Current Research Pertaining to the Correlation of Prion Proteins and Alzheimer's Disease

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Abstract

At present, there are around 50 million AD patients worldwide and this number is projected to double every 5 years and will increase to reach 152 million by 2050. (National Library of Medicine). This neurodegenerative disease has been known to cause cognitive impairment and memory loss. In recent research it seems that this degenerative disease is being correlated with the accumulation of the amyloid-beta (Aβ) peptide as well as the prion protein (PrPC). (PrPC) has been discovered to have inhibitory properties on the Beta-Secretase enzyme (BACE1). The inhibition of BACE1 leads to the essential deprivation of the rate-limiting step, which results in the increase of amyloid-beta.

What is Amyloid-Beta?

The Amyloid-Beta peptide is a product of proteolytic production of the amyloid precursor protein (APP), which is an enzymatic process that essentially is like a blueprint for the breakdown of the APP. APP processing begins with Beta-secretase, in which APP is cleaved into two and releases an N-terminal fragment (sAPPBeta) as well as a membrane-bound C-terminal fragment known as the C99 strand. C99 is then residually cleaved by the presenilin-containing gamma-secretase complex to form amyloid-beta and the amyloid intracellular domain (AICD). Multiple amyloid-beta isoforms are formed by this amyloidogenic cleavage. These isoforms are commonly found in their AB40 and AB42 state. These peptides can subsequently be self-assembled into small soluble oligomers, which are the common oligomers that are found in all human brains.

Amyloid Cascade Hypothesis

However, the amyloid cascade hypothesis, indicates that the amyloid deposition signals the start the progression of Alzheimer's Disease. Amyloid-Beta peptides are known to have a normal function in human brains in the regulation of potassium and calcium channel currents. To prevent its build-up, it is degraded by multiple peptidases. However as humans age, increased BACE1 activity results in the increase in the expression of the amyloid-beta peptide. The reason for the lack of degradation is also due to the reduction in the levels of the amyloid-beta peptidases.

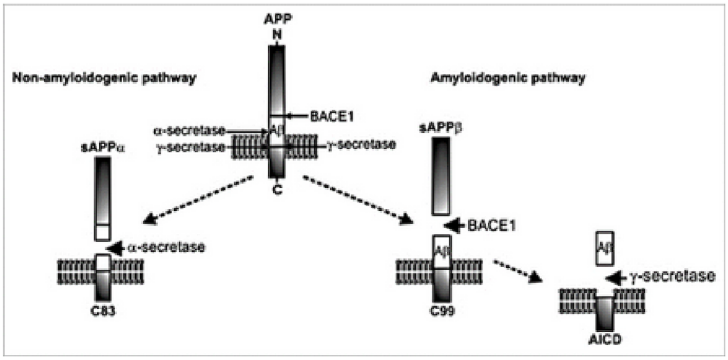

Figure 1. BACE 1 and APP cleavage in the Non-Amyloidogenic Pathway as a result of the Gamma-Secretase

(PrPC) Regulation

In a study conducted in 2007, it was identified that the main reason that the accumulation of Amyloid-Beta peptides is due to the prion protein PrPC. PrPC is known to decrease the rate of cleavage between the BACE1 protein and APP. To investigate this further, researchers examined the effect of mature PrPC on mice. It was here that it was discovered that PrPC must interact with glycosaminoglycans, whose primary role is to facilitate regulation of structural scaffolding. This is how its interaction with BACE1 begins splicing. It was here that they were able to identify that the Met/Val129 genotype polymorphism is the main reason that there is an impact on the PRNP gene (Journal of Biological Chemistry). The PRNP gene itself is known for its role in promoting Amyloid-Beta production.

Through this study, scientists were able to come to the conclusion that humans with higher expression levels of the Met129 genotype in their PRNP gene will most likely have early onset of Alzheimer's seeing as how these specific individuals would report having higher concentrations of the Amyloid-Beta 40 peptides. This essentially means that in the future, certain diagnostic tests for Met129 will allow for the detection of early onset Alzheimer's allowing the patient to properly prepare for the result.

Conclusion

Through this study, scientists have been able to properly understand how PrPC is playing a role in the production and inhibition of the Amyloid-beta proteins, which are the leading indicator of AD. The interactions between PrPC and APP are crucial to the understanding of AD. Through this overall understanding of the correlation between the two factors, it can be stated that the PRNP gene, which is what is controlling the Amyloid-Beta peptide production, can be further examined and regulated through the Met129 phenotype.

In the future, if we can properly identify the upregulation of the Met129 phenotype, we can find possible ways to identify strategies to test for this phenotype, allowing for early detection of onset AD.

References

1. Breijyeh, Z., & Karaman, R. (2020). Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules (Basel, Switzerland), 25(24), 5789. https://doi.org/10.3390/molecules25245789
2. Kellett, K. A., & Hooper, N. M. (2009). “Prion protein and Alzheimer disease”. Prion, 3(4), 190–194. https://doi.org/10.4161/pri.3.4.9980
3. Pauly, Thomas et al. (2022). “Met/Val129 polymorphism of the full-length human prion protein dictates distinct pathways of amyloid formation”. Journal of Biological Chemistry, Volume 298, Issue 10, 102430. https://doi.org/10.1016/j.jbc.2022.102430