An Introduction to Abnormal Protein Aggregation and Its Role in Alzheimer's Research

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Background

Ever since two scientists noticed dark blots in the brain matter of patients with dementia and similar illnesses in 1892, something known as the amyloid cascade hypothesis has made itself known throughout the scientific community. Although bearing an intimidating name, the hypothesis is relatively straightforward. Before the 1900s, those dark blots were already correctly identified as plaques of unwanted material that tangled around neurons. Later, Alois Alzheimer, the namesake of the neurodegenerative disease, made the hypothesis that these plaques were a possible cause of dementia. Soon, in the latter half of the 1900s, those proteins were identified. The main protein that composed the tangle was discovered to be Amyloid-ß (Aß). Aß was found to cluster up in the brain quickly and mess with brain functions (Lowe, 2022).

Beta-Amyloids

In this introduction, it is assumed that the reader is at least vaguely familiar with the monomer structure of proteins, i.e., amino acids, and the structures of primary, secondary, tertiary, and quaternary folding. Amyloid protein generally refers to a protein that is able to aggregate easily and build up quickly. Usually, ß-pleated sheets are found throughout the aggregation in "ultrastructures," and the parallel structure contributed to the fibrous nature of that structure (Liu & Zhang, 2011) (Note that antiparallel sheets were not detected (Holcombe et al., 2023)). These aggregations also tend to contain nucleic acids, with a possible explanation being that nucleic acids tend to be attracted there. As a result, nucleic acids exacerbate and complicate the aggregation, making it even larger (Liu & Zhang, 2011).

The most relevant amyloid protein in this paper is Amyloid-beta. Aß proteins usually come from a bigger protein being broken down. That protein is called an Amyloid Precursor

Protein (APP), which resides in the cell membrane. APP is usually metabolized by the brain to perform regular functions, but it can be broken down into harmful plaque material. When beta-secretase (ß-secretase), an enzyme, cuts the APP into two parts. Then gamma-secretase (ɣ-secretase), another enzyme, cuts through the part of the APP that is still attached to the cell membrane. That cut creates two additional pieces: one attached to the membrane still, and another that is now free-floating. That free-floating piece is Aß. These pieces are insoluble and have an affinity for each other; debris will build up quickly. They can form small, big, and fibrous clumps that are called oligomers, protofibrils, and amyloid fibrils. (Chen et al., 2017). With a constant buildup, it is evident that a problem can be created, and that problem is widely believed to be illnesses like Alzheimer's.

As a result, much research and work have been dedicated to working towards a cure, and usually these treatments revolve around Aß. Attempts at inhibiting ß-secretase and ɣ-secretase have been carried out, as well as antibodies being tested to get the immune system to combat these plaques (Lowe, 2022). However, none of these treatments have worked, and no significant differences have been found between the experimental and control groups. In one study, the treatment actually accelerated symptoms (Lowe, 2022). As a result, doubt has been cast on this theory, in addition to several problems with the integrity of the theory, which will be explored below.

Tau proteins

Another relevant player in Alzheimer's disease is tau proteins (τ). Tau proteins are proteins that assist in the stabilization of microtubules. These proteins are usually found in the brain, as those microtubules are critical for neural communications. Tau has a relatively simple

structure, with the structure even being described as "natively unfolded" (Gholami, 2023). Tau proteins can be messed up in several ways, with one way being affected by prions and another by excessive phosphorylation, which means that there are too many phosphate groups added. As a result of misfolding or damage, Tau proteins can easily begin self-aggregating in a similar fashion to Aβ. These abnormal proteins are generally known as p-tau (Gholami, 2023). These clumps can also be especially dangerous because they clump and damage the microtubules, which are needed for neural connections, and that's why they are also seen as a contributing factor to neurodegenerative diseases such as Alzheimer's.

Issues

There are some issues that have been raised about the amyloid cascade hypothesis, as well as the idea of plaques being the root cause of dementia and other related illnesses.

Firstly, the sheer number of failed trials showed cracks in the theory writ large. Amyloid plaques, although a rather intuitive explanation in hindsight, seemed not to be the underlying cause of Alzheimer's. Rather than focusing on these plaques as the basis of all treatment, it is now more understood that Alzheimer's is an extremely complex disease with many potential physiological contributing factors.

However, a more sinister problem was identified in 2022.

In a 2006 paper by Sylvain Lesné et al., the amyloid Aß-56 was isolated and tested. When tested on rats, Aß-56 seemed to directly cause memory defects in the animals. This paper was seen as groundbreaking and conclusive, but there were issues with the academic integrity and process of these studies despite passing peer review. Specifically, high amounts of image

doctoring and manipulation were found, as well as the generation of non-existent details. For example, protein bands were found to be manipulated and moved. The issue becomes apparent when this paper has been cited over 2000 times (Lowe, 2021). If the findings are sound despite invalid processes, however, other research should corroborate the claims about Aß-56. However, multiple studies and experiments have failed to find Aß-56.

However, it is important to stress that although Lesné's paper was most likely indeed a fraud in many areas, the research on the role that plaques and tau buildup play in Alzheimer's is not irrelevant.

References

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