Disruption of amyloid β-protein processing drives Alzheimer’s

Alzheimer’s disease is a devastating and common condition that causes memory loss and impaired cognitive function. Studies to understand the molecular basis of Alzheimer’s— with pathological features that include cerebral neurodegeneration, build-up of extracellular amyloid plaques, and intraneuronal neurofibrillary tangles— have been ongoing for decades. Deciphering the causes of the disease has been challenging, due to its complexity. No effective treatments have been developed for Alzheimer’s, in part due to an incomplete understanding of the underlying drivers of the disease process.

A rather inherited form of the disease, familial Alzheimer’s disease, presents with similar symptoms and pathology to the more common sporadic Alzheimer’s disease. The only clear differences are that familial Alzheimer’s occurs in middle rather than old age and is caused by single, dominantly inherited mutations. These mutations are found in genes encoding proteins directly responsible for the production of a sticky protein that builds up in the amyloid plaques. The dominant inheritance, early age of onset, and connection to amyloid pathology, makes familial Alzheimer’s easier to study than the common form of the disease in the elderly. Research into familial Alzheimer’s disease is important not only for carriers of these devastating mutations but for all Alzheimer’s patients due to the similarity between these two forms of the disease. Finding new targets and strategies for developing treatments is essential for improving quality of life for patients and their families. While some targets are already known, not all drivers of Alzheimer’s have been discovered.

AMYLOID PLAQUES

One of the key pathologies in the development of the disease is the presence of cerebral amyloid plaques. These plaques are outside the nerve cells in the brain and are made from a build-up of the amyloid β protein (Aβ). This protein is formed when an amyloid β-protein precursor (APP) is cleaved by a protease enzyme called γ-secretase. The Aβ produced can be of varying lengths, but only proteins of 40, 42, or 43 amino acids or fewer in length are secreted from the cells. Aβ that is 42 amino acids in length (Aβ42) is the primary form that builds up in the plaques. In patients with familial Alzheimer’s disease, three genes have been discovered to have inherited dominant missense mutations (mistakes within the DNA leading to incorporation of an incorrect amino acid). These are the amyloid precursor protein (APP) and gamma-secretase components presenilin-1 and -2, enzymes that cut APP to produce Aβ.

Mutations in these genes can cause proportionally more Aβ42 to be produced, leading to development of amyloid plaques. For this reason, Aβ42 and plaque formation is considered integral to triggering the disease process. However, treatments targeting Aβ42 have not shown effectiveness in slowing or halting the decline of Alzheimer’s disease, and not all mutations associated with familial Alzheimer’s disease lead to elevated proportions of Aβ42, suggesting there is more to this process.

PROCESSIVE PROTEOLYSIS

To more fully understand the factors that could be affected in familial Alzheimer’s disease, researchers should investigate the activity of the γ-secretase enzyme more closely. In cleaving the APP, the enzyme does not catalyse only a single cut but also performs a series of processive trimming events. The first cut is carried out at the cytosolic end of the transmembrane domain of the APP. This cut causes the intracellular domain of the APP to be released into the cytosol while either Aβ40 or Aβ42 (42 amino acids in length, respectively) remain membrane bound. The γ-secretase enzyme then continues trimming the membrane-bound protein in increments of three amino acids. This gives two different pathways of processive proteolysis: Aβ42 → Aβ40 → Aβ39 → Aβ38 and Aβ42 → Aβ40 → Aβ38 (this last cut is four amino acids long). Both pathways result in a series of short peptide chains of three (or four) amino acids along with the shortened Aβ proteins being produced. The shorter Aβ proteins are secreted once the cuts remove most of the transmembrane domain and the Aβ protein is no longer bound to the membrane. This is what usually occurs when no mutations are present, but the mutations associated with familial Alzheimer’s disease could also be affecting this part of the process.

These results show that deficient processing of long Aβ by γ-secretase is a common feature of mutations that cause familial Alzheimer’s disease.

MUTANTS AFFECTING TRIMMING STEPS

In order to better understand the effects of mutations that cause familial Alzheimer’s disease on this series of proteolysis trimming events, Professor Michael S Wolfe and his team at the University of Kansas explored this problem further and determined that processive cleaving by γ-secretase was consistently reduced in familial Alzheimer’s disease cases.
These longer Aβ proteins remain bound to the membrane and may be a key driver of disease progression.

**FUTURE THERAPIES**

The importance of understanding the pathological causes of Alzheimer's disease cannot be overemphasized. The experiments undertaken by Wolfe and his team have shed some light on the key process of APP proteolysis by γ-secretase. The discovery that these longer membrane-bound Aβ proteins are overproduced when not cleaved correctly, as a result of disease-causing mutations, could lead to a new line of investigation. The focus of Alzheimer research has primarily been on Aβ42 and its role in amyloid plaque build-up and pathology, but this needs to change, as Aβ42 is clearly not the only cause of the disease. More work needs to be done to understand the role of these long forms of Aβ and how they may be driving familial Alzheimer's disease. These results clearly show that the ineffective processing of Aβ by γ-secretase is key for disease progression. This deficient processing presents a potential target for future therapies that could provide effective treatment for patients suffering across the globe.

**References**


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**Personal Response**

What do you think is the next step in investigating these Aβ that are not secreted?

Key experiments should explore the potential role of these long Aβ peptides and the deficient γ-secretase trimming process in disrupting brain nerve cells and their connections. We are testing effects of Alzheimer-causing mutations in cell and animal models under conditions in which Aβ42 is not produced. Ruling out Aβ12 as responsible for disruption of nerve cells would clearly point to a critical role of deficient trimming of long Aβ peptides in triggering familial Alzheimer's disease. Such findings should also have implications for the aetiology and treatment of the much more common Alzheimer's disease in those over 65 years of age.