

Mechanism and treatment of cell death in Alzheimer's disease

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Abstract. With 60 to 80% of cases, Alzheimer's disease (AD) is the primary trigger of dementia around the globe. The prevalence of people aged 65-69 years increased from 1% to about 30% of people aged 85 years, resulting in more than 50 million affected individuals globally. The AD in the formation of amyloid, the tau protein distribution, the interaction between amyloid and tau protein, clinical symptoms, the genetic background and so on various aspects are heterogeneity exists. Therefore, there is no single pathological process or mechanism of action that can explain why people develop AD. The prevalence of Alzheimer's disease is one of the largest global public health issues today. There have been many different therapy modalities investigated over time. But there is still no cure, and all that can be done for AD is to prevent and delay its progression. Current drug treatments are intended only to alleviate symptoms, not cure the root cause. Based on the universalization and decreasing age of AD, it is particularly significant to study the causes and pathogenesis of AD and how to prevent and treat it. This paper introduces the main stages of the process of AD, introduces two hypotheses -- tau hypothesis and amyloid interpretation, and the role of RNA splicing in this process is summarized. In addition, in order to provide more research ideas, the author describes the current treatment options for AD, from the risk factors that may cause AD to the latest specific treatments. The treatment approach suggests that both at-risk patients and those without underlying diseases make early lifestyle and dietary adjustments and gradually move towards a healthy lifestyle in order to reduce the incidence of Alzheimer's and the financial burden on families and society. This is in addition to early drug treatment to lessen the suffering and life experience of Alzheimer's patients.

Keywords: Alzheimer's disease; treatment; tau protein; Beta-amyloid protein.

1. Introduction

Alzheimer's disease, also known as dementia, is among the six major causes of death worldwide. With the increase of population aging, the problem of Alzheimer's disease will become more and more prominent [1], has become a worldwide problem, and the prevalence will gradually increase. AD brings a huge burden not only to families but also to society. A chronic neurodegenerative condition, Alzheimer's disease typically affects the medial temporal lobe and related neocortical regions. It has a clear pathophysiological mechanism. Alzheimer's disease is divided into three clinical stages. Pre symptom (or pre-clinical) AD, which can develop over a period of years [2]. Excessive amyloid production and accumulation reaches a critical level, triggering the amyloid cascade; The pre-dementia stage of AD (which corresponds to the definition of progressive and amnesic mild cognitive impairment) involves active lesions that vary from moderate neuronal dystrophy to early Braak, which can extend over several years, depending on the resilience and reserves of the human brain; ; a patient is diagnosed stage of dementia in AD, when mental and physical abilities begin to decline; and the amyloid cascade is initiated; In this phase, the affected brain regions have a mass of nerve plexus and neurofibrillary tangles, which are related to the overall severity of the injury [3].

The pathological signs of AD include neuropathic plaques and neurofibrillary tangles, which are linked to cytoskeletal alterations brought on by amyloid beta peptide ($A\beta$) buildup in brain tissue and microtubule-associated Tau protein hyperphosphorylation in neurons, respectively. Nowadays, there are two kinds of pharmaceuticals that have been licensed to treat AD: cholinesterase inhibitors and N-methyl-D-aspartic acid (NMDA) antagonists. These drugs do not address the fundamental cause of AD; they simply serve to alleviate its symptoms. The focus is largely on prevention. AD has a long

early stage in which preventive measures are particularly important. Psychological and social factors, potential diseases, lifestyle, and other aspects can have a potential impact on cognition and provide insights into Alzheimer's disease prevention [4].

Research into future treatments for Alzheimer's will also involve both. But many scholars still disagree about which abnormalities are the best targets for slowing or halting neurological decline. With regard to drug therapy for Alzheimer's disease, drug therapy is on basis of the reduction of symptoms of Alzheimer's disease, not on treating it. Namely, drug therapy can only be used to postpone the development of the disease. This gives us an idea -- early treatment. But it is difficult to accurately diagnose early Alzheimer's based on existing technology. Second, as Alzheimer's disease progresses, we inevitably need to increase the dosage of drugs, but this may also cause other adverse effects. Another limitation is how AD is administered later. When AD is in an advanced stage, drugs are of limited use. Therefore, the early intervention of AD and the discovery of additional biomarkers that can be used to diagnose early AD are very important.

This paper introduced the historical background of Alzheimer's disease and the retrograde neurodegeneration caused by abnormal tau protein function and hyperphosphorylation. The activity of neurons is crucial to the normal brain, and tau, a protein associated with microtubules, plays a certain role in the normal function of human brain neurons. Research into future treatments for Alzheimer's will also involve both. But many scholars still disagree about which abnormalities are the best targets for slowing or halting neurological decline.

2. The Main Mechanism of AD

Despite the loss of functional tau, other microtubule-associated proteins compensate, this is not what happens in a normal body. Functional tau becomes unregulated, becomes toxic, and the functional neurons associated with it slow down later in their work, resulting in retrograde neurodegeneration, which is also characteristic of Alzheimer's disease. The current leading cause of tau dysfunction is abnormal tau hyperphosphorylation. In such a form, it is a major subunit of the paired helical filament (PHFS)/neurofibrillary tangle proteins [5]. Studies have shown that neurofibrosis in Alzheimer's disease may require the activation of PP-2A or inhibition of GSK-2beta and cdk5, or either of these two kinases plus PKA or CaMKII. It can provide a new idea for follow-up treatment [5].

Neurodegenerative diseases are a major challenge for modern healthcare because of the aging population and life style, the amount of patients, the effect of the diseases on the lives of patients and their caregivers, and the economic influence they have. If appropriate preventative or treatment methods are not discovered, the number of persons with neurodegenerative disorders would nearly quadruple to 152 million by the year 2050 [6].

Medications cannot cure AD, but these therapies help to maintain independence for those who are living with its symptoms and enhance the quality of life for both AD patients and those who care for them. Alzheimer's disease is regarded as an illness with several risk factors, including aging, genetics, traumatic brain injury, cardiovascular problems, infections, and environmental factors (Fig 1). (heavy metals, trace elements, etc.). Typical vascular risks include rampant use of cigarettes, alcohol consumption, diabetes, high cholesterol, and physical inactivity. Common vascular risk factors include smoking, alcohol consumption, diabetes, high cholesterol, and physical inactivity. Based on the genetic risk of AD, it is highly recommended that if there is a history of AD in the family, it should be timely. Attention should be paid to the early symptoms of AD in the usual physical examination, and timely treatment [7]. At present, there are mainly two hypotheses for the treatment mechanism of AD: amyloid A- β hypothesis and Tau protein hypothesis.

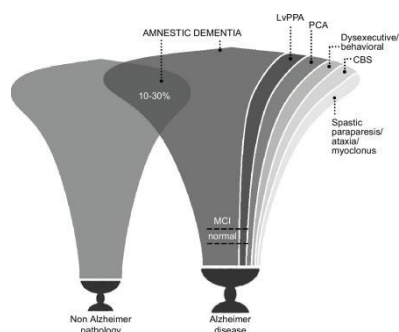


Fig. 1 Non Alzheimer pathology and Alzheimer disease [7].

2.1. Tau protein

Tau is a strongly soluble, internally mixed, non-ordered protein encoded by the MAPT gene on chromosome 17. Its large proto-unfolded region is rich in axons of developing and mature neurons. The microtubule-associated tau protein promotes axonal microtubule (MTS) stability in the brain and is involved in the regulation of axon growth and axonal migration. However, it has been shown that tau knockout in mouse models and touching neurons does not damage onlooker assembly or axon transport [8]. In the experiment, Tau knockout mice did not exhibit a serious phenotype in the experiment, indicating that other microtubule-associated proteins (MAP1A, MAP1B, MAP2, etc.) can take Tau's place and function normally [9]. The same phenomenon is seen in humans with disease-causing tau mutations or complete tau destruction [8]. Pathological markers of AD include Tau phosphorylation, elevated aggregation, and neurofibrillary tangles (NFTS). In known studies, Only tau "hyperphosphorylation" is linked to tau aggregation and toxicity in studies that are known to exist; the causal link between tau phosphorylation and enhanced tau aggregation is unclear. In recent years, the main way to describe the pathological changes of tau is through the detection of tau specific phosphorylation sites, as well as silver or thioflavin staining of beta containing tau aggregates [9]. Protein linked with microtubules (MAP) Tau is the primary paired helix (PHF)/straight filament protein subunit of healthy adult neurons. (SF), These proteins build up in the bodies of dystrophic and infected neurons (as neurofibrillary tangles), (as neurofibrillary lines and AD neutral plaques surrounding beta-amyloid and new dystrophic neurons). In contrast to normal tau, which promotes microtubule assembly and stabilization, abnormally hyperphosphorylated tau prevents assembly and degrades microtubules. MAP1, MAP2, and abnormally hyperphosphorylated tau are linked to each other and compete with tubulin and microtubules. Microtubule breakdown results from aberrant tau storing normal MAP. Tau filament tangles are created when aberrant tau associates with normal tau rather than MAP1 or MAP2. Enzymatic phosphorylation of abnormally hyperphosphorylated tau removes all of these harmful characteristics. In the AD brain, phosphorylation can separate aberrant tau into a normal comparable form by activating phosphoacyl/phosphodiacyl protein phosphatases (PP)-2A and PP-1. In vitro, dephosphorylation of PP-2A, PP-2B, and to a lesser extent PP-1 enhances AD P-tau activity while restoring normal microtubule assembly. Dephosphorylation with PP-2A in vitro also dissociates the PHF neurofibrillary tangles isolated from the AD brain, and tau released in this process can act on microtubule assembly. Therefore, abnormal tau proteins linked to normal tau proteins form neurofibrillary tangles of tau filaments on this basis, which appear to cause neurodegeneration by causing the collapse of microtubule networks. A possible strategy to prevent nerve fiber degeneration and the illness caused by this damage is to increase tau phosphatase activity [8].

2.1.1 Pathological model of Alzheimer's disease

Researchers have created speculative models of the connections between tau and Spliceosomes in AD. According to their hypothesis, clipping factors may be linked to insoluble and soluble Tau species, resulting to the retention or disruption of snRNP assembly and/or stability in the cytoplasm. Tau-spliceosome interactions may result in central nervous system dysfunction in all cases by way of

shearing mistakes, global transcriptome alterations, and finally total loss. Given the significance of splicing, practically all mutations in core spliceosomal proteins that have been previously discovered are deadly in drosophila and other animals. According to research using fruit flies, covert splicing errors were more frequent in elderly animals, genetic modification of multitudinous essential snRNP components increased Tau toxicity, and tau generated splicing errors equivalent to the loss of SmB function. All of these findings imply that tau-induced neurotoxicity in AD and other tau disorders may be mediated by spliceosome disruption and the consequent splicing errors [9].

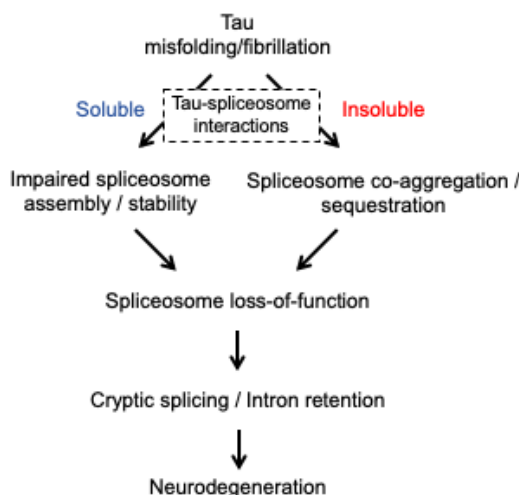


Fig. 2 Tau protein neurodegeneration [9].

2.1.2 RNA-splicing

It has been demonstrated by Hsieh et al. studies that Tau neurofibrillary tangles in Alzheimer's disease pathologically disrupt spliceosomal activity by fusing postmortem human brain tissue with drosophila melanogaster models. Tau-mediated neurodegenerative pathways have been linked to RNA splicing mistakes, including intron retention and unannotated unexplained connections, and the ensuing transcriptome alterations [9]. In eukaryotes, precursor mRNA (pre-mRNA) splicing plays a critical function in controlling gene expression by removing introns and producing mature mRNA transcripts. Neurological illnesses can result from splicing disruption, which also cause the loss of transcriptional diversity and feature in neurons [10]. Many spirochaeta constituents are reportedly diminished by the transgenic expression of human tau, and the reduction of the main spirochaeta protein SmB's activity is enough to trigger progressive neuronal disorder and elimination independent of Tau.

2.2. Beta-amyloid protein (A beta)

Elderly non-dementia (ND) cases and Alzheimer's disease patients have been investigated for beta-amyloid protein (A beta) deposits in the medial temporal lobe (MTL) (AD). MTL in AD has A β deposits all over it, but the hippocampus is less dense than other cortical areas. A β deposits were not found in six of the ND cases, while for the remaining eight, A β deposits were restricted to cortical areas close to the hippocampus. Although there was considerable overlap among both groups, AD cases had an estimated prevalence of A β deposits in the cortical area investigated that was higher than ND cases. In contrast to AD patients, the proportion of mature to diffuse A β deposits in ND cases was greater. Several tissues displayed regular distribution along the cortex in parallel clusters with Piah in patient groups, and A β deposits organized into clusters in the cortex. A beta cluster in AD has a greater average diameter than in ND. Consequently, a number of characteristics of the A beta deposition appear to reliably separate ND instances from AD ones. Nevertheless, determinants in the development of AD may include the spread of beta disease across modular units in the cortex and the hippocampal region [11]. Neuropathological signs of Alzheimer's disease include intracellular braided nerve fibers and extracellular senile plaques (AD). According to the amyloid cascade

hypothesis, the major ingredient of aging plaques, amyloid beta (A β) peptide, and its derivatives, known as amyloid precursor protein (APP), have long been recognized as playing a decisive role in the onset of AD. A β peptide and APP buildup has been demonstrated to cause neurotoxicity and ultimately result in neuronal cell death earlier times. Overproduction of A β peptides and APP triggers a variety of cell signaling cascades, including apoptosis, necrosis, and autophagy, which brings about the demise of neuronal cells. On the other hand, stimulation of this pathway may also result in aberrant APP and A β peptide production [12].

3. Treatment

3.1. Preventive measure

Major lifestyle modifications, including as nutrition, exercise, and regular sleep schedules, are the top recommendations for all patients, regardless of the severity of the cognitive impairment, as they are the only interventions that now demonstrate a lower incidence of AD and may prevent general cognitive decline. In order to accomplish timely diagnosis of lesions, quick treatment, and reduced occurrence of consequences, the number of health examinations for some persons with underlying disorders should be suitably increased. Recent systematic reviews have discovered that people who follow the healthy diet—a diet high in fresh fruits and vegetables, whole grains, olive oil, legumes, and seafood—minimize their risk of acquiring AD and mental decline [4]. Red meat, processed foods, candy, and other sugary foods are also discouraged.

3.2. Future development direction and advice

With the creation of disease-modifying medications that should lessen amyloid plaques in the brain, the identification of individuals with AR-AD or preclinical AD has become crucial. Three anti-A β antibodies, Gandhi ureperizumab, and Aducanumab, have recently been reported to dramatically lessen the retention of amyloid ligand in the brain in PET tests as in comparison to placebo. The identification, creation, and validation of AD-related biomarkers have advanced significantly, opening the door to integrated models and multi-modal studies of various bodily fluids. They originate from neurogenetics, neurophysiology, and the neurochemistry of bodily fluids like CSF and blood (plasma/serum), as well as structural, functional, or metabolic neuroimaging. The sensitivity and/or specificity of the relevant investigators' expectations, as well as their current position, should be taken into consideration when analyzing the prediction performance of this multimodal technique, which has not yet been identified (i.e., isolation or combination). It is recommended that, with regard to the target population, figuring out risk variables might be a crucial step in enlarging the population (including biomarker status) in AD studies. A double-edged sword exists when expanding the population based on risk factors: on the one hand, it can be used to identify subjects who are more prone to disease progression, but on the other, those individuals may not necessarily be the most sensitive to therapies if this reflects accompanying multiple pathological processes that are not all suitable for the effective mechanism of the compound under study. Furthermore, words like "low risk", "medium risk", and "high risk" can leave some room for interpretation. Using all of the patient's risk variables, they can determine if a person is on the path to clinical manifestations of the disease, a process known as staging, or whether they are progressing slowly or quickly. The concept of "risk," which is defined in practice as the likelihood that a patient may suffer pathology for the rest of his or her life or during the experiment, should take into account both dimensions. Comorbidities and lifestyle variables that might impact the course of the disease and its results need to be closely watched [13]. We know from earlier research that the best chance of slowing or halting the advancement of AD 35 is early identification of at-risk individuals and follow-up care at the preclinical stage. Investigations are now enrolling asymptomatic individuals with a genetic susceptibility or biomarker that shows a greater chance of AD, with results anticipated early in the following decade over that time [14].

4. Conclusion

AD is a multifaceted neurological illness that attacks older persons and is distinguished by a progressive decline in memory, language, affection, and cognition [3]. Drug compositions and cholinesterase tablets are readily available and have FDA approval as a kind of AD. Although, with the progress of treatment, it is gradually found that this class of drugs has no effect on eliminating the pathogenic mechanism of AD and can only be used to improve the cognitive outcome and alleviate the symptoms of AD patients. How to find new ways to treat AD from the existing tau hypothesis and amyloid hypothesis in the future? Of course, it should be more about informing the public about how to prevent neurodegenerative diseases like AD. People with family genetic history should increase the early detection of AD and try to carry out interventional treatment for AD at an early stage to increase the survival rate. At the same time, young people should improve their lifestyle, reduce the risk of hypertension, diabetes, hypercholesterolemia and other diseases, avoid excessive smoking and drinking, strengthen physical activity and diet, which can significantly reduce the risk of AD.

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