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Histone Methylation in the Nervous System: Functions and Dysfunctions

Céline Pattaroni · Claire Jacob

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Abstract Chromatin remodeling is a key epigenetic process controlling the regulation of gene transcription. Local changes of chromatin architecture can be achieved by post-translational modifications of histones such as methylation, acetylation, phosphorylation, ubiquitination, sumoylation, and ADP-ribosylation. These changes are dynamic and allow for rapid repression or de-repression of specific target genes. Chromatin remodeling enzymes are largely involved in the control of cellular differentiation, and loss or gain of function is often correlated with pathological events. For these reasons, research on chromatin remodeling enzymes is currently very active and rapidly expanding, these enzymes representing very promising targets for the design of novel therapeutics in different areas of medicine including oncology and neurology. In this review, we focus on histone methylation in the nervous system. We provide an overview on mammalian histone methyltransferases and demethylases and their mechanisms of action, and we discuss their roles in the development of the nervous system and their involvement in neurodevelopmental, neurodegenerative, and behavioral disorders.

Keywords Chromatin remodeling · Histone methylation · Nervous system · Development · Differentiation · Disease

Introduction

In eukaryotes, genetic information is compacted within the nucleus into chromatin. Chromatin is composed of nucleosomes that are themselves formed by DNA wrapped around histone proteins. Chromatin architecture can be rapidly changed by post-translational modifications of residues located on histone tails. These modifications, including methylation, acetylation, phosphorylation, ubiquitination, sumoylation, and ADP-ribosylation, can result in a chromatin structure that is locally either more condensed or more relaxed: A condensed chromatin limits the access for transcription factors to DNA and may lead to transcriptionally inactive regions, whereas a relaxed chromatin facilitates the access for the transcriptional machinery to DNA and is therefore more subject to active transcription. In addition, different histone post-translational modifications can occur simultaneously or subsequently, providing a high degree of complexity in chromatin configurations and thereby allowing for accurate control of gene expression.

In this review, we focus on histone methylation and demethylation. Histone methyltransferases (HMTs) are enzymes that catalyze the addition of methyl groups to target residues of histone tails, while histone demethylases (HDMs) remove these methyl groups. Histone methylation is considered to be very stable as compared with other histone marks that are more dynamic. However, the recent discovery of HDMs [1, 2] revealed that histone methylation is a reversible histone mark. Although our knowledge on the specific functional roles of histone methylation enzymes is still limited, recent progress has highlighted their key functions in gene transcription and cell cycle regulation during development and differentiation, DNA damage, and stress response. Furthermore, several studies indicated that histone methylation may be critically involved in disease and aging (reviewed in [3, 4]).

Interestingly, a lot of effort has been recently invested in elucidating the role of histone methylation in the development and differentiation of neural cells. The mammalian nervous system is mainly composed of neurons and glial cells. Oligodendrocytes in the central nervous system (CNS) and

C. Pattaroni · C. Jacob (✉)
Department of Biology, Unit of Zoology, University of Fribourg,
Chemin du musée 10,
1700 Fribourg, Switzerland
e-mail: claire.jacob@unifr.ch

Schwann cells in the peripheral nervous system (PNS) constitute the myelinating glia that ensheath neurons to provide insulation and fast conduction of electric signals. In addition to myelinating cells, astrocytes and microglia are two other types of glial cells of the CNS involved in different neuronal supporting functions and processes such as inflammation. Sensory neurons and Schwann cells originate from neural crest cells, while other types of neurons, oligodendrocytes, and astrocytes derive from neural stem cells and microglia from hematopoietic stem cells. The specific program of neural development that starts with the specification of precursor cells into distinct neural cell types is controlled by a complex network of transcription factors. In addition, chromatin remodeling enzymes are coordinating the activity of key transcription factors involved in neural development. Indeed, we and others have shown the critical involvement of histone deacetylases (HDACs) 1 and 2 in the development of myelinating cells [5, 6]. Another good example is the enhancer of Zeste homolog 2 (EZH2) HMT that is required to maintain a proper balance between neural stem cell self-renewal and differentiation into neurons [7] and that also plays a critical role in the differentiation of neural stem cells into oligodendrocytes [8]. Altogether, these findings have emphasized the importance of chromatin remodeling enzymes in the differentiation and maturation of the nervous system.

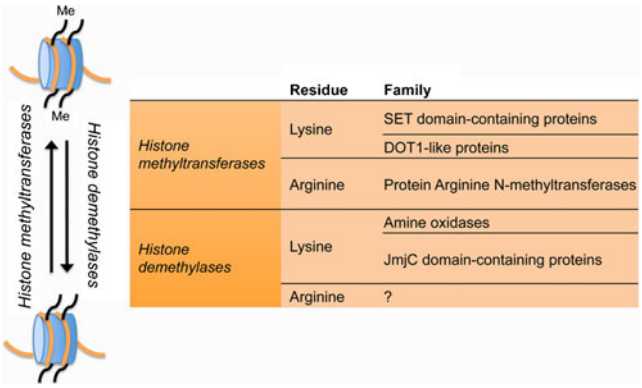
Beyond a critical involvement in development, chromatin remodeling is very likely to be also implicated in pathologies of the nervous system: Accumulation of specific histone marks correlates with several neurological disorders, and recent studies suggest that histone methylation enzymes are essential to the proper function of the nervous system [9, 10].

In this review, we describe the different known mammalian members of histone methyltransferase and demethylase families, their mechanism of action, their critical functions in the development of the nervous system, and their involvement in neurodevelopmental, neurodegenerative, and behavioral disorders.

HMTs and HDMs

HMTs catalyze the transfer of methyl groups from *S*-adenosylmethionine (SAM) to histones [11]. Three families of HMTs have been described: the SET (Su(var)3–9, enhancer of Zeste, trithorax)-domain-containing proteins [12] and DOT1-like proteins [13] catalyzing the methylation of lysine residues, and the protein arginine *N*-methyltransferases (PRMTs) that methylate arginine residues [14] (Fig. 1).

The removal of methyl groups from lysine residues on histones is catalyzed by HDMs. Two families of lysine HDMs, the amine oxidases [1] and the Jumonji C (JmjC) domain-containing proteins, have been identified (Fig. 1). However, the existence of specific arginine HDMs is not



	Residue	Family
Histone methyltransferases	Lysine	SET domain-containing proteins
		DOT1-like proteins
	Arginine	Protein Arginine N-methyltransferases
Histone demethylases	Lysine	Amine oxidases
		JmjC domain-containing proteins
	Arginine	?

Fig. 1 Histone methyltransferase and demethylase families. Histone methylation is catalyzed by histone methyltransferases that belong to three identified families, while the removal of methyl groups on histone residues is catalyzed by histone demethylases that include two described families of enzymes

clear: The JmjC-domain-containing protein JMJD6 has been shown to demethylate arginines [15], but this enzyme is also a lysyl hydroxylase [16]. Another way for cells to get rid of methylated arginines is to use deiminases that convert arginines into citrullines [17]; however, these enzymes are not able to demethylate arginines.

Structure and Catalytic Mechanisms of Histone Methylation Enzymes

HMTs

SET-domain-containing HMTs possess, in addition to their SET domain (containing the catalytic core), a pre-SET domain and a post-SET domain that are involved in the methyltransferase activity and specificity of the enzyme. In order to methylate histone tails, the SET domain of HMTs first recognizes lysines and SAM molecules, which are brought in close proximity, then catalyzes the deprotonation of the ε-amino group of the lysine residue by a nearby tyrosine to allow the transfer of the methyl group from the SAM molecule to the lysine residue [18].

In contrast to SET-domain-containing enzymes that target lysine residues on histone tails, Dot1 HMT was shown in budding yeast to only methylate lysine residues in the globular histone core [19]. Dot1-like HMT (DOT1L) homologs have been identified in mammals [13]. A structural study of the catalytic domain of human DOT1L reveals common features with other methyltransferases that do not methylate lysine residues; however, this study identifies a potential binding channel for lysine residues [20]. Further structural studies are still needed to understand the precise catalytic mechanism of this enzyme.

The catalytic domain of PRMTs, consisting of a SAM binding domain and a substrate binding domain, recognizes arginine residues brought in close proximity to SAM

molecules. Arginine residues are then deprotonated by a nearby glutamate to allow the transfer of the methyl group from the SAM molecule to the arginine residue [21].

For complete review about HMT structures and catalytic mechanisms, see also Wood and Shilatifard [22].

HDMs

Amine oxidases such as LSD1 contain a C-terminal amine oxidase-like domain that includes two subdomains: a FAD-binding subdomain and a substrate-binding subdomain [23]. A large cavity formed by these two subdomains constitutes the catalytic core of the enzyme. LSD1 activity depends on the cofactor FAD. LSD1 catalyzes the transfer of two hydrogens from a methylated lysine to a FAD that is then reduced into $FADH_2$; this reaction eventually results into an unmethylated lysine and a formaldehyde byproduct [1].

JmjC-domain-containing demethylases catalyze hydroxylation reactions. This second family of HDMs introduces a hydroxyl group into a methyl group on a lysine residue using Fe(II) and α-ketoglutarate as cofactors to generate succinate and an unstable carbinol amine intermediate that leads to the formation of an unmethylated lysine and a formaldehyde byproduct [24, 25].

Target Residues and Methylation Outcome

Histone methylation can occur on the three basic residues lysine (K), arginine (R), and histidine; however, histidine methylation is rarely observed. Lysines can be mono- (me1), di- (me2), or trimethylated (me3); arginines can be mono- or dimethylated, whereas only monomethylation of histidine has been described.

Histone methylation sites are mainly located on histones H3 and H4; however, methylation can also occur on histones H1, H2A, and H2B. The most described methylation sites are listed in Tables 1 and 2. The effect of histone methylation on gene expression activity depends on the location of the methylated residue and can also depend on the degree of methylation and the HMT (whether the enzyme catalyzes symmetric or asymmetric methylation): H3K9, H3K27, H4K20, and H3R8 methylations are described as marks of transcriptional repression (reviewed in [26], [27], and [28]) H3K4 [29, 30], H3K36 (reviewed in [31]), H3K79 (reviewed in [32]), H3R17, and H3R26 (reviewed in [33]) methylations are mostly (but not always, e.g., [29]) associated with active transcription, whereas methylation of H3R2 and H4R3 (reviewed in [33]) can either lead to transcriptional activation or repression, depending on the degree of methylation and/or the type of methyltransferase. The most common effects of currently described HMTs and HDMs are summarized in Tables 1 and 2.

Enzyme Recruitment to Histone Target Residues

Several studies have shown that specific DNA sequences, long non-coding RNAs (lncRNAs), small non-coding RNAs, and DNA methylation could direct histone methylation enzymes to their target sites.

In *Drosophila melanogaster*, specific DNA sequences including the polycomb group (PcG) response elements (PREs) and the trithorax group response elements are able to recruit histone methylation enzymes such as, respectively, PcG proteins and the H3K4 methyltransferase Trx [34, 35]. In humans, a D11.12 (region between HOXD11 and HOXD12) genomic element with similar recruitment abilities of PcG proteins as compared with *Drosophila* PREs has been recently identified, suggesting that the recruitment of histone methylation enzymes by specific DNA sequences may as well occur in mammals [36]. In addition, the JmjC protein JARID2 [37] and polycomb-like 2 [38] have been shown to be able to recruit PRC2, a PcG complex having H3K27 trimethylation activity [39].

Several studies have also reported or suggested the ability of lncRNAs to target HMTs and HDMs to regulatory regions of specific genes. Indeed, Hawkins and Morris showed that the suppression of the lncRNA antisense to Oct4-pseudogene 5 in human cells resulted in increased transcription of *Oct4* gene and Oct4 pseudogenes 4 and 5, correlating with loss of the HMT EZH2 at the *Oct4* promoter and therefore indicating the requirement of this lncRNA to target EZH2 to *Oct4* gene [40]. In addition, the lncRNA HOTAIR has been shown to bind and recruit PRC2 and the demethylase LSD1 [41]. Another study reports the recruitment of the protein complex containing the H3K4 methyltransferase mixed lineage leukemia (MLL) and WD repeat-containing protein 5 (WDR5) by the lncRNA HOTTIP [42].

Small non-coding RNAs including microRNAs, small-interfering RNAs and Piwi-interacting RNAs have important functions in transposon silencing, formation of pericentromeric heterochromatin [43], and X-chromosome inactivation [44]. They often play the role of inducers of these mechanisms by recruiting HMTs (reviewed in [45]).

Finally, there is often interplay between DNA methylation and histone methylation. The study of Bartke et al. [46] shows that, in some cases, the recruitment of HMTs is enhanced by the presence of DNA methylation, and in other cases, DNA methylation counteracts the recruitment of HMTs.

For a general review addressing this question, see also, Greer and Shi [3].

Complex Formation and Histone Modification Crosstalk

Changes in chromatin structure often result from a specific combination of post-translational modifications of histones. In many cases, one histone modification serves as a signal for the

Table 1 Mammalian histone lysine methyltransferases and demethylases and prevalent transcriptional outcome of methylation (reported enzymes and their alternative names in brackets are sorted depending on the target residue and the degree of methylation)

Histone and residue		Methyltransferase	Prevalent methylation outcome	Demethylase
H3K4	*me1*	SETD1A/B (SET1A/B, KMT2F)	Transcriptional activation	LSD1/2 (KDM1A/B)
		ASH1L (KMT2H)		KDM5B (JARID1B, PLU1)
		MLL1 (KMT2A, TRX1, HRX, ALL1)	Transcriptional activation	NO66 (MAPJD)
		MLL2 (MLL4, KMT2B, KMT2D, ALR)	Transcriptional activation	
		MLL3 (KMT2C)	Transcriptional activation	
		SETD7 (SET7/9, KMT7)	Transcriptional activation	
	me2	SETD1A/B (SET1A/B, KMT2F)	Transcriptional activation	LSD1/2 (KDM1A/B)
		MLL1 (KMT2A, TRX1, HRX, ALL1)	Transcriptional activation	KDM5A (RBP2, RBBP2)
		MLL2 (MLL4, KMT2B, KMT2D, ALR)	Transcriptional activation	KDM5B/D
		MLL3 (KMT2C)	Transcriptional activation	KDM5C (JARID1C, SMCX)
		SMYD3	Transcriptional activation	NO66 (MAPJD)
	me3	SETD1A/B (SET1A/B, KMT2F)	Transcriptional activation	KDM2B
		ASH1L (KMT2H)		KDM5A (RBP2, RBBP2)
		MLL1 (KMT2A, TRX1, HRX, ALL1)	Transcriptional activation	KDM5B/D
		MLL2 (MLL4, KMT2B, KMT2D, ALR)	Transcriptional activation	KDM5C (JARID1C, SMCX)
		MLL3 (KMT2C)	Transcriptional activation	NO66 (MAPJD)
		SMYD3	Transcriptional activation	
		PRDM9 (MEISETZ)		
H3K9	*me1*	SETDB1 (ESET, KMT1E)	Transcriptional repression	KDM3A/B (JMJD1A/B, JHDM2A/B)
		G9a (EHMT2, KMT1C)	Heterochromatin formation/silencing	PHF8
		GLP (EHMT1, KMT1D)		KDM7 (JHDM1D)
		PRDM2 (KMT8)		
	me2	SUV39H1/2 (KMT1A/B)		KDM3A/B (JMJD1A/B, JHDM2A/B)
		SETDB1 (ESET, KMT1E)		KDM3A/B (JMJD1A/B, JHDM2A/B)
		G9a (EHMT2, KMT1C)	Heterochromatin formation/silencing	PHF8
		GLP (EHMT1, KMT1D)	Heterochromatin formation/silencing	LSD1 (KDM1A)
		PRDM2 (KMT8)		KDM7 (JHDM1D)
	me3	SUV39H1/2 (KMT1A/B)	Heterochromatin formation/silencing	KDM3B (JMJD1B, JHDM2B)
		SETDB1 (ESET, KMT1E)		KDM4A-D (JMJD2A-D, JHDM3A-D)
		PRDM2 (KMT8)		
H3K27	*me1*			KMD7 (JHDM1D)
	me2	EZH1/2	Transcriptional repression	KDM6A/B (UTX/JMJD3)
				KDM7 (JHDM1D)
	me3	EZH1/2	Transcriptional repression	KDM6A/B (UTX/JMJD3)
H3K36	*me1*	SETD2 (KMT3A)	Transcriptional activation	KDM2A/B (JHDM1A/B, FBXL11/10)
		NSD1-3		
	me2	NSD1-3		KDM2A/B (JHDM1A/B, FBXL11/10)
		SMYD2		NO66 (MAPJD)
		SETD2 (KMT3A)	Transcriptional activation	KDM4A-C (JMJD2A-C, JHDM3A-C)
		ASH1L		
	me3	SETD2 (KMT3A)	Transcriptional activation	NO66 (MAPJD)
				KDM4A-C (JMJD2A-C, JHDM3A-C)
H3K79	*me1*	DOT1L (KMT4)	Transcriptional activation	
	me2	DOT1L (KMT4)	Transcriptional activation	
	me3	DOT1L (KMT4)	Transcriptional activation	
H4K20	*me1*	SETD8 (SET8, KMT5A)	Transcriptional repression	PHF8
	me2	SUV420H1/2 (KMT5B/C)		
	me3	NSD1 SUV420H1/2 (KMT5B/C)		

Table 2 Mammalian histone arginine methyltransferases and prevalent transcriptional outcome of methylation

Histone and residue		Methyltransferase	Prevalent methylation outcome
H3R2	*me1*	PRMT4 (CARM1)	Transcriptional activation
		PRMT6	Transcriptional repression
		PRMT5/7	
	me2	PRMT4 (CARM1)	Transcriptional activation
		PRMT6	Transcriptional repression
		PRMT5/7	
H3R8	*me1*	PRMT5 (SKB1)	Transcriptional repression
	me2	PRMT5 (SKB1)	Transcriptional repression
H3R17	*me1*	PRMT4 (CARM1)	Transcriptional activation
	me2	PRMT4 (CARM1)	Transcriptional activation
H3R26	*me1*	PRMT4 (CARM1)	
	me2	PRMT4 (CARM1)	
H4R3	*me1*	PRMT1 (HMT2)	Transcriptional activation
		PRMT5 (SKB1)	Transcriptional repression
		PRMT6/7	
	me2	PRMT1 (HMT2)	
		PRMT5 (SKB1)	Transcriptional repression
		PRMT6/8	Transcriptional activation
		PRMT7	

assembly of protein complexes containing several histone-modifying enzymes. HMTs and/or HDMs are frequently found in these protein complexes. Because of the particular role of histone acetylation and deacetylation in chromatin dynamics of the nervous system, we will focus on the protein complexes containing HMTs or HDMs and histone acetyltransferases (HATs) or HDACs. The PRC2 complex containing EZH2 has also a key role in the development of nerve cells and will be therefore described in this section.

H3K4 HMT Complexes

Most MLL HMTs targeting H3K4 act within multiprotein complexes that contain a three-subunit core composed of WDR5, RbBP5, and ASH2L, necessary for the methyltransferase activity [47]. The MLL1 complex, a key regulator of Hox genes during development, contains also the H4K16 HATs MOF/KAT8 [48] or MOZ [49] and other cofactors that act together to regulate transcription initiation and elongation [50–53]. The activity of this MLL complex is stimulated by the acetylation of H3K9 or H3K14 [50], demonstrating the critical role of crosstalk between different histone modifications for the regulation of target genes.

H3K9 HMT Complexes

In contrast to MLL HMTs, SETDB1 HMT targets H3K9 residue to induce gene silencing or heterochromatin formation. SETDB1 can robustly methylate unmodified histone H3, whereas acetylation of H3K9 or H3K14 strongly inhibits its SETDB1 activity. For this reason, SETDB1 HMT needs to act in concert with a deacetylase complex. Consistent with this, SETDB1 interacts with the co-repressor KAP-1 that serves as a scaffold for KRAB zinc-finger proteins that target the protein complex to specific promoters, for the NuRD complex (containing HDAC1 and HDAC2) required for deacetylation of histone H3, and for HP1 (heterochromatin protein 1) that allows formation of heterochromatin [54, 55].

Similarly to SETDB1, Suv39H1 HMT recruits HP1 by methylating H3K9 and is involved in heterochromatin formation and in transcriptional repression. Suv39H1, such as SETDB1, functionally interacts with HDAC1 or HDAC1/2 [56, 57].

G9a HMT also targets H3K9. G9a plays a critical role in transcriptional repression, and studies in mice revealed that this HMT is essential for early embryonic development [58]. G9a recruits HP1 and has been shown to associate with transcriptional repressors such as HDAC1/2 and DNA methyltransferases [59, 60].

H3K27 HMT Complexes

The polycomb repressive complex PRC2 induces gene silencing by the di- and trimethylation of H3K27 catalyzed by the HMTs EZH2 or EZH1 ([39, 61] and reviewed in Margueron and Reinberg [62]). PRC2 can also methylate H3K9 and H1K26, which leads to the recruitment of the PRC1 complex that represses genes through monoubiquitylation of

histone H2A [63]. PRC2 comprises four core components that are required for its activity: EZH1/2, embryonic ectoderm development protein (EED), RbAp46/48, and SUZ12 (suppressor of Zeste 12 homolog). EZH2 and EZH1 are both able to methylate H3K27; however, EZH1 has lower methyltransferase activity than EZH2 [64]. EED and RbAp46/48 are both WD40 repeat containing proteins. EED allows recognition of the H3 substrate by PRC2 [65] and the propagation of H3K27 methylation [66] while RbAp46/48, which can bind histone H3, SUZ12, and histone H4, may be involved in substrate specificity [39]. SUZ12 contains a zinc-finger domain that is important for the recruitment of PRC2 to its target genes [67, 68]. Beyond these four core components, other proteins are found in PRC2 complexes: the zinc-finger protein AEBP2, the polycomb-like protein PCL1 (also known as PHF1), and the Jumonji protein JARID2. These three proteins are involved in the regulation and enhancement of PRC2 activity and in the recruitment of the complex [69–71]. PRC2 is required for X inactivation and silencing of Hox gene expression during embryonic development and has key functions in stem cell self-renewal, but also in lineage commitment and maintenance of cellular identity [reviewed in Margueron and Reinberg and Walker et al. 62, 72].

HDM Complexes

The first described histone demethylase LSD1 that can target methylated H3K4 or H3K9 is involved in diverse molecular interactions. LSD1 has been initially found to be part of the repressive CoREST complex, which also consists of HDAC1/2, BHC80, and BRAF35 [1, 73]. Additionally, other studies revealed that the CoREST complex is part of another transcriptional corepressor complex, CtBP, which also contains G9a and GLP HMTs and other cofactors [74]. Finally, LSD1 has also been identified as a component of the NuRD complex, where it also acts as transcriptional repressor by demethylating H3K4. The NuRD complex exhibits an ATP-dependent chromatin remodeling activity, together with the presence of HDAC1/2, Mi-2 and histone-binding proteins [75].

NCoR protein, which is known to act within a multimeric protein complex involved in development and neural differentiation, has also been shown to associate with HDMs. Indeed, a repressive complex containing NCoR protein, REST, and HDAC1/2 was found to be associated to G9a HMT and KDM5C, a demethylase of H3K4me2 and H3K4me3 [76]. Another HDM, KDM4A, that demethylates H3K36, seems to be required in the NCoR complex for selective repression of *Ascl2* gene, a basic helix–loop–helix transcription factor essential for proper placental development [77].

Finally, the highly conserved Sin3-HDAC complex, which regulates many genes and has fundamental roles in development, has been shown to associate with the H3K4 HDM KDM5A. This Sin3 complex is constituted of HDAC1/2, Sin3A or Sin3B, RbAp46/48, and SAP18/30, together with other factors such as MRG15, which is involved in the recruitment of KDM5A [78].

As mentioned previously, we only referred to literature that described HMTs or HDMs in complex with HATs or HDACs and to the PRC2 complex. Other important interactions, such as HDMs with nuclear hormone receptors [79, 80], have also been described but are not discussed here.

Histone Methylation in the Nervous System

We and others have shown that several members of the HDAC family are crucial for the development of myelinating cells (reviewed in Jacob et al. [6]). Because HMTs and HDMs are often found in multiprotein complexes where HDACs are present and play an essential role in the activity of these complexes, it is very likely that histone methylation enzymes and HDACs have coordinated functions in the development of the nervous system. In this section, we will first discuss the functions of histone methylation in the development and differentiation processes of nerve cells, including neurons, oligodendrocytes, and Schwann cells, the myelinating cells of the CNS and PNS, respectively, and astrocytes and microglia, two other important types of glial cells in the CNS. As mentioned before, sensory neurons and Schwann cells originate from neural crest cells while other neurons, oligodendrocytes, and astrocytes originate from neural stem cells and microglia are generated from hematopoietic stem cells. Beyond a key involvement in development, histone methylation is very likely to play important roles in diseases of the nervous system. The second part of this section will be focused on suggested implications of histone methylation in neurodevelopmental and neurodegenerative diseases and in behavioral disorders.

Histone Methylation in the Development and Differentiation of the Nervous System

Neurons

Much more information is available regarding the role of histone methylation in neurogenesis, as compared with the differentiation process of other cells of the nervous system. The methylation status of H3K27 is a key determinant of cell fate during neural lineage progression from neural stem cells [8]. Consistent with this, JMJD3, an H3K27me3 demethylase, induces expression of neuronal genes such as Dlx5, Gad1/2, and Dcx [81]. Additionally, studies on embryonic stem cells also demonstrated that JMJD3 is required for commitment to the neuronal lineage [82] and activation of

TGFbeta-responsive genes in neurons [83]. However, methylation of H3K27 by EZH2 in neural stem cells is required to maintain a proper balance between self-renewal of neural stem cells and differentiation into neurons and to prevent massive neurogenesis and depletion of the neural stem cell pool that would eventually result in a decreased number of neurons [7]. Moreover, the nuclear co-receptor SMRT, repressing the expression of JMJD3, is critical for forebrain development and maintenance of the neural stem cell state [81].

Histone methylation at H3K4 has also been shown to play a role in neurogenesis. Indeed, the H3K4 HMT MLL1 promotes neurogenesis in the subventricular zone of the mouse postnatal brain by promoting the expression of Dlx2, a homeodomain-containing transcription factor critical for olfactory bulb interneuron development and migration [84]. Another study in mice revealed that a complex containing MLL2, MLL3, and PTIP is necessary to maintain H3K4 methylation in the neural tube during embryonic development [85]. Consistent with this, the H3K4 HDM KDM5C that acts as a transcriptional repressor has been shown to associate with the REST complex, which represses neuronal genes in non-neuronal tissues. The complex KDM5C and REST associates at a subset of REST-target genes and depletion of KDM5C induces de-repression of several of these target genes [76], suggesting that KDM5C contributes to REST-mediated neuronal gene regulation. In addition to maintaining silencing of neuronal genes in non-neuronal cells, the REST complex is also involved in the differentiation into neurons: The activation of most neuronal genes (designed as class 1) in post-mitotic neurons is only dependent on the release of the REST repressor complex from these genes at the RE1 binding motif, while a smaller group of neuronal genes (designed as class 2) including *Bdnf* remains initially expressed at low levels upon differentiation into neurons even after the release of the REST complex. This is due to the presence of the CoREST and MeCP2 repressor complex on these genes, which is eventually released later by membrane depolarization [86]. The study of Abrajano et al. comparing the different profiles of REST and CoREST target genes in distinct subtypes of neurons shows that the differential presence of these two repressor complexes allows the induction and maintenance of neuronal subtype identity [87].

The status of H3K9 methylation seems also to be involved in neuronal differentiation and in particular in neurite outgrowth. Indeed, Sen and Snyder showed that BDNF, by activating neuronal nitric oxide synthase, induces the degradation of the H3K9 HMT SUV39H1, resulting in the decrease of H3K9 methylation and subsequent increase of H3K9 acetylation. This facilitates CREB binding to DNA and enhances CREB-regulated genes and neurite outgrowth [88]. Consistently, the H3K9/H4K20 HDM PHF8 has been shown to be essential in neurons to promote cytoskeleton dynamics resulting in neurite outgrowth [89]. H3K9 methylation needs to be decreased for neurite outgrowth; however, this histone mark seems necessary for early neurogenesis. Indeed, ablation of the H3K9 HMT SETDB1 in neural stem cells leads to enhanced formation of astrocytes and severe decrease of early born neurons [90]. The authors of this study show that SETDB1 represses the expression of astrocytic genes and thereby prevents precocious differentiation of neural stem cells into the astrocytic lineage. This mechanism could be required for upregulation of neuronal genes and early neurogenesis.

Interestingly, a recent expression study comparing human cortical neurons to neural progenitor cells reports the transcriptional regulation of many chromatin modifiers during human neurodevelopment and identifies the arginine HMT PRMT8 and the lysine HMT EZH1 as new markers of post-mitotic neurons [91].

Oligodendrocytes

Interesting findings on the implication of histone methylation in the development of myelinating cells have just started to emerge.

Histone methylation has been shown to play a critical role in the specification of the oligodendrocyte lineage from neural stem cells. Indeed, the HMT EZH2 is needed for proper in vitro specification of mouse neural stem cells into oligodendrocytes. While EZH2 is highly expressed in proliferating neural stem cells, its expression is decreased upon differentiation into neurons and abolished during differentiation into astrocytes. However, EZH2 expression remains high in oligodendrocytes [8]. A comparative ChIP-Seq analysis of EZH2 target genes in neural stem cells and in premyelinating oligodendrocytes (pOLs) reports the presence of EZH2 at oligodendrocyte, neuronal, and astrocytic lineage-specific genes in neural stem cells, whereas, in pOLs, EZH2 is not anymore present on the oligodendrocyte lineage-specific genes but is still found on astrocytic and neuronal lineage-specific genes [92].

Histone methylation may also play a role in oligodendrocyte development at later stages, from oligodendrocyte progenitor cells into mature myelinating cells. Interestingly, an increase of the repressive histone mark H3K9me3 and HP1α, a marker of stable chromatin compaction, has been observed in mature oligodendrocytes of the rat corpus callosum [93]. This suggests a possible role of histone methylation in maintaining oligodendrocytes in a differentiated myelinating stage, but the underlying mechanisms and enzymes involved in this process remain unknown.

Finally, the REST and CoREST complexes that repress the transcriptional activity of neuronal genes in non-

neuronal cells are also necessary for the differentiation process of oligodendrocytes. Similar to their study in neurons, Abrajano et al. have compared the profiles of REST and CoREST target genes during the different stages of oligodendrocyte development [94].

Schwann Cells

There was no information available about the potential role of histone methylation in Schwann cell differentiation until Heinen et al. recently showed that EZH2 is required for Schwann cell maturation [95]. Indeed, suppression of EZH2 in Schwann cell cultures and dorsal root ganglia cultures leads to the downregulation of myelin genes (P0, PMP22, and MAL) and reduction of process extension. EZH2 binds to and represses the promoter of the cyclin-dependent kinase inhibitor p57kip2 and thereby downregulates the expression of transcriptional repressors of myelin genes such as Hes5 [95]. The same authors of this study previously demonstrated that p57kip2 is a negative regulator of Schwann cell differentiation and in vitro myelination [96]. Altogether, these results suggest that EZH2 activity within the PRC2 complex is necessary to initiate suppression of differentiation inhibitors in Schwann cells, therefore allowing Schwann cell differentiation and maturation.

Astrocytes

As with myelinating cells, little is known about the role of histone methylation in astrocyte development and differentiation. We previously mentioned that EZH2 expression in neural stem cells is downregulated upon differentiation into neurons and abolished during differentiation into astrocytes [8]. Interestingly, important changes in H3 methylation have been observed on the promoter of the *Gfap* gene, a marker of the astrocytic lineage. Indeed, fibroblast growth factor 2 (FGF2) has been shown to induce H3K4 methylation and to reduce H3K9 methylation on the *Gfap* promoter. This facilitates the access of the STAT/CBP complex to the *Gfap* promoter and allows ciliary neurotrophic factor-mediated astrocyte differentiation [97]. However, the underlying mechanism of HMTs and/or HDMs recruitment by FGF2 has not been elucidated yet. Consistently and as mentioned earlier, the H3K9 HMT SETDB1 represses astrocytic genes in neural stem cells and ablation of SETDB1 results in increased astrogenesis [90].

Microglia

Unfortunately, there is currently no evidence concerning the role of histone methylation in microglia development or differentiation. However, some studies reported an implication of histone methylation enzymes in the inflammatory response and the establishment of HIV-1 latency in microglia. Indeed, microglial cells are the principal targets of HIV-1 in the nervous system and constitute a latent reservoir for the virus [98]. Some studies demonstrated a recruitment of a chromatin-modifying complex containing HDAC1/2 and the H3K9 HMT SUV39H1 by the co-repressor COUP-TF interacting protein 2 (CTIP2) at the viral promoter of HIV-1 in microglia [99]. The authors also demonstrated that this complex associates with the promoter of the cyclin-dependent kinase inhibitor *p21*, whose expression is affected in HIV-1 infected microglia [100]. Additionally, they showed that the HDM LSD1 can also interact with CTIP2 to silence HIV-1 promoter [101]. Altogether, these repressive complexes may thus participate in the maintenance of HIV-1 latency in microglia.

In a different context, the CoREST repressor complex containing G9a HMT and LSD1 HDM is recruited by the orphean nuclear receptor Nurr1 to repress the promoters of inflammatory target genes [102]. Since the Nurr1/CoREST complex exerts a regulatory role on inflammatory gene expression, it is likely that histone methylation could play a potential role in the control of inflammation in microglial cells.

Reported functions of histone methylation in the development and differentiation processes of neurons, myelinating cells, and astrocytes are summarized in Table 3 and illustrated in Figs. 2, 3, and 4.

Nervous System Disorders Related to Histone Methylation

As mentioned earlier, accumulations of several histone modifications including methylation have been shown to correlate with neurological disorders. These modifications vary from one disorder to another, and it is not always clear whether they are a cause or a consequence of the disease. Understanding the mechanisms underlying these histone modifications observed in pathological conditions is of utmost importance for the design of novel therapeutic treatments. The following section focuses on recent findings related to histone methylation processes that have been correlated to neurodevelopmental and neurodegenerative diseases and behavioral disorders (summarized in Table 4).

Neurodevelopmental Diseases

Mutations of H3K4 KDM5C [103–107] and of H3K9/H4K20 PHF8 [108–110] HDMs have been linked to mental retardation (for KDM5C and PHF8) and facial deformity (for PHF8) in humans. The genes encoding these two HDMs are located on the X chromosome, where genes affecting cognitive functions seem to be more represented when compared with autosomes. Interestingly, these neurologic phenotypes are consistent with the expression patterns identified in mouse brains. Indeed, KDM5C is highly

Table 3 Functions of histone methylation enzymes in the development and differentiation of neural cells

Cell type	Target residue	Enzyme	Modification	Observation	Suggested role	References
Neurons	H3K27	KDM6B (JMJD3)	Demethylation	Neuronal genes induced when JMJD3 is overexpressed in neural stem cells	Promotes differentiation of neural stem cells into neurons	[81–83]
		EZH2	Methylation	Upregulation of genes involved in neurogenesis in Ezh2-null mouse cortex	Maintenance of appropriate balance between neural stem cell self-renewal and differentiation into neurons	[7]
		EZH1	Methylation	High expression in post-mitotic neurons		[91]
	H3K4	MLL1	Methylation	Neurogenesis impaired in the absence of MLL1 in mouse subventricular zone (SVZ)	Induces postnatal neurogenesis in the SVZ via transcriptional activation of Dlx2	[84]
		KDM5C (SMCX)	Demethylation	KDM5C and REST are released from RE1 binding sites upon differentiation into neurons	Cell identity establishment by REST-mediated silencing of neuronal genes in non-neuronal cells and de-repression of neuronal genes by relase of REST for differentiation into neurons	[76]
	H3K9	SETDB1	methylation	Early neurogenesis severely impaired and increased astrogenesis in the absence of SETDB1	Represses astrocytic genes to prevent precocious differentiation in astrocytes and to allow differentiation of early-born neurons	[90]
		SUV39H1	Methylation	Downregulation of SUV39H1 induced by BDNF enhances CREB-related genes	Neurite outgrowth promoted by downregulation of SUV39H1 and subsequent decrease of H3K9 methylation	[88]
	H3K9/ H4K20	PHF8	Demethylation	Activation of genes involved in cytoskeleton dynamics	Neurite outgrowth	[89]
	H4R3	PRMT8	Methylation	Hig hexpression in post-mitotic neurons		[91]
Oligodendrocytes	H3K27	EZH2	Methylation	EZH2 remains highly expressed in oligodendrocytic lineage where it represses astrocytic and neuronal lineages specific genes	Cell fate choice towards oligodendrocytic lineage upon induction of neural stem cell differentiation and maintenance of oligodendrocyte lineage identity	[8, 92]
	H3K9	not described	Methylation	Increase of H3K9me3 and HP1α levels in mature oligodendrocytes	Maintenance of oligodendrocytes myelination	[93]
Schwann cells	H3K27	EZH2	Methylation	Decrease of myelin gene expression and process extension in Schwann cells upon downregulation of EZH2	Promotes Schwann cell maturation by repressing p57kip2, what downregulates inhibitors of myelination such as Hes5	[95]
Astrocytes	H3K4	SETD7 (SET7/9)	Methylation	Increased H3K4 methylation on the GFAP promoter	Mediates FGF2-dependent astrocyte differentiation via the transcriptional activation of GFAP	[97]
	H3K9	Not described	Demethylation	Decreased H3K9 methylation on the GFAP promoter	Mediates FGF2-dependent astrocyte differentiation via the de-repression of GFAP gene	[97]

expressed and seems to have important functions in brain regions involved in cognition such as the hippocampus [125]. Some studies performed in zebrafish, and primary mammalian neurons showed that these phenotypes could be due to disrupted brain development. Indeed, neuronal survival and dendritic development are affected by mutation of KDM5C [126]. Concerning PHF8, a role for this HDM in zebrafish neuronal cell survival and craniofacial development has been identified [127], providing new insights into the related human pathology.

The Kleefstra syndrome, caused by either deleterious mutations or haploinsufficiency of the H3K9 HMT EHMT1 [111], includes mental retardation and other developmental defects. Interestingly, heterozygous *Ehmt1* knockout mice

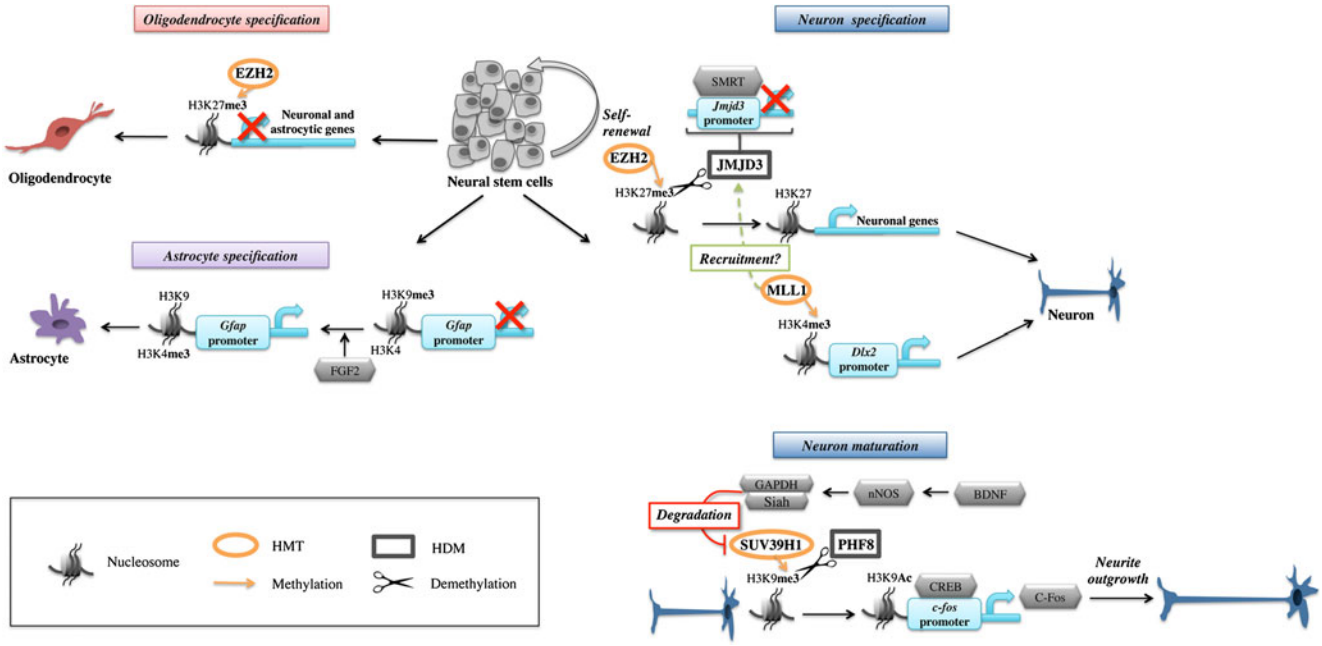


Fig. 2 Known functions of histone methyltransferases and demethylases in the specification and differentiation of neurons, oligodendrocytes, and astrocytes

develop autistic-like behavior that resembles the human pathology [128]. EHMT1 is part of a multiprotein complex that also includes the H3K9 HMT G9a as well as other methyltransferases [129]. Conditional mutagenesis of *Ehmt1* and *G9a* in postnatal mouse brain revealed the importance of this complex for the silencing of non-neuronal genes and progenitor genes in mature neurons. Furthermore, absence of the EHMT1/G9a complex has detrimental effects on cognition and other higher brain functions [130].

Neurodegenerative Diseases

Aberrant histone modifications related to methylation have been detected in Friedreich ataxia, Huntington's disease, and Alzheimer disease (AD), three neurodegenerative diseases of the CNS. Friedreich ataxia is an autosomal neurodegenerative disorder caused by abnormally high copy numbers of GAA repeats in the *frataxin* gene [131]. Interestingly, analyses of human brain tissues revealed increased

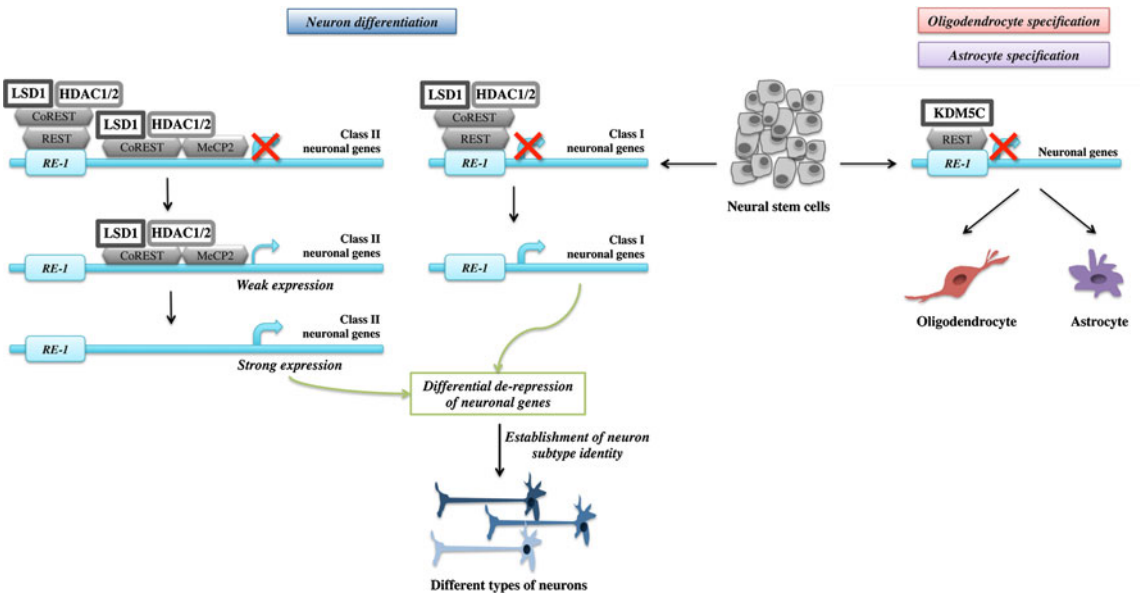


Fig. 3 Functions of REST and CoREST complexes in the specification and differentiation of neurons, oligodendrocytes, and astrocytes. Note that other proteins such as BHC80 and BRAF35 also belong to the CoREST complex, and the HMT G9a can also be associated with REST, but to simplify the figure, these proteins are not represented here

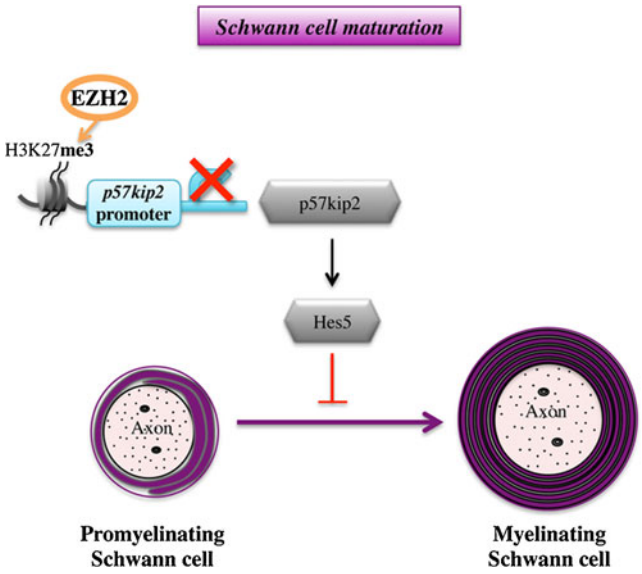


Fig. 4 Role of EZH2 in Schwann cell differentiation

levels of H3K9 methylation together with decreased histone acetylation at the *frataxin* gene, resulting in transcriptional repression of this gene [9].

Similarly, high levels of methylated H3K9 and its corresponding SETDB1 HMT have been detected in postmortem human striatal tissues of patients suffering from Huntington's disease. Huntington's disease is caused by a mutation in the *huntingtin* gene that creates an expansion of a CAG trinucleotide repeat encoding poly-glutamine [112]. Mutated huntingtin interferes with the normal function of neuroprotective factors such as Sp1 and CREB-binding protein, which renders mutated huntingtin neurotoxic [132–134].

Increased levels of H3K9 trimethylation have also been detected in the postmortem brain of a patient suffering from AD, as compared with the levels of H3K9me3 detected in the brain of his twin brother that did not suffer from AD [113]. AD is linked to age-related changes in the metabolism of beta-amyloid (Aβ) precursor protein and tau protein, resulting in aggregates of Aβ fibrils and neurofibrillary tangles that may impact neuronal integrity (reviewed in Huang et al. [135]). The increased H3K9me3 in human brain described above seems rather anecdotic; however, studies in a transgenic mouse model of AD also showed an increase of histone H3 methylation in the presence of Aβ in the prefrontal cortex of these mice [114].

Finally, we can mention the progressive decline of histone methylation marks in oligodendrocytes during aging, which is associated with increased histone acetylation and re-expression of inhibitors of myelin proteins [115]. This loss of histone methylation could play a role in the decreased efficiency of remyelination during aging [116].

Behavioral Disorders

Different histone methylation marks have been associated with behavioral disorders. This topic has been recently extensively reviewed elsewhere [10]. In this section, we have therefore briefly pointed out the most important findings. H3K27, H3K9, and H3K4 methylation marks have been shown to play a role in the development of mood disorders and depression-like behaviors in mice. BDNF is involved in the adaptation of the hippocampus to stress [136], and histone methylation could be part of the regulatory mechanisms mediating its expression. Interestingly, chronic defeat stress induces H3K27 methylation at the *Bdnf* gene in mouse hippocampus, leading to transcriptional repression [117]. Consistent with these results, mice exposed to environmental enrichment demonstrated a strong increase in BDNF mRNA expression in hippocampus, associated with decreased H3K27 and H3K9 methylation together with increased H3K4 methylation [118]. Additionally, studies about global histone methylation in rat dentate gyrus during acute and chronic stress revealed important changes in H3K9, H3K27, and H3K4 methylation levels, giving more evidence to the mechanisms involved in the hippocampal response to stress [137]. Other studies about the effect of social defeat model on gene transcription in the mouse nucleus accumbens, a brain reward region implicated in depression, revealed important histone modification changes. Levels of repressive H3K9me2 and H3K27me2 were increased at several gene promoters in stress-susceptible animals, including at the promoter of the H3K9 HDM KDM3A. Interestingly, mice resilient to the stress model or treated with conventional antidepressants did not show changes in histone H3 methylation, providing new insights into the molecular mechanisms of depression-like behaviors and antidepressant activity [119]. Finally, overexpression of the H3K9 HMT SETDB1 in adult forebrain neurons has been shown to induce antidepressant-like phenotypes in mice, probably resulting from changes in NMDA receptor subunit composition [120].

Chromatin remodeling by post-translational modifications of histones is also critical for the induction and stabilization of long-term memory. For example, contextual fear conditioning in adult mice upregulates H3K4 methylation, a mark of active transcription, in the hippocampus, at specific promoter regions of *Zif268* and *Bdnf* genes. Mice deficient for the H3K4 HMT MLL displayed deficits in fear memory formation, demonstrating that histone methylation is actively regulated in the hippocampus and facilitates long-term memory formation [121]. H3K4 methylation is also increased at the promoters of GABAergic genes such as *Gad1* during human and rodent cerebral cortex maturation [122]. Consistent with this, mice expressing one allele of a truncated *Mll* transgene showed decreased H3K4

Table 4 Correlation of aberrant histone methylation marks with neurodevelopmental, neurodegenerative, and behavioral disorders

	Pathology	Target residue	Enzyme	Enzyme activity	Observation	References
Neurodevelopmental diseases	Mental retardation, autism	H3K4	KDM5C (JARID1C)	Demethylation	KDM5C enzyme mutations in human	[103–107]
	Mental retardation and facial deformity	H3K9	PHF8	Demethylation	PHF8 enzyme mutation in human	[108–110]
	Kleefstra syndrome	H3K9	EHMT1	Methylation	EHMT1 enzyme mutation/gene haploinsufficiency in human	[111]
Neurodegenerative diseases	Friedreich ataxia	H3K9			Increased H3K9me3 levels in post-mortem human brains	[9]
	Huntington's disease	H3K9	SETDB1	Methylation	Increased enzyme and H3K9me3 levels in post-mortem human brains (striatal tissue)	[112]
	Alzheimer disease	H3K9	?		Increased levels of H3K9me3 postmortem human brain (only 1 control brain and 1 AD-affected brain, but similar findings in mouse model of AD)	[113, 114]
	Aging				Decline of histone H3 methylation marks in oligodendrocytes during aging	[115, 116]
Behavioral diseases	Depression, mood disorders (mice)	H3K27			Increased H3K27 methylation at the Bdnf gene (repression) in mice exposed to chronic social defeat stress	[117]
		H3K27/H3K9			Decreased H3K27 and H3K9 methylation and increased Bdnf mRNA levels in mice exposed to environmental enrichment	[118]
		H3K9	KDM3A	Demethylase	Increased H3K9 levels in mice exposed to social defeat	[119]
		H3K9	SETDB1	Methylation	Antidepressant-like phenotype upon SETDB1 overexpression in mice	[120]
	Learning and memory (mice)	H3K4	MLL1	Methylation	Increased H3K4 methylation in mice exposed to fear memory conditioning and deficit in fear memory formation in MLL-deficient mice	[121]
	Schizophrenia	H3K4	MLL1	Methylation	Decreased H3K4me3 at promoters of GABAergic genes such as Gad1 in postmortem Schizophrenic patients brains	[122]
	Addiction	H3K9	G9a	Methylation	Decreased H3K9me2 and G9a levels in the nucleus accumbens of cocaine-addicted rats; increased susceptibility to cocaine-induced social stress when G9a is ablated	[123, 124]

methylation levels at GABAergic gene promoters [122]. Because the brains of schizophrenic patients exhibit decreased levels of H3K4me3 at the *Gad1* promoter and decreased GAD1 expression, this mechanism may be important for the pathophysiology of schizophrenia [122].

Finally, some studies in mice showed an involvement of H3K9 methylation in drug-induced neuronal gene transcription changes that may regulate structural and behavioral plasticity. Indeed, chronic cocaine administration induces the reduction of H3K9me2 and G9a HMT expression in nucleus accumbens neurons, associated with increased dendritic spine plasticity and enhanced cocaine preference, suggesting a role of histone methylation in the molecular mechanisms of drug addiction [123]. Consistent with these findings, repeated cocaine treatment in mice or ablation of the H3K9 HMT G9a in the nucleus accumbens increased mouse susceptibility to social stress, and overexpression of G9a in the nucleus accumbens rendered mice resilient to stress even after repeated cocaine treatment [124]. A recent study also reports a decrease of H3K9 trimethylation at the *Bdnf* promoters II and III after long-term morphine abstinence in the rat brain [138].

Conclusion and Perspectives

Histone methylation is a major chromatin-remodeling process that regulates transcriptional activity. Depending on the exact location of the methyl group transferred by the HMT, this modification can either lead to transcriptional activation or repression. In addition, the combination of histone methylation with other histone modifications allows the fine-tuning of transcriptional activity. Consistently, HMTs and HDMs are often found in multiprotein complexes containing other histone modification enzymes such as HATs and HDACs. In particular, the coordinated action of HDACs with HMTs appears as a very frequent event.

Because of its key function in the regulation of transcriptional activity, histone methylation has become a very active area of current investigation, in particular in cancer research, but also more recently in neurobiology. Our knowledge on the functions of histone methylation in the biology of the nervous system is still very sparse; however, it seems clear that in-depth understanding of these functions will lead to major discoveries and advances in medicine. Histone methylation has critical functions in the development of the nervous system. Detection of a wide range of aberrant histone methylations and other histone modifications in diseases of the nervous system (also reviewed in [139]) suggests that chromatin remodeling also plays an important role in these pathologies. However, whether these histone modifications are a cause or a consequence of these diseases is not yet proven, and a lot more work is needed to elucidate the underlying mechanisms of these aberrant histone modifications. From what we currently know, it seems clear that the consideration of combinations of several histone modifications rather than single ones will be a requirement for the success of future therapeutic strategies. There is therefore an enormous need to concentrate our efforts in the integration of coordinated chromatin remodeling mechanisms in our experimental approaches.

Because of their potential involvement in diseases of the nervous system, HMTs and HDMs could constitute innovative therapeutic targets. Several HMT and HDM inhibitors already exist and have shown very promising results, especially in cancer therapy (reviewed in [140]). In addition, the identification of new compounds that specifically target HMTs and HDMs is a very active area of current investigation. We can thus envision the exciting perspective that novel research tools will be soon available to elucidate the functions of histone methylation in neurobiology and that novel compounds may be useful for the treatment of neurological diseases.

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Conflicts of interest The authors declare that they have no conflict of interest.

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