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Microglia in the pathology of Alzheimer's disease

Yufan Wang

Beijing Huiwen Middle School, Beijing, China, 100000

arryfan@sina.com

Abstract. As the most common neurodegenerative disease, Alzheimer's disease (AD) is troubling countless middle-aged and elderly people. Countless scientists devote themselves to the study of AD in order to help sufferers live happier life. One of the most striking features of AD is the large number of activated microglia around amyloid plaques. This suggests that microglia play an important role in the pathogenesis of AD. But conflicting views have emerged about the specific role of microglia. Some have found that microglia, boosted by proteins such as TREM2 and APOE, can clear plaques in the brain, preventing AD from occurring. Others, however, have found that complement activation mechanisms cause microglia to excessively clear synapses to exacerbate the pathology of AD. This review introduces two opposite opinions about microglia's effects in Alzheimer's disease, which is actually about the theory about how TREM2 and microglia mitigate Alzheimer's disease, and why complement and microglia can exacerbate Alzheimer's disease.

Keywords: microglia, Alzheimer disease, TREM2, complement, dementia.

1. Introduction

Alzheimer's disease (AD), is a neurodegenerative disease, which is the most common form of dementia in the world. Currently, there are at least 50 million AD patients worldwide. People who got AD will always have symptoms of severely impaired memory, aphasia, impairment of visuospatial skills, executive dysfunction, personality and behavior changes etc.

On a pathological level, AD was first described by Alois Alzheimer [1], which is characterized by brain atrophy, amyloid plaques (It is formed by the extracellular deposition of Aβ peptide), neurofibrillary tangles (mostly composed of tau protein), dystrophic neurites, and loss of neurons and synapses.

Microglia is an innate immune cell of the central nervous system (CNS) [2], accounting for about 10% of nervous system cells. In the central system, microglia perform tissue maintenance, injury response, and defense against pathogens [3, 4]. In addition, microglia can also carve neural circuits by Engulf and remove unnecessary synapses and neurons [5, 6].

Recent genetic data show that microglia play an important role in the pathogenesis of AD. However, because of the mechanism of AD and the action mechanism of microglia have not been completely clear, so there are many studies and research presented contradictory conclusions about the role of microglia in the pathogenesis and progression of AD [7-12]. And some researches show that in certain conditions microglia will be acquired by pro-inflammatory activity, which is associated with disease progression [13-16].

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2. TREM2 and microglia in AD

Although the symptoms of cognitive impairment and memory decline in Alzheimer's disease (AD) are ultimately manifested through neuronal dysfunction, AD is also closely associated with neuroinflammation, and glial cells in the AD brain often exhibit chronic activation characterized by an increased number of monocytes, such as microglia [17].

TREM2 is an AD risk site that has the greatest impact on disease risk. In the CNS, TREM2 is mainly expressed in microglia and plays an important role in microglia-associated neurodegenerative diseases [22]. It acts as a cell-surface receptor for microglia, which can promote the phagocytosis, survival, and proliferation of microglia by having interaction with the activating adaptor protein TYROBP/DAP12 [18-22].

An important aspect of microglia's maintenance of nervous system homeostasis is phagocytosis and removal of debris, and TREM2 is required for microglia to perform phagocytosis and clearance (for example Abeta plaques, apoptotic neurons, bacteria, etc.) [23, 24]. The interaction between TREM2 and APOE (TREM2-APOE axis) can facilitate the microglial clearance of extracellular and cellular deposits [25].

3. Two opposite roles microglia plays in AD

3.1. Positive: How do TREM2 and microglia protect the nervous system in AD?

When plaques emerge in the brain, TREM2, DAP12, and phosphotyrosine will cluster near the plaques which means microglia will aggregate around the plaques [26]. These collective microglia will form a barrier around amyloid deposits, and compress them into a denser and less toxic form. Preventing them from accumulating on existing plaques [26].

As I just mentioned, the interaction between TREM2 and DAP12 can facilitate microglia phagocytosis, so this action will promote microglia to have some solution on plaques. As a result, the microglia who has a deficiency in TREM2 that cannot accumulate or multiply around plaques will get a halo of soluble, oligomeric Aβ (the most harmful substance for neurons) that will appear around amyloid plaques. Thus, microglia need the APOE-TREM axis to compact the protofibrillary Aβ [27-29].

For different kinds of deposits, microglia can use different mechanisms to protect CNS: (1) For soluble Aβ species, Microglia will uptake or clear them. (2) For insoluble fibrillar Aβ deposits, Microglia will phagocytose them. (3) For amyloid plaques, Microglia will compact and corralling them.

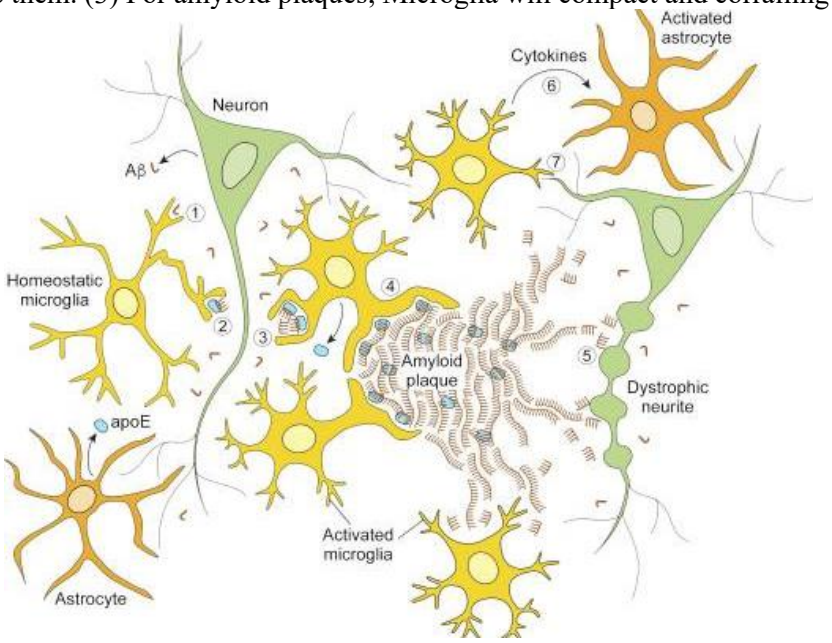

Figure 1. Depiction of microglial cellular activities related to β-amyloid pathology [30].

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The left side of the picture shows how microglia clear deposits, and the right side shows microglial containment mechanisms during a defective or outstripped situation.

3.2. Negative: How do complementand microglia aggregate AD pathology?

Although microglia can prevent AD by cleaning up starch clumps, there is plenty of evidence that activated microglia are harmful to neurons. For example, activated microglia can secrete toxin factors that damage neurons [31], and it will also over-pruning synapses and exacerbating tau pathology [32, 33].

Complement is a serum protein that mediates immune and inflammatory responses and can be activated by antigen-antibody complexes or microorganisms, leading to lysis or phagocytosis of pathogenic microorganisms. When the complement interacts with receptors on the cell surface, it will produce an inflammatory response. And complement activation will cause inflammation and cell damage [34].

Many complement proteins can be synthesized locally in the brain [35-38], and activation of the complement system in the brain has been observed in different neurodegenerative diseases such as AD. The complement proteins of microglia include C1q, C3, receptor: C1qR, CR3, and C5aR. Especially, C1q protein is mainly localized in neurons, and the research finds out that C1q protein only exists in the amyloid plaques that include the β-sheet conformation, which indicates that C1q may affect the amyloid aggregation process [39]. As for how does it exactly affect amyloid plaque accumulation, it needs futher investigation.

There are some interesting experiments that indicate that C1q will act downstream of Aβ [40], and C3 is required in all pathways of complement activation [41].

Because microglia provide most of the Cq1 in the brain and they engulf synapses through C3 as they develop [42], expressing C3a and C5a receptors, which often trigger inflammation due to complement activation. From this, we know that microglia cause synaptic loss, which can further aggravate of AD.

4. Conclusion

As more and more scientists pay attention to and study Alzheimer's disease, a variety of contradictory conclusions emerge. And this review presents the hypothesis about how TREM2 and microglia moderate Alzheimer's disease, and the hypothesis about how complement and microglia fuel Alzheimer's disease. Here, I only briefly discuss the different roles of microglia in Alzheimer's disease using the two most studied proteins TREM2 and complement as vectors, without going into details. This is also because many details are still unknown, such as the phagocytosis mechanism of microglia, the pathology of Alzheimer's disease, and so on. Another shortcoming of this paper is that there is no experimental data to support it. In the future, researchers can focus on the principle on the mechanism by which microglia works, we may get a more certain and clear answer. And I believe that we will get a new way to treat Alzheimer's disease, if we find out the principle on how microglia work.

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