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Alzheimer's Disease Mechanism in Neuroimmunology Perspective

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Abstract. Among the several neurodegenerative illnesses, one of these is the illness Alzheimer's (AD). it is hard to cure completely for now. To find fresh targets for the therapy of AD, neuroimmunology have been getting attention gradually. Neuroimmunology response, which happened in the central nervous system (CNS), is innate immune response of human. In the AD, microglia activated by damage signals lead to a series of cellular cascade responses. Then, a large number of chemokines and inflammatory cytokines are released by microglial cells. The cytokines have neurotoxic effects on the certain brain areas, causing neuronal degeneration. Since microglia can be activated by tau aggregation in addition to alarm signals, with tau protein aggregation releasing from the degenerative neurons, it provokes a positive feedback mechanism of neuroimmunology in hippocampal area. Microglia mainly play a role of neuroprotective by clearing β-amyloid (Aβ) on early stage of AD and have a neurotoxic effects induced by an Aβ-induced phenotypic change on late stage of AD. TREM2 mainly expressed on microglia, it may downregulate the inflammatory response in AD. The review has explained clearly and demonstrated that tau assembly and clearance of Aβ are effective therapeutic targets on AD. In addition, it explained AD nosogenesis from the new view of TREM2 mutations.

Keywords: Alzheimer's Disease, Neuroimmunology, Microglia

1. Introduction

AD is a neurological illness that is resistant to treatment and is characterized by deteriorating cognitive performance and behavioral impairment. Despite The pathogenesis is varied, increasing research have been proved the role of the immune systems in the brain to the process of AD. As a novel field, neuroimmunology combined neuroscience and immunology, focus on the level of molecular mechanisms of diseases. In recent years, there are two main hypothesis were formulated, neuroimmunomodulation and neuroinflammation. The starting of the process mainly determined by Microglia, which play an indispensable role in the AD process. In addition, tau assembly are important to trigger the activation of the microglia. There are some novel therapeutic targets for AD have been found by studying the hypothesis. At present, it is necessary to further research neuroimmunology mechanism of AD for future appropriate therapy [1]. The review will introduce the neuroimmunomodulation and neuroinflammation hypothesis and discuss the correlation between microglia and Aβ，the effects of TREM2 gene mutations in the AD.

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2. The neuroimmunomodulation hypothesis

In the signal pathways, There are many signals can trigger the onset of the AD. From the pathological view, AD shows the two main points: the Senile Plaques (SP) and the Neurofibrillary Tangles (NFT). SP were assembled pathologically by the Aβ peptide. The hyperphosphorylated tau protein variation, which is associated with microtubules, was used to build NFT. Under the pathological conditions, Tau may self-polymerize to cause the death of neurons, leading the shrinkage of the brain. In a general way, the memory areas is common area of tau pathology appears firstly in the brain, such as the hippocampal formation and the entorhinal cortex.

There are many hypotheses indicates the brain immunomodulation are pivotal for the origination and development of AD. The neuroimmunomodulation hypothesis indicates that the starting of AD is mainly because microglia was activated by “alarm signals”/ tau aggregation. These cause the release of Nuclear Factor Kappa, which leads to the production of excessive amounts of inflammation-promoting cytokines such interleukin I beta (IL-1β), Tumor Necrosis Factor Alpha (TNF-α), and interleukin 6 (IL-6). Consequently, these cytokines activating hippocampal neuronal receptors. The activation induce complex signaling pathways, among which CDK5/P35 is very important in the regulating of neuronal migration.

In addition, the glycogen synthase kinase 3 beta (GSK3β) activation also happened at the same time. Hyperactive protein kinases spark hyperphosphorylation of tau and self-agglomeration of tau, which is related to neurodegeneration [2]. According to certain studies, the reactivation of microglial cells can occur as a result of tau aggregation produced from neurodegenerating neurons. As a result, it encourages a molecular signaling continual cascade for neuronal degeneration in the brain of AD patients. [3, 4].

These molecular changes be caused by Tauopathies, which is characterized by Tau wrong misfolding propagation, which is a molecular event causes the cytoskeleton collapse. In the context above, the neuroinflammatory hypothesis may is a more general postulate for several neurodegenerative diseases [3].

3. The neuroinflammation hypothesis

Neuroinflammation is inflammatory response to damage signals in central nervous system. After suffering an injury in the CNS, microglia will cluster quickly and be activated. Then leading to the pro-inflammatory cytokines were secreted. Neuroinflammation have different influences in the CNS, which mostly depend on the duration time of the inflammatory reaction [5]. For example, persistent high level of the secretion of pro-inflammatory cytokines may is the key for leading to AD whereas short period of inflammatory activity may have neuroprotective effect on the brain. Most of evidence have proved that most cytokines have a common feature on inducing the cellular cascade leading to AD and have neurotoxic effects on the middle and late stage of the AD.

In the AD, a long-time inflammatory condition cause neuronal injury and death, which consequently facilitate the process of secreting pathological tau protein to the external environment of neurons. In addition, previous research have confirmed that microglial cells can be triggered by tau oligomers, then with the positive feedback mechanism of neuroinflammation was activated, inducing neurons’ long-period injury.

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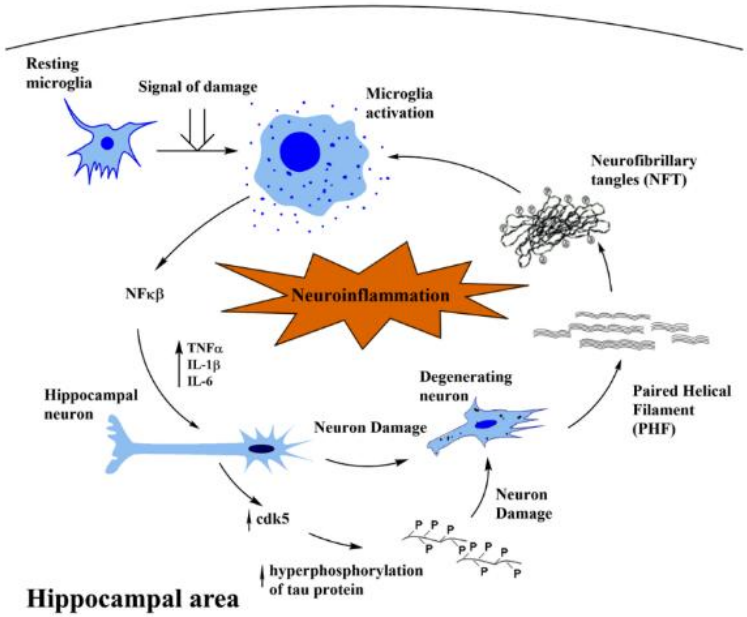

Figure 1. The positive feedback mechanism of neuroinflammation [3].

It have been shown that an important overexpression of inflammatory responses is associate with affected brain areas of the neurodegenerative diseases. The continuous CNS immune reaction, means the neurotrophic factors were produced persistently by the microglial cells, whereas the hyper-activation of the CNS immune response means increased microglia, which induced by lower generative neurotrophins and less liberation of cytotoxic agents to microglia. As the number of activated microglia are increasing, they lead to the positive feedback, which give us new views into the starting and progression in the AD.

4. Microglia and Beta-Amyloid

The primary innate immune cells in the central nervous systems are called microglia. It represented 5–20% of all glial cells. In the process of keeping the brain microenvironment's homeostasis, the cells are crucial [6]. For instance, microglia play a role as activated macrophages and have a reaction to the damage of tissue in the CNS. Microglial activation is a type of innate immune response that results in the production of chemokines, TNF-α, IL-1β, and IL-6. Depending on the form, intension, and circumstance of the stimulus, the progression of microglial activation has two distinct consequences on the brain. The subtle balance between the neurotoxic and neuroprotective determines function of microglia in a certain condition [7].

Aβis one of the abnormal proteins accumulation of pathological changes in Alzheimer's brain. Because intracellular Aβ deposits in microglia in AD brains, it shows that microglial cells play a role of neuroprotection on facilitating Aβ clearance in the early disease process. Therefore microglia's clearance ability of Aβmay is a novel therapeutic target to postpone the AD progression.

With AD progresses, it can be observed that the number of microglia increases and Aβalso constantly accumulate. Therefore, AD pathology keep progressing despite continuous accumulation of microglial cells. Microglia fail to stop AD progressing probably because of an phenotypic change induced by Aβ, which makes microglia play a role in pro-inflammatory instead of the ability of clearing Aβ, lead to a large number of Aβaccumulation. In actuality, it has been discovered that there is interaction between Aβ and a receptor complex composed of the Toll Like Receptors (TLR) TLR4, TLR6, and CD36 which is expressed on microglia. As these cells were activated to create pro-inflammatory cytokines, chemokines and neurotoxins, microglia play a part of neurotoxic in the CNS

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of AD. In addition, these cytokines reduce Aβ degrading enzymes and Aβ phagocytic receptors of signaling pathways in microglia [8] .

5. TREM2

The Trigging Receptor Expressed on Myeloid Cells 2 protein, which belongs to the immunoglobulin family, is encoded by the TREM2 gene. The researchers have discovered numerous heterozygous variants of TREM2, which increase one's susceptibility to late-onset AD. Myeloid cells, particularly microglia, express the gene for TREM2. By using Direct RNA Sequencing (DRS) techniques to analyze the transcriptome of microglia, it identify relevant a cluster of genes. Additionally, it indicates that TREM2 is one of the cell surface receptors in microglial cells that is most abundantly expressed. TREM2 is highly enriched on microglial cells rather than other cells of brain, so TREM2 being taken into account as a possible risk factor in the context of AD genes, and provides a unique angle of view into microglial cells' effect in the AD [9].

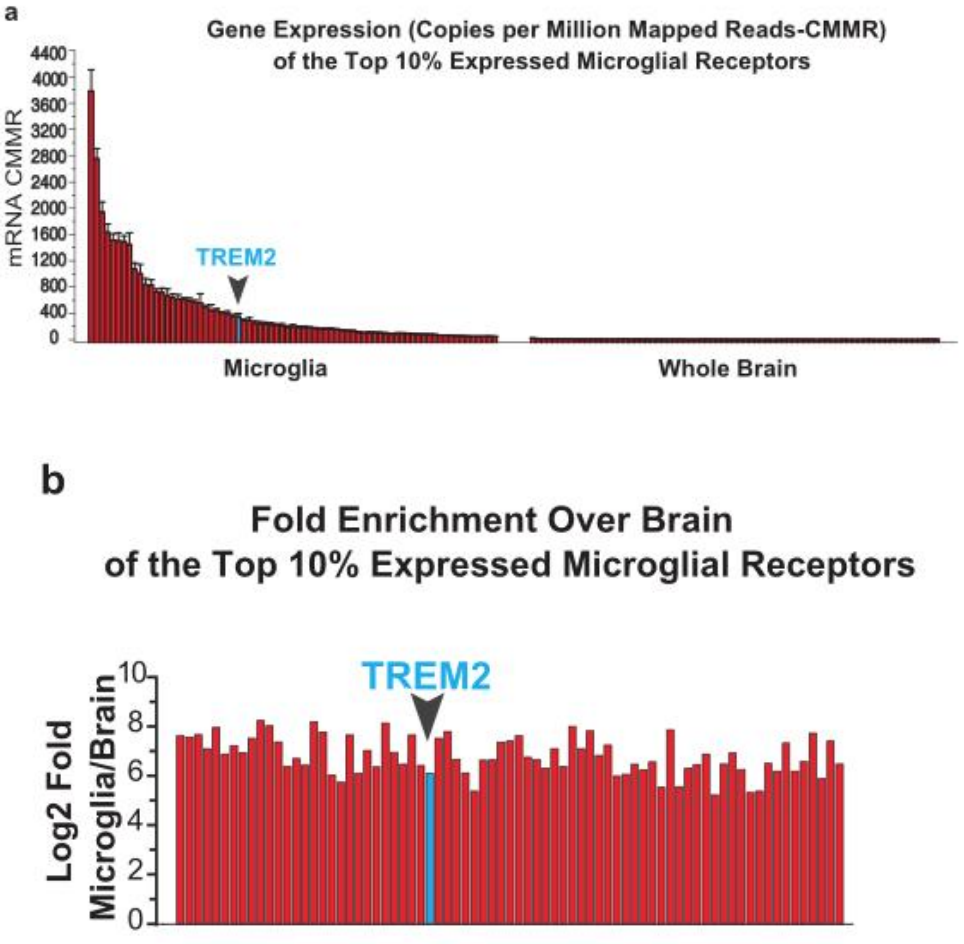

Figure 2. The expression circumstance of TREM2 in microglia [10].

TREM2's precise roles are still not entirely known, however it appears to be involved in the partnering with DAP12, a signaling adaptor, to suppress the inflammatory response and TLR responses. Moreover, the gene is capable of influencing phagocytosis without coming into contact with the granules that have been phagocytized, as well as directly mediating the clearance of bacteria and apoptotic neuronal cells. Uncertainty exists on how TREM2 mutations affect AD. But other studies have revealed that one of the Nasu-Hakola sickness-causing TREM2 mutations is a loss-of-function variation encoding Q33X. It have been found that the same variant is a potential factor for

increasing late-onset AD's risk among carriers of heterozygosity. These suggest AD have a similar mechanism with Nasu-Hakola disease.

TREM2 has been certified the roles of upregulating phagocytosis by myeloid cells and downregulation of the inflammatory response. Therefore, it can be proposed that TREM2 mutations cause AD by upregulating inflammatory reaction in the brain [11]. This pro-inflammatory environment promotes the accumulation of Aβand quicken the progression of AD. Since TREM2 also directly take part in the process of regulating phagocytosis in the brain, the mutations may negatively regulate microglial phagocytic abilities to weaken their clearance ability about Aβ. Additionally, the pro-inflammatory environment may directly improve microglia's neurotoxicity effects and further contributing to the AD nosogenesis [12].

6. Conclusion

Microglial cells were activated by tau aggregation and damage signals, leading to a positive feedback of neuroimmunology, causing a persistent neurons injury in AD brain areas. From the pathological view, tau assembly and formation of Aβ are the key points cause AD. In addition, TREM2 mutations are the risk factors for AD. Blocking tau assembly and improving the ability of clearing Aβ of microglia, appear to key therapeutic methods for AD. In fact, there are some medicine have been applied successfully in animals. For example, the Brain Up-10, which is a nutraceutical compound, have an impact of anti-aggregation on aggregated tau and reducing alarm signals, it also boosts neuron growth. But the effectiveness and side effects of these drugs on human are still undefined.

References

[1] Lao, K., et al., *Therapeutic Strategies Targeting Amyloid-beta Receptors and Transporters in Alzheimer's Disease.* J Alzheimers Dis, 2021. 79(4): p. 1429-1442.
[2] Prasanna, G. and P. Jing, *Self-assembly of N-terminal Alzheimer's beta-amyloid and its inhibition.* Biochem Biophys Res Commun, 2021. 534: p. 950-956.
[3] Maccioni, R.B., et al., *Alzheimer s Disease in the Perspective of Neuroimmunology.* Open Neurol J, 2018. 12: p. 50-56.
[4] Leyns, C.E.G. and D.M. Holtzman, *Glial contributions to neurodegeneration in tauopathies.* Mol Neurodegener, 2017. 12(1): p. 50.
[5] Jha, M.K., W.H. Lee, and K. Suk, *Functional polarization of neuroglia: Implications in neuroinflammation and neurological disorders.* Biochem Pharmacol, 2016. 103: p. 1-16.
[6] Casali, B.T. and E.G. Reed-Geaghan, *Microglial Function and Regulation during Development, Homeostasis and Alzheimer's Disease.* Cells, 2021. 10(4).
[7] Streit, W.J., H. Khoshbouei, and I. Bechmann, *The Role of Microglia in Sporadic Alzheimer's Disease.* J Alzheimers Dis, 2021. 79(3): p. 961-968.
[8] Madhu, P. and S. Mukhopadhyay, *Distinct types of amyloid-beta oligomers displaying diverse neurotoxicity mechanisms in Alzheimer's disease.* J Cell Biochem, 2021. 122(11): p. 1594-1608.
[9] Hickman, S.E., et al., *The microglial sensome revealed by direct RNA sequencing.* Nat Neurosci, 2013. 16(12): p. 1896-905.
[10] Hickman, S.E. and J. El Khoury, *TREM2 and the neuroimmunology of Alzheimer's disease.* Biochem Pharmacol, 2014. 88(4): p. 495-8.
[11] Stefano, L., et al., *The surface-exposed chaperone, Hsp60, is an agonist of the microglial TREM2 receptor.* J Neurochem, 2009. 110(1): p. 284-94.
[12] Yang, J., et al., *TREM2 ectodomain and its soluble form in Alzheimer's disease.* J Neuroinflammation, 2020. 17(1): p. 204.