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The Impact of Post-Translational Modifications on Protein Aggregation in Genetic Disorders

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ABSTRACT

Protein aggregation is a hallmark of various genetic disorders, often resulting from abnormal protein folding that leads to the accumulation of insoluble fibrils within cells. Post-translational modifications (PTMs), which occur after protein synthesis, play a crucial role in regulating protein structure, function, and aggregation propensity. This paper explores the intricate relationship between PTMs and protein aggregation in genetic disorders, focusing on how specific modifications contribute to or prevent the formation of protein aggregates. By examining the molecular mechanisms underlying PTM-induced protein aggregation, this review provides insights into potential therapeutic strategies targeting PTMs to mitigate the effects of protein aggregation in diseases such as Alzheimer's, Parkinson's, Huntington's, and other proteinopathies.

Keywords: Protein Aggregation, Genetic Disorders, Post-Translational Modifications (PTMs), Neurodegeneration, Protein Misfolding.

INTRODUCTION

Genetic disorders arise from abnormalities in genes, leading to the production of dysfunctional proteins. In some cases, this dysregulation contributes to the accumulation and aggregation of proteins, disrupting normal cellular activities and leading to pathology [1]. Typically, proteins aggregate due to aberrant folding resulting in soluble oligomeric structures, which can build up and form deposits of insoluble fibrils [2]. Characterizing and understanding these aggregation phenomena is relevant to elucidate the function of proteins and to decipher the mechanism by which aberrant aggregation leads to diseases [3, 4]. Diverse genetic disorders concerning protein aggregation involve pathogenic mutations related to chartered misfolding states. Most of these misfolding events derive from the intrinsic tendency of polypeptide chains to aggregate (in particular, crystalline and fibrilation of beta structures) coupled with an altered equilibrium between oligomers and aggregates [5]. This latter stands for a more general phenomenon involving a large range of proteins linked to different diseases unrelated to fibril formation (such as cystic fibrosis, a1-antitrypsin, a-2-macroglobulin disorders or galactosemia). In these cases, aggregation occurs because folding processes take place in an unfavorable environment (e.g., mutations affecting solubility or design defects) precluding protein maturation and leading to either soluble oligomers or insoluble aggregates. From the genetic standpoint, diseases concerning protein aggregation fall into two classes: (i) those with dominant mutations that promote aggregation (e.g., sickle cell anemia) and (ii) codominant cases with histo-compatibility mutant genes that inhibit aggregation but do not prevent disease (e.g., estrogen-related breast cancer) [6, 7].

OVERVIEW OF POST-TRANSLATIONAL MODIFICATIONS (PTMS)

PTMs refer to modifications occurring shortly after translation or after folding and localization. Generally, PTMs are catalyzed by specific enzymes modifying a substrate. The modification of a substrate involves the addition of a chemical group that have both steric effect and changes in the electronic density. Sugars or proteins can also be added to specific residues [8]. PTMs account for a large part of the proteomic diversity, complementing the genome and the transcriptome. To date, nearly all cellular processes can be regulated via such chemical modifications. PTMs are usually stable and,

consequently, they can be propagated and sustain functional changes that are impacted by time. The implementation of these changes can involve signal amplification/modulation, phospho-dependent downstream events, and cell memory [9]. Regarding proteins, PTMs may alter the charge and/or the hydrophobicity of a protein, both of which are sterically important, directly influencing protein interactions with their environment. They can also induce structural changes potentially affecting protein structure at the local and global levels, or affecting protein stability and degradation rates [10, 11]. PTMs also target the aggregation propensity of proteins, leading to structural remodeling potentially promoting aggregation. Recently, new classes of PTMs competing for the same target residue were discovered, leading to toggle switches between different structural and functional states of proteins (crucial for signaling in a changing environment) [12]. The specificity of PTM responses often relies on the existence of cross-talk between different types of PTMs. Finally, PTMs can also regulate the clearance of proteins by acting on the functionality of degrons. Degrons are peptide sequences that target a protein for degradation. PTMs on a degron can block or activate degradation pathways controlling protein levels in cells; modifications at residue positions close to, but not part of the degron can also affect the distance between the degradation signal and the potential interaction with the ubiquitin ligase [12, 13,14].

ROLE OF PTMS IN PROTEIN AGGREGATION

Understanding the role of post-translational modifications (PTMs) in protein aggregation is crucial for elucidating the molecular origin of aggregation in genetic disorders. Tau proteins are inherently aggregating and natively unfolded proteins that are the main constituents of paired helical filaments (PHFs) and neurofibrillary tangles (NFTs) in Alzheimer's disease (AD) brains. In this review, the structures and variabilities of tau PTMs are summarized, and a plausible scenario of how these modifications affect tau aggregation is discussed. This PTM-dependent hypo-hyper-enrichment mechanism can be generalized to other aggregation-prone natively unfolded proteins, such as Aβ, α-synuclein, and huntingtin. In the context of aggregation pathologies, aberrant states of PTMs are of great interest as molecular chaperones in AD, fronto-temporal dementia, Down syndrome, and tauopathies and as genetic modifiers in Huntington's disease [15, 16, 17]. PTMs (post-translational modifications) are regarded as a major factor influencing the propensity of proteins to aggregate in many genetic disorders. The aberrant states of PTMs of proteins have been investigated for decades, focusing on understanding how these modifications alter the molecular mechanism of aggregation. Yet, protein aggregation in human genetics is an intricate and complex mechanism that remains elusive. In this article, the efforts made to understand the details of how PTMs influence aggregation are summarized, and the structures and variabilities of tau PTMs, as a model of aggregation-prone natively unfolded proteins, are introduced, which might give an insight for better understanding the role of PTMs in aggregation [18, 19, 20].

EXPERIMENTAL TECHNIQUES FOR STUDYING PTMS AND PROTEIN AGGREGATION

This section is dedicated to discussing the various experimental techniques utilized for studying post-translational modifications (PTMs) and protein aggregation. A range of experimental approaches are covered, including mass spectrometry, chromatography, and other biochemical assays. Readers can learn how these techniques have advanced our understanding of PTMs and protein aggregation, particularly in the context of genetic disorders. The relevance of these experimental methods in identifying potential therapeutic targets is also highlighted [21, 22, 23]. Proteomics of protein post-translational modifications implicated in neurodegeneration have been explored. Neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, Huntington's disease, and prion disorders have been linked to the non-physiological aggregation of proteins. An important mechanism associated with protein aggregation is covalent chemical PTMs. These covalent modifications can occur co-translationally or post-translationally and play vital roles in modulating the activity of proteins, protein-protein interactions, and cellular localization, among others [19, 24, 25]. Significant progress has been made in PTM-specific enrichment methods and MS-based proteomics technologies. PTMs form complex regulatory networks involved in controlling biological functions. Detecting and understanding PTM crosstalk is crucial for developing new therapies. Current methods using antibodies or chemical biology provide qualitative and semi-quantitative characterization. However, challenges in PTM proteomics exist, including sensitivity and accuracy issues. Developing chemoselective pan-specific chemical probes can address these challenges by forming strong covalent bonds with PTMs. These probes allow for the identification of full-spectrum PTMs and cooperative events in proteins [26].

THERAPEUTIC STRATEGIES TARGETING PTMS IN GENETIC DISORDERS

Understanding protein post-translational modifications (PTMs) during aggregation offers promising avenues for therapeutic development, particularly in the context of neurodegenerative diseases [20]. Although research on PTMs in neurodegenerative diseases is still in its early stages, progress is being made in elucidating how these modifications contribute to disease pathology. A prominent area of study is the phosphorylation of tau protein, which plays a crucial role in neurodegenerative diseases such as Alzheimer's Disease (AD) [21]. Tau phosphorylation is commonly observed and is known to lead to tau aggregation, which in turn contributes to neurotoxicity and the progression of AD pathology. The aggregation process can vary depending on whether tau is in its monomeric form or modified by other proteins such as synucleins [22]. Research has shown that synucleins can accelerate tau aggregation. This acceleration is associated with increased construction of PTMs and heightened hydrophobicity of tau, disrupting the protein's normal balance and promoting the formation of neurotoxic aggregates. This interplay between tau and synucleins highlights the complexity of tau aggregation and the role that PTMs play in this process. In Alzheimer's Disease, the cascade of tau PTMs, including phosphorylation and acetylation, is a subject of ongoing research and debate [24]. Phospho-tau, which accumulates in AD cases, often exhibits concurrent threonine phosphorylation, a modification that is linked with downstream pathological lesions. Furthermore, acetylation of tau, in conjunction with phosphorylation, has been associated with severe neurodegeneration, emphasizing the importance of these modifications in disease progression. To better understand how tau PTMs influence aggregation and spreading, further research is needed [25]. This includes studying how different PTMs interact with one another and how they affect tau's aggregation propensity. Current therapeutic strategies are exploring the inhibition of tau kinases, which are responsible for adding phosphate groups, or the activation of phosphatases, which remove these groups, as potential treatments to mitigate tau-related pathology. Overall, while significant strides have been made in understanding the role of tau PTMs in neurodegenerative diseases, much remains to be learned. Continued research into these modifications could provide critical insights into disease mechanisms and lead to novel therapeutic approaches for conditions such as Alzheimer's Disease.

CONCLUSION

Post-translational modifications significantly influence protein aggregation, a process implicated in numerous genetic disorders. Understanding the role of PTMs in this context is essential for elucidating the mechanisms of disease pathogenesis and for developing targeted therapies. The complex interplay between PTMs and protein aggregation offers both challenges and opportunities for therapeutic intervention. Advances in experimental techniques, such as mass spectrometry and proteomics, have enhanced our ability to study these modifications in detail, opening new avenues for therapeutic strategies aimed at modulating PTMs to prevent or reverse protein aggregation. Future research should focus on uncovering the specific PTM pathways involved in various proteinopathies and on designing drugs that can precisely target these pathways to alleviate the burden of genetic disorders associated with protein aggregation.

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