The Beta Bunch: A-beta of Amyloid Precursor Protein

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Abstract

Function: The A-beta section of APP forms aggregates in the brain that are related to Alzheimer’s disease.

The year 2006 marks the 100th anniversary of the identification of Alzheimer’s disease, an ailment affecting an estimated 4.5 million Americans, including it is thought, approximately half of the population aged 85 and older. The ailment typically begins after age 60, and the risk of developing Alzheimer’s disease increases with age since the disease is progressive in nature. A slow moving debilitating affliction, Alzheimer’s disease causes mild forgetfulness in its early stages, but as the disease advances, Alzheimer’s disease destroys nerve cells, disrupting connections between the cells in areas of the brain vital to memory. In addition, it chemically weakens their ability to send messages, which can impair thinking and memory. The subject of our study is the A-beta portion of the amyloid-beta precursor protein (APP), identified in the protein data bank as 1Z0Q; it may contain a potential link to the enigmatic nature of Alzheimer’s disease. APP resides within the cell membrane and the A-beta portion is formed when APP is cleaved by the beta and gamma secretases, leaving a 42 amino acid peptide. After the protein is cut by these secretases sticky surfaces are exposed on the A-beta peptide. In the brain, the A-beta peptide aggregates in extracellular plaques. Presence of these plaques is associated with Alzheimer’s disease; however, it is unknown whether the aggregates are a cause or an effect of the disease. Efforts to stop the progression of the disease target secretase identification and the resulting effect of selective drugs on these secretases as well as the aggregation of the A-beta peptide.

Alzheimer’s Disease

• A progressive brain disorder
• Slowly destroys memory, and affects learning, judgment, communication and the ability to carry out daily activities
• Nerve cells within the brain that process, store and retrieve information undergo degeneration
• Causes holes in the brain matter
• The Alzheimer’s Association and National Institute on Aging estimate that there are about 4.5 million Americans with Alzheimer’s disease, with the majority of those affected above the age of 65

Brain Tissue

A cross section of a normal brain (left) and a brain affected with Alzheimer’s (right). [Image taken from http://alzheimers.about.com/library/brain.htm]

A-beta Structures

Due to the extreme difficulty of determining the crystalline structure of the A-beta peptide, the researchers used a technique called NMR (Nuclear Magnetic Resonance) that allows structure determination of proteins in an aqueous solution, as opposed to a solid crystal. As a result, the researchers obtained 30 distinct possible structures of A-beta. The image below depicts 15 of these structures overlaid on one another. The central helical core is similar in all 15 structures, while the ends are not. It has not been determined whether the ends of the protein are stationary or flexible to some degree.

A-beta Formation

From its residence in the cell membrane, APP is cleaved by beta and gamma secretases, leaving a 42 amino acid chain that is released into the extracellular matrix. The A-beta protein aggregates and localizes into extracellular plaques found within the brain (as shown to the right).

Amyloid Precursor Protein


Beta Bunches

After the A-beta peptide is released from the cell, it aggregates with other A-beta peptides to form plaques, which our team calls “beta bunches,” that are associated with Alzheimer’s disease.

Conclusion

Many things concerning the A-beta peptide are unknown, including the APP’s original function, the precise structure of the A-beta, the structure of the aggregates, and the specific correlation between Alzheimer’s disease and the plaques found in the brains of Alzheimer’s patients. However, knowledge of the formation of the A-beta peptide is crucial to medical advancement in the treatment of Alzheimer’s disease.

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