Review Article

The role of epigenetic modifications in Alzheimer’s disease

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ABSTRACT

Aging is the primary risk factor for various neurodegenerative diseases, including Alzheimer’s disease (AD), which is the most frequent form of Dementia. AD is progressive neurodegenerative disease with abnormal protein production, inflammation and memory deterioration. The main clinical manifestations of this illness are cognitive disturbance and memory deficit. Abnormal of beta-amyloid (Aβ), neurofibrillary tangles (NFTs) and tau deposition are the most common findings pathology in this disease. Recent studies indicate that epigenetic modifications strongly correlate in developing these pathology and disease progression. The hallmarks of epigenetic modifications are DNA (deoxyribonucleic acid) methylation, histone modifications, chromatin remodeling and ncRNA (non-coding ribonucleic acid) expressions. This review aims to explain the potential mechanisms of epigenetic modifications associate with this disease. The general conclusion of this review is that epigenetic modifications play an ultimate role in AD and there are potential biomarkers of AD and future novel treatment of AD based on epigenetics.

Keywords: Alzheimer’s, Epigenetic, DNA methylation, Histone modification, ncRNA

INTRODUCTION

Alzheimer’s disease (AD) is the most common form of Dementia. The clinical manifestations of AD were explained firstly by Alois Alzheimer on a 52-year-old woman. AD can be divided into two categories according to the onset, such as early-onset AD (EOAD) and late-onset AD (LOAD). EOAD is the onset of the disease under 65 years old, while LOAD is the onset of the disease above 65 years old. The prevalence of EOAD is more frequent than LOAD.¹

Worldwide, there are 50 million people who suffer AD. There are almost 10 million new cases of AD every year globally. 60% of those who suffer AD are from low and middle-income countries. The average age of people with AD is 60 years old.² The prevalence of AD will double for every five years after 65 years old. Furthermore, AD is predicted to triple by 2050.³

Impairment in daily activities in AD patients have decreased their quality of life because the patients will depend on others to fulfill their basic needs. Therefore, the annual cost for AD in United States is nearly US$600 billion.³

Slow and progressive cognitive decline is the most common symptom in AD. Short term memory impairment is more frequent than long term memory deficit. Impairment in language ability and visual spatial function are consistent with disease progression.⁴

Beta-amyloid (Aβ) deposition, neurofibrillary tangles (NFTs) and tau abnormal deposition are the pathology in AD.³⁵ Recent studies have shown the correlation between these pathology and epigenetic modifications in this disease. Epigenetic mechanisms play an ultimate role for normal brain function, including learning and memory process. Thus, impairment of these mechanisms is related
to AD pathology. Therefore, this review aims to explain the role of epigenetic modifications in AD.

**REVIEW OF LITERATURE**

**Alzheimer’s disease**

AD is progressive neurodegenerative illness related with abnormal protein deposition, inflammation and memory disturbance. Education level and physical activity are protective factors for AD, while obesity, hypertension and type 2 diabetes mellitus are risk factors in developing AD.

Besides memory dysfunction, AD patients also have difficulty in multitasking and loss of self-confidence, which are manifestations in MCI (mild cognitive impairment) stage, less severe form of AD. AD patients will have trouble in daily activities, whereas MCI patients still can do their daily activities. Usually, most of AD patients die after 8.5 years following the onset of the disease.

Depression, impaired consciousness, anhedonia, irritable, agitation, hypersomnia and increase or loss of appetite can be found in AD. Some psychotic symptoms also can be found in AD, such as delusion and hallucination. Therefore, AD patients will have problems with family, job and social relationship.

Atypical symptoms in AD associate with the brain region which has atrophy. Visuospatial impairment, visuo-perceptual disturbance and dyspraxia can occur in posterior cortical atrophy. Anosmia and working deficit can be occurred in logopenic aphasia. Despite a rare case, frontal AD can cause behavioral changes. Hippocampi atrophy leads to memory deficit, whereas nucleus basalis atrophy results in concentration disturbance.

Aβ, which the deposition of it is the pathology in AD, in physiological condition enhances the level of acetylcholine in hippocampi so that it can improve memory ability. However, the dysregulation of Aβ causes not only neuroinflammation due to mitochondria dysfunction, but also EOAD due to the low level of acetylcholine. Moreover, it can also cause deposition of Aβ plaques and tau phosphorylation, which promotes NF Ts. These mechanisms correlate with neurodegenerative disease, including AD. In addition, epigenetic may play major role in developing AD pathology.

Nowadays the diagnose of AD is based on NIA-AA (National institute on aging and the Alzheimer’s association) criteria. Brain imaging, such as MRI (magnetic resonance imaging), PET (positron emission tomography) and retinal scan, can be done to evaluate AD. Atrophy of hippocampi, temporal lobe and gyrus angular are the most common findings in MRI. PET is used to detect Aβ and tau hyperphosphorylated. Decrease in retinal nerve fiber layer, choroidal layer and volume optic nerve can be observed in retinal scan.

The non-pharmacological treatments of AD, such as behavioral therapy, psychoeducation and care giver support. Nowadays, the available option treatments for AD are cholinesterase inhibitors (which are tacrine hydrochloride, donepezil hydrochloride, galantamine hydrobromide and rivastigmine tartrate) and N-methyl-D-aspartate (NMDA) antagonist receptor (memantine hydrochloride). However, there is no currently effective treatment for AD.

**Epigenetic in AD**

The genome of the eukaryotic organism comprises of plenty amount of genetic information which must be placed in nucleus of each cell. In order to be fitted in the tiny sized of nucleus, the DNA must be stored into higher order configuration. Thus, the DNA is wrapped around the histone octamer (each pair of H2A, H2B, H3 and H4). This structure is termed as nucleosome, which is the primary structure of eukaryotic chromatin. The histone tails consist of amino acid and important for transcription regulation. There is histone H1 protein, also known as linker histone, which binds to linker DNA. Linker DNA is the part of the DNA, which places between two neighbor nucleosomes. These regions play an important role in gene regulation.

Because of the tightly packed form of DNA, the promoter region is hardly approachable for crucial cellular processes which need the DNA template. Therefore, the nucleosome configuration should be changed in order to enable the promoter become accessible. The mechanisms, which involved in this process, are recognized as epigenetic.

Epigenetic is known as the study of phenotype alteration without influencing any changes to the actual DNA sequence. Epigenetic modifications are the basic of gene regulating mechanism. These include DNA (deoxyribonucleic acid) methylation, histone modifications, chromatin remodeling and ncRNA (non-coding ribonucleic acid) expressions.

As a part of aging, human’s epigenome switches toward hypomethylation at particular DNA and global DNA hypermethylation. These also present in AD, which age is the most influence risk factor, the degree of DNA hypomethylation and global DNA hypermethylation are more frequently seen.

**DNA methylation in AD**

One of the most widely understood epigenetic mechanisms is DNA methylation, which process is by adding methyl group to cytosine in cytosine/guanine site, such as CpG island, forming 5-methylcytosine (5-mC). CpG sites are the most crucial sites related with aging,
which is the primary risk factor of AD. DNA methylation is mediated by DNA methyltransferase (DNMT) enzymes, which consist of DNMT1, DNMT2, DNMT 3a, DNAMT 3b and DNMT4.23 Only DNMT1, DNMT 3a and DNAMT 3b are found in human.24

DNMT1 is the enzyme, which play a major role for maintenance of DNA methylation during DNA replication. DNMT 3a and DNMT 3b are entangled in the de novo methylation in nuclear and mitochondria DNA, consecutively.24 Hypermethylation in DNMT1 gene has been related to AD.20

Many recent studies have showed that DNA methylation had involved in AD pathogenesis. There are several genes being key roles in AD. Hypomethylation of amyloid precursor protein (APP) promoter region is observed in the temporal lobe of AD patients.22 This process, together with aging, may result in Aβ deposition.21

A study in China found that a decrease methylation in D-loop region and increase in the 12 S rRNA gene methylation in the hippocampi in APP/PS1 (presenlinin 1) in AD mice. This might due to mitochondria dysfunction. In addition, this study highlighted that this mechanism played a crucial role in developing AD pathology.25

Recent finding in Japan found significantly upregulated of BRCA1 and consistently hypomethylation of it in postmortem brain samples from AD patients. Higher level of BRCA1 was found in response to DNA damage due to Aβ. This might lead to tau accumulation.26 Another study conducted in Japan, which measured DNA methylation in the promoter region of COASY and SPINTI genes in AD and amnestic MCI (aMCI) patient, showed a significantly increase in DNA methylation in both region in AD and aMCI patients compared to control.27

A cross-sectional cohort study in China found that DNA methylation of the BDNF (brain-derived neurotrophic factor) gene promoter and a tag SNP (single nucleotide polymorphism) (rs6265) were elevated in aMCI patients. It also associated with the conversion from aMCI to AD.28 Xu et al demonstrated that BDNF suppression lead to memory and learning impairment, whereas intra-hippocampi injection of BDNF ameliorated cognitive decline.29 Therefore, BDNF might be used as both biomarker of disease progression and potential target therapy for AD.28,29

Smith et al reported that hypermethylation of HOXA gene cluster on chromosome 7 in human cortex associated with AD.30 Li et al. also found that hypermethylation of HOXA gene cluster was observed in postmortem AD patients.31 Sao et al found that higher level of triggering receptor expressed on myeloid cells (TREM) 1 mRNA (messenger RNA) and DNA hypomethylation in the white blood cell of AD patients. This study indicated that hypomethylation in the promoter of TREM1 in leukocytes could be potential as one of blood-based biomarker for AD.32

A systematic review study reported highly expressed of TREM2 in microglial cells in AD.33 A research in United Kingdom found hypermethylation at the transcription start site (TSS) of the TREM2 gene in superior temporal gyrus of AD patients.34 Consistently, a study in Spain also demonstrated hypermethylation at the TSS of the TREM2 gene in AD patients. Higher expression of TREM2 mRNA was observed in hippocampi of AD patients. Dysregulation of TREM2 expression may result in Aβ in mouse model.35

Histone acetylation is mediated by histone acetyltransferase (HAT) enzyme, whereas deacetylation is catalyzed by histone deacetylase (HDAC). Histone acetylation increases the rates of gene transcription, while deacetylation of histone diminishes gene expression by condensing the chromatin.21

Nativio et al reported upregulation of both transcription and chromatin related genes. This finding identified 421 upregulating genes and 434 downregulating genes in AD. There are many chromatin genes which encoding HAT, such as CBP (CREBBP), P300 (EP300), TRAPP and so on. Lysine 27 and 9 on the histone H3 tail (H3K27ac and H3K9ac) are substrates for CBP/P300 and TRAPP, respectively. Thus, increase expressions of those genes also promote acetylation of H3K27 and H3K9. Moreover, increase acetylation of H3K27 and H3K9 enhance Aβ toxicity. Furthermore, this investigation believed that H3K27ac and H3K9ac are potential epigenetic markers in AD.39

Histone modification and chromatin remodeling in AD

Histone can have many post-translational modifications which can affect chromatin structure. These modifications are acetylation, methylation, phosphorylation, ubiquitinylation, sumoylation, ADP (adenosine diphosphate) ribosylation and deamination.38

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Marzi et al found that there was different rate of acetylation of H3K27 in the entorhinal cortex on postmortem AD patient. Hyperacetylation of H3K27 on the genes encoding MAPT (microtubule-associated protein tau), PS1 and PS2 was observed. MAPT enhances microtubule stability and assembly. PS plays a primary role in Aβ deposition from APP. Hypoacetylation of H3K27 of APP gene was significantly in this study.\textsuperscript{40}

Liu et al demonstrated that over expression of HDAC2 enhanced tau hyperphosphorylation, tau aggregation and dendritic disturbance in AD mouse model. Moreover, HDAC2 also contributed in various AD pathogenesis, including Aβ deposition, synaptic dysregulation and memory deterioration.\textsuperscript{41}

HDAC3 are expressed the highest in brain region involved in memory and learning, such as amygdala, hippocampi and cortical area. HDAC3 mediates tau phosphorylation and Aβ metabolism in AD. Thus, HDAC3 inhibitor could be neuroprotective mechanism and potential therapeutic intervention for AD.\textsuperscript{42}

A study in Unites States showed that HDAC levels were dysregulated in frontal cortex of AD patients. HDAC6 was exhibited a significantly increase during disease progression.\textsuperscript{43} 5-aryloindoles was reported to have an inhibitory activity of HDAC6. It diminished the rate of tau phosphorylation and tau aggregation. It could also improve memory and learning impairment. Therefore, it could be a novel target treatment for AD.\textsuperscript{44}

HDAC of SIRT1 (sirtuin 1) is associated with AD hallmarks, such as learning and memory deficit. Low level of SIRT1 promotes Aβ deposition and tau acetylation.\textsuperscript{45} Consistently, Rizzi et al also demonstrated that SIRT1 deacetylation may play a key role in developing AD.\textsuperscript{46} Hadar et al reported that lower expression of SIRT1 correlated with AD. Therefore, the expression of SIRT1 could be used as biomarker of AD.\textsuperscript{47} Resveratrol is potential neuroprotector, including in improving learning and memory deterioration in AD. It has antioxidant and anti-inflammatory properties which can reduce Aβ deposition and inhibit hippocampal damage. The neuroprotective mechanism in resveratrol has been linked with SIRT1 activation.\textsuperscript{48}

ncRNA Expression in AD

ncRNA can cause alteration in gene expression and deposition of protein which associates with the pathology of many neurodegenerative disease, including AD.\textsuperscript{21} Wang et al found that 183 miRNAs (microRNAs), 555 circRNAs (circular RNAs) and 319 mRNAs were significantly dysregulated in the hippocampi of AD mice.\textsuperscript{49} A study in China exhibited that significantly regulated of 315 long ncRNAs (lncRNAs) and 311 mRNAs were observed in hippocampi of AD mice.\textsuperscript{50} A study in Germany showed that miRNA-let-7 were neurotoxic properties in vitro which presented in cerebrospinal fluid (CSF) of AD patients. The selectively upregulation of let-7b and let-7e highlighted the pathway in developing neurodegeneration in AD. Thus, these properties could be potential marker for diagnosis and future target therapy for AD.\textsuperscript{51}

A study in China found the overexpression of miRNA-106b in the brain tissue of APP/PS1 mice. miRNA-106b could activate apoptosis marker, while simvastatin could regulate the expression of apoptosis marker by reversing the activity of miRNA-106b in mice. In addition, simvastatin could improve memory impairment in both human and mouse model of AD. Therefore, simvastatin can be potential drug of choice in AD.\textsuperscript{52}

Kenny et al found that miRNA-206 exhibited strong relationship with cognitive impairment and memory disturbance. The expression of miRNA-206 also increased in AD. Furthermore, miRNA-206 can be used as a predictor in cognitive deterioration and disease progression related to AD.\textsuperscript{53}

BACE1 (beta-amyloid cleaving enzyme) influences the production of Aβ by APP. The transcription of BACE1 is regulated by BACE1-antisense (BACE1-AS) lncRNA. Fotuhi et al demonstrated that BACE1-AS was low in pre-clinical AD (75% sensitivity and 100% specificity) and high in full-AD (68% sensitivity and 100% specificity) compared to control. Moreover, this finding indicated BACE1-AS is potential blood-based biomarker for AD.\textsuperscript{54}

CONCLUSION

Epigenetic mechanisms significantly play major role in AD pathology. There are several properties which can be potential marker in diagnosis and disease progression of AD. Although further studies need to evaluate these mechanisms, there are possibilities of future treatments based on epigenetics mechanism.

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