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Epigenetic regulation in the neurogenic niche of the adult dentate gyrus

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ABSTRACT

The adult dentate gyrus (DG) of the hippocampal formation is a specialized region of the brain that creates new adult-born neurons from a pool of resident adult neural stem and progenitor cells (aNSPCs) throughout life. These aNSPCs undergo epigenetic and epitranscriptomic regulation, including 3D genome interactions, histone modifications, DNA modifications, noncoding RNA mechanisms, and RNA modifications, to precisely control the neurogenic process. Furthermore, the specialized neurogenic niche also uses epigenetic mechanisms in mature neurons and glial cells to communicate signals to direct the behavior of the aNSPCs. Here, we review recent advances of epigenetic regulation in aNSPCs and their surrounding niche cells within the adult DG.

1. Introduction

The subgranular zone (SGZ) of the dentate gyrus (DG) of the hippocampus is one of two regions of the mammalian brain where new neurons are generated at a significant rate under normal physiological conditions during adulthood. The DG and adult-born neurons are implicated in key brain functions such as learning, memory, and mood regulation [1–3]. Each DG of an adult human incorporates an estimated 700 adult-born neurons, known as adult-born granule cells (GCs), to its granule cell layer every day [4]. This ability of the DG to generate and incorporate nascent neurons throughout life demonstrates the capacity of the hippocampus to modulate existing neural circuits and contribute to hippocampal plasticity.

Adult-born GCs derive from resident adult neural stem/progenitor cells (aNSPCs) through a tightly regulated process called adult hippocampal neurogenesis (AHN), ranging from proliferation, differentiation, and maintenance of aNSPCs to maturation and synaptic integration of immature neurons [5,6]. Recent evidence suggests that aNSPCs found in the adult brain are derived from embryonic neurogenesis through a continuous developmental process that initially forms the DG [7,8]. One way to achieve this is to use multi-level regulation, where both intrinsic and extrinsic cues converge to regulate aNSPC behavior. An important regulatory mechanism is epigenetic control of gene expression, which is capable of modulating aNSPC behavior at multiple levels based on environmental signals.

While adult neurogenesis is a continuation of embryonic development, it occurs in a functionally mature microenvironment surrounded by the unique and dynamic neurogenic niche [5]. The cells in the DG that make up this neurogenic niche regulate AHN at its various stages from aNSPC proliferation to immature neuron integration. Transplantation studies highlight the importance of the hippocampal neurogenic niche by demonstrating the ability of this brain region to induce neuronal differentiation from gliogenic aNSPC populations from other brain regions. This work shows that the neurogenic permissive environment of the DG is able to reprogram aNSPC fate through a combination of external factors [9,10]. This result demonstrates the importance of the neurogenic niche of the DG and its role in regulating AHN by producing signals that direct precursor cell differentiation towards neurogenesis [11]. In this review, we will highlight dynamic regulation of gene expression in adult DG cells by their intrinsic epigenetic factors, extracellular signals from the surrounding neurogenic niche, and their crosstalk.

2. Mechanisms of epigenetic regulation in adult hippocampal neurogenesis

Genotypically identical cells can have drastically different phenotypes based on epigenetic regulation of their gene expression. Originally coined by Conrad Waddington as the process by which a genotype results in a phenotype in a developmental context [12], epigenetics is now

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defined as the study of heritable (in both a mitotic and meiotic sense) and stable gene expression modifications during cellular development, proliferation, biological stochasticity, and/or environmental stimuli [13]. Various mechanisms of epigenetic regulation, including DNA base modifications, histone modifications, 3D chromatin structure, and regulation by noncoding RNA (ncRNA), allow for dynamic, multi-level control of gene expression in each cell (Fig. 1). Specifically for AHN, much work has explored how each level of epigenetic control contributes to aNSPC proliferation and differentiation as we will discuss in this section of the review.

2.1. DNA base modifications

The most abundant DNA base pair modification in eukaryotes is the methylation of the 5′-carbon of cytosine (5mC). About 4% of cytosines in the human genome have been reported to be methylated [14,15]. The addition of the methyl group is mediated by DNA methyltransferases (DNMTs) [16]. Traditionally, 5mC is associated with genomic regions that contain a high concentration of CG dinucleotides, which are associated with stable repression of transcription. Promoters that have a high content of 5mC correspond to lowly expressed genes while promoters that lack 5mC correlate with highly expressed genes. Active enhancers and protein binding domains also show a depletion of 5mC, which further suggests an association between 5mC and repression of gene expression [17]. DMNTs have been shown to be essential for aNSPC differentiation and adult-born neuron integration into existing neural networks [18,19]. For example, conditional knockout of DNMT1(a protein that prevents methylation loss during cell division) in aNSPCs using Nestin-CreER^{T2} mouse line does not affect aNSPC proliferation or differentiation but reduces newly generated mature GCs 28 days post-induction, suggesting that DNMT1 is crucial for the survival of adult-born GCs [20]. Furthermore, cranial irradiation or zebularine-mediated DNMT inhibition significantly lowers the expression of DNMT1 and DNMT3a in the hippocampus of Sprague-Dawley rats, which leads to decreased neurogenic proliferation of aNSPCs and cognitive deficits [21].

5mC can be removed by the ten-eleven translocase (TET) proteins, which progressively oxidize the methyl group to form 5′-hydroxymethlyctosine (5hmC), 5′-formylcytosine (5fC), and 5′-carboxylcytosine (5caC) [22–24]. Each of these oxidized methyl cytosines can also be removed by thymine DNA glycosylase and replaced with an unmodified cytosine [25]. A recent study has demonstrated that TET1 knockout in mice impairs AHN by reducing progenitor cell proliferation [26]. Other studies indicate that 5mC removal at specific promoter regions controls various stages of AHN. For example, demethylation at the *Fgf2* promoter induces aNSPCs to proliferate but reduces their ability to differentiate into GCs [27]. These findings suggest that 5mC is a dynamic mark that can be added or removed to modulate aNSPC behavior during development.

Recently, several studies have shown that 5hmC is also a stable epigenetic mark that is enriched in active enhancers and in gene bodies of highly expressed genes across different cell types, including neurons [28–30]. Chromatin accessibility of TET2/TET3 double knockout mice decreases in genomic regions with high 5hmC content in wildtype mice [31]. Further evidence shows that 5′-formylcytosine (5fC) and 5′-carboxylcytosine (5caC) have unique functions. For example, 5fC directs

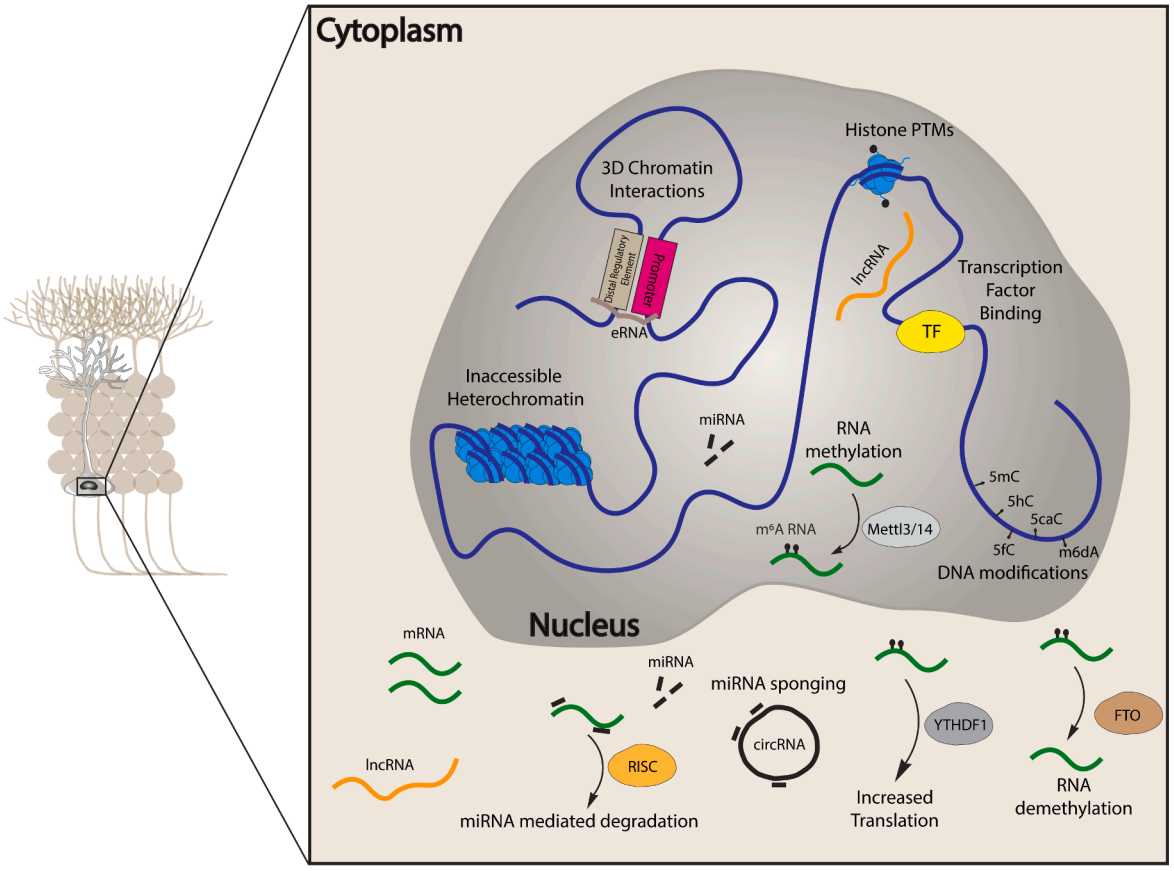

Fig. 1. Epigenetic regulation from 3D architecture to base resolution. Many levels of epigenetic regulation modulate gene expression. 3D chromatin structure consisting of long-range chromatin loops brings together cell-type specific distal regulatory elements and their target promoters aided by eRNAs. Histone modifications, including acetylation and methylation, modulate the accessibility and transcription of genes. DNA modifications at the 5′-carbon of cytosine and at adenosine influence transcription of modified genes and provide differential scaffolds for transcription factor binding. miRNA, lncRNA, and RNA modifications have diverse roles in post transcriptional regulation of gene expression.

nucleosome positioning in a tissue-specific manner through interactions with lysine residues on histones and these interactions occur at enhancers of highly expressed genes [32]. 5caC marks the most active enhancers that have cytosine modifications in mouse embryonic stem cells [33]. Beyond these cytosine modifications, N6-methyl-2′-deoxyadenosine (m6dA) has been recently shown to be an important DNA modification in human cell lines and the murine brain [34]. However, the role that these marks play in AHN is unknown.

Current research methods have lacked the sensitivity to tell the DNA marks apart. However, new techniques such as 5caC clearance (caCLEAR) [35], long read Tet-assisted pyridine borane sequencing (lrTAPs) that measures 5mC and 5hmC dynamics [36], and 5fC pull-down sequencing [32,37] will allow future exploration of the dynamics of each cytosine mark in the context of AHN. The different DNA modifications also impact transcription factor (TF) binding to DNA as the different modification impact TF and other protein affinities for a DNA sequence [38]. In AHN, methyl-CpG-binding domain protein 1 (MBD1) and methyl-CpG-binding protein 2 (MeCP2) specifically bind methylated DNA and repress transcription [39,40]. MBD1 depletion impairs aNSPC proliferation in vitro while MeCP2 knockout mice display delayed maturation of adult-born GCs [39,41]. A new method digital affinity profiling via proximity ligation (DAPPL) allows the high-throughput interrogation of how each DNA mark affects TF preference of DNA modification state [42]. These high-throughput methods, compatible with low cell number samples or rational design, will allow for rapid advancement in the amount of data that can be generated in many fields and permit the precise interrogation of the role of DNA modifications in aNSPCs.

2.2. Chromatin accessibility: Histone modifications

In eukaryotes, DNA is associated with an octamer of histone proteins (two copies of each H3, H4, H2A, and H2B) to form nucleosomes, the functional unit of chromatin [43]. Post-translational modifications (PTMs) can be added to each of these histone proteins in the nucleosome [44]. Many different histone PTMs have been shown to be dynamically regulated through methylation, acetylation, ubiquitination, and phosphorylation. These epigenetic marks can occur at multiple different regions of the histone proteins, and multiple marks can be found on a single histone. The combination of different marks leads to a large variety of post-translational states and can impact how nucleosomes interact with chromatin-binding proteins changing the dynamics of binding site affinities [45,46]. Furthermore, PTMs affect the interaction between neighboring nucleosomes causing them to spread out and form transcriptionally active euchromatin or causing the nucleosomes to clump together forming transcriptionally inactive heterochromatin. This difference in gene expression corresponds to differences in chromatin accessibility. For example, acetylation of histones at lysine residues corresponds to accessible, transcriptionally active euchromatin, whereas methylation at lysine or arginine residues can either increase or decrease accessibility and transcription based on where the mark is placed and how many methyl groups compose the mark (mono-, di, or trimethylation) [47]. Most work on PTMs of histones in AHN focuses on acetylation or methylation, which we discuss below.

Many studies in the adult DG have investigated the roles of different histone acetyltransferases (HATs) and histone deacetylases (HDACs). Broadly, prior studies using HDAC inhibitors, such as calproic acid (VPA), indicate the significance of histone acetylation and HDACs by showing an increase in neurogenesis and a decrease in gliogenic fate decisions of aNSPCs [48]. Studies in the zebrafish retina also demonstrate increased neurogenic fate decisions while suppressing proliferation of aNSPCs in response to HDAC inhibitor treatment following injury [49]. However, the roles of the 18 different HDACs in AHN have since been shown to be more complex. In many systems including the adult brain, HDACs have been found to be redundant [50]. In brain development, HDAC1 or HDAC2 single deletions in mice do not result in a phenotype [51]. However, deletion of both HDAC1 and HDAC2 genes results in abnormalities of the hippocampus and other brain regions [51]. Interestingly, various HDACs, such as HDAC1, HDAC2 and HDAC3, have recently been shown to be only partially redundant [50]. Partial redundancy suggests that they each have distinct roles in the control of different stages of AHN. For example, HDAC1 is highly expressed in glial cells and aNSPCs while HDAC2 levels are elevated in aNSPCs that are differentiating into mature GCs [52]. These findings suggest a complex relationship between HDACs and aNSPC fate decision.

Another group of chromatin modifying proteins important in AHN are histone methyltransferases and histone demethylases. For example, enhancer of zest homolog2 (Ezh2), the methyltransferase component of the Polycomb repressive complex 2 (PRC2), is expressed in actively dividing aNSPCs and mature neurons but not quiescent aNSPCs [53]. The conditional deletion of Ezh2 represses aNSPC proliferation, self-renewal, and neuronal differentiation and leads to impairment in new neuron formation and learning and memory [53]. Furthermore, conditional knockout of the protein EED (embryonic ectoderm development), which interacts with EZH2 to form the PRC2, also results in decreased proliferation and neurogenic impairment. Interestingly, this study has found that EED played distinct and separable roles in aNSPC proliferation and differentiation [54]. Specifically, downregulation of *Cdkn2a*, a downstream target of EED, ameliorates the impairment in proliferation but not differentiation; while overexpression of *Sox11*, another downstream target of EED, reverses the defect in differentiation but not proliferation. Histone demethylases such as Lysine-specific demethylase 1 (LSD1) and JMJD3 also impact AHN. LSD1 knockdown or chemical inhibition leads to reduced proliferation of aNSPC in the adult DG through an interaction with TLX, an orphan nuclear receptor [55]. JMJD3 demethylates H3K27me3 PTMs and the deletion of its gene causes deficits in aNSPC proliferation, neurogenic differentiation, and gliogenic differentiation [56]. The conditional knockout of the Dpy30 subunit of the H3K4 methyltransferase in aNSPCs prevents both their proliferation and differentiation, suggesting that it is essential for AHN [57]. However, Dpy30 has other binding partners, so the methyltransferase activity cannot be confirmed as the cause of the phenotype. These and many other examples demonstrate the impacts that PTMs of histones can have on AHN [58,59], which suggest a very nuanced control mediated by multiple marks on each histone.

Given the above examples, histone PTMs play an important regulatory role in AHN, and further investigation into the mechanisms of control in AHN is needed. High-throughput methods of characterizing changes in histone PTMs like ChIPseq need many cells and deep sequencing, which have prohibited extensive studies on aNSPCs from intact tissues. Because of this, it is still unknown how cellular and molecular manipulations affect PTM distribution throughout the genome. However, methods like CUT&RUN [60], CUT&Tag [61], and single-cell CUT&Tag [62] permit the genome-wide identification of specific proteins like histone modifications bound across the entire genome in far fewer cells. By using an immunotethering approach that targets an enzyme to an antibody labeled chromatin site, these approaches increase their sensitivities and allow for their use at low cell numbers at a lower sequencing depth, thus overcoming the caveats associated with ChIPseq. Furthermore, ATACseq [63] and single-cell ATACseq [64,65] can be used to determine genome-wide accessibility profile of cells that can be coupled with histone PTM data to build more complete picture of chromatin state at various genes. These methods will allow the examination of accessibility and genome features such as enhancers to be analyzed *in vivo* along the neurogenic lineage. The ability to analyze histone modifications and chromatin accessibility changes in response to various physiological, pathological, and environmental conditions will provide valuable information on questions about gene and environment interactions during AHN.

2.3. Chromatin accessibility: 3D chromatin interactions

Cytosine modification and histone PTM analyses are limited in that they analyze the genome in linear space, but the genome is organized in three-dimensional (3D) space within the cell. This chromatin folding, known as DNA looping, permits distal regulatory elements such as enhancers and silencers to be physically close to the promoters they act on in 3D space while far apart in the linear DNA sequence [66]. CCCTC-binding factor (CTCF) is an important insulator protein that plays a role in enhancer-promoter interactions. CTCF has increased binding and loop formation in lineage committed cells, demonstrating its importance in cellular differentiation [67]. Furthermore, conditional knockout of CTCF in postmitotic projection neurons prevents neural development in both the cerebral cortex and hippocampus [68]. Conditional knockout mice are born without apparent abnormalities, but quickly experience growth retardation by P7 and die within 1 month. These 3D interactions also modulate chromatin accessibility and gene expression. Therefore, coupling linear accessibility measurements with methods to measure 3D DNA interaction such as Micro-C [69], and low-input easy Hi-C (eHi-C) [70] would be beneficial for AHN studies in the DG. eHi-C permits the identification of distal *cis*-regulatory regions interacting with promoters from 50 k to 100 k cells. This could help to identify novel enhancers or other distal regulatory units that regulate AHN; however, expanding this technology to require lower cell numbers will make it more beneficial. Another method, single-cell Sprite [71], identifies interactions between distal regulatory regions and promoters but can also detect RNA-chromatin interactions and RNA-protein interactions. However, this field remains largely unexplored in AHN and better low-cost, low-input methods are needed to be able to call differential looping patterns between treatment groups for informative studies.

2.4. Regulation by RNA: Non-coding RNA

The vast majority (~80%) of the mammalian genome is transcribed as RNA, but less than 3% of our genome encodes for proteins [72]. This ncRNA has been shown to regulate gene expression profiles in a cell-type specific manner. The two major classifications of ncRNAs are small (less than 200 nucleotides) and long (greater than 200 nucleotides) ncRNA [73].

The most studied ncRNAs are the microRNAs (miRNAs) a type of small ncRNA that is made when Dicer, an enzyme, cleaves a pre-miRNA into its functional unit. miRNAs are short single strands of 17–25 nucleotides that bind to mRNA and suppress their translation through an interaction with RNA-inducible silencing complex (RISC) in both the cytoplasm and the nucleus [74]. Some miRNAs act in the nucleus to promote alternative splicing [75]. They regulate neurogenesis at all stages from aNSPC maintenance to synaptic integration of immature neurons [76]. Notably, deletion of Dicer in cultured aNSPCs permits self-renewal but prevents aNSPCs from differentiating into either glial or neural cells. Importantly, such phenotypes are rescued by reintroducing Dicer, suggesting an important role of miRNAs in neurogenesis [77]. For one specific example, the expression of miR-132 is low in adult neural stem cells but significantly increases during neuronal differentiation, and its deletion in the adult mouse DG compromises the functional integration of adult-born GCs [78]. The overexpression of miR-132 in aNSPCs of the adult mouse hippocampus induces neuronal differentiation and maturation [79]. In this section of the review, we discuss the emerging role of circular RNA (circRNA) and its interaction with miRNA. For more comprehensive analysis of miRNA contributions to AHN, we refer the reader to Stappert et al. [76] and Esteves et al. [80].

A recent advance in ncRNA biology is the discovery that circRNA are ubiquitous and cell type specific in mammals [81]. circRNAs are a covalently circularized long ncRNA (lncRNA) that consist of 1 or more exons and are generated from a process called backsplicing where the 3′ acceptor site of a transcript is covalently bound to the 5′ donor site [82]. Since they are circularized, they are much more stable than linear RNA and avoid RNase-R exonuclease activity [81,83]. circRNAs have capacity to bind miRNA and suppress their function, a process known as miRNA sponging [83,84]; they can also regulate translation acting as protein sponges [85] and protein complex scaffolds [86]. As there is little published work on the role of circRNA in AHN, here we review the actions of circRNA in the whole brain and during cortical development. Knowledge that is gained from these studies will be instrumental in interpreting the roles of circRNA in aNPSCs and neurogenesis.

circRNAs are especially abundant in the brain compared to other tissues with 20% of all protein coding genes producing circRNA [87]. CDR1as is a circRNA that is enriched in the brain, and its CRISPR-Cas9-mediated deletion causes dysfunction of excitatory neurons and animal behavioral abnormalities in mice [88]. Interestingly, the Cas9-mediated deletion of CDR1as causesd an upregulation miR-671 and down-regulation of miR-7, which demonstrates that CDR1as is involved in more complex regulation than simple miRNA sponging. Knockdown of a different circRNA, circSLC45A4, during murine cortex development reduces the pool of embryonic NSCs and leads to a reduction in the number of neurons in the prefrontal cortex due to a rapid conversion of progenitor cells into neurons without maintaining a sufficient pool of stem cells [89]. In the adult DG, one or more different circRNAs could behave similarly and cause aNSPCs to differentiate too quickly and deplete the aNSPC pool through lack of self-renewal. Conversely, it is possible that other circRNAs induce proliferation of aNSPCs but prevent differentiation. Furthermore, circRNAs could play a putative role in aNSPC maintenance and synaptic integration.

Many other ncRNAs influence aNSPC fate decisions during both development and AHN. For example, the lncRNA *Malat1* is essential in neurite outgrowth, and its knockdown causes a signaling cascade that results in neuronal cell death [90]. lncRNAs also affect aNSPC self-renewal, proliferation, and the fate decision between gliogenesis and neurogenesis. An interesting avenue for future research are enhancer RNAs (eRNAs), which are transcribed from active enhancers and therefore, demonstrate strict lineage and tissue specificity with the highest expression in immune and nervous tissue [91–93]. They play important roles in enhancer promoter loop formation, which is important for cellular differentiation. However, they are unexplored in AHN and how they impact progression through the neurogenic lineage remains an open question in the field. For a comprehensive review of lncRNAs in neurogenesis, we refer the reader to Zhao et al. [94].

2.5. Regulation by RNA: RNA modifications

While epigenetic regulation controls cellular phenotypes through control of the transcription of genes, epitranscriptomic regulation controls the metabolism, translation, localization, and stability/decay of both mRNAs and lncRNAs. N^6-methyladenosine (m^6A) is the most prevalent modification of RNA. This mark is deposited by a protein complex consisting of METTL3 (the catalytic methyltransferase domain) and METTL14, which binds the RNA substrate [95,96]. Germline deletion of Mettl3 in mice gives rise to viable preimplantation epiblasts but culminates in early embryonic lethality of offspring [97]. This study emphasizes the importance of m^6A RNA in lineage commitment and differentiation *in vivo*. In the embryonic mouse cortex, conditional knockout of Mettl14 or knockdown of Mettl3 extends cortical neurogenesis into postnatal stages leading to aberrant brain development [98]. Mettl14 conditional knockout individuals lack m^6A mRNA preventing rapid mRNA decay. Taken together, these results suggest that cell lineage progression mRNA corresponding to genes from the previous cell state are methylated to temporally regulate the decay of transcripts that prevent further specification. The m^6A modification further serves as a direct binding site for proteins with a YTH domain [99]. In humans, there are five YTH domain-containing proteins falling into three distinct families. YTHDC1 (DC1 family), which localizes within the nucleus and exports m^6A RNA from the nucleus. YTHDC2 (DC2 family), which has an unknown role and localization. YTHDF1, YTHDF2, and YTHDF3 (DF

family) reside predominantly in the cytoplasm, playing distinct roles in m^6A RNA signaling pathways [100,101]. These proteins allow for the trafficking, splicing, compartmentalization, translation, and decay of modified transcripts.

Like DNA methylation, m^6A RNA is both reversible and dynamically regulated. The RNA demethylase FTO removes RNA methylation in response to various cues [102]. In the adult DG, loss of FTO reduces proliferation and neurogenic differentiation of aNSPCs and causes learning and memory deficits *in vivo* [103]. In FTO knockout mice, several genes in the NGFR-BDNF signaling pathway, which is important for neuronal differentiation and survival, are downregulated. An important area of research is how these proteins are directed to the transcripts that they methylate or demethylate and how changes in signaling adjusts the transcripts that are targeted.

3. Epigenetics of niche regulation of adult neurogenesis

The DG of the hippocampus is a highly specialized brain region capable of responding to experiences [104,105]. Experiences are sensed by the neurogenic niche, which then provides signals to maintain the resident stem cell population and their progeny to generate nascent neurons or glia throughout life [106]. The aNSPCs need to carefully integrate the signals from the niche in the DG, including mature neurons, long-range neuronal projections into the DG, astrocytes, microglia, and endothelial cells [5,107]. These cells communicate with aNSPCs and other niche cells through activity-dependent signaling and their extracellular secretions. A growing body of evidence suggests that epigenetic changes in niche cells control their signaling impacting aNSPCs.

3.1. Neuronal Activity-dependent epigenetic changes and signaling

GCs are extremely abundant in the DG neurogenic niche and are in close proximity to aNSPCs. Many neuronal circuits send signals to the GCs as intermediates to relay information to the neurogenic niche. Growing evidence supports the idea that GC activity readily influences other niche cells and aNSPCs [108]. A recent study has found that brief stimulation of mature GCs in transgenic mice expressing channelrhodopsin-2 fused to YFP leads to the immediate induction of c-Fos expression (a marker of induced neuronal activation), increases cell proliferation measured by $BrdU^+$ cells, and increases AHN measured by $BrdU^+/NeuN^+$ cells 21 days after BrdU injection [109].

Many studies that interrogate epigenetic mechanisms after neuronal activation use electroconvulsive therapy (ECT), which administers an electric current to anesthetized individuals, inducing controlled electroconvulsive seizures that simultaneously activate all mature neurons in the brain. ECT leads to therapeutic effects through a largely unknown but multifaceted neurobiological mechanism and is used to treat neuropsychiatric disorders, especially severe drug-resistant major depressive disorder with impressive efficacy [110–112]. As with optogenetic stimulation of GCs, ECT significantly increases neurogenic proliferation of aNSPCs in the DG, putatively through ECT-induced GC activation [113]. This study further demonstrates that this neuronal activity-dependent increase in AHN was dose-dependent, suggesting that each progressive seizure caused a greater increase in adult-born GCs. However, the mechanism underlying this increase in adult-born GCs was unknown.

Upon further investigation, ECT induced robust, transient *Gadd45b* expression in GCs of the DG [114]. *Gadd45b* knockout mice have greatly impaired neurogenesis in response to neuronal activity when compared to controls. When overexpressed, *Gadd45b* promotes site specific DNA demethylation of *Fgf-1B* and *BdnfIX in vivo* [114]. The GCs secrete the product of these genes into the DG, causing a broad impact on the neurogenic niche. BDNF promotes dendritic growth and neurogenic proliferation of aNSPCs while FGF proteins are known to cause proliferative effects [115–117]. Interestingly, exercise and enriched environment both upregulate BDNF and FGF expression as well and have similar, but more subtle effects [118,119]. While it remains unclear whether this happens through Gadd45b DNA demethylation or a different mechanism, many studies have shown that exercise improves health through epigenetic mechanisms [120]. Interestingly, TET1 knockout animals exhibit decreased expression of activity-dependent neuronal genes due to hypermethylation of their promoters, decreased synaptic plasticity, and cognitive impairment [121]. A follow-up study has characterized the genome-wide methylome pattern and has found that, after ECT, approximately 1.4% of CpG dinucleotides undergo demethylation and *de novo* methylation, including loci in the *Notch* signaling pathway [122]. These studies provide clear examples of how neuronal activity is regulated by epigenetic mechanisms like DNA methylation state, which control signaling in the neurogenic niche.

Neuronal activity also modifies chromatin accessibility in the adult brain. ATACseq data from before and after ECT indicate that 1 hour post neuronal stimulation, multiple active enhancers and binding sites for AP1-complex components, like c-Fos, became more accessible, which correlates with greater expression of genes corresponding to their target promoters [123]. shRNA-mediated knockdown of c-Fos causes 72.1% of upregulated genes (and all of c-Fos binding sites) to lose the sensitivity of chromatin accessibility to ECT [123]. This finding shows that c-Fos is required for ECT-induced increases in chromatin accessibility at its genomic binding sites. Upon c-Fos overexpression, 56% of the sites of increased accessibility overlap with sites from neuronal activation by ECT [123]. c-Fos binding is only detected 1 hour post-induction and not 4 hours post-induction, but the chromatin is still accessible, signifying that c-Fos is essential for initiation of neuronal activity-based opening of chromatin but not its maintenance. Interestingly, this AP1-induced altered accessibility pattern that persists after AP1 falls off the genome is also seen in mice treated with kainic acid, a glutamate receptor agonist, that is used to model a single epileptic seizure [124]. Enriched environment and exercise studies also show increased AP1 expression however accessibility studies have not been done [125,126]. However, there is increased histone acetylation at *Bdnf* and other genomic loci in mice undergoing exercise [127]. Studies into the mechanism of how accessibility is maintained or how chromatin accessibility is resuppressed post neuronal activation are needed. Methods of prolonging chromatin accessibility may promote beneficial healthy neuronal signaling into the adult brain.

ECT further modulates epitranscriptomic processes in the adult brain. Specifically, in the adult DG, recent work has shown that m^6A mRNA promotes activity-dependent protein translation and that mice with a genetic deletion of the m^6A RNA binding protein locus *Ythdf1* show learning and memory impairment and synaptic deficits that are rescued by acute re-expression of YTHDF1 in the hippocampus [128]. Together, these studies demonstrate epigenetic and epitranscriptomic regulation in neurons of the DG and provides a mechanism for rapid response to experience, induce neurogenic proliferation, and mediate learning and memory (Fig. 2). In response to neuronal activation, these gene regulatory alterations increase the accessibility, transcription, and translation of neurotrophic factors from GCs affecting both the neurogenic niche and AHN. This mechanism provides evidence that experience can induce modifications to the epigenetics of niche cells, which impact aNSPCs.

Many open questions remain in neuronal activity-dependent epigenetic changes. It will be important to confirm whether ECT, exercise, enriched environment, optogenetic stimulation, and chemogenetic stimulation of GCs undergo similar epigenetic regulation or if the epigenetic machinery act on distinct sites in the genome under each condition. Furthermore, other epigenetic modifiers should be examined in the DG. For example, the expression of N6-adenine-specific DNA methyltransferase 1 (N6AMT1), which deposits the m6dA on the transcription start site of highly expressed DNA is activity-dependent in cortical neurons in response to fear conditioning [129]. Furthermore, lentiviral shRNA-mediated knockdown of *N6amt1* in the infralimbic prefrontal cortex (ILPFC) prevents the formation of fear extinction

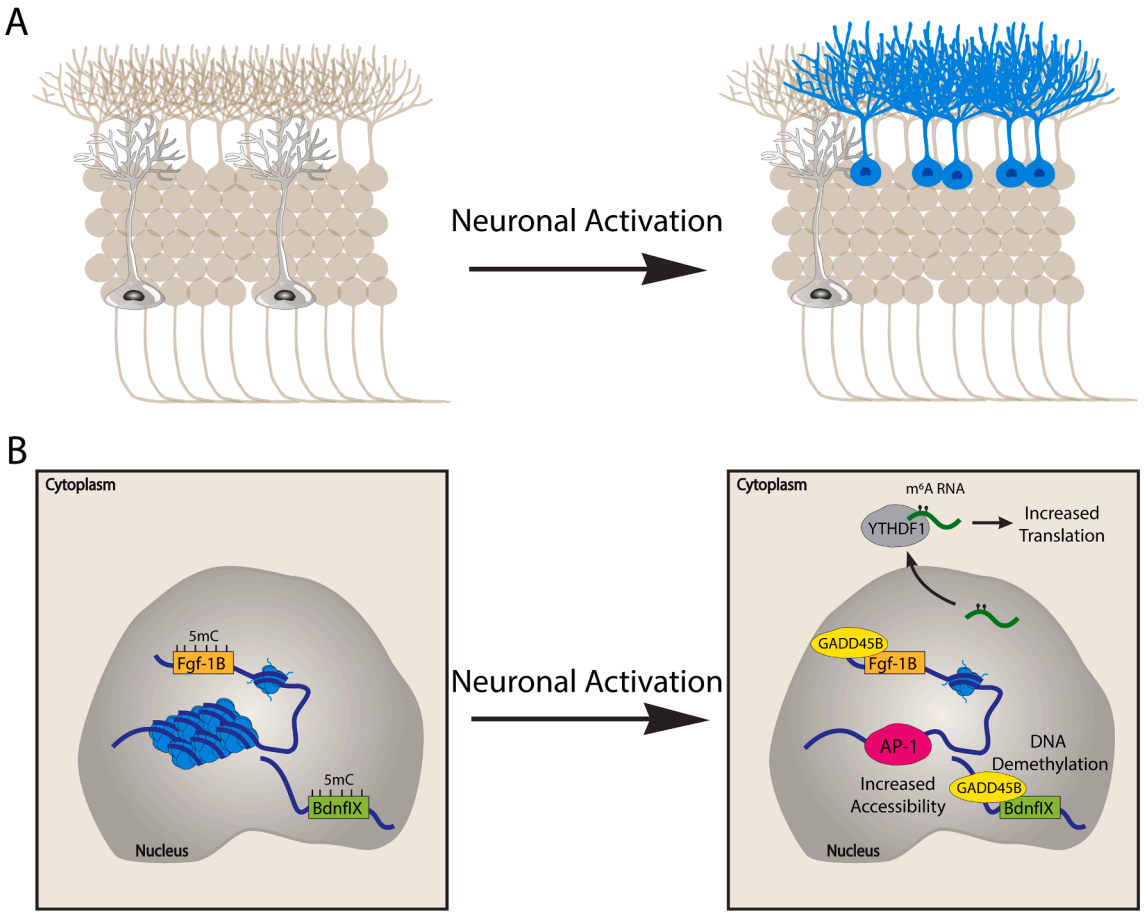

Fig. 2. Neuronal activation influences the neurogenic niche and adult neurogenesis through epigenetic mechanisms. (a) Activation-induced BDNF and FGF-1 secretion by granule cells promotes neurogenic proliferation of aNSPCs, increased dendritic growth, and improvement in learning and memory. (b) Epigenetics and epitranscriptomics provide the molecular mechanisms for increased transcription and translation of key genes through GADD45B-mediated demethylation, c-Fos-dependent chromatin opening, and translation of m^6A mRNA promoted by YTHDF1.

memory [129]. However, *N6amt1* and m6dA have not been studied in the DG. Future studies should examine the activity-dependent regulation of *N6amt1* and m6dA in the DG and if they play a role in hippocampal-dependent behaviors or other processes. Future studies into neuronal activity-dependent epigenetic regulation can elucidate the mechanism by which cells intrinsically control gene expression to modulate neuronal signaling in response to different stimuli.

3.2. Interneuron epigenetic changes and signaling

The DG is populated by many distinct interneurons, such as parvalbumin (PV) basket cells, somatostatin (SST) interneurons, cholecystokinin-expressing (CCK) interneurons, calretinin interneurons, and more reviewed here [130]. These cells are related in their capacity to communicate with aNSPCs through GABAergic signaling to the $GABA_A$ receptors on aNSPCs [131]. Increased expression of DNMT1 in DG interneuron populations resulting from prenatal maternal stress corresponds to methylated *Gad67* and *reelin*, which causes declines in GABA signaling and Reelin signaling in offspring [132]. The mice from this study exhibit depression-like behavior and have decreased neurogenic proliferation. Another group has also found this same result and have treated the offspring of mice that received prenatal stress with 5-aza-CdR, a DNMT1 inhibitor, which rescues the maturation of adult born GCs in the DG and the depression-like behavior of the mice [133]. Unfortunately, these studies fail to specify specific interneuron subtypes leaving unanswered questions about DNMT1 regulation of specific DG interneuron populations. Human hippocampal samples have also implicated DNMT1 in individuals suffering from epilepsy through the differential methylation of endocytosis-related genes that correspond to changes seen in DNMT1 conditional knockout mice mediated by PV-cre [134]. Careful dissection of distinct epigenetic regulatory mechanisms in each interneuron subtype and the effects of signaling changes are needed to achieve a more complete view of how gene expression changes in different subtypes of interneurons affect AHN.

3.3. Astrocyte epigenetic changes and signaling

Astrocytes are known to play an active regulatory role in AHN promoting aNSPC proliferation and differentiation into mature GCs [135]. Astrocytes in the molecular layer of the hippocampus and aNSPCs have been shown to come into contact and share blood vessel coverage [136]. This close association of astrocytes and aNSPCs provides an easy way to transfer signals between the cells. A recent study has demonstrated that astrocytes release glutamate in response to CCK, released by CCK interneurons, causing the neurogenic proliferation of aNSPCs [137]. Furthermore, when CCK signaling decreases, astrocytes become more reactive and release cytokines that decrease the neurogenic potential of aNSPCs. This work demonstrates the complexity of niche control as CCK interneurons regulate astrocytes, which then influence aNSPCs.

Astrocyte epigenetic regulation has the potential to be extremely impactful on aNSPCs because the exosomes that they excrete are known to traffic molecules, including mRNA and miRNAs [138]. Importantly, miR-25, miR-184, miR-34a, and miR-543, which are found in astrocyte exosomes, are known to promote aNSPC proliferation [139–142]. It is

important to note that astrocyte exosomes contain significantly different miRNA profiles than the astrocytes themselves [143]. This evidence suggests that astrocyte exosomes may be a mechanism of direct transmission of epigenetic regulation from astrocytes to aNSPCs and/or other niche cells. Furthermore, epigenetic profiles in astrocytes have more drastic changes than neurons during aging, as astrocytes become more reactive in older individuals [144,145]. So, it is possible that the decline in AHN and aNSPC pool depletion with age may be mediated, in part, by epigenetic changes in astrocytes and changes in their signaling.

3.4. Microglia epigenetic changes and signaling

Microglia, the resident immune cells of the central nervous system, have been shown to communicate with neurons through the CX3CL1-CX3CR1 pathway [146]. This neuronal signaling keeps microglia in the DG in the resting phase and prevents harmful microglia signaling [146,147]. Activated microglia are involved in phagocytosis of the majority of newborn neurons [148]. A recent study has demonstrated that chronic knockout of microglial phagocytosis during embryonic development impairs AHN while inducible acute knockout during adulthood promotes AHN [149]. This finding demonstrates the complex, temporal regulation of neurogenesis by microglia. Interestingly, the phagocytosis secretome created by microglia upregulates many chromatin remodeling factors and impairs neurogenic lineage progression and maintenance. Therefore, chromatin remodeling may play a key role microglia control of AHN.

Furthermore, preventing microglial activation has been shown to improve learning and memory [150]. Many studies have characterized epigenetic alterations that control microglial activation and have been extensively reviewed in Cheray et al. [151]. We discuss some examples of chromatin modifications here. For example, using VPA to inhibit HDACs decreases microglial activation and inflammation, suggesting a role of HDAC proteins in microglial activation [152]. However, this effect may result from inhibitors acting on HDAC2 in glutamatergic neurons in the hippocampus. Recent work has discovered that shRNA knockdown of HDAC2 in $CaMKII^{+}$ neurons in the dorsal hippocampus prevents microglial activation in response to lipopolysaccharide (LPS)-induced inflammation and ameliorates the associated cognitive deficits [153]. The conditional knockout of the *Ezh2* histone methyltransferase locus in microglia of adult mice prevents microglial activation and pro-inflammatory signaling [154–156]. The histone demethylase JMJD3 antagonizes microglial activation and its depletion causes microglia to become activated [157]. Like astrocytes, microglia experience drastic changes in their epigenetic profile during aging [144]. Taken together, these findings suggest that mechanistically epigenetic regulation of astrocytes and microglia, instead of neuronal changes, may play causal roles in regulating learning and memory and AHN as individuals age. The impact of epigenetic changes in microglia during AHN and learning and memory are not well understood and provide exciting avenues for future research.

4. Conclusion and future directions

Epigenetic and epitranscriptomic modifications dynamically regulate aNSPCs in the SGZ of the DG in the hippocampus, controlling their quiescence, proliferation, maintenance, maturation, and integration at different levels. The ability to control transcription at a gene-specific level allows aNSPCs to modulate their behavior in a context-dependent manner after integrating signals from the neurogenic niche. Epigenetic regulation of gene expression permits for rapid changes in aNSPCs transcriptional profiles with spatiotemporal control and allows for functional integration of adult-born new GCs into existing circuits to store new memories.

However, aNSPCs cannot do this on their own. Experiences are sensed by the neurogenic niche, which responds to stimuli by modulating gene expression. Niche cells must coordinate signaling to inform aNSPCs fate decision for a given situation, which can be achieved through the intrinsic epigenetic modifications of niche cells. Furthermore, epigenetic dysregulation of the niche during many diseases impacts stem cell biology and influences the pathogenic outcome in the regulation of mood, learning, and memory.

There is much work to be done to create a complete epigenomic landscape inside niche cells and aNSPCs at their different stages. The field is at an exciting time where it can characterize the specific contribution of each specific DNA modification to aNSPC regulation. Furthermore, promoter interactions with distal regulatory regions and chromatin PTMs can be quickly and robustly identified, given new sequencing technologies. Another avenue for new research is the mechanisms through which ncRNAs and 3D genome conformation dictate aNSPC fate. Furthermore, epigenetic regulation is not happening in a vacuum. Various levels of epigenetic regulation are interacting with each other and responding to different intracellular and extracellular signals [158]. Identifying these interactions will be vital for the future understanding of the complex mechanisms regulating gene expression in aNSPCs. Lastly, more work is needed to understand how the changes in epigenetic states of niche cells impact the neurogenic environment, signaling, and aNSPCs. However, there is a need for more specific models to study the different stages of neurogenesis. Currently, most popular mouse models to study AHN label heterogeneous populations of aNSPCs [159]. The establishment of new models that label cells at a specific stage in AHN will be needed to specifically interrogate the effects of epigenetic regulation along the adult neurogenic lineage. For example, the new $Hopx^{ERCre}$ mouse line specifically labels quiescent neural stem cells in the adult DG and will allow for more controlled interrogation of the initiation of AHN [160,161]. Better understanding of these concepts would provide insights into neuroregeneration in nonneurogenic environments or in degenerated brains and spark the development of new treatment strategies for memory disorders associated with neurodegenerative diseases.

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