BMB
reports

Mini Review

Epigenetic modification is linked to Alzheimer's disease: is it a maker or a marker?

Junghee Lee[1,2] *& Hoon Ryu*[1,2,3,*]

[1]Department of Neurology, Boston University School of Medicine and [2]VA Boston Healthcare System, Boston, MA 02130, USA, [3]WCU Neurocytomics Group, Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul 110-799, Korea

Alzheimer's disease (AD) is the most common age-dependent neurodegenerative disorder and shows progressive memory loss and cognitive decline. Intraneuronal filaments composed of aggregated hyperphosphorylated tau protein, called neurofibrillary tangles, along with extracellular accumulations of amyloid β protein (Aβ), called senile plaques, are known to be the neuropathological hallmarks of AD. In light of recent studies, epigenetic modification has emerged as one of the pathogenic mechanisms of AD. Epigenetic changes encompass an array of molecular modifications to both DNA and chromatin, including transcription factors and cofactors. In this review, we summarize how DNA methylation and changes to DNA chromatin packaging by post-translational histone modification are involved in AD. In addition, we describe the role of SIRTs, histone deacetylases, and the effect of SIRT-modulating drugs on AD. Lastly, we discuss how amyloid precursor protein (APP) intracellular domain (AICD) regulates neuronal transcription. Our understanding of the epigenomes and transcriptomes of AD may warrant future identification of novel biological markers and beneficial therapeutic targets for AD. [BMB reports 2010; 43(10): 649-655]

INTRODUCTION

Abnormal processing of amyloid precursor protein (APP), the Aβ precursor, and hyperphosphorylation of tau are pathological hallmarks of AD. In addition, alteration of the gene expression of these genes significantly impacts the pathogenic pathways of AD (1). Since the temporal and spatial control of gene activity is regulated by other processes in addition to DNA sequence mutation, epigenetic codes have emerged to explain several unknown features and mechanisms underlying the process of neurodegeneration during AD (2). Epigenetic changes encompass an array of molecular modifications to both DNA and chromatin, including transcription factors and cofactors. In general, many genes contain DNA methylation sites (CpG islands) in their promoters (3). Therefore, marked hypomethylation may account for significant aspects of the molecular and pathogenic complexity of a neurodegenerative disease such as AD. For instance, the APP gene promoter is constitutively methylated under normal conditions and becomes hypomethylated with age, which subsequently enhances Aβ production (4, 5). On the contrary, more recent data have shown that there is no difference in methylation of the APP gene promoter in AD (6). Thus, despite controversy, a growing body of evidence suggests that epigenetic modification constitutes a basic molecular mechanism and contributes to AD pathogenesis. Therefore, understanding the role of the epigenome in AD will provide important clues to solving the disease. In this regard, we will provide a brief overview of the recent findings related to DNA methylation, histone modification, and transcription regulators (CBP, SIRTs, and AICD) that are linked to AD pathogenesis and further discuss therapeutic modulations of epigenomes for the treatment of AD.

Why is epigenetic modification considered as a plausible mechanism of AD?

Many studies have examined candidate genes that are associated with AD. Although genetic mutations and their associations have been found in AD, these are still probabilistic rather than inevitable, except in cases of familial AD (2). The circumstantial association between specific genetic components and AD may be derived from genetic complexity that is yet unexplored. In this regard, genetic discordance between rare monozygotic twins having AD can help determine other factors that may contribute to association between genes and AD (7). In this paradigm, reversible epigenetic alteration is expected to be a potential mechanism for explaining unsolved phenomena beyond genetic association with AD.

The status of DNA Methylation is altered in AD

DNA methylation is the most studied epigenetic alteration mechanism to date. DNA methylation involves the addition of a methyl group to the number 5 carbon of the cytosine pyrimidine ring via DNA methyltransferase activity. DNA methyl-

*Corresponding author. Tel: 1-857-364-5910; Fax: 1-857-364-4540; E-mail: hoonryu@bu.edu
DOI 10.5483/BMBRep.2010.43.10.649

Received 28 September 2010

Keywords: Alzheimer's disease, Chromatin remodeling, DNA methylation, Epigenetic modification

ation typically occurs in CpG islands that are present in the 5'-untranslated regions (UTRs) of gene promoters. DNA methylation affects the transcription of genes in two ways. First, methylated DNA physically impedes the binding of transcription factors to the gene. Second, and likely more important, methylated DNAs are occupied by methyl-CpG-binding domain proteins (MBDs). MBD proteins recruit other epigenetic components to the locus, such as histone deacetylases and other chromatin remodeling proteins that can modify histones, thereby forming compact and inactive heterochromatin (3). Thus, in general, DNA methylation in gene promoter regions results in gene inactivation and silencing (Fig. 1).

To determine whether or not epigenetic modifications contribute to the phenotypic differences that emerge in monozygotic twins, Masroeni *et al*. (2009) recently determined the status of DNA methylation in monozygotic twins discordant for AD (8). They studied a male Caucasian chemical engineer who developed symptoms of AD with progressive loss of memory until his death. His identical twin was also a chemical engineer with an identical education who died from complications related to prostate cancer. Immunohistochemical analysis for 5-methylcytosine, a marker of methylated CpG sites, confirmed that DNA methylation was reduced in the anterior temporal neocortex neuronal nuclei of the AD twin. Therefore, this study proved the hypothesis that epigenetic mechanisms may mediate the effects of life events on AD risk, which provides an important clue for AD discordance in a monozygote twin where genetic similarities exist.

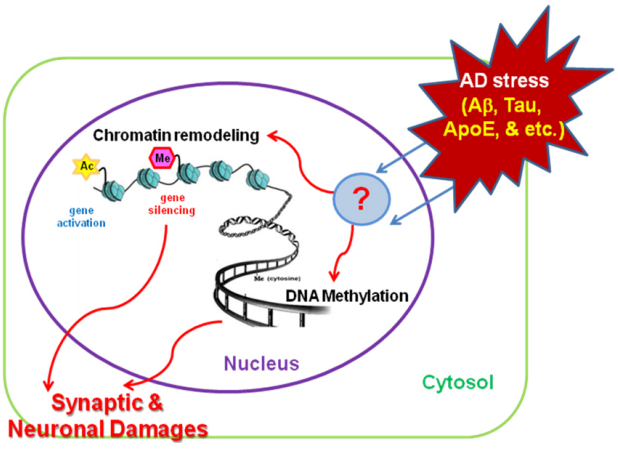

Fig. 1. Epigenetic modification is linked to pathogenesis of AD. DNA methylation is altered in the promoter region of neuronal genes in AD. Altered gene transcription in AD may be associated with alterations in histone acetylation/methylation profiles. Neuronal gene expression is turned on (active) or off (silenced) depending upon the dynamic status of histone post-translational modifications, acetylation versus methylation, respectively. Neurofibrillary tangles (intraneuronal filaments composed of aggregated hyperphosphorylated tau protein) and senile plaques (extracellular accumulations of Aβ) may result in significant transcriptional alterations that lead to synaptic and neuronal damage and ultimately memory loss. However, the mechanisms by which these pathogenic insults modify epigenetic conditions remain to be investigated.

In sporadic AD cases, the DNA methylation states of the SIRT3, SMARCA5, HTERT, and CDH1 gene promoters have been evaluated by Silva *et al*. (2008) (9). Methylation frequencies of SIRT3, SMARCA5, and CDH1 among young, elderly, and AD groups indicate no association with aging or AD. However, the methylation frequency of HTERT, a mRNA component of telomerase, is higher in AD patients compared to elderly controls. The association of HTERT methylation status with AD indicates that this gene may be involved in higher telomerase activity and immune dysfunctions in AD pathogenesis (9). In addition, other inflammatory genes such as iNOS, IL-1, and TNF-α are hypomethylated in the AD cortex (10). This study suggests that many inflammatory genes are activated by epigenetic alterations and are involved in the pathogenesis of AD.

Chromatin remodeling is associated with memory function

Chromatin remodeling is a dynamic, highly regulated process that occurs through interactions between DNA and histone proteins in neurons. Assembled core histone proteins form an octamer around which DNA can flexibly wind, thus leading to distinct histone/DNA conformations, including condensed heterochromatin, which results in gene silencing due to its compact nature, or more relaxed euchromatin, a relatively open region of chromatin associated with gene expression (11, 12) (Fig. 1). The association of histone proteins with DNA is affected by epigenetic histone modifications that influence transcription (13). In this context, gene expression is regulated by two components which act in concert: the binding of transcriptional activators and repressors and the alteration of chromatin structure governed by histone modifications. Amino (N)-terminal tails of the core histones (H2A, H2B, H3, and H4) are strongly basic and contain specific amino acid residues that serve as sites for several post-translational modifications, including acetylation, methylation, phosphorylation, and ubiquitylation (14, 15). In general, acetylation of lysine residues corresponds to transcriptionally active chromatin (euchromatin) that promotes transcription. In contrast, methylation of lysine residues contributes to transcriptionally inactive chromatin (heterochromatin) and represses transcription (15).

Changes in chromatin structure are a prominent pathological feature of many neurodegenerative diseases. In AD, aberrant processing of APP results in significant transcriptional alterations (16, 17). By extension, altered gene transcription in AD has recently been associated with alterations in histone acetylation profiles (2, 18). Ogawa *et al*. (2003) has found that phosphorylated histone H3 is elevated in hippocampal neurons of AD patients. Unexpectedly, activated phosphorylated histone H3 in AD is restricted to the neuronal cytoplasm, as opposed to the nucleus as in actively dividing cells, despite activation of the mitotic machinery. Accordingly, the aberrant cytoplasmic localization of phosphorylated histone H3 indicates

that a mitotic catastrophe may contribute to neuronal dysfunction and neurodegeneration in AD (19).

Transcriptional anomalies are also observed in AD, in which a subset of genes identified by expression profiling is significantly dysregulated (17). In both cases, neuropathogenic alterations in transcriptional activity lead to perturbations in normal neuronal function, resulting in neuronal cell death. CREB binding protein (CBP) functions as a transcriptional co-factor and a histone acetyltransferase (HAT). CBP interacts with diverse transcription factors and with components of the RNA polymerase II (Pol II) complex, thereby acting as a co-activator or repressor of transcription. CBP also plays a role as a HAT in acetylating histones that contribute to transcription by remodeling chromatin structure (20, 21). It was shown that a loss of CBP function interferes with transcription by inhibiting recruitment of the basal transcription machinery to the promoter and by altering the acetylation level of histones in neurons (20, 21). Korzus *et al*. (2004) (21) previously generated transgenic mice expressing CBP that lacks HAT activity. They found that the stabilization of short-term memory into long-term memory is impaired in these mice, whereas acquisition of new information and short-term memory is spared. Concurrent with these findings, p300 (a CBP homologue) mutant mice lacking carboxy-terminal HAT and activation domains have impaired long-term recognition memory and contextual fear memory (22). Moreover, Oliveira *et al*. (2007) demonstrated that p300 is required for certain forms of memory and that the HAT and carboxy-terminal domains play critical roles.

Our group has also investigated the alteration of histone and chromatin modification in a monozygote twin with AD. Interestingly, we found that the trimethylation of histone H3 (K9), a maker of gene silencing, along with the condensation of heterochromatin are markedly increased in the anterior temporal neocortex and hippocampus of a monozygotic twin with AD in comparison to a discordant monozygote twin without AD (unpublished data). Our result suggests that, as an epigenetic alteration, post-translational modification of histones is closely associated with the neuropathological phenotype in a monozygotic twin with AD, where the genetic background is the same but discordant AD exists.

Could chromatin remodeling be a therapeutic target?

Among the prominent post-translational modifications of histones H3 and H4, methylation and acetylation play a significant role in transcriptional activity (23). Histone acetylation is regulated through the concerted activities of histone acetyltransferases (HAT) and histone deacetylases (HDACs) (11). It is widely believed that HAT activity results in increased DNA transcription (23). In contrast, histone deacetylation mediated by HDAC activity is associated with transcriptional repression. Additional chromatin remodeling is also mediated through the activity of histone methyltransferases, the actions of which may have profound implications on transcriptional repression. Methylation of H3 at lysine 9, in particular, is thought to promote gene silencing (24), although recent data suggest that the position of methylated histones along the entire gene can have an equal influence (25).

HDAC inhibitors have been preclinically tested in many neurodegenerative conditions, including animal models of HD, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (26-30). In cell models of HD, polyglutamine decreases histone acetylation, and HDAC inhibitors have been shown to reduce polyglutamine-induced toxicity (28). HDAC inhibitors also improve the phenotypes of transgenic *Drosophila* and mouse models of HD (26-28, 30, 31). By the same token, correction of histone modification abnormalities may be of therapeutic benefit in AD. HDAC inhibitors may improve phenotypes by either upregulating survival genes that are repressed in AD or by repressing pro-death genes that are elevated in AD. However, the underlying mechanisms whereby HDAC inhibitors modulate neuronal function remain to be investigated. Recently, HDAC inhibitors were tested in animal models of neurodegenerative diseases such as AD and HD (32). Enhancement of memory formation was found in mice treated with sodium butyrate or SAHA or subjected to genetic knockout of the HDAC2 gene (33). Thus, modulation of histone acetylation by HDAC inhibitors facilitates learning and memory in mouse models of AD as well as other neurodegenerative diseases. HDAC inhibitors upregulate the expression of beneficial genes implicated in synaptic plasticity and memory formation. In the case of CBP deficiency and HAT deletion mutant animal models, HDAC inhibitors also improve memory and behavioral symptoms. Given their potential benefit on the overall AD phenotype (memory and neuropathology), HDAC inhibitors could be considered for clinical application to AD patients with memory impairment.

How do SIRTs contribute to neuronal activity and neuroprotection in AD?

Mammals contain seven sirtuins (silent mating type information regulation 2 homolog in yeast), which are involved in various functions related to aging, chromatin integrity, and metabolic regulation in various tissues, such as NAD-dependent deacetylase and mono ADP ribosyltransferase. Among the seven SIRTs, the level of SIRT1 in the brain has been well studied in AD patients and controls. Both the mRNA and protein levels of SIRT1 are low in AD patients. However, in contrast to humans, there is no significant alteration of SIRT1 expression in a transgenic mouse model of AD (34). An *in vivo* model involving caloric restriction (CR) and treatment with resveratrol, a CR mimetic, elevates SIRT1 expression and provides protective effects against progression of AD. The catalytic activity of SIRT1 is not modulated by the Class I and II HDAC inhibitor trichostatin. SIRT1 and SIRT2 are cytoplasmic proteins that deacetylate tubulin. SIRT3 is the most abundant homolog among the mammalian sirtuin family of proteins and is expressed ubiquitously and highly in the brain, testis, and skeletal muscle.

SIRT3 localizes to the inner membrane and matrices of mitochondria as well as the nuclei of neurons. CR-conditioned mice and another mouse model having a long lifespan show increased levels of SIRT3 expression, implying that SIRT3 is related with longevity. SIRT3 induces CREB phosphorylation and improves mitochondrial functions by reducing reactive oxygen species (ROS) in brown adipose tissue and preadipocytes. However, the relevance of SIRT3 and SIRT4-7 on neuronal activity has not been explored in an AD animal model yet.

Most recently, an exciting study on the epigenetic modulation of Aβ production and neuronal protective activity of SIRT1 was published by the Guarente group (2010) (35, 36). They showed that production of Aβ production and plaques is reduced by overexpression of the NAD-dependent deacetylase SIRT1 in the brain of AD mice (Fig. 2). Otherwise, knocking out SIRT1 increases Aβ production and plaques in the brain. Interestingly, SIRT1 activates the transcription of the ADAM10 gene, known as α-secretase. As an epigenetic modulator, SIRT1 deacetylates and coactivates retinoic acid receptor β (RARβ), a direct regulator of ADAM10 transcription. Simultaneously, ADAM10 activation by SIRT1 induces the Notch pathway, which prevents neuronal damage in the brain. These findings suggest that SIRT1 activation can be a beneficial therapeutic target for the treatment of AD as well as other neurodegenerative diseases (37, 38).

From a therapeutic point of view, nicotinamide, a competitive HDAC inhibitor of Class III sirtuins, restores some cognitive deficits in AD transgenic mice (3 × Tg-AD) (39). Resveratrol is known to activate SIRT1 and promotes cell survival under stress conditions *in vitro* (40). However, the drug does not fully activate brain SIRT1 in AD transgenic mice (Tg19959), although it still provides beneficial effects such as reduction of amyloid plaques in the brain (41). In this case, resveratrol nullifies systemic oxidative stress rather than regulation of SIRT1 activity in the brain (42). Taken together, future development and testing of SIRTs activators in AD animal models will contribute to the treatment of AD diseases associated with memory impairment.

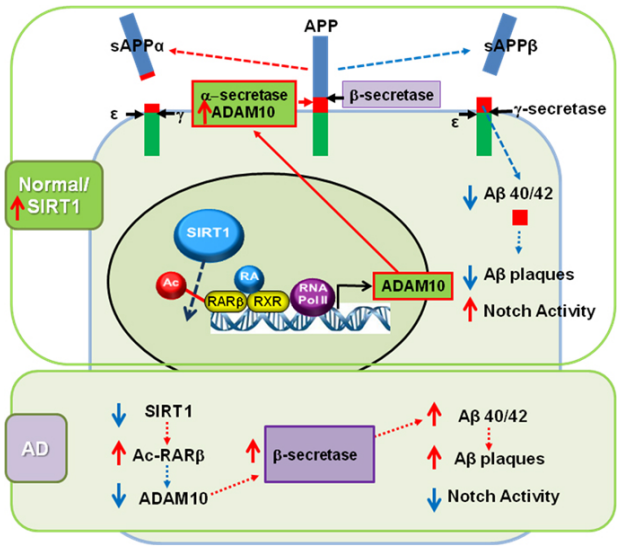

Fig. 2. SIRT1 is an epigenetic modulator of the ADAM10 (α-secretase) gene that prevents neurotoxic Aβ generation in AD. The upregulation of SIRT1 activity deacetylates retinoic acid receptor β (RARβ). Deacetylated RARβ then targets the promoter of the ADAM10 gene with other transcriptional components and subsequently induces gene expression. Next, the increase in ADAM10 activity diminishes β-secretase activity while elevating Notch activity. Then, the level of neurotoxic Aβ production is reduced. As a result, the formation of extracellular Aβ plaques is prevented. In contrast, SIRT1 activity is downregulated in AD. In turn, the high level of acetylated (Ac) RARβ represses the expression of the ADMA10 gene. This eleveates β-secretase activity while decreasing Notch activity in parallel. Consequently, the high level of neurotoxic Aβ leads to the formation of extracellular Aβ plaques. The above findings by the Guarente group highlight the neuroprotective mechanism of SIRT1 through epigenetic cascades.

APP Intracellular Domain (AICD) is a transcriptional cofactor

Does cleavage of APP really turn neuronal genes on and off? The answer is yes! Fig. 3 illustrates how AICD, a small 6-kDa protein, is derived from APP cleavage via a series of α-, β-, and γ-secretases. AICD is detectable in the membrane fraction of brain homogenates, and its level is markedly increased in AD mice (Swedish mutation of human APP) (43). AICD is stained

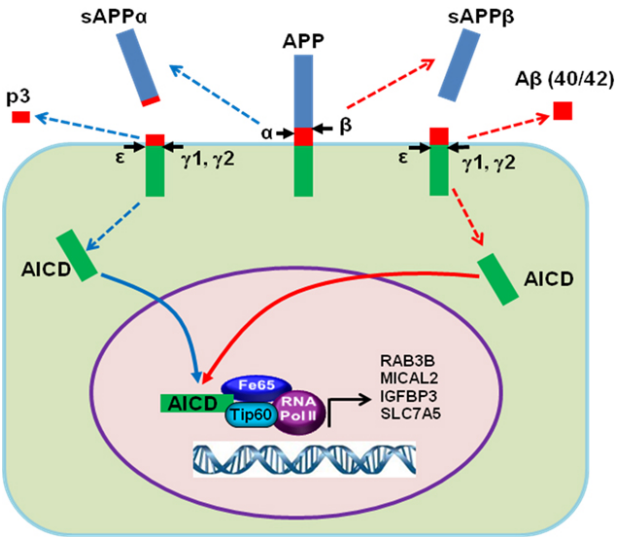

Fig. 3. AICD modulates transcription of neuronal genes. At the first stage of APP processing, α- or β-secretase cleaves and releases the N-terminal fragments sAPPα and sAPPβ. Then, γ-secretases produce p3 or β-amyloid (40-42) by intramembrane digestion. At the same time, AICD, a C-terminal fragment of APP, is released to the cytoplasm and neurons. Thereafter, AICD translocates into the nucleus where it interacts with the transcription complex consisting of the Fe65 and Tip60 proteins. The AICD-containing transcription complex induces neuronal gene expression.

in Hirano bodies in the degenerating neurons of AD patients, suggesting the accumulation of AICD during AD pathogenesis (44).

AICD closely resembles Notch intracellular domain (NICD), which is released from its membrane anchor after γ-secretase–dependent cleavage of Notch (45). NICD translocates to the nucleus where it activates NICD-dependent neuronal gene expression. Similarly, AICD translocates and interacts with several epigenetic components (transcriptional coactivators). Once AICD binds to the phosphotyrosine binding domain 2 (PTB2) of adaptor protein Fe65 via the YENPTY motif (46), the nuclear AICD-Fe65 dimer interacts with a tat-interactive protein (Tip60), a histone acetyltransferase (47, 48). Consequently, this complex can turn on putative target genes such as IGFBP3, MICAL2, RAB3B, SLC7A5, etc. (Fig. 3).

To further understand the role of AICD associated with AD pathogenesis, it is strongly recommended to consult the Mini Review by Dr. Suh, an expert on AICD research, in this issue of *BMB Reports*.

CONCLUSION AND FUTURE PERSPECTIVES

Epigenetic modifications, except a genetic mutation that impacts neuronal gene expression, may provide important molecular mechanisms that contribute to AD pathogenesis. In this context, DNA methylation, histone methylation, acetylation status, and transcription cofactors are all directly or indirectly linked with transcriptional activity and regulate the binding of transcription factors to promoter regions in DNA (14, 23). It seems likely that epigenetic alteration mechanisms, such as DNA methylation and transcriptional dysregulation, are a marker of disease status in AD as well as other neurodegenerative diseases (6, 8, 49, 50). The disruption of transcriptional homeostasis through altered histone methylation and acetylation triggers signaling cascades linked with a number of pathological mechanisms in AD. The abnormal alteration of epigenetic signaling cascades during aging may ultimately promote neuronal dysfunction and subsequent neuronal damage. However, it remains to be determined whether epigenetic alteration is a casual maker of the onset or progression of AD symptoms. In addition, epigenetic alteration during AD pathogenesis is currently less investigated compared to other diseases. Moreover, the association between neuronal death and transcriptional dysfunction is no more evident than in other neurodegenerative diseases such as HD (51). Therefore, accelerated research on the epigenetic components and mechanisms associated with AD will provide essential information that can unveil the cause of AD. It is important to realize that epigenetic modification is reversible while genetic mutation is not. Therefore, from a therapeutic perspective, epigenetic regulation is a strong candidate method. Drug compounds can dynamically modulate the status of DNA methylation and remodel the structure of chromatin through post-translational modifications of histone molecules. Further challenges are the development of such drug agents that subsequently realign the epigenetic balance and thus improve AD-related deficits in epigenomes.

Acknowledgements
We thank KH Seong and YJ Hwang for their assistance in the preparation of the manuscript. This work was supported by a WCU Neurocytomics Program Grant (800-20080848) (H.R.) from the Korea Science & Engineering Foundation (KOSEF).

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