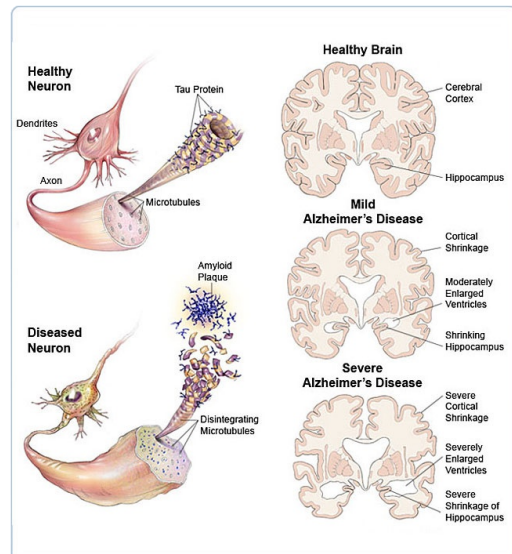# Late-Onset Alzheimer's Disease: Plaques, Tangles, and Genomics
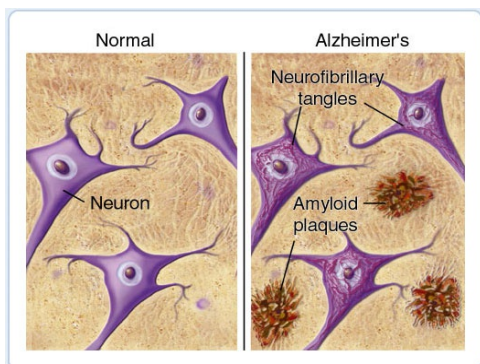
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Introduction

One of today's most well-known and studied diseases, Alzheimer's Disease is becoming more and more prevalent in the elderly as worldwide populations are growing older than ever, affecting 5.2 million Americans over 65.[1] Within the past twenty years, the understanding of the pathology of this disease has increased tremendously with promising implications for finding new treatments and potential cures. Alzheimer's is the leading cause of dementia, or loss of cognitive function that interferes with daily life. Often times, those affected do not display any symptoms until they are over 60, but the disease may have already been present up to twenty years before the patient first exhibits the characteristic symptoms of AD.[1] In AD patients, the brain tissue begins to shrink as a result of neuronal loss (**Figure 1**), which is mainly attributed to the presence of plaques of beta amyloid and tangles of tau protein that interfere with neuronal functions (**Figure2**).[2]

Alzheimer's and Genetics

In approximately 25% of patients with AD, at least two other family members were affected as well, suggesting a strong link between AD prevalence and genetics.[4] Of the two kinds of Alzheimer's, early and late onset, only the early-onset has a causal mutation in one of three genes: amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2).[3] However, only 5% of patients have early-onset AD, so the vast majority develop symptoms of the disease only after age 65.[2] While there are no genetic mutations that can definitively cause this late-onset AD, there are multiple inheritable genetic risk factors associated with AD, the major one being a mutation in the gene coding for apolipoprotein E (APOE4).[2]

Beta Amyloid Plaques

The amyloid precursor protein (APP) contains the beta amyloid fragment, which is found to form detrimental aggregates in Alzheimer's patients. These aggregates of amyloid were first identified in 1984 by Glenner and Wong, and their presence became one of the hallmarks of AD.[5] The mechanism of aggregate formation begins when the APP, which is attached to the surface of neuron membranes, is cleaved by a series of enzymes called alpha-secretase, beta-secretase, and gamma-secretase. [2][6][7] However, the APP can undergo two pathways: a benign cleavage by alpha-secretase, or a harmful cleavage by first beta-secretase and then gamma-secretase that releases the beta amyloid fragment of APP into the space outside of the cell.[2] It is these cleaved beta amyloid fragments that can clump together if there is an excess amount. Unfortunately, the exact mechanism is not fully understood, so it would be very helpful to conduct research on what factors determine which enzyme cleaves APP and when the enzyme does so. Knowing what conditions favor the pathway involving alpha-secretase cleavage and comparing it to the conditions favoring beta- and gamma-secretase cleavage could help

lead to a treatment where the benign pathway is induced and the malignant pathway is inhibited. However, there are also cellular process that can help remove these excess beta amyloid oligomers once they are created, and many ongoing studies have shown optimistic results about inducing such pathways to reverse or slow down AD. Among the most promising that will be discussed later involve analyzing the involvement of the gene APOE and the introduction of lipoproteins that can carry away plaques of beta amyloid. There may be a benefit in research targeting the clearance of beta amyloid as opposed to inhibiting its formation, since so little is known about the overall pathway and processes involving APP, beta amyloid, and other cleaved fragments. It may be that beta amyloid serves a necessary cell function, and while an excess of it has been shown to be detrimental, a deficiency of beta amyloid may be detrimental as well. Thus, it would be useful to study this pathway in more depth by looking at models where the APP and secretase genes have been knocked out or impaired.

The negative effects of beta amyloid plaques have been well documented, and a study conducted in 2008 by Shankar et al. showed that these plaques strongly impair neuronal function.[8] Oligomers of beta amyloid were extracted from Alzheimer's patients and injected into non-afflicted rodent hippocampuses, and these rodents were found to have greatly decreased long term potentiation (which is involved in the plasticity of synapses), long term depression, lowered dendritic spine density (corresponding to neural loss), and impaired memory for learned behaviors.[8] This shows very potent evidence for amyloid plaques being the main cause for the symptoms of dementia, memory loss, and neural death in Alzheimer's patients, and, coupled with the optimistic results of research on mechanisms involving the regulation of beta amyloid, strongly suggests that beta amyloid plaques are the precipitating factor for the disease itself.

Tau Protein Tangles

The second defining hallmark of AD is the presence of tau protein tangles inside neurons. Tau binds to microtubules, supporting them and maintaining the cell's cytoskeleton, as well as promoting transport across microtubules.[9] However, in AD, tau is shown to undergo hyperphosphorylation, which disrupts the structure of tau so that it detaches from the tubulin in microtubules, leading to disrupted cell transport and instability.[10] While these results have been replicated many times, the pathology leading up to the formation of tau proteins and the causal link to Alzheimer's are not clear. It is believed that there are multiple protein kinases involved in the hyperphosphorylation of tau[11], but more importantly, current research suggests that the formation of beta amyloid plaques precedes the formation of tau protein tangles. A study done by Oddo et al. in 2003 claimed that in a transgenic mouse model with three mutations in the APP gene, presenilin 1, and tau gene, the mice first developed amyloid plaques before exhibiting tau tangles.[12] This confirms what they call the "amyloid cascade hypothesis," where the formation of beta amyloid plaques leads to the eventual accumulation of tau aggregates in an unknown process. Therefore, researchers looking for potential treatments for Alzheimer's should not target the tau protein aggregates, as it would not affect the deeper root of the problem, namely the amyloid plaques. However, there is a small chance that the tau protein tangles play some role in AD, so it would be beneficial to study the pathology of tau tangle formations, but it should be of a lower priority due to its limited implications for treating AD.

Apolipoprotein E Gene and Lipoproteins

The protein APOE is involved in the transport and catabolism of lipoproteins, and is coded for by the gene APOE. APOE protein binds to lipids, forming lipoproteins which help transport substances such as cholesterol and amyloid from the blood to the liver.[3]

The APOE gene contains three common alleles: the "protective" APOE 2, the "neutral" and most common APOE 3, and the harmful APOE 4[13] In 1994, Corder et al. showed that across a population, those with the APOE 2 allele had the lowest prevalence of Alzheimer's, and those that did, developed it later in life than those with other alleles.[15] However, it is a relatively rare allele, compared to the approximately 70% of people with the APOE 3 allele[2] The remaining 25-30% of people carry the APOE 4 allele, which is the gene that carries the highest risk for late-onset sporadic Alzheimer's. Around 40% of patients with AD have the APOE 4 allele, so while it is not a causal mutation, it greatly increases the risk of developing AD.[3] Another study conducted by Corder et al. in 1993 calculated the increased risks of developing AD, and found that as the number of APOE 4 alleles increased, the likelihood of getting AD increased from 20% to 90%, and the mean age of onset dropped from 84 to 68.[15] This shows very strong evidence for the involvement of APOE 4 in the pathology of AD, and suggests that the gene would make a good target for AD treatment.

A recent study in 2012 by Cramer et al. were able to do just that, target and induce the APOE gene in Alzheimer's afflicted mice. Using betaroxene, an agonist for receptors known to induce transcription of the APOE gene, the researchers were able to enhance the pathway by which cells naturally clear beta amyloid plaques from outside neurons.[16] Not only were the levels of beta amyloid greatly reduced, but the mice exhibited positive cognitive and behavioral changes that showed the reversal of AD. This confirmed the previous findings that APOE is associated with HDL, high-density lipoprotein, which is known to be responsible degrading plaques of amyloid and transporting them away.[16] Thus, this study shows what may be the most promising potential treatment of Alzheimer's, as it deals with what is most likely the precipitating cause of the disease, the buildup of beta amyloid plaques, and finds a way to enhance the intrinsic processes of the cell to naturally control the excess amounts of amyloid aggregates.

References

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