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Review

New insights on Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD), the most common age-associated dementing disorder, is clinicopathologically manifested by progressive cognitive dysfunction concomitant with the accumulation of senile plaques (SP). SP is consisting of amyloid-β (Aβ) peptides and neurofibrillary tangles (NFTs) of hyper-phosphorylated tau (p-tau) protein aggregates in the brain of affected individuals. Lipid rafts promote interaction of the amyloid precursor protein (APP) with the β-secretase enzyme responsible for generation of the Aβ peptides. Fibrillar Aβ oligomers, which have been shown to correlate with the onset and severity of AD, bind preferentially to cells and neurons expressing cellular prion protein (PrP^C). The binding of Aβ oligomers to cell surface PrP^C, as well as their downstream activation of Fyn kinase, was dependent on the integrity of cholesterol-rich lipid rafts. Rafts also regulate cholinergic signaling as well as acetylcholinesterase and Aβ interaction. Such major lipid raft components as cholesterol and ganglioside (GM1) have been directly implicated in pathogenesis of the disease. Perturbation of lipid raft integrity can also affect various signaling pathways leading to cellular death and AD.

In this review, I will discuss the more recent findings on the biopathological mechanisms, candidate bio-markers, and therapeutic interventions of the elusive AD.

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1. Introduction

Alzheimer's disease (AD) is a common, progressive and devastating neuro-degeneration of human brain structure and function, from which over 37 million people are suffering worldwide [1] with an estimated cost of $600 billion in 2010 [2]. Globally, 5 million new cases of AD are diagnosed annually, with one new AD case being reported every 7 s [3]. The risk of developing AD correlates strongly with aging, resulting in a deterioration of mood, behavior, functional ability, cognition, and memory [4], therefore, AD is becoming an increasing socio-economic crisis as life expectancy increases. Taking care of AD patients places a tremendous socioeconomic burden not only on unpaid caregivers but on our health care system as a whole [5]. In spite of this, there is no current therapy that can halt or reverse AD [6].

The disease is associated with brain pathology involving accumulation of extracellular amyloid aggregates (also known as senile plaques) (SP) of small, toxic, and highly amyloidogenic 42 amino acid amyloid beta (Aβ42) peptides and intracellular neurofibrillary tangles (NFTs) of hyper-phosphorylated tau (p-tau) protein [7,8]. According to the amyloid cascade hypothesis, it is the Aβ which is principally responsible for many of the pathological features of the disease with Aβ oligomers representing the most toxic species [9]. The accumulation of Aβ42 as diffuse plaques triggers the inflammatory responses due to microglial activation with release of pro-inflammatory cytokines and the most affected brain areas are the neocortex and hippocampus. In addition, perturbations in the equilibrium between kinases and phosphatases resulting in hyperphosphorylation of tau protein that results in neuronal degeneration and neuronal loss [10].

Allam et al. [11] strongly suggested through the results of their bioinformatics study that presenilins (PS-1, PS-2) and amyloid precursor protein (APP) play a dominant role in the pathogenesis of AD by inducing a pro-inflammatory state; raises the possibility that genetic components are more important in AD compared to environmental, metabolic, and age related factors.

Although there are strong genetic links, including APP, PS-1, and PS-2 mutations [12], as well as the apolipoprotein ε4 allele [13], sporadic AD is the dominant form. From this point of view pre-dominance of AD research based on the mechanisms of early onset disease versus the broader spectrum of the factors leading to the sporadic form might be one of the reasons for the failure of the majority of therapeutic trials and lack of any preventive measures 20 years since the amyloid hypothesis has been proposed [14].

In this review, I will elaborate on the current status of research addressing the biopathological mechanisms, candidate bio-markers, and therapeutic interventions of the elusive AD.

2. Lipid rafts

The notion of lipid rafts, while not new, has never been far from controversy, their existence frequently questioned. They are small nanodomains (10–200 nm), heterogeneous, highly dynamic of which there are millions in a single cell [15]. They have recently gained considerable attention as these membrane-embedded clusters of phospholipid-sphingolipid- and cholesterol-enriched, integral and peripheral membrane proteins are instrumental in the processing of APP holoprotein and hence the amyloidogenic process itself [16,17]. Small rafts can sometimes be stabilized to form larger platforms through protein–protein and protein–lipid interactions" [15]. The long, saturated acyl chains of sphingolipids allow tight packing hence their juxtaposition with the kinked, unsaturated acyl chains of bulk membrane phospholipids leads to phase separation. The cholesterol molecules can act as "spacers," filling any gaps in sphingolipid packing [18]. Pike [15] showed the importance of lipid rafts in protein sorting and segregation with glycosylphosphatidylinositol (GPI)-anchored proteins, being preferentially localized in lipid rafts. Other lipid modifications of proteins have also been described, such as palmitoylation and myristoylation which may influence raft localization [15]. In describing membrane lipid clusters as moving platforms, or rafts perhaps the most important finding was that proteins could