Eukaryotic peptide chain release factor (ERF3): Aid to research in prion disease

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Abstract

The building blocks of the entire human body—proteins—play many important roles in everyday processes. Proper folding of proteins is important to their function. In some cases, proteins misfold and cannot properly function. The misfolding of a protein can lead to the formation of prion disease. Prion disease is unique since the misfolded protein convinces other proteins to misfold. This self-perpetuating cycle leads to numerous health problems. Prions can be found in many organisms leading to disease like mad cow disease in cattle and Creutzfeldt-Jacob’s disease in humans. Prions can also be found in yeast. Prions can be studied easily in yeast because yeast undergoes prion aggregation, is well studied, and has a rapid duplication rate. Our molecule, eukaryotic peptide chain release factor GTP-binding subunit (ERF3), misfolds and aggregates into prions in yeast. ERF3 is involved in protein biosynthesis. It binds GTP and performs translational termination in yeast. The researchers of the University of Illinois at Chicago’s Laboratory for Molecular Biology are interested in the M region because it is important to prion formation. Having a physical model of the area will allow researchers to understand the actual shape and potential misfolding activity of the molecule.

What is a Prion?

In 1982, Stanley B. Prusiner of the University of California School of Medicine at San Francisco called misfolded proteins ’prions’ for proteinaceous infectious particles. When proteins misfold, they malfunction and the resulting malfunctioning protein, or “prion”, causes prion disease.

Types of Prion Diseases:

Creutzfeldt-Jakob’s disease

Bovine spongiform encephalopathy (BSE—mad cow disease)

Scrapie

Chronic wasting disease

Prion Diseases

Three forms: sporadic, inherited, and acquired.
Sporadic: itching, ataxia (inability to coordinate voluntary movements), and death in sheep.
Bovine spongiform encephalopathy (BSE): Brain tissues have a spongy appearance, showing holes where cells should be in cows.
Creutzfeldt-Jakob disease (CJD): Behavioral changes, hallucinations, loss of coordination and memory, jerking movements, coma, and death after six months of symptoms in humans.

Why Do We Study Yeast?

• The study of the prion disease is challenging because it is pro-pathogenic to humans. Pro-pathogenic diseases such as BSE can be transferred to humans because the cow and human proteins are so much alike.
• A molecule found in yeast misfolds and aggregates into prions.
• Yeast is beneficial to researchers because it undergoes the process of prion aggregation, it is well studied and has a rapid duplication rate.

Eukaryotic peptide chain release factor GTP-binding subunit (ERF3)

• ERF3 is found in the cytoplasm of yeast.
• Active sites:
  • C-terminal region is involved in translational termination.
  • Scientists hypothesize that the M-region is involved in the misfolding process. This area has 40% alpha helixes and 3% beta sheets in its normal form. In the misfolded prion form, the area forms more beta sheets and then can bind to other normal molecules, causing them to misfold.
• In yeast, the spread of prions is not genetic, but prions are passed from one generation of yeast to the next. Researchers have found that misfolded protein in the cytoplasm is transferred to daughter cells, similar to that found in disease like BSE.
• Regions of ERF3:
  • If the C-terminal region is deleted, the cell cannot make proteins and the cell dies.
  • If the N-terminal and M-terminal regions are deleted, a prion cannot be formed.
Therefore, the main function of the N-terminal and M-regions is involved in misfolding and forming of prions.

Process of Protein Misfolding

Normal protein

Misfolding

Conversion

Multiple conversion

Aggregation of ERF3 prion form in yeast

ERF3 is fused to the Green Fluorescent protein. In normal form, ERF3 is found freely in the cytoplasm (left). When in the prion form, the protein aggregates and forms dots in the cytoplasm (right).

Physical model design of ERF3

• The beauty of science lies in its ever-growing ability to advance technology to make our world a better place. The creation of a three-dimensional model of ERF3 has played an essential role in helping scientists gain a better understanding of misfolded proteins so a cure for prion diseases can be found soon.

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