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AMYLOIDβ, APP, AND DISCOVERIES IN THE TREATMENT OF ALZHEIMER'S DISEASE

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Alzheimer's Disease is an age-related disease characterized by amyloidβ plaques that build up in the central nervous system, causing neurogenic effects such as synaptic dysfunction and altered calcium signaling in neurons. APP, amyloidβ's precursor, is a membrane bound protein that has implications in adhesion and synapse specialization (1).

To produce amyloidβ, APP is firstly cleaved by β-secretase and then cleaved again by either α- or γ-secretase to form sAPPα or amyloidβ, respectively1. Both produce the APP intracellular domain AICD which is released to the cytoplasm. Amyloidβ is then released into the extracellular space to form fibrils or oligomers to form the plaques that cause neurotoxic effects. The pathway involving α-secretase is considered the non-amyloidogenic pathway and the pathway with γ-secretase is dubbed the amyloidogenic pathway (2). After elucidating this pathway, researchers have been looking to target specific players in amyloidogenic pathway to reduce the amyloid plaques and the effects they cause.

There are two main approaches in treating the amyloid β plaques: increase clearance of amyloid β from the brain or reduce its synthesis and deposition. Solanezumab, a modified immunoglobin G 1 (IgG1) antibody produced by Eli Lilly, was formulated to attach to soluble monomers of amyloidβ to increase clearance (4). Bound solanezumab would leave the brain and go from the cerebrospinal fluid to the serum of patients, indicating amyloidβ clearance. It also only significantly decreased amyloidβ40 and not amyloidβ42 (3). The difference between these two types of amyloid is that the 1-40 peptides are responsible for amyloid fibril formation which turn into plaques (3). While solanezumab did not effectively reduce cognitive decline in patients and was taken off the shelf by Eli Lilly (4), it provided important breakthroughs on the targeting of amyloidβ for Alzheimer's Disease therapeutics.

Another approach recently published is the inhibition of APP metabolism in general. While it has been shown that reducing APP has limited phenotypic effects due to the attenuation by similar proteins called APLCs, it is integral to note possible effects like decreased grip strength and lowered synaptic potential (2). Methylene blue (MethB) is a known inhibitor by reducing amyloidβ oligomers. One of its metabolites, AzureB, affects β-secretase activity which inhibits the synthesis of both sAPPα and amyloidβ (5).

This editorial showcased two examples of the main and upcoming therapeutic approaches in the treatment of Alzheimer's Disease. As a large population of people, particularly in America, start to grow past the age of 60, innovations in the treatment of Alzheimer's Disease, dementia, and other age-related diseases will be given high priority. The investigation into amyloidβ is particularly interesting for Alzheimer's research to prevent the cognitive decline that is characteristic of the disease.

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