Chapter 2
Deciphering the Molecular and Genetic Basis of Alzheimer's Disease

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Abstract Alzheimer's disease (AD) is a progressive age-related neurodegenerative disease in humans characterized by a decline in cognitive and personal daily activities. AD is considered a multifactorial disease involving different pathological and molecular phenotypes. Several risk factors like aging, genetic factors, infections, and environmental factors play in the onset of AD in humans. The advances in cellular biology have shed light on understanding the molecular mechanism underlying AD. However, current knowledge on the molecular pathogenesis of AD is complex and involves several hypotheses. Several genes and mutations are hallmarks of the molecular pathology of AD. These new discoveries on molecular pathogenesis and the involvement of genetic factors in AD are crucial because they will help us develop new therapeutic strategies for treating different conditions in AD. In the current chapter, we discuss the molecular mechanism inducing the onset of AD and the different genetic factors involved in it.

Keywords Alzheimer's disease · Cholinergic · Tau · Beta-amyloids · NMDA receptors

Abbreviations

Ach	Acetylcholine
AD	Alzheimer's disease
AP	Aβ plaques
ApoE	Apolipoprotein E
APP	Amyloid Precursor Protein
Aβ	Beta-amyloid

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CAA	Cerebral Amyloid Angiopathy
ChAT	Choline acetyltransferase
EC	Entorhinal cortex
EOAD	Early-onset Alzheimer's disorder
LOAD	Late-onset Alzheimer's disorder
LTD	Long-lasting depression
LTP	Long-term potentiation
PSEN-1	Presenilin 1
PSEN-2	Presenilin 2
VAChT	Vesicular acetylcholine transporter

2.1 Introduction

Alzheimer's disease (AD) is a progressive age-related neurodegenerative disease in humans, and it causes the most common form of dementia (Knopman et al. 2021). AD was described first in 1906 by Alois Alzheimer, and he noticed a presence of amyloid plaques and a massive loss of neurons in his first patient who suffered from memory loss and change in personality before dying. Alois Alzheimer described this condition as a peculiar severe disease process of the cerebral cortex (Alzheimer 1906). However, in recent times, AD is considered a chronic or progressive neurodegenerative syndrome characterized by impaired cognition affecting memory, thinking, learning, and behavior (Knopman et al. 2021). Around 50 million people are currently affected by AD worldwide, and the numbers may increase to 82 million by 2030 and 152 million by 2050 (Alzheimer's Association 2021). The main pathophysiological features in AD include (A) amyloid-β (Aβ) plaques aggregation in the extracellular region of neuronal cells and (B) hyper-phosphorylation of the microtubule-associated protein tau, which leads to neuronal disintegration deposits as neurofibrillary tangles in the intracellular region of neurons (Cubinkova et al. 2018; Lee et al. 2019). In addition, cellular impaired antioxidant systems, bioenergetics, and neurotransmitters also contribute to the onset of AD (Gandhi and Abramov 2012; Guan 2008; Liu et al. 2017). The role of oxidative stress in AD pathogenesis is associated with Aβ and tau proteins. The changes in the functional properties of these proteins are strongly associated with neural damages observed in AD (Liu et al. 2017).

The neuropathological changes of AD can be classified into two steps that provide evidence about the progress of AD disease and different types of symptoms. The first step is positive lesions characterized by the accumulation of neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads, and other deposits found in the neural tissues. The second step or negative lesion is characterized by considerable atrophy due to neural and synaptic loss. This will lead to neurodegeneration, neuroinflammation, and loss of cholinergic neurons (Serrano-Pozo et al. 2011; Spires-Jones and Hyman 2014; Singh et al. 2016).

The clinical phases in the patients with Alzheimer's disease can be classified into four stages: (A) a pre-clinical stage with mild memory loss and early pathological changes in cortex and hippocampus. This stage can last for several years or more with no functional impairment in the daily activities. This stage will not show any clinical symptoms of AD (Dubois et al. 2016; De-Paula et al. 2012). (B) Mild or early stage of AD characterized by several symptoms that start appearing in patients. These symptoms include loss of concentration and memory, disorientation of place and time, a change in mood, and slow development of depression (Wattmo et al. 2016). (C) Moderate AD stage where disease spreads to cerebral cortex regions, resulting in increased memory loss. This stage also involves loss of impulse control and difficulty in reading, writing, and speaking (Kumar et al. 2021). (D) Severe or late AD stage involving the spread of the disease to the entire cortex area. This further leads to a severe accumulation of neuritic plaques and neurofibrillary tangles in the cortex area. The patients will have severe functional and cognitive impairment and cannot recognize others. The patients will also suffer from difficulties in swallowing and urination, eventually leading to death due to all the above complications (De-Paula et al. 2012; Wattmo et al. 2016).

Aging is the most critical risk factor in AD, and most cases have late-onset that starts mostly after 65 years of age. Aging is an irreversible process involving a reduction in brain volume, a loss of synapses, and enlargement of ventricles in specific areas in the brain. In addition, aging also involves changes in glucose metabolism, cholesterol homeostasis, mitochondrial function, depression, and decline in cognitive ability. Since these changes also appear in normal aging, it is difficult to distinguish them from the early onset of AD. In general, AD is divided into early-onset AD (EOAD) and late-onset AD (LOAD) based on the age at which primary symptoms of AD appear. EOAD is the rare form with around 1–6% cases, and LOAD is more common with age of onset above 65. However, both EOAD and LOAD may occur in people who have a family with a positive history of AD (Guerreiro and Bras 2015; Hou et al. 2019).

In the following sections, major cellular and molecular causes of AD and different genetic factors influencing the early onset of AD pathology are discussed in detail.

2.2 Major Cellular and Molecular Causes of Alzheimer's Disorders

The underlying mechanism of pathological changes in Alzheimer's disease is still unknown. Several hypotheses were proposed as a cause for AD: the amyloid cascade hypothesis, the tau hyperphosphorylation hypothesis, and the neurotransmitter hypothesis. However, at present, none of these hypotheses are completely accepted for explaining AD pathogenesis. In the following sections, the amyloid cascade hypothesis, the tau hyperphosphorylation hypothesis, and the neurotransmitter hypothesis are discussed in detail.

2.2.1 Amyloid Hypothesis

The amyloid hypothesis was first proposed by John Hardy and David Allsop in 1991 (Hardy and Allsop 1991). The beta-amyloid (Aβ) is a transmembrane protein produced by hydrolysis of the Aβ precursor protein (APP) via the amyloidogenic pathway. For decades, it was proposed that abnormal deposition of Aβ plaques (AP) in the central nervous system has a strong correlation with dementia. This led to the concept of the amyloid hypothesis. However, the AP is also getting deposited in normal healthy brains with aging. This raised some doubts in the scientific community whether AP deposition is really responsible for the progressive development of AD. However, currently, the amyloid hypothesis remains the most accepted pathological mechanism for AD.

Aβ is a peptide having higher resistance for proteolytic degradation. It consists of 37–43 amino acids, in which the isoforms 1–40 and 1–42 are the most common. The 1–42 amyloid peptide isoform is hydrophobic and considered to have the greatest toxicity. Structurally, it often acquires the configuration of β-pleated sheet and shows a greater tendency to aggregate and form the core of the AP (Deane et al. 2009; Jucker and Walker 2015). The amyloid hypothesis suggests that the degradation of Aβ is decreased in AD pathological condition leading to the accumulation of Aβ peptides (Aβ40 and Aβ42) in the neurons. Aβ deposited in the hippocampus and basal segment in the form of AP recruits more Aβ peptides to form insoluble aggregates. This leads to mitochondrial damage, unstable homeostasis, and synaptic dysfunction (Lustbader et al. 2004; Hunt and Castillo 2012). At the same time, immune cells like microglia and astrocytes are activated, leading to some inflammatory reactions. This eventually causes neuronal dysfunction and apoptosis, leading to a series of pathological changes of AD (Ferreira and Klein 2011). The soluble Aβ peptides are suggested to be more toxic than Aβ cellulose bodies, and soluble Aβ peptides are proposed to be the initiating factors of developing pathological changes in AD (Ferreira and Klein 2011) (Fig. 2.1).

2.2.2 Tau Hyperphosphorylation Hypothesis

Tau is a microtubule-associated protein and found mainly in the neuronal axons in the brain. They are functionally involved in maintaining microtubule structure, cytoplasmic transport, maintaining synaptic structure, and regulating neuronal signaling (Kimura et al. 2014). In 1988, Claude Wischik isolated tau protein from AP in AD patients' brains, suggesting that tau protein may be the cause of dementia (Wischik et al. 1988). Tau protein kinase 1 activated by Aβ peptides leads to abnormal phosphorylation of tau protein and the development of tau pathology of AD (Vergara et al. 2019).

The tau protein presents six different isoforms in the central nervous system with variation in the binding sites for microtubules. In AD, initially, a phosphorylation

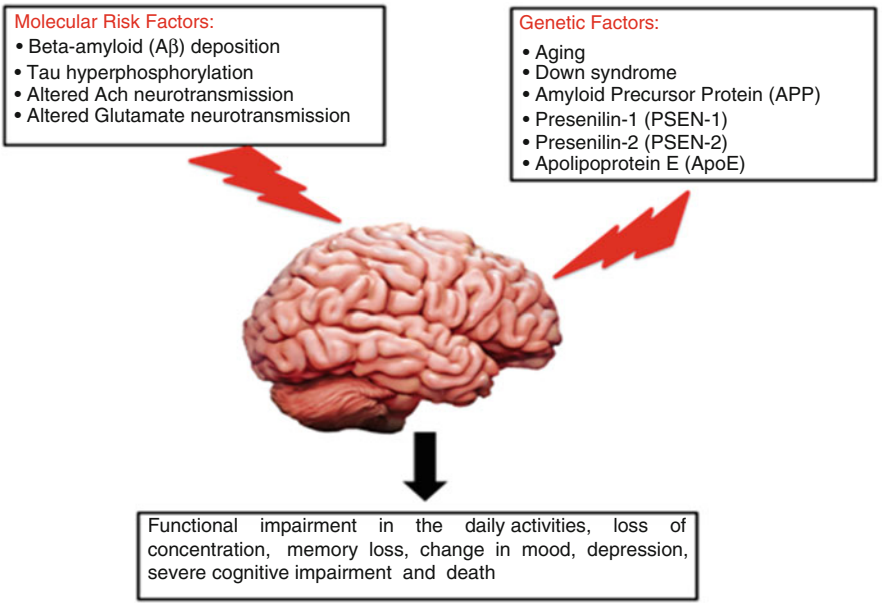

Fig. 2.1 Schematic representation of various molecular and genetic risk factors in the progression of AD and the related symptoms in AD patients

process of tau protein occurs, followed by hyperphosphorylation of tau molecules. The hyperphosphorylated tau protein forms aberrant aggregation with the cytoskeletal proteins. The hyperphosphorylated tau proteins show a lower grade of interaction with microtubules resulting in an increase in the free tau proteins. These extra free tau proteins lead to greater aggregation and fibrilization itself. This leads to subsequent malfunction of axonal transport (Goedert et al. 2006; Kuret et al. 2005; Rafii and Aisen 2009). The changes in the tau proteins and Aβ oligomers are the most important factors responsible for neuronal dysfunction in AD. The neurofibrillary tangles observed initially in the cortex and hippocampus subsequently spread to the amygdala and other cortical areas (Rafii and Aisen 2009), leading to different pathological conditions observed in AD (Fig. 2.1).

2.2.3 Cholinergic Hypothesis

The neurotransmitter acetylcholine (Ach) plays an essential role in cognitive function. The cholinergic hypothesis of AD was proposed based on the significant role of ACh in the cognitive, learning, and memory process. ACh is synthesized in the cholinergic neurons from choline and acetyl-coenzyme A by the choline acetyltransferase (ChAT) enzyme. It is further transported to the synaptic vesicles by vesicular acetylcholine transporter (VAChT). The ACh is involved in several

physiological processes such as memory, attention, sensory information, learning, and other critical functions in the central nervous system. At a molecular level, the cholinergic hypothesis of AD is the first and most studied approach that describes its pathophysiology. It was described 30 years ago as a primary degenerative process in AD capable of selectively damaging cholinergic neurons in different parts of the central nervous system. This cholinergic hypothesis was largely based on the immunohistochemical, neuroimaging, and other analyses revealing a decrease in the density and number of nicotinic acetylcholine receptors in AD patients. A reduction in functional expression of α3, α4, and α7 subunits of nicotinic acetylcholine at the cortex and hippocampus and a decline in the binding ability of α7 nicotinic acetylcholine receptors in the hippocampus and α4 nicotinic acetylcholine receptors in the cortex are observed in AD (Ringman and Cummings 2006; Wu et al. 2010). In AD patients, degeneration of cholinergic neurons was found, causing alternation in cognitive function and memory loss. Aβ is believed to alter cholinergic neurotransmission and cause a reduction in the choline uptake and a release of Ach at the synaptic regions. Various studies have demonstrated that cholinergic synaptic loss and amyloid fibril formation are related to Aβ oligomer neurotoxicity, confirming the interaction between ACh and Aβ (Francis et al. 1999; Ferreira-Vieira et al. 2016). In addition, a reduction in nicotinic and muscarinic Ach receptors is also observed in AD (Ferreira-Vieira et al. 2016) (Fig. 2.1).

The cholinergic and glutamatergic systems significantly interact during neurotransmission. So an alteration in the glutamatergic signaling has been associated with cholinergic disruptions observed in AD. In AD abnormalities of glutamatergic neurotransmission, the initial changes are observed at the entorhinal cortex (EC) followed by neurotransmission defects in the hippocampus, the amygdala, frontal cortex, and parietal cortex (Geerts and Grossberg 2006; Lin et al. 2010). The glutamatergic neurotransmission in the hippocampus mediates synaptic plasticity phenomena such as long-term potentiation (LTP). This facilitates learning and memory consolidation in the brain. The sustained hyperactivation of NMDA glutamate receptors has been associated with excessive depolarization of the postsynaptic membrane promoting the onset of neurodegeneration and cell death in the central nervous system (Beck et al. 2003; Szado et al. 2008). An increase in intracellular calcium as a result of dysfunctional glutamatergic neurotransmission may lead to long-lasting depression (LTD) in the cerebellum. In addition, it also activates nitric oxide synthesis and the generation of free radicals initiating neuronal death (Jung et al. 2009; Ndountse and Chan 2009). Several experiments were carried out to investigate the role of defective glutamatergic neurotransmission in AD. Incubating neurons with glutamate promoted the deposition of filaments similar to neurofibrillary tangles observed in AD. In addition, the neuronal culture exposed to Aβ promotes glutamate-induced neurotoxicity and regulates the expression of NMDA glutamate receptors on the neuronal membrane (Butterfield and Pocernich 2003; Parameshwaran et al. 2008) (Fig. 2.1).

2.3 Genetic Basis of AD

Genetic factors were found to play a major role in the development of AD. Most cases of early onset of AD are inherited in an autosomal dominant pattern. The mutations in the genes for amyloid precursor protein (APP), presenilin 1 (PSEN-1), presenilin 2 (PSEN-2), and apolipoprotein E (ApoE) proteins are associated with AD. Those inheriting mutations to these genes are guaranteed to develop AD if they complete a normal life span. The pathophysiological symptoms tend to develop before age 65 and sometimes as young as age 30. The vast majority of individuals have late-onset AD (Bekris et al. 2010; Goldman et al. 2011) (Fig. 2.1).

People with Down syndrome born with three copies of chromosome 21 (trisomy 21) have an increased risk of developing AD. Chromosome 21 includes the gene that encodes for APP production, and its hydrolysis produces Aβ that accumulates into plaques. An extra chromosome in Down syndrome may increase the production of Aβ fragments in the brain. People with Down syndrome develop AD at an earlier age than people without Down syndrome. By age 40, people with Down syndrome suffering from AD have significant levels of Aβ plaques and tau fibrillar tangles in their brains. According to the report from the National Down Syndrome Society, about 30% of people with Down syndrome have AD dementia by the age of 50, and about 50% of people with Down syndrome have AD dementia by the age of 60 (Lott and Dierssen 2010; Alzheimer's Association 2021) (Fig. 2.1).

In the following section, different genetic risk factors of AD are discussed.

2.3.1 Amyloid Precursor Protein (APP)

APP is a type I transmembrane protein cleaved by α-, β-, and γ-secretase to release Aβ and other proteins. The APP gene encodes APP on chromosome 21. Nearly 30 mutations have been found in the APP gene, and around 25 of them are related to AD. The mutation and functional defect in these genes cause an accumulation of Aβ with elevated concentration. A673T is a protective mutation that acts against the initiation of AD by decreasing the secretion of Aβ, Aβ40, and Aβ42 proteins (Li et al. 2019; Julia and Goate 2017) (Fig. 2.1).

2.3.2 Presenilin-1 (PSEN-1) and Presenilin-2 (PSEN-2)

PSEN1 and PSEN2 genes are autosomal dominant genes located on chromosomes 14 and 1. PSEN-2 and PSEN-1 are homologous with 67% similarity. More than 200 mutations in PSEN1 and around 40 mutations in the PSEN2 gene (Cai et al. 2015; Lanoiselee et al. 2017) are observed. PSEN1 is a core protein that activates the α-secretase complex and plays an important role in Aβ production. Mutations in the

PSEN1 gene increase the ratio of Aβ42/Aβ40 by decreasing Aβ40 secretion. The C410Y or L435F mutations in PSEN1 knock-in mice increased the Aβ42/Aβ40 ratio due to a greater reduction in Aβ40 (Kelleher and Shen 2017). In contrast, PSEN-2 mutations are rare and play a minor role in Aβ production. However, some of the mutations in PSEN-2 cause a significant increase in α-secretase activity with an increased Aβ42 secretion providing a higher Aβ42/Aβ40 ratio and are considered AD pathogenic mutations (Cai et al. 2015; Walker et al. 2005) (Fig. 2.1).

2.3.3 Apolipoprotein E (ApoE)

ApoE protein is a glycoprotein expressed highly in the liver, brain astrocytes, and microglia. It serves as a receptor-mediated endocytosis ligand for lipoprotein particles like cholesterol. Cholesterol is essential for the production of myelin that forms covering around the neurons and helps in normal brain function. The ApoE gene is located on chromosome 19 and has three isoforms: ApoE2, ApoE3, and ApoE4. The ApoE4 allele is a strong risk factor for both early-onset AD and late-onset AD. The ApoE2 and ApoE3 alleles are associated with lower risk and protective (Kim et al. 2009). ApoE4 plays an important role in Aβ deposition as a senile plaque and causes cerebral amyloid angiopathy (CAA). It is considered a marker for AD. In addition, ApoE4 was also associated with vascular damage in the nervous tissues leading to AD pathogenesis (Liu et al. 2013; Giau et al. 2015) (Fig. 2.1).

2.4 Conclusion

AD is currently considered one of the biggest health concerns. During the last decades, extensive studies on AD to understand the molecular pathology, factors influencing the onset of AD, and biomarkers to design therapeutic intervention have been carried out. Many drugs have been designed based on the molecular pathology of AD. However, the molecular pathogenesis of AD is complex, and it is based on different hypotheses. However, none of these hypotheses alone are able to clarify the fundamental aspects of pathology and its molecular regulations. The accumulation of Aβ and cellular mechanism by which it affects cholinergic neurons and following cognitive deficits are still not fully understood. Genetic factors in the form of mutation are also added concern as it is difficult to detect the early onset of AD. Interestingly, the cholinergic hypothesis has served as a basis for the majority of treatment strategies against AD. Most of the drugs were designed as acetylcholinesterase inhibitors, cholinergic precursors, cholinergic receptor agonists, allosteric cholinergic receptor potentiators, and NMDA receptor blockers (Doggrell and Evans 2003). Inhibitors to cholinesterase enzymes, such as galantamine, donepezil, and rivastigmine, and NMDA antagonists, such as memantine, improve memory and alertness. However, it does not prevent the progression of AD. In addition, several

studies have shown that modifications in lifestyles like a healthy diet and good physical exercise can improve brain health and reduce AD progression.

Some of the recent studies were focused on biomarkers of AD such as Aβ and tau peptides. Therefore, further therapies based on these molecules will be a challenging period in the AD treatment strategies. However, many drugs like AN-1792, solanezumab, bapineuzumab, semagacestat, avagacestat, and tarenflurbil targeting Aβ pathways failed to demonstrate their efficacy in the final clinical stages. Several new drugs are currently under investigation. In general, the success of AD treatment depends on its early administration and patient monitoring for disease progression using biomarker diagnosis. Future studies on therapeutic intervention targeting tau pathology and the use of alternative medicinal treatments like Indian Ayurveda or Chinese medicine may potentially influence AD progression. Coming years will be challenging for scientists working on AD as the numbers of people affected with AD and dementia are increasing drastically worldwide.

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Conflict of Interest The authors have no conflicts of interest to declare.

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