Review

Epigenetic Modification and Its Role in Alzheimer's Disease

Yi-Ping Zhu^{a, b} Ya Feng^a Te Liu^c Yun-Cheng Wu^a

Departments of ^aNeurology and ^bUrology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, and ^cShanghai Geriatric Institute of Chinese Medicine, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, PR China

Key Words

Alzheimer's disease · Epigenetics · DNA methylation · Histone acetylation · Noncoding RNA expression

Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disease, and its mechanisms have not been clearly elucidated. A large percentage (more than 95%) of cases are late-onset AD without familial traits. Although some genes have been implicated in the pathogenesis and the risk of developing sporadic AD, they only account for the minority of late-onset AD. Recently, accumulating data have suggested a potential role for epigenetic mechanisms in neurodegenerative processes leading to dementia. Alterations in the epigenetic machinery cause aberrant DNA methylation and histone acetylation. Therefore, these changes trigger alterations on the transcriptional level of genes involved in the pathogenesis of AD. In this review, we summarize recent advances in research on AD caused by common epigenetic modification and the potential treatment strategies targeting the epigenetic machinery.

© 2015 S. Karger AG, Basel

Introduction

Alzheimer's disease (AD) is the leading cause of dementia in the elderly. The histopathological features of AD include senile plaques composed of amyloid- β ($A\beta$) that accumulate extracellularly, neurofibrillary tangles composed of hyperphosphorylated tau protein, and intracellular and selective neuronal cell loss [1]. AD is a complex disease and encompasses many prominent risk factors, such as aging and genetic, environmental, and vascular factors.

Yi-Ping Zhu and Ya Feng contributed equally to this study.

Yun-Cheng Wu, MD, PhD
Department of Neurology, Shanghai General Hospital
Shanghai Jiao Tong University School of Medicine
No. 100 Haining Road, Shanghai 200080 (PR China)
E-Mail yunchw@medmail.com.cn

So far, its pathogenesis has not been clearly elucidated. Mutations in specific genes have been identified; however, they can only explain 5–10% of the AD cases. The genes implicated in early-onset familial AD are the genes encoding for amyloid precursor protein (APP), the gene encoding for presenilin 1, and the gene encoding for presenilin 2. The gene implicated in the pathogenesis and the risk of developing sporadic AD is apolipoprotein E ϵ 4 (APOE ϵ 4) [2].

Recently, epigenetic modifications have been found to be relevant for many complex disorders, whereas the DNA sequence remains essentially the same [3, 4]. Epigenetic modifications comprise all heritable changes in genome function that do not alter the nucleotide sequence within the DNA, including DNA methylation, histone modifications, chromatin remodeling, and noncoding RNA (ncRNA) regulation [5, 6]. Epigenetic modifications are present from as early as the prenatal phase, and a loss of phenotypic plasticity caused by epigenetic modifications is associated with the aging process [7]. Since aging is the most important risk factor for neurodegenerative diseases, in which AD is included, it is speculated that epigenetic modifications might also play a major role in the pathogenesis of AD [8–10].

DNA Methylation in AD

DNA methylation is a biochemical process that is important for normal development in higher organisms. It involves the addition of a methyl group to the 5' position of the cytosine residues within CpG dinucleotides or the number 6 nitrogen of the adenine purine ring (cytosine and adenine are two of the four bases of DNA). This modification is catalyzed by DNA methyltransferases (DNMTs) and can be inherited through cell division [11]. CpG dinucleotides are generally concentrated in regions called CpG islands, which are preferentially located in promoter regions. CpG methylation can directly affect the binding of transcription factors to its homologous DNA; meanwhile, it can also recruit methyl-CpG-binding protein to inhibit gene expression [12]. Many studies have confirmed that a genome-wide decrease in DNA methylation has occurred in aging and AD patients [13].

The novel concentration of one-carbon metabolism-related substances has an influence on the status of DNA methylation. With the help of folate and vitamin B₁₂, homocysteine becomes S-adenosyl methionine (SAM). As a methyl donor, SAM participates in the process of methylation reactions, turning into S-adenosine homocysteine (SAH) and finally homocysteine [14] (fig. 1). The levels of folate and vitamin B₁₂ are decreased in AD patients, whereas levels of SAH (a methyltransferase inhibitor) and homocysteine are high [14, 15]. In addition, compared to controls, patients with late onset of AD have relatively increased plasma homocysteine levels and decreased serum folate values [16]. The abnormal metabolism described above stimulates AD-related gene expression by decreasing the level of DNA methylation, leading to overexpression of A β .

Ageing is a main risk factor for AD, which can decrease the total level of DNA methylation and ultimately cause overexpression of AD-related genes. Studies have indicated that some sites of the promoter region of the APP gene appear to be demethylated when a person is above 70 years of age, which might cause the gene to be overexpressed and finally generate A β in abundance [7] (fig. 2). However, the promoter regions of some specific genes [such as the neprilysin (NEP) gene, which inhibits AD occurrence] turn out to be highly methylated. NEP is one of the important A β -degrading enzymes in the brain, and it plays a critical role in the clearance of A β [17]. Due to the high methylation, expression of the NEP gene is inhibited and the clearance of A β is decreased, resulting in the accumulation of A β . The ApoE gene, closely related to the occurrence of sporadic AD, is characterized by complex DNA methyl-

Fig. 1. Folate and vitamin B₁₂ (V_{B12}) are required for the conversion of homocysteine (Hcy) to methionine (Met) and the formation of SAM. As a methyl donor, SAM participates in DNA methylation, which is catalyzed by DNMT, turning into SAH and finally Hcy. The methyl-CpG-binding domain (MBD), which is characterized by specifically binding to the methylated DNA, can recruit HDACs, producing a more condensed chromatin structure and inhibiting gene transcription. miRNAs bind to complementary nucleic acid sequences in the 3'-UTR of mRNA and bring about mRNA degradation. lncRNA antisense forms an RNA complex with mRNA, preventing mRNA from degradation by RNase to increase the stability of mRNA and boost gene expression. AC/Ac = Acetyl-; Me = methyl-; m⁷G = 7' methylated guanine; 5mC = 5' methylated cytosine.

ation. A few promoter regions of the CpG are less methylated, but the 3' position of the CpG that concerns haplotype ε4 is completely methylated [18]. The abnormal epigenetic mechanism of this CpG island may induce the pathologic alteration in AD [19].

Histone Acetylation in AD

Histone acetylation is a process in which acetyl coenzyme A transfers acetyl to the lysine residues of core histone N terminal domains under the catalysis of histone acetyltransferases (HATs). Histone acetylation can not only neutralize the positive charge in histone, but also reduce the affinity between histone and negatively charged phosphate in DNA. Therefore, it can lose the chromatin structure and activate gene transcription activity. In contrast, histone deacetylase (HDAC) mediates the reverse process and silences some specific genes [20]. It has been demonstrated that histone acetylation was lower in the temporal lobe of AD patients than in aged controls [21]. However, another study has found increased acetyl and total levels in postmortem AD brains [22].

At present, chromatin remodeling mediated by histone acetylation is regarded to be associated with the formation of long-term memory. It has been found experimentally that in the learning and memory process of a 16-month-old mouse, the H4K12 acetylation level decreases and, thus, the expression of the hippocampal memory-related gene is suppressed. SAHA, an HDAC inhibitor, can bring the acetylation level of H4K12 back to a physiological level and can

Fig. 2. The decreased DNA methylation status of the APP gene promoter is correlated with increased gene expression, leading to a higher level of APP. APP is cleaved by β -secretase to form a secreted ectodomain (sAPP β) and a membrane-bound fragment. γ -Secretase cleavage of the latter product by presenilin 1 (PS1) and presenilin 2 (PS2), among others, releases AICD and A β . AICD forms a trimeric complex with Fe65 and the HAT Tip60 and acts on the NEP gene to promote its expression by histone acetylation. NEP, which is the major A β -degrading enzyme in the brain, shows increased promoter methylation with aging. As a class III HDAC, SIRT1 interferes with NF- κ B signaling by deacetylating RelA/p65, reducing neurotoxicity significantly. SIRT1 is also known to activate expression of the α -secretase ADAM10 through deacetylation of retinoic acid receptor- β (RAR β). The activated Notch receptor is proteolysis cleaved sequentially by ADAM10 and γ -secretase to yield NICD, which is implicated in neuronal development and repair mechanisms. HDAC is dynamically implicated in the silencing of the genes related to the formation of long-term memory, promoting the progression of AD. miR-29a/b and miR-107, which both target BACE1, bind to complementary nucleic acid sequences in the 3'-UTR of BACE1 mRNA and lead to BACE1 mRNA degradation and a lower level of β -secretase. lncRNAs may also play a role in regulating the BACE1 gene by antisense transcription. BACE1-ASs form an RNA complex with BACE1 mRNA and prevent the mRNA from degradation by RNase to increase the stability of BACE1 mRNA and expression of β -secretase. AC/Ac = Acetyl-; MBD = methyl-CpG-binding domain; Me = methyl-; m⁷G = 7' methylated guanine; 5mC = 5' methylated cytosine.

recover the expression of related genes, improving cognitive abilities [23]. Neuron-specific overexpression of HDAC2 but not HDAC1 in the mouse leads to a decrease in dendritic spine density and to a reduction in the number of synapses as well as to a decrease in synaptic plasticity and memory [24]. The blockade of epigenetic modification in the process of transcriptional regulation will result in cognitive decline in neurodegenerative diseases, and the effect is mediated by histone deacetylase II [25]. Histone deacetylase II increases significantly in AD patients as well as in vivo and in vitro models, which can lead to transcription of learning- and memory-related genes. Further studies indicated that disinhibition of these genes could recover the neuron structure and synaptic plasticity by reversing the accumulation of histone deacetylase II with small hairpin RNA silencing technology and finally alleviate the cognitive impairment. These studies demonstrated that the decline in gene expression caused by neurodegeneration is not fully caused by blockade of the epigenetic modification mechanism. The development of a selective inhibitor of histone deacetylase II might be helpful in the treatment of cognitive decline in many neurodegenerative diseases [25].

It has been indicated that HDAC inhibitors can reverse the abnormal histone acetylation and improve memory, thus reversing the disease process. When APP/PS1 mice are exposed to a frightening environment, the level of H4 acetylation in the hippocampus is lower than in wild-type mice. After receiving trichostatin A, the acetylation level of H4 increases and the stiffness in the dreaded environment becomes more obvious [26]. If transgenic CK-p25 mice were given trichostatin, the dendrites and synapses were induced to proliferate and the learning and memory ability could be recovered as well [27]. Valproate, an inhibitor of HDAC, could effectively improve the episodic memory of ADAPPswe/PS1dE9 transgenic mice [28]. Another inhibitor of HDAC, such as phenyl butyrate, could reverse the spatial memory loss and the level of phosphorylated tau protein in the hippocampus in Tg2576 mice. However, it could not change the level of A β [29].

Sirtuins are NAD⁺-dependent class III histone deacetylases, and they have a neuroprotective role in neurons. Firstly, sirtuin 1 (SIRT1) can deacetylate and activate the retinoic acid receptor- β and further activate the expression of α -secretase ADAM10. ADAM10 can inhibit the production of A β by an ADAM10-mediated APP proteolysis process [30]; it is also involved in the hydrolysis of the activated Notch receptor, and then the cleaved Notch will facilitate the release of Notch intracellular domain (NICD) by the γ -secretase enzyme. The release of NICD activates the Notch signaling pathway and the transcription of downstream genes and is finally involved in the development and repair of the nervous system [30, 31]. Secondly, overexpression of SIRT1 can also cause deacetylation of RelA/p65 at Lys310 in the NF- κ B family and can finally reverse the neurodegeneration caused by the overproduction of glial cells activated by the NF- κ B family [32] (fig. 2).

In the process of APP hydrolysis into A β , APP intracellular C-terminal domain (AICD) will also be generated [6]. With the transcription of histone acetylation-regulatory genes, AICD, Fe65, and Tip60 (HAT) can form into trimeric complexes. It has been demonstrated that AD-related genes including APP, GSK-3 β , BACE1, and NEP are all regulated by the AICD-Fe65 complex [31, 33]. The AICD-Fe65 complex is also involved in APP processing and management. The overexpression of Fe65 will generate more A β and promote the occurrence and development of AD [33, 34].

ncRNA in AD

In human genes, there are statistically about 98.5% of genetic sequences that could be classified into a noncoding region. These noncoding sequences are mostly transcribed into different forms of ncRNA including microRNAs (miRNAs) [35]. miRNAs are a group of small

ncRNAs which can regulate the translational repression of target messenger RNAs (mRNAs) in a sequence-specific manner. The majority of the presently identified miRNAs in the brain can regulate the expression of the target molecules essential for neuronal and glial development, differentiation, proliferation, apoptosis, and metabolism [35]. Accumulating evidence indicates that aberrant expression and dysfunction of brain-enriched miRNAs can deregulate the target genes in the brain and plays a central role in the pathogenesis of neurodegenerative diseases including AD [36].

In physiological conditions, AD-related gene-homologous miRNA impedes the extension of mRNA transcription through a combination with the coding region (3' untranslated region; 3'-UTR) in the 3' end of the target gene mRNA or through a catalysis to separate ribosomes with mRNA, and finally inhibits gene expression [37]. In AD, the levels of β -secretase 1 (BACE1)-related miR-107 and miR-29a/b [38, 39] (fig. 2) are decreased and their inhibitory effect on BACE1 expression is reduced. In vitro studies with HeLa, COS1, and HEK293 cells indicated that expression of luciferase controlled by the 3'-UTR of the APP gene can be regulated by the miR-20a family including miR-20a, miR-17-5p, and miR-106b, and the instantaneous transfection of these miRNAs can suppress the gene expression of APP [38]. The impediment of the expression of miR-20 leads to an increase in the endogenous APP level by 50% [38]. The level of APP mRNA in the mouse brain is basically stable, while the expression of the APP protein increases, which is closely related to the obvious reduction in miR-20a, miR-17-5p, and miR-106b. Therefore, it is believed that the APP gene is deregulated by miRNAs not through the degradation but through the inhibition of APP mRNA. Further pathological studies demonstrated that miR-106b was dramatically decreased in the cerebral cortex of patients with AD; however, there is no evidence to indicate a correlation of the levels of miR-20a, miR-17-5p, and miR-106b with the concentration of APP protein in the cerebral cortex of patients with AD [38].

It has recently been demonstrated that overexpression or silencing of miR-34a inversely modulated the expression of synaptic targets, including synaptotagmin-1 and syntaxin-1A, in AD patients [40]. Their further results indicate that the p53 family member Tap73 drove the expression of miR-34a, but not miR-34b and -c, by acting on specific binding sites on the miR-34a promoter. Recently, it has been reported that endogenous miR-153 inhibits the expression of APP in human neurons by specifically interacting with the APP 3'-UTR [41]. The same study found that miR-153 significantly reduced reporter expression when co-transfected with an APP 3'-UTR reporter construct, while mutation of the predicted miR-153 target site eliminated this reporter response. Further studies demonstrated that miR-153 delivery in both HeLa cells and primary human fetal brain cultures significantly reduced APP expression, while the delivery of a miR-153 antisense inhibitor to human fetal brain cultures significantly elevated APP expression. Interestingly, in a subset of human AD brain specimens with moderate AD pathology, miR-153 levels were reduced. These results indicate that low miR-153 levels may lead to an increased APP expression in a subset of AD patients [41]. An important study indicated that miRNAs such as Let-7 could also function as signaling molecules and identified TLR7 as an essential element in a pathway that contributes to the spread of central nervous system damage in AD [42].

The long-chain ncRNA (lncRNA) can regulate gene expression with regard to different aspects, such as epigenetic regulation, transcription regulation, and posttranscription regulation, which is involved in the pathogenesis of many complex diseases including AD. lncRNA is transcribed from the antisense strand of AD-related genes (including the gene locus of APP, MAPT, β -secretase 1/2, APOE4, and BSG/CD147) [43]. Concerning the BACE1 gene, for example, lncRNA BACE1 antisense RNA (BACE1-AS) transcribed from the antisense strand of the β -secretase gene (BACE1) can form an mRNA complex with BACE1 RNA, preventing the BACE1 mRNA enzyme from degradation by nucleic acid enzyme to maintain the stability of

BACE1 mRNA, which will lead to greater accumulation of A β . The above positive feedback process accelerates the further development of AD. The specific small interfering RNA of BACE1-AS reduces the expression levels of BACE1-AS; meanwhile, the expression level of A β , as well as BACE1-AS, may be a more ideal drug target of AD treatment [44].

Epigenetic Therapeutics in AD

Neurodegenerative diseases, particularly AD, can cause a significant burden on both the patient and the health care system. Despite extensive research, treatment options for patients with these conditions remain limited and, generally, only provide modest symptomatic relief. Accumulating evidence indicates that aberrant epigenetic posttranslational modifications of proteins are emerging as important elements in the pathogenesis of AD. The current evidence suggests that pharmacologically targeting one such family, namely DNA methylation, histone deacetylases, or ncRNA, may be of potential benefit in the future treatment of AD [5, 45].

The lack of folic acid and vitamin B₁₂, which is involved in one-carbon metabolism, could lead to reduced DNA methylation and the purported occurrence of AD. It has been proved that providing folic acid with the diet can ameliorate the methylation of DNA [46]. Therefore, the treatment of AD with folic acid and vitamin B₁₂ is feasible in theory. Furthermore, clinical trials of vitamin B₁₂ in patients with mild AD have confirmed its effect on delaying the progress of cognitive deficits. However, there was no effect in patients with moderate and severe AD [47]. AD and other neurodegenerative diseases are mainly manifested in impaired learning and memory abilities, which are related to histone acetylation. HDAC inhibitors improve cognitive function in transgenic mouse models of AD [25, 28]. However, these favorable results were not achieved when treating AD patients with 2-valproate (an HDAC inhibitor) [48].

Nicotinamide, a competitive physiological inhibitor of sirtuins, can ameliorate cognitive deficits in 3xTg-AD mice. It could also enhance the level of acetylated α -tubulin by inhibiting SIRT2, which stabilizes microtubules and contributes to neuroprotection [49]. The activation of sirtuin, a new therapeutic approach to AD, could reverse the duration of AD by stimulating the expression of α -secretase and interfering with the NF- κ B signaling pathway. New findings suggest that resveratrol can competitively inhibit phosphodiesterase (PDE) activity and induce cAMP signaling via Epac1, which activates PLC, resulting in increased intracellular Ca²⁺ release via the ryanodine receptor 2 (Ryr2) Ca²⁺ channel. The elevated Ca²⁺ can activate the CamKKb-AMPK pathway and, ultimately, NAD⁺ and SIRT1. Inhibiting PDE4 with rolipram could produce anti-aging effects similar to those of resveratrol, such as increasing mitochondrial function. Therefore, resveratrol may have potential value in treating neurodegenerative diseases [50, 51].

The epigenetic modification of NEP expression, which remained as the principle amyloid-degrading enzyme, may serve as a possible strategy for AD treatment [52]. DNA-demethylating agents, such as 5-azacytidine and decitabine, could decrease the level of NEP methylation by inhibiting DNMT, enhance NEP expression, and eliminate A β . However, it seems more feasible to regulate the expression of NEP by the deacetylation of AICD [52].

In recent years, although encouraging progress has been achieved in our understanding of the role of epigenetic mechanisms in the pathogenesis of AD, the results of the study of epigenetic modification of AD are still not satisfying [5, 6]. It is particularly important to find out how to make the fruits of the basic research accessible in future clinical treatment.

Conclusions

There are many different epigenetic modification mechanisms which interact with and influence each other and finally participate in the pathogenesis of AD. Therefore, different epigenetic mechanisms might target specific disease processes, and the future epigenetic therapy of AD should be comprehensive. Moreover, it is necessary to find a new effective pathway which acts on specific epigenetic mechanisms in specific genes or sets of genes while avoiding side effects on others. The specificity requirements for an AD epigenetic therapeutic agent will be challenging. According to integrative medicine, the interaction of genetic, epigenetic, and environmental toxins might be the real cause of AD, and also the current cocktail treatment of AD indicates that it is important for us to investigate in detail the epigenetic mechanisms in AD [53].

Pathological changes in AD are believed to have happened for more than 10 years before symptoms emerge, and this preclinical stage is the most beneficial period for AD patients to receive epigenetic modification treatment. It is particularly important to make an early diagnosis of AD and focus on identifying new and comprehensive specific biomarkers that will be helpful in the earlier detection of AD.

Acknowledgements

Our work was supported by grants from the National Basic Research Program of China (973 Program; 2011CB707506), the Shanghai Pujiang Program (11PJD019), and the Biomedical Multidisciplinary Program of Shanghai Jiao Tong University (YG2014MS31) to Yun-Cheng Wu. Moreover, this work was supported by a grant from the National Natural Science Foundation of China (No. 81202811), and the project was funded by the China Postdoctoral Science Foundation (No. 2014M550250) and the Shanghai Municipal Health Bureau Fund (No. 20124320) to Te Liu.

Disclosure Statement

The authors declare that they have no competing interests.

References

- 1 Tanzi RE: The genetics of Alzheimer disease. *Cold Spring Harb Perspect Med* 2012;2.
- 2 Hori Y, Hashimoto T, Nomoto H, et al: Role of apolipoprotein E in β -amyloidogenesis: isoform-specific effects on protofibril to fibril conversion of A β in vitro and brain A β deposition in vivo. *J Biol Chem* 2015;290:15163–15174.
- 3 Ruzicka WB: Epigenetic mechanisms in the pathophysiology of psychotic disorders. *Harv Rev Psychiatry* 2015;23:212–222.
- 4 Landgrave-Gomez J, Mercado-Gomez O, Guevara-Guzman R: Epigenetic mechanisms in neurological and neurodegenerative diseases. *Front Cell Neurosci* 2015;9:58.
- 5 Urdinguio RG, Sanchez-Mut JV, Esteller M: Epigenetic mechanisms in neurological diseases: genes, syndromes, and therapies. *Lancet Neurol* 2009;8:1056–1072.
- 6 Lee J, Ryu H: Epigenetic modification is linked to Alzheimer's disease: is it a maker or a marker? *BMB Rep* 2010;43:649–655.
- 7 Marques SC, et al: Epigenetics in neurodegeneration: a new layer of complexity. *Prog Neuropsychopharmacol Biol Psychiatry* 2011;35:348–355.
- 8 Wang J, et al: Epigenetic mechanisms in Alzheimer's disease: implications for pathogenesis and therapy. *Ageing Res Rev* 2013;12:1024–1041.

- 9 Millan MJ: The epigenetic dimension of Alzheimer's disease: causal, consequence, or curiosity? *Dialogues Clin Neurosci* 2014;16:373–393.
- 10 Li L, et al: Epigenetic modulation of Cdk5 contributes to memory deficiency induced by amyloid fibrils. *Exp Brain Res* 2015;233:165–173.
- 11 Yi JM, Kim TO: Epigenetic alterations in inflammatory bowel disease and cancer. *Intest Res* 2015;13:112–121.
- 12 Tahiliani M, et al: Conversion of 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1. *Science* 2009;324:930–935.
- 13 Mastroeni D, et al: Epigenetic mechanisms in Alzheimer's disease. *Neurobiol Aging* 2011;32:1161–1180.
- 14 Fusco A, Scarpa S: One-carbon metabolism and Alzheimer's disease: is it all a methylation matter? *Neurobiol Aging* 2011;32:1192–1195.
- 15 Wainaina MN, Chen Z, Zhong C: Environmental factors in the development and progression of late-onset Alzheimer's disease. *Neurosci Bull* 2014;30:253–270.
- 16 Coppede F, et al: Folate, homocysteine, vitamin B₁₂, and polymorphisms of genes participating in one-carbon metabolism in late-onset Alzheimer's disease patients and healthy controls. *Antioxid Redox Signal* 2012;17:195–204.
- 17 Civitelli L, et al: Herpes simplex virus type 1 infection in neurons leads to production and nuclear localization of APP intracellular domain (AICD): implications for Alzheimer's disease pathogenesis. *J Neurovirol* 2015, Epub ahead of print.
- 18 Caesar I, Gandy S: Evidence that an APOE ε4 'double whammy' increases risk for Alzheimer's disease. *BMC Med* 2012;10:36.
- 19 Wang WX, et al: The expression of microRNA miR-107 decreases early in Alzheimer's disease and may accelerate disease progression through regulation of β-site amyloid precursor protein-cleaving enzyme 1. *J Neurosci* 2008;28:1213–1223.
- 20 Rousseaux S, Khochbin S: Histone acylation beyond acetylation: terra incognita in chromatin biology. *Cell J* 2015;17:1–6.
- 21 Zhang K, et al: Targeted proteomics for quantification of histone acetylation in Alzheimer's disease. *Proteomics* 2012;12:1261–1268.
- 22 Narayan PJ, et al: Increased acetyl and total histone levels in post-mortem Alzheimer's disease brain. *Neurobiol Dis* 2015;74:281–294.
- 23 Peleg S, et al: Altered histone acetylation is associated with age-dependent memory impairment in mice. *Science* 2010;328:753–756.
- 24 Guan JS, et al: HDAC2 negatively regulates memory formation and synaptic plasticity. *Nature* 2009;459:55–60.
- 25 Graff J, et al: An epigenetic blockade of cognitive functions in the neurodegenerating brain. *Nature* 2012;483:222–226.
- 26 Francis YI, et al: Dysregulation of histone acetylation in the APP/PS1 mouse model of Alzheimer's disease. *J Alzheimers Dis* 2009;18:131–139.
- 27 Fischer A, et al: Recovery of learning and memory is associated with chromatin remodelling. *Nature* 2007;447:178–182.
- 28 Kilgore M, et al: Inhibitors of class 1 histone deacetylases reverse contextual memory deficits in a mouse model of Alzheimer's disease. *Neuropsychopharmacology* 2010;35:870–880.
- 29 Ricobaraza A, et al: Phenylbutyrate ameliorates cognitive deficit and reduces τ pathology in an Alzheimer's disease mouse model. *Neuropsychopharmacology* 2009;34:1721–1732.
- 30 Donmez G, et al: SIRT1 suppresses beta-amyloid production by activating the α-secretase gene ADAM10. *Cell* 2010;142:320–332.
- 31 Zhang YW, et al: APP processing in Alzheimer's disease. *Mol Brain* 2011;4:3.
- 32 Chen J, et al: SIRT1 protects against microglia-dependent amyloid-β toxicity through inhibiting NF-κB signaling. *J Biol Chem* 2005;280:40364–40374.
- 33 Pirooznia SK, et al: Tip60 HAT activity mediates APP induced lethality and apoptotic cell death in the CNS of a *Drosophila* Alzheimer's disease model. *PLoS One* 2012;7:e41776.
- 34 Borquez DA, Gonzalez-Billault C: The amyloid precursor protein intracellular domain-Fe65 multiprotein complexes: a challenge to the amyloid hypothesis for Alzheimer's disease? *Int J Alzheimers Dis* 2012;2012:353145.
- 35 Satoh J: Molecular network of microRNA targets in Alzheimer's disease brains. *Exp Neurol* 2012;235:436–446.
- 36 Satoh J, Kino Y, Niida S: MicroRNA-Seq data analysis pipeline to identify blood biomarkers for Alzheimer's disease from public data. *Biomark Insights* 2015;10:21–31.
- 37 Cogswell JP, et al: Identification of miRNA changes in Alzheimer's disease brain and CSF yields putative biomarkers and insights into disease pathways. *J Alzheimers Dis* 2008;14:27–41.
- 38 Hebert SS, et al: MicroRNA regulation of Alzheimer's amyloid precursor protein expression. *Neurobiol Dis* 2009;33:422–428.
- 39 Nelson PT, Wang WX: MiR-107 is reduced in Alzheimer's disease brain neocortex: validation study. *J Alzheimers Dis* 2010;21:75–79.
- 40 Agostini M, et al: Neuronal differentiation by TAp73 is mediated by microRNA-34a regulation of synaptic protein targets. *Proc Natl Acad Sci USA* 2011;108:21093–21098.

- 41 Long JM, Ray B, Lahiri DK: MicroRNA-153 physiologically inhibits expression of amyloid- β precursor protein in cultured human fetal brain cells and is dysregulated in a subset of Alzheimer disease patients. *J Biol Chem* 2012;287:31298–31310.
- 42 Lehmann SM, et al: An unconventional role for miRNA: let-7 activates Toll-like receptor 7 and causes neurodegeneration. *Nat Neurosci* 2012;15:827–835.
- 43 Qureshi IA, Mehler MF: Advances in epigenetics and epigenomics for neurodegenerative diseases. *Curr Neurol Neurosci Rep* 2011;11:464–473.
- 44 Faghihi MA, et al: Expression of a noncoding RNA is elevated in Alzheimer's disease and drives rapid feed-forward regulation of β -secretase. *Nat Med* 2008;14:723–730.
- 45 Gray SG: Epigenetic treatment of neurological disease. *Epigenomics* 2011;3:431–450.
- 46 Durga J, et al: Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. *Lancet* 2007;369:208–216.
- 47 Aisen PS, et al: High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. *JAMA* 2008;300:1774–1783.
- 48 Herrmann N, et al: A placebo-controlled trial of valproate for agitation and aggression in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2007;23:116–119.
- 49 Huber K, Superti-Furga G: After the grape rush: sirtuins as epigenetic drug targets in neurodegenerative disorders. *Bioorg Med Chem* 2011;19:3616–3624.
- 50 Wu Y, et al: Resveratrol-activated AMPK/SIRT1/autophagy in cellular models of Parkinson's disease. *Neurosignals* 2011;19:163–174.
- 51 Park SJ, et al: Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases. *Cell* 2012;148:421–433.
- 52 Nalivaeva NN, et al: Are amyloid-degrading enzymes viable therapeutic targets in Alzheimer's disease? *J Neurochem* 2012;120(suppl 1):167–185.
- 53 Chen X, et al: The treatment strategies for neurodegenerative diseases by integrative medicine. *Integr Med Int* 2014;1:223–225.