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Review article

Histone modifications in neurodifferentiation of embryonic stem cells

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ABSTRACT

Post-translational modifications of histone proteins regulate a long cascade of downstream cellular activities, including transcription and replication. Cellular lineage differentiation involves large-scale intracellular signaling and extracellular context. In particular, histone modifications play instructive and programmatic roles in central nervous system development. Deciphering functions of histone could offer feasible molecular strategies for neural diseases caused by histone modifications. Here, we review recent advances of *in vitro* and *in vivo* studies on histone modifications in neural differentiation.

1. Introduction

Embryonic stem cells (ESCs) are pluripotent cells derived from inner cell mass (ICM) of the early mammalian blastocysts (Evans and Kaufman, 1981; Thomson et al., 1998). ESCs are a promising tool to study early developmental events and possess great potential in regenerative medicines (Adefuin et al., 2014; Amit et al., 2000; Boyer et al., 2005). During embryonic development, ICM differentiates into all three primary germ layers, including ectoderm, mesoderm, and endoderm and subsequently gives rise to all cell types of the adult body (Gaspar-Maia et al., 2011; Meshorer, 2007), including cells of the central nervous system (CNS) (Gage, 2000). The pluripotency of ESCs is tightly regulated by the core transcriptional circuitry that consists of Nanog, Oct4, and Sox2 (Jaenisch and Young, 2008; Young, 2011). Therefore, differentiation of ESCs must initiate a distinct set of lineage-specific genes while silencing these pluripotency genes.

In striking contrast, neural stem cells (NSCs) are multipotent stem cells that can give rise to three neural types cells: neurons, astrocytes, and oligodendrocytes (Gage, 2000; Temple, 2001). Embryonic NSCs arise from the ectodermal germ layer of the early embryo and distribute into the subgranular zone (SGZ) of the hippocampus and the subventricular zone (SVZ) (Gage, 2000). NCSs initially expand their population by symmetric division. Subsequently, the cells undergo asymmetric division to produce neurons at the neurogenic phase and differentiate into glial cells in gliogenesis (Hirabayashi and Gotoh, 2010). Embryonic neurogenesis provides a global architectural framework to support the CNS development, while adult neurogenesis maintains a long-term quiescent state for the CNS. The neuroepithelium is generated from the neural plates and neural tubes and then sequentially aligns along with the apical-apical axis (Gotz and Huttner, 2005). The neuroepithelial cells differentiate into radial glial cells (RGCs) which produce neural progenitor cells (NPCs). In this process, the RGCs lose the epithelial properties. Meanwhile, they obtain neural-lineage properties and produce nascent neural-specific cells (Broccoli et al., 2015). Interestingly, in the embryonic neurogenesis process, histone modifications are associated with either gene activation or suppression. Histone acetylation and methylation play important roles in embryonic neurogenesis. For example, abnormal neural acetylation arises to severe neural tube closure defects in mice (Partanen et al., 1999). In addition, deletion of the histone methyltransferase Ezh2 induces the neural differentiation in the cerebral cortex thought inhibiting the histone H3K27me3 in cortical progenitor cells (Chou et al., 2011). These evidences have shown that histone modifications are highly involved in the embryonic neurogenesis.

Neural lineage cells respond to intrinsic and extrinsic signals to alter their chromatin structure to activate or silence the gene expression in neurogenesis (Juliandi et al., 2010a). Along with the neural differentiation of ESCs, neural lineage genes are activated in the precise time points, whereas the non-neuronal lineages are timely silenced. It is well known that gene expression is regulated by RNA polymerase II, transcriptional factors (TFs), and chromatin regulations (Jaenisch and Young, 2008; Young, 2011). Therefore, to understand the neural differentiation of ESCs, a critical issue needs to be addressed - how do chromatin modifications regulate neurodevelopment spatially and temporally? The presence of NSCs has fostered great interest due to their clinical potentials in regenerative medicine. Understanding the profound roles of histone in

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neurogenesis can provide molecular solutions for precision medicine in treating neural deformity. Here we focus on the crucial roles of histone modifications in neural differentiation of ESCs. We review the recent related advances of *in vivo* and *in vitro* findings. We also discuss chromatin-based stem cell therapies for treating neurological disorders.

2. Chromatin landscape changes of ESCs in neurogenesis

A nearly 2-meter DNA has to be fully packed within a micrometer-level nucleus to maintain a stable status during transcription and replication in eukaryotes. Nucleosomes are the fundamental units of chromatin that contain an octamer of four core histones, H2A, H2B, H3 and H4, which are wrapped by 147 bp genomic DNA and linked with each other by the linker histone, H1 (Kornberg and Thomas, 1974). The surface of the nucleosome contains amino-terminal tails of the histone, which provide the reaction site for histone to undergo multiple post-translational modifications (PTM), including acetylation, methylation, ubiquitylation, phosphorylation and sumoylation (Kouzarides, 2007). The PTMs determine the status of chromatin conformations, the accessibility of TFs, and the recruitment of chromatin remodeling. Hence, each histone modification contributes to either transcriptional activation or inactivation. Acetylation and phosphorylation have a strong propensity to activate the gene expression through unfastening the chromatin condensation. Methylation and ubiquitination, on the other hand, play dual roles in gene activation and suppression, and sumoylation is related to gene repression. Together, post-translational modifications of histone proteins contributes to species diversity and a higher order of chromatin structure (Kouzarides, 2007). Therefore, although nucleosomes are structural repeating units, the transcription status can be completely different due to diverse histone modifications.

ChIP-seq results have demonstrated that many developmental genes in ES cells are marked by both histone H3K4me3 and histone H3K27me3, which are catalyzed by TrxG and PcG complex respectively (Azuara et al., 2006; Bernstein et al., 2006; Pan et al., 2007; Zhao et al., 2007). These "bivalent marks" can regulate the transcriptional state of cell-lineage genes in a poised status. Importantly, the dynamic changes of these bivalent marks can secure ESCs to differentiate into specific lineages in a spatial and temporal manner.

A bivalent domain contains large regions of histone H3K27me3 and smaller regions of H3K4me3 that maintain the lineage genes at a low level (Bernstein et al., 2006). It has been shown that massive neural lineage-specific genes are activated by losing the repressive histone H3K27me3 during neurodevelopment (Broccoli et al., 2015). *In vivo* study has displayed that neural methylation on 5hmC antagonizes to the H3K27me3 in the early neurodevelopment of ESCs (Hahn et al., 2013). Therefore, the bivalent marks provide the molecular interface between gene and cellular cues. They control cell lineage differentiation under regional and temporal manners.

3. Histone acetylation promotes neurodifferentiation

Histone acetylation occurs on histone H2A, H2B, H3 and H4. However, acetylation on histone H3 and H4 is thought to play key roles in neurodevelopment. Acetylation of histone H3 on the lysine residues 9, 14, 18 and 23, while acetylation of histone H4 occurs on lysine residues 5, 8,1 2, 16 (Renthal and Nestler, 2009). Acetylation and deacetylation are a dynamic reversible process mediated by two classes of antagonistic enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs) (Wang et al., 2009b). In histone acetylation, the negative charge of DNA is neutralized by positive charge of acetylated histone. The electrostatic affinity is effectively decreased to relax the higher order of the chromatin condensation. Therefore, transcriptional factors and the RNA polymerase II are allowed to bind to the DNA to promote the transcription. On the other hand, histone deacetylation condenses the chromatin by packing up the DNA and terminates the transcriptional activities. Remarkably, applying ChIP-seq technology is able to predict the heterologous density distribution of nucleosomes. Compared with the upstream regions of the inert gene, the density of the nucleosome of activated genes is significantly downregulated (van Leeuwen and van Steensel, 2005). In other words, gene activation is implicated with the reduction of nucleosome density. The dynamic equilibrium of histone acetylation allows the gene adapt the developmental cues. HATs are considered as epigenetic "writers" that promote the gene expression in the cellular cues. Conversely, HDACs presumably function as epigenetic "erasers" that are implicated in gene repression (Bonnaud et al., 2016).

There are three super-families of HATs: the p300/CBP family, the MYST family and the GNAT family (Liu et al., 2017). Similarly, HDATs are classified into three classes depending on deacetylation pathways (Liu et al., 2017).

CBP/p300 family. HATs in CBP/p300 family are actively involved in mammalian embryonic neurodevelopment. They promote the embryonic spinal neurons differentiation thought regulating Isl1 (Toch and Clotman, 2019). Deletion of CBP/p300 in mouse embryos leads to severe neural tube closure defect (Partanen et al., 1999) and eventually embryonic lethality (Tanaka et al., 2000). During neural differentiation of ESCs, CBP/p300 family drives ESCs to differentiate into three neural lineages which positively correlate with the histone acetylation on H3 (Wang et al., 2010). They promote the transcriptional activity of Smad2-Smad4 complex in TGF signaling (Janknecht et al., 1998). Activation of STAT3 by CBP/p300 complex stimulates the gene expression astrocyte-specific genes and mediate the astrocytic differentiation (Chen et al., 2013). Furthermore, acetylation of the histone proteins provides the docking site for other proteins binding. CBP/p300 provides a linking site to stabilize the transcription machinery. The N-terminal of p300 bridges with STAT3 and the C-terminal of Smad1. The STAT-Smad1-p300 complex stimulates the synergistic astrocytes differentiation in fetal brain (Nakashima et al., 1999). These evidences demonstrate that histone H3 acetylation mediated by CBP/p300 is not only regulated by the substrate, but also the genomic profile or extracellular signalings.

Interestingly, genome-wide studies have shown that CBP is likely to suppress gene transcription while p300 functionally activates gene expression. The heterogeneous region of the complex provides the dual functions of CBP/p300 protein in transcriptional regulation (Ramos et al., 2010). Indeed, genome-wide mapping studies have predicted that histone acetylation is considered as a "mark" of active chromatin (Pokholok et al., 2005; Wang et al., 2009b). However, a large proportion of silent regions are distributed on the CBP/p300 protein (Holmqvist and Mannervik, 2013). Therefore, CBP/p300 may regulate the gene activity in a balanced status that controls temporal/spatial gene expression of the neural lineages.

MYST family. The fundamental functions of MYST in ESCs include maintaining the self-renewal capability and mediating the neural specification in ESCs. Similarly, MYST family members are likely to couple with other domains in paired. In this regard, the overlap of heterologous domains is functionally comparable with CBP/p300.

MOZ and QKF are among the best characterized MYST histone acetyltransferases which can regulate neural differentiation. QKF, a MYST family protein, is highly expressed in the cerebral cortex in early developing murine embryo and other undifferentiated cell populations (Thomas et al., 2000). Deficiency of QKF in developing forebrain leads to less cerebrocortical progenitor cells at early embryonic development, and fewer neurons in the preplate and cortical plate at the late stage of the neurodevelopment (Voss and Thomas, 2009). Further studies have revealed that QKF-deficient mice have fewer neural stem cells which decelerate the migrating neuroblasts in the rostral migratory stream in adult mice (Merson et al., 2006). These observations suggest that, as the member of histone acetyltransferases, QKF is indispensable in maintaining normal neural development and throughout the life.

Unlike canonical histone acetylation in gene regulation, MYST family-mediated acetylation may serve as gene silence via H4 acetylation. Evidently, MOF catalyzes H4K16 acetylation in compacting the

nucleosomal chains (Azuara et al., 2006). Dysfunction of MOF in mice may lead to a global reduction of H4K16 acetylation and embryos can fail to be implanted, subsequently gives embryonic lethal (Kloc and Ivanova, 2012). The histone H4 acetylation is quenched by the existence of Sas2p that block the localization of Sir2p by acetylating histone H4K16 in the telomere distal regions (Kimura et al., 2002). The participation of the MYST family in cellular activities shows their divergent roles in gene regulation. Together, the abnormal expression of MYST protein causes embryonic defects and neural diseases.

GNAT family. The discovery of GNAT family in yeast as a coactivator shows a molecular evidence of the histone acetylation in gene activation (Berger et al., 1992). The functions of GNAT significantly affect the transcription program during the eukaryote development. Aberrant activation of the GNAT superfamily may result in murine embryonic lethality and nerve closure defects. Gcn5 is highly involved in early embryogenesis and survival beyond embryonic neurodifferentiation, while knocking out of Gcn5 in mice induces rapid apoptosis and impedes the mesodermal differentiation (Xu et al., 2000). Gcn5, a typical representative of the GNAT family, maximizes the outcome of transcriptional activation through histone acetylation (Georgakopoulos and Thireos, 1992). In addition, proper neural acetylation of Gcn5 has been considered that it is required to neuronal tube closure (Lin et al., 2008). Besides, they functionally overlap with p300. Double heterozygous knock out of one allele of p300 and Gcn5 leads to embryonic lethality (Phan et al., 2005). These suggest that p300 and Gcn5 maintain the cellular survival by regulating the landscape of histone H3 acetylation.

PCAF is thought to be functional acetyltransferase and thereby regulates a set of transcriptional activities. Gcn5 and PCAF mediate H3K9 acetylation is regulated by and are enriched at the active promoters to enhance gene expression. Deletion of PCAF/Gcn5 complex globally inhibits the activity of the PCAF and H3K9 acetylation (Jin et al., 2014). The activity of p300- and PCAF-mediated HATs and subsequent histone acetylation can be suppressed by the nuclear protein DEK (Ko et al., 2006). In addition, GNAT is able to work with elongator complex and induces the H3 acetylation in a transcription-dependent manner (Han et al., 2008). Elongator is actively involved in the cytoplasm of the cortical projection neurons (Creppe et al., 2009). Deficiency of elongator postpones the radial migration and further globally decreases alpha-tubulin acetylation. In addition, Elp3 has been identified in early-branching protozoa in phylum apicomplexa which is the species that lacks any elongator proteins (Stilger and Sullivan, 2013). With the majority of the coactivators transcribed into the GNAT family, these coactivators likely contribute to neural development and activate other types of acetylation. With further ChIP profiling and state-of-art genomic mapping techniques, scientists will be able to explore more diverse and novel coactivators associated with histone acetylation in the near future.

Histone deacetylases. In contrast to HACs, HDACs dynamically attenuate gene expression by condensing chromatin, resulting in gene silencing. In general, the transcription co-repressors NRSF/REST are coupled with histone deacetylases (HDACs) (Huang et al., 1999). In ESCs, Class I and IIa HDACs are ubiquitously active during neurogenesis (Hsieh and Gage, 2004). HDAC1 is highly expressed while HDAC2 is expressed in neural progenitors and post-mitotic neurons. Strikingly, HDAC2 is not expressed in most of fully differentiated glial cells (MacDonald and Roskams, 2008). Deficiency of class I HDAC1 leads to embryonic lethality in embryonic day of 10, while deletion of class I HDAC2 mice die shortly after birth (Dovey et al., 2010). Class II HDACs are found in myogenesis and neurogenesis through depressing MEF2 signaling pathway (Qin et al., 2017).

Notably HDAC inhibitors have been widely used in biomedical applications. Typical well-documented examples include VPA, TSA, SAHA and PB (Gaub et al., 2010). VPA has been shown to specifically promote the neural progenitor cells differentiation into neurons through a bHLH transcription factor, NeuroD (Hsieh et al., 2004; Juliandi et al., 2010b). VPA-mediated HDAC inhibition activates NeuroD to induce the neural differentiation and suppress the other non-neural lineages gene expression. VPA can initiate ERK pathway by inhibiting GSK-3 or HDACs in cortical neurogenesis (Hao et al., 2004). Administration of VPA promotes the NSCs to differentiate into oligodendrocytes and myelination in a timing manner (Shen et al., 2005).

Apart from NSC differentiation, HDACs are essential for oligodendrocyte progenitor cells. By introducing of TSA, the histone deacetylation is blocked to terminate the oligodendrocyte progenitor's differentiation via chromatin compaction. On the other hand, the negatively regulation caused by the chromatin compaction may decrease myelin gene expression. Sequentially, the progenitors can be differentiated temporally (Marin-Husstege et al., 2002).

4. Histone methylation strengthens neuronal specification

Unlike histone acetylation, histone methylation can be associated with either activation or silencing of gene transcription. Diverse methylations on histone lysine/arginine residues contribute to the high order of chromatin structures. Histone H3K4me3 usually mark gene activation while histone H3K9me3 and H3K27me3 repress gene transcription. In particular, histone H3K27me3 is a key mark in regulating cells fate decision in ES cells (Agger et al., 2007; Lan et al., 2007; Schwartz and Pirrotta, 2007; Shen et al., 2008). In ESCs, histone H3K4me3 mediated by TrxG complex and histone H3K27me3 mediated by PcG complex play important roles in pluripotency and differentiation (Bracken et al., 2006; Jiang et al., 2011; Schuettengruber et al., 2017; Simboeck et al., 2013).

PcG protein. PcG proteins were originally identified in *Drosophila* in which they suppress the homeotic genes which regulate segment identity in developing embryos. PcG proteins are highly conserved from *Drosophila* to vertebrates (Sher et al., 2008). PcG proteins are essential for stem cell identity and maintenance of epigenetic memory during metazoan development (Shen et al., 2008). Depletion of PcG proteins increases the timing of neurogenic phase of the NPCs and delays the timing of the astrogenic stage (Hirabayashi et al., 2009). Depending on the genetic characteristics, PcG proteins are subdivided into two distinct complexes: PRC1 and PRC2. Deletion of the PRC2 are likely to induce neuronal differentiation in mouse ESCs, while the role of PRC1 strengthens gene suppression (Sher et al., 2011).

As PRC1 processes either a polycomb domain for histone H3K27me3 (Gao et al., 2012) or a Ring domain for ubiquitination (Wang et al., 2004), PRC1 is able to undergo the multiple histone modifications, rather than histone methylation alone. In ESCs, PRC1 recruits H3K24 through the ubiquitin ligase Ring1 for continuously PcG-mediated repression (Sher et al., 2011). The PRC2 catalyzes histone H3K27m3 is EZH-containing histone methyltransferases to form a complex (Cao et al., 2002). The complex sequentially recruits PRC1 to condense the chromatin structure and gives a long-term gene silencing (Boyer et al., 2006). On the other hand, PRC2 protein with suppressing the expression of Eed and EZH2 initiates the neural lineage markers expression. PRC2 binds with DNA regulatory elements that activate the gene transcription and initiate differentiation while suppressing the transcriptional activities timely during terminal differentiation.

Interestingly, unlike conical roles of PRC1 in gene silencing, when PRC1 recruits Aus2, the complex is able to promote the transcriptional expression in brain development. Aus2 is able to bind to various domains that undergo multiple histone modifications including histone H3 acetylation expect H3K27me3. Aus2 is also involved in the early brain development and gene activation in a timely manner to ensure proper brain development. In particular, Aus2 is highly expressed in prefrontal cortex of the brain. Aus2/PRC1 complex is a transcriptional activation rather than a conical transcriptional repression since no histone H3K27me3 is detected (Gao et al., 2014).

PRC2 contains Ezh2 (catalyzes histone H3K27me3), Eed and Suz12. Ezh2 is transcriptional repressor that is involved in the NSC differentiation into neurons and astrocytes. Deletion of Ezh2 suppresses histone H3K27me3 level in cortical progenitor cells, leading to the neural differentiation in the cerebral cortex (Chou et al., 2011). Reduction of Ezh2

drives NSCs to differentiate into nerve cells and astrocytes cells (Sher et al., 2011). Evidently, Ezh2 mutated embryos failed to be formed from the blastocyst, while lacking of Eed in ESCs were prone to differentiate (Boyer et al., 2006). On the other, Ezh2 is expressed in the NSCs in the differentiation of oligodendrocytic cell lineages from immature oligodendrocyte stage (Sher et al., 2008).

TrxG protein. In undifferentiated ESCs, large number of developmental genes are marked with both histone H3K4me3 and H3K27me3 (Jaenisch and Young, 2008; Young, 2011). H3K27me3 is mediated by PcG proteins with set of sub-units. H3K27me3 marks are reduced efficiently upon the differentiation of the developing embryo and the stem cell differentiation which means that there are some specific histone demethylases for H3K27me3 and timely response to the differentiation. TrxG family proteins mediate histone H3K4 methylation. There are six HMTs of TrxG proteins (hSet1a, hSet1b, MLL1-4), non-redundant function and SET/COMPASS domains (Schuettengruber et al., 2007). Although these proteins are structurally different, they all process the evolutionary conserved SET domains (Simboeck et al., 2013). These proteins secure the proper activation of H3K4 upon the differentiation requirement of ESCs.

In eukaryotic cells, MLL1 family comprised of the SET domain is the key TrxG-HMT enzymes catalyzing H3K4 methylation in the cell fate decision of NSCs (Lim et al., 2009). Genome-wide analysis identifies deletion in the MLL1 proteins slightly cause global reduction of H3K4 methylation which is attributed to redundancy among the MLL complex (Wang et al., 2009a). MLL is essential for neuronal differentiation in the subventricular zone, rather than in other neuronal lineages. Knocking down MLL1 in mice suppresses the expression of transcriptional factor, Dlx2 (Lim et al., 2009) and Brn4 (Potts et al., 2014), but not in Mash1 and Oligo2 (Brightman et al., 2018) that the promotor of Set1/COMPASS in MLL1 family is the key promotor to regulate the H3K4 methylation (Wang et al., 2009a). In other words, conditionally knock out of MLL1 in mice reduces the neurogenesis. MLL mutation allows the NSCs to survive but not in the differentiation into specific neuronal lineages. However, the global reduction of H3K4 methylation caused by MLL mutant is not completely serve (Wang et al., 2009a). So, there is another candidate to prevent the reduction in the MLL. In the regard, Dpy-30 is identified as a new member mediated by MLL proteins. Phenotypically, deletion of Dpy-30 in ESCs fails to differentiate into neural lineages (Jiang et al., 2011). Given know Dpy-30 is the substrate of all SET-domain MLL proteins as mentioned, they are proposed to involve in the H3K4 methylation directly. knocking down of Dpy-30 significantly decreases the global level of H3K4 methylation-marked active chromatin, and thereby reduce the proliferation of cells and exhibits a senescent phenotype (Simboeck et al., 2013). Indeed, Dpy-30 is less likely to promote gross methyltransferase activity *in vitro*, and gives heterotypic allosteric regulation of HMTs (Haddad et al., 2018). Therefore, TrxG is able to switch the PcG-mediated renewal status to neuronal lineage differentiation. Although TrxG are thought to work oppositely to PcG family to switch on or off the transcription, the antagonistic mechanism is still significantly diminished.

Histone demethylases. During differentiation process of ESCs to NSCs, a number of bivalent marks are resolved in the lineages specific fractions, leaving univocal signatures of either activation (H3K4me3) or repression (H3K27me3) (Burgold et al., 2008). Histone H3K27me3 is related to final transcriptional repression. On the other hand, histone methylation and demethylation are a dynamic equilibrium process. The reversible removal of H3K27me3 marks is mediated by three classes of histone demethylases, including JmjC-domain-containing proteins, Jmjd3 and UTX.

Recent studies have shown that upregulation of Jmjd3 is essential for the cell fate decision of neuronal development. Jmjd3 is required for H3K27me3 demethylation at promoter regions of Myt1, Slc32a1, and Gjb6 for transcriptional activation in NSC populations (Park et al., 2014). *In vivo* evidence shows Jmjd3-mutant mice cannot survive after birth due to the respiratory failure (Burgold et al., 2008). Jmjd3 recruits Smad3 to occupy genomic regions of TGFß-mediated repressive genes in the NSCs for proper regulation (Estaras et al., 2012). This might be caused by the elongated RNA polymerase II progression and histone H3K27me3 is enriched in these TGFß-mediated repressive genes (Estaras et al., 2013).

Similar to Jmjd3, Utx process a JmjC domain responsible to the histone demethylases. In ESCs, many factors of the HOX genes are repressed upon to differentiation, but not in UTX. Therefore, UTX is mediated by the H3K27me3. H3K27me3 is correlatedly responded to the HOX gene expression. Both JMJD3 and UTX share the HOX domain. When they are bound together to for a complex, H3K27me3 marks regulated the Utx/Jmjd3 derived to the appreciated differentiation (Agger et al., 2007). Together, these evidences predict that preserving high levels of H3K27 by inhibiting JmjC-domain-containing proteins is essential for maintain the proper neural-specific lineage differentiation of ESCs. These studies are consistent with the deletion of epigenetic regulation of repressed chromatin observed upon differentiation.

5. Other histone modifications in neurodevelopment

Histone ubiquitination. Ubiquitination is a PTM mechanism that covalently attaches ubiquitin molecules to modify the protein after the translation (Kawabe and Brose, 2011). Histone H2A and histone H2B are the most common site to undergo histone ubiquitination, particularly at lysine 119 and 123 and mono-ubiquitination of H2A is likely to compact the chromatin (Cao and Yan, 2012). Recent evidence has shown that a number of the ubiquitin ligases are effectively functional in neural lineage specification. Knocking out of an H2B ubiquitin ligase Bre1a prevents normal NPC differentiation (Ishino et al., 2014). Ubiquitination of H2A also has an effect on the differentiation of NPCs (Tsuboi et al., 2018). REST is downregulated when it is ubiquitinated thereby maintaining the proper neural differentiation (Westbrook et al., 2008).

Mono-ubiquitinated histone H2A is highly involved in the bivalent marks (Endoh et al., 2012; Srivastava et al., 2017). Histone H2A suppresses the extension of RNA polymerase located at the bivalent domains. In this case, PRC protein recruits the H2A to form a complex through ubiquitination reaction. Consequently, the H2A ubiquitination activity of the PRC proteins provides a target site for binding that compacts the chromatin (Endoh et al., 2012). Transcriptional factors such as Fbxo45 can also be ubiquitinated and this will induce neural differentiation (Saiga et al., 2009). Deletion of Fbxo45 in embryo results in neural disease and abnormal brain development (Saiga et al., 2009). Therefore, these studies have suggested that histone ubiquitination contributes to higher diversity of histone modifications which are critical to the neural differentiation.

Histone phosphorylation. Histone phosphorylation is a post-transcriptional modification of histone that control the specification of chromatin in either activation or suppression ways. Early evidence shows that high percentage of histone H1 and H3 phosphorylation presented in the cultured mammalian cells during mitosis (Gurley et al., 1974). Basically, histone phosphorylation occurs in mammalian cells with two phases: the chromatin is first highly compacted as aggregates and then access into the chromosome (Gurley et al., 1978). Unlike other histone modifications, histone phosphorylation occurs at the sites of serine and threonine residues. Phosphorylation of histone H3 at serine 10 is occurred in mitosis and meiosis in various specifies (Garcia et al., 2005) that shows high degree of spatial-temporal distribution (Sawicka and Seiser, 2012). Proper phosphorylation ensure the appreciated chromosome segregation in mitosis and chromosomes access in meiosis (Wei et al., 1999).

Phosphorylation on histone H3 at the specific residues can dynamically modulate the chromatin into either open or compact status which have neural effectives during brain development (Sawicka and Seiser, 2012). Mitogen-and stress-activated kinase 1 (MSK1) plays key roles in neurodevelopment in response to the phosphorylation of histone H3. MSK1 is a ubiquitously expressed kinase which is required for maintaining the neural plasticity of the brain (Brami-Cherrier et al., 2005). Apart from it, NSCs differentiation requires chromatin modification in presence of JNK, a MAP kinase which phosphorylates histone H3 at

Table 1. List of histone modification enzymes in embryonic stem neurodevelopment.

Category	Substrate	Functions in histone modifications	Function in neurodifferentiation	References
HATs	CBP/ p300	Essential for HATs and alter chromatin landscape in mediating neural specification.	Promotes ESCs differentiation into three neural lineages, stimulates the gene expression astrocyte-specific genes and mediate the astrocytic differentiation, stimulates the synergistic astrocytes differentiation in fetal brain.	Wang et al. (2010)
	MYST	Catalyze H4K16 acetylation.	Highly expressed in cerebral cortex in early developing murine embryo.	Merson et al. (2006); Thomas et al. (2000)
	GNAT	Acetylates with other HATs to maximize the outcome of transcriptional activation via histone acetylation, maintains cell survival via histone H3 acetylation, positively correlated with histone H4 acetylation.	Affects rapid apoptosis and impedes mesodermal differentiation, and essential for neuronal tube closure.	Georgakopoulos and Thireos (1992); Lin et al. (2008); Xu et al. (2000)
HDACs	Class I-III	Dynamically attenuate gene expression by compacting chromatin structure.	Promotes neural progenitor cells to differentiate into neurons.	Hsieh et al. (2004); Juliandi et al. (2010b)
HMTs	PcG	Regulates lineage-specific gene expression programs in ESCs.	Deletion of PRC2 likely induces neuronal differentiation in mouse ESCs while PRC1 strengthens gene suppression for neural specification.	Schuettengruber et al. (2017); Sher et al. (2011)
	TrxG	Mediates H3K4 methylation.	Catalyzes histone H3K4 methylation in cell fate decision of NSCs.	Lim et al. (2009); Wang et al. (2009a)
HDMTs		Bivalent marks are resolved in the lineage specific fractions leaving univocal signatures of either activation or repression.	Upregulating of Jmjd3 is essential for cell fate decision in neuronal development.	Agger et al. (2007); Burgold et al. (2008)
Histone ubiquitination		Covalently attaches to ubiquitin molecules to modify proteins.	Has an effect on the differentiation of NPCs	Kawabe and Brose (2011); Tsuboi et al. (2018)
Histone variants		Replace either H2A or H3.	Essential for proliferation of NSC and neuronal differentiation	Santoro and Dulac (2015); Xia and Jiao (2017)

serine 10. Downregulation of JNK in post-mitotic neurons reduces the affinity to phosphorylation of H3Ser10 (Tiwari et al., 2011). These studies suggest that Histone H3 phosphorylation significantly affects the neural functions of the brain.

Histone variants. Many metazoan proteins are synthesized by the canonical histone proteins which are encoded by the DNA replication-dependent histone genes with conventional non-polyadenylated mRNAs in the 3'stem-loop sequence (Marzluff et al., 2008). Histone variants are not replication-dependent and are transcribed from the polyadenylated mRNAs (Meshorer, 2007). Histone variant is a post posttranscriptional modification in which one or more residues at either H2A or H3 are replaced. The slightly different composition in the histones gives non-allelic isoforms of the canonical histone proteins and significant structural dissimilarities (Santoro and Dulac, 2015). Histone variant can be grouped as replication dependent, replication independent depending on the developmental patterns (Banaszynski et al., 2010).

Specific or multiple histone modifications can alter a series of downstream cellular activities in accordance with the chromatin conformation. In eukaryote, H3.3 can occur with many histone replacements during differentiation of mouse germ cells (Hajkova et al., 2008). In addition, the replacement histone H3.3 is necessary at the early stage of cranial neural crest (Cox et al., 2012). Early studies have identified that the replacement on the replication-dependent histone H3.2 with the replication-independent activates the gene expression in *Drosophila* (Ahmad and Henikoff, 2002; Hake et al., 2006). Histone H3.3 contains a serine residue on which modifications may activate the chromatin. In addition, the expression of histone H3.3 is highly involved in embryonic brain. Histone H3.3 is essential for of NSC proliferation and neuronal differentiation by activating PAX6 (Xia and Jiao, 2017). Histone variants also participate in the neural differentiation. H2A.X is significantly phosphorylated after NMDA receptor is activated in rat cortical neurons (Crowe et al., 2006). These studies indicate the essential role of histone variants in embryonic neural development.

6. Histone modifications in neurodifferentiation of induced pluripotent stem (iPS) cells

Induced pluripotent stem cells (iPS) cells have provided excellent platforms for disease modeling, drug screening and other clinical applications (Shi et al., 2017). Based on the high similarity between iPS cells and ES cells, scientists have successfully differentiated iPS cells into nerve cells in vitro (Wernig et al., 2008; Chambers et al., 2009; Soldner et al., 2009). However, Hu et al. found that human iPSCs utilize the same temporal program as that of hESC to differentiate into neurons but with variation and lower efficiency (Hu et al., 2010). Hence the emerging interesting question is how histone modifications play roles in neurodifferentiation of iPS cells.

Yang et al. found that HDAC3 negatively regulates the differentiation of hPSCs towards neural precursor cells (NPCs) at an earlier stage of neural differentiation. Consistently HDAC inhibitor can enhance the differentiation of human iPS cells towards neural progenitor cells (Yang et al., 2014). Another study showed that the histone H3K27ac-marked enhancer regions had more active changes than the histone H3K4 me3-marked promoters (Choi et al., 2020). Interestingly, NEUROD1 concerts iPSC differentiation to NPC by interacting with the accessible enhancer regions (Choi et al., 2020). These reports support that histone acetylation has positive role in directing iPS cells into neural lineages.

Meng et al. discovered that Inhibition of KDM6 (histone H3K27me3 demethylase) can improve neuroectoderm induction from both ES cells and iPS cells (Meng et al., 2021). In addition, deletion of KMT2D (encoding histone H3K4 methyltransferase) may cause precocious iPSC-derived neuronal maturation due to transcriptional suppression of metabolic genes and proliferation defects (Carosso et al., 2019). These studies suggest that histone methylation play important roles in neurodifferentiation of iPS cells.

It must be noted that until now, not many studies have been focused on roles of histone modifications in neurodifferentiation of iPS cells. For better personized iPS cell therapy, more efforts should be put into investigating how histone modifications are exactly involved in this process.

7. Concluding remarks

Researches over past decades have clearly established the crucial roles of histone modifications in neurodifferentiation in embryos and ESCs (Table 1). However, some open and intriguing issues are still remained. First, the environmental interventions, such as oxidation stress, in histone modifications will be an intriguing issue. Second, it will

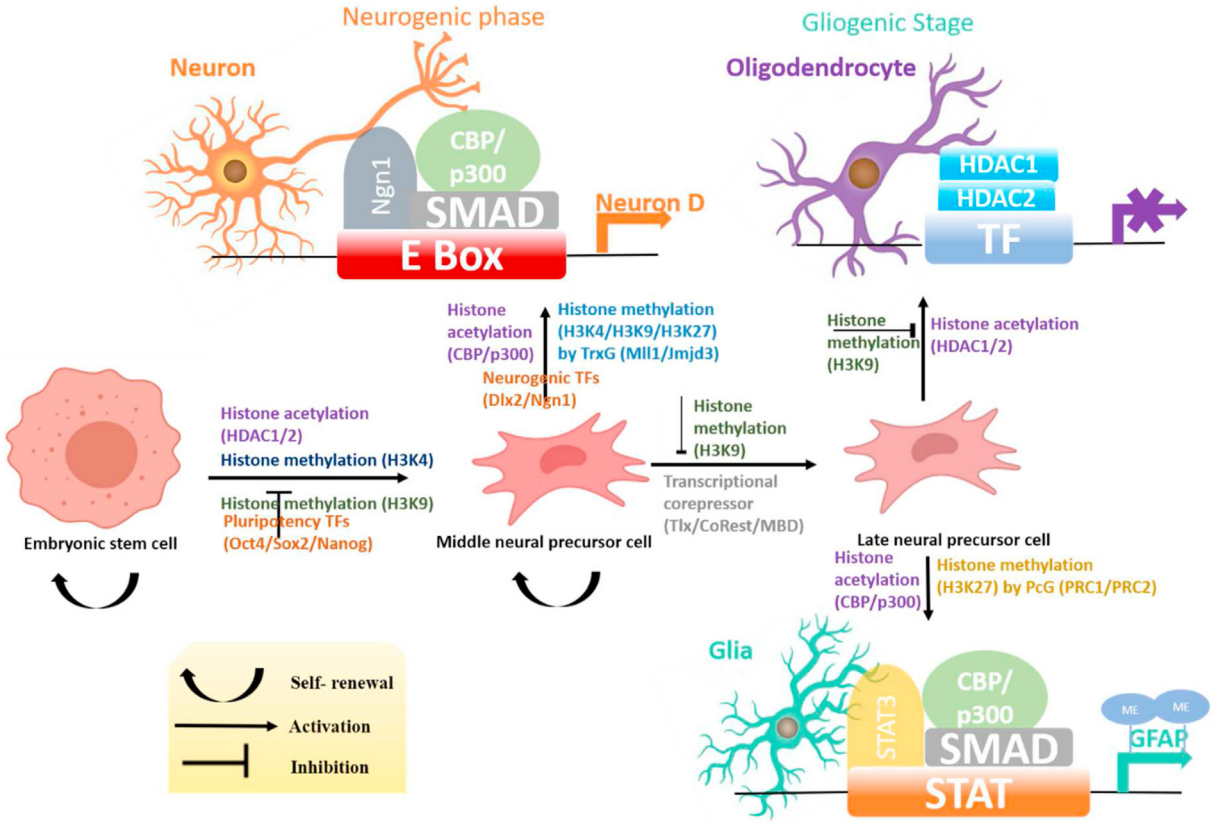

Figure 1. Neurodifferentiation is regulated by histone modifications. Initially, ESCs exit from pluripotency while bivalent histone marks are changing. In neurogenesis process, both histone acetylation and histone methylation play roles in neurodifferentiation of ESCs. In the neurogenic phase, the neurogenic TFs drives neuron formation. Second, CBP/p300 binds to SMAD and Ngn1 to the E Box domain to eventually activate the neuron D expression. TrxG proteins catalyze histone H3K4 methylation to promote neuronal specification. Third, neural precursor cells are associated with relative repressive chromatin, which is represented by deacetylation of histones and histone H3K9 methylation. Finally, neural precursor cells differentiate into more cells types to complete the development of the CNS. Histone deacetylation is involved in strengthening oligodendrocyte specification with repressive histone H3K9 methylation. In glia cells, CBP/p300 recruits SMAD to activate STAT signaling to activate GFAP.

be important to explore the redistribution of histone modifications in cell sub-populations. Third, identification of novel histone modifying enzymes and more types of histone modifications will not only be beneficial to understanding the nature of histones but also can contribute to the precision medicine for neural diseases. Further studies on specific histone functions in neurodifferentiations may delineate the mechanisms of neural development and provide new insights into therapeutic strategies.

In summary, neurodifferentiation is a complicated process that requires concerted effects of multiple signaling pathways and transcription regulation. Post-translational modifications of histones secure neural differentiation in a spatial and temporal manner by controlling the correlated gene expression (Figure 1). Aberration of histone modifications impairs proper neural differentiation and results in neural diseases. Hence further studies are required to develop novel epigenetic strategies for neuro diseases.

Declarations

Author contribution statement

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Additional information

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References

Adefuin, A.M., Kimura, A., Noguchi, H., Nakashima, K., Namihira, M., 2014. Epigenetic mechanisms regulating differentiation of neural stem/precursor cells. Epigenomics 6, 637–649.

Agger, K., Cloos, P.A., Christensen, J., Pasini, D., Rose, S., Rappsilber, J., Issaeva, I., Canaani, E., Salcini, A.E., Helin, K., 2007. UTX and JMJD3 are histone H3K27 demethylases involved in HOX gene regulation and development. Nature 449, 731–734.

Ahmad, K., Henikoff, S., 2002. The histone variant H3.3 marks active chromatin by replication-independent nucleosome assembly. Mol. Cell 9, 1191–1200.

Amit, M., Carpenter, M.K., Inokuma, M.S., Chiu, C.P., Harris, C.P., Waknitz, M.A., Itskovitz-Eldor, J., Thomson, J.A., 2000. Clonally derived human embryonic stem cell lines maintain pluripotency and proliferative potential for prolonged periods of culture. Dev. Biol. 227, 271–278.

Azuara, V., Perry, P., Sauer, S., Spivakov, M., Jorgensen, H.F., John, R.M., Gouti, M., Casanova, M., Warnes, G., Merkenschlager, M., et al., 2006. Chromatin signatures of pluripotent cell lines. Nat. Cell Biol. 8, 532–538.

Banaszynski, L.A., Allis, C.D., Lewis, P.W., 2010. Histone variants in metazoan development. Dev. Cell 19, 662–674.
Berger, S.L., Pina, B., Silverman, N., Marcus, G.A., Agapite, J., Regier, J.L., Triezenberg, S.J., Guarente, L., 1992. Genetic isolation of ADA2: a potential transcriptional adaptor required for function of certain acidic activation domains. Cell 70, 251–265.
Bernstein, B.E., Mikkelsen, T.S., Xie, X., Kamal, M., Huebert, D.J., Cuff, J., Fry, B., Meissner, A., Wernig, M., Plath, K., et al., 2006. A bivalent chromatin structure marks key developmental genes in embryonic stem cells. Cell 125, 315–326.
Bonnaud, E.M., Suberbielle, E., Malnou, C.E., 2016. Histone acetylation in neuronal (dys) function. Biomol. Concepts 7, 103–116.
Boyer, L.A., Lee, T.I., Cole, M.F., Johnstone, S.E., Levine, S.S., Zucker, J.P., Guenther, M.G., Kumar, R.M., Murray, H.L., Jenner, R.G., et al., 2005. Core transcriptional regulatory circuitry in human embryonic stem cells. Cell 122, 947–956.
Boyer, L.A., Plath, K., Zeitlinger, J., Brambrink, T., Medeiros, L.A., Lee, T.I., Levine, S.S., Wernig, M., Tajonar, A., Ray, M.K., et al., 2006. Polycomb complexes repress developmental regulators in murine embryonic stem cells. Nature 441, 349–353.
Bracken, A.P., Dietrich, N., Pasini, D., Hansen, K.H., Helin, K., 2006. Genome-wide mapping of Polycomb target genes unravels their roles in cell fate transitions. Genes Dev. 20, 1123–1136.
Brami-Cherrier, K., Valjent, E., Herve, D., Darragh, J., Corvol, J.C., Pages, C., Arthur, S.J., Girault, J.A., Caboche, J., 2005. Parsing molecular and behavioral effects of cocaine in mitogen- and stress-activated protein kinase-1-deficient mice. J. Neurosci. 25, 11444–11454.
Brightman, D.S., Grant, R.L., Ruzycki, P.A., Suzuki, R., Hennig, A.K., Chen, S., 2018. MLL1 is essential for retinal neurogenesis and horizontal inner neuron integrity. Sci. Rep. 8, 11902.
Broccoli, V., Colasante, G., Sessa, A., Rubio, A., 2015. Histone modifications controlling native and induced neural stem cell identity. Curr. Opin. Genet. Dev. 34, 95–101.
Burgold, T., Spreafico, F., De Santa, F., Totaro, M.G., Prosperini, E., Natoli, G., Testa, G., 2008. The histone H3 lysine 27-specific demethylase Jmjd3 is required for neural commitment. PLoS One 3, e3034.
Cao, J., Yan, Q., 2012. Histone ubiquitination and deubiquitination in transcription, DNA damage response, and cancer. Front. Oncol. 2, 26.
Cao, R., Wang, L., Wang, H., Xia, L., Erdjument-Bromage, H., Tempst, P., Jones, R.S., Zhang, Y., 2002. Role of histone H3 lysine 27 methylation in Polycomb-group silencing. Science 298, 1039–1043.
Carosso, G.A., Boukas, L., Augustin, J.J., Nguyen, H.N., Winer, B.L., Cannon, G.H., Robertson, J.D., Zhang, L., Hansen, K.D., Goff, L.A., et al., 2019. Precocious neuronal differentiation and disrupted oxygen responses in Kabuki syndrome. JCI Insight 4.
Chambers, S.M., Fasano, C.A., Papapetrou, E.P., Tomishima, M., Sadelain, M., Studer, L., 2009. Highly efficient neural conversion of human ES and iPS cells by dual inhibition of SMAD signaling. Nat. Biotechnol. 27, 275–280.
Chen, E., Xu, D., Lan, X., Jia, B., Sun, L.C., Zheng, J., Peng, H., 2013. A novel role of the STAT3 pathway in brain inflammationinduced human neural progenitor cell differentiation. Curr. Mol. Med. 13, 1474–1484.
Choi, W.Y., Hwang, J.H., Cho, A.N., Lee, A.J., Jung, I., Cho, S.W., Kim, L.K., Kim, Y.J., 2020. NEUROD1 intrinsically initiates differentiation of induced pluripotent stem cells into neural progenitor cells. Mol. Cell. 43, 1011–1022.
Chou, R.H., Yu, Y.L., Hung, M.C., 2011. The roles of EZH2 in cell lineage commitment. Am. J. Transl. Res. 3, 243–250.
Cox, S.G., Kim, H., Garnett, A.T., Medeiros, D.M., An, W., Crump, J.G., 2012. An essential role of variant histone H3.3 for ectomesenchyme potential of the cranial neural crest. PLoS Genet. 8, e1002938.
Creppe, C., Malinouskaya, L., Volvert, M.L., Gillard, M., Close, P., Malaise, O., Laguesse, S., Cornez, I., Rahmouni, S., Ormenese, S., et al., 2009. Elongator controls the migration and differentiation of cortical neurons through acetylation of alpha-tubulin. Cell 136, 551–564.
Crowe, S.L., Movsesyan, V.A., Jorgensen, T.J., Kondratyev, A., 2006. Rapid phosphorylation of histone H2A.X following ionotropic glutamate receptor activation. Eur. J. Neurosci. 23, 2351–2361.
Dovey, O.M., Foster, C.T., Cowley, S.M., 2010. Histone deacetylase 1 (HDAC1), but not HDAC2, controls embryonic stem cell differentiation. Proc. Natl. Acad. Sci. U. S. A. 107, 8242–8247.
Endoh, M., Endo, T.A., Endoh, T., Isono, K., Sharif, J., Ohara, O., Toyoda, T., Ito, T., Eskeland, R., Bickmore, W.A., et al., 2012. Histone H2A mono-ubiquitination is a crucial step to mediate PRC1-dependent repression of developmental genes to maintain ES cell identity. PLoS Genet. 8, e1002774.
Estaras, C., Akizu, N., Garcia, A., Beltran, S., de la Cruz, X., Martinez-Balbas, M.A., 2012. Genome-wide analysis reveals that Smad3 and JMJD3 HDM co-activate the neural developmental program. Development 139, 2681–2691.
Estaras, C., Fueyo, R., Akizu, N., Beltran, S., Martinez-Balbas, M.A., 2013. RNA polymerase II progression through H3K27me3-enriched gene bodies requires JMJD3 histone demethylase. Mol. Biol. Cell 24, 351–360.
Evans, M.J., Kaufman, M.H., 1981. Establishment in culture of pluripotential cells from mouse embryos. Nature 292, 154–156.
Gage, F.H., 2000. Mammalian neural stem cells. Science 287, 1433–1438.
Gao, Z., Lee, P., Stafford, J.M., von Schimmelmann, M., Schaefer, A., Reinberg, D., 2014. An AUTS2-Polycomb complex activates gene expression in the CNS. Nature 516, 349–354.
Gao, Z., Zhang, J., Bonasio, R., Strino, F., Sawai, A., Parisi, F., Kluger, Y., Reinberg, D., 2012. PCGF homologs, CBX proteins, and RYBP define functionally distinct PRC1 family complexes. Mol. Cell 45, 344–356.
Garcia, B.A., Barber, C.M., Hake, S.B., Ptak, C., Turner, F.B., Busby, S.A., Shabanowitz, J., Moran, R.G., Allis, C.D., Hunt, D.F., 2005. Modifications of human histone H3 variants during mitosis. Biochemistry 44, 13202–13213.
Gaspar-Maia, A., Alajem, A., Meshorer, E., Ramalho-Santos, M., 2011. Open chromatin in pluripotency and reprogramming. Nat. Rev. Mol. Cell Biol. 12, 36–47.
Gaub, P., Tedeschi, A., Puttagunta, R., Nguyen, T., Schmandke, A., Di Giovanni, S., 2010. HDAC inhibition promotes neuronal outgrowth and counteracts growth cone collapse through CBP/p300 and P/CAF-dependent p53 acetylation. Cell Death Differ. 17, 1392–1408.
Georgakopoulos, T., Thireos, G., 1992. Two distinct yeast transcriptional activators require the function of the GCN5 protein to promote normal levels of transcription. EMBO J. 11, 4145–4152.
Gotz, M., Huttner, W.B., 2005. The cell biology of neurogenesis. Nat. Rev. Mol. Cell Biol. 6, 777–788.
Gurley, L.R., D'Anna, J.A., Barham, S.S., Deaven, L.L., Tobey, R.A., 1978. Histone phosphorylation and chromatin structure during mitosis in Chinese hamster cells. Eur. J. Biochem. 84, 1–15.
Gurley, L.R., Walters, R.A., Tobey, R.A., 1974. Cell cycle-specific changes in histone phosphorylation associated with cell proliferation and chromosome condensation. J. Cell Biol. 60, 356–364.
Haddad, J.F., Yang, Y., Takahashi, Y.H., Joshi, M., Chaudhary, N., Woodfin, A.R., Benyoucef, A., Yeung, S., Brunzelle, J.S., Skiniotis, G., et al., 2018. Structural analysis of the Ash2L/Dpy-30 complex reveals a heterogeneity in H3K4 methylation. Structure 26, 1594–1603 e1594.
Hahn, M.A., Qiu, R., Wu, X., Li, A.X., Zhang, H., Wang, J., Jui, J., Jin, S.G., Jiang, Y., Pfeifer, G.P., et al., 2013. Dynamics of 5-hydroxymethylcytosine and chromatin marks in Mammalian neurogenesis. Cell Rep. 3, 291–300.
Hajkova, P., Ancelin, K., Waldmann, T., Lacoste, N., Lange, U.C., Cesari, F., Lee, C., Almouzni, G., Schneider, R., Surani, M.A., 2008. Chromatin dynamics during epigenetic reprogramming in the mouse germ line. Nature 452, 877–881.
Hake, S.B., Garcia, B.A., Duncan, E.M., Kauer, M., Dellaire, G., Shabanowitz, J., Bazett-Jones, D.P., Allis, C.D., Hunt, D.F., 2006. Expression patterns and post-translational modifications associated with mammalian histone H3 variants. J. Biol. Chem. 281, 559–568.
Han, Q., Lu, J., Duan, J., Su, D., Hou, X., Li, F., Wang, X., Huang, B., 2008. Gcn5- and Elp3-induced histone H3 acetylation regulates hsp70 gene transcription in yeast. Biochem. J. 409, 779–788.
Hao, Y., Creson, T., Zhang, L., Li, P., Du, F., Yuan, P., Gould, T.D., Manji, H.K., Chen, G., 2004. Mood stabilizer valproate promotes ERK pathway-dependent cortical neuronal growth and neurogenesis. J. Neurosci. 24, 6590–6599.
Hirabayashi, Y., Gotoh, Y., 2010. Epigenetic control of neural precursor cell fate during development. Nat. Rev. Neurosci. 11, 377–388.
Hirabayashi, Y., Suzki, N., Tsuboi, M., Endo, T.A., Toyoda, T., Shinga, J., Koseki, H., Vidal, M., Gotoh, Y., 2009. Polycomb limits the neurogenic competence of neural precursor cells to promote astrogenic fate transition. Neuron 63, 600–613.
Holmqvist, P.H., Mannervik, M., 2013. Genomic occupancy of the transcriptional co-activators p300 and CBP. Transcription 4, 18–23.
Hsieh, J., Gage, F.H., 2004. Epigenetic control of neural stem cell fate. Curr. Opin. Genet. Dev. 14, 461–469.
Hsieh, J., Nakashima, K., Kuwabara, T., Mejia, E., Gage, F.H., 2004. Histone deacetylase inhibition-mediated neuronal differentiation of multipotent adult neural progenitor cells. Proc. Natl. Acad. Sci. U. S. A. 101, 16659–16664.
Hu, B.Y., Weick, J.P., Yu, J., Ma, L.X., Zhang, X.Q., Thomson, J.A., Zhang, S.C., 2010. Neural differentiation of human induced pluripotent stem cells follows developmental principles but with variable potency. Proc. Natl. Acad. Sci. U. S. A. 107, 4335–4340.
Huang, Y., Myers, S.J., Dingledine, R., 1999. Transcriptional repression by REST: recruitment of Sin3A and histone deacetylase to neuronal genes. Nat. Neurosci. 2, 867–872.
Ishino, Y., Hayashi, Y., Naruse, M., Tomita, K., Sanbo, M., Fuchigami, T., Fujiki, R., Hirose, K., Toyooka, Y., Fujimori, T., et al., 2014. Bre1a, a histone H2B ubiquitin ligase, regulates the cell cycle and differentiation of neural precursor cells. J. Neurosci. 34, 3067–3078.
Jaenisch, R., Young, R., 2008. Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming. Cell 132, 567–582.
Janknecht, R., Wells, N.J., Hunter, T., 1998. TGF-beta-stimulated cooperation of smad proteins with the coactivators CBP/p300. Genes Dev. 12, 2114–2119.
Jiang, H., Shukla, A., Wang, X., Chen, W.Y., Bernstein, B.E., Roeder, R.G., 2011. Role for Dpy-30 in ES cell-fate specification by regulation of H3K4 methylation within bivalent domains. Cell 144, 513–525.
Jin, Q., Zhuang, L., Lai, B., Wang, C., Li, W., Dolan, B., Lu, Y., Wang, Z., Zhao, K., Peng, W., et al., 2014. Gcn5 and PCAF negatively regulate interferon-beta production through HAT-independent inhibition of TBK1. EMBO Rep. 15, 1192–1201.
Juliandi, B., Abematsu, M., Nakashima, K., 2010a. Chromatin remodeling in neural stem cell differentiation. Curr. Opin. Neurobiol. 20, 408–415.
Juliandi, B., Abematsu, M., Nakashima, K., 2010b. Epigenetic regulation in neural stem cell differentiation. Dev. Growth Differ. 52, 493–504.
Kawabe, H., Brose, N., 2011. The role of ubiquitylation in nerve cell development. Nat. Rev. Neurosci. 12, 251–268.
Kimura, A., Umehara, T., Horikoshi, M., 2002. Chromosomal gradient of histone acetylation established by Sas2p and Sir2p functions as a shield against gene silencing. Nat. Genet. 32, 370–377.
Kloc, A., Ivanova, N., 2012. Chromatin and pluripotency: the MYSTerious connection. Cell Stem Cell 11, 139–140.

Ko, S.I., Lee, I.S., Kim, J.Y., Kim, S.M., Kim, D.W., Lee, K.S., Woo, K.M., Baek, J.H., Choo, J.K., Seo, S.B., 2006. Regulation of histone acetyltransferase activity of p300 and PCAF by proto-oncogene protein DEK. FEBS Lett. 580, 3217–3222.
Kornberg, R.D., Thomas, J.O., 1974. Chromatin structure; oligomers of the histones. Science 184, 865–868.
Kouzarides, T., 2007. Chromatin modifications and their function. Cell 128, 693–705.
Lan, F., Bayliss, P.E., Rinn, J.L., Whetstine, J.R., Wang, J.K., Chen, S., Iwase, S., Alpatov, R., Issaeva, I., Canaani, E., et al., 2007. A histone H3 lysine 27 demethylase regulates animal posterior development. Nature 449, 689–694.
Lim, D.A., Huang, Y.C., Swigut, T., Mirick, A.L., Garcia-Verdugo, J.M., Wysocka, J., Ernst, P., Alvarez-Buylla, A., 2009. Chromatin remodelling factor Mll1 is essential for neurogenesis from postnatal neural stem cells. Nature 458, 529–533.
Lin, W., Zhang, Z., Srajer, G., Chen, Y.C., Huang, M., Phan, H.M., Dent, S.Y., 2008. Proper expression of the Gcn5 histone acetyltransferase is required for neural tube closure in mouse embryos. Dev. Dynam. 237, 928–940.
Liu, N., Li, S., Wu, N., Cho, K.S., 2017. Acetylation and deacetylation in cancer stem-like cells. Oncotarget 8, 89315–89325.
MacDonald, J.L., Roskams, A.J., 2008. Histone deacetylases 1 and 2 are expressed at distinct stages of neuro-glial development. Dev. Dynam. 237, 2256–2267.
Marin-Husstege, M., Muggironi, M., Liu, A.X., Casaccia-Bonnefil, P., 2002. Histone deacetylase activity is necessary for oligodendrocyte lineage progression. J. Neurosci. 22, 10333–10345.
Marzluff, W.F., Wagner, E.J., Duronio, R.J., 2008. Metabolism and regulation of canonical histone mRNAs: life without a poly(A) tail. Nat. Rev. Genet. 9, 843–854.
Meng, Y., Zhang, T., Zheng, R., Ding, S., Yang, J., Liu, R., Jiang, Y., Jiang, W., 2021. Depletion of demethylase KDM6 enhances early neuroectoderm commitment of human PSCs. Front. Cell Dev. Biol. 9, 702462.
Merson, T.D., Dixon, M.P., Collin, C., Rietze, R.L., Bartlett, P.F., Thomas, T., Voss, A.K., 2006. The transcriptional coactivator Querkopf controls adult neurogenesis. J. Neurosci. 26, 11359–11370.
Meshorer, E., 2007. Chromatin in embryonic stem cell neuronal differentiation. Histol. Histopathol. 22, 311–319.
Nakashima, K., Yanagisawa, M., Arakawa, H., Kimura, N., Hisatsune, T., Kawabata, M., Miyazono, K., Taga, T., 1999. Synergistic signaling in fetal brain by STAT3-Smad1 complex bridged by p300. Science 284, 479–482.
Pan, G., Tian, S., Nie, J., Yang, C., Ruotti, V., Wei, H., Jonsdottir, G.A., Stewart, R., Thomson, J.A., 2007. Whole-genome analysis of histone H3 lysine 4 and lysine 27 methylation in human embryonic stem cells. Cell Stem Cell 1, 299–312.
Park, D.H., Hong, S.J., Salinas, R.D., Liu, S.J., Sun, S.W., Sgualdino, J., Testa, G., Matzuk, M.M., Iwamori, N., Lim, D.A., 2014. Activation of neuronal gene expression by the JMJD3 demethylase is required for postnatal and adult brain neurogenesis. Cell Rep. 8, 1290–1299.
Partanen, A., Motoyama, J., Hui, C.C., 1999. Developmentally regulated expression of the transcriptional cofactors/histone acetyltransferases CBP and p300 during mouse embryogenesis. Int. J. Dev. Biol. 43, 487–494.
Phan, H.M., Xu, A.W., Coco, C., Srajer, G., Wyszomierski, S., Evrard, Y.A., Eckner, R., Dent, S.Y., 2005. GCN5 and p300 share essential functions during early embryogenesis. Dev. Dynam. 233, 1337–1347.
Pokholok, D.K., Harbison, C.T., Levine, S., Cole, M., Hannett, N.M., Lee, T.I., Bell, G.W., Walker, K., Rolfe, P.A., Herbolsheimer, E., et al., 2005. Genome-wide map of nucleosome acetylation and methylation in yeast. Cell 122, 517–527.
Potts, M.B., Siu, J.J., Price, J.D., Salinas, R.D., Cho, M.J., Ramos, A.D., Hahn, J., Margeta, M., Oldham, M.C., Lim, D.A., 2014. Analysis of Mll1 deficiency identifies neurogenic transcriptional modules and Brn4 as a factor for direct astrocyte-to-neuron reprogramming. Neurosurgery 75, 472–482 discussion 482.
Qin, H., Zhao, A., Fu, X., 2017. Small molecules for reprogramming and transdifferentiation. Cell. Mol. Life Sci. 74, 3553–3575.
Ramos, Y.F., Hestand, M.S., Verlaan, M., Krabbendam, E., Ariyurek, Y., van Galen, M., van Dam, H., van Ommen, G.J., den Dunnen, J.T., Zantema, A., et al., 2010. Genome-wide assessment of differential roles for p300 and CBP in transcription regulation. Nucleic Acids Res. 38, 5396–5408.
Renthal, W., Nestler, E.J., 2009. Histone acetylation in drug addiction. Semin. Cell Dev. Biol. 20, 387–394.
Saiga, T., Fukuda, T., Matsumoto, M., Tada, H., Okano, H.J., Okano, H., Nakayama, K.I., 2009. Fbxo45 forms a novel ubiquitin ligase complex and is required for neuronal development. Mol. Cell Biol. 29, 3529–3543.
Santoro, S.W., Dulac, C., 2015. Histone variants and cellular plasticity. Trends Genet. 31, 516–527.
Sawicka, A., Seiser, C., 2012. Histone H3 phosphorylation - a versatile chromatin modification for different occasions. Biochimie 94, 2193–2201.
Schuettengruber, B., Bourbon, H.M., Di Croce, L., Cavalli, G., 2017. Genome regulation by polycomb and trithorax: 70 Years and counting. Cell 171, 34–57.
Schuettengruber, B., Chourrout, D., Vervoort, M., Leblanc, B., Cavalli, G., 2007. Genome regulation by polycomb and trithorax proteins. Cell 128, 735–745.
Schwartz, Y.B., Pirrotta, V., 2007. Polycomb silencing mechanisms and the management of genomic programmes. Nat. Rev. Genet. 8, 9–22.
Shen, S., Li, J., Casaccia-Bonnefil, P., 2005. Histone modifications affect timing of oligodendrocyte progenitor differentiation in the developing rat brain. J. Cell Biol. 169, 577–589.
Shen, X., Liu, Y., Hsu, Y.J., Fujiwara, Y., Kim, J., Mao, X., Yuan, G.C., Orkin, S.H., 2008. EZH1 mediates methylation on histone H3 lysine 27 and complements EZH2 in maintaining stem cell identity and executing pluripotency. Mol. Cell 32, 491–502.
Sher, F., Boddeke, E., Copray, S., 2011. Ezh2 expression in astrocytes induces their dedifferentiation toward neural stem cells. Cell. Reprogr. 13, 1–6.
Sher, F., Rossler, R., Brouwer, N., Balasubramaniyan, V., Boddeke, E., Copray, S., 2008. Differentiation of neural stem cells into oligodendrocytes: involvement of the polycomb group protein Ezh2. Stem Cell. 26, 2875–2883.
Shi, Y., Inoue, H., Wu, J.C., Yamanaka, S., 2017. Induced pluripotent stem cell technology: a decade of progress. Nat. Rev. Drug Discov. 16, 115–130.
Simboeck, E., Gutierrez, A., Cozzuto, L., Beringer, M., Caizzi, L., Keyes, W.M., Di Croce, L., 2013. DPY30 regulates pathways in cellular senescence through ID protein expression. EMBO J. 32, 2217–2230.
Soldner, F., Hockemeyer, D., Beard, C., Gao, Q., Bell, G.W., Cook, E.G., Hargus, G., Blak, A., Cooper, O., Mitalipova, M., et al., 2009. Parkinson's disease patient-derived induced pluripotent stem cells free of viral reprogramming factors. Cell 136, 964–977.
Srivastava, A., McGrath, B., Bielas, S.L., 2017. Histone H2A monoubiquitination in neurodevelopmental disorders. Trends Genet. 33, 566–578.
Stilger, K.L., Sullivan Jr., W.J., 2013. Elongator protein 3 (Elp3) lysine acetyltransferase is a tail-anchored mitochondrial protein in Toxoplasma gondii. J. Biol. Chem. 288, 25318–25329.
Tanaka, Y., Naruse, I., Hongo, T., Xu, M.-J., Nakahata, T., Maekawa, T., Ishii, S., 2000. Extensive brain hemorrhage and embryonic lethality in a mouse null mutant of CREB-binding protein. Mech. Dev. 95, 133–145.
Temple, S., 2001. The development of neural stem cells. Nature 414, 112–117.
Thomas, T., Voss, A.K., Chowdhury, K., Gruss, P., 2000. Querkopf, a MYST family histone acetyltransferase, is required for normal cerebral cortex development. Development 127, 2537–2548.
Thomson, J.A., Itskovitz-Eldor, J., Shapiro, S.S., Waknitz, M.A., Swiergiel, J.J., Marshall, V.S., Jones, J.M., 1998. Embryonic stem cell lines derived from human blastocysts. Science 282, 1145–1147.
Tiwari, V.K., Stadler, M.B., Wirbelauer, C., Paro, R., Schubeler, D., Beisel, C., 2011. A chromatin-modifying function of JNK during stem cell differentiation. Nat. Genet. 44, 94–100.
Toch, M., Clotman, F., 2019. CBP and p300 coactivators contribute to the maintenance of Isl1 expression by the Onecut transcription factors in embryonic spinal motor neurons. Mol. Cell. Neurosci. 101, 103411.
Tsuboi, M., Kishi, Y., Yokozeki, W., Koseki, H., Hirabayashi, Y., Gotoh, Y., 2018. Ubiquitination-independent repression of PRC1 targets during neuronal fate restriction in the developing mouse neocortex. Dev. Cell 47, 758–772 e755.
van Leeuwen, F., van Steensel, B., 2005. Histone modifications: from genome-wide maps to functional insights. Genome Biol. 6, 113.
Voss, A.K., Thomas, T., 2009. MYST family histone acetyltransferases take center stage in stem cells and development. Bioessays 31, 1050–1061.
Wang, H., Wang, L., Erdjument-Bromage, H., Vidal, M., Tempst, P., Jones, R.S., Zhang, Y., 2004. Role of histone H2A ubiquitination in Polycomb silencing. Nature 431, 873–878.
Wang, J., Weaver, I.C., Gauthier-Fisher, A., Wang, H., He, L., Yeomans, J., Wondisford, F., Kaplan, D.R., Miller, F.D., 2010. CBP histone acetyltransferase activity regulates embryonic neural differentiation in the normal and Rubinstein-Taybi syndrome brain. Dev. Cell 18, 114–125.
Wang, P., Lin, C., Smith, E.R., Guo, H., Sanderson, B.W., Wu, M., Gogol, M., Alexander, T., Seidel, C., Wiedemann, L.M., et al., 2009a. Global analysis of H3K4 methylation defines MLL family member targets and points to a role for MLL1-mediated H3K4 methylation in the regulation of transcriptional initiation by RNA polymerase II. Mol. Cell Biol. 29, 6074–6085.
Wang, Z., Zang, C., Cui, K., Schones, D.E., Barski, A., Peng, W., Zhao, K., 2009b. Genome-wide mapping of HATs and HDACs reveals distinct functions in active and inactive genes. Cell 138, 1019–1031.
Wei, Y., Yu, L.L., Bowen, J., Gorovsky, M.A., Allis, C.D., 1999. Phosphorylation of histone H3 is required for proper chromosome condensation and segregation. Cell 97, 99–109.
Wernig, M., Zhao, J.P., Pruszak, J., Hedlund, E., Fu, D., Soldner, F., Broccoli, V., Constantine-Paton, M., Isacson, O., Jaenisch, R., 2008. Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease. Proc. Natl. Acad. Sci. U. S. A. 105, 5856–5861.
Westbrook, T.F., Hu, G., Ang, X.L., Mulligan, P., Pavlova, N.N., Liang, A., Leng, Y., Maehr, R., Shi, Y., Harper, J.W., et al., 2008. SCFbeta-TRCP controls oncogenic transformation and neural differentiation through REST degradation. Nature 452, 370–374.
Xia, W., Jiao, J., 2017. Histone variant H3.3 orchestrates neural stem cell differentiation in the developing brain. Cell Death Differ. 24, 1548–1563.
Xu, W., Edmondson, D.G., Evrard, Y.A., Wakamiya, M., Behringer, R.R., Roth, S.Y., 2000. Loss of Gcn5l2 leads to increased apoptosis and mesodermal defects during mouse development. Nat. Genet. 26, 229–232.
Yang, J., Tang, Y., Liu, H., Guo, F., Ni, J., Le, W., 2014. Suppression of histone deacetylation promotes the differentiation of human pluripotent stem cells towards neural progenitor cells. BMC Biol. 12, 95.
Young, R.A., 2011. Control of the embryonic stem cell state. Cell 144, 940–954.
Zhao, X.D., Han, X., Chew, J.L., Liu, J., Chiu, K.P., Choo, A., Orlov, Y.L., Sung, W.K., Shahab, A., Kuznetsov, V.A., et al., 2007. Whole-genome mapping of histone H3 Lys4 and 27 trimethylations reveals distinct genomic compartments in human embryonic stem cells. Cell Stem Cell 1, 286–298.