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Short-Review Article

Misfolded Structures | A Brief Insight into Protein Aggregation Criteria, which May Lead to Proteopathy Diseases

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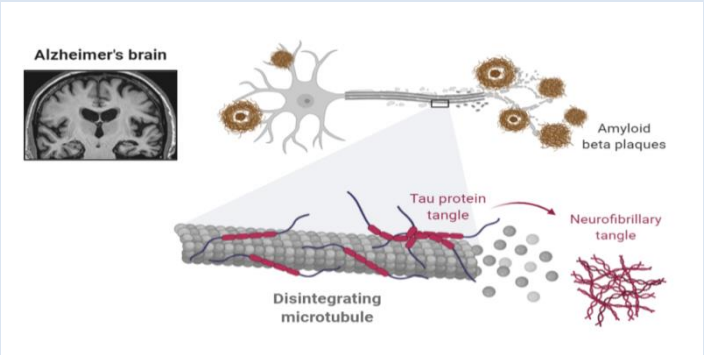
Abstract: Diseases resulting from protein accumulations can be described mainly by improper folding and aggregation of endogenous proteins in affected tissues such as the brain or the heart. During misfolding and aggregation, the affected protein often loses its normal function, becomes more resistant to degradation, and often acquires toxic functions that can cause organ damage. Proteins generally require specific three-dimensional conformations to be soluble and function correctly in the body. Under the stress conditions, normally soluble proteins can undergo structural changes and self-assembly, leading to their aggregation into insoluble deposits, referred to as amyloids. Amyloids from different proteins share several structural properties: they all have a fibrillar morphology and cross-β structure, whereby intermolecular main-chain hydrogen bonding acts as one primary stabilizing interaction. So, protein aggregation is the process by which misfolded proteins adopt a conformation that causes its polymerization into aggregates and organized fibrils. Many neurodegenerative diseases (amyloidoses) are associated with protein aggregation, though smaller oligomeric forms of the misfolded (amyloid genic) proteins have been implicated as the causative agent. This study investigated the factors involved in disease and abnormalities arising from protein aggregation one by one. Also, it can be reviewed as a comprehensive glance for the process of protein aggregation whether from a structural or clinical point of view.

Keywords: Protein Misfolding; Protein Aggregation; Amyloid; Proteopathy and Toxicity

Graphical Abstract:



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Introduction

The last decade has seen a vast increase in the development of biomolecules as therapeutic agents to treat a wide array of diseases. Almost all that have reached the market, are protein-based drugs [1]. There is stated that protein aggregations have been displaying the most common patterns of protein instability. This phenomenon can be considered a potential challenge in generating protein products as a way of treatment [2]. Furthermore, one of the most significant challenges in the pharmaceutical industry concerning protein products is the chemical and physical stability of the products [3], as well as delaying in their expiration dates, which means the processes that limit the storage and shelf life of these products is the process of protein accumulation severely [4]. From an *In vivo* point of view, the manifestation of protein accumulation and its related disease/disorders have been the significant mind challenging questions over the years. It is now known that protein accumulation is engaged with many diseases' pathogenesis. For instance, in a large group of diseases known as Amyloidosis; one or more proteins inside or outside the cell convert to amyloid aggregate structures [5]. Amyloid diseases linked to neurodegenerative diseases [6], including Alzheimer's [7], Parkinson's [8], Huntington's [9], and prion diseases [10], along with diseases such as type II diabetes [11]. A better understanding of protein aggregation can demonstrate the necessity of increasing industrial development in production [12], sterilization [13], storage [13], and distribution for the protein products [14]. This study provides both structural and clinical approaches to the various factors associated with protein aggregation and the subsequent incidence of Proteopathy (Proteinopathy) diseases [15]. Accordingly, the most important research studies about this subject have been collected, categorized, and discussed based on the quality and level of pieces of evidence.

Discussion

1. Mis folded Proteins

Under the physiological conditions inside the cell, the correct folding process is not conducive to many proteins, especially those with multiple subunit structures, and conditions are provided to produce a variety of incorrectly folded forms, and biologically inactive aggregates [16]. In a cell, the folding process takes place in a crowded environment with the help of a wide range of auxiliary proteins [17]. Recent studies demonstrated that the cumulative process that results in the formation of amyloid filaments; has similar behavior to the folding process [18], except that the residues connected to the amyloid structure may be located in different regions of the amino acid sequence. However, the folding process residues are mostly located in the inner regions of a protein structure [19]. Inside the cell, controlling the folding of proteins in the

right direction is most often done by molecular chaperones. Therefore, any dysfunction of chaperones, and other polypeptide spatial regulators, can lead to incorrect folding of the protein and diseases associated with protein accumulation [20]. The improper folding of proteins, protein aggregations, and the production of fibrillar structures are correlated with a series of diseases [21], including Alzheimer's, Parkinson's, Huntington's, prion diseases, and many other disorders that are now classified as protein conformational disorders (PCDs) [22]. Although each of the PCDs shows different symptoms, there are many similarities at the molecular level [23]. The conformational disease title was first suggested by Carrel and Lomas; they displayed that improper folding of proteins causes spontaneous accumulation (self-association) of the polypeptides and subsequently leads to deposition of accumulated proteins in the relevant tissues [24]. Depending on the type of tissue, both characteristic of tissue and its location, whether intracellular or extracellular; the disease manifestations considering the biological effects of these protein deposits will be seen differently [24, 25]. While in terms of histology, they are usually in the form of strings and have similar structural and morphological features. The protein involved in these diseases is rich in beta plates. The stability of protein against oligomerization or accumulation is determined by the rate of intermolecular reactions in the beta sheets [23].

2. Protein Aggregations

Protein aggregation is the process by which protein molecules that are naturally present in monomers or small oligomers in solution gradually bind to each other to form larger particles [26]. These particles either remain dispersed in the solution or are precipitated and separated from the solution step by step [27]. An essential feature of protein aggregates is that the spatial protein structure in the resulting aggregates is abnormal. Thus, it is assumed that the natural form of the protein does not tend to accumulate [28]. For such a process to begin, it is necessary first to change the conformational structure of the protein and find the abnormal form with the potential for accumulation. It is then necessary that the abnormal protein molecules bind to each other and form large protein particles [29]. With this explanation, the accumulation of protein is distinguished from its crystallization under particular conditions or the deposition of protein due to the addition of salts such as ammonium sulfate [30].

2.1. Effective Conditions in Protein Accumulation

Protein accumulation can occur either in an irregular structure or in a wide variety of conditions. For example, acidic [31, 32] or alkaline [32], chemicals such as guanidine hydrochloride [33], pH [34], and various factors such as high pressure [35] or temperature [36], alcohols such as trifluoroethanol [37], as well as the presence of high concentrations of protein [38] can be considered among these situations and may not arise in the body. However, the presence of substances like glycosaminoglycans [39] as well as heparin [40], is of utmost importance in the formation of amyloid sheets [41].

2.1.1. Temperature Effects

Although heat denaturation is reversible in some cases, high temperatures usually lead to permanent opening of the structure, which in most cases, it is produced irreversible protein accumulation [42]. In most

samples, high temperatures can change the protein structures to such an extent that the process of protein accumulation begins [43]. Usually, due to the thermal accumulation of protein at a temperature lower than the melting temperature (T_m), the process of protein unfolding can take place [44], and this is interpreted as meaning that protein accumulations do not start from a fully open protein form, but rather relatively unfold forms of protein move towards aggregation [45].

2.1.2. PH Effects

Soluble pH can affect the spatial structure of the protein [46]. As we move away from the pI of the protein, the net charge of the protein increases, and because the protein molecule is not normally open, it is smaller in size and has a higher charge density. As a result, the native form of the protein becomes somewhat unstable compared to its open conformation, and the stability of the protein spatial protein structure decreases [47]. In such a way that if the pH change is sufficient, the opening of the protein conformation may happen [34, 47]. Also, changing the pH with a specific effect on the charged groups involved in the salt bridges of protein structure can affect the stability in the spatial protein design [48]. Moreover, it may even lead to the opening (unfolding) of the protein formation [49]. Eventually, the open form of the protein structure resulting from pH changes may modify toward aggregation [50].

2.1.3. Salt Effects

The effect of salts on protein stability has been studied in detail for many years [51]. Regardless of the type of salts, the ionic strength has a stabilizing or destabilizing effect on the spatial structure of the protein by attenuating the electrostatic interaction [47, 52, 53]. Salts may also have specific interactions with specific sites in some proteins, thereby affecting the stability of their spatial structure [54].

2.1.4. Alcohol Effects

The influence of alcohol on proteins and peptides has also been extensively studied in recent decades [55]. Most non-aqueous solvents, such as alcohols, in specific concentrations, abnormalize the natural structure of the protein by solubilizing the internal non-polar residues of the protein [56]. This process leads to complex formation with high alpha-helix content [57]. Various alcohols, especially those substituted with fluorine such as 2, 2, 2, trifluoroethanol (TFE), and 3, 3, 3, 3´, 3´, 3´ hexafluoro-2-propanol (HFIP), abnormalize the protein and induce an effective alpha-helix structure in peptides [58]. This condition is probably due to the low dielectric constant of alcohols; decreased solvent polarity attenuates hydrophobic interactions that lead to stabilizing compact natural protein structures while enhancing electrostatic interactions such as hydrogen bonds by stabilizing the local secondary structures, especially the alpha-helix [59]. The main driving force of the accumulation process is hydrophobic forces. The similarity of the type of dependence of hydrophobic forces and the introduced process on ambient temperature changes confirms the mentioned claim. Since hydrophobic forces are endothermic, the strength and intensity of hydrophobic forces arise with increasing temperature [60]. However, the role of other factors, such as electrostatic forces in the formation of inactive protein masses during the phenomenon of protein corrosion, should not be neglected [61].

2.2. Mechanism of Protein Accumulation

Protein aggregations generally take place in three stages, as will be described in the following.

2.2.1. Partially Folded Intermediate Phase

Soluble native proteins are converted into primary molecules prone to aggregation. Therefore, the ease of creating the folded/unfolded state is considered as an essential parameter in gaining the tendency of a protein to accumulate [62]. Proteins that are not naturally folded have faced with a lack of tertiary structure, making them more subjected to aggregation than compact proteins. As expected, most known amyloid-producing proteins (Amyloidogenic) are typically uncompressed and unstructured [63, 64]. In the protein folding process, folding protein mediators are more potential to aggregate than folded protein [65, 66]. Comparative folding can lead to relatively distant hydrophobic residues, resulting in a disposed of the continuous hydrophobic surface accumulation [67]. In addition to spatial conformation, protein mediators' longevity is also a determining factor for the protein accumulation process [68].

2.2.2. Nucleation phase

The intermediates accumulate with a specific pattern; they can form oligomers with a separate structure (Nucleus) [69]. Core formation is kinetically undesirable and does not determine the rate or delay phase (Lag phase) of the protein accumulation process [70]. It is believed that the structure of oligomers depends on the type of protein and environmental conditions both together [71].

2.2.3. Polymerization phase

At this stage, the oligomers form amyloid fibrils or dense protein masses [72]. This phase is kinetically desirable and, therefore, much faster than the nucleation phase [73]. The addition of pre-formed nuclei boosts the acceleration of the previous two phases by reducing the Lag phase [74].

3. Proteopathy terminology

From a medical point of view, the term Proteopathy refers to a group of diseases in which specific proteins become structurally abnormal and further impair the function of cells, tissues, and organs [75]. Proteins can no longer achieve the correct folding in terms of spatial conformation and become toxic (in other words, they acquire a toxicity property) or lose the normal function of a protein [76]. Proteopathy, also known as Proteinopathy, is a group of diseases that refer to protein conformational disorders, or protein misfolding diseases, including Creutzfeldt–Jakob disease [77], prion diseases [10, 78], Alzheimer's disease [76, 79], Parkinson's disease [76, 80], amyloidosis [81, 82], multiple system atrophy [77, 83], and a wide range of other problems. The term Proteopathy was first mentioned by Lary Walker and Harry Levine in 2000 [15, 84]. Naming this word dates back to the early nineteenth century when Rudolf Virchow (in 1854) expressed the term Amyloid; to describe a series of substances in the body that exhibits a similar chemical reaction associated with cellulose [85]. In 1859, it was shown by two people named Friedreich and Kekulé that the ingredients of amyloid compounds are full of protein instead of cellulose [86]. Subsequent studies demonstrated that many other proteins also can form amyloid, and all of them are able to deflect cross-polarized light such as fibrillar ultrastructures when studied under an electron microscope after treated with Congo red dye [87, 88]. However, some proteinaceous lesions lack birefringence and contain few or no classical amyloid fibrils, such as the diffuse deposits of amyloid-beta (Aβ) protein in the brains of people with Alzheimer's disease [89]. In addition, evidence

revealed that non-protein and fibrillar aggregates identified as oligomers are considered toxic to damaged tissue cells [90]. In contrast, Amyloidogenic proteins in their fibrillar structure may be relatively less harmful [91]. The development and production of effective therapies is a severe challenge for many Proteopathies because they often involve different proteins from different sources [92, 93]. Treatment strategies should be tailored to the type of abnormality; however, general treatment strategies include maintaining the function of damaged organs, reducing the formation of pathogenic proteins, preventing malnutrition and/or protein accumulation, or promoting their elimination [94].

Conclusion

In all, protein aggregation is a biological phenomenon in which intrinsically disordered proteins or misfolded proteins aggregates (i.e., accumulate and clump together) either intra- or extra-cellular. Misfolded protein aggregates are often correlated with a disease. Protein aggregates have been implicated in a wide variety of diseases known as amyloidosis, including ALS, Alzheimer's, and Parkinson's, and prion disease. Recent studies have shown that in addition to known amyloidosis issues, several other degenerative diseases that molecular basis is currently unknown may be diagnosed as a problem by sediments and intracellular or extracellular, accumulations that are not currently disease-causing. According to the studied considerations, it can also be understood that protein accumulations take place in a biological environment to perform a specific and physiological function. This article briefly tried to investigate the factors involved in changing the spatial/conformational structure of a polypeptide and finally presents the consequences of these unprincipled changes in the form of academic classification.

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