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Prion Protein Structure and Human Disease

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Prions, mis-folded proteins that act as pathogenic and infectious agents, are a topic of great biochemical and medical importance. They are the underlying cause of several neurodegenerative diseases including Creutzfeldt-Jakob disease (CJD), Gerstmann-Staussler-Scheinker syndrome (GSS), and fatal familial insomnia, which although rare, are rapid in their progression and unquestionably fatal. The misbehavior of the culprit protein, relates to one of the most essential concepts in the study of biomolecules; mainly, that the sequence of a protein determines its shape which in turn dictates its function. A key area of research for studying the effects and causes of familial prion disease includes in depth examination of the protein structure in both the normal and diseased states. Recent investigations in this area have made use of a wide range of technological methods including molecular dynamic simulations and nuclear magnetic resonance imaging. These articles have contributed to a deeper understanding of prions and will hopefully lend to further investigations that may determine methods of treating these deadly diseases.

Introduction

Upon assembly, proteins spontaneously arrange themselves into a specific 3-dimensional conformation. This process is dictated by the amino acid sequence and due to specific properties of the various amino acid side chains' chemical properties as well as fundamental principles of thermodynamics. Interactions between neighboring amino acids and the cytoplasmic environment contribute to a protein structure that exists in a minimal free energy state. The specificity of protein shapes makes the amino acid sequence essential for proper function. The majority of prion related diseases can be attributed to single amino acid mutations, a difference that may sound small, but has a profound impact on the function of these proteins. Thus, the altered sequence causes the protein to mis-fold, or take on an abnormal conformation. Such conformations are considered toxic and often aggregate in fibrillar masses that result in amyloid deposits.[i]

Prions are considered "infectious" proteins because of the mutant prion protein's (PrP) ability to induce abnormal folding in other regularly folded PrP proteins in the brain.[ii] The disease states that are the consequence of this are known as transmissible spongiform encephalopathies. These diseases include Creutzfeldt-Jakob disease, Gerstmann-Staussler-Scheinker syndrome, Kuru, and fatal familial insomnia and are neurodegenerative, meaning they contribute to deterioration of the nervous system.[iii] Some may be inherited genetically, like classic CJD, while others are caused by importing prion proteins into the body through food, as is the case in mad-cow disease. [iv] Familial, or genetic, prion diseases (e.g.- CJD, GSS, and fatal familial insomnia) are caused by mutations in the PRNP gene.[v] Studying the sequence and structure that these various mutations produce is a critical step unfolding the mystery of how to cure these seemingly untreatable diseases.

An important development in the field of biochemical and molecular sciences in recent years has been the development of technologies that allow the visualization of protein structure. Nuclear magnetic imaging (NMR) is one such critical technology in the study of proteins because it allows their 3D structure to be determined while the protein is in solution, eliminating the difficulty of trying to crystallize a sample.[vi] Another useful technique in studying protein structure and especially their folding patterns in different environments is molecular dynamics (MD) simulations. Such simulations may be used to detect changes in protein shape based on calculations of specific coordinates' variations in trajectory.[vii] Recent studies have made use of technologies such as, nuclear magnetic resonance imaging and molecular dynamics simulations to study the structure of prion proteins. Three of these original research articles

contributions to the field are examined in the following section.

Recent Progress

In a recent study by Biljan, et al, NMR structural determination was used to investigate the differences in cellular architecture between normal human Prp and that with the mutation associated with CJD (the V210I mutation). While the overall structure of the two proteins was quite similar, the mutant strain showed localized divergence in specific regions. The valine residue that is altered to leucine in this mutation and results in altered structure localized in the hydrophobic region that includes several inter-helices and loops. This mutation interrupts one of these α-helices as well as changes in the orientation of two of the α-helices and exposes the α-β loop region to the solvent. [viii]

A previous study by Van der Kamp and Daggett examined the effects of similar mutations in this region by using molecular dynamic simulation, and focusing more specifically on the structure of the hydrophobic core region. The results of this study showed how specific point mutations in this region affect the mis-folding of PrP proteins and contribute to structural instability in the overall protein structure. Wild type PrP proteins were compared with five variations of this mutation including V180I, T183A, F198S, V203I, and V201I. Structure as the result of spontaneous folding was examined in these proteins using molecular simulations that identified coordinate variation and changes in flexibility. Each of the mutants studied produced to some degree an essential change in the hydrophobic region. Some specifically induced mis-folding (i.e.- V180I and F198S), others increased the protein's flexibility (i.e.- T183A and F198S), while others produced various and more subtle changes. Overall, it was deduced that these conformational alterations contributed to instability and mis-folding in PrP proteins, lending to the pathogenic nature of these prions. [ix]

Another structural examination of prion proteins was conducted by Rossetti, et al. A major finding of this research which was conducted using MD simulations was that disease-linked mutations in human PrP often disrupt the salt bridge network that normally connects the α2 and α3 helices with α1 and each other. These disease-linked mutants also notably showed specific weaker interactions in the β2-α2 loop portion of the protein's hydrophobic region resulting in diminished π-stacking. Their results also displayed localized exposure of the hydrophobic region to solvent. These structural variations that were found throughout pathogenic PrP mutants potentially play a critical role in the etiology of prion related diseases.[x]

Discussion

Overall, these three studies display results that are consistent with one another regarding the influence of point mutations in the hydrophobic region of PrP proteins. These results underscore the importance of protein sequence not only in folding but also in potentially initiating a diseased state in organisms. The use of MD simulations and NMR to view, in detail, the conformation and differences between wild type and pathogenic mutant proteins, provides opportunity for further pharmacological and medical research that could potentially produce a cure for these deadly neurodegenerative diseases caused by prions. Insight into the structure of specific proteins is an excellent starting point in discovering the greater detail and mechanisms involved in their function, and how mutations may impede on it since protein structure is inextricably linked with the specificity of its function. Thus, the detailed examination of conformational changes as a result of alterations of α-helices and β-α loops caused by point mutations could lead to the discovery of specific drugs that either inhibit the action or aggregation of prion proteins or may as Biljan, et al, suggest help stabilize the folding of the PrP protein, limiting its pathogenic effects. Medical discoveries and solutions linked to the study of prion protein structure may even present insight for solutions for other diseases linked to neurological amyloid deposits, such as Alzheimer's.

References

[i] Reynaud, Enrique, Ph.D. "Protein Misfolding and Degenerative Disease." *Nature.com*. Nature Publishing Group, 2010. Web. 04 Oct. 2012. <http://www.nature.com/scitable/topicpage/protein-misfolding-and-degenerative-diseases-14434929>.

[ii] Alberts, Bruce. "Ch. 4- Protein Structure and Function." *Essential Cell Biology*. New York: Garland Science, 2010. N. pag. Print. Pg. 125.

[iii] "Prion Diseases." *Centers for Disease Control and Prevention*. Centers for Disease Control and Prevention, n.d. Web. 04 Oct. 2012. <http://www.cdc.gov/ncidod/dvrd/prions/>.

[iv] "Creutzfeldt-Jakob Disease, Classic." *Centers for Disease Control and Prevention*. Centers for Disease Control and Prevention, n.d. Web. 04 Oct. 2012. <http://www.cdc.gov/ncidod/dvrd/cjd/index.htm

"Prion Disease." - *Genetics Home Reference*. U.S. National Library of Medicine, May 2007. Web. 04 Oct. 2012. <http://ghr.nlm.nih.gov/condition/prion-disease>.

[vi] Alberts, Bruce. Glossary. *Essential Cell Biology*. New York: Garland Science, 2010. N. pag. Print. G:15.

[vii] Li, Ju. "Basic Molecular Dynamics." Web. 04 Oct. 20112. http://li.mit.edu/Archive/Papers/05/Li05-2.8.pdf

[viii] Biljan, Ivana, and Gregor Ilc, Gabriele Giachin, Andrea Raspadori, Igor Zhukov, Janez Plavec, Giuseppe Legname. "Toward the Molecular Basis of Inherited Prion Diseases: NMR Structure of the Human Prion Protein with V210I Mutation." *Journal of Molecular Biology*. Volume 412, Issue 4, 30. September 2011. Pages 660-673. ISSN 0022-2836, 10.1016/j.jmb.2011.07.067.<http://www.sciencedirect.com/science/article/pii/S00222836110084 5X>.

[ix] Van der Kamp, Marc W., and Valerie Daggett. "Pathogenic Mutations in the Hydrophobic Core of the Human Prion Protein Can Promote Structural Instability and Misfolding." *Journal of Molecular Biology*. Volume 404, Issue 4. 10 December 2010. Pages 732-748, ISSN 0022-2836, 10.1016/j.jmb.2010.09.060. <http://www.sciencedirect.com/science/article/pi i/S0022283610010788>.

[x] Rossetti, Giulia, and Xiaojing Cong, Rocco Caliandro, Giuseppe Legname, Paolo Carloni. "Common Structural Traits across Pathogenic Mutants of the Human Prion Protein and Their Implications

