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Opinion

How Histone Sensing Drives Alzheimer's Disease

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Abstract

The human DNA double helix is wrapped around proteins known as histones, which play a critical role in regulating gene expression. The goal of this opinion piece is to provide an overview of how histone sensing drives Alzheimer's disease (AD). Histones are proteins enriched in basic amino acids. Histone acetylation plays an important role in the progression of AD as its dysregulation can lead to neuroinflammation and neurodegenerative diseases. Specifically, abnormal histone acetylation, a post-translation modification, is a key factor in AD as it contributes to brain cell inflammatory pathology. Thus, higher levels of histone acetylation could potentially serve as important biomarkers for the progression of AD. Here, we report that increased levels of acetylation of histones H2B, H3, and H4 in the promoter regions of Tip60 lysine acetyltransferase protein, p300/CREB-binding protein (CBP), GCN5-related N-acetyltransferases, p300/CBP-associated factor, elongator protein 3, brain-derived neurotrophic factor, and *Tau* genes in the hippocampus and temporal lobe are associated with the development of AD-associated learning and memory impairment.

Keywords: histone; Alzheimer's disease; impaired learning; memory; histone acetylation; neuroinflammation

1. Introduction

The development of Alzheimer's disease (AD) is considered to have a genetic risk factor. The human brain with AD often shows abnormal build-up of histone proteins. Although recent research has identified how histone sensing drives AD, it remains unclear whether histone acetylation of AD-related proteins in the temporal lobe (TL) and hippocampus (HIP) mediates the targeting of genes by the acetylation machinery [1]. Over time, these proteins lead to plaques, tangles, large brain chambers large, and brain atrophy. Histone acetylation is the most extensively characterized epigenetic mechanism involved in memory formation and consolidation, learning, and synaptic plasticity [2]. In eukaryotic cells, nucleosomes are the main structural units of chromatin, and the histone octamer is composed of two copies of each of the core histones H2A, H2B, H3, and H4, forming the core particle around which the DNA double helix wraps [3]. Histones are proteins that tightly bind DNA and are composed of two copies each of H2A, H2B, H3, and H4 proteins. Histone modification is involved in the development of AD [4]. In the nucleus, histone acetylation and histone deacetylation are in a dynamic equilibrium and are jointly regulated by histone acetyltransferase (HAT) and histone deacetylase (HDAC). HAT transfers the acetyl group of acetyl coenzyme A (acetyl-CoA) to a specific lysine residue at the amino terminus of a histone protein. HDAC deacetylates histone, resulting in a more positively charged histone, which then binds more tightly to the negatively charged DNA, leading to densely coiled chromatin that inhibits gene transcription [5]. Some histones function as spools for thread-like DNA to wrap around. Chromatin structure is closely related to eukaryotic gene expression and directly affects the expression of genetic information carried by DNA assembled in the nucleus in the form of chromatin. When genes are activated, there are certain structural changes in the corresponding regions of chromatin; this transcriptionally active chromatin is called euchromatin [6]. Histones play an important role in packing these long DNA molecules into the nucleosome, giving the chromosome a more compact shape. Each nucleosome comprises DNA wrapped around a core of eight histone proteins into a 30 nm spiral solenoid [7]. Histones help DNA condense into chromatin by acting as spools around which DNA wraps in the nucleus. H1 histone protein is crucial for maintaining the chromosome structure. Modification sensing of histones by acetylation has been shown to modulate the chromatin structure by changing protein-DNA or protein-protein interactions. Systematic sensing induced histone acetylation is associated with local chromatin opening that mediate change in chromatin structure and gene expression. This histone sensing is histone acetylation induces crosstalk between gene expression open and close.

For this review, we gathered information from different studies that describe how histones display both immunologic and inflammatory effects, which can be either beneficial or detrimental in specific circumstances. Histones are basic proteins, and their positive charge allows them to bind tightly to the negatively charged DNA backbone [6]. The amino end of each histone protein protrudes from the nucleosome, forming a histone tail. These tails form links between nucleosomes and are also sites for histone modification [8].

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2. Role of Histone Acetylation in AD

Histone modifications include acetylation, phosphorylation, ubiquitination, ADP-ribosylation, and methylation of positively charged basic amino acids such as lysine, arginine, and histidine, which are abundant in histones. In general, acetylation can neutralize the positive charge of basic amino acid residues on histone tails, thereby weakening the binding between histones and negatively charged DNA, leading to a looser chromatin structure. This chromatin remodeling allows for easier access of transcription factors to DNA, which in turn enables the transcription of specific genes and enhanced expression levels of those genes [9]. Interestingly, like the H2B mutant, the H3 mutant is minimally incorporated into chromatin in cells but still enhances colony formation ability. Cancer-associated mutations of histones H3 and H2A also induce nucleosome instability. Histones in chromatin in transcriptionally active regions are characterized by less lysine-rich H1 histones; increased instability of H2A-H2B dimers; and modifications such as acetylation, phosphorylation, and ubiquitination on histones H3 and H4. Modification of histones H3 and H4 makes nucleosomes loose and unstable, reducing the affinity of nucleosome proteins to DNA and facilitating gene transcription, which lead to diseases. Histones can mediate detrimental effects on cells in various human diseases as they can be released from cells in their free form, leading to tissue damage [10]. The scientific community has increasingly shown interest in histones as potential biomarkers and therapeutic targets in AD, because they play a key pathophysiological role in inflammation and thrombosis [11].

Histones have been studied as potential therapeutic targets in many pathologies where deregulated inflammatory processes play a key role. Histones act as damage-associated molecular patterns to promote immune cell activation and pro-inflammatory cytokine release, causing cytotoxicity and immune stimulation. Histone modification triggers and accelerates inflammation, depending on the cell type affected. HDAC is a class of enzymes that play an important role in the structural modification of chromosomes and the regulation of gene expression. In general, the acetylation of histones is conducive to the dissociation of DNA and histone octamers, and the nucleosome structure is relaxed, allowing various transcription factors and co-transcription factors to specifically bind to DNA-binding sites and activate gene transcription. Deacetylation of histones, on the other hand, plays the opposite role [12].

3. Development of AD through Histone Acetylation

AD is a neurodegenerative disease characterized by changes in the level of a specific histone modification, namely, histone H3 lysine acetylation, which is potentially driven by the actions of its associated corepressors [13]. AD is associated with epigenetic modulation, which affects the level of neuroinflammation in the brain, leading to cognitive decline and memory impairment due to the loss of neuronal cell loss. Acetylation of histones H3 and H4 in the brain of patients with AD promotes the progression of neuroinflammation in the central nervous system. In addition, altered acetylation activity on non-histone proteins is also closely associated with the pathogenesis of AD. There is increased histone acetylation in AD; thus, HDAC inhibitors (HDACis) are considered potential therapeutic agents due to their protective functions [14]. In general, histone acetylation is associated with enhanced AD; conversely, the removal of acetyl groups from histones is catalyzed by HDACs, which reduces neuroinflammation mainly by regulating inflammation towards ameliorating AD. Indeed, increasing evidence has shown that regenerative neurogenesis has the potential to improve brain repair in AD in humans. More specifically, HDACs promote a healthy neuronal state. Conversely, increased deacetylation, particularly at gene promoters, is linked to the progression of AD. Increasing histone acetylation in the HIP by HATs can improve cognitive deficits and enhance memory formation, whereas HDAC levels are increased in the HIP of patients with AD [15]. Some protein molecules, such as HAT enzymes, require covalent histone modification. HDAC regulates gene expression at the DNA level [16]. The acetylation of histones by HATs leads to a relaxed chromatin structure, making DNA more accessible for the transcription of genes, thus acting as a transcriptional coactivator. On the other hand, HDAC promotes the deacetylation of histones and represses the transcription of genes, acting as a transcriptional co-repressor. HDAC is a class of enzymes that play an important role in the histone modification of chromosomes and the regulation of AD. The acetylation of histones promotes the dissociation of DNA and histone octamers, leading to a more relaxed nucleosome structure, which makes it easier for transcription factors and co-transcription factors to bind to DNA and activate gene transcription [17]. Several mechanisms in the human brain depend on histone acetylation development of AD. In the nucleus, histone acetylation and histone deacetylation are in dynamic equilibrium and are jointly regulated by HAT and HDAC [18]. The increased histone acetylation occurs in AD and repressed functions of HDACis. HAT transfers the acetyl group of acetyl-CoA to a specific lysine residue at the amino terminus of histone, and development AD; excessive HAT activity is linked to the development of AD. HDAC deacetylates the histone of lysine residue, which may inhibit AD development (Fig. 1). Inhibiting HDAC contributes to a reduction in inflammation; accordingly, some HDACis have been shown to exert therapeutic effects against AD. Histone acetylation in the HIP plays an important role in the formation of long-term memory, and its dysregulation is associated with impaired memory and the development AD. Moreover, histone acetylation seems to be increased in brain regions with inflammation. HDACis increase his-

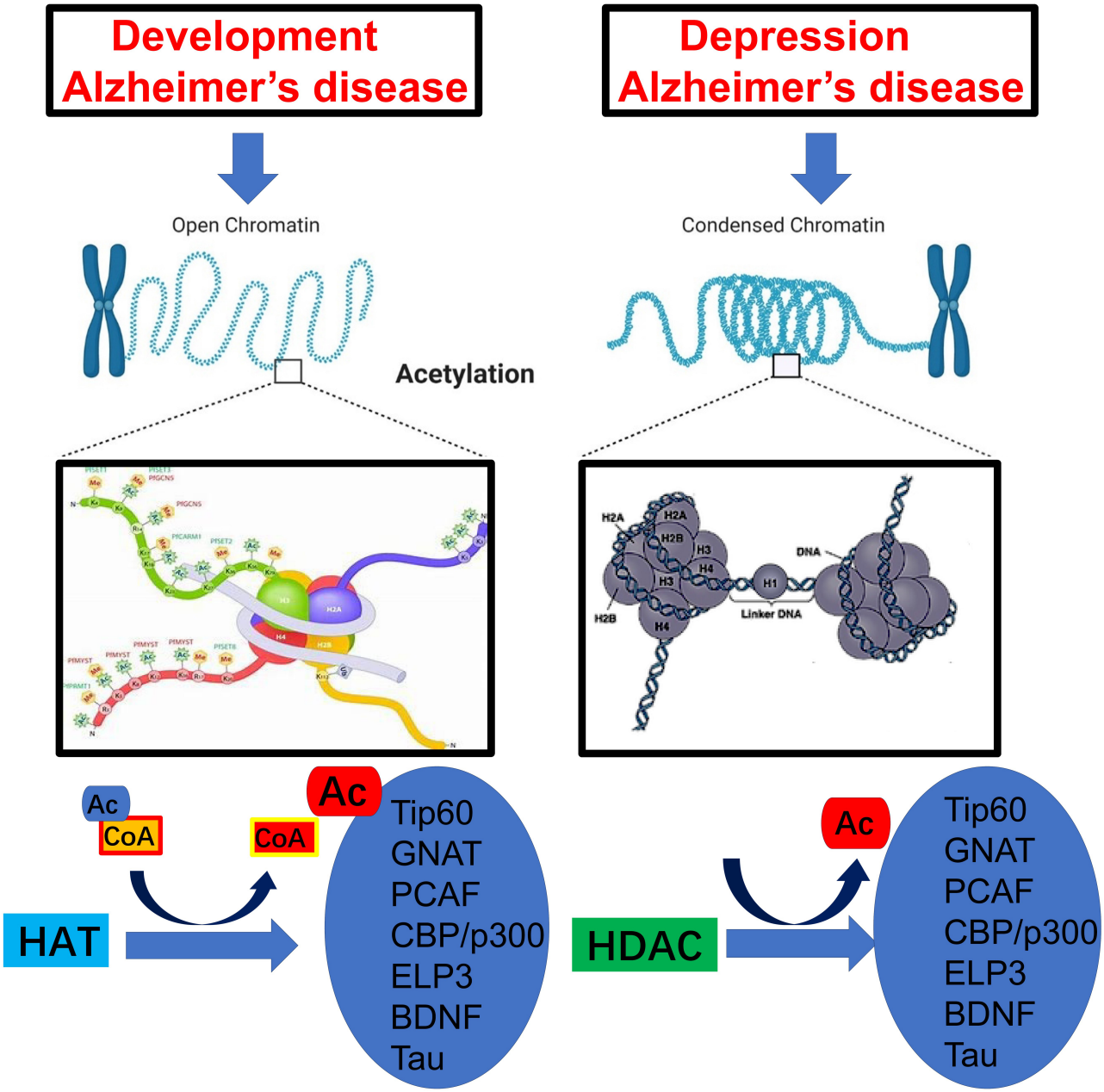

Fig. 1. Repression and activation of gene expression in Alzheimer's disease via histone acetylation. Created with BioRender.com.

tone acetylation and prevent histone deacetylation, making them promising therapeutic agents for AD [19].

4. Acetylation Molecular Mechanisms of Development of AD

HDAC binds tightly to negatively charged DNA, leading to densely coiled chromatin and inhibition of gene transcription. HDACs indirectly regulate their own expression levels by modifying chromatin structure and also stabilize age-related proteins including Tip60 lysine acetyltransferase protein (Tip60), p300/CREB-binding protein (CBP), General control non-depressible 5 (GCN5)-related N-acetyltransferase (GNAT), p300/CBP-associated factor (PCAF), elongator protein 3 (ELP3), brain-derived neurotrophic factor (BDNF), and Tau. HDACs are emerging as a new class of drugs to treat neurodegenerative diseases due to their ability to increase histone deacetylation in specific regions of chromatin, potentially offering a therapeutic approach to neurological disorders [20]. Interestingly, a study in adult mice with impaired long-term memory due to expression of mutant CBP with suppressed HAT activity, showed that the phenotype could be re-established upon the reversal of HAT activity or use of HDACis. Due to Alzheimer's disease development involving HDACs in an amyloid-beta accumulation, tau abnormalities, neuroinflammation, mitochondrial dysfunction, and synaptic loss by exploring the connections between aging mechanisms

and AD pathogenesis, thus, HDACIs have been suggested as agents for the treatment of AD. Histone acetylation inhibitors (HDACis) not only have promising therapeutic effects against AD but also have the advantages of relatively high selectivity and reversal of HAT activity [21]. Interestingly, aging is also associated with a decrease in HDAC activity [22]. Increased levels of acetylation of histones H2B, H3, and H4 in the promoter regions of *Tip60*, *p300/CBP*, *GNAT*, *PCAF*, *ELP3*, *BDNF*, and *Tau* genes are associated with the development AD.

Furthermore, repaired AD has also been observed in *Tip60*, *p300/CBP*, *Tau*, *GNAT*, *PCAF*, *ELP3*, *BDNF*, and HDACis evidencing the role of histone in memory and synaptic plasticity to repress AD (Table 1). A study involving AD models has extensively shown the role of histone acetylation in learning, memory, and synaptic plasticity [23]. Histone acetylation involves the addition of acetyl groups from acetyl-CoA to lysine residues on the N-terminal tails of histones, mostly H3 and H4, weaking the interaction between DNA and histones and allowing the transcriptional machinery access to gene promoters, thereby enabling posttranslational modifications to occur such as methylation, acetylation, phosphorylation, ubiquitylation, and SUMOylation [24]. The main histone acetylation changes involved in AD pathology are enrichment of H3K27ac and H3K9ac in the TL and HIP, and loss of H3K18ac, H3K23ac, H4K16ac, H3K122ac in the TL of patients with AD compared to controls. Moreover, the development of HDACis has brought promising results for AD therapeutics [25]. Some studies have made great advances in understanding the role of histone acetylation in AD. For example, inhibition of HDAC3 in AD has been shown to increase histone H3 and H4 acetylation and decrease the accumulation of amyloid beta plaques and tau phosphorylation. AD is associated with the upregulation of gene acetylation by HATs such as Tip60, p300/CBP, GNAT, PCAF, ELP3, BDNF, Tau, and HDACs (e.g., [26]). By contrast, histone deacetylation involves the removal of the acetyl groups by HDACs, leading to reconfiguration of the epigenome as a mechanism involved in AD pathology [27]. Furthermore, immediate early genes, including BDNF, are potential targets in AD. It has been reported that increased levels of H3 acetylation at BDNF and p300/CBP in the HIP are associated with the development of AD; however, a mutant form of p300/CBP and BDNF with suppressed HAT activity showed histone deacetylation.

Table 1. Modified acetylation and deacetylation of histone substrates play a regulatory role in the development of Alzheimer's disease.

Activation of genes in Alzheimer's disease (AD)	
Tip60 acetylation	H3 and H4 acetylation
p300/CBP acetylation	H2B and H4 acetylation
GNAT acetylation	H2B and H4 acetylation
PCAF acetylation	H2B and H4 acetylation
ELP3 acetylation	H3 acetylation
BDNF acetylation	H3 and H4 acetylation
Tau acetylation	Acetylation
Repression of genes in Alzheimer's disease (AD)	
Tip60 deacetylation	H3 and H4 deacetylation
Tau deacetylation	Deacetylation
GNAT deacetylation	H2B and H4 deacetylation
PCAF deacetylation	H2B and H4 deacetylation
ELP3 deacetylation	H3 deacetylation
BDNF deacetylation	H3 and H4 deacetylation
p300/CBP deacetylation	H2B and H4 deacetylation

5. Discussion

An understanding of the genetic mechanisms underlying AD and the genes potentially implicated in histone acetylation will lead to a better understanding of AD development [28]. Moreover, the acetylation of histones in Tip60, p300/CBP, GNAT, PCAF, ELP3, BDNF, and Tau appear to be increased in brain regions with inflammation. HDACs remove acetyl groups from histones and are emerging as a new class of drugs to treat neurodegenerative diseases [29]. AD is regulated via histone acetylation in the temporal lobe (TL) and hippocampus (HIP), such as *Tip60*, *p300/CBP*, *GNAT*, *PCAF*, *ELP3*, *BDNF*, and *Tau* genes. Several genes that do not undergo changes in histone acetylation have been implicated in AD, such as amyloid precursor protein, presenilin-1, triggering receptor expressed on myeloid cells 2, apolipoprotein E. Furthermore, several genes have been implicated as neurodegenerative disease targets, including synuclein alpha, Parkin RBR E3 ubiquitin protein ligase, and leucine-rich repeat kinase 2 [30,31]. Moreover, histone acetylation seems to be increased in brain regions with inflammation, particularly in regions targeted by the nuclear factor kappa B gene, which is implicated in the development of AD [32]. This opinion piece provides an overview of the genetic acetylation of AD and the relationship between these gene acetylation and deacetylation in AD.

6. Conclusion

Alzheimer's disease development is a condition of *Tip60*, *p300/CBP*, *GNAT*, *PCAF*, *ELP3*, *BDNF*, and *Tau* gene expression *open* gene expressions by histone acetylation by the gradual nervous system degeneration. This opinion will summarize histone-sensing acetylation and histone-sensing reversible deacetylation. It has been therefore suggested that Alzheimer's disease develops by *Tip60*, *p300/CBP*, *GNAT*, *PCAF*, *ELP3*, *BDNF*, and *Tau* gene expression acetylation, but suppression by deacetylation.

Abbreviations

Tip60, Tat-interactive N-acetylase; p300/CBP, p300/CREB-binding protein; GNAT, Gcn5-related N-

acetylase; PCAF, p300/CBP-associated factor; ELP3, elongator complex protein 3; BDNF, brain-derived neurotrophic factor.

Author Contributions

JPW was responsible for the conception of ideas presented, writing, and the entire preparation of this manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The author declares no conflict of interest.

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