

Alzheimer's Disease and Immune Response: A Brief Overview

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Abstract

Alzheimer disease (AD) is a chronic neurodegenerative disease, which it occurs degeneration of the neurons. The early symptom of AD is short-term memory loss and in chronic, it is characterized by language problems, insidious in onset problems, impairment of activities, mood swings, loss of motivation, hoarding, not managing self-care and behavioral issues. AD is neuropathologically characterized by amyloid beta plaques surrounded by neurons containing neurofibrillary tangles in the brain. The molecules of amyloid beta become toxic to the area, and they are flagged by the body to be cleared. Immune cells as Microglia, Astrocytes and neurons are liable for inflammatory reaction that activate and produce inflammatory mediators to clear cellular debris from the damage area. However, these clearing processes are triggered by the different immunological processes, which can provide through immunotherapeutic approach. The purpose of this review article is to brief cellular neuroimmunological aspects of AD, describes advances in the use of immunotherapy for treatment of AD and highlights ongoing efforts to develop novel therapies.

Keywords: Alzheimer's disease; Immune cells; Immunotherapy; Inflammation

Introduction

Alzheimer disease (AD) is a chronic neurodegeneration disease, which it occurs degeneration of the neurons. 60% to 70% of cases of dementia are caused by AD [1]. The early symptom of AD is short-term memory loss and in chronic, it is characterized by language problems, insidious in onset problems, impairment of activities, mood swings, loss of motivation, hoarding, not managing self-care and behavioral issues. Finally, bodies' functions are lost and leading to death. It is mostly occurred in people over 65 years of age [2]. AD is neuropathologically characterized by amyloid beta plaques surrounded by neurons containing neurofibrillary tangles in the brain [3]. Formative event in AD, production of Amyloid beta is the result of cleavage of amyloid precursor protein (APP) which amyloid beta is high in AD [4]. APP plays important role in developmental processes in cell differentiation and establishment of synapses [5] whereas the function of APP is not clear properly in adult brain [4]. Tau protein is an integral part of microtubules in healthy neurons and support to nutrients, vesicles, mitochondria and chromosomes. The hyperphosphorylation of the tau protein results into formation of neurofibrillary tangles which aggregates intracellularly and cause neuronal death [6]. Inflammation is clearly seen in pathologically vulnerable region of the AD brain [7]. Immune cells as Microglia, astrocytes and neurons are liable for inflammatory reaction that activate and produce inflammatory mediators to clear cellular debris from the damage area [8]. The purpose of this review article is to brief introduction about Alzheimer disease and the related concept of immune response. The article emphasizes cellular neuroimmunological aspects of AD. In addition, the article describes advances in the use of immunotherapy for treatment of AD and highlights ongoing efforts to develop novel therapies.

Role of Immune System in AD

The immune system is capable of recognizing the proteins that aggregate in the brain in AD. Immune system is responded two different complementary forms of activation-innate and adaptive. Neurodegeneration is caused by immune reactions in AD that amyloid plaques are often surrounded by microglial cells [9]. Amyloid beta monomer treats as normal by immune system with no response but after aggregation large amount of polymers as isomers confuse the

immune system, which it responds like as foreign particle and activates immune cells as well as mass inflammation [10]. In the AD, occurred increasing the filtration of blood derived microglial cells, which could be good therapeutic approach for preventing the formation of beta amyloid deposits [11].

Microglia is constituted approximately 10% of the cells in nervous system and they are the first line of defense against the foreign particles or any injury in brain. In the pathological condition, these cells become activate, migrate and surround damaged cells to clear the cellular debris from the damaged area [12]. The activation of the microglial cells is directly dependent on the amount of amyloid proteins and precursor protein APP [13] and may be activated by neurodegeneration rather than amyloid protein deposition [14].

Astrocytes is important for the clearance and degradation of the amyloid beta, they provide trophic support to neurons and form the protective barrier between amyloid beta. The association of the astrocytes and amyloid beta protein in AD creates lesions, which generate the chemotactic molecules that mediate recruitment of the astrocytes [15].

Complement system is activated by inflammation and cell damage and it essentials for the eliminating the cell debris and potentially aggregates toxic proteins for destroying the damage cells [16]. Without the presence of antibody, amyloid beta peptides can activate the complement pathway because in addition they can produce complement components (C1q) which is mainly localized in neurons [17]. Due to changes in receptor expression, enhanced activation of different complement pathways, imbalance complement factors levels, and complement cascade inhibitors may all contribute to dysregulate the

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Therapy	Targets on AD	Results
Cholinesterase Inhibitors (Donepezil, Galantamine, Rivastigmine)	Prevent breakdown of acetyl choline in the brain	Cognitive symptom progression shown slow but does not seem to slow disease progression [24].
NMDA Receptor Antagonist (Memantine)	Regulate glutamate activity and NMDA receptor activity	Cognitive symptom progression shown slow but doesn't seem to slow disease progression [25].
Melatonin Treatment	Inhibit Aβ aggregation	Greatly help sleep disorders and symptoms of sun-downing and to slow cognitive impairment [26].
THC Treatment	Block Aβ production, Disrupt Aβ plaque formation by binding to Aβ	Effects may be similar to melatonin and caffeine; studied little on animal models or humans
Caffeine Treatment	Blocks β-and γ-secretases forming Aβ monomers	Shown to help reduce cognitive impairment in the mouse model [27].
Young Lymphocyte Infusion	Young blood shown to change the molecular, structure and cognitive function of older mice	Young blood seen to reverse effects of aging in brain of mice [28].
Free Radical Scavengers and Anti-inflammatory Drugs	Oxidative stress and free radicals in the AD brain	Some improvement in terms of Aβ deposition, inflammation and symptoms [29].

Table 1: Summary of available therapeutics targets of Alzheimer's disease.

Complement components	Function	Complement components presence in AD's brain [30].
C1q	Binding to Ag-Ab complex and pathogen surface	Plaques, tangles, neuropil threads, dystrophic neurites
C3d	Membrane binding proteins and Oponins	Plaques, tangles, neuropil threads, dystrophic neuritis, diffuse deposits.
C4d	Membrane binding proteins and Oponins	Plaques, tangles, neuropil threads, dystrophic neuritis, diffuse deposits.
C7	Membrane attack protein	Plaques, tangles, neuropil threads, dystrophic neurites.
C9	Membrane attack protein	Plaques, tangles, neuropil threads, dystrophic neurites.
C5b-9	Membrane attack protein	Tangles, neuropil threads, dystrophic neurites.

Table2: Summary of potential therapeutics in future based on complement system.

complement system in AD [18]. There are many possible approaches which can Neurons can generate the inflammatory molecules and can serve as source of complement systems and others. Many cytokines produce by neurons or glia, moreover, cytokines are secreted by variety of immune cells, the level of cytokines fluctuate in AD brain. The numbers of interactions are reported between cytokines and the components of the AD [4].

Neuroinflammation in AD is served to aggravate AD and is promoted the progression of disease. Plaques and peptides of Amyloid Beta are greatly cytotoxic which trigger chronic inflammation in the brain cells and they are responsible to the infiltration of macrophages within the brain. After activation of macrophages, it releases pro-inflammatory cytokines, which further promote the neurotoxicity and apoptosis in brain cells [19].

Microglial activation is inducted by pro-inflammatory molecules and related signaling pathways that leading to Aβ aggregation, tau formation, synaptic damage, neuronal loss and the activation of other inflammatory participants. Pro-inflammatory cytokines may have multiple roles both neurodegeneration and neuroprotection. It is difficult to know the precise role of pro-inflammatory cytokines in AD [20].

Immunotherapeutic Approach

Various immunotherapeutic approaches for AD are under research process. Synthetic Aβ42 evaluated in transgenic mice models with direct immunization and this evaluation has been provided the Aβ immunotherapy that stimulates the T-cells, B-cells and microglial immune responses. With active immunization administrated of synthetic fragment of Aβ conjugated to a carrier protein that responds the T-cell directly against antibodies. Last approach is passive administration with monoclonal antibodies directed against Aβ which under investigation. Other mechanisms like as plaque breakdown, peripheral sink and aggregation sink are trying as new immunotherapy of AD [21]. Active immunizations developed with minimize T-cell reaction and maximize antibody production but passive immunizations

are being devised [22]. Various therapeutic approaches and their results are mentioned briefly in Table 1.

Many studies have shown that broad amyloid and tau pathologies are already present at mild impairment stage of AD [23]. Some research articles indicated that the microglial activity could be manipulated by the complement factors towards protective or harmful [18]. Various research groups tried to show the role of complement system in Alzheimer's disease and also trying to find out the suitable therapeutic approaches targeting complement system as mentioned in Table 2.

Conclusion

Previous studies by various research groups have suggested that the inflammation is the significant cause of the pathogenesis of the AD. Proinflammatory mediator's secretions and generation may contribute to multiple levels of the neurodegeneration. Many research papers have reported that the complement system in brain is activated due to AD. The amyloid beta proteins can activate the complement pathways without antibodies because in addition they can produce complement components. In future studies need to determine the complement system's components contribution in AD and these components may use to immunotherapeutic approach in future.

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