Epigenetic modulation during hippocampal development (Review)

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Abstract. The hippocampus is located in the limbic system and is vital in learning ability, memory formation and emotion regulation, and is associated with depression, epilepsy and mental retardation in an abnormal developmental situation. Several factors have been found to modulate the development of the hippocampus, and epigenetic modification have a crucial effect in this progress. The present review summarizes the epigenetic modifications, including DNA methylation, histone acetylation, and non-coding RNAs, regulating all stages of hippocampal development, focusing on the growth of Ammon's horn and the dentate gyrus in humans and rodents. These modifications may significantly affect hippocampal development and health in addition to cognitive processes.

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Abbreviations: DG, dentate gyrus; PM, postnatal month; EW, embryonic week; SGZ, subventricular zone; GCL, granular cell layer; GD, gestational day; NPCs, neural progenitor cells; ED, embryonic day; RGCs, radial glial cells; VZ, ventricular zone; DNMTs, DNA methyltransferases; MBD3, methyl-CpG-binding domain-3; MeCP2, methyl CpG binding protein 2; GFAP, glial fibrillary acidic protein; HDACs, histone deacetylases; ESCs, embryonic stem cells; lncRNA, long non-coding RNA; miRNA, microRNA; IPS cells, induced pluripotent stem cells; LTP, long-term potentiation; APT1, acyl-protein thioesterase 1; SynCAM1, synaptic cell adhesion molecule 1; NLGN1, neuroligin 1

Key words: hippocampal development, epigenetic modification, DNA methylation, histone acetylation, non-coding RNA

1. Introduction

The hippocampus is a part of the limbic system that is vital in learning ability, memory formation, and emotion regulation (1-3). It is also associated with the emergence of several neuropsychiatric disorders, including epilepsy, mental retardation and Alzheimer's disease (AD) (4). During development of the rodent hippocampus, aberrant neuronal migration results in anomalous hippocampal lamination, neuronal differentiation disorders and neural circuit defects, leading to severe epilepsy syndrome following birth (5). Exposure to ethanol during fetal development can cause apoptosis of hippocampal neurons, leading to postnatal mental retardation (6). It has been demonstrated that the abnormal proliferation of neuronal cells and disordered differentiation of neurons appear in the dentate gyrus (DG) of offspring when pregnant rats are exposed to depleted uranium for a prolonged period; the neonatal rats exhibited depressive symptoms at 2 months postnatally (7). In advanced eukaryotes, epigenetic modifications exist in the normal developmental progress of eukaryotic cells, including DNA methylation, histone acetylation and non-coding RNAs. These major epigenetic modifications for the regulation of mammalian gene expression are crucial in ontogenesis and phenotypic transmission. Epigenetic regulation is defined as a genetic variation in gene expression in which the DNA sequence remains unaltered (8). Several epigenetic modifications affect the growth of the hippocampus therefore, the present review summarizes the various stages of human and rodent hippocampal development and discusses their effects from the perspective of DNA methylation, histone acetylation and non-coding RNAs.

2. Development of the hippocampus

Humans. The mammalian nervous system originates from its embryonic ectoderm, which differentiates into the neural tube and neural crest. The neural tube expands gradually and forms into a brain vesicle, following which the hippocampus appears in the prosencephalon vesicle. A previous study showed that the cortical hem, a region of the dorsomedial telencephalon, mediates hippocampal development by producing a bone morphogenetic protein and wingless-related signal (9). In the process of human neurogenesis, the neural tube forms in

embryonic week (EW)3 and prosencephalon vesicles occur in EW5. The local parietal lobe then thickens to form the hippocampal primordium in EW6 (in EW14 the hippocampus disappears from the parietal lobe), and another hippocampal primordium derives from the temporal lobe in EW7 via a series of spins and folds to eventually form a complete hippocampus, of which the developmental hallmarks are shown in Table I (10). The hippocampal primordium is composed of neuroepithelium, and in EW8, the neuroepithelium is initiated to migrate and generate the sub granular zone (SGZ), the middle layer and the marginal layer, respectively (10). Between EW10 and EW11, the earliest granular cell layer (GCL) of the DG emerges from the middle hippocampal layer of the temporal lobe, which marks the beginning of DG development (2,10). The DG is a specific region of the hippocampus that possesses the capacity of neurogenesis in adulthood (1). A previous study showed that the ability of the DG to sustain neurogenesis is associated with the neurogenic niche, which is maintained in the SGZ (11). Another study traced the key markers of hippocampal neurogenesis to confirm that the neurogenic niche was formed in the hippocampus prior to the mammal reaching adulthood (12).

In EW13 through EW14, the Ammon's horn and the DG starts to fold, and the DG is narrowed into a U-shape; however, the CA1, CA2 and CA3 fields of Ammon's horn are linearly arranged (13). The primal Ammon's horn appears on EW14, and the boundary between the Ammon's horn and the DG is divided by the hippocampal fissure. In EW15, the undifferentiated cells of the middle hippocampal layer begin to differentiate into hippocampal pyramidal cells, which gradually form the pyramidal layer of the CA1, CA2 and CA3 regions (10). The settling and generation of pyramidal cells occurs in opposing order between the CA1 and CA3 regions. The early-generated pyramidal cells are destined to settle in the late-forming stratum pyramidal of the CA3 region, whereas the late-generated pyramidal cells settle in the early-forming CA1 region (1). Between EW16 and EW18, the Ammon's horn and the DG are stacked in the temporal lobe, the CA1-3 regions are curved, and the hilus of the DG is occupied by the CA4 region (13). In EW30, the hippocampal fissure disappears; subsequently, the Ammon's horn and the DG already have a typical three-tier structure, which is the fundamental structure of the hippocampus (14).

Approximately 80% of dentate granule cells (DGCs) appear in the prenatal period of humans and reach peak proliferation in EW15 (10,15). Following birth, the proliferation of neural progenitor cells (NPCs) in the SGZ gradually evolve into DGCs, which is known for neurogenesis in the DG; these newly generated DGCs become increasingly mature by a complicated process and eventually settle in the GCL (3,16). The new neurons from neurogenesis establish a synaptic connection with the other neurons and are incorporated into the trisynaptic circuit [entorhinal cortex (EC)-DG-CA3-CA1-EC], which is formed in the prenatal hippocampus; it gives rise to corresponding neurological functions and is associated with the learning and memory functions of humans (1). The role of SGZ neurogenesis in emotional control has been investigated previously; it was found that stressors inhibit the proliferation of NPCs in SGZ and antidepressants exert an opposite effect (17). The volumes of the hippocampus and temporal lobe increase markedly in 2-year-old children, following which the rate of increase plateaus and the proportion of the hippocampus in the temporal lobe declines with age (18). The right-left asymmetry of the hippocampus and temporal lobe has been suggested in previous studies; as a statute, the right side is larger than the left side (19,20).

Rats. The neural tube of the rats takes shape between ED10.5 and ED11 (15,21). The hippocampal primordium of the rats is composed of neuroepithelium, which appears in the dorsomedial telencephalon by ED14 (22). On ED16, the incrassate hippocampal primordium is categorized into three forms: Primary dentate neuroepithelium, fimbria glioepithelium and ammonic neuroepithelium. These forms evolve into the DGCs, the glial cells of the hippocampal fimbria and the pyramidal neurons of Ammon's horn, (1,11,22). The formation of DGCs in rats is divided into two phases: The first phase begins on ED16 and produces ~15% DGCs prior to birth; the second phase begins at birth when ~85% of the DGCs take shape, and peak proliferation occurs on postnatal day (PD)7 (2,23). The multiple migration transforms the primary dentate neuroepithelium cells into secondary dentate matrix or tertiary dentate matrix and SGZ, which further differentiates into DGCs sequentially (24). On ED18, the migration of primary dentate neuroepithelial cells form the secondary dentate matrix; these cells transplant into the DG fields following proliferation (25). There are two stages in the process of migration of the secondary dentate matrix cells to the DG fields. The first dentate migration develops into the shell of the GCL on ED20 (22), and the secondary dentate matrix disappears on PD5 (25); after 5 days, the first stage is complete (1). The second dentate migration is diffused in the polymorph layer of the DG, between PD3 and PD10 (25). Consequently, the tertiary dentate matrix begins to form, which evolves into the SGZ on PD20 through PD30 (1). Subsequently, the second stage is completed, however, the SGZ persists and generates DGCs during adolescence and adulthood. Furthermore, radial glial cells (RGCs) are crucial in the formation of DGs. The earliest RGCs appear in the neuroepithelium, and the radial glial fibers of RGCs originate from the ventricular zone (VZ) throughout the DG fields. In addition to the migration of RGCs from the VZ to the SGZ, the primary dentate neuroepithelium cells migrate along the fiber scaffold of RGCs and differentiate into DGCs. Whether antenatal or postpartum, RGCs are divided into primary and secondary RGCs, which affect the two production phases of DGCs as described above (2).

Between ED15 and ED17, the primary Ammon's horn appears in the hippocampus of rats, and the hippocampal fissure divides the boundary between Ammon's horn and DG (22). On ED17 through ED19, a large number of pyramidal cells are present in the middle layer of Ammon's horn; the later-generated pyramidal cells are settled earlier in the CA1 region; however, the earlier-generated pyramidal cells are deposited into the CA3 region following formation of the GCL (24,26,27). This phenomenon is described as the opposite of the generation time and the settling time of the pyramidal cells in the Ammon's horn. The development of the pyramidal stratum of CA1 is complete on ED20 (24,26). The formation of the shell of the GCL is the immediate cause for the pyramidal

Table I. Comparison of the hippocampal development process in humans and rodents.

Author, date	Humans	Rats	Mice	Hippocampal development milestone	Refs.
Deng *et al*, 1996; Bayer, 1980; Berg *et al*, 2018	EW6	ED14	ED10-11	Differentiate into hippocampal primordia	(10,22,30)
Xu *et al*, 2015; Deng *et al*, 1996; Radic *et al*, 2017; Berg *et al*, 2018	EW10-11	ED16	ED12-14	Appearance of DGCs	(2,10,23,30)
Deng *et al*, 1996; Altman and Bayer, 1990; Bayer, 1980; Altman and Bayer, 1990; Nakahira and Yuasa, 2005	EW15	ED17-19	ED14	Earliest pyramidal cells emerging in Ammon's horn	(10,24,26,27,31)
Xu *et al*, 2009; Deng *et al*, 1996; Rice and Barone, 2000; Radic *et al*, 2017	EW15	PD7	PD1	Peak DGC growth spurt	(2,10,15,23)
Li *et al*, 2009; Humphrey, 1967; Berg *et al*, 2018	EW30	PD30	PD14	Generation of SGZ	(1,14,30)

EW, embryonic week; ED, embryonic day; PD, postnatal day.

layer of CA1-3 to begin to turn inwards (1); between days E18 and E22, the CA3 extends into the hilus of the DG to transform into the CA4 field (the hilus) (22). Consecutively, the pyramidal cells in the middle layer of Ammon's horn settle in the C-type pyramidal stratum, which disappears gradually with the thickening of the pyramidal stratum (24). Generally, the structure of the pyramidal layer in Ammon's horn is almost complete during the embryonic period. Following birth, the arrangement of cells in the pyramidal layer gradually increases from the inside to the outside (28); the arrangement of cells increases from the outside to the inside in the GCL (29), and the pyramidal layer of Ammon's horn thins due to a reduction in the number of cells and increased volumex(22). By contrast, the morphological development of the DG is mainly postnatal; the number of DGCs increase and exhibit a large volume (22).

Mice. The neural tube takes shape in mice between ED9 and ED9.5 (21). Subsequently, the hippocampal primordium emerges between ED10 and ED11 (30). The process involved in the morphological development of the DG is similar in rats and mice; however, there are differences in the time. The production of DGCs in the DG of mice can be divided into two phases: ~85% of the DGCs are generated in the second phase postnatally, and peak proliferation is observed on PD1 (23). The DGCs in rats are mature 4-6 days earlier than in mice, although the peak proliferation appears later (23). The secondary dentate matrix is formed on ED15, and the cells migrate to the DG field following proliferation (30). The rudimentary GCL shell is generated on ED18 by the first dentate migration (31). In the secondary dentate migration, the tertiary dentate matrix is also generated on ED18, and turns into the SGZ on PD14 (30). Furthermore, severe morphological defects of the DG and loss of the hippocampal fissure have been found in Nfib-deficient mice, demonstrating the vital function of RGCs in the formation of the DG (32). Between days P10 and P14, the secondary RGCs differentiate into astrocytes following formation of the radial glial fiber scaffold, which accompany GCL migration to the molecular layer of the DG (2).

On ED14, the primary Ammon's horn appears in the hippocampus of mice (31). Subsequently, a large number of pyramidal cells is observed in the middle layer of Ammon's horn (31,33), and the settlement process of the pyramidal cells in the CA1 and CA3 regions is consistent with that of rats (34). The pyramidal layer of Ammon's horn is bent into type C on ED15, followed by the appearance of the CA4 field (35); on ED18, the middle layer disappears with complete settlement of the pyramidal cells in Ammon's horn (33). Between PD10 and PD15, the abundance of pyramidal cells in Ammon's horn increases rapidly; the structure of Ammon's horn stabilizes in postnatal month (PM)3 (36).

The extreme of entorhinal fibers reaches the molecular layer of the DG in mice by ED17 and the axon of Cajal-Retzius cells in the DG act as scaffolds for neuronal projection in the EC, which is the starting signal of the trisynaptic circuit (1). At ~PW1, the neonatal DGCs extend the dendrites into the granular and molecular layers of the DG and project axons into the hilus of the DG (CA4 field), which receive the input of excitatory GABA-ergic neurons (16). The DGCs begin to receive Glu-ergic neurotransmitter by the performant pathway on PW3. With the completion of synapse integration at PW4,

the transmission of GABA signals changes from excitability to inhibitory; until PM2, the structure and function of the newborn DGCs matures (1,16). Previous studies have shown that in PW3 in rodents, the regenerative capacity of the brain, particularly the DG of the hippocampus, is minimal (21). When the DG is damaged, the damaged neurons are not replaced, resulting in long-term memory defects (21).

3. Epigenetic modifications in hippocampal development

DNA methylation. DNA methylation refers to the conversion of cytosine to 5-methylcytosine (5mC), catalyzed by DNA methyltransferases (DNMTs) and acquisition of a methyl group from S-adenosylmethionine (37,38). Among the three types of DNMTs, DNMT1 and DNMT3 function as the maintenance methylase and nascent methylase, respectively; however, the role of DNMT2 remains to be fully elucidated (38-40). The non-5'-C-phosphate-G-3' (CpG) dinucleotide is localized and clustered close to the transcription regulation domain, which is the major site of DNA methylation in vertebrates; the methylation of this site causes inactivation of the corresponding gene (37,41). DNA demethylation is effectuated by two methods: Active demethylation is the translation of 5-hydroxymethylcytosine (5hmC) into 5mC under the action of 5mC hydroxylase (Ten-eleven translocation 1/2/3; TET1/2/3), and the passive demethylation is caused by the lack of DNMTs during cell replication (37). 5hmC is a relatively stable epigenetic marker persistent during the life cycle of neurons (37). The 5hmC preferentially binds to methyl-CpG-binding domain-3 (MBD3), which antagonizes the combination of methyl CpG binding protein 2 (MeCP2) with 5hmC. Consequently, the weak bond between DNMT1 and 5hmC decreases the effect of DNMT1 and promotes DNA demethylation; however, 5mC binds to MeCP2 and MBD1 (combination with MeCP2 precedes MBD1) and maintains the methylation status of DNA (37,42).

The mature sperm and eggs of humans and rodents are highly methylated, followed by genome-wide demethylation in the preimplantation embryo and the re-emergence of DNA methylation by embryo implantation (42,43). Studies have confirmed that the concentrations of 5mC and 5hmC increase during the proliferation and differentiation in the mouse neuroepithelial cells (44). The point at which 5mC surges coincide with the time at which neuroepithelial cells proliferate prior to differentiation; however, the 5hmC surge is in accordance with the differentiation of NPCs (44). Setoguchi *et al* showed that the differentiation of neuroepithelial cells in mice was closely associated with the methylation status of the glial fibrillary acidic protein (GFAP) gene (45). Until day E14.5, the neuroepithelial cells of mice start to differentiate into astrocytes, which previously evolved only into neurons (45). The CpG in the signal transducer and activator of transcription (STAT) protein binding site of the GFAP gene promoter is hypermethylated at an early developmental stage, which results in GFAP gene silencing. However, with demethylation during the developmental process, STAT protein binds to the promoter and leads to activation of the GFAP gene; gradually, the neuroepithelial cells evolve into astrocytes (45). Another study showed that neural stem cells (NSCs) in DNMT3a-deficient mice exhibit a low level of hypomethylation and a proliferation rate significantly higher than that of normal mice. In addition, the NSCs of DNMT3a-deficient mice differentiate into astrocytes in early development with increase in quantity (46). DNMT1 promotes the development of secondary RGCs by regulating the Reelin signaling pathway. Noguchi *et al* utilized the TAM-inducible Cre recombinase system to knock out the DNMT1 gene in mice NSCs at the onset of DG development; this resulted in the inability of NSCs to establish appropriate secondary radial gliosis scaffolds (47). Therefore, a subset of NPCs and granulosa cells migrate into the SGZ unsuccessfully, followed by accumulation in the molecular layer of the DG. Although NPCs and granulosa cells began to differentiate, they fail to enter the GCL and ultimately die. DNMT1-deficiency also promotes the differentiation of NSCs into astrocytes (47). The above-mentioned factors lead to a decrease in the volume of postnatal GCL.

DNA methylation of the hippocampal Ammon's horn (CA1-4) in mice shows a patterned progression. Between P15 and P17, the 5mC appears first and the cells multiply in the pyramidal and neuroepithelial layers of the hippocampus; in the subsequent hours of the first day, the progression of 5hmC is synchronized with cell migration, followed which 5mC and 5hmC continue to increase throughout the migration process (48). Until the pyramidal cells are colonized in the CA regions, the 5mC in the pyramidal cells are reduced, and the 5mC in the nucleus translates into the 5hmC, which activates the corresponding gene, allowing the pyramidal cells to differentiate further and mature. Here, the 5mC in the pyramidal cells of the pyramidal layer turn from the inside out into 5hmC, completing the inside-out maturity (48). By P17, 5mC and 5hmC continually persist in mature pyramidal cells that are aggregated in different regions of the nucleus (48). DNMT1 and DNMT3 maintain DNA methylation, regulate the division of neural progenitors and mature neurons, and are crucial in the synaptic plasticity of mature neurons. Feng *et al* showed that abnormalities in synaptic plasticity occur in the CA1 field of the DNMT1 and DNMT3 double-knockout mice hippocampus; thus, learning and memory disorders are also exhibited (49). In addition, the genome-wide analysis of NSCs in postnatal mice showed that DNMT3a catalyzes the methylation of a large number of proximal non-promoter sequences (50). The methylation of these DNMT3a-dependent proximal non-promoters facilitates the transcriptional expression of neurogenic genes by functional antagonism of polycomb inhibition in order to maintain the active chromatin status of the core developmental genes (50). The mRNA expression levels of DNMT (DNMT1, DNMT3a and DNMT3b) peak on PW1 and decrease with age in various brain structures of rats, however, global DNA methylation continues to increase in the hippocampus (51).

DNA methylation is involved in the development of hippocampal DG. During migration to the DG, the neuroepithelial cells are first presented at 5mC, followed by 5hmC, ac companied by the decrease of 5mC which converts to 5hmC (48). As Sex determining region Y-box 2 (Sox2) and Ki67 markers are lost in the cells and eventually differentiate into mature granule cells, the earlier granule cells that reached the DG region aggregate to form the GCL shell (48). Consecutively, with development of the DG matrix, a class of

NPCs derived from the secondary DG and expressing Sox2 and Ki67 accumulate in the innermost layer of the DG to form the SGZ (48). The changes in NPC migration and differentiation and maturation of DNA methylation in the SGZ are similar to those described above, and neurogenesis in the adult SGZ also follows this pattern. The prenatal deletion of DNMT1 leads to the increased expression of cyclin-dependent protein kinase (CDK) inhibitors, p21 and p57, resulting in decreased proliferation of NSCs in the postnatal SGZ and impaired neurogenesis in the adult SGZ (47). The investigation of neurogenesis in the postnatal hippocampus of TET1-deficient mice indicates that TET1 deficiency results in a decrease in the number of NPCs in the SGZ (~45% decrease). In addition, the self-replication ability of NPCs decreases; however, the differentiation ability of NPCs is unaffected, as the deficiency of TET1 has its function replaced by TET2 and TET3, leading to the marginal increase of 5hmC in the NPC (52). Further investigations have demonstrated that the function of TET1 primarily maintains the hypomethylated state of specific genes to activate them transcriptionally (52). Larimore *et al* focused on the effect of MeCP2 on the terminal differentiation of rat hippocampal neurons, it was found that the overexpression of MECP2 increased axon length, and the number of dendrites and axons, whereas the knockdown of MECP2 only shortened dendrite length. This suggests that MeCP2 is an important factor in the terminal differentiation of hippocampal neurons (53).

It is suggested that the destruction of DNA methylation processes during human embryogenesis, triggering synaptic plasticity damage in hippocampus, leads to postnatal Autism and Rett syndrome (54). In addition, the reduction of neuropils in the hippocampus of patients with schizophrenia leads to structural changes in the hippocampus and the interference of synaptic plasticity and regenerative mechanisms, which have been shown to arise from the abnormal epigenetic regulation (55). Falkai *et al* reported that more severe synaptic plasticity damage was accompanied by more marked negative symptoms of schizophrenia (55). The downregulation of GABA-ergic gene expression caused by hypermethylation of the GABA-ergic promoter in the hippocampus has been confirmed as a characteristic pathological phenotype of schizophrenia (56). This is different from the static state of DNA methylation in the hippocampus in human health, autism and AD; there is extensive gene promoter hypermethylation in the hippocampus of patients with temporal lobe epilepsy (57). This may be a mechanism for persistent hyperexcitability in chronic epilepsy. Similarly, Blanco-Luquin *et al* showed that the downregulation of expression caused by hypermethylation of the phospholipase D family, member 3 gene is closely associated with late-onset AD (58). Studies have suggested that childhood neglect or abuse can cause methylation and histone modifications in the child's hippocampal glucocorticoid receptor promoter region, which reduces the child's hippocampal glucocorticoid receptor expression and increases the adulthood stress response leading to depression and anxiety (59,60). There is also a significant correlation between hypermethylation of the zinc finger and BTB domain containing 20 gene in the hippocampal CA1 region with major depressive disorder (61). A study showed that the overexpression of Dnmt3a2 in the hippocampus consolidated memory and improved anxiety and phobia (62).

Histone acetylation. The basic unit of chromatin is nucleosome consisting of DNA and histone (37). Histone modifications include methylation, phosphorylation, acetylation and ubiquitination. These modified histones recruit other proteins to bind to DNA in a synergistic or antagonistic manner at the transcriptional level. This mechanism regulates the transcription dynamically, and is termed as the 'histone code hypothesis' (63). The most well-known histone modification is histone acetylation, wherein the acetyl group from acetyl-CoA is transferred to the N-terminus of the lysine residue in histone. Histone acetylation can reduce the electrostatic interaction between histones and DNA, altering the conformation of histones, which leads to the relaxation of chromatin structure and binds the transcription factors to corresponding sites; thus, the expression of these modified genes is activated (37,64). By contrast, when histones are deacetylated, the chromatin structure condenses and the transcription factors cannot combine with the corresponding sites, leading to expression of the genes being inhibited (37,64). Histone deacetylases (HDACs) are modulators of histone acetylation. Currently, HDAC-containing complexes are known to be exhibit two types of HDAC structures (HDAC1 and HDAC2); usually, histone deacetylation requires the involvement of two HDAC domains (65).

HDAC1 and HDAC2 have different expression characteristic functions in the development of the hippocampus. HDAC1 is expressed at a high level in proliferating NPCs but disappears following the differentiation of NPCs; however, it appears in glial cells persistently (66). By contrast, HDAC2 is expressed during the proliferation of NPCs, increases following the differentiation of NPCs into neurons and continues to emerge in mature neurons; however, it does not exist in the majority of glial cells (66). In the neurodevelopment of HDAC1 and HDAC2 double-knockout mice, the early nerve cells migrate normally and the proliferation of NPCs increases, although the NPCs do not differentiate into neuronal cells. On ED15.5, a large number of NPCs demonstrate apoptosis, and Montgomery *et al* found that the hippocampal structure was damaged, the cortex was disorganized and cerebellar foliation was lacking postnatally (67). The defect of HDAC1 or HDAC2 in mice does not cause variations in the overall anatomy of the brain (68). Although HDAC1-deficient mice can survive and multiply, HDAC2-deficient mice die within hours of birth, suggesting that HDAC2 is an essential histone deacetylase for survival and brain development (68).

The transcription factor Ski serves as a scaffolding protein to link HDAC, Sin3, cell type-specific transcription factors (69). The early hippocampal neuroepithelial cells of Ski-deficient mice differentiate into neurons, such that the number of proliferating neuroepithelial cells is reduced in early hippocampal development. The possible mechanism is that Ski acts as an inhibitor of the transforming growth factor-β pathway, which recruits Sin3/HDAC complexes to mothers against decapentaplegic (Smad)s, followed by inhibition of the entry of Smads into the nucleus and regulation of the transcription of target genes, which in turn, regulates the balance of proliferation and differentiation of neuroepithelial

cells (69). Furthermore, Ski binds to MeCP2 and is involved in MeCP2-mediated transcriptional repression (70). Bromodomain- and PHD finger-containing protein 1 (BRPF1) is an activator of three types histone acetyltransferases, lysine acetyltransferase (KAT)6A, KATB and KAT7. The hippocampal neuroepithelial cells in BRPF1-deficient mice were reported to be significantly reduced and the distribution of RGCs was sustained in an abnormal state from embryonic to the postnatal stage, which significantly affected the migration of primary dentate neuroepithelium cells (71). Consecutively, the cell cycle of the migrating cells was abnormal, which led to an abnormal state of proliferation during migration and affected the formation of the SGZ as the number of NPCs in the SGZ decreased; the hippocampal anatomy in the adult mice suffered maldevelopment, particularly in the DG (71).

Histone H3 lysine 9 acetylation (H3K9Ac) is an epigenetic marker that exists in transcriptionally active chromatin. Qiao *et al* showed that H3K9Ac declined gradually within 4 days prior to the neural differentiation of human ESCs and increased with the differentiation of nerves on days 4-8 (72). In phase one, the addition of histone deacetylase inhibitors (HDACIs) resulted in enhanced pluripotency and decreased neural differentiation of ESCs. By contrast, the use of HDACIs on days 4-8 promoted neural differentiation, which indicates that H3K9Ac exerts different effects in various stages of ESC development (72). Another study revealed that the expression levels of H3K9Ac and H3K14Ac in the hippocampal CA3 region of hypoxic rats were decreased, causing the neurodegeneration of neurons and impaired neurotransmitter transmission (73). HDACIs can increase the survival of neonatal neurons in the mouse hippocampus at a specific postnatal time and enhance the neurogenesis in adult hippocampus (74). HDAC2 is extensively distributed in the pyramidal cells and the DGCs of hippocampal CA1 and CA3 regions of postnatal rats. Furthermore, with the development and maturation of nerve cells, the expression of HDAC2 is decreased gradually and transferred from the nucleus to the cytoplasm; until PW4, HDAC2 is maintained at a relatively low level (75). The level of histone acetylation in the hippocampus of mice overexpressing HDAC2 is decreased (acetylation levels of H4K12 and H4K5, but not H3K14), which was most pronounced in the pyramidal cells of Ammon's horn. Subsequently, the dendritic spine density of pyramidal cells and DGCs in the CA1 field is significantly reduced (76). However, the density of dendritic spines in these regions of HDAC2-knockdown mice is significantly increased, suggesting that HDAC2 regulates the formation of hippocampal synapses and affects the functions of learning and memory (76).

In the early stage of AD, Gräff *et al* (77) found that HDAC2 was significantly elevated and accumulated gradually in the hippocampus CA1, and the degree of HDAC2 elevation was associated with the process of cognitive decline in the human brain. It concluded that the current treatment of AD has limitations and should consider treatment options to increase HDAC2. Subsequent rat experiments have shown that the use of HDACIs was effective against a range of neurodegenerative diseases (78). HDACIs can also treat abnormal behavioral symptoms in schizophrenic rats and reverse the structure of ventral hippocampal lesions (79). In addition, the increase of histone acetylation in the hippocampus can counter emotional stress and reduce the emotional behavior of depression (80). However, exposure to HDACIs of the embryonic stage hippocampus may cause autism-like symptoms following birth (81).

Non-coding RNAs. Non-coding RNAs mainly include two types: Long non-coding RNA (lncRNAs) and microRNAs (miRNAs) that effectuate in epigenetic mechanisms. The length of lncRNAs is >200 nucleotides. They do not encode proteins but affect the chromatin structure, chromatin transcription activity and stability, translation, post-transcriptional processing of mRNAs, and gene expression (82,83). miRNAs are a class of non-coding small RNAs that typically consist of ~20 nucleotides. miRNAs bind to mRNAs in a complementary pairing manner, resulting in the degradation of mRNAs or inhibition of their translation, thereby being involved in regulating gene expression (84-86).

The Cre-loxP system was previously used to knock out the expression of Dicer and inhibit the formation of miRNAs in the development of the hippocampus of three Cre mouse lines. Li *et al* showed that the deficiency of miRNA leads to a significant decrease in the number of proliferating NPCs in the hippocampus, which increases apoptosis and promotes early differentiation into hippocampal neurons; however, their development and maturation is impaired (87). The deletion of miRNAs leads to a decrease in the number of NPCs in all hippocampal formations, and the apoptosis of NPCs is most pronounced in CA1 and the DG. The lack of miRNAs in the late stages give rise to prominent early differentiation of neurons in CA1 and the DG on ED10.5, CA3 is mainly affected by ED13.5, and the proliferation and apoptosis of CA3 and DG cells increase; subsequently, the learning and memory functions of mice are enhanced (87,88). In summary, miRNA deletions primarily affect the development of CA1 and DG at an early stage, and CA3 at a later period.

In the hippocampus of mice, lncRNAs are abundant, and as the expression of lncRNAs in the different regions of hippocampus has tissue-cell specificity, it is hypothesized that lncRNAs are involved in the differentiation of hippocampal NSCs (89). A study on the differentiation of induced pluripotent stem cells (IPS cells) into neurons showed that the lncRNA-HOTAIRM1 in the homeobox (HOX) genome was not expressed in IPS cells; however, the level of its transcripts increased 54.6-fold in early differentiated neurons. In addition, the expression of other lncRNAs in the HOX genome was also augmented significantly, indicating that lncRNAs are involved in regulating the differentiation of NSCs into neurons (90). Nigro *et al* demonstrated abnormal proliferation, morphological disorder in the RGCs of the telencephalon, and abnormal migration of neuroepithelial cells in the hippocampus in Dicer-deficient mice. Between days E16.5 and E18.5, the number of proliferating cells in the DG decreased significantly; however, by day P15, the DG structure of the deficient mice was severely disordered, and cell proliferation and neurogenesis were distinctly reduced in the SGZ (91). The re-expression of miRNA (miR)-30e and miR-181d in the telencephalon of deficient mice, led to the return of RGCs to the normal state. The underlying mechanism may be that miR-30e and miR-181d binds to the 3' UTR of the HtrA serine peptidase 1 gene, inhibiting its expression (91). Another study confirmed that the expression of miR-124 was upregulated

by embryonic period methyl donor deficiency (vitamin B9 and vitamin B12) which downregulated Stat3 signaling, leading to atrophy of the hippocampal CA1 pyramidal layer and the DGL of rats (92). Monteleone *et al* (93) showed that prenatal stress can eliminate the alterations in the methylation pattern at three specific CpGs, which are rooted in two CpG islands of the glycoprotein M6A (gpm6a) gene in the hippocampus, significantly upregulating the expression of miR-133b in the hippocampus, with the subsequent specific interaction of miR-133b with gpm6a affecting mRNA expression and protein levels and function and leading to abnormal hippocampal synapse formation. miR-338-3p exerts a regulatory effect during the proliferation and development of DG neurons. With the maturation of DG neurons, the expression of miR-338-3p increases gradually and eventually reaches a peak in the $NeuN^+$ mature neurons (94). The knockdown of miR-338-3p results in decreased dendritic branching, abnormal distribution, and increased length of dendritic spines in the hippocampal neurons, leading to the abnormal proliferation of hippocampal cells and tumorigenesis (94). By contrast, the overexpression of miR-338-3p leads to decreased hippocampal glioblastoma activity and increased apoptosis (94). miR-9-5p/3p has been shown to effectuate neuronal development and maturation (95-97). The long-term potentiation (LTP) of the hippocampus was impaired in miR-9-3p-knockdown mice, following which the memory and learning function were affected postnatally (97). The intrinsic mechanism may be that the knockdown of miR-9-3p results in the overexpression of synapse-associated protein 97, which is void on synaptic transmission of mature neurons but damages LTP (97). The transcription factor cAMP response element-binding (CREB) is a key regulator of synaptic growth and refinement in mature neurons; however, there is no direct target between CREB and neuronal plasticity (98). CREB binds to the miR-132 promoter in the hippocampal neurons of mice and facilitates its expression, which inhibits the translation of p250GAP, thereby regulating changes in the dendritic morphology of neurons (98). miR-134 inhibits the translation of LIM domain kinase 1 and is involved in regulating neuronal dendritic spine morphology (99). The dendritic spines of neurons become smaller when miR-134 is overexpressed and larger with miR-134 knockdown (99). Subsequent studies have shown that miR-138 exerts a similar effect to miR-134 by regulating the expression of acyl-protein thioesterase 1 (100). Bond *et al* found that in lncRNA-Evf2-knockout mice, the number of GABA-ergic interneurons in the early postnatal period was significantly decreased in the Ammon's horn and DG, and the number gradually returned to normal; however, the number of GABA-ergic pyramidal cells in the CA1 region were maintained at a low level, resulting in the impaired function of neural circuits in the hippocampus (101). Evf2 recruits distal-less homeobox 5 (DLX) and MeCP2 to Dlx5/6, and regulates the expression of Dlx5, Dlx6 and GAD67, consequently regulating the production of GABA interneurons (101). The lncRNA-Malat1 regulates the synaptic density between hippocampal neurons. Of note, lncRNA-Malat1-knockout decreases the expression of synaptic cell adhesion molecule 1 (SynCAM1) and downregulates the expression of neuroligin 1 (NLGN 1), resulting in decreased synaptic density between hippocampal neurons (102).

The lncRNA-Uc.173 originates from the transcribed ultraconservative region of the genome in humans and rodents. Nan *et al* demonstrated that lead induced the apoptosis of hippocampal neurons in developing and maturing rats. Additionally, the expression of lncRNA-Uc.173 in the lead-exposed cells decreased over a period, whereas the overexpression of lncRNA-Uc.173 significantly reduced the apoptosis of these cells, suggesting that lncRNA-Uc.173 regulates the genes involved in hippocampal neuronal apoptosis and maintains hippocampal development (103). In the hippocampus of adult mice, lncRNA-AK089514 is expressed in the GCL; lncRNA-BC051426 appears in the pyramidal layer of Ammon's horn and lncRNA-AK037594 emerges in the GCL and the pyramidal layer of the CA3 region (89).

Partial miRNAs can target key enzymes in the regulation of epigenetic mechanisms, termed epigenetic-miRNA (epi-miRNA). Epi-miRNA can inhibit the expression of DNMT by binding to the 3'-UTR of DNMT mRNA, which in turn affects the genome-wide methylation pattern (104). miR-290, a type of epi-miRNA, affects the differentiation of embryonic stem cells by controlling the *de novo* DNA methylation of embryonic stem cells, and differentiation is inhibited when miR-290 is deficient (105). Epi-miRNA inhibits DNA methyltransferase by regulating B cell-specific Mo MLV insertion site-1 (BMI-1) and enhancer of zeste homolog-2 (EZH2), promoting the senescence of pluripotent stem cells (106). Epi-miRNAs (miR-125 and miR-181) act as modulators of chromobox 7, mediate the expression of the polycomb genes and are key in establishing embryonic stem cell pluripotency (107). Epi-miRNA can target Bmi-1 to regulate the expression of polycomb genes (108). The downregulation of miR-128 has been shown to result in the upregulation of Bmi-1, which induces the abnormal proliferation of brain cells (109). Ezh2, which interferes with the expression of polycomb genes, is regulated by Epi-miRNA. The overexpression of miR-137 inhibits the appearance of Ezh2 and promotes neurogenesis in the hippocampal SGZ (110). HDACs are also regulated by Epi-miRNA, miR-134 mediates the post-transcriptional modification of CREB, leading to increased activation of the NAD-dependent deacetylase Sir2, which disrupts the plasticity of hippocampal synapses and leads to memory impairment (111). Zovoilis *et al* (112) showed that the expression of miRNA 34c was increased in the hippocampus of AD mice, and that miR-34c was able to activate the NAD-dependent deacetylase sirtuin 1 and cause memory impairment.

Miller-Delaney *et al* (57) indicated that there are multiple miRNA differential methylation events in the human hippocampus in temporal lobe epilepsy, leading to the upregulation and downregulation of corresponding miRNA expression; in particular, the upregulation of miR-876-3p and miR-193a-5p is most valuable, suggesting that miRNA dysregulation in the hippocampus causes epilepsy. It has been found that miRNAs cause Glu-ergic and GABA-ergic synaptic dysfunction of the hippocampus by regulating fragile X mental retardation protein, leading to fragile X syndrome epilepsy (113). In addition, lncRNA-BC1 and lncRNA-Evf2 were reported to act on Glu-ergic and GABA-ergic interneurons, respectively, and the excited interneurons induced epilepsy when lncRNA-BC1 and lncRNA-Evf2 were absent (101,114).

Impaired synaptic plasticity in AD is associated with the dysregulation of specific miRNAs. Hu *et al* showed that miR-34c was significantly increased in amyloid-β (Aβ) accumulation in hippocampal neurons, whereas decreased miR-34c improved Aβ-induced synaptic failure and memory deficits (115). Furthermore, deletions on chromosome 22q11.2 caused by the upregulation of miR-185 in the hippocampus is an important genetic risk factor for schizophrenia, which indicates that miR-185 can be used as a novel target for the development of therapeutic drugs (116). A study on the schizophrenia risk gene MIR137 in rat hippocampal neurons indicated that MIR137 is key in the pathophysiological progression of schizophrenia as a hippocampal gene network node (117).

4. Conclusions

Humans and rodents exhibit marked similarity in the basic process of the development of the hippocampus. However, a marked difference is observed in the generation time of the DGC; ~80% of the human DGC is formed at the embryonic stage, whereas ~85% of the rodent DGC appears postnatally. The RGCs, including cell migration scaffolds, are crucial in the development of the hippocampal DG in humans and rodents.

Epigenetic inheritance is important in various stages of development of the hippocampus, and affects the proliferation, differentiation, migration and maturation of nerve cells. DNA methylation, histone acetylation and non-coding RNAs significantly influence the formation of synapses in the hippocampal neurons; this affects the construction of hippocampal neural circuits, and postnatal learning and memory function. Notably, future investigations are likely to considerably affect the analysis of clinically relevant disease mechanisms in addition to clinical diagnosis and treatment. DNA methylation, histone modifications and non-coding RNAs may act on the same gene or different aspects of the same mechanism of action, for example, the negative correlation between DNA methylation and histone tagging (H3K4me3) (118); histone modifications and lncRNAs regulate the Sox gene (119,120), and lncRNAs and miRNAs act on mRNAs differently to affect gene expression. These phenomena suggest the occurrence of interactions between different epigenetic regulatory mechanisms to produce synergistic or antagonistic effects in the same regulatory process. With an increasing number of epigenetic mechanisms revealed, further correlations can be identified to provide in-depth insight into the role and significance of epigenetic modifications in the development of the hippocampus.

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Authors' contributions

SJF searched the related literature and wrote the manuscript. ABS aided with the literature search and edited the manuscript. LL drafted the manuscript and revised it critically for important intellectual content. All authors aided to prepare the manuscript and approved the final version to be published.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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