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Decoding the path from amino acids to architecture: Understanding protein folding

DRx. Snigdha Mohanty[1] and Amisha Biswal[2]

[1]Department of Pharma Chemistry, Institute of Pharmacy and Technology, Cuttack, Odisha, India
[2]Department of Biotechnology, MITS School of Biotechnology, Bhubaneswar, Odisha, India

ABSTRACT

Protein folding is a crucial biological mechanism where linear sequences of amino acids, produced by ribosomes during translation, attain a specific three-dimensional shape that dictates their biological role. Although created as unstructured polypeptides, proteins experience a complicated but carefully regulated process that leads to the formation of secondary, tertiary, and, in certain instances, quaternary structures. This change is directed by the amino acid sequence itself, a principle recognized as Anfinsen's dogma, but is also affected by multiple intra- and intermolecular forces, including hydrogen bonds, hydrophobic interactions, and van der Waals interactions. Correctly folded proteins are crucial for almost all cellular functions, including enzymatic catalysis, signal transduction, structural support, and immune defense. On the other hand, improper or incomplete folding may result in nonfunctional proteins that are either quickly broken down or build up as harmful aggregates, frequently associated with various degenerative diseases like Alzheimer's, Parkinson's, and cystic fibrosis. Grasping the principles and mechanisms of protein folding is therefore essential for both basic biology and practical biomedical research.

KEYWORDS

Alzheimer's disease; Protein; Amino acid sequence; AlphaFold; Intramolecular interaction

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Introduction

Proteins are crucial macromolecules that act as the engines of the cell, performing numerous biological functions such as catalyzing metabolic processes, offering structural support, moving molecules, and enabling cell signaling and immune reactions [1]. Every protein is produced as a linear sequence of amino acids a primary structure through the process of translation in the ribosome. Nevertheless, this linear arrangement by itself is not effective; a protein's biological function is fundamentally linked to its three-dimensional structure [2].

The progression from a basic sequence of amino acids to a completely folded and operational protein entails a sophisticated yet well-structured process referred to as protein folding. This change is dictated by the chemical characteristics of the amino acids in the sequence and affected by interactions in the cellular setting, such as molecular chaperones, cofactors, pH levels, and ionic strength. Notably, the majority of proteins can naturally fold into their native structure, but many need help to prevent misfolding and aggregation. The accuracy of this process is essential mistakes in folding may result in loss of function or disease states. Grasping the mechanisms of protein folding is essential to molecular biology, carrying important consequences for medicine, biotechnology, and synthetic biology [3,4].

The Protein Folding Problem

The protein folding problem, a concept well-known in molecular biology since the 1950s, pertains to the intriguing issue of how proteins swiftly and precisely fold into their functional three-dimensional shapes despite the vast array of potential conformations. Even a tiny polypeptide has an enormous number of possible folding pathways, but in nature, the majority of proteins fold in milliseconds to seconds [4]. This seeming paradox how proteins efficiently traverse such an extensive conformational space is key to grasping protein biophysics.

A key understanding of this issue originated from Christian B. Anfinsen's experiments in the 1950s, which showed that the primary amino acid sequence of a protein holds all the essential information required to establish its native structure [5,6]. This concept, referred to as Anfinsen's dogma, suggests that the ultimate structure is thermodynamically stable and dictated by inherent interactions including hydrogen bonds, hydrophobic effects, ionic interactions, and van der Waals forces (Figure 1).

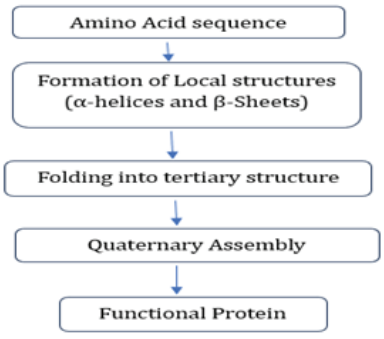

Figure 1. Flowchart showing the key stages of protein folding.

***Correspondence:** DRx. Snigdha Mohanty, Department of Pharma Chemistry, Institute of Pharmacy and Technology, Cuttack, Odisha, India. e-mail: mohantysnigdha326@gmail.com

Nonetheless, in the cellular setting, folding is not always an individual process. Proteins frequently need help from molecular chaperones to fold properly or to avoid clumping together [5]. Moreover, the crowded intracellular environment introduces further complexity, transforming protein folding into a dynamic, multi-stage process that showcases both the beauty and complexity of cellular existence.

The hierarchy of protein structure

Protein folding consists of multiple stages that is primary structure that includes, the sequential arrangement of amino acids. Secondary structure involves local formations such as α-helices and β-sheets maintained by hydrogen bonds where the tertiary structure involves the entire three-dimensional arrangement created by the interactions between side chains and the quaternary structure construction of several polypeptide units [7,8].

Mechanisms and pathways of folding

Folding is not an arbitrary process. Proteins typically navigate a funnel-like energy landscape, with partially folded intermediates directing the molecule towards its native form (Table 1). Essential processes consist of hydrophobic collapse, nucleation, zipping and docking [9].

Table 1. Key factors influencing protein folding.

Factor	Description
Amino Acid Sequence	Dictates the folding pathway and final structure (Anfinsen's principle).
Hydrophobic Effect	Drives nonpolar residues to the protein core, reducing exposure to water.
Chaperones	Assist in folding and prevent misfolding or aggregation.
pH & Ionic Strength	Affect electrostatic interactions and protein solubility.
Temperature	Alters folding rates; extreme heat may cause denaturation.

Role of chaperones and cellular environment

Cells utilize molecular chaperones to aid in folding includes the Hsp70 and Hsp60 families assist in avoiding aggregation and facilitate correct folding and proteasomes and autophagy mechanisms remove improperly folded proteins [7,10].

The crowded conditions of the cytoplasm, along with its pH, ionic strength, and cofactors, also affect folding dynamics.

Misfolding and disease

Improperly folded proteins can result in aggregates and plaques, frequently associated with illnesses like Alzheimer's disease, Parkinson's disease, Cystic fibrosis [11,12]. Grasping these misfolding routes creates opportunities for treatment options.

Computational approaches to folding

Recent developments, particularly AlphaFold from DeepMind, employ deep learning to forecast protein structures with impressive precision. Additional tools consist of rosetta, simulations of molecular dynamics [13]. These methods are revolutionizing bioinformatics and drug design.

Uses in biotechnology and healthcare

Drug design includes aiming at particular protein structures or fixing improperly folded proteins [14]. Synthetic biology also includes designing proteins with new capabilities. Also, the diagnostics involves recognizing biomarkers associated with folding [15].

Conclusions

Protein folding is a crucial but complex biological process that connects genetic information with functional cellular machinery. The exact folding of a protein influences its structure, which in turn affects its function highlighting the principle that structure governs activity in biological systems. Although the basic comprehension of protein folding has significantly improved due to years of biochemical and biophysical investigations, the intricacy of the process still encourages fresh scientific exploration. Even with these advancements, numerous facets of protein folding are still not completely understood, particularly the real-time folding processes in living cells and the management of folding errors during stressful conditions. Ongoing investigation into folding pathways, mechanisms of cellular quality control, and the impact of folding on disease advancement is crucial. Grasping protein folding is crucial not just to molecular biology but also essential for influencing the future of medicine, biotechnology, and synthetic biology.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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