The role of microglia in Alzheimer's Disorder

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Abstract. Alzheimer's disease (AD) is a neurodegenerative disorder with insidious onset and gradual development. Its symptoms include loss of memories, impaired language, reduced spatial perception, mood swings, and reduced ability to perform calculations and abstract thinking. AD is the most common type of dementia in the aged. Around the globe, more than 40 million people suffer from AD, and the number continues to rise. At present, there are many hypotheses about the pathogenesis of Alzheimer's disease, but the specific pathogenesis is not clear. Currently, due to unclear pathogenesis, this disease has no specific treatment methods, mainly symptomatic treatment and supportive treatment. Nowadays, most of the treatments being studied focus on reducing levels of neurotoxic Aβ and Tau. However, these therapeutic targets appear to be secondary and not causally related to the development of AD. Microglia, as one of the most significant immune cells in the central nervous system (CNS) has shown considerable clinical efficacy against neurodegenerative diseases. Furthermore, one of the causes of AD progression also includes neuroinflammation mediated by malfunctioning microglia cells. Microglia may exhibit great therapeutic benefits in treating AD. There are currently three approaches to ameliorate pathological changes in AD patients through microglia: modifying microglia to reduce neurological damage caused by dysfunction, targeting microglia immune receptors to improve their immune response, and targeting microglia-mediated inflammatory response to reduce inflammatory damage.

Keywords: Alzheimer's disease; Microglia; Treatment.

1. Introduction

Alzheimer disease (AD) is a neurodegenerative disease that is connected with deposition of tau and amyloid in the brain [1]. Specific causes of AD are not clear, existed hypotheses are genetic hypothesis, vascular pathway hypothesis, psychological hypothesis, etc [2]. Its features include gradual cognitive and functional disability, behavioral disorder and psychiatric symptoms, difficulties in carrying out daily activities [3].

Age is one of the most essential risk factors of AD, it has a prevalence that grows exponentially from 3 to 32% between 65 and 85 years old. Despite those uncertainties for AD, some known risk factors exist, such as insulin-resistant diabetes mellitus and repeated head trauma including concussions, they may increase the possibility of developing AD. Inheritance contributes to the formation of AD, —first degree relatives of those who have AD are likely to have 10-40% higher risk than unrelated people [3].

At present, more than 25 million people who have dementia are mostly influenced by AD. Based on the estimates, about 4.0% of people aged 60+ have dementia, with the prevalences of around 4.0% in China and the Western Pacific, around 2% in Africa, around 5% in Western Europeand Latin America, and about 6% in North America. Every year, there will be about 5 million new cases appeared. Currently, dementia is prioritized by WHO as a public health issue.

Pre-dementia, mild dementia, moderate dementia and severe dementia stages are the four phases of AD's dementia. During pre-dementia and mild dementia stage, patients may not be capable of acquiring new information, they mainly perform symptoms like aphasic and visual deficits, but patients can mostly live by themselves. In moderate and severe dementia stages, patients seem to live

in memories form the past. Abilities of reasoning with logic, organizing and planning drastically degrade. Eventually they can lose early biographical memories and may only be able to speak in simple phrases or even single words. Patients will need support since their bodies' basic functions may be in extreme apraxia. Expect dementia, there are also numerous symptoms of AD that may differ from man to man. Anxiety, irritability and mild to moderate depressive symptoms may occur in the early phrase of AD. In later stages, the common symptoms may be presented as disinhibition, disturbances of sleep and appetite, etc.

The target of existing therapies is to slow down the progression of AD instead of curing completely. Symptomatic and disease-modifying therapies (DMTs) are the two categories of pharmacotherapeutic approaches to AD. Since up to 90% of dementia patients have experienced symptoms such as cognitive impairment, anxiety, psychosis and sleep disturbance, symptomatic treatment has a great impact on these symptoms. The amyloid cascade hypothesis and tau-based therapies have received the majority of attention in the seeking for DMTs [4]. The primary cause of AD is β-amyloid peptide (Aβ) accumulation according to amyloid cascade hypothesis, followed by a number of post-stage pathological cascades including inflammatory responses, neuronal loss, and neurofibrillary tangle formation [5]. For tau-based therapy, the failure of trial targeting amyloid may be explained by the evidence of neurodegeneration connected with normal amyloid levels, axonal injury, and tau lesions within late myelinating regions.

Since AD is featured by the accumulation of Aβ and tau protein, and the gradual decline of neurons lead to dementia, a cell is found useful for AD—microglia cell. Microglia have a vital role in the regulation of human brain's advanced cognitive functions and the development of CNS. In order to provide researchers with the newest progress of research of microglia's effect in AD, this paper has been divided into three parts, summarizing the relationship between microglia and AD and therapies targeting microglia to treat AD.

2. The relationship between Microglia cells and Alzheimer's disease

Microglia are very important cells in human brains derived from progenitors within the yolk sac and it is an important defense of the CNS. Microglia cells are highly active in a healthy brain, constantly on the move, investigating brain parenchyma. They are activated in response to inflammation or injury and their activation occurs in any pathological lesion of the brain. However, previous studies have revealed that there are two types of activation states of microglia cells noted as M1and M2 [6]. In general, M1 is a pro-inflammatory state, which primarily induces nitric oxide synthase 2 (iNOS/NOS2) through up-regulation of interferon-γ and bacterial cell wall components, thus producing nitric oxide and inflammatory cytokines. By contrast, M2 is an anti-inflammatory state, which can relieve neuroinflammatory response by releasing anti-inflammatory factors such as IL-4 and IL-13, which has a general neuroprotective effect [7].

AD is associated with Aβ accumulation, Tau-like protein phosphorylation, neurofibrillary tangles formation and neuroinflammation [8]. A previous study showed that Aβ and Tau proteins can activate microglia. Microglia differentiated into different phenotypes near Aβ deposits and increased inflammatory expression. Also, transfer of tau-like proteins can take place through synapses in microglia, as well as through phagocytosis and secretion in microglia [9]. In addition, aging is one of the related determinants of AD. Another study showed that microglia cells in older brains are more likely to activate and release inflammatory cytokines [10]. Moreover, previous studies have shown that cognitive problems in humans are independent of Aβ and Tau during the course of AD, but decreased protrusion and branching of microglia cells and increased pro-inflammatory factors expression may cause a gradual decline in cognitive ability [11]. However, as mentioned earlier, microglia have a two-sided role in the AD process. One is that it can promote AB clearance, and the other is that its overactivation can lead to the release of more inflammatory mediators, causing damage to nerves. Therefore, preventing the overactivation of microglia and utilizing the protective effect of microglia may become an important therapy for AD.

3. The microglia therapies

In recent years, various experiments on the management and treatment of AD have been performed. However, only a few can be applied to clinical treatment and mostly fail to have discernible effect on the development of the illness or symptoms when used singly. Healthy microglia help to guard against the onset of AD, while dysfunctional microglia can worsen the disease. Therefore, developing therapies targeting microglia in the direction of reducing neuroinflammation to treat AD is feasible and expected.

3.1. Modifying microglia

Current observations show that early microglial activation has neuroprotective effects by regulating Aβ clearance and maintaining tissue homeostasis, while late excessive activations of microglia will damage the synapses, secrete neurotoxic cytokines, and promote the spread of Tau pathology, which lead to intensification of neuroinflammation and deterioration of AD symptoms. Thus, supplementation of healthy microglia or removal of dysfunctional microglia may be used to reduce neurological damage caused by dysfunction.

3.1.1 Practical Examples & Efficacy

1) CSF-1R Inhibitors

CSF-1R receptor is primarily expressed on cell membranes of microglia in CNS and is crucial for development, steady-state maintenance, proliferation, and survival. In order to remove malfunctioning microglia with precision, chronic continuous infusion of CSF-1R inhibitors may be a useful and non-invasive technique. Animal models, preclinical research, and clinical trials have all been used to evaluate a number of CSF-1R inhibitors, such as PLX3397 (Pexidartinib) and PLX5622. In a study utilizing five-month-old 5XFAD mice, after PLX3397 treatment, the number of microglia decreased to 20-30% and almost completely eliminated (99%) the area occupied by microglia [12]. Meanwhile, in 5XFAD transgenic rodent models, PLX3397 treatment reduced syptoms and pathology in AD-affected brain regions [13]. In addition to PLX3397, after PLX5622 blocked the CSF-1R, there was also less overall plaque load [14], and PLX5622 also demonstrated adequate oral bioavailability and brain penetration.

2) Stem Cell Therapy

In addition to possibly improving AD pathogenesis, repopulating healthy microglia has the ability to treat dysfunctional microglia in AD patients. Considering the potential of stem cells to differentiate into other cell types, massive proliferation of functional microglia can be achieved. In fact, many microglial cells have already been created through this method. These microglial cells from stem cells also have effective phagocytosis and respond quickly to noxious stimuli. In vivo and in vitro experiments, the regenerated microglia showed effective protection of the nervous system, reducing symptoms, and pathology [15,16].

3.1.2 Limitations & challenges

1) CSF-1R Inhibitors

It is important to carefully examine any possible negative effects of CSF-1R inhibitor therapy, especially during organogenesis and neurodevelopment.

2) Stem Cell Therapy

Several restrictions should be taken into account, such as the absence of an adaptive immune system, the variable grafting efficacy of pluripotent stem cells.

3.2. Targeting microglia immunoreceptors

In the early stage of AD, microglia can control the progression of AD by phagocytosing Aβ clumps, releasing cytokines to maintain nervous system stability. However, in the late stage of AD, the overactivated microglia appear dysfunctional, and the immune response mediated by them instead damages the neuronal synapses and accelerates the cognitive, language, and memory functions of

patients. Several studies have shown that by targeting certain immune receptors, the effects of their downstream-mediated immune response beneficial to AD treatment can be enhanced, producing obvious therapeutic effects.

3.2.1 Practical Examples & Efficacy

1) Targeting TREM2 Gene

A lot of research has been done on TREM2 and CD33 because of their significance as important AD risk factors. TREM2 has been shown to be crucial for the microglia's reaction to Aβ. A number of TREM2 agonistic antibodies induced increased microglial responses to Aβ and improved Aβ pathology to exercise their neuroprotective effects. A study shows either by intracranial, intraperitoneal or systemic administration, antibody AL002a was able to cause immune responses, activate microglia, reduce the formation and deposition of amyloid protein, and ultimately improved cognitive function [17]. In a different study, mice given AL002c showed neither an increase in microglia clumping near Aβ plaques nor a decrease in the overall Aβ load. The rapid accumulation of Aβ seen in the 5XFAD model may be too much for AL002c-mediated activation of microglia to handle [18]. However, AL002c was enough to lessen the toxicity of Aβ plaque and to lessen neuritic dystrophy, one of the key pathological traits connected to AD and age-dependent neuronal failure.

2) Targeting CD33 Gene

It is conceivable that the sialic acid-binding domain of Aβ might be the target of CD33-mediated reduction of Aβ phagocytosis given that CD33 gene polymorphisms are linked to the development of AD. As a result, therapeutic approaches targeting the sialic acid-binding domain may be potential therapies for AD. The new sialic acid mimic P22 is subtype-selective, which increases Aβ phagocytosis by P22-ligand-carrying microparticles based on CD33-dependence. Moreover, some kinds of CD33 antibodies might protect against the neurotoxic effects of CD33. In mouse models of AD, CD33 knockout decreased FA-soluble A42 levels and the burden of amyloid plaques, slowed neurodegeneration, and enhanced cognition [19].

3.2.2 Limitations & challenges

1) Targeting TREM2 Gene

Clinical characteristics and laboratory findings of AD patients show that, it is still difficult to enhance TREM2 expression locally without triggering the potentially dangerous immune evasion and tumor development that can occur when TREM2-expressing macrophages are activated in other organs. Bexarotene and other drugs that increase TREM2 expression have led to negative effects in mouse models, including weight loss, hepatomegaly, and respiratory problems [20,21]. These findings imply that additional research is needed into medicinal medicines that target TREM2.

2) Targeting CD33 Gene

Careful patient selection may be necessary in some situations (based, for example, based on the CD33 risk allele for AD). Also, it's thought that before anti-CD33 antibody advantages could be examined in clinical studies for AD, antibody conjugates would need to be improved.

3.3. Targeting microglia-mediated inflammatory response

Microglia play an important immune function in the CNS. Under normal circumstances, the microglia-mediated inflammatory response is well able to remove pathogenic substances from the brain and retain the healthy structure and function of CNS. However, in the CNS of AD patients, the microglial-mediated immune response is excessive and destructive, which also promotes the deterioration of patient pathology and symptoms. By regulating microglia, the inflammatory response mediated by them can be improved, and AD patients can be treated.

3.3.1 Practical Examples & Efficacy

1) Non-Steroidal Anti-Inflammatory Drugs

At present, many research have focused on non-steroidal anti-inflammatory drugs (NSAIDs). In various experimental observations, these drugs have demonstrated the ability to mediate some

neuroprotective properties. For example, PPARγ is connected to this ability. PPARγ is able to suppress inflammatory factors after being activated by NSAIDs, contributing to the regulation of transcription. Until now, the results are complex. However, it seems that long-term use of NSAIDs may be effective to the pathogenesis of AD. In vivo and in vitro, for instance, decreases the levels of pro-inflammatory cytokines, Aβ plaque load and microglial activation.

2) NLRP3 Inflammasome Inhibitors

NLRP3 is an inflammasome that acts on microglia and is a risk factor for AD. Inflammatory response of microglia can be decreased by inhibiting the NLRP3 inflammasome [14]. Many preclinical studies have provided positive support for the effectiveness of various inhibitors targeting NLRP3 inflammasome [15,16]. Minocycline may reduce microglia activation and Aβ accumulation by inhibiting NLRP3 inflammasome. However, numerous clinical analyses have demonstrated that it does not prevent people with AD from developing cognitive impairment.

3) P2X7R Inhibitors

P2X7R effectively activates the NLRP3 inflammasome and promotes inflammation, which is detrimental to the progression of AD pathology. As a result, inhibiting P2X7R can be used to reduce the inflammatory response of microglia cells. In vitro microglia cells and AD mouse models have verified these findings [22,23]. Brilliant blue G, a kind of P2X7R inhibitor, has been shown to diminish microglial proliferation and counteract the induced inflammatory response in a prior study utilizing mouse models of AD.

3.3.2 Limitations & challenges

1) Non-Steroidal Anti-Inflammatory Drugs

Most of the studies were relatively short in duration and involved people with symptoms who had already been diagnosed with AD. It is commonly acknowledged that processes of inflammatory contribute to the development of AD, future clinical trials may need to evaluate the preventive effects of anti-inflammatory drugs.

2) NLRP3 Inflammasome Inhibitors

Future drugs that can be put into clinical application for the treatment of AD and other neurodegenerative disease still need more experimental data support.

3) P2X7R Inhibitors

Although P2X7R antagonists have shown promising results in animal and cellular studies, they have not been included in clinical studies.

4. Conclusion

This research paper showed an overview of the relationship between microglia and Alzheimer's Disorder (AD), decreased branching and protrusion of microglia cells may lead to cognitive disability. Microglia increase inflammatory expression, and they can transfer tau-like proteins; they are more likely release inflammatory cytokines in the brains of elderly. Furthermore, the suggested microglia therapies are categorized into three sections. Firstly, modifying microglia performs good oral bioavailability and brain-penetration activities, it could also improve memory lesions and relating neuropathology. Secondly, targeting microglia immunoreceptors reduces amyloid deposition and improves cognition, attenuating neurodegeneration. Thirdly, targeting microglia-mediated inflammatory response may result in reduction in the levels of microglial activation, proinflammatory cytokines and Aβ accumulation. Nonetheless, the effect of microglia on AD is two-sided. It might promote AB clearance, causing the release of more inflammatory mediators and damage to nerves. There are also numerous limitations in these treatments using microglia, they may include unknown side effects or lack of adaptivity in human bodies; they may contain toxic components or lack of suitable patients for testing; they may not be accepted widely or require further experiments to ensure it can be used for clinical treatment. The latest information of the impact and role of microglia in the curing of AD is provided in this review, which helps future researchers to summarize data. Since researchers have limited access of knowledge about the causes and treatments of AD, this article may

be able to enhance their understanding for better and further investigation. However, there are a lot of deficiencies in this review. The dates of some collected information were be published ages ago, which might reduce their credibility. It can be improved by verifying specific dates and selecting from recent reports.Because there are still plenty of uncertainties in the discovery of AD, under the circumstances of insufficient information about AD, patients will have enormous social and financial burdens, leading to decreasing living standards. Hopefully, the cure of AD will be found in the near future and reduces the suffering of patients.

References

[1] Apostolova LG. Alzheimer Disease. Continuum (Minneap Minn). 2016 Apr;22(2 Dementia):419-34.

[2] Qiu C, Kivipelto M, et al. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues Clin Neurosci. 2009;11(2):111-28.

[3] Burns A, Iliffe S. Alzheimer's disease. BMJ. 2009 Feb 5;338:b158.

[4] Pais M, Martinez L, et al. Early diagnosis and treatment of Alzheimer's disease: new definitions and challenges. Braz J Psychiatry. 2020 Aug;42(4):431-441.

[5] McQuade A, Blurton-Jones M. Microglia in Alzheimer's Disease: Exploring How Genetics and Phenotype Influence Risk. J Mol Biol. 2019 Apr 19;431(9):1805-1817.

[6] Hanisch UK, Kettenmann H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. Nat Neurosci. 2007 Nov;10(11):1387-94.

[7] Hu X, Leak RK, et al. Microglial and macrophage polarization—new prospects for brain repair. Nat Rev Neurol. 2015 Jan;11(1):56-64.

[8] Ziegler-Waldkirch S, d'Errico P, et al. Seed-induced Aβ deposition is modulated by microglia under environmental enrichment in a mouse model of Alzheimer's disease. EMBO J. 2018 Jan 17;37(2):167-182.

[9] Sarlus H, Heneka MT. Microglia in Alzheimer's disease. J Clin Invest. 2017 Sep 1;127(9):3240-3249.

[10] Njie EG, Boelen E, et al. Ex vivo cultures of microglia from young and aged rodent brain reveal age-related changes in microglial function. Neurobiol Aging. 2012 Jan;33(1): 195.e1-12.

[11] Feng Z, Gao F. Stem cell challenges in the treatment of neurodegenerative disease. CNS Neurosci Ther. 2012 Feb;18(2):142-8.

[12] Haenseler W, Sansom SN, et al. A Highly Efficient Human Pluripotent Stem Cell Microglia Model Displays a Neuronal-Co-culture-Specific Expression Profile and Inflammatory Response. Stem Cell Reports. 2017 Jun 6;8(6):1727-1742.

[13] Sosna J, Philipp S, et al. Early long-term administration of the CSF1R inhibitor PLX3397 ablates microglia and reduces accumulation of intraneuronal amyloid, neuritic plaque deposition and pre-fibrillar oligomers in 5XFAD mouse model of Alzheimer's disease. Mol Neurodegener. 2018 Mar 1;13(1):11.

[14] Casali BT, MacPherson KP, et al. Microglia depletion rapidly and reversibly alters amyloid pathology by modification of plaque compaction and morphologies. Neurobiol Dis. 2020 Aug;142:104956.

[15] Kim JA, Ha S, et al. Neural stem cell transplantation at critical period improves learning and memory through restoring synaptic impairment in Alzheimer's disease mouse model. Cell Death Dis. 2015 Jun 18;6(6):e1789.

[16] Lee IS, Jung K, et al. Human neural stem cells alleviate Alzheimer-like pathology in a mouse model. Mol Neurodegener. 2015 Aug 21;10:38.

[17] Price BR, Sudduth TL, et al. Therapeutic Trem2 activation ameliorates amyloid-beta deposition and improves cognition in the 5XFAD model of amyloid deposition. J Neuroinflammation. 2020 Aug 14;17(1):238.

[18] Wang S, Mustafa M, et al. Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. J Exp Med. 2020 Sep 7;217(9):e20200785.

[19] Griciuc A, Serrano-Pozo A, et al. Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. Neuron. 2013 May 22;78(4):631-43.

[20] Tesseur I, Lo AC, et al. Comment on "ApoE-directed therapeutics rapidly clear β-amyloid and reverse deficits in AD mouse models". Science. 2013 May 24;340(6135):924-e.

[21] Tachibana M, Shinohara M, et al. Rescuing effects of RXR agonist bexarotene on aging-related synapse loss depend on neuronal LRP1. Exp Neurol. 2016 Mar;277:1-9.

[22] Wang Y, Cella M, et al. TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease model. Cell. 2015 Mar 12;160(6):1061-71.

[23] Ruganzu JB, Zheng Q, et al. TREM2 overexpression rescues cognitive deficits in APP/PS1 transgenic mice by reducing neuroinflammation via the JAK/STAT/SOCS signaling pathway. Exp Neurol. 2021 Feb;336:113506.