Get Hooked: Cross-beta Structure Leads to Domino Effect in Prion Disease

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Abstract

In the study of protein function, one of the most important factors to the outcome of a molecule is the way it folds. If a protein does not fold properly, it will be unable to meet its function. The cells in our body contain ways to correct or rid our body of these misfolded proteins. In some cases, when a protein misfolds, it can aggregate and/or form fibers to create a prion, which then can induce other proteins to misfold and aggregate. Baker’s yeast has been known to have a number of prions including [PSI+], which is the prion form of the Sup35 protein. The Sup35 protein is important in translational termination, but when in the prion form, it loses the ability to efficiently perform this process. Within prion domain of Sup35, located in the Nterminus, a seven amino acid region, GNNQQNY, has been found to form a “cross-beta spine” structure, which is thought to contribute to the fibrillar structure of the prion. The researchers at University of Illinois-Chicago’s Laboratory for Molecular Biology are interested in the structure of GNNQQNY because it helps in understanding the structural change of Sup35 from a normal form to the prion form. Furthermore, it can provide insight to how prions fold in human/mammalian systems.

Prion Sup35 [PSI+]

- Structure of the Sup35 Prion we have modeled GNNQQNY
- It is located in the cytoplasm
- What does it do normally?
  - Sup35 in yeast participates in making other proteins in the cell
  - 20% of all misfolded proteins are not corrected; some do not cause problems while others cause brain diseases
- [PSI+] is the misfolded infectious prion form of Sup35
- The molecule begins to misfold at the N-terminus of Sup35
- The C-terminus does not change
- These seven amino acids form interlocking beta sheet-like structures

Process of Protein Misfolding

A normal protein misfolds to prion state and is added to another normal protein. As more normal proteins are added they begin to misfold.

Conclusion

The most important reason for this research is that the understanding of the process of prion disease is essential to discovering a cure. Our model shows the sequence and structure of the GNNQQNY section of the prion, which may signal the prion and other normal proteins to misfold. This model may help scientists decide the best approach to finding possible cures for prion diseases. The similarities between prion disease and Alzheimer’s found in recent research may help scientists discover cures for both disorders.

Why Do We Study Yeast?

- Yeast prion misfolding is very similar to human protein misfolding
- Research is safer because the risk of human infection is lessened
- Human form of disease is contagious to study even after the autoclaving process
- Yeast makes it possible for the whole process of the disease’s misfolding to be studied
- In humans we can not study the beginning of the process because it can only be studied once the patient is dead

Comparison of Normal Sup35 Protein vs. Misfolded Protein

Normal Protein

Misfolded Protein

Alterations in Brain Tissue Caused by Prions

Normal human cerebral cortex showing no significant pathological changes

Prion Diseases

The prion diseases in mammalian species are:
- Scrapie (sheep): acquired
- Transmissible mink encephalopathy (mink); acquired
- Chronic wasting disease (deer, elk); acquired
- Bovine spongiform encephalopathy (cows); acquired

Prion diseases in humans are:
- Creutzfeldt-Jakob disease: inherited
- Gerstmann-Straussler-Scheinker syndrome: inherited
- Fatal familial insomnia: inherited
- Kuru: acquired and inherited
- Alpers: inherited

Structure of GNNQQNY from yeast Prion Sup35

Images and Information Courtesy of:
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Microbiology @ Leicester Website; http://www.micro.msb.le.ac.uk/3DStruct.html
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