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Epigenetics: A novel therapeutic approach for the treatment of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common type of dementia in the elderly. It is characterized by the deposition of two forms of aggregates within the brain, the amyloid β plaques and tau neurofibrillary tangles. Currently, no disease-modifying agent is approved for the treatment of AD. Approved pharmacotherapies target the peripheral symptoms but they do not prevent or slow down the progression of the disease. Although several disease-modifying immunotherapeutic agents are in clinical development, many have failed due to the lack of efficacy or serious adverse events. Epigenetic changes including DNA methylation and histone modifications are involved in learning and memory and have been recently highlighted for holding promise as potential targets for AD therapeutics. Dynamic and latent epigenetic alterations are incorporated in AD pathological pathways and present valuable reversible targets for AD and other neurological disorders. The approval of epigenetic drugs for cancer treatment has opened the door for the development of epigenetic drugs for other disorders including neurodegenerative diseases. In particular, methyl donors and histone deacetylase inhibitors are being investigated for possible therapeutic effects to rescue memory and cognitive decline found in such disorders. This review explores the area of epigenetics for potential AD interventions and presents the most recent findings in this field.

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, with over 35 million cases worldwide (Selkoe, 2012). The four acetylcholinesterase inhibitors, donepezil, rivastigmine, galantamine and tacrine, along with the NMDA receptor antagonist memantine are the only FDA-approved drugs for AD; however, they merely target

the symptoms and do not prevent the progressive loss of memory, cognitive and executive functions in AD patients. With the increase in life expectancy and the absence of disease-modifying agents, the number of people with AD is expected to triple within the upcoming 40 years (Barnes & Yaffe, 2011; Huang & Mucke, 2012; Tricco et al., 2012). The annual costs for AD and other dementias in the US in 2013 are estimated to be over \$200 billion and are expected to reach \$1.2 trillion in 2050 (Alzheimer's Association, 2013). With such a heavy socioeconomic burden, there is an urgent need to find novel and improved treatments for AD. Throughout the last century, the advances acquired in health related fields were able to increase the lifespan of AD patients, yet this needs to be matched with discoveries that improve the quality of life of people with this debilitating disorder. New targets should be identified and investigated for possible AD therapeutics that tackle its core pathophysiology as well as prevent the decline in memory and cognitive functions associated with the disease.

Abbreviations: A β , amyloid β ; AD, Alzheimer's disease; APP, amyloid β precursor protein; BACE, β -site APP cleaving enzyme; CBP, CREB binding protein; CREB, cAMP response element-binding protein; CSF, cerebrospinal fluid; DNMT, DNA methyltransferase; FAD, familial AD; HAT, histone acetyltransferase; HDAC, histone deacetylase; LOAD, late onset AD; MeCP2, methyl CpG binding protein 2; NFTs, neurofibrillary tangles; PS, presenilin; SAM, S-adenosyl methionine; SIRT, sirtuin; Sp1, specificity protein 1.

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AD is characterized by progressive loss of memory and other cognitive and executive functions, with two types of pathological deposits found in the brain, the extracellular amyloid β ($A\beta$) plaques and the intracellular tau neurofibrillary tangles (NFTs). Senile plaques are mainly composed of $A\beta$ which is cleaved off the larger amyloid β precursor protein (APP) by β -site APP cleaving enzyme (BACE), also known as β -secretase, and γ -secretase (Shoji et al., 1992; Citron et al., 1995). According to the amyloid hypothesis, $A\beta$ and its aggregates are responsible for the neurodegeneration and dementia in AD through mechanisms that involve disturbances in calcium homeostasis which make cells more vulnerable to toxicants that can cause further damage and NFTs (Hardy & Higgins, 1992; Mattson et al., 1992; Selkoe, 1993). The hypothesis was supported by the fact that mutations on APP are connected to hereditary types of AD (Hardy & Higgins, 1992). Early onset familial AD (FAD) could also be due to mutations on genes encoding the presenilin (PS) membrane proteins PS1 and PS2 (Tanzi et al., 1996; Czech et al., 2000). PS mutations increase the production of the more aggregative 42 amino acid-long $A\beta$ ($A\beta_{42}$) from APP and elevated $A\beta_{42}$ levels were observed in the blood and brains of FAD patients with PS abnormalities (Czech et al., 2000). In addition, neurons lacking the PS1 gene fail to produce $A\beta$ peptides (De Strooper et al., 1998; Naruse et al., 1998). PS1 was found to be related to the enzyme γ -secretase (De Strooper et al., 1998; Shimojo et al., 2007). These findings suggest that $A\beta$ and its aggregates are involved in the pathology of AD as proposed in the amyloid hypothesis.

NFTs are composed of tau protein which belongs to a family of microtubule-associated proteins that normally promote microtubule assembly (Weingarten et al., 1975). When hyperphosphorylated, tau loses its normal function and becomes prone to form pathological aggregates causing disorders known as tauopathies of which AD is the most common (Alonso et al., 1997; Lee et al., 2001). Both $A\beta$ and tau have been associated with neurodegeneration and memory decline and have been extensively targeted for AD interventions such as immunotherapeutics, enzyme modulators, and aggregation inhibitors (Hardy & Higgins, 1992; Selkoe, 1993; Hutton et al., 1998; Lee et al., 2001; Hardy & Selkoe, 2002; Iqbal et al., 2009).

Epigenetics deals with acquired and heritable modifications on DNA that regulate the expression and functions of genes without affecting the DNA nucleotide sequence. These include DNA methylation and hydroxymethylation, histone modifications and non-coding RNA regulation. Histone modifications consist of acetylation, methylation, crotonylation, ubiquitination, sumoylation, phosphorylation, hydroxylation and proline isomerization (Davie & Spencer, 1999; Peterson & Laniel, 2004; Kouzarides, 2007; Houston et al., 2013). All these pathways act as mediators between the environment and the genome, these epigenetic changes are activated by various conditions such as stress or exposure to environmental toxicants and in turn they result in a variety of responses including gene transcription or silencing. Epigenetic changes are dynamic and unlike genetic mutations, they can be reversed for therapeutic purposes by targeting enzymes or other factors that control or maintain them (Henikoff & Matzke, 1997; Feinberg, 2008; Liu et al., 2008; Mill, 2011; Caraci et al., 2012). As changes within the genetic makeup itself are limited and the environment cannot freely amend the DNA sequence, epigenetics is the mechanism through which the environment can affect gene expression and function which can be employed as a medical intervention for diseases where epigenetics play a pathological role (Jaenisch & Bird, 2003; Mill, 2011). Furthermore, some age related changes are also mediated through epigenetics (Feinberg, 2008).

The majority of AD cases are sporadic or late onset AD (LOAD). Only about 5% of cases are familial or early onset AD which is associated with rare mutations on the APP, PS1 and PS2 genes (Goate et al., 1991; Sherrington et al., 1995; Tanzi, 2012). The sporadic nature of AD suggests that epigenetics plays an important role in the pathology of the disease; a hypothesis that is supported by recent findings from our laboratory and others (Zawia & Basha, 2005; Lahiri et al., 2008; Wang et al.,

2008a; Wu et al., 2008b; Lahiri et al., 2009; Zawia et al., 2009; Mastroeni et al., 2011; Mill, 2011). This review explores epigenetic mechanisms as possible targets for AD therapeutics and highlights the current status of epigenetics in AD pathology and drug discovery.

1.1. Epigenetics of the brain and memory formation

Epigenetic dynamics within cells play a major role in their differentiation and in determining their functional type as hepatocytes in the liver, neurons in the brain, skin cells, or other cells, as well as becoming cancerous or not (Feinberg, 2008; Chadwick, 2012). Epigenetics is involved in various brain related disorders and physiologic responses that genetics alone does not completely explain including AD, depression, schizophrenia, glioma, addiction, Rett syndrome, alcohol dependence, autism, epilepsy, multiple sclerosis and stress (Shahbazian & Zoghbi, 2002; Jaenisch & Bird, 2003; Zawia et al., 2009; Nguyen et al., 2010; Qureshi & Mehler, 2010; Maze & Nestler, 2011; Mifsud et al., 2011; Taqi et al., 2011; Heim & Binder, 2012; Kreth et al., in press; Maric & Svrakic, 2012; Orr et al., 2012; Inkster et al., 2013). As neurons do not divide and cannot be replaced after degeneration, epigenetic changes resulting in neuronal dysfunction need to be targeted and modified to prevent neurodegeneration (Bird, 2007; Selvi et al., 2010).

Recent studies have pointed out the importance of epigenetics in brain development and functions including learning and memory (Feng et al., 2007; Miller & Sweatt, 2007; Molfese, 2011; Sultan & Day, 2011). In particular, DNA methylation and histone acetylation both play an important role in memory formation (Levenson et al., 2006; Miller et al., 2008). Other histone modifications involved in memory are methylation and phosphorylation (Chwang et al., 2006; Gupta et al., 2010; Molfese, 2011).

DNA methylation is catalyzed by DNA methyltransferases (DNMTs) in the presence of the methyl donor S-adenosyl methionine (SAM) (Yen et al., 1992). The DNMT family of enzymes includes DNMT1, DNMT2, DNMT3a, and DNMT3b (Okano et al., 1999). It is found that DNMT3a and DNMT3b are responsible for de novo methylation and establish DNA methylation patterns while DNMT1 has preference for hemimethylated DNA (Hsieh, 1999; Okano et al., 1999; Chen et al., 2003). DNA methylation occurs on the 5' position of cytosine in CpG rich regions (Bird, 1986). This epigenetic mechanism regulates gene transcription and plays a particular role in memory functions (Liu et al., 2009; Day & Sweatt, 2010; Korzus, 2010). Memory and learning abilities decline with age which correlates with an overall reduction in DNA methylation (Liu et al., 2009). Furthermore, methylation on certain locations of the APP promoter in the human cortex is reduced with age (Tohgi et al., 1999).

DNMTs are considered crucial for memory functions (Miller & Sweatt, 2007). DNMTs regulate methylation within the promoter of reelin, an extracellular glycoprotein that is involved in memory formation in the adult brain (Weeber et al., 2002; Levenson et al., 2006). Protein levels of DNMT1 and DNMT3a are reduced in the cortex of aged monkeys compared to early time points (Bihagi et al., 2011). Moreover, conditional knockout mice lacking the expression of *Dnmt1* and *Dnmt3a* genes in forebrain neurons perform worse on the Morris water maze hippocampus related memory task than wild-type littermates or knockout mice lacking the expression of only one of the genes (Feng et al., 2010). The gene expression of *Dnmt3a2* decreases with age in mouse cortex and hippocampus (Oliveira et al., 2012). This age-related decline in *Dnmt3a2* gene expression is linked to memory decline that can be recovered by restoring DNMT3a2 levels (Oliveira et al., 2012).

Hydroxylation of 5-methylcytosine to 5-hydroxymethylcytosine by ten-eleven translocation (TET) enzymes is an important regulatory pathway involved in brain development, aging and disease (Szulwach et al., 2011). Levels of 5-hydroxymethylcytosine are significantly higher in neurons than in cells of other tissues (Globisch et al., 2010; Szulwach et al., 2011). DNA hydroxymethylation, levels of 5-hydroxymethylcytosine

and 5-methylcytidine increase with age, and alterations in DNMT3a have also been reported with aging in mouse hippocampus (Chouliaras et al., 2011, 2012a, 2012b). Such epigenetic changes could be prevented by 50% caloric restriction diet throughout the mice lifetime after weaning (Chouliaras et al., 2011, 2012a, 2012b).

Moreover, mutations on methyl CpG binding protein 2 (MeCP2) may contribute to the development of Rett syndrome; a life-long neurodevelopmental disorder with marked learning disabilities (Amir et al., 1999). Other neurological abnormalities such as autism and infantile encephalopathy have been associated with disturbances in MeCP2 (Moretti & Zoghbi, 2006; Chahrouh et al., 2008). MeCP2 binds to methylated cytosine in CpG dinucleotides and inhibits or promotes gene expression by recruiting transcription repressors or activators like cAMP response element-binding protein 1 (CREB1) (Jones et al., 1998; Nan et al., 1998; Chahrouh et al., 2008). This also involves MeCP2 binding to histone deacetylase complex (Jones et al., 1998; Nan et al., 1998). MeCP2 levels are found to decrease with age in primates (Bihagi et al., 2011).

Histone acetylation is also involved in the regulation of learning and memory (Levenson et al., 2004; Martin & Sun, 2004). The most widely studied histone modification is regulated by two groups of enzymes, histone acetyltransferases (HATs) and histone deacetylases (HDACs). The HDAC family of enzymes has been studied extensively for implications in cancer. Aberrant overexpression of various HDACs has been reported in different cancer types including gastric, pancreatic, breast, lung and colon cancer (Johnstone, 2002; Barneda-Zahonero & Parra, 2012; New et al., 2012). Many HDAC inhibitors are in clinical trials for cancer therapy, vorinostat and romidepsin have been approved by the FDA for cutaneous T-cell lymphoma (Mann et al., 2007; Kim et al., 2012; Nebbioso et al., 2012). There are 18 HDACs identified that belong to four classes I, II, III and IV according to their sequence homology (Xu et al., 2007). Class I HDAC2, class IIb HDAC6 and class III sirtuins (SIRT1) 1 and 2 are linked to AD pathology (de Oliveira et al., 2012; Karagiannis & Verweris, 2012). Acetylation of histone H3 in the hippocampus accompanies long-term memory formation in rats as determined in hippocampal tissues collected 1 h after fear conditioning experiments (Levenson et al., 2004). Increasing histone acetylation by the administration of the HDAC inhibitor sodium butyrate to rats prior to contextual fear conditioning improves memory formation (Levenson et al., 2004). Class I HDAC inhibitors sodium butyrate, sodium valproate and vorinostat enhance cognition in APP/PS1 double transgenic AD mouse model as evaluated by contextual fear conditioning tests (Kilgore et al., 2010). Overexpression of HDAC2 and not HDAC1, both Class I HDACs, in mice impairs memory and the chronic administration of the HDAC inhibitors vorinostat or sodium butyrate enhances cognition (Guan et al., 2009). HDAC2 knockout mice display improved memory in fear conditioning experiments over wild-type mice (Guan et al., 2009). Consequently, downregulation or inhibition of HDACs 2 and 6 constitutes important therapeutic targets for memory related disorders.

1.2. Epigenetic changes in AD

1.2.1. Histone modifications in AD

Increased levels of HDAC2 have been associated with cognitive impairment in CK-p25 AD mouse model which seems to be mediated through glucocorticoid receptor induced HDAC2 transcription (Graff et al., 2012). Postmortem studies reported that HDAC2 and not HDAC1 or HDAC3 is increased within the hippocampus of AD patients (Graff et al., 2012). Class II HDAC6 levels are elevated in AD cortex and hippocampus by 52% and 91% respectively (Ding et al., 2008). Tau co-localizes with HDAC6 in AD hippocampus and *in vitro*, and downregulation of HDAC6 decreases tau phosphorylation at Thr231 (Ding et al., 2008). Hyperphosphorylation of tau inhibits its normal functions and promotes its aggregation (Alonso et al., 1997). In particular tau phosphorylation at Thr231 restrains its normal function of binding to microtubules (Sengupta et al., 1998). Class III HDACs or sirtuins are a family of

enzymes that includes seven members named SIRT1–7 (Gray & Ekstrom, 2001). In addition to histones, SIRT1s are responsible for deacetylation of other molecules like some proteins involved in AD pathology. For example SIRT1 accounts for tau deacetylation which is considered neuroprotective while tau acetylation contributes to tau dysfunction and aggregation (Min et al., 2010; Cohen et al., 2011; Stunkel & Campbell, 2011). SIRT1 is lower in the AD cortex which correlates with the presence of tau pathology and memory impairment (Julien et al., 2009). There is evidence that SIRT1 also stimulates α -secretase which cleaves APP within the A β sequence and protects against A β accumulation (Donmez et al., 2010; Wang et al., 2010; Raghavan & Shah, 2012). SIRT1 is the most studied sirtuin, other sirtuins are also expressed in the brain and SIRT2 has been presented as a drug target for neurodegenerative diseases such as Parkinson's and Huntington's diseases (de Oliveira et al., 2012).

1.2.2. DNA methylation in AD

DNA methylation and factors such as DNMT1 are significantly reduced in neurons of entorhinal cortex layer II in AD patients (Mastroeni et al., 2010). Reductions in methylation are particularly localized in tangles containing neurons (Mastroeni et al., 2010). Other studies have demonstrated that there is abnormal methylation in AD patients (Wang et al., 2008a; Bakulski et al., 2012). When studying DNA methylation within the cerebral cortex of AD and control subjects, two out of the fifty loci examined were differentially methylated in AD which represent an acceleration of aging-linked alterations (Siegmund et al., 2007). In an AD discordant pair of monozygotic twins, extensive plaques and NFTs were present and less methylation was found in the cortex of the AD twin compared to the non-AD twin (Mastroeni et al., 2009). However, some studies found no differences in the methylation patterns of AD related genes (Barrachina & Ferrer, 2009). The difficulties in obtaining postmortem AD brain tissues for such studies and the variability among the available tissues as well as the different end points of methylation analyzed within these studies account for their various findings.

The promoter region within the APP gene is GC rich suggesting that it can be modulated through methylation (Pollwein et al., 1992). APP promoter displays differential methylation within the human brain (Rogaev et al., 1994). Hypomethylation of the APP promoter was reported to correlate with APP overexpression in AD (West et al., 1995). DNA methylation controls BACE and PS1 expression and consequently A β levels (Fuso et al., 2005). PS1 expression and methylation are altered in LOAD (Wang et al., 2008a). However, the changes on PS1 gene methylation in AD brains were not significant (Wang et al., 2008a). Another study did not detect significant changes in PS1, APP and tau genes methylation in the cortex and hippocampus of AD patients compared to controls (Barrachina & Ferrer, 2009). Lower paternal age was significantly associated with the increase in LOAD risk which might involve DNA methylation (Farrer et al., 1991). The challenges in acquiring and handling human brain tissues make it difficult to have a large number of matched controls and AD samples, however the available studies along with the sporadic and non-Mendelian inheritance nature of the disease suggest that epigenetics is indeed involved in AD. Further research is needed to examine the epigenetic changes affecting AD biomarkers including APP, tau, BACE, PS1 and PS2 among others, as well as global gene methylation patterns which would help with the early diagnosis of the disease.

1.2.3. Non-coding RNA in AD

Non-coding RNA can influence gene expression via epigenetic mechanisms affecting DNA methylation, histone modifications and chromatin remodeling (Costa, 2008). Various microRNAs are differentially expressed in AD and alter the expression of AD pathological intermediates (Cogswell et al., 2008; Nunez-Iglesias et al., 2010; Provost, 2010). An example is microRNA-101 which negatively regulates APP levels and is reduced within the brain cortex of AD patients (Hebert et

al., 2008; Vilardo et al., 2010). Another example is microRNA-107 which is lowered early in AD and regulates BACE1 expression (Wang et al., 2008b). BACE1-AS is a long non-coding RNA antisense transcript of BACE1 that improves BACE1 stability and expression and is upregulated in the hippocampus and cortex of AD patients (Faghihi et al., 2008). Additional changes on non-coding RNAs are reported in AD and have been reviewed recently (Schonrock & Gotz, 2012). However, due to the current limitations and the absence of methods that can target or modify non-coding RNAs for therapeutic purposes, only few are mentioned within this review.

2. Epigenetic therapeutic approaches for AD

2.1. HDAC inhibitors

HDAC inhibitors show promise for cognitive improvement and are being considered for drug development for AD (Fischer et al., 2007; Abel & Zukin, 2008; Guan et al., 2009). Epigenetic changes play a role in cognitive decline and reversing such changes by inhibiting HDAC2 improves memory and cognitive functions (Graff et al., 2012). Treatment of hippocampal neurons with A β promotes HDAC2 transcription suggesting that the traditional target of A β lowering in AD should be complemented with the reversal of epigenetic changes that were caused by increased A β levels (Graff et al., 2012). This might explain why A β lowering is not always successful in improving memory and cognitive deficits when subsequent epigenetic changes are not reversed as well (Graff et al., 2012). Crebinostat, an HDAC inhibitor, improves memory in mice (Fass et al., 2013). Administration of any of the three Class I HDAC inhibitors sodium valproate, sodium butyrate and vorinostat, which is an HDAC inhibitor approved by the FDA for cancer, improves memory in the APPswe/PS1dE9 AD mouse model (Kilgore et al., 2010). Hence, HDAC inhibitors could be promising therapeutic agents for AD and other disorders associated with dementia and cognitive impairments.

Valproic acid, which is used as an anticonvulsant in epileptic patients and as a mood stabilizer in bipolar disorder patients (Phiel et al., 2001), is a known HDAC inhibitor and has therefore been proposed for use in cancer and AD (Gottlicher et al., 2001; Kramer et al., 2003; Nalivaeva et al., 2009). In addition, valproate seems to have multi-target effects that can be useful for AD including the inhibition of the enzyme responsible for tau phosphorylation glycogen synthase kinase 3 beta (GSK3 β) (Loy & Tariot, 2002). Valproic acid lowers A β in the PDAPP transgenic mouse model of AD (Su et al., 2004). However, in a 2-year clinical trial, valproate did not improve cognitive function or slow memory decline in moderate AD patients and was associated with adverse effects such as somnolence, tremor, weakness and dyspnea (Fleisher et al., 2011; Tariot et al., 2011).

Another HDAC inhibitor, sodium phenylbutyrate was found to improve memory and lower tau phosphorylation by GSK3 β in APPswe transgenic AD mice (Ricobaraza et al., 2009). EVP-0334 is an HDAC inhibitor developed for AD by EnVivo Pharmaceuticals that successfully completed phase I clinical trials and was deemed safe for further testing, however, detailed information on the trial have not been made available yet (Mack, 2010; Arrowsmith et al., 2012; Caraci et al., 2012). A class II HDAC inhibitor referred to as W2 lowers A β , tau phosphorylated at Thr181 and improves cognition in hAPP transgenic mice (Sung et al., 2013). The authors also found that W2 and I2, a class I and II HDAC inhibitor, both downregulated genes involved in A β production and promoted genes responsible for A β degradation *in vitro* (Sung et al., 2013).

2.2. Sirtuins

Class III HDACs or SIRT1s are epigenetic targets for cancer and AD (Outeiro et al., 2008; Albani et al., 2010; Huber & Superti-Furga, 2011). The natural product found in red grape skin and wine resveratrol is a SIRT1 activator that improves cognition in mice (Kim et al., 2007).

However, resveratrol cognitive benefits involve other mechanisms besides SIRT1 activation and its epigenetic functions (Kim et al., 2007; Huber & Superti-Furga, 2011). A phase II study is currently recruiting mild to moderate AD patients to study the effects of resveratrol on AD biomarkers including cerebrospinal fluid (CSF) tau and A β levels as well as memory and daily performance using tests like Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) (ClinicalTrials.gov., identifier: NCT01504854, 2013). Two SIRT1 activators developed by GSK were in phase I clinical trials, SRT2104 and SRT2379, recently the results from one of the trials were published and showed that SRT2104 was well tolerated by human subjects and suitable for further clinical trials (Townsend, 2011; Hoffmann et al., 2013). Interestingly, the nonselective SIRT1 inhibitor nicotinamide lowers phosphorylated tau and improves cognition in mice demonstrating that SIRT1 modulation involves complex mechanisms (Green et al., 2008; Stunkel & Campbell, 2011). Nicotinamide is in phase II clinical trial for AD (ClinicalTrials.gov., identifier: NCT00580931, 2012). Furthermore, the administration of the SIRT2 inhibitor AK1 directly into the hippocampus protects against neurodegeneration in tau transgenic mice without altering tau tangles (Spires-Jones et al., 2012).

2.3. HATs

Less attention has been given to HAT enzymes as epigenetic targets for AD. Three HATs are involved in memory formation CREB binding protein (CBP), p300 and p300/CBP associated factor (PCAF) which might represent more specific targets than HDACs (Korzus et al., 2004; Selvi et al., 2010). CBP plays an important role in memory as CBP deficient mice display impaired long-term memory formation (Oike et al., 1999; Wood et al., 2005). In humans, mutations on the CBP gene result in Rubinstein-Taybi syndrome which is characterized by mental retardation (Rubinstein & Taybi, 1963; Petrij et al., 1995). Inducing the expression of CBP within the brains of 3 \times Tg-AD triple transgenic AD mouse model recovers the impaired memory functions in these mice (Caccamo et al., 2010). On the other hand, inhibition of the HAT p300 by using the commercially available p300 inhibitor C646 reduces the levels of acetylated tau and phosphorylated tau at Ser202 *in vitro* (Min et al., 2010). The natural plant product curcumin possesses p300/CBP HAT inhibitor activity and is in phase II clinical trial to study its cognitive effects and A β lowering potential in AD patients (Balasubramanyam et al., 2004; Marcu et al., 2006; ClinicalTrials.gov., identifier: NCT01383161, 2012). Previous trials with a smaller number of AD subjects reported no significant changes between curcumin- and placebo-treated groups (Hamaguchi et al., 2010; Ringman et al., 2012). While in transgenic animal models, curcumin decreased oxidative damage and A β pathology by affecting anti-inflammatory pathways (Lim et al., 2001; Yang et al., 2005; Begum et al., 2008; Hamaguchi et al., 2010).

2.4. DNA methylation

There are multiple ways for targeting DNA methylation for therapeutic purposes (Klose & Bird, 2006). DNA methylation affects the expression of the AD related intermediates APP, PS1 and A β (Fuso et al., 2005). It has been hypothesized that hypomethylation of the promoter regions of such genes like PS1 leads to the overexpression of their products including A β (Mulder et al., 2005). Overexpression of DNMT3a2 within the hippocampus of old mice increases overall methylation and improves memory (Oliveira et al., 2012).

The levels of the methyl donor SAM are lower in the CSF and within the brains of AD patients (Bottiglieri et al., 1990; Bottiglieri et al., 1994; Morrison et al., 1996). However, in another study, there was no difference in SAM-CSF levels in AD patients vs. healthy subjects (Mulder et al., 2005). Nevertheless, treatment with SAM reduces BACE1, PS1 and A β production *in vitro* in human neuroblastoma cells (Scarpa et al., 2003; Fuso et al., 2005). Moreover, the administration of SAM adjunct

to antidepressants in depressed patients enhances their cognitive symptoms and ability to remember as determined by cognitive and physical symptoms questionnaire (CPFQ) (Levkovitz et al., 2012).

Betaine, the methyl donor used conventionally for homocystinuria treatment (Key, 2000), was tested in 8 AD patients for 24 weeks and failed to demonstrate cognitive improvement (Craig, 2004; Knopman & Patterson, 2001). However, the small number of patients and the lack of a placebo-treated control group suggest that further trials are needed to properly evaluate betaine's efficacy in AD (Knopman & Patterson, 2001), especially that elevated homocysteine has been associated with dementia and AD and betaine lowers homocysteine (Seshadri et al., 2002). In a more recent study in mice, betaine was able to improve memory that was compromised by prior lipopolysaccharide administration (Miwa et al., 2011).

2.5. Non-coding RNA

Several non-coding RNAs are involved in AD pathology and could present specific diagnostic and therapeutic targets for the disease (Costa, 2008; Provost, 2010). These include BACE1-AS, microRNA-34c, microRNA-101, and microRNA-107 (Cogswell et al., 2008; Faghihi et al., 2008; Wang et al., 2008b; Vilardo et al., 2010; Zovolis et al., 2011). However, concerns about ways to alter such targets, off target effects, and delivery methods still need to be adequately addressed before having epigenetic treatments capable of affecting non-coding RNAs. Targeting non-coding RNA regions on APP by the antibiotic erythromycin, the antidepressant paroxetine and N-acetyl cysteine has been found to reduce A β in TgCRND8 transgenic mice (Tucker et al., 2005; Tucker et al., 2006).

2.6. Beyond epigenetics: epigenetics and transcription

Epigenetics is an important mediator that influences DNA transcription and translation. The aim of AD therapy is to enhance the transcription of genes involved in memory formation and reduce the transcription of pathogenic intermediates in the disease process like tau, APP, and BACE1. Hence, transcription factors constitute valid targets for developing novel treatments for AD. One of the important transcription factors for learning and memory is CREB (Silva et al., 1998). CREB is an essential mediator of memory improvement following HDAC inhibition as CREB has histone acetylation activity through recruitment of the histone acetyltransferase CBP (Vecsey et al., 2007). HDAC inhibitors, such as phenylbutyrate or crebinostat promote the transcription of genes involved in memory functions as seen with crebinostat which upregulates the CREB target gene early growth response 1 (egr1), which is involved in memory formation (Ricobaraza et al., 2009; Fass et al., 2013). A clinical trial studying the effects of the antiplatelet drug cilostazol on cognition in AD patients co-administered with donepezil is currently in progress (ClinicalTrials.gov., identifier: NCT01409564, 2011). The rationale behind choosing cilostazol is to promote the phosphorylation of CREB which regulates its activity and consequential expression of genes that are controlled by CREB (Bito et al., 1996; Silva et al., 1998; ClinicalTrials.gov., identifier: NCT01409564, 2011). Cilostazol protects against A β triggered cognitive impairment in mice and improves memory following cerebral hypoperfusion damage in rats (Watanabe et al., 2006; Hiramatsu et al., 2010).

An important transcription factor involved in AD is specificity protein 1 (Sp1). It binds to GC-rich regions within the promoters of APP, tau and BACE1 and upregulates their expression (Pollwein et al., 1992; Hoffman & Chernak, 1995; Docagne et al., 2004). Sp1 is able to bind to CpG sites in gene promoters that have such specific binding motifs and activate their transcription whether they are methylated or non-methylated (Holler et al., 1988). Furthermore, Sp1 can trigger epigenetic modifications as it regulates the expression of DNMT1 (Kishikawa et al., 2002). Tolfenamic acid promotes Sp1 protein degradation and lowers APP, tau, and BACE1 expression as well as A β levels and improves cognition

in mice (Abdelrahim et al., 2006; Adwan et al., 2011; Adwan et al., unpublished observation; Subaiea et al., in press). Tolfenamic acid is scheduled to be tested in AD patients in the near future.

3. Discussion and conclusions

Epigenetic changes that occur early in life can impact our health decades later. Various studies suggest that pathologic changes in AD can be reversed prior to the development of symptoms through epigenetic modifications (Fig. 1). Developmental exposure to lead (Pb) upregulates genes involved in AD late in life through mechanisms that involve DNA methylation and histone acetylation (Wu et al., 2008a; Bihagi et al., 2011; Bihagi & Zawia, 2012). Persistent bidirectional changes in DNA methylation in response to earlier Pb exposure are reported with hypermethylation resulting in a latent reduction in gene expression (Alashwal et al., 2012; Dosunmu et al., 2012). Moreover, cognitive impairment accompanies overexpression of Sp1, BACE1, APP and A β late in life following early exposure to Pb and consequential epigenetic alterations (Bihagi et al., in press). Such environmentally-induced changes on AD related intermediates could be reversed via epigenetic mechanisms. Alternatively, active epigenetic changes are involved in memory formation and could be targeted for AD therapy. Modulation of epigenetic intermediates could be a means for the upregulation of genes that promote learning and memory, or reversing epigenetic changes that are responsible for the overexpression of genes involved in AD pathology. As neurons have a very limited ability to regenerate, reversing pathological changes through targeting epigenetic intermediates seems to be a promising therapeutic approach.

Interestingly, epigenetic targets in AD are also implicated in the pathophysiology of schizophrenia and depression (Covington et al., 2009; Gavin & Sharma, 2010). Depression is a common comorbidity in demented patients (Holtzer et al., 2005; Alzheimer's Association, 2012). Psychotic symptoms, especially at later stages of the disease, are also frequent in AD (Ropacki & Jeste, 2005; Alzheimer's Association, 2012). Besides AD, HDAC inhibitors have been explored for other disorders including schizophrenia and depression. For example, the HDAC inhibitor sodium butyrate shows antidepressant activity in mice (Schroeder et al., 2007). Sodium butyrate also protects against phencyclidine induced psychotic-like behavior in mice (Koseki et al., 2012). It would be interesting to study the effects of HDAC inhibitors as epigenetic modifiers on cognitive as well as depressed and psychotic symptoms in AD patients.

Epigenetic alterations reported in AD are summarized in Table 1. A major challenge for AD management is early diagnosis. Currently, no standard criteria are available for early or accurate detection of AD through reference values of biomarkers from patient CSF and blood samples or imaging results. Epigenetic changes in AD could offer a diagnostic tool for the disease especially that some changes occur long before the molecular pathology of AD develops. If such changes are identified and detected early, reversing them via epigenetic therapeutic approaches would prevent the triggering of alterations in gene expression and transcriptional cascade associated with the neuropathology of AD. Also establishing criteria for epigenetic changes in AD can help administer disease-modifying drugs, once they become available, early in the disease process. The use of epigenetics will likely be even more crucial as the field moves towards early and pre-symptomatic case detection and earlier attempts at intervention (Sperling et al., 2011).

The side effects of epigenetic targeting should also be studied. Attention should be made for the consequences of epigenetic modifications that are involved in multiple pathways and which might serve various functions within different cells and organs. Identification of more specific targets and agents could be a way for minimizing toxicity. It is important to realize that drugs with epigenetic effects are already present on the market. Some drugs used for years like the antihypertensive agent hydralazine and the antiepileptic drug valproate are found to interfere with epigenetic pathways which explains their previously unknown mechanisms of action or some of their adverse effects and

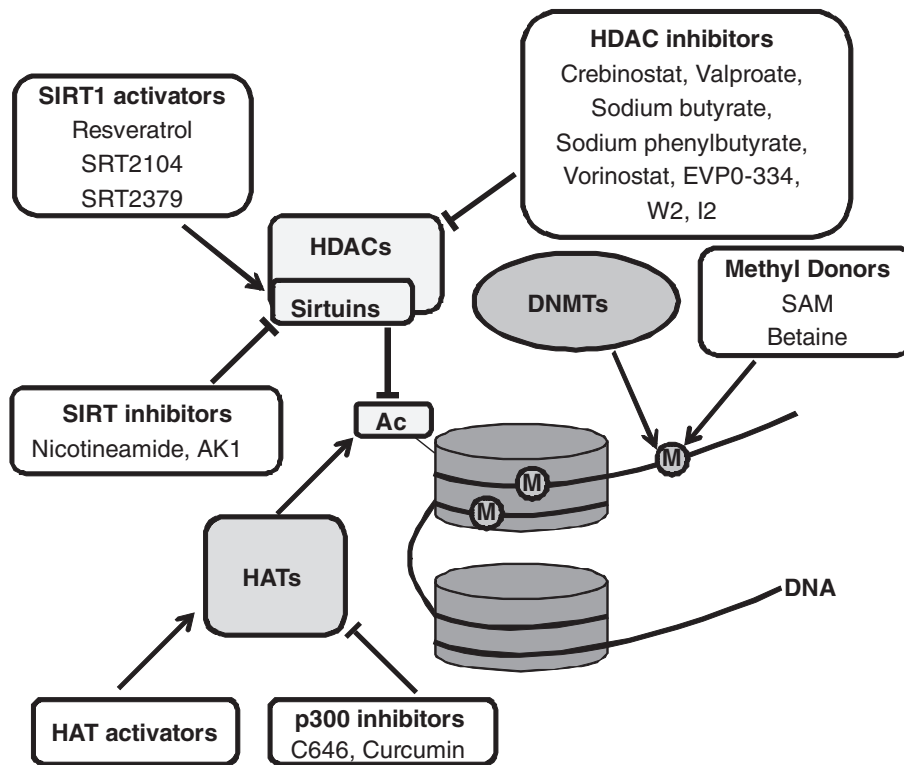


Fig. 1. Epigenetic targets and therapeutic approaches for AD. DNA methylation and histone modification mediators involved in AD and potential therapeutic interventions under development reported in literature. Barrels = histones; (M) = methyl group; (Ac) = acetyl group. Abbreviations in the figure are as follows: DNMT, DNA methyltransferase; HAT, histone acetyltransferase; HDAC, histone deacetylase; SIRT, sirtuin.

suggests that their use could be repurposed for other disorders where epigenetic alterations are desired (Csoka & Szyf, 2009).

Our knowledge about epigenetics is still limited, some mechanisms have been studied more thoroughly like histone acetylation and DNA methylation, yet much remains to be revealed, especially when it comes to AD, memory and cognitive functions. Epigenetics is more upstream in AD pathology than the more common or conventional targets such as BACE, γ -secretase, A β and tau and thus could be beneficial especially in early stages of the disease to prevent further transcription and accumulation of pathological intermediates. Screening for such modifications and diagnosis of AD at an early stage remain a challenge. Nevertheless, promoting epigenetic mechanisms that trigger memory formation and inhibit pathological events could be a novel and effective therapeutic approach for preventing or at least delaying the development of dementia. Epigenetics offer potential for AD where epigenetic changes are integrated in the disease pathology. While no disease-modifying candidate is available, more research is needed for the refinement of epigenetic targets and identification of specific agents that can improve cognition and prevent or slow AD. Although knowledge is still being gathered about this field of study, there is evidence

that epigenetics could provide multi-target therapeutic approaches for AD.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Table 1
Some epigenetic changes in AD reported in literature.

| Epigenetic Mark | Change | Reference |
|------------------------------|----------------------|----------------------------|
| HDAC2 | Increase | Graff et al. (2012) |
| HDAC6 | Increase | Ding et al. (2008) |
| SIRT1 | Decrease | Julien et al. (2009) |
| DNMT1 | Decrease | Mastroeni et al. (2010) |
| MicroRNA-101 | Decrease | Hebert et al. (2008) |
| MicroRNA-107 | Decrease early in AD | Wang et al. (2008b) |
| BACE1-AS | Upregulated | Faghihi et al. (2008) |
| Methylation on APP gene | Hypomethylation | West et al. (1995) |
| Methylation on APP, PS1, tau | No change | Barrachina & Ferrer (2009) |

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