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Biochemistry of Protein Folding and Misfolding in Human Disease

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Introduction

Proteins are the workhorses of the cell, carrying out a vast array of structural, catalytic and regulatory functions essential for life. To fulfill these roles, proteins must adopt specific three-dimensional conformations, a process known as protein folding. The precise folding of a polypeptide chain into its functional structure is dictated by its amino acid sequence but is also influenced by the cellular environment and molecular chaperones that assist in this process. When folding proceeds correctly, proteins achieve their native states and contribute to cellular health. However, failures in folding, referred to as misfolding, can have devastating consequences, leading to aggregation, loss of function, or toxic gain of function. Protein misfolding underlies a range of human diseases, from neurodegenerative disorders such as Alzheimer's and Parkinson's disease to systemic conditions like cystic fibrosis and certain cancers. Understanding the biochemical principles of protein folding and misfolding is therefore central to unraveling the molecular basis of disease and identifying therapeutic strategies [1].

Description

Protein folding is a highly coordinated process that begins as the polypeptide chain emerges from the ribosome. The amino acid sequence provides the information necessary for folding, often summarized by Anfinsen's thermodynamic hypothesis, which states that the native structure corresponds to the lowest free energy state of the protein. Folding proceeds through intermediate states, forming secondary structures such as α-helices and β-sheets, which then assemble into the tertiary structure. The process is guided by non-covalent interactions, including hydrogen bonds, hydrophobic interactions, van der Waals forces and electrostatic interactions, as well as covalent disulfide bonds in some proteins. Cells employ molecular chaperones to ensure efficient folding and to prevent aggregation. Heat shock proteins (HSPs), for example, bind transiently to exposed hydrophobic regions of nascent polypeptides, stabilizing them until proper folding can occur. Other chaperones, such as chaperonins, provide enclosed environments that facilitate correct folding by isolating polypeptides from the crowded cytoplasm [2].

Additionally, protein disulfide isomerases and peptidyl-prolyl isomerases catalyze the formation of correct disulfide bonds and cis-trans isomerization of proline residues, respectively. These biochemical safeguards highlight the delicate balance required for protein homeostasis, or proteostasis. Despite these mechanisms, errors in folding are inevitable. Misfolding can occur due to mutations that destabilize the native state, errors during translation, or stress conditions that overwhelm the folding machinery. Misfolded proteins may expose hydrophobic regions that promote aggregation, leading to the formation of insoluble fibrils or amorphous deposits. In many cases, these aggregates are toxic to cells, either through direct disruption of cellular structures or by sequestering essential proteins.

Neurodegenerative diseases are among the most well-studied examples of protein misfolding disorders. In Alzheimer's disease, misfolded amyloid-β peptides aggregate into extracellular plaques, while hyperphosphorylated tau proteins form intracellular neurofibrillary tangles. Both processes disrupt neuronal communication and lead to cell death. Structural studies have shown that amyloid-β peptides misfold into β-sheet-rich conformations that stack into fibrils, a hallmark of amyloid pathology. Similarly, in Parkinson's disease, the protein α-synuclein misfolds into fibrils that form Lewy bodies, impairing neuronal function. Huntington's disease results from expanded polyglutamine repeats in the huntingtin protein, which destabilize its structure and promote aggregation.

These disorders illustrate how subtle changes in protein structure can trigger cascades of misfolding with catastrophic effects. Protein misfolding is not limited to neurodegeneration. In cystic fibrosis, a mutation in the CFTR chloride channel protein leads to its misfolding and subsequent degradation by the cell's quality control systems, preventing its proper localization to the plasma membrane. The result is defective ion transport and the accumulation of thick mucus in the lungs and other organs. Similarly, in certain forms of cancer, mutations destabilize tumor suppressor proteins such as p53, preventing them from folding correctly and impairing their ability to regulate cell growth and apoptosis.

In type II diabetes, misfolding and aggregation of islet amyloid polypeptide (IAPP) in pancreatic β-cells contribute to the decline in insulin secretion. These examples underscore the wide-ranging impact of protein folding errors on human health. The biochemical mechanisms underlying misfolding are diverse. Some proteins are inherently unstable and rely heavily on chaperone assistance; others may adopt alternate conformations that are thermodynamically stable but non-functional.

Conclusion

The biochemistry of protein folding and misfolding lies at the heart of understanding human disease. Proteins must fold into precise three-dimensional structures to function correctly, yet the same complexity that enables their versatility also makes them vulnerable to error. Misfolding can arise from genetic mutations, environmental stress, or stochastic events and its consequences range from subtle functional impairments to catastrophic aggregation and cell death. Diseases such as Alzheimer's, Parkinson's, cystic fibrosis and cancer all highlight the devastating impact of disrupted proteostasis on human health. By uncovering the molecular principles of folding and misfolding, researchers are developing innovative strategies to restore balance, prevent aggregation and stabilize functional proteins. As structural and biochemical techniques continue to advance, our ability to understand and intervene in protein misfolding diseases will expand, offering hope for new therapies against some of the most challenging medical conditions.

Acknowledgement

None.

Conflict of Interest

None.

Reference

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