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Exploring the Clinical Importance of Protein Structures as Vital Contributors to Cellular Function and Life Processes: Implications for Health and Disease

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ABSTRACT

Proteins are essential components of all living cells and play vital roles in numerous biological processes. These intricate molecules contribute to structural support, catalyze biochemical reactions, regulate cellular functions, and facilitate immune responses. Their varied functions arise from their unique three-dimensional structures, which are determined by sequences of amino acids encoded in genetic material. Gaining insight into the chemical structure of protein molecules is crucial for understanding their clinical significance, which is vital for advancing medical research and therapeutic development. This paper emphasizes their importance in both health and disease, examining recent advancements in protein research. Furthermore, it delves into the implications of protein folding, misfolding, and aggregation in the development of various diseases, such as Alzheimer's, Parkinson's, and cystic fibrosis. Through a thorough review of current literature, this research aims to clarify the potential of targeting proteins for diagnostic and therapeutic applications. By leveraging proteomics and bioinformatics, we can gain a deeper understanding of protein functions and interactions, paving the way for personalized medicine approaches that improve patient outcomes.

Keywords: Amino Acid; Protein, Folding; Misfolding; Aggregation

Abbreviation: C: Carbon; H: Hydrogen; O: Oxygen; N: Nitrogen; mRNA: Messenger RNA; Aβ: Amyloid-Beta Peptide; AD: Alzheimer's Disease; DMT: Develop Potential Disease-Modifying Therapies; AβO: Aβ Oligomer; NMDA: N-Methyl d-Aspartate; AChEIs: Acetylcholinesterase Inhibitors; BChE: Butyrylcholinesterase; PD: Parkinson's Disease; CF: Cystic Fibrosis

Introduction

Grasping the chemical structure of proteins is essential for understanding how they misfold. The three-dimensional shape, which dictates their function, is entirely shaped by the amino acid sequence and the physicochemical interactions among them. Protein misfolding happens when a polypeptide strays from its correct folding pathway, often revealing hydrophobic regions that are typically hidden within the core [42].

Misfolded proteins cause various diseases, called proteinopathies, such as Alzheimer's, Parkinson's, and cystic fibrosis. Ongoing research aims to understand the complexities of protein folding and misfolding.

Amino Acids

Amino acids (The Building Blocks of Proteins) serve as the fundamental components of proteins. They belong to a class of chemicals characterized by two functional groups: the amino group (NH_2) and the carboxyl group (COOH). The amino group (NH_2) is basic, while the carboxyl group (COOH) is acidic [1-7]. There are three classifications of amino acids: acidic, basic, neutral. While some amino acids can be synthesized by the body, others must be obtained from dietary sources and are known as essential amino acids. On the other hand, amino acids that the body produces independently and do not require external supplementation are termed non-essential amino acids. Additionally, there are semi-essential amino acids, which the body can produce, but not in sufficient quantities [8]. An amino acid is part of a group of organic molecules characterized by the presence of a basic

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amino group ($-NH_2$), an acidic carboxyl group (−COOH), and a unique organic R group (or side chain) (Figures 1 & 2) specific to each amino acid. The term "amino acid" is short for α-amino [alpha-amino] acid. Each amino acid molecule features a central carbon (C) atom known as the α-carbon. This α-carbon is bonded to both an amino group and a carboxyl group. The remaining two bonds of the α-carbon are typically occupied by a hydrogen (H) atom and the distinctive R group [1-6,9].

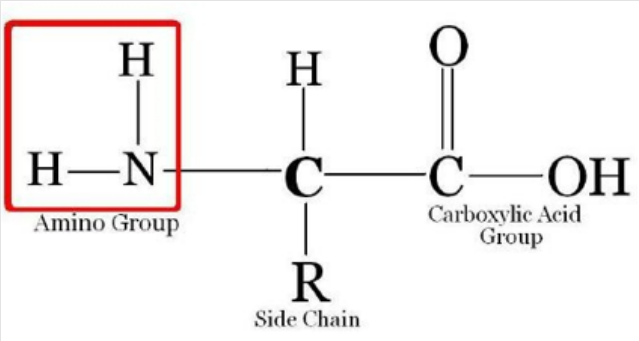

Figure 1: General structure of amino acids.

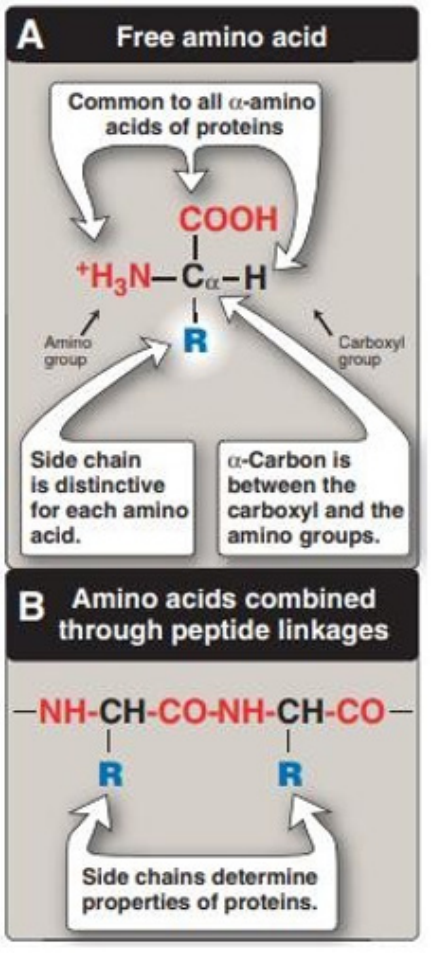

Figure 2: Structural characteristics of amino acids (Displayed in their fully protonated form) [10].

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The fundamental components of an amino acid include carbon (C), hydrogen (H), oxygen (O), and nitrogen (N). Additionally, various other elements can be found in the side chains of specific amino acids. Currently, around 500 amino acids are identified, although only 20 are represented in the genetic code. Amino acids can be classified based on the positions of their core structural-functional groups as: alpha (α-) amino acids, Beta (β-) amino acids, gamma (γ-) amino acids, and delta (δ-) amino acids [9]. At physiological pH (around pH 7.4), the carboxyl group dissociates, resulting in the formation of the negatively charged carboxylate ion (–COO–), while the amino group becomes protonated (–NH3 +) [1-6,7]. In proteins, nearly all these carboxyl and amino groups are linked via peptide bonds and are generally not reactive, except for participating in hydrogen bonding. Consequently, the characteristics of the side chains are what ultimately determine the function of an amino acid within a protein [10]. Therefore, it is beneficial to categorize amino acids based on the attributes of their side chains, distinguishing between nonpolar amino acids (with an even distribution of electrons) and polar amino acids (with an uneven distribution of electrons, such as acids and bases; (Figures 3 & 4). Conversely, amino acids that the body can produce without needing supplementation are termed non- essential amino acids [8].

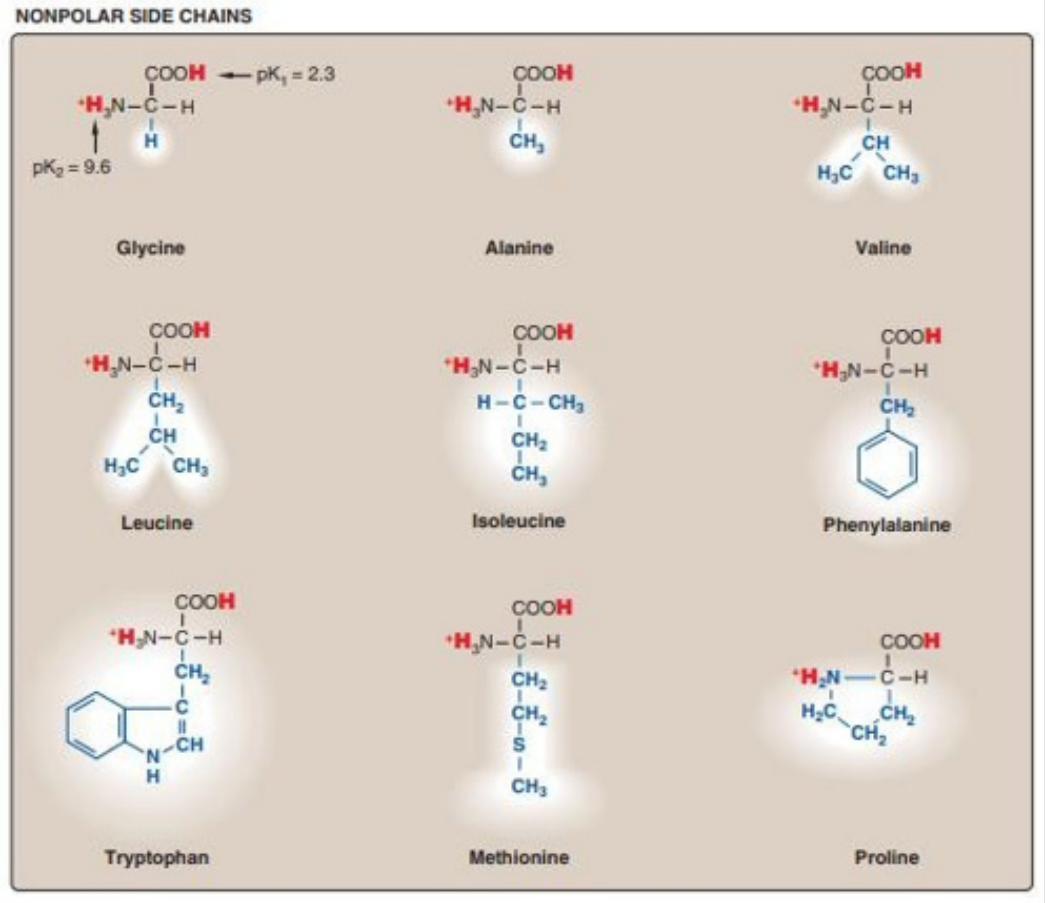

Figure 3: This illustration categorizes the 20 amino acids found in proteins according to the charge and polarity of their side chains at acidic pH. Each amino acid is depicted in its fully protonated form, with dissociable hydrogen ions highlighted in red [10].

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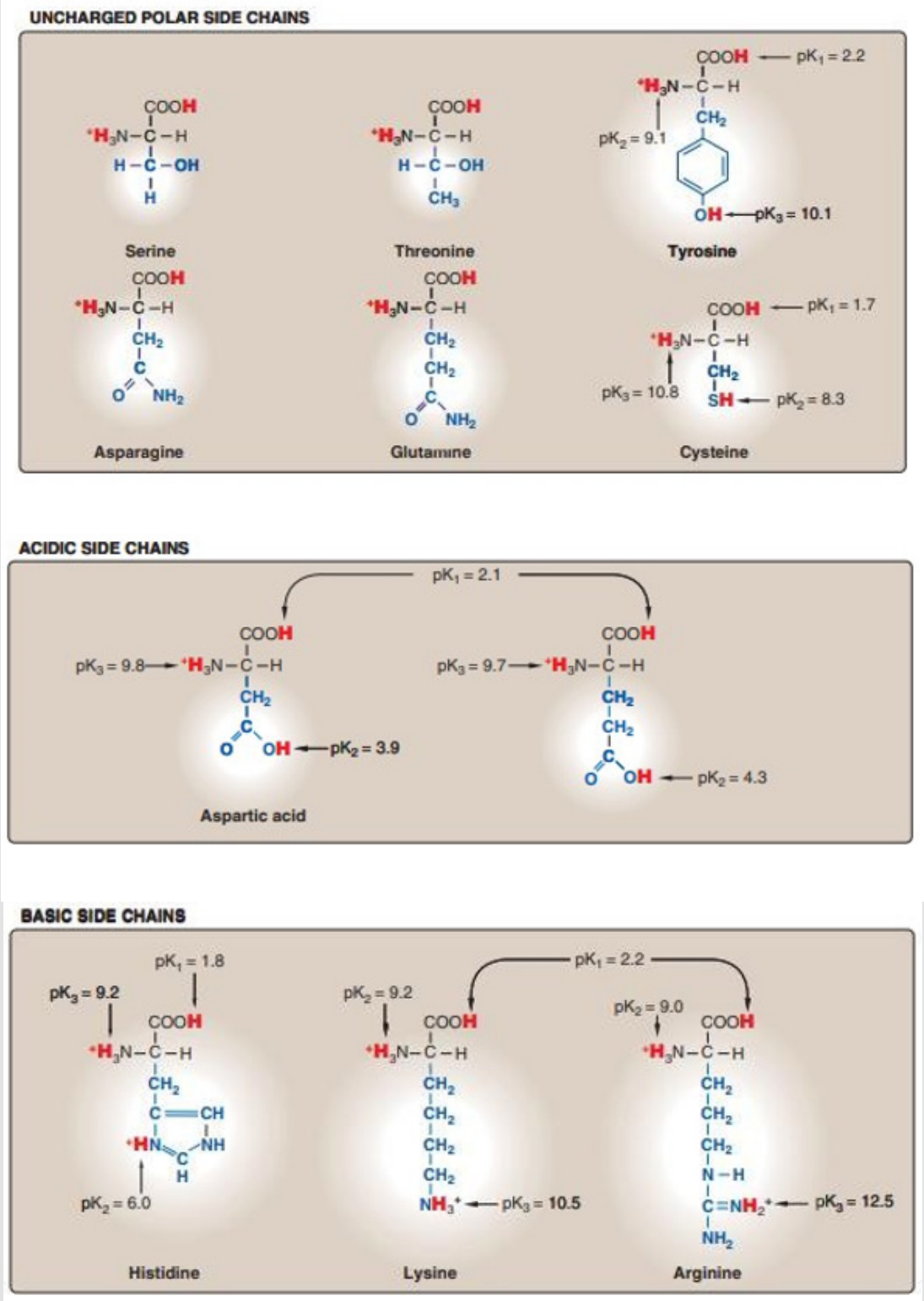

Figure 4: Classification is determined by the charge and polarity of the side chains at an acidic pH [10].

Amino acids play a crucial role in regulating various processes related to gene expression, particularly in controlling the function of proteins involved in messenger RNA (mRNA) translation [7]. Proteins evolve through natural selection, adapting to their specific functions and locations within biological systems. For processes such as DNA replication, RNA transcription, and ribosome protein translation, proteins must be water-soluble within the aqueous cytosol. Similarly, secreted proteins require aqueous environments to facilitate diffusion or circulation [11,12]. The hydrophobic and nonselective lipid bilayer, membrane proteins play crucial roles in various functions, including photosynthesis, transport, ion channels, ATP synthases, and membrane receptors. These proteins act as communication systems embedded within the lipid bilayer, effectively dividing and regulating the internal and external cellular environments [11,12].

Amino Acids with Nonpolar Side Chains

Each amino acid in this category features a nonpolar side chain that neither gains nor loses protons, nor engages in hydrogen or ionic bonds (Figure 3). These side chains can be described as "oily" or lipid-like, a characteristic that encourages hydrophobic interactions [10]. According to [10] in proteins situated in aqueous solutions polar environment the side chains of nonpolar amino acids tend to gather in the protein's interior (Figure 5). This occurrence, referred to as the hydrophobic effect, arises from the hydrophobic nature of the nonpolar R-groups, which behave similarly to droplets of oil merging in water. The nonpolar R-groups occupy the center of the folded protein, contributing to its three-dimensional structure (Figure 6). Conversely, in hydrophobic environments like membranes, the nonpolar R-groups are located on the exterior surface of the protein, interacting with the lipid surroundings [10]. Sickle cell anemia, a sickling disease of red blood cells, results from the substitution of polar glutamate by nonpolar valine at the sixth position in the β subunit of hemoglobin [11,12]. Hydrophobic interactions are crucial driving forces in nature. They play a key role in various phenomena, such as the separation of water and oil, the effectiveness of detergents, the distribution of minerals in the Earth's crust, and much more. In the field of biology, they play a crucial role in determining the structure of proteins and cells, as well as facilitating the self-assembly of membranes [11,12].

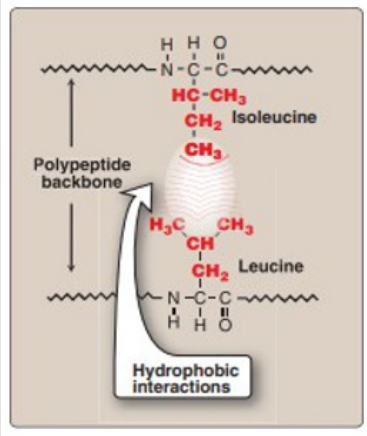

Figure 5: Hydrophobic interactions occurring among amino acids that possess nonpolar side chains [10].

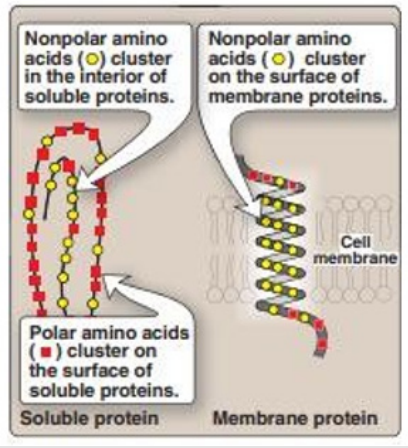

Figure 6: Distribution of nonpolar amino acids in soluble and membrane proteins [10].

Furthermore, the hydrophobic effect is crucial in ligand binding processes and must be considered in drug design [13,14]. In all these systems, apolar groups generally group together in a polar liquid, such as water, to reduce the surface area between differing polarities [15,16]. The study of hydrophobic properties in compounds is complex, requiring careful analysis of size, shape, and chemical group positioning for thorough understanding [17-19]. Proline is distinct from other amino acids due to its side chain and α-amino nitrogen forming a rigid five-membered ring structure (Figure 7). As a result, proline possesses a secondary amino group rather than a primary one, which is why it is often termed an amino acid [10]. This unique geometric configuration of proline plays a significant role in creating the fibrous structure of collagen and frequently disrupts the α- helices present in globular proteins [10].

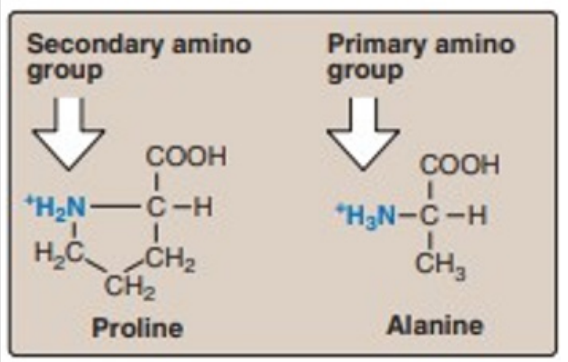

Figure 7: A comparison of the secondary amino group present in proline alongside the primary amino group found in other amino acids, like alanine [10].

Amino Acids with Uncharged Polar Side Chains

These amino acids maintain a net charge of zero at neutral pH. However, the side chains of cysteine and tyrosine can lose a proton in an alkaline environment (Figure 4) [10]. Serine, threonine, and tyrosine each feature a polar hydroxyl group that can form hydrogen bonds (Figure 8) [10]. Additionally, the side chains of asparagine and glutamine possess both a carbonyl group and an amide group, which can also engage in hydrogen bonding [10]. Disulfide bond: The side chain of cysteine features a sulfhydryl group (–SH), which plays a crucial role in the active sites of numerous enzymes. In proteins, the –SH groups of two cysteine residues can undergo oxidation, resulting in the formation of a dimer known as cystine [10]. This dimer contains a covalent cross-link referred to as a disulfide bond (–S–S–). Many extracellular proteins achieve stability through the formation of disulfide bonds. A notable example is albumin, a blood protein that functions as a transporter for a variety of molecules [10]. Side chains as attachment sites for other compounds: The polar hydroxyl groups found in serine, threonine, and occasionally tyrosine can act as attachment points for various structures, including phosphate groups. Additionally, the amide group in asparagine, along with the hydroxyl groups in serine or threonine, can function as sites for attaching oligosaccharide chains in glycoproteins [10].

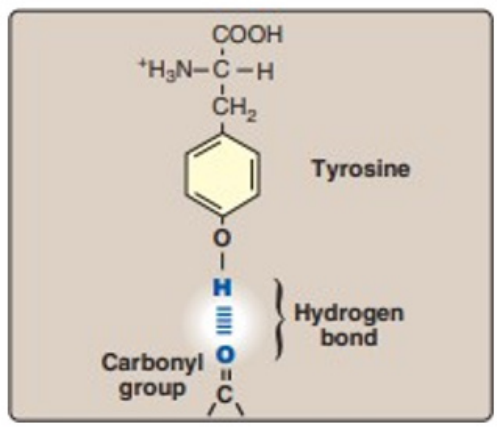

Figure 8: A hydrogen bond forms between the phenolic hydroxyl group of tyrosine and a separate molecule that contains a carbonyl group [10].

Amino Acids with Acidic Side Chains

The amino acids, aspartic acid, and glutamic acid act as proton donors. At physiological pH, the side chains of these amino acids are completely ionized, featuring a negatively charged carboxylate group (–COO–). Consequently, they are referred to as aspartate or glutamate to highlight their negative charge at physiological pH (Figure 4) [10].

Amino Acids with Basic Side Chains

The side chains of basic amino acids have the ability to accept protons (Figure 4). At physiological pH, the side chains of lysine and arginine are fully ionized and carry a positive charge [10]. [20] concluded that charged amino acids play a crucial role in numerous biological processes, as they facilitate both short-range and long-range interactions essential for: protein folding [21], helix aggregation [22], membrane protein anchoring [23], sensing membrane potentials [24,25], deforming phospholipid bilayers via cell-penetrating peptides (CPP) [26-29] and antimicrobial peptides (AMP) [30-33]. In contrast, histidine is considered weakly basic, and in its free form, it is predominantly uncharged at physiological pH. However, when histidine becomes part of a protein, its side chain can exist in either a positively charged or neutral state, depending on the ionic environment created by the protein's polypeptide chains. This characteristic of histidine is crucial, as it influences its role in the functionality of proteins like hemoglobin [10].

Optical Properties of Amino Acids

The α-carbon of an amino acid is bonded to four distinct chemical groups, making it a chiral or optically active carbon atom [10]. Glycine is the notable exception, as its α-carbon features two hydrogen substituents, rendering it optically inactive. Amino acids with an asymmetric center at the α-carbon can exist in two configurations, known as D and L, which are mirror images of one another (Figure 9) [10]. Each pair of forms is referred to as stereoisomers, optical isomers, or enantiomers. All amino acids present in proteins possess L-configuration, while D-amino acids can be found in certain antibiotics as well as in the cell walls of plants and bacteria [10].

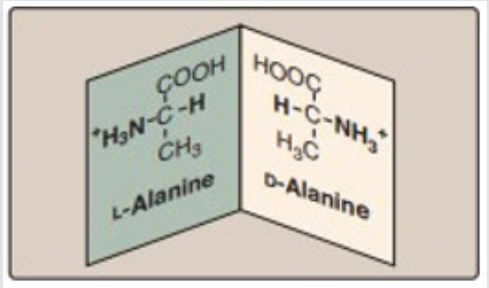

Figure 9: The D and L forms of alanine are mirror images of each other [10].

Proteins: Essential Cellular Components for Functionality

Proteins are essential cellular components for functionality. Proteins play a crucial role as cellular components, vital for the optimal functioning of cells [34]. These intricate molecules are engaged in numerous cellular processes, including maintaining cell structure, providing mechanical support, facilitating chemical reactions and regulating communication between cells [35,38]. Grasping the significance of proteins in cellular function is essential for deciphering the intricacies of cell biology and enhancing our understanding of health and disease [36]. In the complex realm of cellular biology, proteins are crucial elements that perform a wide array of essential functions [37,38]. Proteins are biopolymeric structures made up of amino acids, with 20 commonly occurring in biological chemistry [39]. They play various roles, including providing structural support, acting as biochemical catalysts, functioning as hormones and enzymes, serving as building blocks, and initiating cellular death [39]. The functions of proteins are remarkably varied. They serve as enzymes, facilitating the chemical reactions essential for metabolism and cellular activities. Enzymes boost the reaction rate by reducing the activation energy needed for the reaction to take place. Furthermore, proteins help to preserve cell shape and integrity [40].

Proteins form the cytoskeleton, which is a dynamic network of protein filaments essential for cellular movement, division, and organization. They play a crucial role in cellular signaling, enabling communication between cells and their responses to external stimuli [41].

Receptor proteins located on the cell surface identify and bind to specific molecules, triggering a series of events that transmit signals and elicit appropriate cellular reactions. Additionally, proteins are vital for the transport of molecules across cell membranes and within the cell, aiding in the movement of nutrients, ions, and signaling molecules. Moreover, proteins are key players in the immune system, contributing to immune defense mechanisms. Antibodies, which are specialized proteins, identify and neutralize pathogens, effectively preventing infections [42]. Proteins play a crucial role in regulating gene expression by determining when and how genes are transcribed into RNA and subsequently translated into proteins. This regulation

significantly impacts cellular identity and function [34]. According to [10,43] the 20 amino acids typically found in proteins are linked by peptide bonds. The linear arrangement of these connected amino acids carries the information required to create a protein molecule with a distinct three-dimensional shape. To understand the complexity of protein structure, it is useful to examine the molecule through four organizational levels: primary, secondary, tertiary, and quaternary (Figure 10). Analyzing these tiers of increasing complexity has shown that certain structural elements recur across a diverse range of proteins, indicating that there are overarching "rules" governing how proteins attain their native, functional forms.

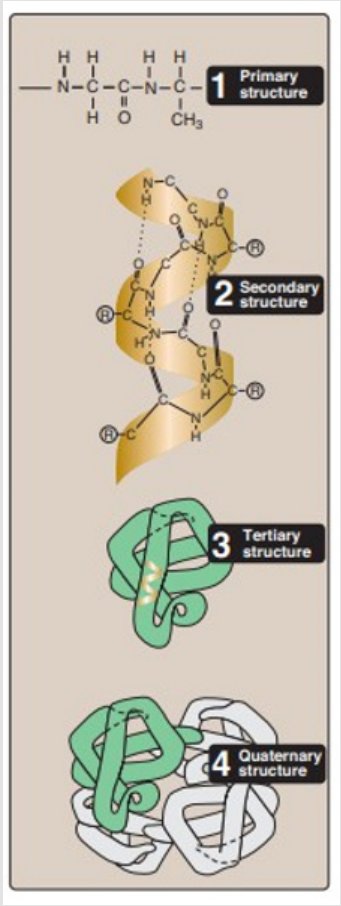

Figure 10: The four levels of protein structure [10].

These recurring structural components can range from simple combinations of α-helices and β-sheets forming small motifs to the intricate folding of polypeptide domains in multifunctional proteins [10,43]. Amino acids form polypeptide chains that fold into unique protein shapes through weak interactions, such as van der Waals forces, hydrogen bonds, and electrostatic interactions [43]. For example, lysine's non-polar hydrocarbon chain and positively charged end allow diverse interactions, while glutamic acid, though similar in size, has a negative charge and fewer interaction options [43]. Additionally, peptide bonds possess a dipole, facilitating hydrogen bonding. With 20 amino acids arranged in countless combinations, organisms create thousands of different proteins. These proteins are versatile, serving functions like enzymes, messengers, or structural scaffolds, unlike DNA, which maintains a consistent double-helix structure for genetic information storage [43]. Interactions among amino acid side chains play a crucial role in stabilizing protein structures and facilitating interactions. Here is a breakdown of the key interactions involved [43]:

- Van der Waals interactions: These create weak electrostatic attractions between uncharged, non-polar molecules, capable of
- Hydrophobic effect: Non-polar groups tend to attract one another, influencing the folding of proteins.
- Hydrogen bonding: This occurs between molecules with polar covalent bonds, where the orientation of the atoms is essential for bond strength; optimal alignment is achieved when hydrogen, nitrogen, and oxygen are positioned correctly.
- Ionic interactions (salt bridges): These are strong attractions between oppositely charged ions.
- Disulfide bonds: These are robust covalent bonds formed between cysteine residues and can be disrupted in reducing environments.

All these interactions are essential for proper protein folding and stability [43].

Primary Structure of Protein

The fundamental structure of a protein is determined by the linear arrangement of amino acids in a polypeptide chain [44]. Even when the types and quantities of amino acids are identical, varying sequences lead to the formation of different proteins. For instance, the sequence Leu-Gly-Thr-Val-Arg-Asp-His is different from Val-His-Asp-Leu-Gly-Arg-Thr [44]. This sequence serves as the initial step in defining a protein's ultimate three-dimensional shape [44]. By understanding the primary structures of both normal and mutated proteins, we can potentially diagnose or investigate related diseases [10].

Secondary Structure of Protein

Secondary structure refers to the specific folding patterns of the peptide backbone, the alpha helix and beta-pleated sheet. These structures are formed through hydrogen bonds between the amide N—H and carbonyl C=O groups [44]. It is essential to note that side chain conformations are not included in the secondary structure [44]. The polypeptide backbone does not randomly form a three-dimensional structure; instead, it typically organizes into regular configurations of amino acids that are close to one another in the linear sequence [10]. These configurations are referred to as the secondary structure of the polypeptide. Common examples of secondary structures found in proteins include the α-helix, β-sheet, and β-bend (β-turn) [10].

Tertiary Structure of Globular Protein

The tertiary structure represents the complete three-dimensional arrangement of all atoms within a single polypeptide, encompassing side chains and prosthetic groups (non-amino acid components) [44]. This structure defines the protein's overall shape and functionality [44]. When a protein consists of multiple polypeptide chains, known as subunits, their spatial arrangement leads to the formation of the quaternary structure. Interactions between subunits are stabilized by noncovalent forces, including hydrogen bonds, electrostatic attractions, and hydrophobic interactions [44]. A protein's amino acid sequence, referred to as its primary structure, ultimately determines its three-dimensional shape, which in turn influences the protein's function and characteristics [44].

Quaternary Structure of Protein

While many proteins are composed of a single polypeptide chain and are classified as monomeric proteins, others consist of two or more polypeptide chains that may be structurally identical or completely unrelated [10]. The configuration of these polypeptide subunits is referred to as the quaternary structure of the protein. These subunits are held together by noncovalent interactions, such as hydrogen bonds, ionic bonds, and hydrophobic interactions [10]. Subunits may function independently or in a cooperative manner, as seen in hemoglobin, where the binding of oxygen to one subunit of the tetramer enhances the affinity of the other subunits for oxygen [10].

Protein Folding, Misfolding and Aggregation

Interactions among the side chains of amino acids dictate how a lengthy polypeptide chain folds into the complex three-dimensional structure of a functional protein [10]. Protein folding, which takes place within the cell in a matter of seconds to minutes, utilizes a shortcut to navigate through the myriads of possible folding configurations [10]. As peptide folds, the side chains of its amino acids experience attractions and repulsions based on their chemical properties [10]. For instance, positively and negatively charged side chains draw each other in, conversely, like-charged side chains repel one another [10]. Moreover, various interactions, including hydrogen bonds, hydrophobic interactions, and disulfide bonds, all play a role in the folding process. This trial-and-error approach explores many, but not all, configurations to find a balance where attractions surpass repulsions. This leads to a correctly folded protein that achieves a low-energy state (Figure 11) [10].

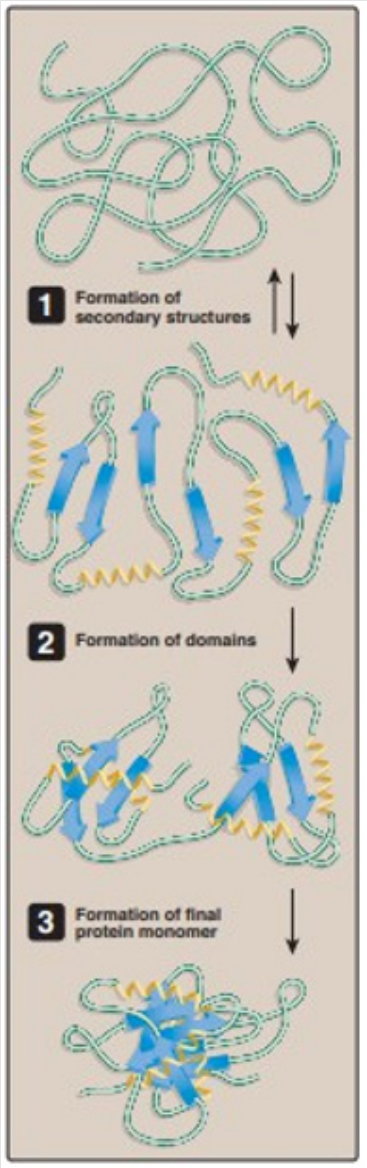

Figure 11: Steps in protein folding [10].

The Importance of Proper Protein Folding

Proper folding is essential for protein functionality; however, every protein has the potential to misfold and aggregate instead of forming its native structure [44-47]. While stably folded proteins usually exhibit only one native conformation, sometimes two in specific cases [48] the number of conformations for a polypeptide chain grows exponentially with its length [49] This increased ratio of nonnative to native conformations heightens the chances that larger proteins will exist in a misfolded state [50].

Signs of Selective Pressure

Certain markers of the selective pressure to avoid stable, misfolded states can be observed in protein sequences.

These include:

- Selection against hydrophobic residues in larger proteins [51].
- Avoidance of long stretches of hydrophobic residues [52,53].
- Low sequence conservation between consecutive domains of similar structure in multidomain proteins [54].

Folding Mechanisms of Larger Proteins

Although research has demonstrated that larger, multidomain proteins can fold translationally—simultaneously with the vectorial emergence of the nascent chain [55,56]. This includes the competing processes that decide whether a polypeptide chain will achieve its native state or result in a misfolded and/or aggregated state. This knowledge gap arises from the more complex folding mechanisms of larger proteins [57] and the technical difficulties in structurally characterizing the subtle differences between the fleeting intermediate states that lead to proper folding versus misfolding.

Insights into Protein Folding Mechanisms

While small proteins are less likely to misfold, research has revealed strategies that could be applicable to the successful folding of larger proteins with more intricate energy landscapes [45]. For instance, even the straightforward folding processes of small proteins can involve nonnative interactions. The immunity protein Im9, derived from colicin-producing bacteria, folds via a two-state mechanism, whereas its homolog Im7 utilizes a three- state mechanism that includes a nonnative, yet on-pathway, folding intermediate [58]. Remarkably, just a few differing amino acid residues between Im9 and Im7 can change the folding mechanism without compromising the thermodynamic stability of the native state by stabilizing an intermediate conformation with nonnative, long-range contacts [59]. Similarly, a recent investigation into influenza nucleoprotein revealed that a single point mutation can modify the folding pathway, resulting in the formation of an aggregation-prone intermediate [60]. The energy landscapes of small proteins may also present unusually large energy barriers, which can lead to kinetic traps [45]. A notable example of kinetic trapping is kinetic stability, where a protein's folded state is less stable than its unfolded structure but remains in a folded form due to being obstructed by a high energy barrier, unfolding at an extremely slow rate [45]. A classic case of kinetic stability is α-lytic protease, which maintains a native state lifetime of over one year, despite its native structure being less stable than its unfolded state due to a sufficiently high energy barrier for unfolding [61,62].

The Role of "Bridge" Interactions in α-Lytic Protease Stability

The "bridge" interaction created between the N- and C-terminal regions of α-lytic protease plays a significant role in the remarkably high energy of its transition state [63]. Interestingly, another kinetically stable protease, SbtE, has a homolog known as ISP1, which is thermodynamically stable instead. This highlights two unique strategies that Nature employs to preserve the native, functional structure of proteases [64]. At present, it remains uncertain how nonnative interactions and/or kinetically trapped states influence the folding of large proteins, promoting the formation of productive (on-pathway) intermediates while preventing unproductive misfolded (off-pathway) conformations [45]. Furthermore, the specific mechanisms by which large proteins evade kinetic traps that lead to misfolding are still not fully understood.

Protein Kinases

Cellular signaling depends on precise molecular interactions, with protein kinases serving as key switches for transmitting information [65]. They phosphorylate substrates to regulate cellular activities and respond to cues. Dysregulated kinase signaling can lead to diseases such as cancer, characterized by uncontrolled cell growth [65]. Kinase inhibitors have revolutionized cancer therapy and are also used for autoimmune and neurodegenerative disorders. Moreover, insights into kinases aid personalized medicine for tailored treatments [65].

Cellular Signaling: The Language of Life

Cellular signaling represents the intricate and meticulously coordinated communication system of life, allowing cells to interact, respond to their surroundings, and synchronize essential biological functions [66]. At the core of this complex network of intercellular dialogue are protein kinases, the molecular architects responsible for transmitting critical information within cells [66]. Cellular signaling serves as the bedrock for coordinating various biological processes [67]. It enables cells to exchange information, respond to external stimuli, adapt to changing environments, and perform vital functions. This intricate web of signaling pathways is fundamental to everything from cell growth and differentiation to immune responses and tissue repair [67]. At its essence, cellular signaling entails the transfer of molecular signals, typically in the form of chemical messengers, which communicate information from the cell's exterior to its interior [68]. These signals activate a series of events within the cell, culminating in specific responses. For instance, a signaling pathway may direct a cell to divide, specialize into a particular cell type, or even trigger programmed cell death (apoptosis) [68].

The Role of Protein Kinases

Protein kinases are pivotal players in cellular signaling. They comprise a large family of enzymes dedicated to a vital function: the phosphorylation of proteins [69]. Phosphorylation, the addition of a phosphate group to a protein, acts as a molecular switch that can turn proteins on or off. Protein kinases facilitate this process by transferring phosphate groups from adenosine triphosphate (ATP) to specific amino acids on target proteins [69]. The phosphorylation events driven by protein kinases set off a series of intracellular reactions that lead to the activation or inhibition of various cellular processes [70]. These reactions are notably specific and finely tuned, enabling cells to respond selectively to diverse signals. This specificity is crucial, as it ensures that the correct message reaches the appropriate destination within the cell [70].

Implications for Health and Disease

Understanding the role of protein kinases in cellular signaling transcends mere academic interest; it carries significant implications for human health and disease [71]. Dysregulation of kinase-driven signaling pathways is a hallmark of various diseases, including cancer, autoimmune disorders, and neurodegenerative conditions [71]. For instance, cancer, mutations, or overactivity of protein kinases can result in uncontrolled cell growth and tumor formation. On the other hand, leveraging the power of kinase inhibitors—drugs that selectively block specific kinases—has transformed cancer treatment, providing targeted therapeutic options [71].

The Significance of Proteins in Biological Processes and Disease Management

According to [72] many proteins are associated with infectious diseases, including bacterial proteins that facilitate adhesion to host epithelium, bacterial toxins, and viral membrane glycoproteins. Additionally, components of the host's innate immune system, such as Toll-like receptors and Nod-like receptors, along with adaptive immune elements like immunoglobulins, are essential proteins that help defend against pathogens [72]. Acid and heat shock proteins, protect cells from elevated temperatures, metabolic toxins, and various stressful conditions. Furthermore, numerous natural and synthetic proteins serve as components of vaccines, which are a vital strategy for controlling deadly diseases that lack effective treatments [72]. Investigating these proteins is essential for developing new biomedical tools and technologies aimed at eradicating various diseases. Infectious diseases are caused by agents that invade a host, harm tissues, and can be transmitted to others [72]. These diseases result from the infection and growth of pathogens like viruses and bacteria. Proteins play critical roles in both causing and protecting against infections, including membrane proteins and heat shock proteins. Various antimicrobial peptides and antibiotics help treat these diseases by targeting microorganisms [72]. Understanding these mechanisms is vital for developing biomedical tools to combat diseases and improve human quality of life.

Antibodies are naturally generated by plasma cells in the human body to facilitate an adaptive immune response against invading pathogens [73]. There are five main types of antibodies, each tailored to perform specific functions, through genetic recombination of various structural elements, antibodies develop the capability to recognize a wide array of antigens, while their affinity for antigens stems from affinity maturation and somatic recombination processes [73]. Antibodies have numerous clinical applications, the most significant of which include fighting autoimmune disorders and cancer, providing passive immunity, and serving diagnostic purposes. [74] concluded that enzymes are specialized proteins made up of amino acids arranged in one or more polypeptide chains. The sequence of these amino acids in a polypeptide chain is referred to as the primary structure, which influences the enzyme's three-dimensional shape, including the configuration of its active site [74]. The complete three-dimensional folding of a polypeptide chain into a protein subunit is referred to as its tertiary structure [10]. The overall three-dimensional arrangement of these subunits is termed as its quaternary structure. The structure of the subunits is determined by the sequence and properties of the amino acids within the polypeptide chain [10,75,76]. The active site is a specific groove or crevice on an enzyme where a substrate binds to promote the catalyzed chemical reaction. Enzymes are typically specific because the arrangement of amino acids in the active site stabilizes the precise binding of the substrate. This active site usually occupies a relatively small portion of the entire enzyme and is filled with free water when not engaged with a substrate [10,75,76].

Protein Clinically Significant

In their review [100] included that proper protein folding and the elimination of misfolded proteins are crucial for maintaining cellular functions [101]. Despite the presence of sophisticated cellular monitoring systems, around 30% of newly synthesized proteins are susceptible to misfolding [102,103]. Misfolded proteins can lead to various cellular issues, such as mitochondrial dysfunction, calcium dysregulation, and inflammation [104].

Alzheimer's

The amyloid cascade hypothesis has long been central to understanding Alzheimer's disease (AD) but has evolved over time. Initially, it focused on large Aβ fibrils as the main cause of neuronal damage. Recent evidence suggests that soluble Aβ oligomers can also induce neurotoxicity independently, leading to the Aβ oligomer (AβO) hypothesis, which posits that these oligomers trigger AD pathogenesis [77]. Alzheimer's disease (AD) leads to brain cell degeneration, causing dementia and a decline in cognitive abilities [77]. It is multifactorial, with the cholinergic and amyloid hypotheses proposed as causes, and risk factors including age, genetics, and environmental influences [77]. Currently, approved treatments only manage symptoms, with two drug classes: cholinesterase inhibitors and NMDA antagonists. Research focuses on understanding AD pathology by targeting mechanisms like tau protein metabolism and β-amyloid to develop potential disease-modifying therapies (DMT), chaperones, and natural compounds for more effective treatments [77]. Alzheimer's disease (AD), named after the German psychiatrist Alois Alzheimer, is the most prevalent form of dementia [78]. It is characterized as a gradually progressive neurodegenerative condition marked by the presence of neuritic plaques and neurofibrillary tangles (Figure 12), resulting from the accumulation of amyloid-beta peptide (Aβ) in the brain, particularly affecting the medial temporal lobe and neocortical structures [78].

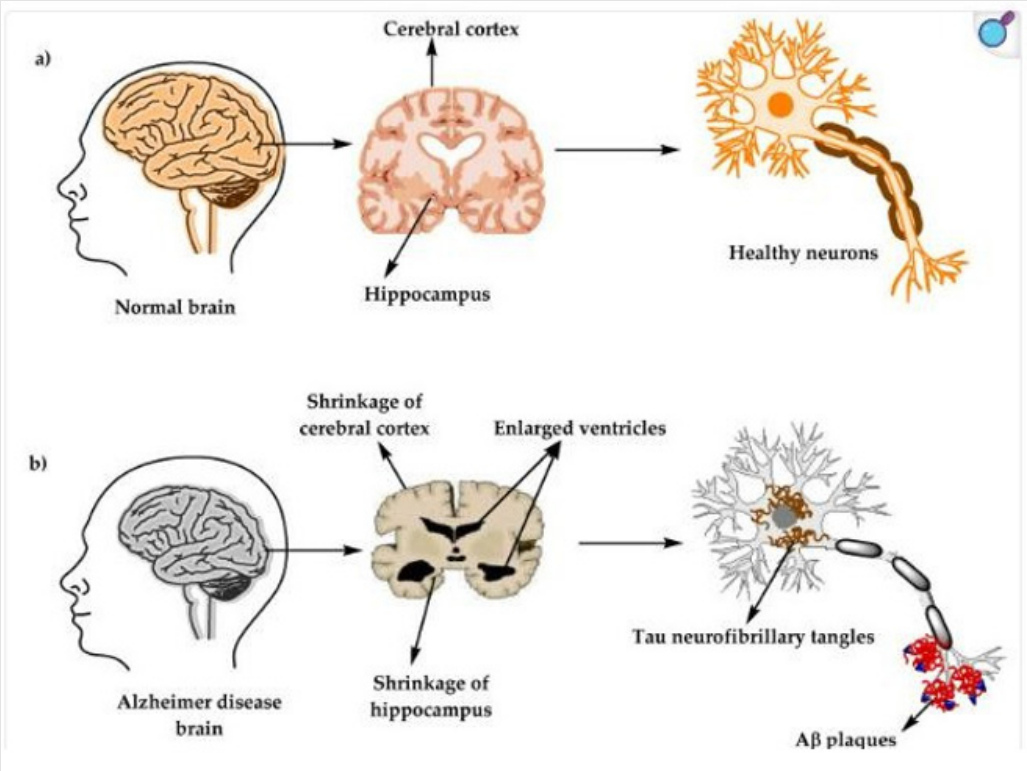

Figure 12: The physiological composition of the brain and neurons in:
(a) A healthy brain
(b) A brain affected by Alzheimer's disease (AD) [77].

Alois Alzheimer identified amyloid plaques and neuronal loss in his first patient with memory loss and personality changes. He characterized the condition as a serious disease of the cerebral cortex. The term "Alzheimer's disease" was introduced by Emil Kraepelin in his psychiatry handbook's eighth edition [79,80]. The decline in cognitive functions can result from cerebral disorders like Alzheimer's, as well as factors such as intoxications, infections, pulmonary and circulatory issues reducing brain oxygen supply, nutritional deficiencies, vitamin B12 deficiency, and tumors [81,82]. A patient suspected of having Alzheimer's Disease (AD) should undergo a series of evaluations, which include:

- A neurological examination.
- Magnetic resonance imaging (MRI) to assess neurons.
- Laboratory tests, such as vitamin B12 levels
- Additional assessments, alongside a review of the patient's medical and family history [83].

Vitamin B12 deficiency is associated with neurological issues and a higher risk of Alzheimer's disease. Elevated homocysteine levels, a marker of this deficiency, can cause brain damage via oxidative stress and apoptosis. Diagnosis includes measuring serum vitamin B12, complete blood count, and serum homocysteine levels [84,85].

Neuropathological Changes in Alzheimer's Disease: According to [86-88] Alzheimer's Disease (AD) is associated with two primary types of neuropathological changes that indicate disease progression and symptoms:

- Positive Lesions (resulting from accumulation):
- These lesions are marked by the buildup.
- of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads, and various other deposits found in the brains of AD patients.
- Negative Lesions (resulting from losses):
- These lesions are characterized by significant atrophies linked to the loss of neural connections, neuropil, and synaptic structures.

Additionally, other factors contributing to neurodegeneration include neuroinflammation, oxidative stress, and damage to cholinergic neurons [86-88].

Clinical Phases of Alzheimer's Disease: The clinical progression of Alzheimer's disease can be categorized into four distinct phases:

- Pre-clinical or Pre-symptomatic Stage

It is characterized by mild memory loss and early pathological changes in the cortex and hippocampus, yet there is no functional impairment in daily activities, and clinical signs and symptoms of Alzheimer's disease are absent [78,89,90].

- Mild or Early Stage of Alzheimer's Disease

During this phase, various symptoms begin to manifest in patients. These may include difficulties in daily life, such as loss of concentration and memory, disorientation in time and place, mood changes, and the onset of depression [90,91].

- Moderate Stage of Alzheimer's Disease

In this stage, the disease extends to areas of the cerebral cortex, leading to increased memory loss. Patients may struggle to recognize family and friends, experience a loss of impulse control, and face challenges with reading, writing, and speaking [90].

- Severe or Late-stage Alzheimer's Disease

This final phase involves the spread of the disease throughout the entire cortex, resulting in a significant accumulation of neuritic plaques and neurofibrillary tangles. Patients experience profound functional and cognitive decline, often failing to recognize family members, becoming bedridden, and facing difficulties with swallowing and urination, leading to death due to these complications [78,92].

Causes and Risk Factors of Alzheimer's Disease: Alzheimer's Disease (AD) is recognized as a multifactorial condition influenced by various risk factors (Figure 13) [77], including advancing age, genetic predispositions, head trauma, vascular disorders, infections, and environmental elements such as heavy and trace metals. The precise cause behind the pathological changes associated with Alzheimer's Disease, including amyloid beta (Aβ), neurofibrillary tangles (NFTs), and synaptic loss, remains elusive [151,152]. While several hypotheses have been proposed regarding the origins of AD, two are considered predominant: one posits that a dysfunction in cholinergic activity is a significant risk factor, while the other suggests that changes in the production and processing of amyloid β-protein trigger the disease. Nonetheless, as of now, no universally accepted theory exists to explain the pathogenesis of AD.

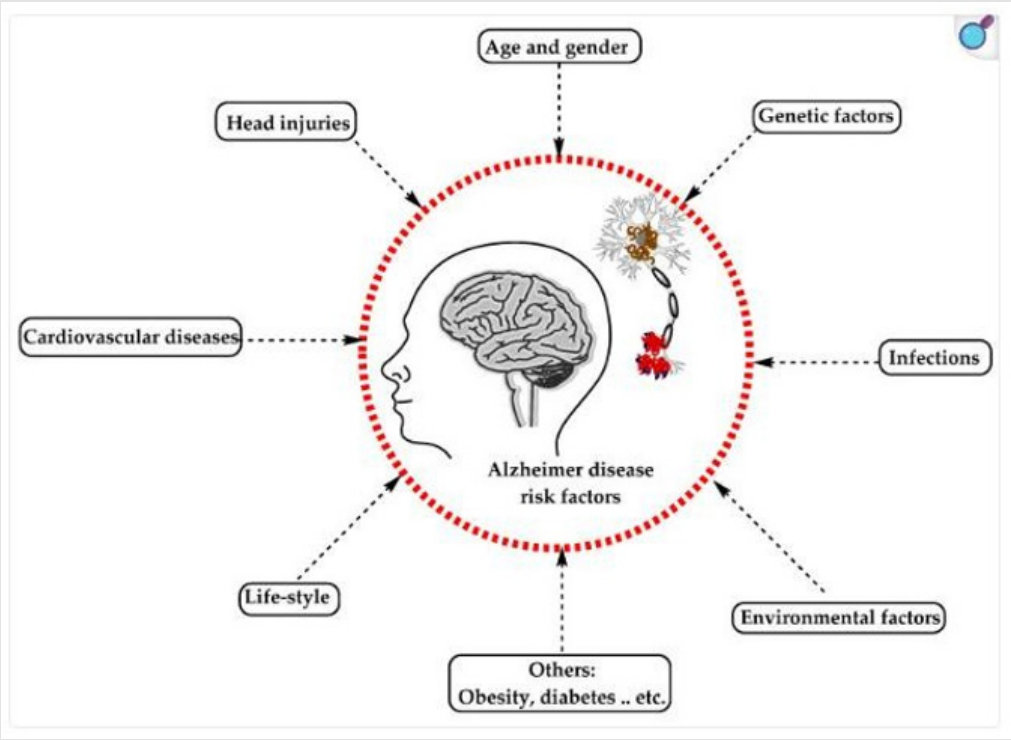

Figure 13: The risk factors for Alzheimer's disease [77].

Treatment: As it stands, there are only two classes of drugs approved for the treatment of Alzheimer's Disease (AD): cholinesterase enzyme inhibitors (which include naturally derived, synthetic, and hybrid analogues) and N-methyl d-aspartate (NMDA) antagonists [93-95]. Various physiological processes in AD lead to the destruction of acetylcholine (ACh)-producing cells, which ultimately decreases cholinergic transmission throughout the brain [93-95]. Acetylcholinesterase inhibitors (AChEIs) are categorized as reversible, irreversible, and pseudo-reversible and work by inhibiting cholinesterase enzymes (both AChE and butyrylcholinesterase (BChE)) from degrading ACh. This action results in elevated ACh levels in the synaptic cleft [93-95]. On the flip side, excessive activation of NMDAR results in heightened levels of Ca2+ influx, which can lead to cell death and synaptic dysfunction. An NMDAR antagonist helps to prevent this overactivation of the glutamate receptor, thereby reducing Ca2+ influx and restoring normal receptor activity. While both classes have therapeutic effects, they are only effective in alleviating the symptoms of Alzheimer's disease and do not offer a cure or prevent the progression of the condition [96,97]. Unfortunately, only a limited number of clinical trials focused on Alzheimer's Disease (AD) have been initiated in the past decade, and their results have largely been disappointing [98].

Various mechanisms have been suggested to help clarify AD pathology, aiming to alter its progression and create effective treatments. These mechanisms include [98]:

- Abnormal tau protein metabolism
- β-amyloid accumulation
- Inflammatory responses
- Cholinergic dysfunction
- Free radical damage

On the other side, many modifiable risk factors for Alzheimer's Disease (AD), such as cardiovascular issues and lifestyle choices, can be prevented without medical intervention [99]. Research indicates that engaging in physical activity enhances brain health and may lower the risk of AD by promoting brain vascularization, plasticity, neurogenesis, and reducing inflammation through decreased Aβ production—all of which contribute to improved cognitive function in older adults [99]. Additionally, following the Mediterranean diet, participating in intellectual activities, and attaining higher education levels may help slow the progression of AD and memory decline while boosting brain capacity and cognitive abilities [99]. Numerous studies have shown that a multi- domain approach, which encompasses lifestyle changes (including diet, exercise, and cognitive training), addressing AD symptoms, and managing cardiovascular risk factors, can enhance or sustain cognitive function and prevent new cases of AD in older individuals [99].

Parkinson's

According to [105] the occurrence and frequency of Parkinson's Disease (PD) rise with age, affecting approximately 1% of individuals over 65 years old [106]. Early-onset Parkinson's Disease (EOPD) is characterized by the emergence of parkinsonian symptoms before the age of 40, representing 3-5% of all PD cases. EOPD is further categorized into two groups: 'juvenile' PD, which occurs before 21 years of age, and 'young-onset' PD (YOPD), which occurs between 21 and 40 years of age [107]. In most populations, PD is twice as prevalent in men compared to women. This disparity may be attributed to the protective effects of female sex hormones [108,109]. Additionally, the presence of gender-associated genetic factors and/or gender-specific differences in exposure to environmental risk factors may help explain this male predominance [108-110]. The pathophysiology of Parkinson's Disease (PD) is characterized by the loss or degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the accumulation of Lewy bodies, which are abnormal intracellular aggregates that contain proteins such as alpha-synuclein (aSyn) and ubiquitin [111,112]. Research indicates that approximately 60-70% of the neurons in the SNpc are lost before any symptom's manifest [113]. Studies have shown that the pathogenic process in PD involves not only the dopaminergic neurons of the SNpc but also regions of both the peripheral and central nervous systems. Lewy body pathology begins in cholinergic and monoaminergic neurons in the brainstem as well as in neurons associated with the olfactory system. As the disease progresses, it extends to limbic and neocortical brain regions [114,115]. Ultimately, the loss of dopaminergic neurons, which initially occurred in the SNpc, became more widespread by the time end-stage disease is reached [116].

Parkinson's Disease: A Growing Concern

In their research [117] included that Parkinson's disease (PD) ranks as the second most prevalent neurodegenerative disorder globally [118]. Between 1990 and 2015, the number of diagnosed individuals surged by 118%, leading to a worldwide prevalence of 6.2 million cases [119]. Remarkably, by 2019, this number climbed again, reaching approximately 8.5 million confirmed cases, which signifies a 37% increase in just four years [120]. Alarmingly, projections indicate that the prevalence of PD could surpass twelve million cases by 2040 [121], positioning it as the fastest-growing neurological disorder globally [119]. It is important to note that these increases might not solely indicate a true rise in incidence but could also stem from factors such as heightened awareness of PD and adjustments in diagnostic criteria. Nonetheless, Bloem and colleagues pointed out that while enhanced diagnostic accuracy by experienced clinicians contributes to the rise in incidence, it does not fully explain why the age-adjusted prevalence of PD is increasing at a rate faster than that of other neurological disorders [122]. The increasing prevalence of Parkinson's disease (PD) is a significant concern, as it presents a substantial economic burden projected to exceed $79 billion in the United States by 2037 [123].

Consequently, there is an urgent need for earlier and more accurate diagnosis to enable effective therapeutic management. Recently, an international dialogue has emerged regarding the classification of PD and other alpha-synuclein (α-syn) diseases based on their biological characteristics [124-126]. Parkinson's disease (PD) ranks among the most common chronic progressive neurological disorders and is the second most prevalent neurodegenerative condition, impacting over 1.5% of individuals worldwide aged sixty-five [127] and older. This disorder typically arises from reduced dopamine production due to the death of dopaminergic neurons in the midbrain's substantia nigra, resulting in a deficiency of striatal dopamine, which is responsible for the motor symptoms associated with PD [128].

Contributing Factors, several suggested mechanisms include:

- Exogenous toxins
- Inflammation
- Genetic alterations
- A combination of these factors

It is widely accepted that PD stems from the interplay between genetic and environmental influences. This theory posits that cell death in the nigral neurons occurs due to the interaction of environmental conditions and genetic susceptibility, leading to mitochondrial respiratory failure and oxidative stress [129].

Affected Neurons and Symptoms

The primary targets of PD are the median spiny neurons of the midbrain. However, the additional loss of dopaminergic neurons and the accumulation of Lewy bodies in the substantia nigra pars compacta (SNpc) disrupt normal neuronal functioning [126]. Furthermore, excitability of GABAergic neurons in PD is heightened at the dopaminergic D2 receptor while diminished at the D1 receptor, resulting in an imbalance between the direct and indirect pathways. During this period, symptoms such as stiffness and bradykinesia re-emerge [130]. The upregulation of the alpha-synuclein gene leads to the production of abnormal mutant alpha-synuclein protein, which aggregates to form Lewy bodies and neuritis, contributing to neurodegeneration and manifesting symptoms akin to those of PD. Nevertheless, oxidative stress and mitochondrial dysfunction are the underlying causes of cellular malfunction and mortality [130]. PD can be diagnosed based on the patient's clinical features and exclusion of other possible causes of PD since there are no practical laboratory tests to diagnose PD (Figure 14) [126]. Despite significant efforts to uncover the cause of Parkinson's Disease (PD), its etiology and precise origins remain unclear, which restricts treatment options [131]. Managing PD necessitates a personalized treatment approach at every stage of the disease's progression [132].

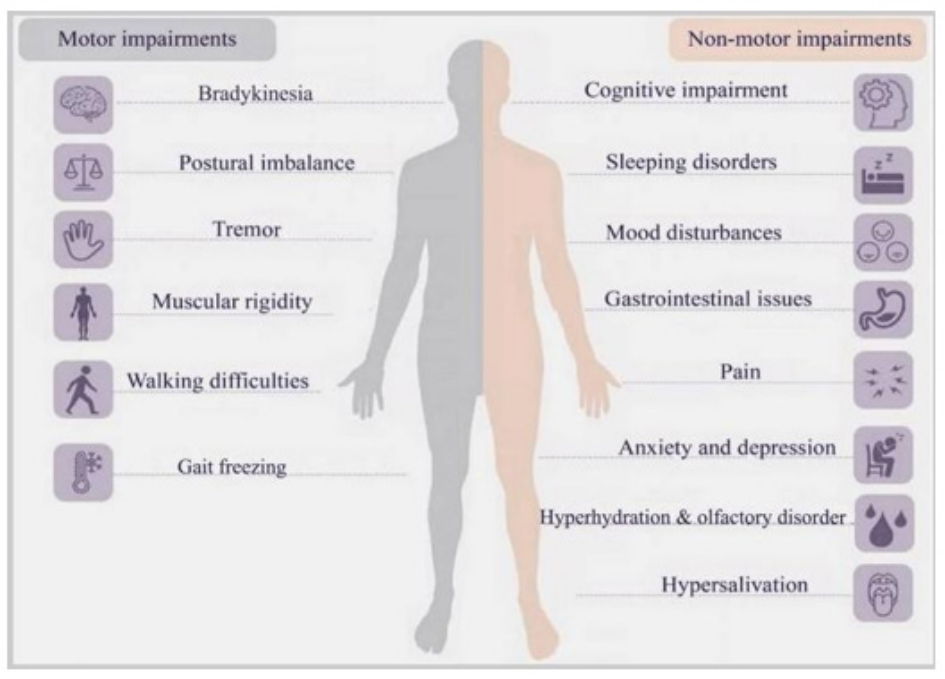

Figure 14: Clinical manifestations of Parkinson's Disease [126].

Management strategies and supportive methods for PD are advancing, with new therapeutic options being developed each year. While medical therapy is the most prevalent approach, addressing dopamine deficiency—the primary factor associated with PD—other surgical interventions may be considered for patients experiencing a chronic progressive course of the disease [133].

Commonly prescribed medications include:

- Levodopa/carbidopa
- Carbidopa/levodopa/entacapone (Stalevo)
- Dopamine receptor agonists (bromocriptine, ropinirole, pramipexole, apomorphine)
- Selective monoamine oxidase-B inhibitors (selegiline and rasagiline)
- Anticholinergic agents (muscarinic receptor antagonists: Artane, Cogentin, Benadryl)
- Amantadine (Symmetrel) [133].

Current surgical options consist of ablative procedures (lesional therapy), dopaminergic medication infusion devices, and deep brain stimulation (DBS) [134]. Dopaminergic neuron loss in the substantia nigra is a defining feature of Parkinson's Disease (PD). Another key characteristic of PD is the presence of Lewy bodies, which are neuronal inclusions primarily composed of aggregated α-synuclein protein. The Braak hypothesis serves as the most referenced theory to elucidate the neuropathological progression of PD (Figure 15) [133]. According to [126] Parkinson's Disease (PD) initially presents itself in the medulla and olfactory bulb during stages 1 and 2. Symptoms linked to this early phase include rapid eye movement sleep behavior disorder—where individuals lose the usual paralysis associated with REM sleep and exhibit physical actions while sleeping—and a diminished sense of smell [126]. As the disease progresses to stages 3 and 4, it impacts the substantia nigra pars compacta and other regions of the midbrain and basal forebrain. Motor symptoms of PD are connected to pathology in these areas, and it is typically at this stage that the disease is diagnosed. As PD advances further, it spreads to the cerebral cortex, leading to cognitive decline and the onset of hallucinations. The aggregation of proteins in Parkinson's is associated with the degeneration of dopamine-producing cells. Consequently, dopamine supplementation remains the cornerstone of treatment for PD [126].

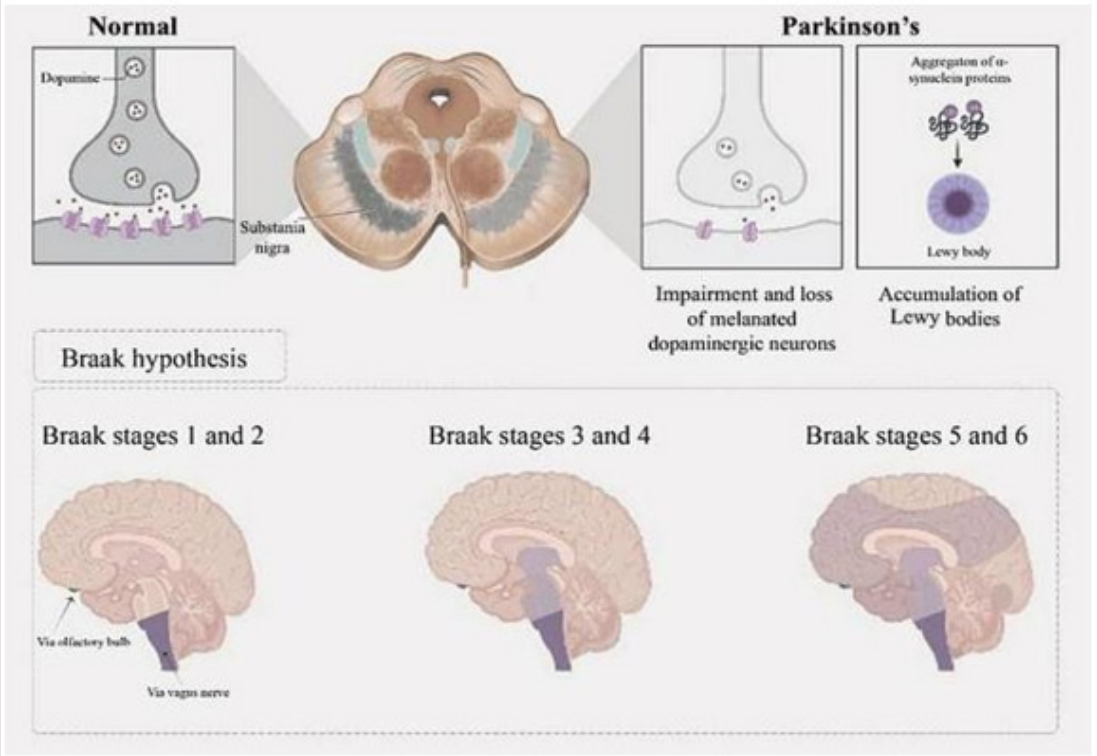

Figure 15: Pathophysiology of Parkinson's disease and break staging [126].

Pharmacological Treatment of Parkinson's Disease

Present evidence-based treatment for PD focuses on symptomatic relief, primarily through dopaminergic

replacement or modulation. This evidence is summarized in the latest guidelines from the National Institute for Health and Care Excellence (NICE) and the International Parkinson and Movement Disorder Society [135-137].

- Medications licensed for initial therapy in PD include:
- Levodopa
- Dopamine agonists
- Monoamine oxidase B inhibitors (MAOB-I)

Anticholinergics are no longer commonly prescribed due to the potential risk of cognitive decline [137].

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder that affects multiple systems and is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [138]. The majority of morbidity and mortality associated with this condition is related to lung disease [139,140]. In the lungs, the defective or insufficient CFTR protein in the airway epithelium results in a detrimental cycle characterized by mucus accumulation and airway obstruction. This leads to:

- Impaired pathogen clearance
- Development of airway inflammation
- Progression to irreversible structural lung disease, including bronchiectasis [139,140].

It was reported that most infants with cystic fibrosis, as young as 0 to 4 months, displayed mucopurulent airway blockage and bronchial wall inflammation. Furthermore, all children diagnosed with cystic fibrosis showed detectable bronchiectasis by the age of two [139,140]. Subsequent clinical studies have revealed various evidence in infants with cystic fibrosis (CF) within their first year of life, including:

- Bacterial infections.
- Neutrophilic airway inflammation.
- Structural lung disease, characterized by bronchial dilation, thickening of bronchial walls, and air trapping [141-144].
- Decreased lung function [142-148].

The early introduction of CFTR modulator therapy small molecules aimed at correcting the underlying defects in the CFTR protein—combined with newborn screening, is anticipated to alter the progression of CF lung disease by restoring CFTR protein functionality early on [138]. Furthermore, a deeper understanding of the initial pathophysiology of CF lung disease may uncover additional therapeutic targets. If these are addressed early in life, they could significantly enhance clinical outcomes, especially for individuals with CF (pwCF) who are not currently eligible for or benefiting from CFTR modulator therapies [138].

Treatment

The main goal of cystic fibrosis (CF) treatment is to alleviate symptoms, slow disease progression, and enhance patients' quality of life and longevity. This can be accomplished through the following measures:

- Proper airway clearance.
- Control of respiratory infections.
- Reduction in inflammation.
- Optimization of nutritional status.
- Annual vaccinations for Influenza A and B [149].

In addition, emerging therapies focus on correcting the underlying dysfunction of the CFTR protein, tackling the root cause of the disease, and potentially altering its natural trajectory. Regular monitoring and personalized treatment adjustments are crucial for effectively managing the various complications associated with CF [150-152].

Summary

In our ongoing research, we delve into the essential role of proteins as crucial components of cells, emphasizing their significant functions in preserving cellular integrity and enabling a wide range of biological processes. Proteins, made up of chains of amino acids, serve multiple purposes, including providing structural support, catalyzing biochemical reactions, and regulating cellular activities. Their distinctive three-dimensional structures, shaped by genetic coding, are fundamental to their varied functions. Also this study underscores the significance of proper protein folding and the detrimental effects of misfolding, which can lead to severe diseases such as Alzheimer's, Parkinson's, and cystic fibrosis. By examining the molecular intricacies of protein kinases and their regulatory roles, we can better understand the pathways involved in disease progression and identify potential therapeutic targets. Advancements in proteomics and bioinformatics are pivotal in unraveling the complex interactions and functions of proteins, offering insights into personalized medicine approaches. These technologies enable a more precise understanding of protein behavior, ultimately leading to improved diagnostic methods and innovative treatments that enhance patient outcomes. Through this comprehensive review, we aim to illuminate the profound impact of proteins on health and disease, emphasizing their potential in disease management and therapeutic development.

Conclusion

In conclusion, our research highlights the indispensable role of proteins in maintaining cellular function and integrity, emphasizing their multifaceted contributions to health and disease. By elucidating the molecular dynamics of proteins, particularly through the study of protein kinases and their regulatory mechanisms, we have gained valuable insight into the pathways that underpin disease progression. Our findings stress the importance of proper protein folding and the consequences of its disruption, linking it to various severe health conditions. The integration of proteomics and bioinformatics has proven crucial in deciphering the complex protein interactions that hold promise for advancing personalized medicine. These technologies are paving the way for more precise diagnostic tools and innovative therapeutic strategies, ultimately aiming to improve patient outcomes. As we continue to explore the vast potential of proteins, our research underscores their critical impact on both understanding and managing diseases, heralding a new era of targeted and effective treatments.

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