

Deep Learning in the Inflammation in Alzheimer's Disease

Bohan Zhang *

Wycombe Abbey School, High Wycombe, UK

* Corresponding Author Email: lyang@qqmail.org.uk

Abstract. Alzheimer's disease (AD) refers to the most prevalent neurological disease, which is caused by amyloid plaque deposition and tau tangles accumulation. Several recent clinical investigations have suggested that many immune system components may play essential roles in AD pathogenesis. Both adaptive and innate immune system shows a bi-directional regulation to AD and the over-activated immune system could lead to neurons' inflammation. In this article, the critical role of microglia in the non-specific immune system and T lymphocytes in specific immune system are mainly focused. Microglia and T cells both play important roles in regulating the cytokines and multiple signaling pathways which are associated with memory loss. Other immune cells including B lymphocytes and neutrophils are possibly associated with the pathology of AD, although their roles still need to be studied. Here, research showing the link among dysfunctional immune cells and AD pathophysiology are reviewed in this project. In addition, the potential treatment and therapeutics target for AD are also discussed.

Keywords: Inflammation, Alzheimer's Disease, Beta-amyloid Peptides, Microglia.

1. Introduction

AD refers to the most widespread reason of dementia globally, impacting around 50 million people [1]. AD has traditionally been seen as a neurodegenerative disease that mostly results in dementia [2]. Though the pathology of AD is unclear, the most convincing hypothesis proposed that the extracellular accumulation of misfolded amyloid-beta ($A\beta$) peptide, form extracellular amyloid plaques to prompt the progress of AD [3]. The other primary hypothesis of AD pathology is tau hypothesis. Tau proteins aggregate and cause the formation of the intracellular neurofibrillary tangles (NFTs) under hyperphosphorylated state. Moreover, epidemiological research indicates a crucial role of innate the immunological system activation in the pathophysiology of AD [4]. The formation as well as accumulation of $A\beta$ will result in chronic neuroinflammation and downregulation of microglial phagocytosis [5]. The inflammation in neurons can also contribute to the neurodegeneration and thus lead to the disease. Simultaneously, the cellular inflammation could be assessed through the presence of pro-inflammatory microglia and the infiltration of T lymphocytes. The function of immune systems is highlighted in AD. Innate immune cells protect human body as sentinel cells [6]. The non-specific immune system could recognize the pathogen-related molecules and molecules secreted by damaged cells through pattern recognition receptors. Such pathogen recognition patterns play an essential role to allow the host to clear foreign pathogens or substrates without damaging body cells. When the innate immune cells realize that they cannot clear foreign substrates on their own, antigen presenting cells will then present the foreign antigens to recruit lymphocytes. The recruited antigen-specific T and B cells are vital in the specific adaptive immunity which is highly associated with pathogenesis. Deep understanding of inflammation in this kind of dementia including both innate immune system and adaptive immune system are reviewed in this project. The contribution of dysregulation of the immunologic cells to the pathophysiology of AD also involved in the following sections.

2. Innate immune system

2.1. Microglia

When pathogens intrude human body, the immune system could be activated to response the foreign antigens. The immune system is classified as two types: non-specific immune system and specific immune system. Among them, innate immune cells are responsible for protecting human body in the first line through multiple defense approaches. Innate immunity detects pathogens and stresses invading the body and clean them through specific inflammatory responses such as phagocytosis. It is composed of different cells such as natural killer cells, macrophages, dendritic cells [7]. Microglia cells are identified as the resident macrophage cells in the central nervous system (CNS) and served as a special macrophage which exists in human's brain. Recently, scientists report that overactivated microglia cells can be a hallmark of inflammation in AD. Microglia are the only myeloid cells which mainly exist in our brain with large quantities. It plays vital role in maintain homeostasis of human brain through appropriate immune response. However, the abnormal activation of microglia cells might deteriorate AD symptoms by binding to the beta-amyloid ($A\beta$) peptides. In the past, research mainly interprets microglia stimulation as conducted by oxidative and inflammatory response of fibrillar $A\beta$ peptides, which is the soluble form of $A\beta$ peptides. By responding to this stimulation, microglia can further secrete more cytokines into the synapses. As can be seen in Figure 1, the highly upregulated cytokines are associated with hyperphosphorylation of tubulin associated unit (tau) protein, which is another key hallmark of AD [8]. Furthermore, the mutations of microglia receptor triggering receptor expressed on myeloid cells 2 (TERM2) highly developing risks of getting the dementia by two to three times, as it is highly critical to maintain metabolism of microglia. The TERM2 variants disrupt the crosstalk between TERM2 and extracellular ligands, and increase the risk of AD. On the other hand, researchers revealed the protective role of microglia in AD. what's more, the increased accumulation of amyloid plaques might lead to the microglia dysfunction, resulting in its ineffective phagocytosis. Through the progressing of this disease, microglia may also be dysregulated and loses their protective functions for neurons with ageing. However, previous studies also demonstrated the mechanism of microglia to maintain brain homeostasis. TERM2 is vital to promotes the phagocytosis of apoptotic neurons, and the activated microglia has been implicated in the toll-like receptors (TLR) -induced inflammatory response. The lack of TERM2 will lead to the dysfunction of endocytosis of microglia to the amyloid plaques. As part of immune system, microglia engulf the $A\beta$ peptides. Moreover, multiple studies suggest microglia have the ability to build a physical barrier surround the amyloid plaques[9]. It wraps and condenses the amyloid fibrillar, and potentially transfer into a less toxic form. Additionally, microglia could produce enzymes which help in reducing the number of amyloid plaques.

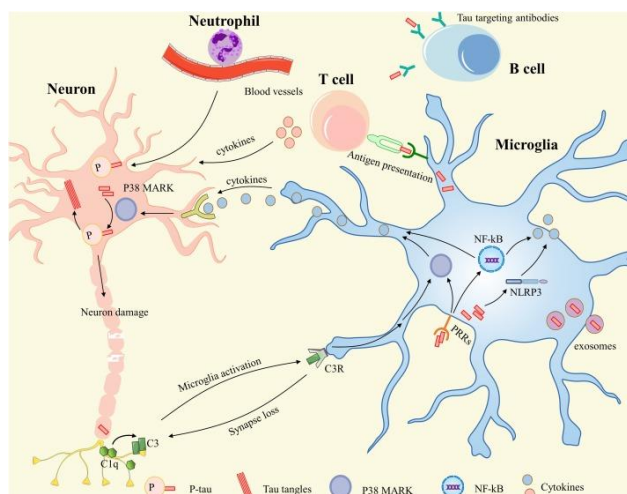


Figure 1. The schematic of microglia causing AD [5]. Tau can induce microglia to secrete more pro-inflammatory cytokines, further prompt inflammation and regulating other immune cells.

2.2. The peripheral system

In addition, the peripheral system is essential for controlling inflammation [8]. Pro-inflammatory cytokines change peripheral levels and are significantly associated with AD progression. When innate immune cell receptors identify certain molecular patterns derived from unknown pathogens, an inflammatory response is set off. Also, evidence indicate that peripheral cells include neutrophils, monocytes and macrophages contribute promote the development of AD.

2.3. Monocytes

Non-classical monocytes are mostly associated to the fragment crystallizable (Fc) region mediated adhesion and phagocytosis, whereas classical monocytes are vital in phagocytosis, immunological responses, and differentiation. Besides, intermediate monocytes are important in the control releasing toxins like cytokine as well as antigen presentation. Monocytes could differentiate into phagocytic cells including macrophages that can be recruited to the injury areas to clear pathogens or cellular debris. Moreover, the relationship between the change of monocyte amounts and the formation of amyloid plaques was studied. Classical monocytes explicitly decline as AD progresses, whereas monocytes in different forms imply an increase through the accumulation of amyloid plaques. Infiltrating monocytes could indeed control inflammatory reaction in the brain while also prevent the synapses from damaged by toxins in A β peptides. Furthermore, monocytes enable to transport amyloid plaques in blood, which will significantly reduce them in neurons [9].

2.4. Neutrophils

The most prevalent and prominent peripheral immune cells, neutrophils, are crucial in homeostasis recovery process via ingesting pathogens and releasing cytokines. Inside the brains of AD patients, neutrophil levels considerably rise, hitting the peak while memory impairment occurs. Additionally, they boost the formation on neutrophil extracellular traps and toxins cytokines which formed by inflammatory reaction, which in turn lead to the activation of microglia and neuro-inflammation in AD.

3. Adaptive system

3.1. T cells

In contrast with the extensively studied non-specific immune system, the relationship between lymphocytes and AD is remain unknown. However, more researchers have started to focus on how T cells and B cells contribute to neuroinflammation. The percentage of T cells considerably rises with A β peptides accumulation and the upregulation in tau protein of AD patients. When the brain blood barrier is breached, peripheral T lymphocytes might infiltrate the CNS and migrate into the regions where typically associate to AD neuropathology, for example, hippo- campus, corpus, cortex and callosum. There has been information suggesting T cells proliferation inside the cingulate bundle seems linked to enhance cognitive performance. Misfolded A β might well be clearly given to T lymphocytes through antigen presenting cells, leading them to be activated and differentiated. However, the contribution of this kind of T cell in AD is indeed disputed. Several research indicates that A β antigen caused T cells could perhaps lessen A β deposition, reduce microglia function, as well as strengthen spatial memory through limiting the production of cytokines including interleukin-2, interleukin-4 (IL-4), α -tumour necrosis factor, and factors which stimulate the granulocyte macrophage colony, whereas other research suggests that A β activated T lymphocyte cells promote disease's development by manufacturing the pro-inflammatory toxins cytokines interferon gamma. For example, T regulatory (Treg) cells increase A β phagocytosis via microglia and as well as, this helps to relieve cognitive impairment, therefore, showing a regulatory role in the early stage of AD. These inconsistent results of mouse models' studies have been related to the various function in T cells' subpopulations. By producing pro-inflammatory cytokines, T helper 1 (Th1) and type 17 T

helper (Th17) cells might elevate A β deposition or accelerate neurodegeneration. T helper 2 (Th2) cells, by contrast, may partially regulate the production of A β autoantibodies via an IL-4 dependent mechanism. Treg cells block leukocyte immigration throughout the final stages of the disease, resulting in higher amyloid deposition as well as worsened cognitive deterioration [10]. As a result, T cells shows a complicated position in A β pathogenesis, demanding a better knowledge of distinct T cell subtypes in AD. Tau protein-related spatial memory issues are exacerbated by infiltrating T cells, which elevate inflammatory responses, whereas systemic T cell reduction might assist in reverse behavioural defects. Furthermore, previous research in AD mice suggests that T cells are strongly related to tau hypothesis. There is a positively correlation between the level Treg cells and the hyperphosphorylation level of tau. As a result, the level of T cells may be a possible indication in terms of the progression of AD.

3.2. B cells

B lymphocyte cells are vital in the adaptive immune system of the human body. B cells release immunoglobulins to control humoral immunity and also take part in antigen presentation to T lymphocytes, triggering T cell-mediated adaptive responses. B cells are widely expressed in clinical AD patients and build an intimate interaction with inflammation-related proteins. Certain pro-inflammatory B cell receptors, including C-C motif chemokine receptors 6 and 7, can be increased in certain AD patients. A β peptides' misfolding will stimulate production of A β targeting autoantibodies, this lowers the toxic effects of A β oligomers and protofibrils which largely strength the spatial memory of patients who experience AD [10]. One of the recent projects discovered that transient depletion in B cells one of the recent studies discovered that transitory B cell depletion at the outset of AD decreases A β plaque accumulation and microglia that related to the disease while benefiting memorial and behavior capacity.

4. Conclusions

The trend is now becoming more clearer that the inflammation needs to be highlighted in the pathogenesis in AD. Dysregulation of innate and adaptive immunity may accelerate the development of AD pathophysiology and neuroinflammation. Furthermore, immunity-related indicators including cytokines could give useful information for the diagnosis and therapy for disease's patients. Even though previous research has revealed unique insights in the involvement of peripheral-immune cells in AD, various features are currently unknown. Innate-immune cells are thought to be a main factor in amyloid pathology, however, their functions in tau hypothesis remain unknown. Furthermore, T and B lymphocyte cells' function cells in AD's pathology is currently being investigated. Later, studies might need to dig deeper into these concerns. Dysfunction in glymphatic and meningeal lymphatic outflow has been linked to deteriorating AD pathology, but the precise mechanism under how lymphatic channels affect the immunological reaction in the CNS stays unknown. So far, major AD research involving immunology have been restricted to animal models, yet it is still incredibly difficult to apply the findings of these animal models to the treatment of AD patients with various intersecting pathologies. To obtain a better learning of the crosstalk among the inflammation and AD, massive clinical investigations are required to demonstrate various functions of the immunological systems in future. Furthermore, it's appropriate for developing advanced adaptable systems or margin slicing technologies in order to investigate possible beneficial therapies based on multifaceted immune responses. Moreover, present biomarkers are unreliable in identifying disease phases and predicting disease severity. It is necessary to develop new immune-related biomarkers. When the disease is at its early stages, immune cells transformed, this is strongly connected to AD etiology. Biomarkers that relate to immunity could contribute to the early disease's diagnosis and detection. Modifying immunological therapeutics is continued to be investigated in Alzheimer's disease. Even though most immunotherapies are ineffective to treat Alzheimer's disease, there are many possible

medications that have demonstrated high safety and tolerability. As a result, immunotherapy remains a viable treatment option for AD.

References

- [1] Guerchet M, Prince M, Prina M. Numbers of people with dementia worldwide: An update to the estimates in the World Alzheimer Report 2015[J]. 2020.
- [2] Hansen D V, Hanson J E, Sheng M. Microglia in Alzheimer's disease[J]. Journal of Cell Biology, 2018, 217(2): 459-472.
- [3] Knopman D S, Amieva H, Petersen R C, et al. Alzheimer disease[J]. Nature reviews Disease primers, 2021, 7(1): 1-21.
- [4] Webers A, Heneka M T, Gleeson P A. The role of innate immune responses and neuroinflammation in amyloid accumulation and progression of Alzheimer's disease[J]. Immunology and cell biology, 2020, 98(1): 28-41.
- [5] Wu K M, Zhang Y R, Huang Y Y, et al. The role of the immune system in Alzheimer's disease[J]. Ageing research reviews, 2021, 70: 101409.
- [6] Shastri A, Bonifati D M, Kishore U. Innate immunity and neuroinflammation[J]. Mediators of inflammation, 2013, 2013.
- [7] Hato T, Dagher P C. How the innate immune system senses trouble and causes trouble[J]. Clinical Journal of the American Society of Nephrology, 2015, 10(8): 1459-1469.
- [8] Sarlus H, Heneka M T. Microglia in Alzheimer's disease[J]. The Journal of clinical investigation, 2017, 127(9): 3240-3249.
- [9] Heneka M T, Golenbock D T, Latz E. Innate immunity in Alzheimer's disease[J]. Nature immunology, 2015, 16(3): 229-236.
- [10] Marsh S E, Abud E M, Lakatos A, et al. The adaptive immune system restrains Alzheimer's disease pathogenesis by modulating microglial function[J]. Proceedings of the National Academy of Sciences, 2016, 113(9): E1316-E1325.