Neurogenesis-based epigenetic therapeutics for Alzheimer's disease (Review)

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Abstract. Alzheimer's disease (AD) is a worldwide health problem with multiple pathogenic causes including aging, and genetic and environmental factors. As the interfaces between genes and the environment, epigenetic mechanisms, including DNA methylation, histone modification and microRNAs, are also involved in the pathogenesis of AD. Neurogenesis occurs throughout life in the normal adult brain of mammals. The neurogenic process, consisting of the proliferation, differentiation and maturation of neural stem cells (NSC), is regulated via epigenetic mechanisms by controlling the expression of specific sets of genes. In the pathology of AD, due to impairments in epigenetic mechanisms, the generation of neurons from NSCs is damaged, which exacerbates the loss of neurons and the deficits in learning and memory function associated with AD. Based on neurogenesis, a number of therapeutic strategies have shown capability in promoting neuronal generation to compensate for the neurons lost in AD, thereby improving cognitive function through epigenetic modifications. This provides potential for the treatment of AD by stimulating neurogenesis using epigenetic strategies. The present review discusses the epigenetics of AD and adult neurogenesis, and summarizes the neurogenesis-based epigenetic therapies targeted at AD. Such a review may offer information for the guidance of future developments of therapeutic strategies for AD.

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1. Introduction

Alzheimer's disease (AD) is a worldwide health problem, which has a complicated pathogenesis involving diet, aging, and genetic and environmental causes (1). As the interfaces between genes and the environment, epigenetic mechanisms, which include DNA methylation, histone modification and microRNAs (miRNAs) are also implicated in the pathogenesis of AD (2). Experimental evidence has shown that the epigenetic mechanisms are altered in AD pathology, including the DNA methylation of AD-associated genes, which may promote the accumulation of β-amyloid (Aβ) in plaques, intracellular formation of neurofibrillary tangles (NFTs), as well as loss of neurons, which result in dementia (3). A number of therapeutic strategies have been shown to alleviate the cognitive and memory impairments caused by AD through epigenetic modification. Thus, AD-associated epigenetics are of particular interest in investigations of the pathogenesis of AD and therapeutic options (4).

Neurogenesis is considered to occur throughout life within the brain of adult mammals, including humans; it contributes thousands of new neurons each day to the hippocampus to assist in the maintenance of normal cognition and memory function in humans (5,6). Neurogenic processes include the proliferation, fate specification, maturation and final integration of neural stem cells (NSCs) into the existing neural circuitry; this process is regulated by intracellular programs and extracellular niche signals. Epigenetic mechanisms may be involved in the regulation of neurogenesis by translating extracellular niche signals into long-lasting changes in gene expression. In AD, neurogenesis-associated epigenetic mechanisms are altered due to changes of intracellular programs and surrounding microenvironments of NSCs (7). These include the hypermethylation of neurogenesis genes, histone de-acetylation and miRNA dysfunctions, which halt or delay NSC generation. As a consequence, the generation of neurons from neurogenesis are significantly reduced, exacerbating the loss of neurons due to AD and thereby accelerating the disease process (8-10).

Based on neurogenesis, a number of therapeutic strategies have been designed to modify the altered epigenetic mechanisms in AD pathology (11). For example, histone deacetylase (HDAC) inhibitors, including valproic acid (VPA), have been shown to promote neuronal generation through histone modification with cognitive improvement in experiments on animals, which offers potential for the treatment of AD through epigenetic modifications (12). However, epigenetic mechanisms are complex as a regulatory system, and no epigenetic drugs have been successfully applied for the treatment of patients with AD. In the present review, the neurogenesis-based epigenetic therapies for AD were examined, with the aim of providing novel insight for future therapy development. To improve understanding of the underlying molecular mechanisms, the epigenetic changes associated with AD and neurogenesis were first discussed. The review may provide novel insights for the development of strategies to treat AD in the future.

2. Epigenetics in AD

Epigenetics is used to describe heritable changes in the patterns of gene expression without alterations to DNA sequences, generally including DNA methylation, histone modifications and miRNA regulation. AD, as the most common type of dementia, is considered to arise from the formation of Aβ in plaques and NFTs (13). Although this hypothesis may, in part, explain the formation of Aβ and NFTs, the exact pathophysiology of AD remains to be fully elucidated. Emerging evidence has shown that epigenetic mechanisms and their changes are involved in the pathogenesis of AD.

DNA methylation in AD. As one of the most common epigenetic mechanisms, DNA methylation adds a methyl group to the 5-position of the pyrimidine ring of the DNA base, cytosine, leading to the production of 5-methylcytosine (5-mC). DNA methylation primarily occurs in CpG-rich sites and usually results in gene silencing; this process can be reversed by DNA methyltransferases (Dnmts). In investigations of AD, DNA methylation is the most widely examined, predominantly on the promoter methylation of known AD genes, particularly for APP. Duplication of the *APP* gene increases the risk of AD through gene overexpression, and epigenetic changes of *APP* promoters can also enhance gene expression and the susceptibility to AD. However, existing reports of DNA methylation in AD are controversial; with reports of hypomethylation of APP promoters in patients with AD relative to controls (14), others reporting hypermethylation (15) and others reporting no significant AD-associated abnormalities (16). These may be associated with differences in the brain regions assessed across the studies (17), however, it is more likely due to the drift and diversity in epigenetic modifications, rather than specific methylation changes, which occur at APP promoters (18). This viewpoint is supported by several other studies showing that the levels of 5-mc and Dnmt3a are increased in the hippocampus of aging mice, but were reduced in APP/PS1 transgenic mice, and in the hippocampus, enthorhinal cortex and cerebellum of patients with AD (19,20).

In addition to *APP*, no significant differences have been observed in the methylation of microtubule-associated protein tau (*MAPT*), *GSK3B* and *PSEN1* promoters in the frontal cortex and the hippocampus in patients with AD and controls, even at different stages of AD (16). However, certain genes are affected by DNA methylation in AD. The *S100A2* genes, which encode a calcium binding protein, have been found to be hypomethylated in AD, with a resulting increase in gene expression to promote corpora amylacea formation (21). By contrast, *NEP* genes, which encode a protease controlling Aβ degradation, and *SORBS3* genes, which encode a cell adhesion molecule, are hypermethylated (22). The reduced gene expression levels of *NEP* and *SORBS3160* contribute to Aβ deposition and synaptic disturbances, respectively (23,24). In addition, the methylation levels of the *MAPT* gene are higher in the aged human hippocampus and cerebral cortex, compared with those in young individuals (15,25). Based on these findings, it is possible that the disturbances in DNA methylation are implicated in AD pathogenesis. However, the functional impacts of AD-associated DNA methylation remain to be fully elucidated.

Histone modifications in AD. Histone modification is another important epigenetic mechanism, which modifies DNA and includes acetylation, methylation, phosphorylation, ubiquitination and isomerization. These modifications can alter the accessibility of DNA to transcription regulators by inducing changes to the structural configuration of nucleosomes. Alterations in histone acetylation have been reported in studies of AD. The levels of histone H3 and histone H4 acetylation were significantly increased in AD brain tissues post-mortem, compared with those in age-matched controls (26). Increased histone H3 acetylation is considered to be due to disruptions in its homeostasis, induced by soluble Aβ, in AD pathology (27), and it is associated with increased levels of β-secretase 1 (*BACE1*), a protease that cleaves APP in the amyloidogenic pathway (28). Abnormal histone H4 acetylation leads to differential gene expression, and is associated with impaired learning and memory functions in AD-associated insults (2,29). In addition, non-nuclear histone H1 has been reported to be upregulated in the neurons and astrocytes of brain regions susceptible to AD (30).

Histone acetylation is a dynamic reversible process, which is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDAC2 is an important regulator for memory and synaptic plasticity, and has been shown to be disturbed in AD-associated process (31). In AD mice, a significant increase in the expression levels of HDAC2 were detected in the hippocampus and prefrontal cortex of the mice, however, no notable changes in the expression of HDAC2 were observed in the amygdala, an area not affected by AD (32). These findings are supported by other observations showing aberrant histone acetylation levels in patients with AD (32). Notably, increased levels of HDAC2 and hypoacetylation have been found to negatively correlate with the mRNA expression levels of genes associated with learning, memory and synaptic plasticity (32). By contrast, the inhibition of HDAC2 reinstates the structural and synaptic plasticity, eliminating the AD-associated memory impairments (32). These findings suggest that the levels of HDAC2 are significantly enhanced in the AD-affected brain regions, and disruption of HDAC2 activity can increase the development of AD.

miRNAs in AD. miRNAs, a broad class of small non-coding RNAs involved in gene post-transcriptional control, constitute another important epigenetic mechanism. By binding to the 3'-untranslated regions (3'-UTR) of messenger RNAs (mRNAs), miRNAs can inhibit the translation of target mRNAs. The dysregulation of miRNAs has been demonstrated to be implicated in the pathophysiology of AD. As noted above, the increased expression of APP leads to enhanced Aβ production, and consequently to AD pathogenesis. In parallel, miRNA-mediated regulation of the expression of APP has been investigated extensively in order to elucidate relevant mechanisms underlying AD (33,34). As a result, a number of miRNAs have been shown to be associated with APP metabolism and Aβ production, including miR let-7, miR-16, miR-101, miR-106b, miR-124, miR-137, miR-153, miR-181, miR-644 and miR-645 (35-38). Specifically, miR-124 is able to alter the splicing of APP exons 7 and 8 in neuronal cells by repressing the polypyrimidine tract binding protein 1 (*PTBP1*) transcript, the level of which has been found to be reduced in a subset of patients with AD (39), indicating that the miR-124/*PTBP1* pathway is important for *APP* splicing in neurons. Simultaneously, miR-124 has been shown to regulate the expression of *BACE1*, which correlates with Aβ-induced cell death (40). The inhibition or overexpression of miR-124 may upregulate or downregulate the expression of BACE1. miR-16 has also been found to target *APP* to potentially modulate AD-associated pathogenesis in mice. The increased expression of miR-16 leads to decrease in the protein expression of APP (41). In addition, miR-106b, which is negatively correlated with the expression of APP, has been found to be significantly reduced in patients with sporadic AD (42).

Disruption in the expression of tau also implicates miRNA in the pathology of AD. For example, miR-15, miR-16, miR-26b, miR-34a, miR-125b, miR-132 and miR-497 have been linked to aberrant tau regulation, of which miR-132 has been shown to regulate the alterative splicing of tau exon 10 through repression of *PTBP2* transcription (43). The repression of *PTBP2* transcription interferes with the physiological phosphorylation of tau and thus leads to the dysfunction of miR-132 to a disease state. Of note, the overexpression of miR-132 has been found to reduce the protein levels of APP in the brains of senescence-accelerated mouse prone 8 (SAMP8), however, reduced expression of miR-132 causes APP protein accumulation in AD mice (41). Aberrant expression of miR-16 is also of vital importance for the pathogenesis of AD, with the overexpression of miR-16 leading to NFT formation and a decrease in its expression leading to APP protein accumulation (41). miR-26b, another epigenetic regulator of the expression of tau, has been found to arise in the substantia nigra at an early stage of AD stage, and is maintained at a high level in the brain areas exhibiting AD pathology during disease progression. miR-26b targets the mRNA of Retinoblastoma (Rb), and its overexpression downregulates the expression of Rb. The overexpression of miR-26b and downregulation of Rb enhances tau phosphorylation and aggregation, followed by neuronal apoptosis and neurodegeneration (44). In addition, overexpressed miR-125b has been found to induce tau hyperphosphorylation and cognitive deficits in AD mice through upregulation in the levels of p35, cdk5 and p44/42-*MAPK* signaling, and downregulation of the *USP6* and *PPP1CA* phosphatases, and anti-apoptotic factor, B cell lymphoma (Bcl)-W, suggesting the involvement of miR-125 in the pathogenesis of AD (45).

Microenvironmental epigenetics in AD. The epigenetics of microenvironments are also affected by changes in the pathology of AD. Studies have shown that the expression of the growth arrest and DNA-damage inducible 45 (Gadd45) family protein, which has been identified as a vital mediator of the DNA demethylation process (46), is upregulated at the early stage of AD (47), but decreased at the late stage of the disease (48). Although the early upregulation of Gadd45 suggests DNA damage in AD (47), its late decrease indicates impairment of intracellular pathways involved in sensing and repairing DNA damage (48). The disrupted expression of Gadd45 may be associated with aberrant *APP* processing, as Aβ1-42 and Aβ25-35 have been shown to provoke an early and marked increase in the level of Gadd45 in cultured human neurons (49). Methyl-CpG-binding protein 2 (MeCP2), another important epigenetic regulator in the extracellular microenvironment, has also been found to be significantly reduced in *in vivo* and *in vitro* studies of AD (50,51). The reduction of MeCP2 may be caused by Aβ-induced neuroinflammation and may lead to notable defects in the production of brain-derived neurotrophic factor (BDNF), axonal transport, synaptic efficacy and neuronal maturation in AD (52-54).

AD-associated neuropathology can also induce changes in microenvironmental epigenetics. Aβ has been reported to affect aberrant CpG methylation in *APP*, *NEP* and *MAPT* genes of the AD brain, with resulting *APP* and *MAPT* dysfunction, which is important for the pathogenesis and progression of AD (55,56). Of note, the presence of a small number of highly methylated neurons among normal neurons has been found to contribute to the methylation differences in *APP* and *MAPT* CpGs (56). Chronic inflammation is involved in neurodegenerative diseases, including AD (57), which correlates with the promoter hypermethylation of synaptophysin and BDNF, and the hypomethylation of BCL-2-associated X protein, which are important for neuronal maintenance (58,59). In addition, oxidative stress occurs in AD, which can induce the hypermethylation of genes associated with neuronal and synaptic plasticity (60). Hypermethylated genes appear to be more vulnerable to toxic effects caused by Aβ, further increasing oxidative stress-induced damage to DNA (61). Oxidative stress may also, through epigenetic changes, activate certain gene pathways, which are hyperactive in AD, including those associated with inflammations (3).

3. Epigenetics in neurogenesis

Neurogenesis occurs throughout life within the mammalian adult brain, which generates thousands of new neurons to assist in the maintenance of normal cognition and memory function. Neurogenesis is regulated by multiple epigenetic mechanisms, including DNA methylation, histone acetylation and miRNAs. As the interface between genes and the environment, epigenetic mechanisms can translate environmental signals into gene expression levels within NSCs. The extracellular microenvironment may also be involved in the regulation of neurogenesis via epigenetic mechanisms.

Neurogenesis in adults. Neurogenesis persists throughout life in two brain regions of adult mammals: The subventricular zone (SVZ) and the subgranular zone (SGZ). Neurogenic processes include the proliferation, migration, differentiation, maturation and functional integration of NSCs into the local brain network (11,62). In SVZ, NSCs are relatively quiescent radial glia-like cells, which divide infrequently to produce fast-dividing precursor cells (NPCs). NPCs act as intermediate cell types, which generate neuroblasts (63,64), the majority of which move along the rostral migratory stream to the olfactory bulb where they largely differentiate into GABAergic neurons (65). In SGZ, primary NSCs also have low proliferative activity and classical astrocytic features. These cells can give rise to two types of transit-amplifying neuroblasts, which can migrate into the dentate granule cell layer of hippocampus in which they differentiate into glutamatergic neurons and integrate into the local circuitry (66). It is estimated that neurogenesis contributes thousands of new neurons each day to the hippocampus in adult mammals (67), which benefits the maintenance of normal cognitive and learning function (68,69).

NSCs reside in a highly specialized microenvironment, termed a 'niche', which is composed of structural cells, extracellular matrix proteins, microvasculature and soluble factors (70). The niche has an important effect on neurogenesis, and can protect NSC populations from differentiation stimuli and apoptotic signals in a stable balance with proliferation (71). It has been shown that NSCs can proliferate and differentiate into neurons when transplanted into neurogenic niches (72), whereas NSCs destined for the neuronal lineage can switch to glial differentiation when transplanted into non-neurogenic regions (73). In addition, neural precursors have been isolated from the spinal cord, white matter, entorhinal cortex, amygdala and striatum of adult mammalian brains, which have traditionally been considered to be non-neurogenic (6,74). These precursors can generate neurons following transplantation back to neurogenic regions of the adult brain (72). In addition, several types of brain injury, including ischemia and seizures, have been shown to promote the proliferation, migration and differentiation of precursors in non-neurogenic regions (5,75). All the above data indicate that multi-potent precursors exist in non-neurogenic regions, their proliferative capacity is limited by local microenvironments, and that injury or disease can rescue neurogenesis by inducing microenvironmental changes.

DNA methylation in neurogenesis. Specific attention has been paid to the performance of DNA methylation and Dnmts in neurogenesis. Cultured neurospheres have been observed to exhibit DNA methylation, and the expression of Dnmt1 and Dnmt3a (72). Upon cell differentiation and migration, the expression levels of Dnmt1 and Dnmt3a are severely decreased in NSCs, whereas DNA methylation has been found to increase and decrease in these differentiating/migrating cells at different loci (72). If methylation is inhibited, NSC differentiation and migration are markedly reduced (76). These observations suggest that, in addition to changes of DNA methylation following decreases in Dnmts, the repression of stem cell maintenance genes and combined activation of cell differentiation genes occurs in the active NSCs (70,77). In further studies of DNMT3a in neuronal differentiation, it has been found that DNMT3a is expressed in the SVZ and SGZ in postnatal mice (78), whereas NSC differentiation is markedly decreased in DNMT3a-knockout mice (79). Epigenetic analysis has shown that, in addition to the downregulation of neurogenic genes, the genes associated with glial differentiation are upregulated in Dnmt3a-knockout mice (80), suggesting that Dnmt3a may serve as an important regulator, switching gene expression towards either a neuronal or non-neuronal lineage.

The regulation of neurogenesis induced by DNA methylation is modulated by methyl-CpG binding proteins (MBDs). MBD1 is primarily expressed in adult neurons, which can repress the expression of genes encoding fibroblast factors by binding to the promoters (81). The expression of MBD1 is lowered in undifferentiated NSCs, increased at the initiation of their differentiation, and promptly decreased at the onset of migration (82). When MBD1 is inhibited, neurogenesis is significantly reduced, accompanied by an increase in new astrocytes (83). These findings suggest that MBD1 is involved in the maintenance and differentiation of adult NSCs. As another member of the MBDs, MeCP2 shares a similar mechanism with MBD1 in regulating gene expression. It has been found that MeCP2 is expressed at high levels in mature neurons of the adult mouse hippocampus, but absent in oligodendrocytes and astrocytes (7). When MeCP2-expressing neural progenitors are transplanted into non-neurogenic regions, notable neuronal differentiation is observed (84). By contrast, impaired neuronal maturation characterized by decreases in dendritic spine formation and spine density has been detected in MeCP2-knockout mice (53). It appears that MeCP2 is important in multiple stages of neurogenesis, including the maturation, differentiation and fate determination of NSCs (85).

Histone modification in neurogenesis. Histone modification can mediate neurogenesis at various stages by controlling gene expression. Studies have shown that HAT-mediated histone acetylation can increase the proliferation and differentiation of NSCs (86), whereas HDACs-induced de-acetylation has more important effects on neurogenesis. HDAC3, HDAC5 and HDAC7 have been shown to be expressed simultaneously in undifferentiated NSCs from adult mice, the expression levels of which are decreased at the start of differentiation (87). When HDACs are inhibitors with inhibitors, including VPA, NSC proliferation is markedly reduced, particularly for cells of a glial lineage, however, neuronal progression is increases, even with the presence of factors favoring non-neuronal differentiation (88). Further analysis has shown high levels of H3 and H4 acetylation in undifferentiated NSCs, and lower levels of H3 and H4 acetylation in stem cells progressing to astrocytes and oligodendrocytes (89,90). However, their levels have been shown to increase upon the differentiation of NSCs into neurons in VPA-treated cells. These findings suggest that HDAC activity is crucial for the proliferation and fate determination of NSCs, in which histone acetylation maintenance is required for neuronal progression, and its de-acetylation is necessary for glial differentiation.

HDAC2, another member of the HDAC family, appears to be more important in the maturation of adult NSCs. HDAC2 is specifically expressed in dividing cells in the adult SVZ and SGZ (91). The depletion of HDAC2 in mice induces a notable

increase of transit-amplifying cells, however, these fail to progress into mature neurons. This increased but impaired neuronal generation in HDAC2-deficient mice may be associated with the lack of HDAC2-induced gene repression, which may upregulate transcription activators, including SRY-box 2 (Sox2), promoting NSC proliferation, but damaging their maturation capacity (92). These results indicate that HDAC2 activity is important for NSC proliferation, and that sufficient histone de-acetylation is required for neuronal maturation.

Histone methylation is also involved in the regulation of adult neurogenesis (93), which is a process mediated by two antagonistic chromatin complexes of the polycomb and trithorax group (PcG and TrxG) proteins, which can activate or silence their target genes, respectively (94). The PcG complex promotes histone 3 lysine 27 tri-methylation (H3K27me3), whereas the TrxG protein enhances histone 3 lysine 4 tri-methylation (H3K4me3). B lymphoma Mo-MLV insertion region 1 homolog (Bmi-l) is a typical member of the PcG complexes, acting as a key epigenetic regulator in neurogenesis (95). It has been shown that the overexpression of Bmi-l markedly increases the number of adult NSCs in the SVZ, and also improves their developmental capacity to neuronal lineages *in vitro* and *in vivo* (96,97). When Bmi-l is knocked down, the self-renew ability of NSCs is severely impaired (98). The action of Bmi-1 may be associated with repression of the expression of cell cycle inhibitors of p16 and p19 (99) or interaction with the transcription factor, Foxg1, which is important for NSC multipotency and self-renewal maintenance (100). Studies have also reported that the PcG complex promotes NSC self-renew by silencing genes required for differentiation through PcG-mediated H3K27 tri-methylation (101-103).

In contrast to the PcG complex, TrxG proteins predominantly contribute to the neural progression between NSCs and neuronal phenotypes, with mixed-lineage leukemia 1 (Mll1) as an example (104). The distal-less homeobox 2 (Dlx2) protein is a key target of Mll1 and serves as a crucial regulator for adult neurogenesis in the SVZ. Studies have shown that SVZ Mll1-deficient NSCs survive, proliferate and efficiently progress into glial lineages without neuronal differentiation, however, the overexpression of Dlx2 has been observed to rescue neurogenesis in these cells (104,105). Previous chromatin immunoprecipitation analysis showed that Mll1 bound directly to the Dlx2 promoter, and a high level of H3K4 trimethylation was observed in a wide range of differentiating NSCs. By contrast, chromatin at Dlx2 was markedly bivalent by H3K4 and H3K27 trimethylation in Mll1-deficient SVZ cells (104). It appears that the bivalent histone methylation leads to failure of the Dlx gene to activate normally, and Mll1 recruits H3K27 demethylase to resolve the silenced bivalent loci in SVZ NSCs for neuronal, but not glial, differentiation (104,106). This finding is supported by another previous study which showed that Jmjd3, an H3K27 demethylase, can activate the neurogenic program, which ensures the progression of NSCs along a neuronal pathway (107). Thus, PcG- and TrxG-dependent histone methylation are required for adult neurogenesis, and the expression of Mll-1 may assist in maintaining NSC neuronal fate without glial conversion.

miRNAs in neurogenesis. A number of miRNAs have been identified at different stages of NSC generation, and different miRNAs perform different functions at different developmental stages. In addition, these miRNAs constitute complex regulatory networks with transcription factors and chromatin modifiers. For example, miR-184, a direct target of MBD1, has been demonstrated to promote NSC proliferation, but inhibit NSC differentiation (108,109), whereas the inhibition of miR-184 rescues the phenotypes in MBD1 deficiency (Liu, *et al* 2010), suggesting its importance in modulating NSC self-renew. Mechanical analysis has shown that miR-184, which can be directly repressed by MBD1, regulates the expression of Numblike (Numbl), a known regulator of neuronal differentiation during development, by binding to the 3'-UTR of Numbl mRNA and affecting its translation (108). By contrast, restoration of the expression of endogenous Numbl rescues the defects in NSCs resulting from either the overexpression of miR-184 or MBD1 deficiency (108). From these observations, it appears that MBD1, miR-184 and Numbl form an interaction network with miR-184 as a central modulator, controlling the balance between the proliferation and differentiation of NSCs.

miR-124, as one of the most abundant miRNAs, is crucial for neural differentiation from stem cells in the adult SVZ. Studies have shown that miR-124 is distinctively expressed in neuroblast cells, and its level increases until the cell cycle exit of neuroblasts (70,110). The knockdown of miR-124 maintains purified SVZ NSCs as dividing NPCs, however, the ectopic expression of miR-124 leass to precocious and increased neuron formation (110), indicating that the expression of miR-124 is important for the transition of adult NSCs between transit-amplifying cells and neuroblasts. In subsequent functional studies, miR-124 has been found to interact with the transcription factor, Sox9, the expression of which can specifically commit neural progenitors to glial fate via the Notch signaling pathway (110,111). The expression of miR-124 induces downregulation of the Sox9 protein in NSCs, leading to the correction of cell state differentiation towards neuronal fates (110). Thus, miR-124-induced post-transcriptional repression of Sox9 is crucial for progression of SVZ NSCs along the neuronal lineage.

miR-137 is specifically expressed in adult neurons and has been shown to be involved in the process of neuronal maturation (112,113). Whereas the overexpression of miR-137 inhibits dendritic morphogenesis, phenotypic maturation and spine development in the brain and cultured primary neurons, the repression of miR-137 produces the opposite effects (104). Further studies have shown that miR-137 targets the mind bomb 1 protein, a ubiquitin ligase important in neurodevelopment (112), and miR-137 represses the translation of Ech2, a histone methyltransferase and PcG protein, leading to a global reduction of H3K27me3 in adult SGZ NSCs (105). In addition, miR-137 is epigenetically regulated by MeCP2 and Sox-2, which are important for neuronal differentiation and maturation (113). It appears that miR-137, MeCP and PcG form a cross-talk loop, which modulates the bivalent H3K27 levels at specific gene domains and thus affects gene expression. In contrast to miR-137, miR-132 promotes neuronal maturation by promoting dendritic morphogenesis, spine density, synaptic integration and the survival of newborn neurons (114) through post-transcriptional repression of the expression of nuclear receptor related 1 (115) and reducing repressor element-1 silencing transcription factor (116).

Microenvironmental epigenetics in neurogenesis. The extracellular microenvironment in which the NSCs reside changes with aging, brain trauma, stroke and seizures, and is also involved in the regulation of neurogenesis through epigenetic mechanisms. Whereas NSCs and their progeny directly adapt to environmental changes, microenvironmental cells, including mature neurons, can mobilize their own epigenetic mechanisms to translate environmental signals into long-lasting gene modifications. In addition, microenvironmental cells can regulate neurogenesis by establishing cross-talk with NSCs in their epigenetic mechanisms (117,118).

The Gadd45 family proteins can respond to microenvironmental changes by repressing specific genes through the promotion of DNA demethylation within their promoters (70). Gadd45b is an activity-induced immediate early gene, specifically expressed in mature dentate granule neurons in the SGZ, and its transcription is particularly sensitive to transient stimulation (46). The expression of Gadd45b induced by neuronal activity can promote DNA demethylation in several genes important for neurogenesis, including those encoding BDNF and fibroblast growth factor (FGF), which can stably increase adult neurogenesis (101). The importance of Gadd45b in neurogenesis is underlined in studies of transgenic mice lacking Gadd45b, which showed that the increase in neuronal proliferation of neural progenitors and the dendritic growth of newborn neurons following electroconvulsive therapy were notably decreased in the Gadd45b-deficient mice (46). Methylation analysis has shown that Gadd45b is essential for the demethylation of several genes associated with neurogenesis, including FGF1 (119). These findings suggest that Gadd45b functions as a sensor for microenviromental signals in mature neurons, and the neuronal activity-induced expression of Gadd45b may regulate adult neurogenesis through epigenetic DNA modifications.

MeCP2, also abundant in mature dentate granule neurons, is another important mediator, which regulates the expression of BDNF in an activity-dependent manner (120,121). By adjusting the DNA methylation status of activity-dependent genes (101), MeCP2 is involved in the regulation of neuronal maturation (46,122). Although the extent to which MeCP2 impacts neuronal maturation remains to be fully elucidated, marked defects in the maturation of neurons, including delayed differentiation and reduced dendritic spine density, have been noted in the SGZ of MeCP2-knockout mice (123). Similar to DNA methylation, histone modifications can be dynamically mediated through the activity-dependent regulations of chromatin remodeling and modifying enzymes, including HATs and HDACs in mature neurons (124-126). In addition, several miRNAs, including miR-138, have been found to integrate environmental changes in the regulation of neurogenic processes (113,127,128).

As important microenvironmental cells, endothelial and glial cells are also involved in the regulation of adult neurogenesis in the SGZ and SVZ. In addition to providing structural supports for neurogenesis (1), these cells can interact with NSCs via cross-talk, mediated by cytokines, including endothelial cell growth factor and glial-derived nerve factor (GDNF), which can activate multiple signal pathways and increase NSC proliferation through epigenetic mechanisms (129). There are also several inducible positive feed-back signal loops between NSCs and cells in the microenvironment mediated by cytokines, which ensures the homeostasis and balance between these two groups of cells (130,131). In addition, several signaling molecules have demonstrated involvement in different stages of neurogenesis (132,133). From these results, it appears that microenvironmental epigenetics is involved in the regulation of neurogenesis and may be used as a therapeutic target for regulating adult neurogenesis.

4. Neurogenesis in AD

As stated above, epigenetic mechanisms are altered in AD, and neurogenesis is regulated by epigenetic mechanisms. Due to altered epigenetic mechanisms in the pathology of AD, the neurogenesis considered to persist throughout life in the mammalian brain is impaired, which contributes to the loss of neurons and deficits in learning and memory. Neurogenic impairment and associated epigenetic therapies have been investigated intensively in studies of AD.

Neurogenic impairment in AD. Increasing evidence has shown that the disease symptoms of AD may be partly be attributed to the impaired formation of neurons from NSCs in the SGZ and SVZ, which is important for the maintenance of normal learning and memory function (134). The epigenetic mechanisms altered in AD may cause direct impairments to neurogenesis. As discussed above, DNA methylation, which is crucial for NSC proliferation, differentiation and migration, is disrupted in AD pathology, with resulting neurogenic impairment (8). In the SVZ of AD mice, increased histone H3 acetylation significantly reduces cell proliferation throughout life (9). Deregulation in the expression of miRNAs lead to a decrease in the expression of growth factors, including BDNF, and thus impair synaptic plasticity and neurogenesis in AD (10). Oxidative stress and inflammation can also lead to dysfunction in neurogenesis via multiple epigenetic alterations (135-137).

Neurogenic impairment in AD can also be caused by epigenetic alterations associated with the formation of Aβ plaques and NFTs. The dysfunction of DNA methylation in the APP, PSEN1 and tau promoters can cause overexpression of these genes and lead to the excessive production of Aβ and phosphorylated tau proteins. Although the impacts of Aβs on neurogenesis remain controversial, Aβ plaques and NFTs can cause severe damage to neurons (138) and astrocytes (139), leading to a gradual loss of neurons responsible for AD symptoms. As a result, the reduction in neuronal numbers and activity decrease the function of Gadd45b and MeCP2, promotes the demethylation of neurogenic genes, including FGF1 and BDNF (119), and finally impairs neurogenesis. Damaged astrocytes not only abate the structural supports for neurogenesis, but also reduce the expression of nerve growth factors (NGFs), including GDNF. In addition, certain subtypes of Aβ proteins, including Aβ25-35, has been shown to be toxic to neurogenesis (1), and tau aggregation can lead to neurodegeneration and neuronal death (140). Based on these findings, it can be concluded that neurogenesis is impaired in AD due to epigenetic dysfunctions, which provide opportunities for therapeutic intervention.

Neurogenesis-based epigenetic therapies for AD. Based on neurogenesis, a number of epigenetic therapies have been developed in the treatment of AD. Notably, HDAC inhibitors, which can increase histone acetylation by inhibiting histone deacetylation, have been suggested as potential treatments for AD, of which VPA has been shown to reduce NSC proliferation, induce the differentiation of neural progenitors specifically towards a neuronal lineage, and inhibit progression to an astrocyte or oligodendrocyte fate (141). In animal models of AD, VPA has been reported to improve learning and memory deficits by promoting NSC generation and synaptic development (12,34). VPA has also been found to increase the protein levels of NGF in the hippocampus of transgenic AD mice, correlating with cognitive improvement (142). In addition, ercaptoacetamide-based class II HDAC inhibitors have been shown to lower levels of Aβ, and to improve learning and memory in a mouse model of AD (143). In addition, γ-hydroxybutyrate has been found to induce HDAC inhibition and the gene expression of neprilysin, to reduce the levels of Aβ and simultaneously ameliorate clinical symptoms in AD mice (144). Gallic acid, an HDAC inhibitor, has also been demonstrated to suppress Aβ neurotoxicity by inhibiting microglial-mediated neuroinflammation (145).

Compared with HDAC inhibitors, a number of drugs, which are specifically designed at DNA methylation, exhibit neurogenic effects in the treatment of AD. For example, S-adenosylmethionine and l-methylfolate, which provide methyl groups in the body to enhance DNA methylation (4,146), have been found to improve the learning and cognitive performance associated with AD (147-149). In other studies, S-adenosylmethionine and l-methylfolate have been used as adjunctive therapies for combating AD (148,149), and these therapies have been shown to enhance the expression of genes associated with neurogenesis more than those associated with apoptosis (150). Fortunately, a number of these treatments, including as l-methylfolate, have been used as an adjuvant therapy in the treatment and prevention of patients with a high risk of AD (151,152).

Several miRNA regulators have also been developed for treating AD. For example, the injection of AM206, a neutralizing inhibitor of miR-206, into the cerebral ventricles of AD mice has been shown to increase the brain levels of BDNF and improve memory function (10). In parallel, AM206 enhances hippocampal neurogenesis and synaptic density. By using RNA interference, the knockdown of long-form phosphodiesterase-4D, using a lentiviral RNA construct containing a specific miRNA, increased the level of BDNF in the hippocampus and reversed the memory impairment caused by Aβ in mice (153). miR-34c, which is essential for normal brain development (154), has also been recognized as a therapeutic target for treating AD, as miR-34c is elevated in the hippocampus of patients with AD and AD mouse models, and targeting the miR-34c seed rescues learning ability in these mouse models (155).

To date, no drugs have been designed to specifically target the epigenetic alterations of the microenvironments in AD. However, certain therapeutic strategies have been shown to enhance the expression of genes associated with neurogenesis in the treatment of AD, indicating the modification of epigenetic mechanisms (156-158). For example, granulocyte colony stimulating factor has been found to induce neurogenesis, reduce oxidative stress and the levels of acetylcholinesterase, and increase antioxidant enzymes and total RNA expression levels in rat AD models, which is followed by improvements in memory and neurobehavioral function (159). Similar observations have been made in AD animals treated with neurotrophic peptide and IGF2 (156-158). It may be that these therapies attenuate the epigenetic alterations of the microenvironments by alleviating inflammation and oxidative stress in the brain in AD (160).

5. Conclusions

As discussed, significant advances have been made in the understanding of epigenetics in AD and neurogenesis, and in investigations of neurogenesis-based epigenetic therapies for the treatment of AD. In AD, epigenetic mechanisms are altered due to neurodegenerative conditions, which include the dysfunction of DNA methylation, histone acetylation and miRNA regulation. Neurogenesis exists in the normal adult mammalian brain and contributes to the maintenance of normal brain function. The neurogenic process is regulated by multiple epigenetic mechanisms. Epigenetic dysfunctions due to AD impair the formation of neurons from NSCs, which contributes to the loss of neurons and cognitive impairment. Restoration of the epigenetics altered in AD can enhance neurogenesis, which provides novel promise for combating this disease. A number of epigenetic therapies have been shown to alleviate cognitive impairments by promoting neurogenesis in preclinical studies. However, understanding of epigenetic regulations in neurogenesis remains at an early stage, particularly in the field of AD, and further investigations are required. It is anticipated that targeting the epigenetic modifications of adult neurogenesis as a potential therapy may ultimately become feasible in patients with AD in future.

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