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Review

Like a rolling histone: Epigenetic regulation of neural stem cells and brain development by factors controlling histone acetylation and methylation ☆

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ABSTRACT

Background: The development of the nervous system is a highly organized process involving the precise and coordinated timing of many complex events. These events require proper expression of genes promoting survival, differentiation, and maturation, but also repression of alternative cell fates and restriction of cell-type-specific gene expression.
Scope of the review: As the enzymes mediating post-translational histone acetylation and methylation are regulating higher order chromatin structure and controlling gene transcription, knowledge of the roles for these enzymes becomes crucial for understanding neural development and disease. The widespread expression and general biological roles for chromatin-modifying factors have hampered the studies of such enzymes in neural development, but in recent years, in vivo and in vitro studies have started to shed light on the various processes these enzymes regulate. In this review we summarize the implications of chromatin-modifying enzymes in neural development, with particular emphasis on enzymes regulating histone acetylation and methylation.
Major conclusions: Enzymes controlling histone acetylation and methylation are involved in the whole process of neural development, from controlling proliferation and undifferentiated, "poised", state of stem cells to promoting and inhibiting neurogenic and gliogenic pathways and neuronal survival as well as neurite outgrowth.
General significance: Aberrant enzymatic activities of histone acetyl transferases, deacetylases, and demethylases have been chemically and genetically associated with neural developmental disorders and cancer. Future studies may aim at linking the genetic and developmental studies to more in-depth biochemical characterization to provide a clearer picture of how to improve the diagnosis, prognosis, and treatment of such disorders. This article is part of a Special Issue entitled Biochemistry of Stem Cells.

1. Introduction

The control of transcription is crucial in cell differentiation and development of the nervous system. In the last decade, histone modifications have been shown to control many aspects of transcription including higher order chromatin structure and gene expression. The enzymes mediating post-translational histone modifications are therefore at the heart of development that requires precise control of gene expression patterns. The concept of the self-renewing, multipotent neural stem cells generating the main cell types of the nervous system has received a lot of attention and identification of adult neural stem cells residing in spinal cord and dentate gyrus has excitingly triggered a vision of enabling neural-replacement strategies solving severe disease situations, like spinal cord injuries or neurodegenerative diseases, by promoting a functional recovery (cf [1]). Characterizing epigenetic cell state regulation is essential in many aspects for normal development but also to understand developmental disorders. Importantly, epigenetic processes are also influenced by environmental cues like maternal behavior or prenatal stress and have shown to be central in influencing responses in the offspring [2,3]. From epigenetic studies it has become clear that histone-modifying enzymes control transcription both through their cell-type specific expression and their specific activity. Histones can be post-translationally modified in many ways, for example by acetylation, methylation, phosphorylation, ubiquitination, and sumoylation [4]. These modifications have profound effects on the local chromatin environment and the modifications can be regulated by active addition or removal. Hence, the enzymes regulating these modifications become focus of attention when dissecting the epigenetic mechanisms influencing neural stem cell state and fate and nervous system development. In this review we aim to present the implications of the specific enzymes with activities modulating acetylation, i.e. histone acetyl transferases and histone deacetylases, and methylation, i.e. histone methyl transferases and histone demethylases, of lysines of the histone tails identified to be involved in neural development. These findings have

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strong implications for the teratogenic effects of widely used medical substances, such as valproic acid, neurodevelopmental disorders including mental retardation, pediatric tumors of the nervous system, and predisposition for developing disease in adulthood.

2. Histone acetyl transferases (HATs)

Histones H3 and H4 can be acetylated on several lysines on their N-terminal tails and the acetylation level of histones in a promoter is positively correlated to an active transcription, but the enzymes that acetylate the histones in vivo are not well studied in a developmental context, not even in cellular systems. The fact that the substrate specificity of the HATs is fairly low when studied in vitro makes it difficult to couple specific acetylated residues to any single enzyme. Many of the HATs also acetylate non-histone proteins, which also complicate the interpretation of the phenotypes observed in acetyl transferase (AT) knock-out mice [5]. CBP and p300 are large, similar proteins that interact with many different transcription factors and are shown to have both AT activity as well as non-enzymatic functions where they act as scaffolds bringing the general transcriptional machinery and the DNA binding transcription factors together [6]. Mutations in either factor cause Rubinstein–Taybi syndrome, a disease in part characterized by mental retardation. One example of a non-enzymatic function of CBP is the finding that ES cells from CBP AT activity deficient mice surprisingly respond to bone morphogenetic protein 2 (BMP2) signaling by upregulating BMP-inducible genes to a similar if not higher level than wild type ES cells [5]. However, the AT activity of the enzymes is essential to mouse development since deficiency in AT activity is embryonic lethal [5]. Nevertheless, there are several studies linking HATs to neural development (Table 1, Fig. 1) even though knockouts of the whole protein do not differentiate between CBP/P300 activities on histone acetylation and other functions of the proteins. Mice mutant for CBP die around embryonic day (E) 12 with malformations of the central nervous system as a result of failure to close the dorsal tube cranially [7], which implicates CBP function during early neural development. Similar observations were made early in the p300 mutant mice [8]. In addition, neural lineage decision has been linked to functional CBP activity [9] and development of motor neurons in the spinal cord has been shown to be dependent on CBP through a synergistic interaction with retinoic acid receptor (RAR) and Neurogenin2 [10]. CBP and p300 can be modified post-translationally at several positions, and phosphorylation of CBP by atypical protein kinase Cζ controls the AT activity. This phosphorylation has been shown to be necessary for histone acetylation of neural promoters and neuronal differentiation [11]. Regeneration in response to injury is also related to development and nerve injury models have been used to study the formation of nerves. Thus, in an ocular nerve model of nerve damage, p300 overexpression was observed to promote axonal regeneration [12].

Apart from neurogenesis, HATs have also been implicated in astrocytic differentiation. Neural stem cell differentiation into astrocytes has been shown to be dependent on synergistic signaling between leukemia inhibitory factor (LIF) and BMP2 [13]. These signals are coordinated by p300 acting as a bridge between STAT3 and Smad1 representing the downstream signals in the LIF and BMP2 signaling cascades [13]. CBP and p300 have also been implicated in astrocytic differentiation in differentiating Ntera2 cells, where CBP and p300 are recruited directly to the astrocytic marker glial fibrillary acidic protein (GFAP) promoter and facilitate transcription [14].

In several of these studies, CBP/p300 has been suggested to act as signaling hubs that integrate the activity of several transcriptional activators from different signaling pathways [10,13] and it is important to note that this seems to be a general role for CBP and p300 in neural development. In addition to the CBP and p300 studies the Gcn5 HAT has also been implicated in neural development since mice with a point mutation in the HAT domain of Gcn5 show neural tube closure effects [15]. More studies on other HATs than CBP and p300 in neural stem cells and brain development will be of interest to increase the understanding for specific roles of histone acetylation in these events.

Table 1
Histone modifying enzymes involved in neural development. References for the table: [7,10–15,21,22,24–27,31–34,36,40,47,49,51–54,66,67,69,70].

Function	Enzyme	Effect on neural development	References
HAT	CBP	Required for neuronal development	Tanaka, 2000; Lee, 2009; Wang, 2010
	P300	Required for astrocyte development, promotes axonal regeneration	Cheng, 2011; Nakashima, 1999; Gaub, 2011
	GCN5	HAT activity needed for neural tube closure	Bu, 2007
HDAC	HDAC1	Blocks premature differentiation of NSCs, required for oligodendrocyte differentiation	Ye, 2009; Jacob, 2011; Chen, 2011; Akhtar, 2009
	HDAC2	Blocks premature differentiation of NSC, required for oligodendrocyte differentiation	Ye, 2009; Jacob, 2011; Chen, 2011; Akhtar, 2009
	HDAC1-3	VPA stimulates neurogenesis, inhibits oligodendrocyte differentiation	Hsieh, 2004; Laeng 2004
	HDAC5	Promotes neural stem cell proliferation	Sun, 2007
	HDAC9	Regulates dendritic growth	Sugo, 2010
	Sirt1	Influences neuronal differentiation	Zhang, 2011; Prozorovski, 2008; Wallenborg, 2009
DNMT	DNMT1	Required for neural cell viability	Fan, 2001
	DNMT3a	Required for neuromuscular junction	Nguyen, 2007
HMT	Mll1	Controls neurogenesis	Lim, 2009
	G9a	Prevents misexpression of neural genes, required for neurogenesis	Roopra, 2004
	Ezh2	Controls neural stem cell state, prevents premature differentiation	Rai, 2010 Pereira, 2010
HDM	LSD1	Controls neural stem cell proliferation	Sun, 2010
	Jarid2a	Control repression of pluripotency genes during neural differentiation	Schmitz, 2011
	JMJD3	Promotes neuronal differentiation	Jepsen, 2007
	KDM7	Required for neural development	Tsukada, 2010
	Jarid1c/SMCX	Required for neuronal survival and dendrite development	Iwase, 2007

3. Histone deacetylases (HDACs)

HDACs are generally divided into four classes. Class I HDACs (HDAC1, 2, 3 and 8) are most closely related to the yeast transcriptional regulator Rpd3 and are sensitive to the HDAC inhibitor Valproic acid (VPA) that is clinically widely used to treat epilepsy and bipolar disorder [16]. Class II HDACs (HDAC4, 5, 6, 7, 9 AND 10) share domains that have similarities in the yeast deacetylase HDA1. Common HDAC inhibitors, such as Trichostatin A (TSA), block HAT activities from both class I and class II HDACs. Class III HDACs are also called sirtuins after the founding member Sir2 in yeast. These are NAD + dependent enzymes and at least a subset of these can be activated by the well-studied and discussed polyphenol resveratrol. Class IV only contains one HDAC (HDAC 11) and has characteristics of both class I and Class II HDACs. The expression of HDAC 11 is cytoplasmic which suggest a non-histone deacetylation function (for extensive review on HDACs, please see [17]).

4. Effects of chemical inhibitors of HDACs

As HAT activity is affecting neural differentiation it is not surprising that also HDAC activity, which counteracts histone acetylation, can affect neural differentiation. Many studies have used chemical means of inhibiting HDAC activity in different systems. In neuronal cells, the histone deacetylase inhibitors TSA and sodium butyrate were observed

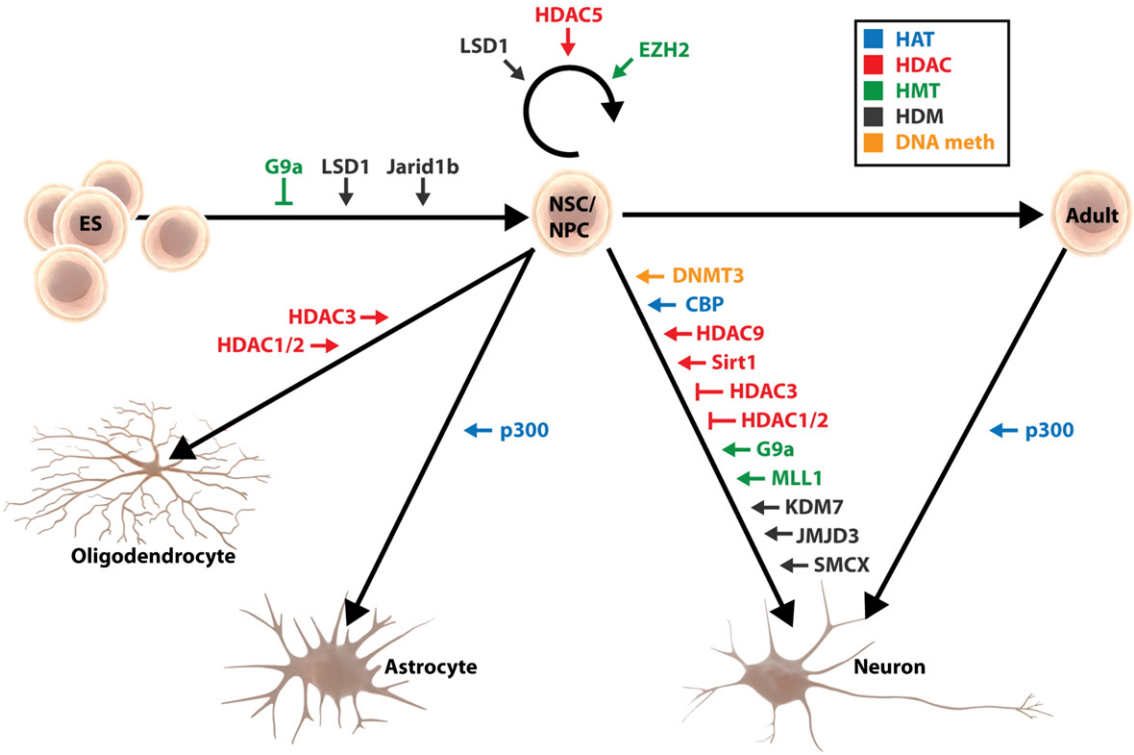

Fig. 1. Graphical summary of histone-modifying enzymes in neural development and differentiation. The classes of enzymes are color coded following the order of the abbreviations in the square upper right. Abbreviations: HAT, histone acetyl transferase; HDAC, histone deacetylase; HMT, histone methyl transferase; HDM, histone demethylase: DNA meth, DNA methyl transferase; ES, embryonic stem cells; NSC, neural stem cell; NPC, neural precursor cell; Adult, adult neural stem cell.

to induce apoptosis when protein synthesis is inhibited by cycloheximide [18]. This apoptotic effect of TSA was seen when used at a concentration of 1–3 μM. However, using a 15–30 fold lower TSA concentration in another system where rat neonatal cortical progenitors normally differentiate into oligodendrocytes in response to mitogen withdrawal, TSA treatment inhibits the differentiation and the progenitors remain in an undifferentiated state [19]. Similar to these results is the finding that HDAC inhibition by TSA in oligodendrocyte precursors can cause developmental plasticity whereby the cells can develop into astrocytes and neurons [20].

Also the unrelated HDAC inhibitor VPA can affect neurogenesis by stimulating neuronal development towards GABAergic neurons while inhibiting astrocytic differentiation in rat and human fetal neural stem cells [21]. In adult neural stem cells, VPA has been shown to stimulate neurogenesis through an up-regulation of NeuroD, while inhibiting glial fates [22].

It is important to note that histone deacetylase function and thus histone acetylation has been implicated in many diseases, including the neurodevelopmental disorder Rett syndrome, and it has therefore been discussed whether HDAC inhibitors such as VPA can be used therapeutically in treatment of some of these diseases [23]. Please note therefore that many patients with such disease, including Rett syndrome, due to epilepsy or other diagnoses, already are being treated with VPA. Thus although HDAC inhibitor treatment may be promising in many cases, a lot of caution should be taken when speculating in the beneficiary effects of such drugs.

5. Class I HDACs

As chemical inhibitors against class I and class II HDACs thus have profound effects on neural differentiation, it becomes interesting to couple such effects to the specific HDAC enzymes (Table 1, Fig. 1). Mice harboring gene deletions in the oligodendrocyte lineage for HDAC1 or HDAC2 respectively have weak effects. However, in double knock-out mice where both HDAC1 and HDAC2 are eliminated, the oligodendrocyte differentiation has been shown to be affected due to effects on β-catenin signaling [24]. Also, conditional gene deletion of HDAC1 and HDAC2 in peripheral Schwann cells leads to loss of cells and absence of myelin [25]. HDAC2 was found to be required for proper Sox10 expression and HDAC1 to regulate β-catenin activity. In agreement with this, it was found that acetylation of the protein NFκB is affected in HDAC1/2 double knock-out Schwann cells, which does affect Sox10 expression as well as myelination of peripheral nerves [26]. In hippocampal neurons, HDAC1 and HDAC2 were shown to control synapse maturation and combined gene deletion of HDAC1 and HDAC2 resulted in premature synapse maturation [27]. Since both VPA and TSA have been seen to have an inhibitory effect on differentiation of glial fates this correlates well with the findings that HDAC1 and 2 are used during glial differentiation in several systems.

HDAC3 is not as extensively studied during neural development but in hippocampal pyramidal neurons it has been reported to influence the acetylation levels of H4K8 and diminish long term memory formation [28], and forced expression of HDAC3 results in increased cell death of cortical neurons [29] indicating that it also contributes to the neuronal function in adult. Interestingly, the toxicity of HDAC3 has been suggested to be regulated by a balance in activity of the kinases Akt and GSK3ß [29], similar to the associated corepressor NCoR1 [30].

6. Class II HDACs

Class II HDACs are not as well studied as class I HDACs in relation to neural development, and it has been shown that class I HDACs are required for the activity of class II HDACs. Nevertheless, specific functions of at least two class II HDACs have been reported. HDAC5 is interacting with the orphan nuclear receptor Tlx (NR2E1) and repress p21 expression thereby controlling neural stem cell proliferation [31]. In addition, dendritic growth is regulated by the translocation of

HDAC9 from the nucleus into the cytoplasm in developing cortical neurons [32].

7. Class III HDACs (sirtuins)

Also the class III HDAC Sirt1 has been implicated in neuronal differentiation albeit with conflicting activity since it has been implicated in both promotion and inhibition of neuronal differentiation. Inhibition of Sirt1 by nicotinamide improved motor neuron differentiation from ESC [33]. Similarly, Sirt1 has been suggested to act together with Hes1 and TLE1 to repress Mash1 expression and neural differentiation in neural precursor cells [34] associated with an effect on lysine 9 on histone H3 (H3K9). It should be noted that the effects of Sirt1 on H3K9 acetylation is debated as it is primarily targeting lysine 16 on histone H4 (H4K16; [35]). Also in rat cortical neural stem cells, stimulation by resveratrol inhibited neuronal differentiation in a Sirt1-dependent way [36].

On the other hand, overexpression of cytoplasmic Sirt1 stimulated nerve growth factor dependent neurite outgrowth whereas a dominant negative cytoplasmic Sirt1 suppressed it [37]. Sirt1 has also been found to bind repressor complexes, and overexpression of Sirt1 promoted neuronal differentiation of neural precursor cells (NPCs) while knockdown inhibited differentiation. This could supposedly be an effect of Sirt1 in the nucleus as overexpression of cytoplasmic Sirt1 did not promote differentiation [38] indicating that the nuclear function of Sirt1 is needed for this effect. It is rather likely that Sirt1 is involved in many complex events in a cell, and the outcome of Sirt1 activity on neural development could be secondary to, e.g., the metabolic context and global changes in gene expression due to the regulation of H4K16 acetylation.

8. HDAC associated transcriptional regulatory complexes

The function of HDACs in various differentiation pathways depends on which genes the HDAC is recruited to and where it is located. In many cases the recruitment of HDACs occurs in the context of transcriptional regulatory protein complexes (Table 2). The nuclear receptor corepressor (NCoR) and the homologous protein NCoR2 (silencing mediator for retinoid or thyroid hormone receptor, SMRT) are co-repressors that recruit HDAC3. HDAC3 has been suggested to achieve a repressed state and a stable corepressor complex by ordered deacetylation of H4 tail lysines [39]. A specificity with regard to controlling lineage fate of the NCoR versus the NCoR2/SMRT complexes have been observed in neural stem cells (NSCs) which may be explained by recruitment target site or possibly by variable protein complex components including HDACs. It has been demonstrated that NCoR controls astrocyte differentiation at least in part by directly repressing GFAP transcription [30] while NCoR2/SMRT specifically controls neuronal differentiation by repressing retinoic acid receptor target genes in the absence of retinoic acid [40]. HDAC1, HDAC2 and HDAC3 can be recruited to chromatin through interactions with Sin3 (HDAC1, HDAC2) or via complexes including NCoR or NCoR2/SMRT to which HDAC3 binds directly (Table 2), which bind chromatin through interactions with deacetylated histone H3 in vitro [41]. In Ntera2 cells, which share some features with adult neuronal precursor cells Sin3a has been shown to be associated with the GFAP promoter when the cells are kept undifferentiated, whereas during differentiation Sin3a is downregulated [14]. This indicates that Sin3a repression and associated HDAC activity are needed to prevent premature expression of GFAP in differentiating Ntera2 cells.

In HeLa cells, repression by NCoR and NCoR2/SMRT complexes is dependent not only on the receptor that recruits the complex but also on interactions with deacetylated histones mediated by the associated HDAC activity [42]. Any possible substrate specificity for HDAC-associated complexes in neural development remains however to be elucidated.

Table 2
Protein complexes containing histone modifying enzymes implicated in neural development. References for the table: [74–80].

Complex	Proteins	References:
CoREST	CoREST	Lakowski, 2006; Perissi, 2010
	CtBP1	
	CtBP2	
	HDAC1	
	HDAC2	
	LSD1	
	Sin3	
NCoR/SMRT	NCoR/SMRT	Li, 2000; Underhill, 2000
	CORO2A	
	GPS2	
	HDAC3	
	KAP1	
	TAB2	
	TBL1	
	TBLR1	
NURD	CHD4	Denslow, 2007; Perissi, 2010
	HDAC1	
	HDAC2	
	LSD1	
	MBD3	
	MTA1–MTA3	
Sin3	SIN3	Silverstein, 2005
	HDAC1	
	HDAC2	
	RBAP46	
	RBAP48	
	SAP18	
	SAP30	
PRC1	RING1	Simon, 2009
	PHC1	
	PHC2	
	CBX4	
	BMI1	
PRC2	EZH2	Simon, 2009
	SUZ12	
	EED	

Repressor element 1 silencing transcription factor (REST) is functioning together with a complex of several other proteins (Table 2) with several enzymatic activities such as HDAC1/2, the histone methyl transferase G9a and the histone demethylase LSD1, and is further reviewed in [43]. The REST complex inhibits neural specific genes through interactions with Sin3a and HDAC2 [44] and is needed for maintenance of pluripotency of embryonic stem cells as well as for neural induction. When REST is ablated in radial glia like neural stem cells, the generated astrocytes and oligodendrocytes do not stop expressing neuronal genes [45]. The REST cofactor CoREST has functions independent from REST in NSC and is associated with pluripotency genes. Differentiation of NSC from CoREST deficient cells leads to a bigger fraction of neurons while the number of astrocytes and oligodendrocytes are diminished [46]. Taken together this indicates an involvement of REST and CoREST complexes in controlling the timing of neural differentiation.

9. Histone methyl transferases (HMT)

The methylation of histones especially of histone 3 at residues H3K4, H3K9 and H3K27 is emerging as some of the key epigenetic marks that control transcription in stem cells and progenitors. Methylation of H3K4, especially trimethylation, has been tightly linked to active transcription whereas methylation of H3K9 and H3K27 are *bona fide* marks of repressive chromatin. H3K9me is bound by HP1 and regulates heterochromatin formation and H3K27me recruits the well-studied PRC1 polycomb complex.

Mll1 is a histone methyl transferase methylating H3K4 and has been associated with the trithorax group of transcription factors. In mice where Mll1 is knocked out in neural stem cells, postnatal

neurogenesis is impaired (Table 1). Mll1 is associated with the Dlx2 promoter and in knock out NSC Dlx2 expression is diminished. Surprisingly, the loss of Mll1 did not affect the methylation of H3K4 on the Dlx2 promoter but H3K27me3 is increased, indicating that Mll1 is recruiting a H3K27 demethylase [47]. Ezh2, the histone methyl transferase of the PRC2, is needed for correct gene repression in the developing cortex since genetic deletion leads to a premature differentiation and loss of H3K27me3 in the mid-gestation cortex thereby indirectly promoting astrocytic differentiation [48,49]. The demand for modulation of H3K27me during neural development has also been seen genome wide during differentiation of ES cells to neural progenitors and further to terminal pyramidal neurons [50]. During this process H3K27me is highly variable on many promoters highlighting the need for enzymes that add and remove H3K27me.

The methyl transferase G9a interacts with REST and methylates H3K9 on REST target genes, and expression of a dominant negative G9a lead to dysfunctional regulation of neuronal genes (Table 1; [51]). In zebrafish, the histone methyl transferase G9a is also needed for neurogenesis through repression of Lef1. In this setting G9a cooperated with the DNA methyl transferase DNMT3 which also represses Lef1 expression [52] illustrating the cooperativity between DNA methylation and H3K9 methylation in repression (Fig. 1). The DNA methyl transferase DNMT1 is needed to maintain DNA methylation in dividing cells after replication when the newly synthesized DNA strand needs to be methylated similarly to the older strand to maintain methylation levels. DNMT1 knockout mice die at gastrulation, which makes it impossible to study requirements of DNMT1 during later development. Whereas the effects of deleting DNMT1 are detrimental [53] the effects of knocking out the de novo methylase DNMT3a in the nervous system are less severe but lead to neuromuscular defects and a shortened lifespan [54]. Conditional mice models for DNA methyl transferases have been generated, but also in these models, the cellular effects are severe and specific roles for the enzymes in neural stem cells and development have been difficult to elucidate. Postnatally, it has been demonstrated that a double knockout of DNMT1 and DNMT3a in forebrain excitatory neurons as targeted by CaMKII expression has effects on long-term plasticity in the hippocampal CA1 region as well as learning and memory deficits [55]. It will be helpful in future studies to use inducible or a wider range of transgenic mice expressing Cre recombinase regulated by various promoters expressed in different classes of neural progenitors during embryonic development.

10. Histone demethylases (HDMs)

For a long time it was unclear whether histone methylation was regulated by enzymes with opposing effects, in a similar way as other histone modifications. Before demethylating enzymes were identified, the general idea was that histone or histone-tail replacement was required in order to remove a methyl-mark. However, identification of the arginine deiminase PADI4/PAD4 in 2004 suggested a dynamic regulation of the modification even though it was not a demethylase per se [56,57]. Shortly after this finding, the first evidence of an enzyme with a histone demethylase activity was presented as LSD1/KDM1 and was shown to demethylate H3K4 mono and dimethylation [58].

Enzymes belonging to the JmjC-domain containing protein family that targets trimethylation marks were identified a couple of years later (JHDM1 [59], GASC1 [60], Jmjd2b [61], JHDM3A [62], JMJD2 [63]). Since then, several classes of demethylases have been reported, reviewed in [64,65]. Histone demethylases are today recognized as crucially involved in regulating cell function including differentiation. Specifically enzymes regulating H3K4, H3K9 and H3K27 methylation have a key role in differentiation since these modifications are potent effectors of chromatin environment. A limited but nonetheless crucially important list of demethylases has so far been shown to regulate neural development (Table 1, Fig. 1).

The consequence of genetic deletion of NCoR2/SMRT was a derepression of genes that promote neuronal differentiation both in isolated cortical progenitor cells as well as in vivo [40]. One of those derepressed genes were found to be JMJD3/KDM6B (Table 1), a gene belonging to the JmjC-domain protein family, and it was shown to be actively involved in promoting specific pathways in the neurogenic program by demethylation of H3K27me3.

KDM7, another JmjC-domain containing gene has been reported to catalyze the demethylation of mono- or di-methylated H3K9 and H3K27 [66]. These histone marks have been associated with transcriptional silencing and KDM7-dependent removal of the specific residue methylation load was found to affect the tectum size due to loss of neurons in this area and thereby affecting brain development in zebrafish. In addition, KDM7 dependent demethylation directly regulates the Follistatin gene in mouse Neuro2A cells implicating this enzyme to be involved in neural development also in mammals.

LSD1, the first demethylase from 2004, has been shown to serve as a key regulator of neural stem cell proliferation (Table 1; [67]). This effect was mediated through Tlx-dependent recruitment to known cell proliferation genes like p21 and Pten. Using LSD1 inhibitors or siRNA against LSD1 the mono- and-dimethyl levels on H3K4 at p21 and Pten promoters specifically increased. This epigenetic change induced the expression of the p21 and Pten genes and inhibited cell proliferation. In a different study, LSD1 was recently found to be crucially involved specifically in embryonic stem cell differentiation but however dispensable for maintaining ES cell state including proliferation (self-renewal) [68].

An essential role for the H3K4 di- and tri-demethylase Jarid1b controlling ES cell differentiation along the neural lineage was recently reported. Removal of the enzyme with shRNA in cultivated ES cells did not affect self-renewal but did affect a proper repression of pluripotency genes during differentiation [69].

Jarid1c/SMCX is another JmjC-domain protein specifically demethylating H3K4me3 to a mono- or di-methylated product [70]. Iwase et al. showed that SMCX plays a role in neuronal survival and dendrite development both in zebrafish and importantly also in primary mammalian neurons. As the authors point out, the clinical syndrome X-linked mental retardation has interestingly been associated with several point mutations in the SMCX gene [71–73]. Importantly, these mutations are linked to a dysfunctional H3K4me3 demethylase activity providing a molecular mechanism involving a histone-modifying enzyme directly underlying an intellectual disability condition.

Overall, although histone demethylases have only been recognized for a few years, the implications of these enzymes in stem cell regulation, including neural stem cells, and development are profound. It will be of great interest in the near future to study the dynamic regulation of histone methylation in neural stem cell lineage decision as well as during neuronal and glial differentiation and nervous system development in health and disease.

11. Conclusion

Taken together, enzymes controlling histone acetylation and methylation seem to be involved in the whole process of neural development, from controlling proliferation and undifferentiated but “poised” state of stem cells to promoting and inhibiting neurogenic and gliogenic pathways and neuronal survival as well as neurite outgrowth (Table 1, Fig. 1). Aberrations in the enzymatic activity of histone acetyl transferases, deacetylases, and demethylases have already been chemically (VPA) and genetically (Rubinstein–Taybi Syndrome, X-linked mental retardation) linked to neural developmental disorders, and aberrancies in the activities of histone deacetylation and demethylases have been associated with pediatric tumors in the nervous system. Future studies need to link the genetic and developmental studies to more in-depth biochemical characterization to provide a clearer picture of how to improve the diagnosis, prognosis, and treatment of such disorders.

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