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# Lysine methylation regulates nervous system diseases

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ABSTRACT

Lysine methylation is an important dynamic modification which is essential in the epigenetic regulation of gene transcription. Unlike acetylation markers, lysine methylation signals at gene promoters could be viewed as markers that either activate or silence gene expression in different contexts or states. This article briefly reviews lysine methylation sites involved in nervous system diseases. The methyltransferases and demethylases which cause abnormal methylation signals in nervous system diseases are also discussed. Methylated proteins correlated with nervous system biological processes are extracted from databases and known writer-code-eraser patterns are analyzed, which could provide insight into the design of methylation-based interference peptides for the investigation of nervous system diseases.

## 1. Lysine methylations are involved in nervous system disease

Genomic DNA and the associated histone proteins form the nucleosomes, which are the elementary units of eukaryotic chromatin. The dynamic change of chromatin structure and gene transcription is mainly controlled by epigenetic regulation, including DNA methylation and histone modification (Pan et al., 2018). Compared to DNA methylation, posttranslational modification of histone proteins is more complicated. The modification types, modification positions, modification degrees and the crosstalk are usually different between different modifications (Hamamoto et al., 2015; Pan et al., 2018; Yang and Bedford, 2013). Here we'll give a brief review of lysine methylation and its role in nervous system disease.

Lysine methylation in histones was first reported in the mid-1960s (Murray, 1964). The addition of the methyl group to lysine of histone proteins is carried out by histone lysine methyltransferases. Because these enzymes methylate both histone and non-histone substrates, they are also named protein lysine methyltransferases (KMTs) (Pan et al., 2018). Up to date, KMTs are divided into two families on the basis of catalytic domain. One is the suppressor of variegation 3–9 (Su(var) 3–9), Enhancer of zeste (E(z)) and Trithorax (SET) family that contains a unique functional SET domain originally found in Drosophia polycomb proteins (Alvarez-Venegas and Avramova, 2002). The other is the disrupter of telomeric silencing 1-like (DOT1L) (Pan et al., 2018). Deletion of DOT1l in the murine telencephalon leads to cortical layering defects(Franz et al., 2019). Their data also suggested that DOT1L balanced transcriptional programs necessary for proper neuronal composition and distribution in the six cortical layers (Franz et al., 2019). The incorporated methyl group on protein lysine can be removed by lysine demethylases (KDMs). The lysine demethylase (KDMs) are divided into two families based on sequence homology and catalytic mechanism. One includes lysine-specifc demethylase (LSD1, also known as KDM1A) and LSD2 (KDM1B), and they catalyze the demethylation reaction *via* generation of an imine intermediate (Maes et al., 2015; Shi et al., 2004). The other one is a large group of histone demethylases with a unique Jumonji-C (JMJC) domain. JMJC demethylases exhibit dioxygenase activity and remove the methyl groups from lysine in an iron and α-ketoglutarate-dependent fashion (Agger et al., 2007; Whetstine et al., 2006).

The ε-NH2 of amino acid lysine has the capacity to accept multiple methyl groups from lysine methyltransferases (KMTs) using the methyl donor substrate S-adenosylmethionine (SAM), resulting in three modification states: mono-methyl (me1), di-methyl (me2) and tri-methyl (me3). These epigenomic markers are removed by lysine demethylases (KDMs). Extracted from HIstome Infobase, Uniprot database and literatures, we generated the network of Kme writer, reader and eraser by NAViGaTOR software (Fig. 1). Due to the specificity of KMTs or KDMs in alternating methylation degrees, each methylation state should be defined as a different modification. A complex combination of DNA methylation, non-conding RNAs (ncRNA), histone modifications (*e.g.* methylation, acetylation, phosphorylation and ubiquitination), and their cross communications encode a finely tuned epigenetic code, leading to repression or activation of the targeted gene without altering the original sequence. Many epigenetic modifications have been

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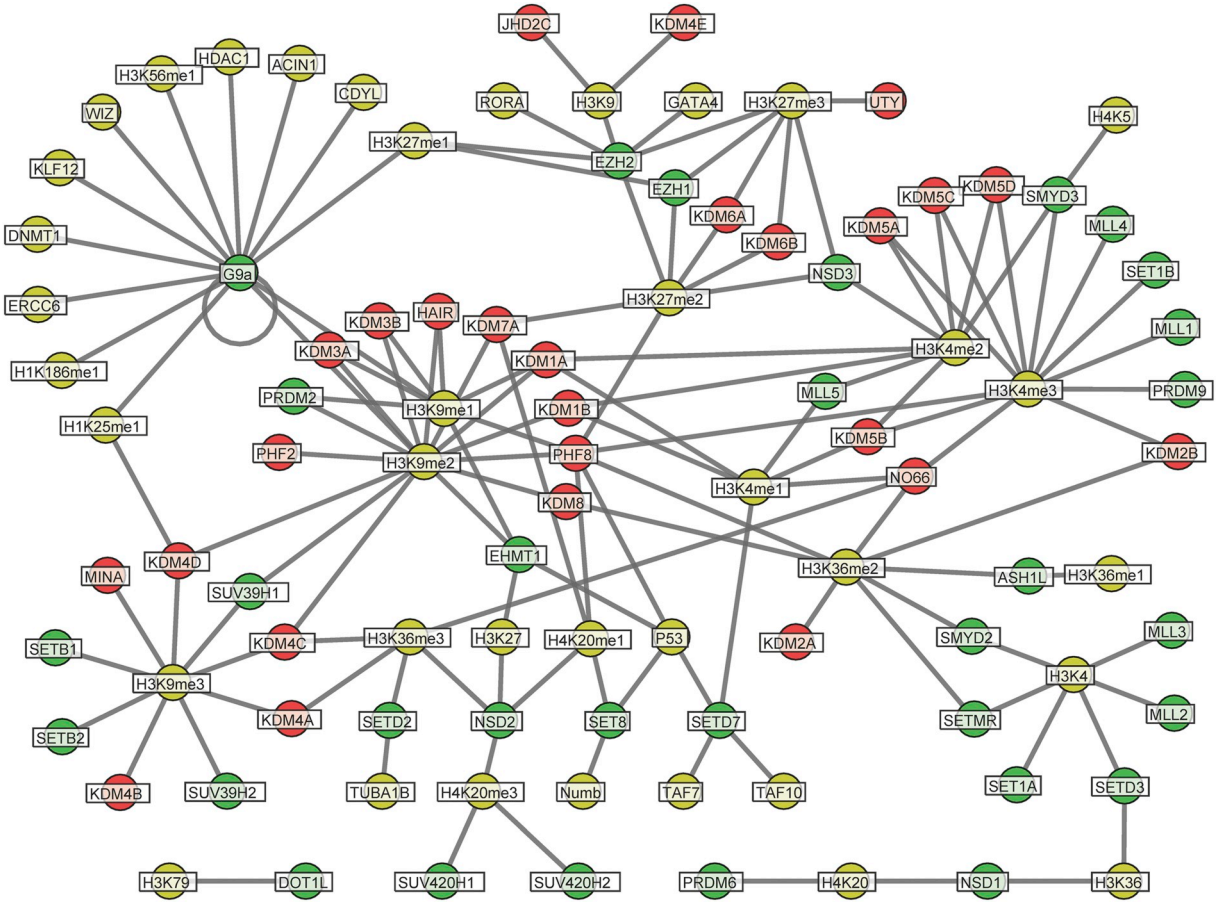


**Fig. 1.** The writer-code-eraser network of lysine methylation. The network of lysine methylation sites (yellow), methyltransferases (green) and demethylases (red) were generated by NAViGaTOR software, using information extracted from HIstome Infobase, Uniprot database and literatures. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

implicated in the regulation of chromatin structure in the nervous system (Kundakovic et al., 2017; Penas and Navarro, 2018) and abnormal epigenetic modifications have been detected in various neuropsychiatric disorders (Nestler et al., 2016; Shimada et al., 2018). Herein, we focus on the function of lysine methylation and corresponding writing or erasing enzymes in nervous system diseases.

H3K4 methylation plays an important role in neuronal differentiation, particularly in axon growth and the development of myelin cells (Qiao et al., 2018; Shen et al., 2014). H3K4me3 is proposed to be an active marker involved in the development of human prefrontal cortex (PFC) from prenatal to peripubertal ages and throughout adulthood. The level of H3K4me3 has been found decreased in schizophrenia, resulting in decreased glutamate decarboxylase 1 (GAD1) expression and the impaired glutamatergic neurotransmission (Bator et al., 2018; Huang et al., 2007). However, in many other diseases, H3K4me3 levels are increased. In the polyalanine (polyA)-expansion-encoding mutations of aristaless-related homeobox (ARX)-mediated X-linked ID (XLID) diseases and chronic epilepsy, H3K4me3 levels were elevated (Poeta et al., 2013). In specific gene promoter regions (early growth response 1 (ZIF268) and brain derived neurotrophic factor (BDNF)), the level of H3K4me3 increased in the hippocampus 1 h following contextual fear conditioning, and returned to baseline levels by 24 h (Gupta et al., 2010). Increasing level of H3K4me3 was also found to be correlated with increasing level of DNA 5hmc in area (Cornu Ammonis 1) CA1 of the hippocampus, indicating an important link between histone methylation and DNA hydroxymethylation mechanisms in the epigenetic control of *de novo* gene transcription triggered by memory retrieval (Webb et al., 2017). Downregulation of Kmt2b, a key regulator in memory function, was linked to reduced level of H3K4me3 in the corresponding promoter regions, revealing a specific role of H3K4me3 in the regulation of plasticity genes in the dorsal dentate gyrus of the hippocampal formation (Kerimoglu et al., 2013). Investigation in post-mortem brain samples found that H3K4me3 levels were significantly enriched at the promoter region of synapsin gene (*SYN2)* distinctly for bipolar disorder (BD) and major depression disorder (MDD). The gene expression of *SYN2a* in BD, and *SYN2b* in MDD, are regulated, at least in part, by changes in H3K4me3 levels at the SYN2 promoter (Cruceanu et al., 2013). Interestingly, acute and chronic stress showed different effect on H3K4me3 levels. Acute stress had no effect on levels of H3K4me3. Seven days of restraint stress reduced levels of H3K4me3 in the CA1 (Hunter et al., 2009). H3K4me3 also plays vital role in neurodegenerative disease. H3k4me3 was found to be cytoplasmic accumulated in human Alzheimer's disease (AD) brain, indicating that cytoplasmic accumulation of H3K4me3 as an early event in AD cell pathology (Mastroeni et al., 2015). In two different models of MPTP-induced Parkinson's disease (PD), dopamine depletion was associated with a reduction in H3K4me3 (Habibi et al., 2011). H3K4me3 levels were lowered at *Bdnf* and other promoters in R6/2 mice and key neuronal genes in human HD brain cortex and striata, and H3K4me3 specifically played a critical role in the pathway leading to transcriptional dysregulation in Huntington disease (HD) (Vashishtha et al., 2013).

H3K9me2 is a complicatedly regulated marker in the nervous system. Primary cultures of 3xTg-Alzheimer's disease (AD) mouse showed increased H3K9me2 levels, and this elevated level of H3K9me2 could diminish *Bdnf* expression, more dominantly than the hyperacetylated marks in 3xTg-AD neurons (Walker et al., 2013). Elevated H3K9me2 at the promoter region of synaptosome associated protein 25 (SNAP25) affects small NF90 (ILF3) associated RNA E (SNARE)

complex assembly and hence synaptic vesicle fusion events regulated by α-synuclein. The H3K9me2 increased mark results in transcriptional repression. Accordingly, *L1CAM* and *SNAP25* mRNA levels were reduced afer αS induction. Conversely, mRNA expression of the zinc transporter *SLC39A3* was increased. (Sugeno et al., 2016). However, lower H3K9me2 levels have been observed in a TAU drosophila AD model and in human samples, and mRNA expression detection indicated that Su(var)3–9, which encodes the main histone methyltransferase responsible for H3K9 dimethylation, and Su(var)205, which encodes HP1α, were equal between control and tau transgenic Drosophila heads, indicating that the loss of H3K9me2 and HP1α in tauopathy was not a result of transcriptional changes in these genes (Frost et al., 2014). Similarly, contextual fear learning increased the global levels of H3K9me2 in CA1 region (Gupta-Agarwal et al., 2012) while a decrease in H3K9me2 levels was observed in the nucleus accumbens (NAc) of mice with subchronic social defeat stress, which was indicated to mediate resilience to chronic social stress. (Covington 3rd et al., 2011). As to memory storage, increasing level of H3K9me2 levels in the lateral amygdala (LA) at 1 h following auditory fear conditioning, which continued to be temporally regulated up to 25 h following behavioral training. While inhibiting the H3K9me2 histone lysine methyltransferase G9a (H/KMTs-G9a) in the LA impaired fear memory, while blocking the H3K9me2 histone lysine demethylase LSD1 (H/KDM-LSD1) enhanced fear memory (Gupta-Agarwal et al., 2014). Interestingly, H3K9me2 levels increased in the hippocampus of aged adults, and LSD-1 histone demethylase inhibitor treatment increased baseline resting H3K9me2 levels in the young adult hippocampus (Morse et al., 2015). H3K9me2 also plays important roles in schizophrenia and Fragile X Syndrome. The baseline levels of H3K9me2 increased in patients with schizophrenia, and there was a significant negative correlation between age at onset of illness and levels of H3K9me2 (Gavin et al., 2009). The undifferentiated Fragile X Syndrome (FXS) hESC lines exhibited a decreased H3K9me2 level. However, in differentiated FXS cells, the FMR1 promoter switched to the repressive H3K9me2 mark (Colak et al., 2014). Besides H3K9me2, the level of histone H3 lysine 9 trimethylation (H3K9me3) was substantial and regionally specific induced an increase in hippocampal by acute (30 min) restraint stress (Hunter et al., 2012). H3K9me3 is associated with heterochromatin formation and the large changes observed suggested a rapid (less than 2 h) and global chromatin reorganization (Hunter et al., 2009). In addition, H3K9me3 in the hippocampus improves spatial memory in aged mice but not in young mice and H3K9me3 inhibition improves memory, promotes spine formation, and increases BDNF levels in the aged hippocampus (Snigdha et al., 2016).

H3K27 methylation is dynamically regulated in the mature brain and is involved in the pathogenesis of major psychiatric diseases (Braidy et al., 2018; Ernst et al., 2009; Guo et al., 2018; Singh-Taylor et al., 2018; Tsankova et al., 2006). PRC2 is the primary writer of di- and tri- methylation of H3K27, which leads to the recruitment of PRC1 (Nichol et al., 2016). EZH2 specifically trimethylates H3K27, leading to target gene silencing (Bracken et al., 2006). Counterparts of these repressive complexes are the histone demethylases KDM6A and KDM6B, which can specifically remove methyl marks of H3K27, and are able to activate silenced genes (Bracken et al., 2006). Defeat stress robustly increased H3K27 dimethylation (H3K27me2) at the brain derived neurotrophic factor (*Bdnf*) promoter and induced lasting down-regulation of its transcripts III and IV (Tsankova et al., 2006). This chromatin modification leads to a more 'closed' chromatin state and thereby mediates the stable repression of the *Bdnf* gene. The total H3K27 methylation level was also increased in the brains of people who committed suicide, statistically correlated with the expression level of the BDNF receptor tropomyosin-related kinase B.T1 (TrkB.T1) (Ernst et al., 2009). Interestingly, H3K27me3 levels were reduced in the dentate gyrus (DG) and CA1 after acute stress, and reducing level of H3K27me3 may contribute to chronic stress induced remodeling of the hippocampal formation (Hunter et al., 2009). This provides a perfect example that a single methylation state doesn't reflect the total methylation levels even on the same residue, which is reasonable because H3K27me1 is an active marker while H3K27me3 is a repressive one (Wang et al., 2008). H3K27me3 levels increased in male rats retrieval of a contextual fear memory, and EZH2-mediated H3K27me3 plays a critical role in the repression of *Pten* transcription necessary for AKT-mTOR activation and memory reconsolidation following retrieval (Jarome et al., 2018). In HD, increased H3K27 methylation tend to rescue HTT-induced HD pathology while those that tend to decrease H3K27 methylation lead to more aggressive HD pathology (Song et al., 2018).

Other lysine methylation sites also play an important role in nervous system diseases. For example, H2BK108me1 was decreased in the frontal cortex from human donors with AD (Anderson and Turko, 2015). H3K9me3 levels were increased in the DG and CA1 following acute stress (Hunter et al., 2009). H4K20 methylation as critically important for the biological processes. SET8/PR-Set7 that catalyses monomethylation of H4K20, whereas SUV4-20H1 and SUV4-20H2 enzymes mediate further H4K20 methylation to H4K20me2 and H4K20me3. (Jorgensen et al., 2013). H4K20 methylation is important for genome integrity, such as DNA damage repair, DNA replication and chromatin compaction. Lysine methylation occurs on both histone and non-histone proteins, but our knowledge on the methylation of non-histone proteins has lagged behind. Our knowledge on the methylation of non-histone proteins remained to be determined at the proteome level. On the genome level, data on protein methylation are sparse compared to protein phosphorylation. (Liu et al., 2013; Moore et al., 2013). In recent years, a large number of Lys methylation (Kme) sites and Arg methylation (Rme) sites from non-histone proteins have been identified, indicating that non-histone lysine methylation is more prominent than expected (Liu et al., 2013b; Ong et al., 2004). To further understand the function of lysine methylation, we firstly extracted human proteins involved in nervous system relating biological process from Uniprot database. Then we checked their lysine methylation conditions documented by PhosphoSitePlus database (Hornbeck et al., 2015). The methylated nervous system relating proteins were analyzed by String database. The interactions within them were presented in Fig. 2 with high confident cut-off. Interestingly, lysine methylation seems like enriched in gene expression pathways (in blue), especially in SWI/SNF superfamily-type complex (in red).

## 2. Lysine methylation writers and erasers in nervous system diseases

Mixed-lineage leukemia 1 (MLL1) is a H3K4me3 specific KMT. Although less than 5% of promoters' signal is regulated by MLL1 (Wang et al., 2009), it may play a more important role in the nervous system than the general regulators SET1A/B. Mutations in MLL1 are thought to be responsible for the majority of Wiedemann–Steiner syndrome cases (Jones et al., 2012). Neuronal ablation of MLL1 in mouse postnatal forebrain and adult PFC is associated with the increased anxiety and robust cognitive deficits. In contrast, only mild behavioral phenotypes were observed after ablation of the MLL2 in the PFC (Jakovcevski et al., 2015). Similarly, Shen et al. reported that conditional deletion of MLL1, but not MLL2, in postnatal forebrain, is associated with the excessive nocturnal activity and the absent or blunted responses to stimulants or dopaminergic agonist drugs, in conjunction with a substantial loss of spike-timing-dependent long-term potentiation in medium spiny neurons (MSNs) (Shen et al., 2016). H3K4me2/3 specific KDMs, such as KDM5A, KDM5C and KDM5D, may be erasers of the H3K4me3 mark in the nervous system (Fig. 1). Missense mutations in KDM5A have been linked to an autosomal recessive form of intellectual disability (Najmabadi et al., 2011). Deleterious mutations of KDM5C were detected in autism patients (Adegbola et al., 2008), and in individuals with mental retardation and short stature and hyperreflexia (Abidi et al., 2008).

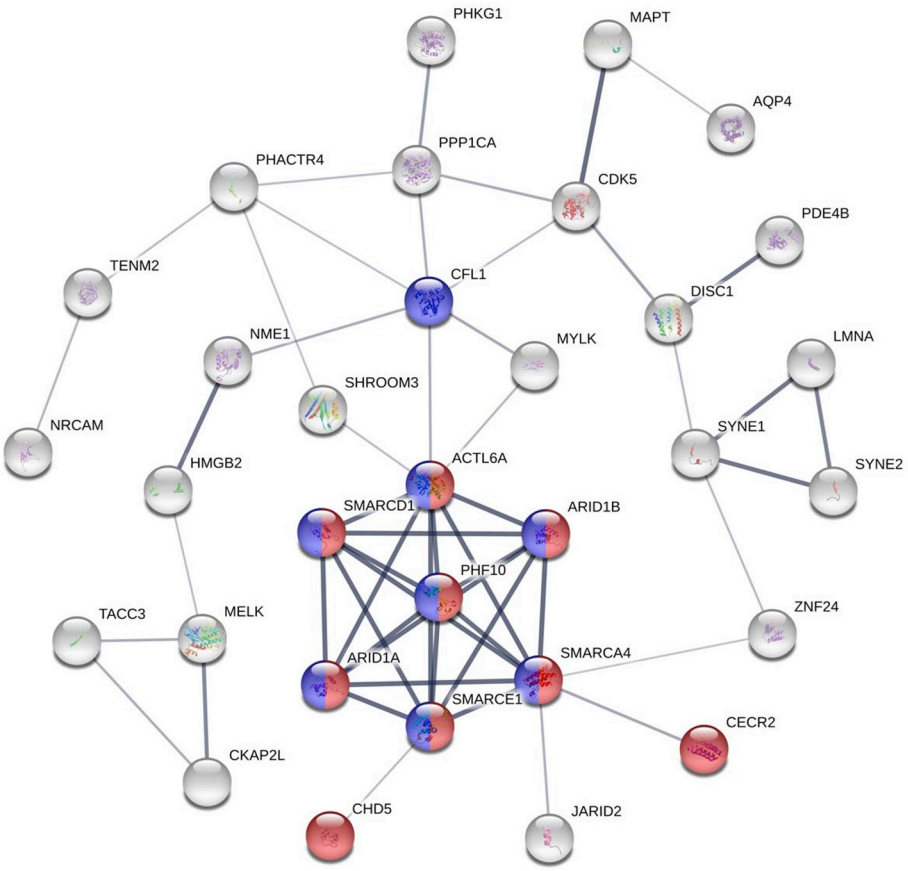


**Fig. 2.** Lysine methylated nervous system relating proteins. Human proteins involved in nervous system relating biological process were extracted from Uniprot database. Their lysine methylation conditions were documented by PhosphoSitePlus database. The interaction between methylated nervous system relating proteins were presented by String database using high confident cut-off score (Blue, involved in gene expression; Red, SWI/SNF superfamily-type complex proteins). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The EZH1 and EZH2 of polycomb repressive complex 2 (PCR2) are KMTs responsible for creating all three states of methylation on H3K27 (Fig. 1). EZH2 is essential for cortical progenitor cell and neuron production, and loss of EZH2 depletes H3K27me3 in cortical progenitor cells. This is associated with severe thinning of the cerebral cortex and a disproportionate loss of neurons residing in the upper cortical layers I–IV (Pereira et al., 2010). EZH2 competes with MLL1 in forming a complex with polycomb protein embryonic ectoderm development (EED). The EZH2-EED complex is common during neurodevelopment while EED-MLL1 is associated with brain maturation, which is the main reason for the fluctuation in H3K27me3 and H3K4me3 levels during the neurodevelopment (Kim et al., 2007). KDM6B specifically removes H3K27me3 in ES cells to release lineage-specific gene repression in differentiated cells (Burgold et al., 2008). In KDM5C knockdown mice, multiple genes involved in GABAergic neurotransmission were upregulated, and promoters of these genes contain increased levels of H3K4me3 (Xu and Andreassi, 2011).

G9a mediated H3K9me2 critically regulates ethanol-induced neurodegeneration in the developing brain (Subbanna et al., 2013). G9a leads to derepression of numerous non-neuronal and neuron progenitor genes in adult neurons. G9a controlled histone H3K9me2 in regulation of brain function through maintenance of the transcriptional homeostasis in adult neurons (Schaefer et al., 2009). Overexpression of G9a in the NAc after repeated doses of cocaine protected mice from the consequences of subsequent stress (Covington 3rd et al., 2011). Inhibition of G9a in the entorhinal cortex (EC) enhanced contextual fear conditioning relative to control animals. Interestingly, the decreasing of G9a activity in the EC enhanced H3K9me2 levels in the CA1, resulting in transcriptional silencing of the non-memory permissive gene COMT in the hippocampus (Gupta-Agarwal et al., 2012). It is likely that other H3K9 specific KMTs (Fig. 1) play roles subsequent to G9a inhibition. PRDM2, another H3K9me1/2 KMT (Congdon et al., 2014; Kim et al., 2003), contributed to gene expression changes that alter synaptic functioning, particularly by affecting calcium channel activities in the dorsomedial prefrontal cortex of alcohol dependence rat (Barbier et al., 2016). Although the mechanism is not clear, mutations on PHF8, a H3K9me1/2 demethylase, results in mental retardation and facial deformity such as cleft lip and palate(Feng et al., 2010; Kleine-Kohlbrecher et al., 2010).

## 3. Implication of lysine methylation-based interference in nervous system

Due to the importance of lysine methylation, lysine methylation-based interference has huge application potential in nervous system disease therapy. The KDM1 family member KDM1A had been known to form part of nuclear complexes (Maes et al., 2015), and it was involved in transcriptional regulation and was identified as a lysine specific demethylase in the normal brain and in neurodegenerative disease (Kegel et al., 2002; Van Raamsdonk et al., 2005). KDM1A can demethylate mono- and dimethylated H3K4, and it exhibits high specificity over dimethylated H3K9, 20, 27, 36 and 79 *in vitro* and in cells (Shi et al., 2004). The old antidepressant and anxiolytic agent TCP (Parnate) was reported that it can also inhibit KDM1A. Currently the selective irreversible KDM1A inhibitor ORY-1001 has already been developed, which provokes a time and dose-dependent induction of the *Cd11b* differentiation (Morera et al., 2016). In additiona, several selective EZH2 inhibitors have been developed and implicated in nervous system disease treatment (Pan et al., 2018). Furthermore, one EZH2 inhibitor EPZ-6438 (tazemetostat or E7438) progresses quickly and is now in three phase 2 clinical trials (NCT01897571, NCT02860286 and NCT02601950) (Pan et al., 2018). This shows that the design of methylation-based interference has great potential in the nervous system disease investigation and therapy.

## 4. Future directions

Studies about histone methylation bear great promise to enhance knowledge regarding the mechanisms of nervous system diseases. Advanced approaches will also shed light on how the histone methylation landscape of the human brain is shaped during development and altered in psychiatric diseases. The in-depth research on nervous system epigenetics may provide potential therapeutic targets for nervous system diseases. Despite our growing understanding of these mechanisms, future studies, particularly on the cross talk of histone codes, KMT or KDM specificities and the function of non-histone protein methylation, is needed to address a large amount of challenges.

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