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Experimental studies linking Alzheimer's Disease and changes in immune cell function

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Abstract. Alzheimer's disease (hereafter referred to as AD), which is a neurodegenerative malady, featured basically by memory deficiency and cognitive decrease, has been increasingly linked to immune system dynamics in recent studies. This paper aims to review experimental studies that elucidate the relationship between AD and alterations in immune cell functionality. Recent research has shown progress in this area through experiments, highlighting quantitative and functional shifts in T cells, macrophages, neutrophils, and B cells on the growth of AD. The assay insinuates pro-inflammatory cells rising and a decrease in inflammation-suppressing cells. These findings offer valuable insights for future mechanistic investigations and drug development. However, there remain numerous unexplored aspects in this field, such as specific factors exacerbating AD, drug treatments, and the identification of signaling pathways. Future research may benefit from focusing on uncovering signaling pathways as a key avenue for further exploration and understanding.

Keywords: AD, neurodegenerative disorders, immune cells, inflammation, signaling pathways.

1. Introduction

AD is named after the German neurologist Alois Alzheimer, who first described the disease in 1906. In the course of her work, Alzheimer encountered a patient named Auguste Deter, who developed severe memory and cognitive dysfunction in her 50s. Alzheimer observed and studied for a long time and performed an autopsy after her death. After the autopsy, Alzheimer found abnormal pathological changes in the brain, including amyloid plaques and neurofibrilla tangles. These pathological features become important hallmarks of AD. Her findings were published in 1906. In honor of her contribution, the disease was named AD.

WHO claims that over 50 million, about 10 million people increase each year [1]. The United States sufferers will reach 14 million in 2060 [2], while in the European Region, this figure is expected to rise to 18 million by 2050. In China, more than 10 million people are projected to be affected by AD. Despite these alarming statistics, a cure for AD remains elusive. Consequently, the emphasis has shifted towards prevention, early detection, and effective treatment as crucial strategies to alleviate the impact of AD on individuals and society.

This review will first delve into the pathomechanism of AD. Subsequently, it will explore the connection between AD and immune cells, highlighting changes in various types of T cells, macrophages, neutrophils, and B cells during the onset of AD. Additionally, it will examine drugs or

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pertinent exocytotic proteins that exhibit promise in slowing the progression of AD. Ultimately, the paper aims to consolidate information on drugs or relevant exocytotic proteins that could potentially decease the increasing of AD, which is aiming to offer insights into future therapeutic and preventative measures for this condition.

2. Pathogenesis of AD

Because of the imprecision of AD, it is supposed that alterations in immune cell function may be crucial in its onset and progression. Therefore, investigating changes in immune cell function in mice afflicted with AD can offer relevant understanding, which can offer new creative therapy.

2.1. Relationship between the T lymphocytes and AD

T cells are the key cells in the immune system, which are responsible for recognizing and killing abnormal cells. T lymphocytes include T helper (Th) cells, effector T cells and so on. table.

2.1.1. Th1 cells and Th17 cells

Most Th1 cells secrete IFN-γ(interferon-γ, hereafter), which is called CD4+IFN-γ+. An increase in Th1 cells leads to an exacerbation of AD. Several experiments have shown that Th1 not only promotes inflammation but also exacerbates the deposition of Aβ(β-amyloid, hereafter referred to as Aβ). In addition, Aβ-Th1 and Aβ-Th17 clones were transportted to specific mice and the same results were observed [3]. Similar to Th1, an increase in Th17 leads to an increase in AD. In addition, IL-23 plays an important role and can be considered as a therapeutic target.

Gene sequencing and protein analysis revealed that the intestinal flora changes during AD, leading to an increased accumulation of phenylalanine and isoleucine, which stimulates the proliferation and differentiation of Th1 cells in turn. Finally, it was found that the cellular changes in Th1 are consistent not only in the brain but also in the nose, cervical lymph nodes and spleen, which are the same results [4].

2.1.2. Th2 cells

Most Th2 cells produce interleukin 4 (IL-4), referred to as CD4+IL-4+, which differs from Th1 cells in their ability to regulate inflammation, making them a promising therapeutic avenue for Alzheimer's patients. Studies have shown that administering small portion Th2-specific cells can reverse cognitive impairments by reducing amyloidosis through pathological assessments. Previous research has suggested that elevated standards of tumor necrosis factor-α lead to increased expression of formyl peptide receptor 2 (mFPR2) in mouse microglia, exacerbating amyloid-β (Aβ) deposition. In contrast, IL-4 inhibits TNF-α upregulation by inhibiting the sensitization of extracellular-signal Regulated Kinase, p38,mitogen-activated protein kinases, and enhancement of kappa light chain in B cells activated by nuclear factors, consequently hindering Aβ deposition.

2.1.3. Treg cells

Regulatory T cells (Treg cells) are commonly recognized as CD4+CD25+FoxP3+, with FoxP3 serving as not only a crucial marker of Treg cells but also being involved in their differentiation and function. Deficiencies in FoxP3 can lead to autoimmune disorders in both humans and mice, similar to Th2 cells, Treg cells also play a role in suppressing inflammation and have been investigated in AD. The engineered TCR Aβ-Treg, created through Clustered Regularly Interspaced Short Palindromic Repeats. It has demonstrated some sustained immunosuppression, reduced microglial responses, and amyloid burden. This over-expression of TCR Aβ-Treg leads to the restoration of brain homeostasis, ultimately enhancing learning and memory functions [5].

2.2. Relationship among neutrophils and AD

Being the initial responders to inflammation in the body, neutrophils feature chronic inflammation. this has prompted an uptick in research dedicated to unraveling this phenomenon. Initially, scientists

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uncovered Lymphocyte Function-Associated Antigen 1 can interplay with neutrophils, exacerbating cognitive decline in AD. Subsequent investigations revealed that the binding of Aβ to neurons in the brain triggers the release of mitochondrial DNA (mtDNA) from damaged neurons,which can cause to the permeation to neutrophils into the brain. This process also triggers an increase in STING, NLRP3, and IL-1β levels [6]. The adhesion of neutrophils to brain capillaries can impede or halt capillary blood flow, impacting cognitive and memory functions. The neutrophil-to-lymphocyte ratio (NLR) has emerged as a diagnostic marker in AD [7], with studies indicating that vitamin D-induced ischemic lesions in Alzheimer's are not linked to elevated NLR. Therapeutically, targeting neutrophil trafficking from the bone marrow to the bloodstream using anti-IL-17A and anti-IL-23 antibodies has shown promise in inhibiting their infiltration into brain tissue and stands as a potential therapeutic avenue [8]. Furthermore, certain inflammatory stimuli can exacerbate AD, as observed when acute enteritis triggers neutrophil infiltration into various tissues, thereby aggravating the disease onset in patients or laboratory animals [9].

2.3. Relationship between macrophages and AD

Macrophages primarily tasked with engulfing and eliminating pathogens and waste materials from the body. These immune cells can be categorized into two main types based on their functions - M1 and M2 [10]. M1 macrophages are known for their pro-inflammatory properties and their role in promoting Th1-type immune responses. They exhibit high cytokine and eliminate pathogens. The other side of the shield, M2 macrophages are anti-inflammatory in nature. The M2 category is diverse and has several subsets: M2a, M2b, M2c, and M2d.M2a enables them to engulf apoptotic cells and metabolic waste. M2b are sensitized from some complexes. M2c macrophages, on the other hand, are induced by IL-10 and glucocorticoid signaling. M2d macrophages are activated by adenosine receptor agonists or IL-6.

When macrophages appear in Alzheimer's mice, a number of immune cells are also altered. Initially, it was found that TASTPM transgenic mice (APPswe×PS1M146V)underwent SNI (selective nerve injury model)conditions in which partial abnormal pain occurred, but exhibited full abnormal pain in the presence of peripheral opioid receptor antagonists. Subsehuaequent experimental investigation revealed that the infiltrating macrophages were predominantly M2 phenotype and it was the enkephalins secreted by the macrophages that attenuated the pain [11].

2.4. Relationship between B lymphocytes and AD

B cells, similar to Th cells, are primarily involved in antibody production and immune responses. For mice, studies have revealed that the improvement of AD, which is connected to a dropping with the number of B cells and alterations in their functioning, further contributing to the accumulation of pathological proteins and neuronal damage [12]. Similar reductions in B cell count have also been observed in other neurodegenerative diseases.

In conclusion, immune cells experience substantial functional and numerical changes on the enhancement for AD. The transformations of the function and quantity of macrophages, T cells, and B cells give rise to intensify inflammation and neuronal damage deteriorated. These insights offer new avenues for understanding the pathogenesis of AD and emerge newfangled concepts and tactics.

3. Mice used in the study

The mouse serves as a commonly utilized experimental model in AD research. Presently, there exist a minimum of 10 mouse models designed for studying AD. While these mouse models offer valuable insights, none can fully replicate all the cognitive impairments observed in human AD. AD is a sophisticated status encompassing not only memory deficits but also a series non-cognitive symptoms. These non-cognitive manifestations are exhibited across various mouse models for AD, warranting increased attention to both cognitive and non-cognitive traits of the disease. By focusing on these comprehensive deficits, researchers can better select suitable mouse models to investigate AD pathology and progression.

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4. Current status of drug research in AD

AD research extensively explores drug treatment options. Firstly, studies focus on traditional Chinese medicine, indicating that a combination of Paeonia lactiflora and licorice soup enhances the cognitive performance of Alzheimer's mice by targeting the NLRP1 and NLRP3 structural domains [13]. Secondly, the monoclonal antibody Lecanemab, a human IgG1 monoclonal antibody, exhibits a strong affinity for binding to Aβ soluble protofibers and is employed in the treatment of individuals with AD [14]. Lastly, the protein NR is recognized for its ability to elevate NAD+ levels within the brains of transgenic Alzheimer's mice, thereby reducing inflammation and decelerating the aging process [15]. Research efforts into therapeutic medications for AD adhere, and the future keeps on undertaking the increasing for additional drugs capable of mitigating or potentially eradicating this debilitating condition.

5. Conclusions

In conclusion, this study demonstrates functional and quantitative alterations in immune cells in mice affected by AD. The observed changes signify a rise in inflammation within the organism, providing a factual basis for subsequent investigations. According to specific models, unchecked inflammation could potentially escalate to life-threatening levels. While recent years have witnessed the discovery of medications capable of mitigating inflammation and delaying the onset of AD, a definitive cure remains elusive. Further exploration into the underlying mechanisms is essential, encompassing the sequencing of inflammatory processes, identification of signaling pathways, and elucidation of the upstream and downstream connections of each factor. By delving into these mechanisms, it may be possible to develop targeted drugs that could effectively treat or even eradicate the disease. These therapeutic interventions aim to enhance both the quantity and functionality of immune cells in individuals with Alzheimer's, thereby decelerating the progression of the condition.

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