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The pathology, diagnosis and treatment of Alzheimer's disease

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Abstract. Alzheimer's disease (AD) is the main cause of dementia worldwide. Although the pathology of AD is not yet completely understood, it has been widely acknowledged that the biomarkers including beta-amyloid plaques, neurofibrillary tangles and the neuroinflammation induced by these hallmarks contributed to the AD's pathology. Different from the conventional diagnosis of AD which is based on clinical criteria, the modern methods relay on biomarkers imaging and fluid test. Currently, although the treatment of AD is targeted to symptomatic therapy, advanced therapies that target the hallmarks of AD such as anti-beta-amyloid and APOE related therapies are under developing. Here, we will first review the major hypothesis of AD's pathological mechanism and then discuss the methods of diagnosis and treatment of AD which is developed in progress.

Keywords: Alzheimer's Disease, Amyloid Beta, Tau, Neuroinflammation, Therapy.

1. Introduction

Dementia is a degenerative condition marked by a deterioration in cognitive functions, which goes beyond the expected decline associated with normal aging. According to the World Health Organization's 2022 estimate, over 50 million people worldwide suffer from dementia. The considerable costs of medications and caregiver fees impose a substantial financial strain on patients, their families and the social healthcare system. Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia, accounting for more than 70% of all cases[1, 2] and primarily affecting older adults. The condition is characterized by a gradual decline in cognitive functions, including memory, language, problem-solving, and decision-making abilities, which eventually leads to a loss of independence and a diminished quality of life. Up to date the widely acknowledged hallmark pathological features of Alzheimer's disease are the accumulation of amyloid-beta (Aβ) plaques, neurofibrillary tangles composed of hyperphosphorylated tau proteins in the brain and the sustained neuroinflammation caused by these protein aggregates[3].

Diagnosing Alzheimer's disease can be challenging, as its symptoms often overlap with those of other neurological disorders. Traditionally, diagnosis involves a comprehensive assessment of patient's clinical criteria, including clinical history, physical and neurological examinations, cognitive testing. Despite their widespread use, traditional diagnostic methods for neurodegenerative disorders often exhibit low sensitivity and specificity. To enhance diagnostic accuracy, cutting-edge techniques like positron emission tomography (PET) scans and the analysis of amyloid-beta (Aβ) and hyperphosphorylated tau (p-tau) levels in cerebrospinal fluid (CSF) have been developed.

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Although there is currently no cure for Alzheimer's disease, various treatments and interventions were developed aiming to manage symptoms, slow disease development, and improve the quality of patients' as well as their families' life, including pharmacological therapies such as cholinesterase inhibitors and memantine as well as non-pharmacological interventions, like physical exercise and maintaining a healthy diet. Based on the guidance of AD pathology hypothesis, new methods and medicine such as anti- Aβ antibody, APOE related genetic therapy and natural products therapies are developed and discovered.

In this article, we will review the latest acknowledgement of the pathological pathway, newly developed diagnosis methods, and the recently approved therapeutic strategies of AD.

2. Amyloid Hypothesis

The first paragraph after a heading is not indented (Bodytext style). Among the various hypotheses related to AD pathology, the principal one, and most widely accepted, is the extracellular accumulation of amyloid-beta (Aβ). This hypothesis suggests that AD results from a pathological disruption involving the accumulation and deposition of Aβ, which forms amyloid plaques. These plaques subsequently lead to synaptic and neuronal damage.

Aβ is a highly insoluble peptide that is extremely challenging to degrade. Aβ peptides can vary in length, with the most common forms being Aβ40 and Aβ42. While both forms can aggregate and contribute to amyloid plaque formation, Aβ42 is considered more neurotoxic. Typically, Aβ42 adopts a β-pleated sheet-like structure, which has a high tendency to aggregate, forming the primary component of amyloid plaques [4–8]. Aβ peptides, including Aβ42, are generated through the abnormal hydrolysis of amyloid precursor protein (APP), a transmembrane glycoprotein ubiquitously expressed on the membrane of human cells.

The degradation of APP can have two different pathways: the non-amyloidogenic and amyloidogenic pathways. In a healthy human brain, the degradation of APP recruits an enzyme called ADAM (A Disintegrin and Metalloproteinase), cutting the APP at the α-site. This process produces a soluble peptide called APPsα (soluble APP-alpha) and a second peptide fragment that remains within the membrane. The second peptide, after being cleaved by ADAM, is further broken down by γ-secretase into smaller peptide fragments called p3 and AICD (APP Intracellular Domain). All the peptides produced through this degradation pathway involving ADAM and γ-secretase are soluble and nontoxic[9, 10], making this the non-amyloidogenic processing pathway for APP. However, in an AD patient brain, APP is cleaved by beta-secretase and gamma-secretase, producing Aβ peptides, which can aggregate and form amyloid plaques in the brain, contributing to the development and progression of AD. The amyloidogenic processing of APP involves the following steps: 1. Beta-secretase (also called BACE1) cleaves APP at its extracellular domain, generating a soluble fragment called sAPPβ and a membrane-bound peptide called C99) [11]. 2. Gamma-secretase then cleaves the C99 fragment within the transmembrane region, releasing the Aβ peptide and an intracellular domain called APP intracellular domain (AICD).

While Aβ plaques have a significant role in the development of AD, the underlying mechanisms are not yet fully understood and warrant further research. Recent studies have demonstrated that Aβ oligomers, smaller aggregates of Aβ peptides, also exhibit cellular toxicity. They can impact cellular components such as the nucleus, leading to damage to genomic information, and can penetrate cell membranes, causing an imbalance in membrane potential.

Additionally, the research of immunological has shown that Aβ aggregation can activate immune cells in the brain, such as microglia and astrocytes, leading to the secretion of various inflammatory mediators that can be harmful to neurons. This suggests that Aβ accumulation may contribute to neuroinflammation in the brain, further exacerbating the pathology of AD.

3. Tau hypothesis

The Tau hypothesis presents an alternative perspective in AD research, positing that the abnormal behavior of tau proteins such as hyperphosphorylation and aggregation, resulting in neurofibrillary

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tangles, are central to the disease's development and progression. Tau proteins are microtubule-associated proteins that help stabilize microtubules in neurons, essential for maintaining the structural integrity and function of these cells[12, 13]. The Tau hypothesis suggests that abnormal hyperphosphorylation causes tau proteins to detach from microtubules and aggregate into paired helical filaments, forming neurofibrillary tangles inside neurons. These tangles disrupt neuronal function by destabilizing microtubules, hindering synaptic function, and leading to neuronal death.

4. Neuroinflammation hypothesis

While it is known that Aβ plaques and hyperphosphorylated tau proteins are toxic and can directly damage neurons, recent research suggests that they may also induce inflammation in the brain by activating immune cells like microglia and astrocytes.

Neuroinflammation refers to the inflammatory responses that occur within the brain. In the context of AD, the neuroinflammatory process involves the activation of microglia and astrocytes by Aβ or hyperphosphorylated tau (p-tau) proteins, followed by the release of inflammatory mediators such as cytokines, chemokines, neurotransmitters, and reactive oxygen species (ROS) [14]. These mediators can attract monocytes and lymphocytes to cross the blood-brain barrier (BBB) and stimulate resting microglial cells [15, 16]. This process creates a positive feedback loop in which an increasing number of microglial cells become involved, releasing even more inflammatory factors that accelerate the pathology of AD.

Microglia are immune cells in the central nervous system (CNS) and play crucial roles in maintaining neuronal function, including clearing unnecessary plaques and damaged neurons. The activation of microglia involved the triggering of receptor for advanced glycation end products (RAGE) and macrophage colony-stimulating factor (M-CSF) [17]. When Aβ plaques are detected by these receptors, microglia congregate around the plaques but are unable to engulf the hydrophobic Aβ plaques due to their size. Consequently, more mediators, such as cytokines and chemokines like IL-1/6/8 and TNF-α1 [17, 18], are secreted to activate additional microglia, promoting the clearance process [17, 19]. However, during the clearance process, microglia release toxic substances, such as reactive oxygen species (ROS) and free radicals, which are harmful to neuronal cells. As a result, numerous cells undergo apoptosis, and further neuroinflammation takes place. Understanding this complex interplay between microglia activation, Aβ plaques, and neuroinflammation is essential for developing potential therapeutic interventions to address AD progression.

Astrocytes are star-shaped cells responsible for maintaining ion balance and repairing damage within the brain and spinal cord. Similar to microglia, astrocytes are activated by Aβ plaques and gather around them. Astrocytes release mediators, such as prostaglandins, thromboxane, complement factors, interleukins (ILs), leukotrienes, proteases, protease inhibitors, and coagulation factors, to stimulate additional astrocytes. However, the increased involvement of astrocytes leads to an overproduction of reactive oxygen species (ROS) and cytokines, which can exacerbate neuronal inflammation.

5. Current diagnosis of AD

Patient symptom observation is the most traditional method used for diagnosing Alzheimer's disease (AD). In 2011, the National Institute on Aging-Alzheimer's Association (NIA-AA) published clinical criteria for symptom observation of AD patients, building upon the original 1984 version [20–22]. However, this traditional method has low accuracy and specificity. For example, it can be tough to distinguish between early-stage AD symptoms and memory loss resulting from normal aging. To overcome these limitations, contemporary diagnostic techniques with greater accuracy have been introduced.

Positron emission tomography (PET) is a technique that employs radiotracers to pinpoint and image changes in particular metabolic activities. When undergoing a PET scan, patients receive an injection of a radiotracer that circulates through the bloodstream and specifically binds to Aβ plaques. The PET scan subsequently detects the presence and quantity of Aβ plaques in the patient's brain. This

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diagnostic approach boasts a sensitivity of 96% and specificity of 100% [23]. However, due to the high expense of amyloid PET imaging, it remains inaccessible for many individuals, restricting its broad application. Another method that is more affordable but also more invasive is the examination of cerebrospinal fluid (CSF). This approach measures the concentrations of Aβ and p-tau proteins in the CSF, obtained via a lumbar puncture procedure. The accuracy of CSF analysis is lower than PET scans, ranging from 85% to 90%. Despite PET and CSF tests, a serum test can also be performed to measure the levels of specific proteins involved in AD. This method is less invasive compared to the other options.

6. Current Treatment of AD

Current treatments for Alzheimer's disease (AD) primarily focus on managing symptoms, as there is no cure for the disease yet. These treatments can be categorized into pharmacological and non-pharmacological interventions. The first type of pharmacological therapy is cholinesterase inhibitors. These medications, including donepezil, rivastigmine, and galantamine, work by ether increasing the secretion levels of acetylcholine which is a neurotransmitter involved in memory and learning or reducing the hydrolysis of it to increase the lifetime of acetylcholine. They help improve cognitive function and may alleviate some behavioral symptoms in mild to moderate AD. Nonetheless, cholinesterase inhibitors are primarily effective for individuals in the initial stages of Alzheimer's disease. The second type of pharmacological therapy is memantine. Memantine is N-methyl-D-aspartate (NMDA) receptor antagonist and functions by blocking the entry of calcium ions (Ca^{2+}) into the cell, reducing or preventing calcium influx [24]. This results in a more significant charge difference, enhancing signal transmission strength. All five drugs have been shown to effectively alleviate AD symptoms. Donepezil, galantamine, and rivastigmine are beneficial for all AD and Parkinson's patients, whereas memantine is appropriate for individuals with moderate or severe AD stages [25, 26].

Non-pharmacological interventions include cognitive stimulation and rehabilitation, occupational therapy, physical exercise and social engagement. Cognitive stimulation and rehabilitation involve engaging in mentally stimulating activities to improve cognitive function and maintain existing abilities. They can be carried out individually or in a group setting. Occupational therapists can help patients adapt to their environment and develop strategies to maintain independence in daily activities. Regular physical activity has been shown to improve overall well-being and may help slow cognitive decline in individuals with AD. Participating in social activities can help maintain cognitive function and emotional well-being. Additionally, it is believed that individuals following a Mediterranean diet could lower the risk of developing AD. The Mediterranean diet typically includes seafood, fresh produce, and plant-based products like olive oil while limiting the consumption of processed foods (particularly red meat and oil) and refined grains. The primary reason this diet may reduce the risk of AD is that olive oil and fish lipids can inhibit receptors on human immune cells, preventing their activation and the subsequent release of reactive oxygen species (ROS) and chemokines.

7. Future treatment

The accumulation of Aβ peptides, particularly Aβ42, in the brain is considered a primary event in the development of Alzheimer's disease. Thus, understanding the processing of APP and the factors that influence the balance between non-amyloidogenic and amyloidogenic pathways is crucial for developing therapeutic strategies aimed at reducing amyloid plaque formation and treating AD.

Anti-Aβ antibodies can be developed and introduced into a patient's body to specifically target and break down Aβ plaques. In 2014, two monoclonal antibodies were developed, but neither demonstrated significant improvement in patients with moderate-stage Alzheimer's disease. Subsequent research suggested that this treatment is only effective for patients in the early or mild stages of AD. An alternative approach to preventing Aβ plaque formation is to inhibit the production of beta-secretase. As previously mentioned, beta-secretase plays a crucial role in the abnormal

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processing of APP. In the absence of beta-secretase, amyloid β would not be produced, and consequently, plaques would not form.

Besides Aβ plaques, hyperphosphorylated tau protein is also important in causing Alzheimer's disease. Tau vaccines and anti-tau medications, aimed at eliminating the build-up of hyperphosphorylated tau protein, are under development. At present, these anti-tau treatments and vaccines have only undergone testing in animals.

Gamma oscillations are high-frequency brainwaves related to neuronal communication, potentially involved in verifying the accuracy of certain memory elements. Researchers at MIT have found that in a mouse model of Alzheimer's disease, increasing gamma oscillations resulted in a reduction of Aβ aggregates and an improvement in cognitive function. For humans, this method has been utilized to stimulate patients' visual and auditory capacities.

8. Conclusion

In this review, we have summarized the primary hypotheses of AD pathology, including Aβ, p-tau, and neuroinflammation. However, each of these can only partially explain the pathology of AD, necessitating further research in the future.

We also reviewed advancements in AD diagnosis and treatment methods. In contrast to symptom-based clinical criteria, advanced imaging and fluid tests are paving the way for more effective diagnostic approaches. As for treatment, while currently approved drugs can improve memory and alertness in AD patients, the overall progression of AD remains unaddressed. To enhance treatment efficacy, several advanced methods based on Aβ and p-tau theories have been developed, including antibodies and vaccines targeting Aβ plaques, BACE1 enzymes, and p-tau.

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