Beta-amyloid and Alzheimer's disease

In Alzheimer's disease, brain cells that process, store and retrieve information break down and die. Although Alzheimer's is complex and scientists do not yet know the underlying causes of this destruction, there are numerous factors that may contribute. Some examples include inflammation, vascular changes, metabolic changes and the buildup of proteins including proteins known as beta-amyloid and tau in the brain.

A buildup of beta-amyloid has long been recognized as a hallmark of Alzheimer's disease. This microscopic protein fragment is sticky and accumulates outside of nerve cells into plaques in the brain, disrupting communication between brain cells and eventually contributing to their death. Some versions of beta-amyloid are chemically "stickier" than other fragments and are more likely to accumulate into the plaques found in the brain of a person with Alzheimer's. While beta-amyloid's exact role in the disease process is not completely understood, research has demonstrated that drugs that remove beta-amyloid from the brain slow the progression of the disease for people in the early stages. There are now new FDA-approved treatments for Alzheimer's disease that target beta-amyloid.

What evidence is there that beta-amyloid plays a role in Alzheimer's disease?

- In a few hundred extended families worldwide, scientists have identified rare genetic mutations that result in an overproduction of beta-amyloid, virtually guaranteeing an individual will develop Alzheimer's, often decades earlier than what is considered typical (age 65 and older). These mutations occur in any of three genes. Each of these genes is involved in biological processes associated with beta-amyloid production or accumulation. Globally, only an estimated 1% of people living with Alzheimer's disease have one of these mutations.

- Scientists have developed mice genetically engineered to carry some of these genetic mutations. The mice develop amyloid plaques, have difficulty remembering their way through mazes and develop other symptoms that mimic Alzheimer's in humans.

- Another gene related to the risk of Alzheimer's disease is APOE, which exists in multiple forms in the human population, with the three most common forms being APOE-e2, APOE-e3 and APOE-e4. Research has shown that APOE-e4 increases the risk of the disease in individuals of White European descent. Recently, it has been shown that the APOE-e4 version impairs the ability of

the brain to remove beta-amyloid, leading to a possible accumulation of amyloid plaques, a hallmark of the disease. It's important to note that APOE-e4 has not been shown to have the same impact on risk in all populations, so more research is needed.

- In contrast, individuals of White European descent with the APOE-e2 gene have a reduced risk of Alzheimer's. These individuals appear to produce lower amounts of beta-amyloid in the brain.

- Other genes linked to increased risk of Alzheimer's disease have been identified. Further research on the functions of these genes has suggested a link to some aspect of beta-amyloid production or clearance, pointing to beta-amyloid as a key player in the disease process.

- Individuals with Down syndrome have three copies of chromosome 21, which means they have an additional copy of genes that play a role in increasing beta-amyloid production and almost invariably develop amyloid plaques by age 40. Not all people with Down syndrome develop dementia, but according to the National Down Syndrome Society, about 30% of people with Down syndrome in their 50s and 50% in their 60s are living with dementia due to Alzheimer's disease.

- Research has demonstrated that removing beta-amyloid from the brain can slow the progression of the disease for people in the early stages, preserving their ability to remember and perform routine daily activities longer. In addition, research has also shown that lowering beta-amyloid may impact other underlying biology that contributes to Alzheimer's disease, such as lowering the accumulation of tau protein inside of nerve cells.

In addition to beta-amyloid accumulation, researchers worldwide are investigating a variety of other possible triggers and potential interventions for the destructive series of events over many years that eventually kill brain cells.

How do treatments that attack beta-amyloid work?

There are currently two anti-amyloid therapies that have received approval as treatments for early Alzheimer's from the U.S. Food and Drug Administration (FDA): aducanumab (Aduhelm™), which was approved in June 2021, and lecanemab (Leqembi™), approved in January 2023.

Anti-amyloid treatments work by targeting and reducing beta-amyloid in the brain. Although aducanumab and lecanemab both target beta-amyloid in the brain and belong to the same class of treatments, no two treatments are the same.

Both drugs are intravenous (IV) infusion therapies, which means they are given directly into the bloodstream through a vein. And both aducanumab and lecanemab are known as anti-amyloid monoclonal antibody therapies. *Monoclonal* ("mono" or "one") refers to the fact that each drug was developed in a lab using a single cellular source. *Antibodies* are protective proteins made by our immune system or generated in a lab as a way to respond to foreign or problematic substances in the body. In this instance, the substance is amyloid. By targeting amyloid in the brain, both drugs address the underlying biology of Alzheimer's and slow the progression of the disease for people in the early stages of the disease.

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