment possibilities including gene therapy as well as proteostasis modulators and pharmaceutical chaperones. It has been concluded that many diseases known as protein folding disorders exist because of fundamental protein misfolding events that lead cells or tissues toward aggregation and accumulation. Several negative outcomes appear from these conditions after genetic mutations alongside environmental stress and aging produce loss of function and gain of function with oxidative stress and cellular dysfunction. The complexity of these illnesses has enabled researchers to understand better the protein misfolding process and develop sufficiently reliable treatment strategies. Scientists are currently exploring four promising therapeutic methods that include antioxidants alongside gene therapy and proteostasis regulators and pharmacological chaperones. Treatment approaches involve lowering pathogenic protein misfolding symptoms and proteostasis restoration together with misfolded protein reduction. Current pharmaceutical development maintains optimism about protein folding disorder treatments although additional barriers remain before success becomes achievable.

INTRODUCTION

Proteins serve as fundamental macromolecules that control essential cell processes including holding cell shapes and speeding up metabolic changes. The outcome of protein folding depends on its specific polypeptide chain arrangement which gives proteins their necessary functioning shapes. Prolonged protein folding problems appear due to mismatches between the normal process and harm from age changes plus environmental strain and mutation effects. The PQC system fails to repair or remove abnormal proteins which form harmful collections inside cells that lead to cellular malfunction and disease. Systemic amyloidosis and neurological diseases along with metabolic problems make up the group of protein folding disorders known as conformational diseases that affect human health. Protein damage that turns into aggregated masses within cells or tissues leads to these disorders. The various protein misfolding disorders follow a basic pathogenic process that affects the overall balance of protein quality control in cells. Our aim is to study how protein folding difficulties become damaging to human health and how researchers treat them through new therapies. We will examine PQC operations along with gene and protein folding mutations and explain how these things damage cells through oxidative stress and protein buildup.

Proteins which handle essential cellular processes occur through ribosome-mediated biosynthesis of amino acids. Native conformation refers to folded structures that comprise tertiary and in some cases quaternary structures of proteins. The acquired compact three-dimensional arrangement results from both amino acid sequence and cellular environmental factors. The natural configuration of proteins houses all its biochemical traits that enable cellular operations. The folding process of proteins depends strongly on chain topology according to Makarov, D.E.; Plaxco,2003. The native state structure displays contact order as the average distance between sequence-residing contacts. Small protein folding rates demonstrate direct correlation with protein structures' contact order (Plaxco, K.W.; Simons, K.T. Baker,2018). This correlation stands separate from the protein dimensions or their helix and sheet structure content (Branden, C.; Tooze,2020). The diverse structural protein group demonstrates matching folding behaviors which validates the fundamental protein folding process (Dobson, C.M.; Šali, A,2018). A longer time period will be needed to perform the search when residues form the protein nucleus.

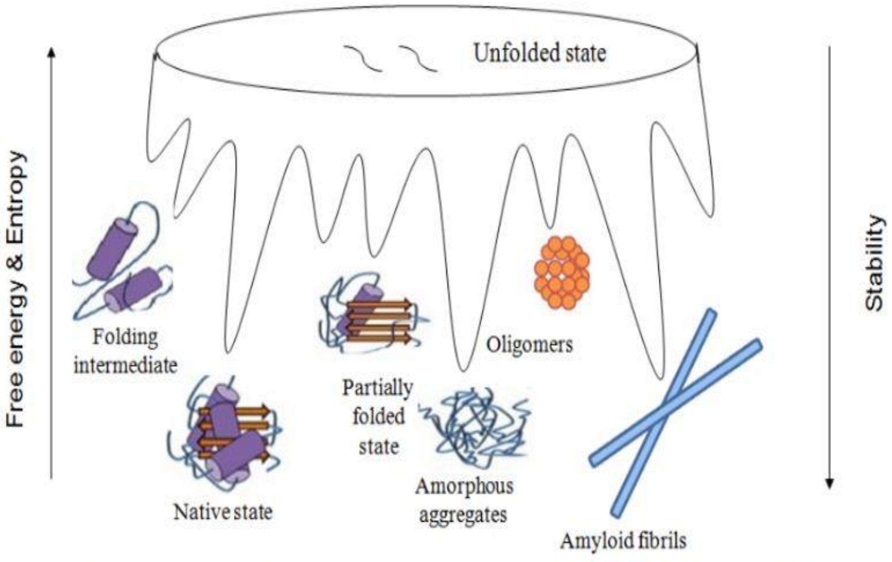

Fig. (1). Energy state of protein folding under physiological (left portion) and misfolded and aggregated conditions (right portion).

LITERATURE REVIEW

Protein Folding: The Role of Amino Acid Sequence The polypeptide chain's amino acid composition holds all instructions to create both the natural and working form of the protein during folding. In 1973 Christian Anfinsen showed that physiological conditions produce the most stable protein shape which became known as the Anfinsen Creed (Anfinsen 1973). Various conditions in the cell alongside molecular helpers and the specific protein makeup complicate the intricate protein folding process. According to Levinthal's concept protein folding cannot be achieved through random searches since it would need more time than what cells survive (Levinthal, 1968). Cells have designed a network of chaperone molecules that guide proteins to proper folding structure because random folding takes too much time. During folding and aggregation prevention molecular chaperones join misfolded and newly formed proteins to facilitate their correct structure formation. Through their role in protein refolding and elimination of damaged proteins these chaperone molecules protect cellular proteins from changes that could harm normal function. When proteins fail to form their natural shapes it becomes protein misfolding which results primarily from folding problems and external pressure alongside genetic changes. Proteins that fold incorrectly create resistant and long-lasting toxic clumps. Unfolded proteins create damage through stress and block protein activity while also holding essential molecules inside (Dobson, 2003). Protein folding failure creates protein clusters that affect both Parkinson's and Alzheimer's patients. Protein misfolding occurs mainly because of genetic mutations. Nonsensical mutations create protein design errors that adjust its energy map to generate misformed shapes which disrupt protein folding (Gregersen et al., 2006). The PQC system works to destroy damaged proteins or they become disruptive when they accumulate in large groups. Studies of various keratin diseases and heart disorders confirm that abnormal proteins disrupt normal protein operation but damage it more severely (Bross et al., 1999).

Protein Misfolding

During folding the individual molecules develop incorrect interactions while getting trapped in temporary local energy minimums. Scientists label this phenomenon as misfolding. The protein misfolding refers to a mechanism where proteins develop multiple nonnative interactions that modify their shape together with their functional characteristics. Protein misfolding occurs due to multiple reported elements that contribute to this process. Protein misfolding occurs as a result of somatic or genetic mutations together with organellar DNA deletion and conditions like high temperature and acidic or basic pH and high glucose or oxidative stress and metal ion and aging etc. (Aliev, G.; Seyidova, D.; Neal, M.L.; Shi, J.2020). Misfolded proteins experience two main possible outcomes during their biochemical processes. A degenerative protein clearance process removes misfolded proteins thereby causing function deterioration of the specific protein. The aggregation of misfolded protein results in toxic gain of function as its second major consequence. The diagrams illustrating both fates appear in Figure 2. Molecular chaperones (A) work to fold the recently synthesized protein according to Fig. (2). Misfolding occurs to the chain of polypeptides which stems from a gene mutation during protein synthesis (B). The misfolded mutant protein moves through the degradation (clearance) pathway which requires sequential action of ubiquitin activating enzyme (E1), ubiquitin conjugating enzyme (E2) and ubiquitin ligase enzyme (E3) (C). The proteasome system receives ubiquitinated protein complex for breakdown (D). Through proteasome system the unfolded protein is degraded to produce short peptides while releasing ubiquitin (E). The conversion of alpha-helix structure to beta-sheets during destabilization leads to mis-folded proteins referred to as F. Molecular chaperones have the capability to route misfolded proteins into the proteasome system for destruction (G).

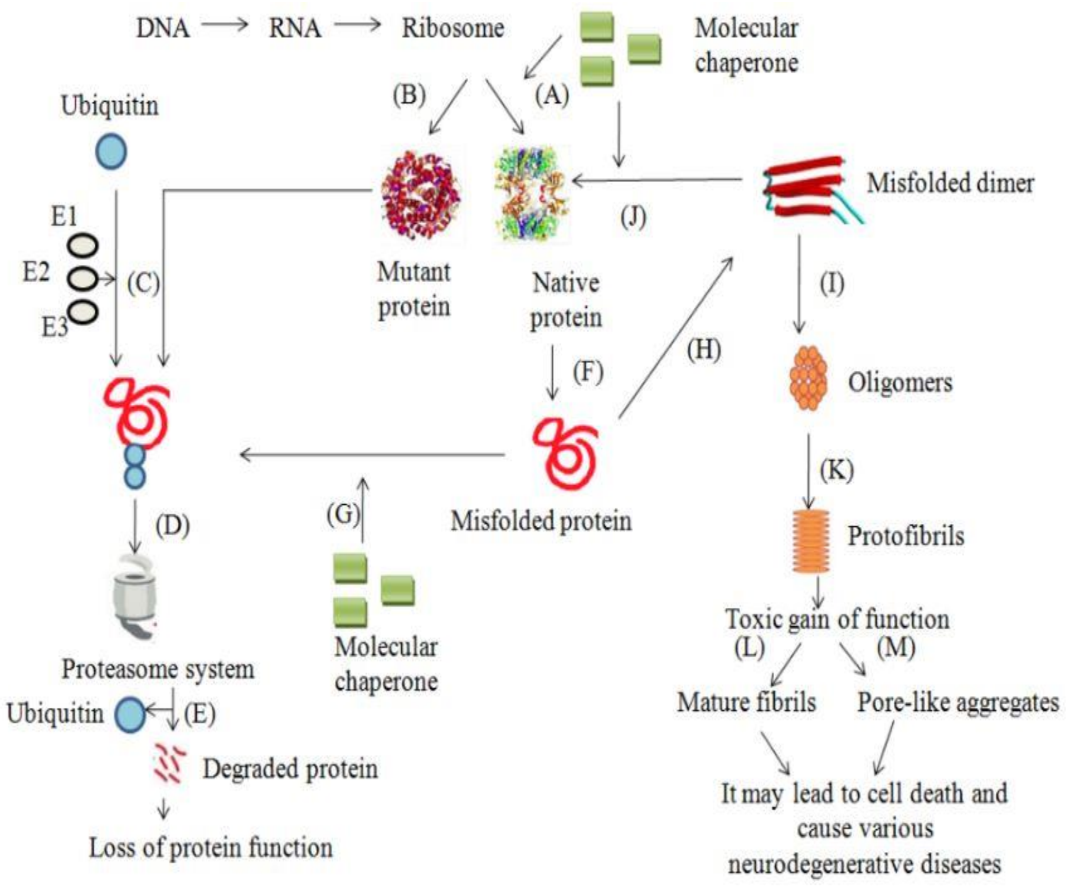

Fig.2. Protein misfolding and degradation pathways

Protein Quality Control Systems

Molecular chaperones are key components of the PQC system, which is responsible for maintaining proteostasis by ensuring that proteins are properly folded and functional. Chaperones such as Hsp70 and Hsp90 bind to nascent or misfolded proteins, preventing their aggregation and facilitating their refolding (Hartl & Hayer-Hartl, 2002). In cases where refolding is not possible, chaperones can target misfolded proteins for degradation by the ubiquitin-proteasome system (UPS) or autophagy.

The Ubiquitin-Proteasome System

Among the critical mechanisms for protein breakdown exists the ubiquitin-proteasome system (UPS). The proteasome acts as a big enzymatic complex which destroys proteins marked with ubiquitin regulatory proteins (Glickman and Ciechanover, 2002). The UPS functions to remove problematic misfolded proteins that could develop dangerous aggregates thus maintaining cellular stability. The UPS becomes overwhelmed by misfolded protein accumulation which leads to cellular abnormalities together with protein aggregate formation within various protein folding diseases.

Autophagy and Lysosomal Degradation

The vital process of autophagy enables breakdown of harmed organelles together with misfolded proteins. Autophagy works to splurge organelle ruins and protein misfolding incidents into autophagosomes until these vesicles enter the lysosomes for decomposition (Levine and Klionsky, 2004). The autophagy process performs a critical role in eliminating large protein clusters which the proteasome system cannot degrade. The degenerative conditions of lysosomal storage disorders together with several forms of neurodegenerative disease have shown strong links to autophagy dysfunction.

PATHOLOGICAL IMPLICATIONS OF PROTEIN MISFOLDING

Loss-of-Function and Gain-of-Function Pathogenesis

Protein misfolding produces two types of diseases: when harmful changes in protein function occur and when essential proteins become unusable. Strong protein breakdown causes loss-of-function disease when it prevents normal protein production. The defective enzyme in quest of its damaged state represents the primary symptom of PKU and other metabolic conditions. During gain-of-function pathogenesis protein aggregates in cells disturb regular operations and destroy the cells. Many types of brain-destroying disorders including ALS and PD develop from the buildup of misfolded proteins. In Parkinson's disease (PD) mutations to the α-synuclein gene lead α-synuclein protein to misfold then aggregate into pathogenic structures that disrupt nerve cell operations and bring about neuronal death according to Moore et al. 2005.

Oxidative Stress and Cellular Dysfunction

Oxidative stress leads to cellular breakdown in protein folding diseases because protein mis formation and clumping create it. The misfolding of proteins creates Reactive Oxygen Species (ROS) that attacks DNA, lipids and proteins inside cells according to Dunlop et al. in 2002. Oxidative stress damages both PQC functions and protein-folding enzymes when it enters the PQC system at the molecular level. Aggregated misfolded proteins lead to oxidative stress which makes more proteins cluster and misalign.

Aggregation and Toxicity

Pagans of protein folding diseases lead to an abnormal buildup of proteins. The presence of protein clumps causes severe cell damage because they bind useful proteins while blocking proteasome activity and generating oxidative harm (Bucciantini et al., 2002). Soluble oligomers leak through cell walls and disturb ions to cause damage according to research by Kayed and colleagues (2003). The buildup of protein clusters serves as a main culprit behind protein folding diseases without researchers fully grasping their exact causes of damage.

METHODOLOGY

Therapeutic Strategies for Protein Folding Disorders

Pharmacological Chaperones

Pharmacological chaperones make up small chemical compounds that fix folded proteins by returning them to their natural structures to achieve proper functioning capabilities. Tests indicate that these compounds demonstrate potential uses in handling lysosomal storage disorders along with cystic fibrosis (CF) and additional protein folding conditions. The misfolded CFTR protein in CF receives improvement of function and folding through pharmacological chaperones ivacaftor and lumacaftor according to (Van Goor et al., 2011).

Proteostasis Regulators

Proteostasis modulators make the PQC system more efficient by promoting breakdown of all proteins including those that misfolded. These substances help PQC function by supporting autophagy and improving proteasome activity plus promoting molecular chaperone production. Research shows that proteostasis modulators could improve cellular functions and reduce toxic protein clumps so they offer hope for treating neurodegenerative diseases (Balch et al., 2008).

Gene Therapy and Genome Editing

Advances in protein folding disorders treatment utilize gene therapy coupled with CRISPR-Cas9 genome editing tools as potential solutions. The technology enables improvements to PQC system operations together with protein production restoration and disease mutation correction. Scientists have demonstrated successful restoration of CFTR expression through gene therapy in preclinical cystic fibrosis studies together with genome editing implementation of PAH mutation corrections in preclinical PKU studies (Griesenbach et al., 2011; Schwank et al., 2013).

Targeting Oxidative Stress

Oxidative-stress-blocking substances and antioxidants are being researched as medicines because oxidative stress strongly affects these protein folding problems. The PQC system works better with these substances while it destroys fewer harmful proteins and protects cells from ROS damage. Researchers have found promising outcomes with N-acetylcysteine and coenzyme Q10 antioxidants when testing them for neurodegenerative diseases in early study stages (Emerit et al., 2004).

CONCLUSION

Many diseases known as protein folding disorders exist because of fundamental protein misfolding events that lead cells or tissues toward aggregation and accumulation. Several negative outcomes appear from these conditions after genetic mutations alongside environmental stress and aging produce loss of function and gain of function with oxidative stress and cellular dysfunction. The complexity of these illnesses has enabled researchers to understand better the protein misfolding process and develop sufficiently reliable treatment strategies. Scientists are currently exploring four promising therapeutic methods that include antioxidants alongside gene therapy and proteostasis regulators and pharmacological chaperones. Treatment approaches involve lowering pathogenic protein misfolding symptoms and proteostasis restoration together with misfolded protein reduction.

Current pharmaceutical development maintains optimism about protein folding disorder treatments although additional barriers remain before success becomes achievable.

REFERENCES

Anfinsen, C. B. (1973). Principles that govern the folding of protein chains. Science, *181(4096), 223-230.*

Balch, W. E., Morimoto, R. I., Dillin, A., & Kelly, J. W. (2008). Adapting proteostasis for disease intervention. Science, *319(5865), 916-919.*

Bross, P., Corydon, T. J., Andresen, B. S., Jørgensen, M. M., Bolund, L., & Gregersen, N. (1999). Protein misfolding and degradation in genetic diseases. Human Mutation, *14(3), 186-198.*

Bucciantini, M., Giannoni, E., Chiti, F., Baroni, F., Formigli, L., & Stefani, M. (2002). Inherent toxicity of aggregates implies a common mechanism for protein misfolding diseases. Nature, *416(6880), 507-511.*

Dobson, C. M. (2003). Protein folding and misfolding. Nature, *426(6968), 884-890.*

Dunlop, R. A., Rodgers, K. J., & Dean, R. T. (2002). Recent developments in the intracellular degradation of oxidized proteins. Free Radical Biology and Medicine, *33(7), 894-906.*

Ellis, R. J. (1990). The molecular chaperone concept. Seminars in Cell Biology, *1(1), 1-9.*

Emerit, J., Edeas, M., & Bricaire, F. (2004). Neurodegenerative diseases and oxidative stress. Biomedicine & Pharmacotherapy, *58(1), 39-46.*

Gamez, A., Perez, B., Ugarte, M., & Desviat, L. R. (2000). Expression analysis of phenylketonuria mutations: Effect on folding and stability of the phenylalanine hydroxylase protein. Journal of Biological Chemistry, *275(38), 29737-29742.*

Glickman, M. H., & Ciechanover, A. (2002). The ubiquitin-proteasome proteolytic pathway: Destruction for the sake of construction. Physiological Reviews, *82(2), 373-428.*

Gregersen, N., Bross, P., Vang, S., & Christensen, J. H. (2006). Protein misfolding and human disease. Annual Review of Genomics and Human Genetics, *7, 103-124.*

Griesenbach, U., Alton, E. W., & UK Cystic Fibrosis Gene Therapy Consortium. (2011). Gene transfer to the lung: Lessons learned from more than 2 decades of CF gene therapy. Advanced Drug Delivery Reviews, *63(4-5), 269-276.*

Hartl, F. U., & Hayer-Hartl, M. (2002). Molecular chaperones in the cytosol: From nascent chain to folded protein. Science, *295(5561), 1852-1858.*

Kayed, R., Head, E., Thompson, J. L., McIntire, T. M., Milton, S. C., & Glabe, C. G. (2003). Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science, *300(5618), 486-489.*

Levine, B., & Klionsky, D. J. (2004). Development by self-digestion: Molecular mechanisms and biological functions of autophagy. Developmental Cell, *6(4), 463-477.*

Levinthal, C. (1968). Are there pathways for protein folding? Journal de Chimie Physique, *65, 44-45.*

Moore, D. J., West, A. B., Dawson, V. L., & Dawson, T. M. (2005). Molecular pathophysiology of Parkinson's disease. Annual Review of Neuroscience, *28, 57-87.*

Schwank, G., Koo, B. K., Sasselli, V., Dekkers, J. F., Heo, I., & Demircan, T. (2013). Functional repair of CFTR by CRISPR/Cas9 in intestinal stem cell organoids of cystic fibrosis patients. Cell Stem Cell, *13(6), 653-658.*

Van Goor, F., Hadida, S., Grootenhuis, P. D., Burton, B., Cao, D., & Neuberger, T. (2011). Correction of the F508del-CFTR protein processing defect in vitro by the investigational drug VX-809. Proceedings of the National Academy of Sciences, *108(46), 18843-18848.*