

Dilemma of Glial in Alzheimer's: A Review of the Role of Glial Cells in Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative brain disease worldwide. Though related studies are persistently conducted, the disease pathogenicity is yet to be fully deciphered. Most previous trails ended in failure and an effective treatment is an acute requirement. Current investigations attributed the cause of AD to neuronal cells. Nevertheless, non-neuron (i.e., glial cells) make up a considerable population of whole brain cells in the central nervous system and are highly associative with AD onset and progression. This review summarises some current findings of Alzheimer's in the context of glial, highlighting the multiple functions of microglial cells and astrocytes in AD brains. The discussion was followed by crosstalk of Alzheimer's, blood brain barrier, and glial cells, which broaden our understanding of the complexity and heterogenous dynamic of the disease. Extended studies are needed to further characterise the role of glial cells in neurodegenerative disorders, aiming to develop better therapeutic strategies in the coming years.

Keywords: Neuroscience, Neurodegenerative disorder, Alzheimer's disease, Glial cells.

1. Introduction

1.1. An Overview of Alzheimer's

Alzheimer's disease (AD) is the most prevalent chronic neurodegenerative disorder, accounting for approximately 60-70% of dementia worldwide[1]. Statistics showed that approximately 10% of people aged ≥ 65 years suffered from AD, which rises to 32% among individuals of ≥ 85 years. AD is characterised by phenotypic formation of intracellular tau neurofibrillary tangles (NFTs), extracellular amyloid-beta ($A\beta$ or senile plaques) accumulation, neuroinflammation, neuronal death, synaptic demise, and brain dysfunction[2], which contribute to its common clinical outcomes include cognitive impairment, progressive memory loss, dementia, confusion, dysfunctional thoughts, and personality changes.

Alzheimer's can be classified into two subgroups. Familial AD (FAD), characterised by an early onset, is a rare autosomal dominant genetic disease and accounts for only minor cases of AD. Sporadic AD (SAD), on the other hand, occurs at much later stages between the age of 35 and 50 and caused by mutations of tau protein hyperphosphorylation and amyloid precursor protein.

1.2. Dilemma of the Mechanism behind Alzheimer's

AD has drawn the attention of scientists for decades, yet due to cell heterogeneity and the dynamic of disease, no pharmacologic cure developed today slows or stops the neuronal damage which caused the detrimental effect of Alzheimer's. Among the top 10 fatal diseases, AD is the only disorder with no available treatment. Current therapeutic treatments approved by the U.S. Food and Drug Administration (FDA) include donepezil, galantamine, rivastigmine, tacrine, memantine, and memantine combined with donepezil[3]. Memantine temporarily improved the symptoms through eliciting its effect on certain receptors to impede excess damage to the nerves, while other drugs increase the amount of neurotransmitters in the brain. An effective treatment for early intervention is thus urgently demanded.

Previous findings mainly focused on the amyloid hypothesis, suggesting a linearity of disease progression with accumulation of $A\beta$ and identifying β -amyloid as the main cause of Alzheimer's. The production of $A\beta$ involves a two-step proteolytic process where amyloid precursor protein (APP)

is initially cleaved by β -site APP-cleaving enzyme 1 (BACE1), yielding C99. C99 is then further cleaved by γ -secretase and leads to A β synthesis, followed by the oligomerization of A β monomers to form toxic aggregates, which causes AD. Nevertheless, a study of Gordon et al. implied that a prominent increase of A β levels was noted 22 years before the symptoms of AD were intended to develop. Glucose metabolism started decreasing 18 years prior to supposed symptom onset, and brain atrophy began 13 years ahead. The central nervous system (CNS) therefore sustains homeostasis decades before cognitive impairment turns apparent in later stages of the disorder, which imply the linear model of hypothesis needs to be reconsidered.

1.3. Glial Cells and Alzheimer's

CNS is consisted of neuronal and non-neuronal cells, also known as glial cells. While neurons participate in cognitive functions, their consistent activity mainly depends on the support of glial. Glial cells, occupying most brain cell populations, include astrocytes, microglia, oligodendrocytes, polydendrocytes (NG2 glia), ependymal cells, enteric glial cells, satellite cells, and Schwann cells, which serve to maintain the homeostasis of CNS, proper function of synapses, and the formation of myelin sheaths[4].

Since the first description of Alzheimer's in 1906, most studies recognised AD as neuro-related and neuron have been the subject of research with less characterisation in the context of glial cells. It is now apparent non-neuron and the interactions within different cell types are also crucial factors in neurodegenerative disorders, and an increase in interest towards their pathophysiological function has been noticed. First studied by Dr. Alois Alzheimer, glial cells were found in neuritic plaques[5]. Indeed, a proliferation in abundance of astrogliosis (increased levels of astrocytes), microgliosis, and pro-inflammatory cytokines are observed in clinical Alzheimer's outcomes. In this review, the role of non-neuronal cells, mainly microglia and astrocytes, will be addressed and the correlation between glial cells and AD progression is elucidated. This emphasises the complex circular and parallel pathways involved in Alzheimer's and enhances our understanding of these interactions between and among different cells during AD pathogenesis, which is crucial to developing effective therapeutic interventions for the disorder.

2. Microglial Cells in Alzheimer's

2.1. Neuroprotective Responses in Microglia

Microglial cells are present throughout the brain, spinal cord, retina, and optic nerves, while predominantly locate at the substantia nigra and hippocampus[5]. Activated microglia sever key roles in the innate immune system and are responsible for most proinflammatory molecules causing neuroinflammation during AD onset and progression[6]. Its neuroprotective role has been proposed in 1993 by Dickson et al. where microglia was postulated to eliminate amyloid plaques to remodel synapses. Another group of researchers also detected plaque deposition in microglia-ablated mice of 2-month-old[7]. Noticeably, there is a lack of direct relationship between microglial and formation of A β . Instead, receptors on microglia are involved in the pinocytosis of A β in the soluble forms and the phagocytosis of the fibrillar forms[8], including receptor for advanced glycation end products (RAGE), scavenger receptor class A type 1 MARCO, scavenger receptor class B member 1 CD36, toll-like receptor (TLR2), TLR4, chemokine-like receptor 1 (CMKLR1), G protein-coupled receptors formyl peptide receptor 2, CD14 co-receptor, and $\alpha 6 \beta 1$ integrin[9]. CX3C chemokine receptor 1 (CX3CR1), expressed merely by microglia and acts as microenvironmental cues to facilitate the communication between microglial and neuronal cells, has also been widely studied.

These receptors, in turn, allow microglial cells to respond to multiple stimuli, including A β plaques and NFTs[10]. Once activated, microglia synthesis and secrete increased levels of proinflammatory mediators including tumour necrosis factor- α (TNF- α), interleukin-1 α (IL-1 α), IL-1 β , IL-6, IL-8, IL-12, IL-18, IL-23, macrophage chemotactic protein-1 (MCP-1), MCP-113, macrophage inflammatory

protein-1 α (MIP-1 α), interferon (IFN- γ), and granulocyte-macrophage colony stimulating-factor (GM-CSF) in AD patients[9]. The number of IL-1 β rises particularly in response to an overexpression of tau protein. Promoted abundance of TNF- α are noticed in AD brains and appear at proximal levels of β -amyloid, which helps reflect the severity of disease. Other molecules such as IL-34, transforming growth factor- β 1 (TGF- β 1), and macrophage colony stimulating factor (M-CSF) have also been indicated to reduce A β plaques formation.

Triggering receptors expressed on myeloid cells 2 (TREM2), a transmembrane receptor encoded by TREM2 gene, is a significant genetic risk factor of Late-Onset AD (LOAD) and is predominantly expressed on microglia. Findings showed that overexpression of TREM2 promoted the phagocytic genes synthesis and improved the phagocytic capacity of microglia to amyloid deposits. This neuroprotective effect is also validated by Zhong et al. where sTREM2, the hydrolysate of TREM2, increase microglia proliferation, migration, and β -amyloid uptake and degradation[11].

2.2. Ambiguity of Microglia Toxicity

However, some studies have suggested otherwise. While IL-18 levels elevate extensively in various regions of the brains, they also promote the expression of glycogen synthase kinase-3 β (GSK-3 β) and cyclin-dependent kinase 5 (cdk5), molecules involved in tau hyperphosphorylation[12]. Cytokines IL-12 and IL-23, normally synthesised by leucocytes, are synthesised by microglial cells in AD mouse models, and their inhibition reduces AD pathology. Although microglia are constantly activated and recruited by senile plaques during AD progression, they gradually lose the capacity to recognise and degrade A β when aged[13]. It was demonstrated that cytokines released by microglia and chronic neuronal damage could in turn overactive microglia, causing immune responses that further stimulated microglia to synthesis cytokines[14]. Indeed, besides proinflammatory mediators, microglia also produce cytotoxic factors including nitric oxide (NO), reactive oxygen species (ROS), and superoxide radicals (O $_2^{\cdot-}$) upon activation[15].

Therefore, at resting state, microglia play a role in neuroprotection, neurogenesis, and synaptic pruning, yet persistent activation leads to ineffective β -amyloid plaques deposition clearance and results in proinflammatory state[14]. Whether microglial cells function as neuroprotective or neurotoxic in AD brains remain under debate, yet it can be postulated that the principle of microglia's function in Alzheimer's lay between the fine balance between being neuroprotective and neurotoxic and between proinflammatory and anti-inflammatory.

3. Astrocytes Heterogeneity and Alzheimer's

3.1. Relating Astrocytes with Alzheimer's

Locating in the central nervous system, astrocytes originate from neuroepithelium-derived radial glial cells [2] and function to maintain ion balance, support endothelial cells (ECs) of blood brain barrier (BBB) and provide nutrients to the brain[5]. There are at least 11 different astrocyte classes identified to date[16]. Studies have identified astrocytes in the process of forming tripartite synapses, encompassing microvessels, and interacting with neuronal and nearby glial cells[17]. Morphological studies of post-mortem Alzheimer's patients illustrated an interaction between astrocytes and A β depositions, and reactive astrocytes were detected in both mice models and human patient brains. Astrogliosis near A β plaques are also observed in Alzheimer's brains[18], and an analysis of astrogliosis revealed a correlation between astrogliosis and the level of cognitive dysfunction.

Astrocytes are activated after exposure to amyloid- β and increase excretion of cytokines, chemokines, glial fibrillary acidic protein (GFAP), nestin, synemin, and vimentin. Activated microglia, in fact, also activate astrocytes through factors such as IL-1 α , TGF- β , C1q, and TNF- α , which cause astrocytes to produce additional mediators including TGF- β , TNF- α , IL-6, and IL-1 β , thereby exacerbating neuroinflammatory response. Additionally, dysfunctions between astrocytes and surrounding neurons and astrocytes damage could interrupt synaptic homeostasis and initiate a

cascade of neuronal injury, which further enhances ROS release, leading to astrocytes loss and death of neuronal cells.

3.2. Astrocytes in amyloid elimination

It was suggested that astrocytes likely take part in β -amyloid elimination and clearance. They are involved in the glymphatic system and produce water channels aquaporin 4 (AQP4) in vascular endfeet, whose expression is suppressed in AD patients and its deletion has been indicated to exacerbate β -amyloid accumulation. Ries and Sastre uncovered the expression of insulin-degrading enzyme (IDE), metalloendopeptidases neprilysin (NEP), and endothelin-converting enzymes 1 (ECE1) and 2 (ECE2) by astrocytes that facilitated monomeric A β degradation. Furthermore, clearance is mediated by Apolipoprotein E (APOE), α 1-antichymotrypsin (ACT), α 2-macroglobulin (α 2-M), and ApoJ/Clusterin, all of which are produced by astrocytes and assist the transportation of β -amyloid across BBB into circulation either by itself or with low density lipoprotein receptor-related protein 1 (LRP1) and very low-density lipoprotein receptor (VLDLR). APOE, which is another risk gene of LOAD, mainly locates on astrocytes in healthy brains and contributes to A β aggregation[19]. It affects the size and neuritic dystrophy of plaque instead of the total amyloid load[20]. Compared to APOE3, APOE4 causes pericytes degeneration and facilitates BBB breakdown, leading to the cognitive impair in APOE4 carriers and increasing the risk of disorder development by 3-fold[21]. Mouse and human astrocytes expressing APOE4 display less efficiency in eliminating amyloid plaques than those with APOE3[22]. Besides, other AD-associated genes including Fermitin family member 2 (FERMT2) and Clusterin (CLU) are also highly expressed by astrocytes.

3.3. Intercellular and Intracellular Activities of Astrocytes

At the molecular level, reactive astrocytes surrounding amyloid deposits exhibit aberrant Ca^{2+} dynamics and astrogliotic remodelling induced by β -amyloid is mediated by the synthesis of Ca^{2+} [23]. Inhibition of Ca^{2+} has been shown to impede astrocytic reactivity[24]. Calcium hyperactivity increases release of detrimental mediators, disturbs neuronal-glia communication and damages synaptic plasticity and transmission. Distinctively, reactive astrocytes also alter their GABA excretion by putrescine-MAO-B pathway in AD brains. This shifts the excitation-inhibition balance of astrocytes, which is postulated to be a defensive mechanism against AD-associated neuronal hyperexcitability[25].

Of note, neuroinflammation also attributes to the interactions of astrocytes with neurones, microglia, and oligodendrocytes. NF- κ B cascade is activated in both mouse model and human AD brains, triggered by β -amyloid to release complement protein C3. The binding of C3 to microglial receptor C3aR changes A β plaques phagocytosis and disrupts dendritic morphology and network function, exacerbating AD pathogenesis[26]. Once activated by microglia-released cytokines, a promoted level of classical complement pathway genes including C3 were expressed by astrocytes to diminish synapse formation, function, and the capacity to phagocytose myelin and synapses debris.

Extensive transcriptomics and proteomics investigations have further correlated mitochondrial bioenergetics with Alzheimer's[27], implying the effect of mitochondrial dysfunction and metabolic deficits on AD pathogenesis[28]. Astrocytic mitochondria mainly locate at sites of homeostatic transport, providing energy for Na^+/K^+ -ATPase and accumulating neurotransmitters including glutamate[29]. A β -stimulated astrocytes promote superoxide dismutase levels and oxidative stress, in turn lead to an extensive increase in hydrogen peroxide production when β -amyloid continuously infuse into brains[30]. Amyloid plaques and APP in mitochondrial inner membrane disrupts the activity of Complex IV [31], which is subsequently manifested by mitochondrial deposition and loss of Ca^{2+} homeostasis.

3.4. Populations of Astrocytes

Due to their diversity, astrocytes are challenging to study. Current understanding of astrocytes mainly emphasis the significant role of astrocytes in neurodegeneration, highlighting that

compromised astrocytic function potentially define the severity of disease. Nevertheless, Habib et al. recognised a group of disease-related astrocytes in Alzheimer's mouse model through single-nucleus RNA sequencing, which appeared in early stages and increased in abundance as disease progressed[32]. Similar population of astrocytes are found in aging wild-type mice and human brains, implying their correlation with aged-associated factors. Different population of astrocytes therefore vary in the type and extent of disease-related effects in different brain regions, thereby astrocytes in some regions might be neuroprotective whereas being toxic in others, assumptions of which should be validated in future investigations.

4. Relating Alzheimer's with Glial Cells and Blood Brain Barrier

The blood brain barrier (BBB), comprising of endothelial cells (ECs), astrocyte endfeet, pericytes, and basement membrane (BM), is a dynamic interface and selective barrier that maintains CNS homeostasis and impedes peripheral pathogens and toxins from entering the brain[33]. Recent indications correlated BBB with neurodegenerative disease, suggesting BBB alterations were extensively detected in AD brains with various methods[34]. As BBB mediators, glial are recognised to be highly associative in this process.

It is widely recognised that microglia are the major regulators of neuroinflammation, which contributes to pathomechanistic alterations throughout AD continuum and commences decades prior to disease clinical onset. Microglia with podosomes release destruction factors including cathepsin S to adhere and degrade extracellular matrix (ECM), layers of proteins that make up BM. Evidence also referred that cytokine (e.g., IL-6, IL-1 β , and TNF- α) secreted by reactive microglia impair lipoprotein receptor-related protein 1 (LRP1) in brain microvascular ECs by concentration-dependent means, thereby disrupts the bidirectional transport coordinated by BBB[35]. TNF- α was also uncovered to upregulate MHC class I molecule expression on ECs and enhances T cells migrating into CNS[36]. An *in vitro* study revealed lipopolysaccharide-activated microglia (LPS-MG) reduced trans-endothelial electrical resistance (TEER) and alters tight junction protein expression, causing BBB to collapse[34]. In addition, it was indicated that LPS-MG enhanced tau protein spreading to hippocampus from entorhinal cortex. Intriguingly, a study detected a BBB-protective subpopulation of microglia that express gene coding claudin CLDN5 during early phase of inflammation, implying microglial cells might affect the formation of TJs to impair BBB destruction[37].

In the context of astrocytes, evidence denoted that extensive astrocyte reactivity compromised BBB integrity through decoupling of ECs and endfeet[38]. Astrocytes activated by A β 1-42 secrete vascular endothelial growth factor (VEGF) to activate endothelial MMP9, thereby reducing claudin-5 expression and promote BBB permeability. Moreover, microglia-induced astrocytes lose their normal function and further exacerbate the BBB. Yet some others indicated the overexpression of RALDH2 by astrocytes promoted retinoic acid (RA) synthesis and protected BBB function.

5. Conclusion

Alzheimer's is the most prevailing neurodegenerative disease. Its heterogeneous nature makes its full elucidation challenging and pharmaceutical treatments remain elusive. Recent research starts to attribute AD onset and progression to non-neuronal cells and their interactions with neuron and BBB, some of which have been discussed in this review. In principle, immune response of CNS mediated by inflammatory factors can be considered as a double-edged sword with both beneficial and adverse effects. Neuroprotective cascades at early stages, including antioxidant mechanisms against ROS and amyloid plaque clearance, are effective. However, oxidative stress elevates the immune response and results in overproduction of pro-inflammatory molecules as AD progresses. Higher resolution characterisation of glial cells in upcoming studies are required to further validate the role of glial in AD and potentially initiate new avenues of identifying new targets for therapeutic strategies of Alzheimer's.

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