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The Connection Between Alzheimer's Disease and Prion Diseases: A Mini-Review

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Abstract

Alzheimer's disease and prion diseases are progressive neurodegenerative disorders that have no cure. These illnesses share some similar mechanisms for misfolding, aggregation, accumulation, and dispersion of proteins; moreover, one of the receptors for amyloid beta is the normal prion protein, so several neurodegenerative diseases may share a pathological pathway.

Keywords: Alzheimer's Disease; Prion; Protein Misfolding

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease with a slow progression that worsens over time [1]. AD is the main cause of dementia and this syndrome can be characterized by any reduction in cognitive capabilities that interferes with daily life [2]. There are two main forms of AD: early-onset AD, which is rare (≤ 1%), occurs in individuals under 65 years of age, and is caused by genetic mutations. The other form is late-onset AD and this is the most common form. Late-onset AD occurs in individuals 65 years of age and older and it is multifactorial [1]. Prion diseases, also known as transmissible spongiform encephalopathies, are a group of rare infectious neurodegenerative and fatal illnesses that includes Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease, fatal familial insomnia, and kuru [3]. In addition to the loss of synapses and neurons in specific brain areas, prion diseases, AD, and other neurodegenerative diseases such as Parkinson's and Huntington's disease have several other common features such as the progressive accumulation of misfolded proteins that form amyloid [4].

The main proteins involved in the accumulation of misfolded aggregates in AD are extracellular amyloid beta 42 (Aβ42), which forms amyloid plaques, and hyperphosphorylated tau (hp-tau), which forms intracellular neurofibrillary tangles [5]. In contrast, in prion diseases, the aggregates are formed by extracellular abnormal prion protein (PrPSc) [3]. These proteins, in their native form, undergo a misfolding process that produces a structure with β-sheet-rich structures [4]. Several studies support the hypothesis that misfolding, oligomerization, and accumulation of these proteins are the main events that trigger the pathological events in neurons in both AD and prion diseases [6]. Aβ42, hp-tau, and PrPSc aggregation seems to adjust better to the seeding-nucleation model first proposed by Jarret and Lansbury [7].

In their current form, this model can be summarized as follows: the first event is the formation of a nucleus or seed from the misfolded monomeric protein; then, this structure evolves to oligomers, protofibrils, and mature fibrils, which eventually suffer fragmentation and the fragments produced can migrate and function as a new seed which can recruit soluble normal protein and the cycle repeats [4,8]. Of all the structural conformations previously mentioned, the oligomers are the more toxic form [6,9,10]. Experimental evidence shows that normal prion protein (PrPC) can function as an Aβ42 receptor and this interaction produces a decrease in long term potentiation in neurons of the hippocampus [11,12]. Other studies have shown that activation of PrPC stimulates hp-tau [13,14], which suggests that PrPC is an intermediary between Aβ42 and the hyperphosphorylation of tau.

Conclusion

Strong evidence supports the hypothesis that AD and prion diseases have some similar mechanisms for misfolding, aggregation, and propagation, and also that PrPC can function as an Aβ42 receptor which is an intermediary for the hyperphosphorylation of tau. This evidence may suggest a new method for finding new therapeutic agents.

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