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Alzheimer's disease and Aβ pathways

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease which is one of the major health issues globally. It is the 6th cause of death in the United States. Approximately, 60–70% of cases of dementia are caused by AD. The disease advances with age worsening the symptoms that include problems with declining memory, language, mood swings, loss of motivation, self-neglect, and other behavioral issues. AD patients need a long-term health care and hospital services as the disease worsens with the advancing of their age. However, proper medications and treatment is still unavailable as the cause of AD is poorly understood.

Keywords: Amyloid beta pathway; Alzheimer's disease; Dementia; Global health; Global economy

1. Alzheimer disease is a global major issue

Alzheimer disease (AD) is known to be the most common cause of dementia among the elderly people. The progressive neurodegeneration of AD leads to progressive loss of memories and other cognitive deficits such as confusion with time/place and poor judgment etc. In United States, it is presently reported one individual diagnosed with Alzheimer in every 33 seconds accounting nearly 1 million AD cases per year [1,2]. With the record of 121404 people dead in 2017 caused by the disease [3], AD was officially listed as sixth-leading cause of death in this country since many years [3,4]. According to the report in 2015, the cost for the care of affected individuals by AD and other dementia's exceeded $221 billion dollars [5], which is further increased by 69 billion dollars (~$290) in 2019 [3]. On the other hand, number of individuals with AD is increasing faster. According to the latest report by Alzheimer's association (2021), more than 6 million Americans of all ages have been diagnosed with AD. In 2021, 6.2 million Americans with the age of 65 years and older were found to be living with dementia accompanied with AD, of which 72% were at the age of 75 or older [6]. Accordingly 1 out of 9 Americans at the age of 65 years and older (11.3%) have Alzheimer's dementia and the two-thirds of the AD patients are women [6]. As the disease largely affects general public health as well as global economy, there is an urgent need of finding a solution. The last few decades of research have largely increased understanding the pathophysiology of AD; however, due to highly complex nature of the disease, an appropriate drug to cure or slow down the disease could not be available until now which leads to greater challenge for the scientists. To overcome these challenges, deeper understanding of the operating molecular mechanism underlying the disease and to find a drug target for cure or slow down through those molecular players, are necessary.

2. Dynamic role of Aβ in AD

The deposition of neuritic plaques (Aβ aggregates) and neurofibrilary tangles (filamentous hyperphosphorylated tau protein aggregates) in the brain of AD patients are two hallmark discoveries in AD [7,8]; and considered as well established molecular markers for diagnosis of the disease [9,10]. While the extracellular deposition of Aβ and tau

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largely defined neuropathological conditions of AD, very little is understood about their direct influence on the progressive cognitive declination and neurodegeneration of AD and moreover, they are found with the dead neurons at the late stage of the disease. This may be the reason why the drugs designed for decreasing the Aβ aggregate have not been successful in the clinical trials. On the other hand development of new biomarkers and imaging techniques revealed that the Aβ and tau deposition have occurred a decade or more prior to the clinical diagnosis of dementia [11]. It directs to the belief that synaptic loss, plasticity changes, neural loss, and the presence of microscopic Aβ and even tau, may contribute to progressive neural system dysfunction over the decades [11]. To cite a few, intranuronal accumulation of Aβ within pyramidal neurons inducing neuronal and synaptic dysfunction [12] and it may alter cellular metabolism inducing conformational and phosphorylation-specific changes of tau protein in AD (Oddo et al., [13]; besides, extracellular association of APP and tau fibrils affecting intracellular tau aggregates [14] have been evidenced. Cleavage and phosphorylation of tau, which are crucial for neurofibrillary tangle formation, may also be controlled by soluble Aβ as phosphorylation of tau is regulated by several kinases, including GSK3β and cdk5, both of which are activated by extracellular Aβ [15,16,17,18,19,20]. In addition, controversy on relative toxicities between intracellular and extracellular Aβ cannot be rule out, because intracellular injection of Aβ42 but not Aβ40 also killed neurons and intracellular Aβ is seen early in AD [21]. It has been well documented that apoptosis leads to dead of neurons in neurodegenerative diseases including Alzheimer's and Huntington's disease [22,23,24,25]. Besides, intracellular Aβ-42 induces neuronal apoptosis but not extracellular soluble Aβ peptides [26]. Now a day, clinical trials for AD in human approach the therapies on Aβ production, tau aggregation, oxidation, and inflammation (http://www.alz.org/trialmatch) which shows promising [27]. Considering these developments, thoughtful approaches towards finding molecular targets linking Aβ deposition, could be the promising solution in the treatment and early detection of AD.

3. Conclusion

Alzheimer's disease is a life threatening disease caused by progressive degeneration of neurons. It is one of the most leading causes of death. It affects both the human health as well as the economy. However, underlying mechanism or pathophysiology is still unclear and thereby no treatment or medication for cure or reversing the disease is available. Abnormal Aβ deposition in brain is one of the most common symptoms and diagnostic criteria of Alzheimer's disease. Several lines of study reports have evidenced the association of Aβ accumulation in the brain with the loss of neuron functions. Therefore, further deeper research in finding the molecular pathways linking to Aβ accumulation and the loss of neuronal function is essential. This can help in finding the appropriate therapeutic target site for Alzheimer disease.

Compliance with ethical standards

Disclosure of conflict of interest

Authors declare no conflict of interest.

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