THE ROLE OF INFLAMMATORY MEDIATORS IN ALZHEIMER'S DISEASE AND THE POTENTIAL FOR TARGETING THE IMMUNE SYSTEM FOR DISEASE TREATMENT

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Alzheimer's disease is the most common age related neurodegenerative disorder the main clinical feature is gradual loss of memory[1]. Synaptic degradation, loss of neurons, neurofibrillary tangles and senile plagues are the neuropathological hallmarks of Alzheimer's disease. Senile plagues are formed of amyloid-β neurotoxic protein (Aβ), which derived from amyloid precursor protein (APP), Accumulation and deposition of amyloid-β protein in the brain is seen as the primary factor in the pathogenesis of Alzheimer's disease[2]. Amyloid-β protein deposits extracellular in senile plaques while paired helical filaments (PHFs) and hyper-phosphorylated tau protein accumulate abnormally in neurofibrillary tangles, neuropil threads and dystrophic neuritis[1,3]. Also formations of neurofibrillary tangles by hyper-phosphorylated tau constitute the primary neuropathological features of Alzheimer disease[4].

Amyloid β is a normal soluble metabolite protein of around 4-kDa produced by processing a large transmembrane glycoprotein, APP, by β- and γ-secretase[5]. Platelets are also considered as main source of amyloid-β in the circulatory system[6]. The main component of Aβ plaques is continuously producing in brains of normal people and patients with AD. Normally, Aβ-associated proteins have been involved in the Aβ amyloidogenic process regulation. However, in Alzheimer's disease brains there seem to be an imbalance between those Aβ-associated proteins that stimulate fibril formation and deposition and those Aβ-associated proteins that prevent it[7].

Aβ plaques are formed from the accumulation and precipitation of secreted Aβ in extracellular space. This perspective suggests that Aβ deposition is a result of production higher than clearance mechanisms by a small amount, and the excess becomes converted to a more stable form that deposits and builds up in a time-dependent manner[8]. This review will discuss the role of inflammatory components in Alzheimer's disease with reference to microglia, astrocytes, complement proteins, and cytokines. Then, it will illustrate the possibilities of targeting the immune system for the disease treatment.

The role of inflammatory mediators in Alzheimer's disease

Microglia and astrocytes, the complement system, cytokines and chemokines are inflammatory components related to AD neuroinflammation[9]. In addition, aggregation of activated microglia and complement factors, leukocytes and astrocytes are increased in brain affected areas which strongly suggests the presence of an ongoing inflammatory process[10]. Microglia represents the first line immune cells against invading pathogens or other types of brain tissue injury. They compose about 10% of the cells in the nervous system[11]. Pathological conditions, like traumatic injury, neurodegenerative disease or tumour, have affected on microglia to become activated, migrated, and surround damaged or dead cells[12]. Amyloid-β plaques and tangles enhance inflammatory reaction to clear this debris[13]. These plaques compose of reactive astrocytes, dystrophic neuritis and activated microglia[14,15]. Long-term activated microglia secrete inflammatory mediators such as Cytokines and chemokines, TNF-α, IL-6 and Complement proteins and amyloid fibrils[16,17]. Moreover, activated microglia can destroy surrounding normal neurons by releasing highly toxic products such as nitric oxide (NO), proteolytic enzymes, reactive oxygen intermediates, complementary factors or excitatory amino acids[18]. However, in some situation the function of microglia has established to be beneficial. Activated microglia can minimize amyloid β aggregation by increasing its phagocytosis, degradation, and clearance[19, 20].

Amyloid β also induce astrocytes to activate and secrete different pro-inflammatory mediators such as leukotrienes, prostaglandins, complement factors, chemokines, ROS and NOS-mRNA that may result in neuronal damage[21,22]. Another study showed that high levels of nitrous oxide synthase (NOS)-positive astrocytes in the AD brains compared to controls which suggest increased production of nitrous oxide in the AD brain[23]. The astrocytes tendency to produce pro-inflammatory molecules is thought to enhance and accelerate the progression of AD[24].

Astrocytes can express all the complements of classical pathway and alternative pathway like C1-C9, many complement receptors such as C1qR, C3aR and C3aR and regulatory factors B, D, H, I[25,26]. The classical pathway activation can be achieved by interaction between C1q and serum amyloid protein[27, 28]. Complement system activation causes inflammation, and cell degradation and damage[29].

Inflammatory mediators may stimulate amyloid precursor protein processes and lead to establish a vicious cycle that could be essential in the pathological progression of AD[30]. APP synthesis and Aβ

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production in vitro can be regulated by interleukin-1 with other cytokines[31]. In vivo Il-1 induced production may initiate a vicious circle whereby Aβ deposition stimulates microglia activation to produce further cytokine[32].

Possibilities for targeting the immune system for the disease treatment

The immune system appears to participate in AD pathogenesis. Down-regulation of immune system associated with aging may blunt the immune response to Aβ[33]. Long-term exposure of humans and mouse models immune system to Aβ might lead to hypo responsiveness in terms of cellular and humoral immune responses to Aβ itself, which could contribute to the disease process[34].

Moir and his colleagues have measured the titer of anti-Aβ 42 antibodies in serum from individuals with and without late onset AD by using an ELISA[35]. They illustrated that IgG titer of anti-Aβ 42 peptide antibodies was considerably higher in serum from elderly controls than from AD patients. However, the low titer of anti-Aβ 42 antibodies in AD patients does not reflect the well-established, age-associated defect in the antibody response to most protein antigens. The lower titer of serum anti-Aβ 42 peptide antibodies in AD patients may reflect specific impairment of helper T-cell activity for B cells that produce anti-Aβ 42 peptide antibodies[36]. Also a study of by Du and his colleagues, states that the plasma level of anti- Aβ antibodies that bind to accumulated Aβ were extensively lower in AD patients than in healthy controls, while there was no difference in anti-Aβ antibodies binding to Aβ monomers[37]. Therefore, natural antibodies to aggregated Aβ may have great importance against AD pathology[37].

The conception of immunological treatment of AD becomes a therapeutic approach to enhance brain Aβ plaques clearance[38]. Different active and passive immunizations are providing significant therapeutic benefits in transgenic mouse models of AD by targeting beta-amyloid plaques[38].

Active immunization approaches

Schenk and his colleagues have shown that the transgenic mice over-expressing mutant human amyloid precursor protein V717F (PDAPP mice)[39]. Gradually develop several neuropathological sings of Alzheimer's disease in time dependent manner. The transgenic mice were treated with full-length Aβ1-42, either before the onset of AD or at an older age[39]. They reported that immunization of transgenic mice leads to produce high serum antibody titers against Aβ 42 which inhibit amyloid plaques formation and markedly reduce the extent and progression of these AD-like neuropathologies[40]. Weiner and hiss flowers (2000) have found that PDAPP mice who treated with nasal mucosal administration of human Aβ 1-40 peptide results in reduced Aβ aggregation and deposition in the brain by a 52% and consequently decrease astrocytosis, microgliosis and neuritc dystrophy. This action was specifically related with an anti-Aβ antibody response and with expression of IL-4, IL-10, TGFβ[40]. Transgenic mice that carrying the human amyloid precursor protein, familial AD (hAPPFAD) were immunized with antigen based on Aβ 1-15. The result shows high serum level of anti-Aβ titers, specifically isotypes (IgG1 and IgG2b). These isotypes markedly decreased Aβ plaque and reduced Aβ level. Moreover, compared with mice controls the memory of immunized hAPPFAD mice was improved[40].

Passive immunization approaches

Passive immunization requires administrating anti-Aβ antibodies frequently in order to keep steady state levels of the antibody[40]. They act either directly within the CNS or periphery to provide a therapeutic benefit[41]. Such antibodies have a limit amount access to the brain, since only 0.1% of an intravenous antibody dose can pass through the blood-brain barrier into the brain[41]. In old mice the peripherally administrated antibodies were able to induce clearance of pre-existing amyloid and change plaques shape, whereas in young mice the passive route antibodies prevent plaque formation[42]. Passive immunization of antibodies against Aβ peptide decreased the extent of amyloid burden in the brain of PDAPP Tg mice[43]. These experiments illustrate that although monoclonal antibodies have limited access to the CNS, they may be considered not only for the treatment of Alzheimer disease, but possibly for other CNS disorders as well[43].

In conclusion, Alzheimer's disease is the most neurodegenerative disorder causing dementia and loss of neurons. Amyloid-β protein accumulates abnormally and form plagues which are the main feature of AD. Microglia and astrocytes represent the defence line in the brain. Under certain pathological situations such as Alzheimer's disease these cells become active and release different inflammatory mediators. Inflammatory mediators like complement proteins and cytokines stimulate cell damage and consequently accelerate the AD progression. Increasing evidence has supported that Immune system participates in AD pathogenesis. Therefore, targeting the immune system is the main approach for the disease treatment. Active immunization leads to the production of serum antibodies against amyloid proteins. Passive immunization with anti-Aβ antibodies is another alternative therapeutic goal to decorate plagues and induce clearance of pre existing amyloid.

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