Role of the histone methyltransferases Ezh2 and Suv4-20h1/Suv4-20h2 in neurogenesis

Christopher T. Rhodes¹, *, Chin-Hsing Annie Lin², *  

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Abstract

Mechanisms regulating neurogenesis involve broad and complex processes that represent intriguing therapeutic targets in the field of regenerative medicine. One influential factor guiding neural stem cell proliferation and cellular differentiation during neurogenesis are epigenetic mechanisms. We present an overview of epigenetic mechanisms including chromatin structure and histone modifications; and discuss novel roles of two histone modifiers, Ezh2 and Suv4-20h1/Suv4-20h2 (collectively referred to as Suv4-20h), in neurodevelopment and neurogenesis. This review will focus on broadly reviewing epigenetic regulatory components, the roles of epigenetic components during neurogenesis, and potential applications in regenerative medicine.

Key Words: adult neurogenesis; epigenetic; Ezh2; histone co-regulation; histone modification; neurodevelopment; neurogenesis; regenerative medicine; Suv4-20h

Overview of Epigenetic Mechanisms in the Context of Neurogenesis

Neurogenesis, neural stem cell proliferation, and cellular differentiation are broad and complex processes. The process of determining which cell type a neural stem cell will become involves genetic factors, epigenetic components, extrinsic signaling cues, and the microenvironment of a cell (Flitsch et al., 2020; Nasu et al., 2021). Exactly how intrinsic and extrinsic components integrate to specify cell fate has long been a central question in biology (Schaum and Guillemot, 2002; Guillemot, 2007; McKenzie et al., 2019). The development of the nervous system requires fidelity in the expression of specific genes determining different neural cell types and is regulated, in part, by a multitude of intracellular signals interacting with the extracellular microenvironment temporally and spatially. These signals induce the expression of genes involved in lineage commitment, differentiation, maturation, migration, and cell survival (Lim et al., 2018). The silencing of genes responsible for the maintenance of stem cells in a pluripotent state and for cell fate decisions are important hallmarks of neurodevelopment. Intracellular effectors of neurogenesis including cell-cycle inhibitors (p16/IPK4A and p21) and transcription factors have been previously reported. More recently, how epigenetic status influences neural stem cell proliferation and cellular differentiation during neurogenesis has become better characterized (Podobinska et al., 2017).

Epigenetic regulation is one of the most influential players in broad aspects of biology including neurogenesis. It is loosely described as heritable changes in gene expression without alterations in DNA sequence. The term “epi” means “over or above” and generally refers to changes associated with DNA, but not directly altering the nucleotide sequence of DNA. An important concept is each cell type has a distinctive epigenetic signature giving rise to a unique gene expression profile (transcriptome) (Lacal and Ventura, 2018; Zhang et al., 2021). Epigenetic regulation includes four main mechanisms to regulate gene expression levels within a cell: (1) DNA methylation; (2) histone post-translational modifications and histone variants; (3) non-coding RNAs and (4) higher order chromatin architecture (Podobinska et al., 2017). DNA methylation and non-coding RNAs are the best investigated epigenetic mechanisms, have been reviewed extensively, and will not be covered here. Neither will higher order chromatin architecture nor dynamic chromatin topology be discussed here. Cataloging large-scale chromatin features is a nascent research area with fewer studies evaluating potential roles in neurogenesis. Consequently, regulation via chromatin structure (DNA plus associated histone proteins) and its potential for directing neurogenesis will be the focus of this review.

Search Strategy and Selection Criteria

The search strategy and selection criteria were limited to articles published in peer-reviewed journals. A literature review of articles was conducted by searching PubMed and Web of Science databases, updated until April 2022, searching for the following topics: histone modifications and neurogenesis, histone modifications and neurodevelopment, adult neurogenesis, Ezh2, and KMT5c. The selected articles focused on histone modifications in the context of neurogenesis and neurodevelopment and basic and translational therapeutic applications of histone enzyme modulators.

Regulation of Intrinsic Cellular Processes by Histone Modifications

Within the nucleus of each cell, genomic DNA interacts with structural proteins to form chromatin. The fundamental unit of chromatin is the nucleosome. A nucleosome is comprised of 146 base pairs of DNA wrapped approximately 1.7 times in left-handed super-helical turns around a “core” of 8 histone proteins. The core is comprised of 4 related core histone proteins denoted H2A, H2B, H3, and H4. Each core contains 2 copies of each core histone protein to form a histone octamer containing 2 H2A, 2 H2B, 2 H3, and 2 H4 proteins. The core histone proteins are arranged into an (H3-H4), tetramer flanked by two H2A-H2B dimers to form the cylinder-like “core” around which DNA wraps. Core histones contain a globular C-terminal domain and an N-terminal tail that extends away from a histone core (Podobinska et al., 2017).

The N-terminal tail of each core histone protein is the site of numerous post-translational modifications (PTMs). Each histone PTM is highly associated with a specific effect on chromatin structure and consequently influences the expression of nearby genes. Additionally, multiple modifications are often added concurrently and interact with one another in agonistic or antagonistic ways. The shear breadth of histone PTMs and the outcomes of different PTM combinations has led to the “histone code” hypothesis. This model states that different combinations of histone PTMs confer different chromatin states. A
Histone code suggests that each type of PTM can be recognized by one or more effector molecules. Such a hypothesis conceptually echo's the view of the "genetic code" which provides rules to interpret linear sequences of DNA into genotypic information. Thus epigenetic modifications convey information about a chromatin state to transcriptional machinery (Baker, 2011). Indeed, recent evidence indicates that transcription factors not only recognize DNA sequence motifs but also read the epigenetic state of chromatin when initiating gene expression (Hughes and Lambert, 2017).

One mechanism of histone PTMs is regulating the accessibility of DNA to transcription factors and RNA polymerase binding. Histone cores and genomic DNA are not covalently bound together; the spatial relationship of histones and DNA is dynamic. Consequently, histone PTMs can affect the accessibility of multiple PTMs often displace histones along with DNA. Depending on the PTMs present, nucleosomes reversibly alternate between a form of chromatin with a high packing density (heterochromatin) and a form with low packing density (euchromatin). By altering combinations of histone modifications within the same genomic region, histone PTMs can alter the structure of chromatin. Because the highly dense form of chromatin is inaccessible to DNA binding proteins, all genes contained within the region are often repressed. In contrast, the low nucleosome density associated with chromatin activation marks promotes open chromatin and transcriptional activity. In sum, histone PTMs regulate gene expression by altering the accessibility of transcription proteins to DNA via reversibly switching between heterochromatin and euchromatin states that allows changing and resetting cell fate capability within germline cells and multipotent lineage progenitors, such as neural stem progenitor cells. These PTMs consist of acetylation, methylation, phosphorylation, ubiquitination, and ubiquitin conjugation of histones (Ponder et al., 2017).

While the addition of acetyl groups to the aforementioned histone tails renders chromatin for activation, the site-specific addition of methyl groups can signify the active, poised, or repressed status of gene expression. For example, tri-methylation on histone 3 lysine 4 (H3K4me3) is associated with poised or active gene expression, whereas tri-methylations at histone 3 lysine 9 (H3K9me3) and lysine 27 (H3K27me3) as well as at histone 4 lysine 20 (H4K20me3) suppress gene expression.

Histone methylation is the reversible process of transferring methyl groups onto the N-terminal tail of core histones, often at lysine or arginine residues. Up to three methyl groups are transferred onto an arginine or a lysine, respectively. There are two main enzymes that catalyze histone methylation (HMTs) transfer a methyl group to lysine or arginine positions. Lysine-specific HMTs are further subdivided into SET domain HMTs and non-SET domain containing HMTs. The vast majority of HMTs are lysine-specific and part of the SET domain superfamily proteins. The SET domain is a large family of enzymes named after the first three HMTs identified in D. melanogaster. Suppressors of variegation 3–9 (Su(var)3-9), enhancer of zeste (E(z)), and trithorax (Trx) (Dillon et al., 2005; Bennett et al., 2017; Zhu et al., 2020; Sterpe et al., 2021; Michurina et al., 2022). The catalytic mechanism of SET domain enzymes involves transferring a methyl group from S-adenosyl-L-methionine to a lysine residue in the SET domain. In general, histone modifications are actively removed by one of two groups of lysine-specific demethylases (LSD). Members of the first group, LSD1, are flavin adenine dinucleotide dependent amine oxidases. Members of the second group, the Jumonji domain containing enzymes (JmJC) act on methyl groups and are further divided into seven subgroups: JHD1M, JHD2M, JHD3M/JMD2, JARID, JmIC domain only, PHF2/PHF8 and UTX/UTX (Khare et al., 2012).

The remaining sections will focus on three chromatin modifiers relevant to regulating neuronal stem cell proliferation and/or differentiation and may represent therapeutic targets. Enhancer of zeste homolog 2 (Ezh2) catalyzes tri-methylation on histone 3 lysine 27 (H3K27me3). Suppressor of variegation 4-20 homologs (KMT5B (human)/Suv4-20h1 (mouse) and KMT5C (human)/Suv4-20h2 (mouse)) catalyze tri-methylation on histone 4 lysine 20 (Suv4-20h/H4K20me3). Nuclear receptor binding SET domain protein (NSD) family, such as NSD1, which methylate H3K36. These enzymes have been well characterized in other tissues but may have novel roles in the brain or have clinical relevance in neuro-regeneration. These enzymes have been well characterized in other tissues but may have novel roles in the brain or have clinical relevance in neuro-regeneration.
while sorting single cells has enormous potential in expanding the types of cellular components that can be characterized by single-cell sequencing, furthering the high throughput capability to glean cell type signals from heterogeneous stem cell niches and complex tissue microarchitectures. Using this cutting-edge technology, the authors found that Ezh2/H3K27me3 and Suz4-20h/H3K27me3 co-regulate developmentally critical genes required for the maintenance of undifferentiated mitotic neural stem progenitor cells, possessing high cell fate capacity. Assessing potential modulators of Ezh2 and/or Suz4-20h may prove a useful method of reprogramming neural cell lineages or increasing neurogenic activity in the hippocampus.

Distinct Roles of Ezh2/Suz4-20h during Adult Neurogenesis

The individual roles of the histone modifiers Ezh2 and Suz4-20h had been characterized less in the adult brain, particularly in the adult SVZ and the DG of the hippocampus. A recent report utilized stereotaxic injection to administer peptide tagged-Cre protein into targeted brain regions, the SVZ and the DG, to assess the long-term in vivo effect of region-specific knockout of Ezh2 or Suz4-20h (Rhodes et al., 2018). The finding demonstrated distinct roles of two chromatin repressors; Ezh2 plays an important role in the maintenance of the neural stem progenitor cell population while Suz4-20h regulates the cell cycle in these adult neurogenic niches (Figure 1). This Cre protein-based approach presents a technical breakthrough that offers myriad tightly controlled knockouts in multiple cell types simultaneously for studying many other regulatory mechanisms and is optimal for region-specific manipulation within complex, heterogeneous tissue architectures.

Taken together, the roles of histone modifications in regulating hippocampal development and adult neurogenesis make these epigenetic mechanisms attractive therapeutic targets for neuronal regeneration, especially in neurodegenerative and neurodevelopmental disorders (Pereira et al., 2010; Feng et al., 2016; Pursani et al., 2017; Yu et al., 2017).

Cross-regulation between EZH2/PRC2 and the Nuclear Receptor Binding SET Domain Protein Family of Histone H3K36 Methyltransferases

Underlies the Mechanism of Oncohistone Mutations in Pediatric Gliomas

Histone H3.3 mutation (H3F3A) occurs in 50% of cortical pediatric high-grade gliomas, impairing H3K36me3, altered H3K27me3 enrichment, contributing to genetic instability, favoring a brain tumor phenotype and signature associated with tumorigenesis (Suzuki et al., 2017). Further, nuclear receptor binding SET domain protein 1 (NSD1) which catalyzes H3K36 methylation is frequently mutated in head and neck squamous cell carcinoma, the sixth most common cancer by incidence, and a leading cause of cancer-related death (Brennan et al., 2017). NSD1 is a repressor gene and has been implicated in the development of several cancer types. NSD1 is therefore among several epigenetic modifying enzymes (such as NSD2, DNMT3a, SETD2, and Ezh2) that represent causative genes for developmental growth disorders that are also frequently mutated in cancer (Brennan et al., 2017).

NSD1 is a SET-domain containing histone methyltransferase, which catalyzates methylation of histone 3 at lysine 36 (H3K36). Intriguingly, H3K36 methylation is bound by polycomb repressive complex 2 (PRC2) which contains Ezh2. This is done through accessory components PHF1 and PHF19 engaging H3K36 methylated regions with their Tudor motifs (Cai et al., 2013). In addition, the Hoxb5/Hoxb6 gene locus and differentiation-associated genes (Otx2, Hoxa5, Fgf15, and Meis1) are selectively H3K27me3 enriched by PRC2 via the Tudor domain of PHF1 and PHF15 (Suzuki et al., 2017). This suggests that indirect interactions between EZH2/PRC2 and the NSD family members co-regulate developmentally critical genes that interact destructively to take place in adult forms of brain tumors, where increased enrichment of H3K27me3 and H3K36me3 occur in MIR-classified SVZ-associated glioblastomas (Lin et al., 2017).

The potential for crosstalk between EZH2/PRC2 and the NSD family of histone H3K36 methyltransferases is a very intriguing topic. Both histone modification families, the SET domain superfamily containing EZH2 and the NSD family, are very pertinent to neuronal development as well as neuronal stem cell proliferation, differentiation, and plasticity and likely represent pharmacological targets for drug discovery, either individually or in combination.
References
Alkaslasi MR, Piccus ZE, Hareendran S, Silberberg H, Chen L, Zhang Y, Petros TJ, Le Pichon CE (2021) Single nucleus RNA-sequencing defines unexpected diversity of cholinergic neuron types in the adult mouse spinal cord. Nat Commun 12:2471.
Allaway KC, Gabitto MI, Wapinski O, Saldi G, Wang CY, Bandler RC, Wu SJ, Bonneau R, Fishell G (2021) Genetic and epigenetic coordination of cortical interneuron development. Nature 597:693-697.
Alvarez-Buylla A, Lim DA (2004) For the long run: maintaining germinal niches in the adult brain. Neuron 41:683-686.
Ardvisson A, Collin T, Kirk D, Kokaia Z, Lindvall O (2002) Neuronal replacement from endogenous precursors in the adult brain after stroke. Nat Med 8:963-970.
Baker M (2011) Making sense of chromatin states. Nat Methods 8:717-722.
Bennett RL, Swaroop A, Troche C, Licht JD (2017) The role of nuclear receptor-binding SET domain family histone lysine methyltransferases in cancer. Cold Spring Harb Perspect Med 7:a026708.
Brennan K, Shin JH, Tay JK, Prunello M, Gentles AJ, Sunwoo JB, Gevaert O (2017) NSO1 inactivation defines an immune cold, DNA hypomethylated subtype in squamous cell carcinoma. Sci Rep 7:17064.
Cai L, Rothbart SB, Lu R, Xu B, Chen WY, Tripathy A, Rockowitz S, Zheng D, Patel DJ, Allis CD, Strahl BD, Song L, Wang GG (2013) An H3K36 methylation-engaging Tudor motif of polycomb-like proteins mediates PRC2 complex targeting. Mol Cell 49:571-582.
Chan KM, Fang D, Gan H, Hashizume R, Yu C, Schroeder M, Gupta N, Mueller S, James CD, Jenkins R, Sarkaria J, Zhang Z (2013) The histone H3.K27M mutation in pediatric glioma reprograms H3K27 methylation and gene expression. Genes Dev 27:985-990.
Chang KC, Rhodes CT, Zhang JQ, Rockowitz S, Zheng D, Patel DJ, Allis CD, Strahl BD, Song L, Wang GG (2013) An H3K36 methylation-engaging Tudor motif of polycomb-like proteins mediates PRC2 complex targeting. Mol Cell 49:571-582.
Collin T, Arvidsson A, Kokaia Z, Lindvall O (2005) Quantitative analysis of the generation of different striatal neuronal subtypes in the adult brain following excitotoxic injury. Exp Neurol 195:71-80.
Dillon SC, Zhang X, Trievel RC, Cheng X (2005) The SET-domain protein superfamily: histone lysine methyltransferases. Genome Biol 6:227.
Ekins TG, Mahadevan V, Zhang Y, D’Amour JA, Agul K, Petros TJ, McBain CJ (2020) Emergence of non-canonical parvalbumin-containing interneurons in hippocampus of a murine model of type I lissencephaly. Elife 9:e62373.
Ernst A, Alkass K, Bernard S, Salehpour M, Perl S, Gartner ZJ, Abate AR (2017) Printed droplet microfluidics for ondemand dispensing of picoliter droplets and cells. Proc Natl Acad Sci U S A 114:8728-8733.
Feng X, Juan AH, Wang HA, Ko KD, Zare H, Sartorelli V (2016) Polyclom Ezh2 controls the fate of GABAergic neurons in the embryonic cerebellum. Development 143:1971-1980.
Filippov V, Kronenberg G, Pinveva T, Reuter K, Steiner B, Wang LP, Yamaguchi M, Kettenmann H, Kempermann G (2003) Subpopulation of nestin-expressing progenitor cells in the adult murine hippocampus shows electrophysiological and morphological characteristics of astrocytes. Mol Cell Neurosci 23:373-382.
Flitsch LJ, Laumann KE, Brustle O (2020) Transcription factor-based fate specification and forward programming for neural regeneration. Front Cell Neurosci 14:121.
Franjic D, Skarcia M, Ma S, Arellano JJ, Tebbenkamp ATN, Choi J, Xu C, Li Q, Morozov YM, Andrijevic D, Vrslajs Z, Spajic A, Santpere G, Li M, Zhang S, Liu Y, Spurrier J, Zhang L, Gudeli J, Rapan L, et al. (2022) Transcriptional taxonomy and neurogenic trajectories of adult human, macroaque, and pig hippocampal and entorhinal cells. Neuron 110:452-469.
Gallo V, Deneen B (2014) Glial development: the crossroads of regeneration and repair in the CNS. Neurosurgery 8:283-308.
Ganesan A, Arimond PB, Rots MG, Jeronimo C, Berdasco M (2019) The timeline of epigenetic drug discovery: from reality to dreams. Clin Epigenetics 11:174.
Golomb SM, Gucliner IH, Zhao A, Wang Q, Palakurthi B, Aleksoff J, Lopez JA, Lee SW, Yang K, Zhang S (2020) Multi-modal single-cell analysis reveals brain immune landscape plasticity during aging and gut microbiota dysbiosis. Cell Rep 33:108438.
Goritz C, Frisen J (2012) Neural stem cells and neurogenesis in the adult. Cell Stem Cell 10:657-659.
Gottz M, Huttner WB (2005) The cell biology of neurogenesis. Nat Rev Mol Cell Biol 6:777-788.
Guillemot F (2007) Cell fate specification in the mammalian telencephalon. Prog Neurobiol 83:37-52.
Habib N, Avraham-Davidi I, Basu A, Burks T, Shekhar K, Hofree M, Choudhury SR, Aquet Y, Geld ef A, Adikie K, Weitz DA, Rozenblatt-Rosen O, Zhang R, Regev A (2017) Massively parallel single-nucleus RNA-seq with DroNc-seq. Nat Methods 14:955-958.
Hughes TR, Lambert SA (2017) Transcription factors read epigenetics. Science 356:489-490.
Hwang WW, Salinas RD, Siu JU, Kelley KW, Deigano RN, Paredes MF, Alvarez-Buylla A, Oldham MC, Lim DA (2014) Distinct and separable roles for EZH2 in neurogenic astroglia. Elife 3:e02439.
Ihrie RA, Alvarez-Buylla A (2011) Lake-front property: a unique germinal niche by the lateral ventricles of the adult brain. Neuro 70:674-686.
Jessberger S, Gage FH (2014) Adult neurogenesis: bridging the gap between mice and humans. Trends Cell Biol 24:558-563.
Jurboksi MP, Betto L, E KW, Patten A, Yau SY, Gil-Mohapel J (2020) Beyond the Hippocampus and the SVZ: adult neurogenesis throughout the brain. Front Cell Neurosci 14:576444.
Kalin JH, Wu M, Gomez AV, Song Y, Das J, Hayward A, Adejola N, Wu M, Panova I, Chung HJ, Kim E, Roberts HJ, Roberts JM, Prusevich P, Jeliakov J, Roy Burman SS, Fairall L, Milano C, Eroglu A, Proby CM, et al. (2018) Targeting the CoREST complex with dual histone deacetylase and demethylase inhibitors. Nat Commun 9:53.
Kase Y, Shimazaki T, Okano H (2020) Current understanding of adult neurogenesis in the mammalian brain: how does adult neurogenesis decrease with age? Inflamm Regen 40:40.
Kempermann G, Gast D, Kronenberg G, Yamaguchi M, Gage FH (2003) Early determination and long-term persistence of adult-generated new neurons in the hippocampus of mice. Development 130:391-399.
Kempermann G (2014) Off the beaten track: new neurons in the adult human striatum. Cell 156:877-881.
Khare SP, Habib F, Sharma R, Gadewal N, Gupta S, Galande S (2012) HIstome--a relational knowledgebase of human histone proteins and histone modifying enzymes. Nucleic Acids Res 40:D337-342.
Knudton SK, Kawano S, Minoshima Y, Warholic NM, Huang KC, Xiao Y, Kadowaki T, Uesugi M, Kuznetsov G, Kumar N, Wigele T, Kraus CR, Aliajn CI, Raimondi A, Waters NJ, Smith JH, Porter-Scott M, Chesworth R, Moyer MP, Copeland RA, et al. (2014) Selective inhibition of EZH2 by EPZ-6438 leads to potent antitumor activity in EZH2-mutant non-Hodgkin lymphoma. Mol Cancer Ther 13:842-854.
Kronenberg G, Reuter K, Steiner B, Brandt MD, Jessberger S, Yamaguchi M, Kempermann G (2003) Subpopulations of proliferating cells of the adult hippocampus respond differently to physiologic neurogenic stimuli. J Comp Neurol 467:455-463.
Kralj I, Ventura R (2018) Epigenetic inheritance: concepts, mechanisms and perspectives. Front Mol Neurosci 11:292.
Lee DR, Rhodes C, Mitra A, Zhang Y, Maric D, Dale RK, Petros TJ (2022) Transcriptional heterogeneity of ventricular zone cells in the ganglionic eminences of the mouse forebrain. Elife 11:e71864.
Lim DA, Huang YC, Swigut T, Mirick AL, Garcia-Verdugo JM, Wysoka J, Ernst P, Alvarez-Buylla A (2009) Chromatin remodelling factor MIL1 is essential for neurogenesis from postnatal neural stem cells. Nature 458:529-533.

Lim L, Mi D, Llorca A, Marín O (2018) Development and functional diversification of cortical interneurons. Neuron 100:294-313.

Lin CA, Rhodes CT, Lin C, Phillips JJ, Berger MS (2017) Comparative analyses identify molecular signature of MRI-classified SVZ-associated glioblastoma. Cell Cycle 16:765-775.

Mahadevan V, Mitra A, Zhang Y, Yuan X, Peltekian A, Chittajallu R, Ensaunt C, Maric D, Rhodes C, Pelkey KA, Dale R, Petros TJ, McBay CN (2021) NMADs drive the expression of neuropsychiatric disorder risk genes within GABAergic interneuron subtypes in the juvenile brain. Front Mol Neurosci 14:72609.

Maksour S, Ooi L, Dottori M (2020) More than a corepressor: the role of CoREST proteins in neurodevelopment. eNeuro 7:E1199-13.2020.

Matt SM, Zimmerman JD, Lawson MA, Bustamante AC, Uddin M, Johnson RW (2018) Inhibition of DNA methylation with zebularine alters lipopolysaccharide-induced sickness behavior and neuroinflammation in mice. Front Neurosci 12:636.

McKenzie MG, Cobbs LV, Dummer PJ, Petros TJ, Halford MM, Stacker SA, Zou Y, Fishell GJ, Au E (2019) Non-canonical Wnt signaling through Ryk regulates the generation of somatostatin- and parvalbumin-expressing cortical interneurons. Neural Prog 103:853-864.

Michurina A, Sakib MS, Kerimoglu C, Kruger DM, Islam MR, Joshi PD, Schroder S, Centeno TP, Zhou J, Pradhan R, Cha J, Xu X, Eichele G, Zeisberg EM, Kranz A, Stewart AF, Fischer A (2012) Postnatal expression of the lysine methyltransferase SETD1B is essential for learning and the regulation of neuron-enriched genes. EMBO J 41:e106459.

Ming GL, Song H (2011) Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron 70:687-702.

Moreno-Jimenez EP, Tereceros-Roncal J, Flor-Garcia M, Rabano A, Llorens-Martin M (2021) Evidences for adult hippocampal neurogenesis in humans. J Neurosci 41:2541-2553.

Nasu M, Esumi S, Hatakeyama I, Tamamaki N, Shimamura K (2021) Two-phase lineage specification of telencephalon progenitors generated from mouse embryonic stem cells. Front Cell Dev Biol 9:63381.

Natarajan R (2011) Drugs targeting epigenetic histone acetylation in vascular smooth muscle cells for restenosis and atherosclerosis. Arterioscler Thromb Vasc Biol 31:725-727.

Ninomiya M, Yamashita T, Araki N, Okano H, Sawamoto K (2006) Subventricular zone-derived neuroblasts migrate and differentiate into functional circuits. Science 225:1046-1048.

Paton JA, Nottebohm FN (1984) Neurons generated in the adult brain are recruited into functional circuits. Science 225:1046-1048.

Pereira JD, Sansom SN, Smith J, Dobenecker MW, Tarakhovsky A, Livesey FJ (2010) Ezh2, the histone methyltransferase of PRC2, regulates the balance between self-renewal and differentiation in the cerebral cortex. Proc Natl Acad Sci U S A 107:15957-15962.

Podobinska M, Szabolcs-Gadomski I, Augustyniak J, Sandvig I, Sandvig A, Buzanska I (2017) Epigenetic modulation of stem cells in neurodevelopment: the role of methylation and acetylation. Front Cell Neurosci 11:23.

Pursani V, Pethe P, Bashir M, Sampath P, Tanavde V, Bhartiy A (2017) Genetic and epigenetic profiling reveals EZH2-mediated down regulation of OCT-4 involves NR2F2 during cardiac differentiation of human embryonic stem cells. Sci Rep 7:13051.

Rhodes CT, Zunino G, Huang SA, Cardona SM, Cardona AE, Berger MS, Lemmon VP, Lin CA (2018) Region specific knock-out reveals distinct roles of chromatin modifiers in adult neurogenic niches. Cell Cycle 17:377-389.

Richards LJ, Kilpatrick TJ, Bartlett PF (1992) De novo generation of neuronal cells from the adult mouse brain. Proc Natl Acad Sci U S A 89:8591-8595.

Schuurmans C, Guillermot F (2002) Molecular mechanisms underlying cell fate specification in the developing telencephalon. Curr Opin Neurobiol 12:26-34.

Semenov MV (2019) Adult hippocampal neurogenesis is a developmental process involved in cognitive development. Front Neurosci 13:159.

Sorrells SF, Paredes MF, Cebrian-Silla A, Sandoval K, Qi D, Kelley KW, James D, Mayer S, Chang J, Augustine KJ, Chang EF, Gutierrez AJ, Kriegstein AR, Mathern GW, Oldham MC, Huang EJ, Garcia-Verdugo JM, Yang Z, Alvarez-Buylla A (2018) Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. Nature 555:377-381.

Stazi G, Taglieri L, Nicolai A, Romaneli A, Fantiotti N, Maroncelli M, Ragona R, Taurone S, Nebbirotto M, Carletti R, Artico M, Valente S, Scarpa S, Mai A (2019) Dissecting the role of novel EZH2 inhibitors in primary glioblastoma cell cultures: effects on proliferation, epithelial-mesenchymal transition, migration, and on the pro-inflammatory phenotype. Clin Epigenetics 11:173.

Stripe A, Guidotti N, Northall SJ, Kilic S, Hainard A, Vadas O, Fierz B, Schalch T (2021) SUV39 SET domains mediate crosstalk of heterochromatic histone marks. Elife 10:e62682.

Suzuki S, Murakami Y, Takahata S (2017) H3K36 methylation state and associated silencing mechanisms. Transcription 8:26-31.

Wester JC, Mahadevan V, Rhodes CT, Calvigioni D, Venkatesh S, Maric D, Hunt S, Yuan X, Zhang Y, Petros TJ, McBain CJ (2019) Neocortical projection neurons inhibit instructive interneuron circuit development in a lineage-dependent manner. Neuron 102:960-975.

Wu D, Qiu J, Jiao Y, Qiu Z, Liu D (2020) Small molecules targeting HATs, HDACs, and BRDs in cancer therapy. Frontiers in oncology 10:560487.

Xie W, Schultz MD, Lister R, Hou Z, Rajagopal N, Ray P, Whitaker JW, Tian S, Hawkins RD, Leung D, Yang H, Wang T, Lee AY, Swanson SA, Zhang J, Zhu Y, Kim A, Nery JR, Ulrich MA, Kuan S, et al. (2013) Epigenomic analysis of multilineage differentiation of human embryonic stem cells. Cell 153:1134-1148.

Yamashita T, Ninomiya M, Hernandez Acosta P, Garcia-Verdugo JM, Sanabria T, Sakaguchi M, Adachi K, Kojima T, Hirota Y, Kawase T, Araki N, Abe K, Okano H, Sawamoto K (2006) Subventricular zone-derived neuroblasts migrate and differentiate into mature neurons in the post-stroke adult striatum. J Neurosci 26:6627-6636.

Yu Y, Deng Y, Yu B, Zymianski JM, Aghaloo T, Hong C, Wang CY (2017) Inhibition of EZH2 promotes human embryonic stem cell differentiation into mesoderm by reducing H3K27me3. Stem Cell Reports 9:752-761.

Zhang C, Macchi F, Magnani E, Sadler KC (2021) Chromatin states shaped by an epigenetic code confer regenerative potential to the mouse liver. Nat Commun 12:4110.

Zhang H, Zhu D, Zhang Z, Kaluz S, Yu B, Devis NS, Olson JJ, Van Meir EG (2020a) EZH2 targeting reduces medulloblastoma growth through epigenetic reactivation of the BAII/p53 tumor suppressor pathway. Oncogene 39:1041-1048.

Zhang J, Ji F, Liu Y, Lei X, Li H, Ji G, Yuan Z, Jiao J (2014) Ezh2 regulates adult hippocampal neurogenesis and memory. J Neurosci 34:5184-5199.

Zhang JQ, Siltanen CA, Liu L, Chang KC, Gartner ZI, Abate AR (2020b) Linked optical and gene expression profiling of single cells at high-throughput. Genome Biol 21:49.

Zhu Y, Sun D, Jakovecvisi M, Jiang Y (2020) Epigenetic mechanism of SETD2B1 in brain: implications for neuropsychiatric disorders. Transl Psychiatry 10:115.