Jumonji family histone demethylases in neural development

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Abstract

Central nervous system (CNS) development is driven by coordinated actions of developmental signals and chromatin regulators that precisely regulate gene expression patterns. Histone methylation is a regulatory mechanism that controls transcriptional programs. In the last 10 years, several histone demethylases (HDM) were identified as important players in neural development, and their implication in cell fate decisions is beginning to be recognized. Identification of the physiological roles of these enzymes and their molecular mechanisms of action will be necessary for completely understanding the process that ultimately generates different neural cells in the CNS. In this review, we provide an overview of the Jumonji family of HDMs involved in neurodevelopment, and we discuss their roles during neural fate establishment and neuronal differentiation.

Keywords

Histone demethylation, Jumonji family, neural specification, neuronal differentiation, developmental signals

Introduction

The CNS is formed by different cell types that are generated during neural development. Neural progenitor cells (NPCs) proliferate to maintain their population, and at the same time, they differentiate, first to generate neurons, then oligodendrocytes and astrocytes (Guillemot, 2005). These complex processes occur in response to a variety of developmental cues, and their completion requires close coordination between transcription factors, extrinsic signals, and chromatin-modifying enzymes. The developmental signals and transcription factor families that control neurogenesis have been studied for many years, and they are quite well established (Lee and Pfaff, 2001,

Guillemot, 2007). However, recently, factors that interact with chromatin have emerged as regulators of neurogenesis and neural development. During the last decade, great efforts have been made to elucidate the role of epigenetic regulators that govern the transcriptional programs involved in neural development.

Eukaryotic DNA is organized into nucleosomes; this organization provides both a compact package of genetic material and a new layer of regulation for controlling its activity. Each nucleosome is composed of a DNA strand of 145-147 base pairs and two molecules each of histones H3, H4, H2A, and H2B. Moreover, the linker histone, H1, is required to compact the chromatin into high-order structures (Luger, 2003, Kouzarides, 2007). The amino-terminal domains of H3, H4, H2A, and H2B undergo different types of post-translational modifications, mainly acetylation, methylation, phosphorylation, ubiquitination, and sumoylation (Kouzarides, 2007, Bannister and Kouzarides, 2011). These modifications evoke dynamic changes in the chromatin structure, which are essential for responding to both extrinsic and intrinsic signaling cues. In many cases, these responses lead to changes in gene expression that ultimately control transcriptional programs during development.

Although histone acetylation is the most studied and characterized histone modification (Kouzarides, 2007, Bannister and Kouzarides, 2011), in the last few years, many enzymes that catalyze the addition or removal of methyl groups from histones have been identified and widely studied. Methylation of histones can occur on lysine (K) and arginine (R) residues; in addition, K residues can undergo mono- (me1), di- (me2), or tri-methylation (me3), and R residues can undergo me1 and me2, positioned either symmetrically or asymmetrically.

For many years, it was believed that histone methylation was an irreversible modification, and that the removal of methyl groups required a histone exchange. However, the finding that histone methylation patterns could respond to many signals in a reversible manner suggested that methylation/demethylation is a much more dynamic process than previously thought. The identification of the first histone demethylase (HDM) in 2004 (Shi, et al. 2004) confirmed this possibility. During the last decade, many HDMs have been identified (Table1). They were classified into two families: (i) the KDM1 family, whose members demethylate H3K4me2/1 and H3K9me2/1 in a flavin-adenine-dinucleotide dependent reaction (Shi, et al. 2004, Metzger, et al. 2005, Ciccone, et al. 2009); and (ii) the Jumonji (JMJC) family (Jumonji-c domain containing proteins), whose members utilize Fe(II) and 2-oxoglutarate in the demethylation reaction. The first JMJC HDM was identified in 2006 (Tsukada, et al. 2006). Since then, this family has greatly grown in number, and it includes enzymes that target me1, me2, and me3 histones [(Kooistra and Helin, 2012), Table 1].

Histone methylation is associated with both transcriptional activation (H3K4me3, H3K36me3, and H3K79me3/me2/me1) and repression (H3K9me3/me2, H4K20me3, and H3K27me3/me2). Interestingly, a combination of active and repressive histone methylations occurs in many promoters, and mainly in embryonic stem cells (ESCs). In particular, sites that carry H3K27me3 are often also enriched in H3K4me3. Sites marked by this combination of histone modifications with opposite regulatory potential are called bivalent domains, and they are thought to be responsible for maintaining genes in a poised state for activation (Azuara, et al. 2006, Bernstein, et al. 2006). Accordingly, many chromatin-acting complexes contain both histone methyltransferases (HMT) and HDMs that catalyze functionally opposing modifications. For example, the one comprising MLL3-MLL4 H3K4me3 HMTs

combined with a H3K27me3 HDM, UTX (Agger, et al. 2007, Lee, et al. 2007b); another containing a H3K4me3 HDM, JARID1A (jumonji, AT-rich Interactive domain 1A) together with polycomb responsive complex 2 (PRC2), which is responsible for H3K27me3 methylation (Pasini, et al. 2008). These close associations might facilitate coordinated chromatin modifications and ensure methylation balance is maintained for regulating proper development. Moreover, histone methylation occurs together with other histone modifications, mainly histone acetylation. Accordingly, HDMs are present in large protein complexes that often contain other histone-modifying enzymes; for example, the JARID1C H3K4me3/me2 HDM is associated with histone deacetylases (HDAC) HDAC1 and HDAC2, the HMT G9a, and the transcriptional repressor REST [(Tahiliani, et al. 2007), see below]. These associations facilitate coordinated interactions of different enzymes with multiple histone sites. Then, although a particular modification might correlate with either transcription activation or repression, the combination of histone modifications will determine the final biological output (de la Cruz, et al. 2005, Taverna, et al. 2007, Lois, et al. 2010).

During the last few years, it was proposed that HDMs played a central role in development, particularly in a neural context, and in diseases (Lee and Lee, 2010, Pedersen and Helin, 2010, Pattaroni and Jacob, 2013) (Table 2). However, we are just beginning to understand the molecular mechanisms through which HDMs cooperate with signals, to coordinate neural development. In this review, we briefly summarize the roles of Jumonji family members in different aspects of neurogenesis. In addition, we will highlight the major questions that remain open for future investigation.

Function of Jumonji demethylases in neural development

The first identified protein containing Jumonji-c domain was JARID2 that interestingly lacks the histone demethylase activity. However, it is essential for normal embryonic development and in particular for neural development (Landeira and Fisher, 2011). JARID2 associates with PRC2 to facilitate the latter's recruitment to target genes (Peng, et al., 2009, Shen, et al., 2009, Pasini, et al., 2010). As PRC complexes are required at different steps of neurogenesis, JARID2 might contribute to neural development by regulating PRC recruitment. The rest of proteins with a Jumonji-c domain are catalytically active and they are classified into subfamilies (HDM2/7). Each one contains different enzymes that target a particular lysine/s mainly on histones H3 and H4. They are highly specific for both K residues and degree of methylation (Table 1). Recently, many reports highlight the importance of the equilibrium between HMT and HDM enzymatic activities in the control of the final state of histone methylation during neural development. This is a key determinant of both neural commitment in ESCs and cell fate determination in NSCs. In accordance with that notion, many reports have proposed an essential role of PRC2 during neural development. PRC2 occupies and represses many neural-developmental regulators in ESCs (Boyer, et al. 2006, Bracken, et al. 2006, Lee, et al. 2006); moreover, H3K27me3 levels decrease in many neural-specific genes during neural differentiation (Boyer, et al. 2006, Burgold, et al. 2008). PRC complexes are also required for NPCs differentiation. High levels of Enhancer of Zeste Homologue 2 (EZH2), the enzyme in PRC2 that methylates H3K27me3/me2, are required for NPC differentiation to oligodendrocytes. Conversely, *Ezh2* expression decreases to allow neuronal and astrocytic differentiation (Sher, et al., 2008). Finally, during the neurogenic to astrogenic transition, PRC proteins suppress neurogenic competence of NPCs by inhibiting *Neurog*1 expression. At the late stage of

NPCs, histone acetylation of the *Neurog*1 promoter decreases and H3K27me3 increases leading to repression of *Neurog*1 (Hirabayashi, et al., 2009).

Another good example remarking the importance of the balance between the histone methylation and demethylation is the regulation of the *GFAP* promoter during differentiation of NPCs into astrocytes. At this stage of development, FGF2 induces the decrease of H3K9me3 and the increase of H3K4me3 levels on the *GFAP* promoter leading to the activation of this astrocyte-specific marker (Song and Ghosh, 2004).

In this review we will discuss the function of the different HDMs controlling the histone methylation levels during neural development. Among them, we will mainly focus on those targeting H3K4 and H3K27 sites, because they have been associated with the major neural phenotypes.

KDM5 Subfamily

The KDM5 subfamily members catalyze the demethylation of H3K4me3/me2 (Christensen, et al. 2007, Iwase, et al. 2007, Klose, et al. 2007, Lee, et al. 2007a, Tahiliani, et al. 2007, Yamane, et al. 2007). The mammalian family comprises the JARID1A-D proteins (Table 1). These enzymes, particularly JARID1B and C, are involved in different aspects of neural development.

Recent work with *Jarid1B* knockout mouse embryos revealed that this HDM performs essential functions in neural development. Deletion of *Jarid1B* led to several neural defects, including disorganized cranial nerves, defects in eye development, and an increased incidence of exencephaly (Albert, et al. 2013). JARID1B binds to neural master regulator genes such as *Pax*6 and *Otx*2, to maintain low levels of H3K4me3. In

Jarid1B KO embryos, increased levels of H3K4me3 were associated with both repressed and bivalent genes, which made these genes more susceptible to activation (Albert, et al. 2013) (Fig. 1). Furthermore, ESCs require JARID1B activity for proper differentiation into neurons (Schmitz, et al. 2011). On the other hand, *Jarid1B* over-expression in ESCs decreased the expression of other genes that regulate cell fate decisions, like *Egr1*, *p27*, and *BMI1*. These findings demonstrated that JARID1B plays an important role in balancing proliferation and differentiation during development (Dey, et al. 2008).

The best-known member of the KDM5 subfamily is JARID1C. JARID1C is strongly related to X-linked mental retardation (XLMR) and epilepsy (Jensen, et al. 2005, Tzschach, et al. 2006, Tahiliani, et al. 2007, Jensen, et al. 2010). The mutations found in patients with XLMR frequently compromise JARID1C HDM activity (Iwase, et al. 2007, Tahiliani, et al. 2007). Shi's group has shown that, in combination with REST, G9a, and HDAC1/2, JARID1C repressed a subset of the REST target genes by binding to the neuron-restrictive silencing elements in their promoters. Thus, the JARID1C/REST complex maintains the neuronal genes silenced in non-neuronal cells. Additionally, when *Jarid1C* was knocked down in primary rat cerebellar granule neurons, dendritic morphogenesis was impaired. Moreover, studies in zebrafish demonstrated that Jarid1C plays a role in brain-patterning establishment and neuronal survival (Iwase, et al. 2007).

Taken together, the published data indicate that the JARID1 family is critical for normal neural development. Its major role is to fine-tune the expression of important neural regulators by maintaining appropriate H3K4me3 levels to ensure a balance between active and repressive histone modifications. An alteration in this balance can

affect phenotypical outcome when the developmental transcription potential takes advantage of that.

The KDM6 subfamily

KDM6 subfamily members catalyze H3K27me3/me2 demethylation. This family includes UTX, JMJD3, and UTY proteins, although HDM activity has not been shown for UTY (Agger, et al. 2007, De Santa, et al. 2007, Lan, et al. 2007, Lee, et al. 2007b).

As described above, the H3K27 methylation status is essential for cell fate determination in stem cells. Accordingly, H3K27me3/me2 HDMs are involved in important aspects of neural development. Several studies have demonstrated that *JMJD3* (unlike *UTX*) is highly regulated at the transcriptional level in response to different developmental, differentiation, and stress-related signals. In a developmental context, *Jmjd3* was up-regulated during differentiation of ESCs to a neural lineage, and it was required for neuronal commitment (Burgold, et al. 2008). Besides, over-expression of *Jmjd3* in NPCs induced the expression of various neuronal genes in a HDM activity-dependent manner (Jepsen, et al., 2007). Moreover, it has been described a direct relation between JMJD3 and the corepressor SMRT (silencing mediator of retinoic acid and thyroid hormone receptor) that is essential for proper forebrain development. SMRT is necessary to maintain the NSC state, mediating the retinoic-acid- and Notch-dependent transcriptional response. In isolated NPCs, SMRT prevented retinoic-acid-receptor-dependent induction of neuronal differentiation in the absence of any ligand by repressing *Jmjd3*, which in turn participates in the activation of the neurogenic program (Fig. 2). Mechanistically, JMJD3 has been shown to cooperate with

a number of different signals during neural development. (i) In P19 cells, in response to retinoic acid (RA), JMJD3 was recruited by the Hes1 transcription factor to the *Mash1* promoter to facilitate efficient expression of the *Mash1* gene and to drive RA-induced neuronal differentiation (Dai, et al. 2010). (ii) *In vivo* experiments in the chick neural tube have demonstrated that TGFβ-induced neuronal differentiation was dependent on JMJD3 HDM activity (Estarás, et al. 2012). Moreover, in neural stem cells (NSCs), upon signaling activation, SMAD3 recruited JMJD3 to the promoter of TGFβ-responsive genes to facilitate transcription elongation, which allowed the TGFβ developmental program to proceed (Estarás, et al. 2012, Estarás, et al. 2013) (Fig. 3). (iii) In response to BMP pathway activation, JMJD3 interacted with SMAD1/SMAD4 to demethylate and activate the *NOGGIN* promoter during spinal cord development. At the same time, NOGGIN antagonized the BMP pathway, generating a negative-feedback regulatory loop, which controlled the dorsal interneuron generation mediated by JMJD3 HDM activity (Akizu, et al. 2010). These data point to JMJD3 as a critical integrator of neural developmental cues. Accordingly, a knockout of the mouse *Jmjd3* caused perinatal lethality due to an immature respiratory neuronal network (Burgold, et al. 2012). Furthermore, JMJD3 was shown to be essential for M2 microglia polarization. Suppressing *Jmjd3* in N9 microglia led to the inhibition of M2 polarization, an increase in M1 microglial inflammatory responses, and induction of neuronal death *in vitro* (Tang, et al. 2014).

These data suggested that JMJD3 is the member of the KDM6 subfamily that plays a central role in regulating H3K27me3/me2 levels in neural genes. Nevertheless, UTX has also been reported to play a functional role in neural development. Incorporation of UTX, but not JMJD3, into the *HOX* gene regions was required for RA-induced neural differentiation in hESCs (Shahhoseini, et al. 2013).

Several reports have suggested that non-histone proteins can also be targeted and regulated by both HMT and HDM enzymes (Huang, et al. 2007). Recent data have indicated that JMJC-mediated demethylation of non-histone substrates might contribute to neural differentiation. The interaction between JMJD3 and p53 during mouse NSC differentiation resulted in nuclear accumulation of p53 (Sola, et al. 2011). Another member of the p53 family, p63 (TAp63g), is a direct target of JMJD3 HDM activity. Through demethylation, JMJD3 stabilizes p63 and influences its cellular distribution to promote the correct expression of *p63*-regulated neural-specific genes (Fonseca, et al. 2012).

The KDM7 subfamily

The KDM7 subfamily, also called PHF (plant homeodomain finger), is the most recently identified HDM subfamily. In mammals, it consists of three proteins: KIAA1718 which targets H3K9me2/me1 and H3K27me2/1 (Horton, et al. 2010, Huang, et al. 2010b, Tsukada, et al. 2010); PHF8, which demethylates H3K9me2/me1 and H4K20me1 (Horton, et al. 2010, Liu, et al. 2010, Loenarz, et al. 2010, Qi, et al. 2010); and PHF2, which targets H3K9me2/me1 and H4K20me3 (Wen, et al. 2010, Baba, et al. 2011, Stender, et al. 2012,).

PHF8 is the best-known member of the subfamily, partly because *PHF8* mutations have been found in patients with XLMR or cleft lip/palate (Laumonnier, et al. 2005, Abidi, et al. 2007, Koivisto, et al. 2007). Interestingly, many of these mutations impair the HDM catalytic activity (Loenarz, et al. 2010, Qiu, et al. 2010, Yu, et al. 2010). How mutations on *PHF8* lead to XLMR remains unclear. Many studies have implicated PHF8 in the regulation of XLMR-related genes, including *JARID1C* (see

above). Moreover, PHF8 associates with a zinc finger protein that is related to XLMR, ZNF11 (Kleine-Kohlbrecher, et al. 2010). Recent data demonstrated that PHF8 HDM activity was essential for promoting cytoskeleton dynamics, and it was required for proper neurite outgrowth in mouse primary cortical neurons (Asensio-Juan, et al. 2012). Consistent with those findings, depletion of the zebrafish *PHF* homolog led to a decrease in tectum size, a loss of neurons, and craniofacial alterations (Qi, et al. 2010, Tsukada, et al. 2010). Although PHF8 is the most studied member of the KDM7 subfamily, another HDM of this subfamily has been associated with neural development. When *KIAA1718* was knocked down, neural differentiation was blocked in mouse ESCs. This proneural effect was due to the direct transcriptional activation of *FGF4,* a signaling component implicated in neural differentiation (Huang, et al. 2010b). In addition, KIAA1718 promoted neural induction in early chick embryos; its over-expression led to an expansion of the neural plate (Huang, et al. 2010a).

The HDM2/3/4 subfamilies

Although not so many data support a definite role for the KDM2, KDM3, or KDM4 subfamilies in neural development**,** we will point to some studies that reveal their importance in such a context. JMJD1C, a member of the KDM3 subfamily, that targets H3K9me2/me1 (Yamane, et al. 2006, Kim, et al. 2010, Kim, et al. 2012), has been recently shown to repress neural differentiation. JMJD1C binds and demethylates miR-302 promoter to induce miR-302 expression, which prevents neural induction (Wang, et al. 2014). The mammalian KDM4A subfamily includes four members: KDM4A (Klose, et al. 2006, Whetstine, et al. 2006, Trojer, et al. 2009), KDM4B (Fodor, et al. 2006, Whetstine, et al. 2006, Trojer, et al. 2009), KDM4C (Cloos, et al.

2006, Whetstine, et al. 2006, Trojer, et al. 2009) and KDM4D (Whetstine, et al. 2006, Shin and Janknecht, 2007, Trojer, et al. 2009). Interestingly, it was recently shown that KDM4A drives neural crest specification in the chick embryo; loss of KDM4 leads to a down-regulation of neural crest specifier genes due to demethylation of regulatory regions (Strobl-Mazzulla, et al. 2010). The KDM2 subfamily, which targets H3K36me2/me1 (Tsukada, et al. 2006, He, et al. 2008, Lagarou, et al. 2008) and H3K4me3 (Frescas, et al. 2007) was reported to be involved mainly in oncogenesis (Suzuki, et al. 2006, Pfau, et al. 2008).

Role of jumonji family in neurodevelopmental diseases

As described in the Introduction, histone methylation/demethylation equilibrium plays an essential role in development, particularly during neural development. Thus, it is not surprising that specific alterations in HMT and HDM activities correlate with neurodevelopmental disorders (Table 2). For example, changes in HDM activity, due to mutations in *JARID1C* and *PHF8*, have been linked to mental retardation and facial morphological alterations in humans. A close analysis of the *Jarid1C* expression pattern in mice indicated that it was highly expressed in the hippocampus, which points to a role in cognition. Moreover, studies performed in different animal models have demonstrated that JARID1C is involved in neuronal survival and dendritic development (Iwase, et al. 2007). Similarly, PHF8 HDM activity is required for neurite outgrowth (Asensio-Juan, et al. 2012). Thus, the XLMR associated with *PHF8* mutations might be due to deficient neuronal network establishment during development. Interestingly, the genes that encode *JARID1C* and *PHF8* are located on the X chromosome, where the genes that regulate cognitive functions are more represented than in autosomes

(Pattaroni and Jacob, 2013). Taken together, these data provide new insights into XLMR in humans, and they hint that HDM activity plays a critical role.

Other developmental diseases that have been directly or indirectly related to alterations in HDM activity include: (i) the Kabuki syndrome, which causes developmental delay and congenital anomalies; it has been recently associated with a deletion of the *UTX* gene (Lederer, et al. 2012); (ii) autism spectrum disorders (ASD) have been related with alterations in the activity of at least two HDMs: JARID1C (Adegbola, et al. 2008) and JMJD2C (Kantojarvi, et al. 2010).

Finally, several reports have suggested that JMJD3, UTX, and KDM2B HDMs might play critical roles in cranial neural tube development (Cox, et al. 2010, Fukuda, et al. 2011, Tsurubuchi, et al. 2013). For example, *Kdm2B*-deficient mice exhibited failure of neural tube closure, which led to exencephaly (Fukuda, et al. 2011). In addition, decreased levels of JMJD3 were found in the amniotic fluid and serum of pregnant women with neural tube defect-affected embryos (Tsurubuchi, et al. 2013). These data have opened the possibility that these HDMs, or their enzymatic activities, may serve as potential therapeutic targets and as biomarkers for associated conditions.

Conclusions and future perspectives

During neural development, a complex regulatory network controls transcriptional programs. In the last decade, HDMs have been identified as key components of this network (Fig. 4). In addition to methylation, other modifications on histones can fine-tune transcriptional activity at each developmental stage. Consequently, many HDMs and HMTs are found in multiprotein complexes that

contain other histone-modifying activities that coordinate the establishment of the final epigenetic landscape.

Although enormous progress has been made in the last few years in understanding the regulatory mechanisms that control the activity of HDMs, many questions remain open. It is particularly important to clarify how HDMs find their appropriate target genes in each different developmental context. HDMs act in coordination with intrinsic transcriptional programs and extrinsic signals. Thus, we speculate that direct interactions with transcription factors and the responses to developmental signals will determine how HDMs are recruited to specific sets of genes to provide a time- and space-appropriate response. How extrinsic signals control HDM activity remains an unanswered question. Developmental cues might affect their association with other histone-modifying enzymes, with transcription factors, or with other cellular components. In addition, extrinsic signals may directly modify the HDMs to alter their enzymatic activity, their stability, or their cellular localization.

Another unresolved question is: what is the cellular role of HDMs? Many data in the literature indicate that, although they contribute to transcriptional control, they do not play an instructive role during gene transcription; instead, they modulate the response to fine-tune the transcriptional output. The importance of non-histone substrate demethylation could also be relevant in HDM modulation of transcription. Moreover, many studies have confirmed that several HDMs play a role that is independent of HDM activity (Koyama-Nasu, et al. 2007, Secombe, et al. 2007, Lagarou, et al. 2008, Li, et al. 2008, Lee, et al. 2009, Miller, et al. 2010, DiTacchio, et al. 2011, Landeira and Fisher, 2011, Shpargel, et al. 2012). Experiments that address the role of HDM activity are essential for fully understanding the contribution of these enzymes to cellular responses.

To comprehend the role of HDMs, it will be important to characterize dynamic changes in genome-wide histone modification patterns and changes in their specific targets during development. Finally, the generation of more animal models to analyze *in vivo* functions at different developmental stages will be crucial for understanding the role of these enzymes in neural development and in neurodevelopmental diseases.

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Figure Legends

Fig. 1 Function of JARID1B in mouse neural development. **a** JARID1B maintains the low levels of H3K4me3 that are needed to repress key neural development genes, such as *Pax*6 and *Otx*2. **b** In *Jarid1b* KO embryos, H3K4me3 levels are increased, and a high neonatal lethality is observed together with several neurodevelopmental defects (Albert et al. 2013). Red arrows mean gene silencing, green arrows depict transcription activation

Fig. 2 SMRT repression of retinoic acid-dependent JMJD3 expression avoids neuronal differentiation**. a** SMRT blocks the expression of JMJD3 by counteracting its retinoic

acid-dependent activation. As a consequence, H3K27me3 at *Dlx5* promoter is not removed, the gene remains silent, and the NSC state is maintained. **b** In SMRT KO mice retinoic acid receptor (RAR) binds to the retinoic acid responsive element (RARE) and promotes *Jmjd3* transcription activation. Demethylation by JMJD3 causes *Dlx5* gene induction and NSC differentiation into neurons (Jepsen et al. 2007). Red arrows mean gene silencing, green arrows depict transcription activation

Fig. 3 JMJD3 cooperates with TGFβ signaling to induce expression of the neurogenic gene *Neurog2*. **a** In the absence of the signal, *Neurog2* remains silent due to the high levels of H3K27me3 on its promoter and coding region. **b** Upon TGFβ stimulation SMAD3 is recruited to the *Neurog2* promoter and targets JMJD3 to this region. **c** JMJD3 interacts with RNA polymerase II phosphorylated in serine 2 and promotes transcription elongation by demethylating the gene body (Estaras et al. 2012, Estaras et al. 2013). Red arrows mean gene silencing, green arrows depict transcription activation (small arrowhead: initiation, big arrowhead: high expression)

Fig. 4 JMJC histone demethylases are essential for progression from ESCs to terminal differentiated neurons. In ESCs, JMJD1C is necessary to maintain the stem cell state, while JARID1C, UTX, JMJD3 and KIAA1718 are required to promote neural commitment and differentiation from ESCs to NSCs. In addition, JMJD3 is fundamental to induce neurodifferentiation from NSCs, collaborating with RA, TGFβ and BMP pathways. Finally, the HDMs JARID1C and PHF8 contribute to the correct development and maintenance of axons and dendrites in mature neurons

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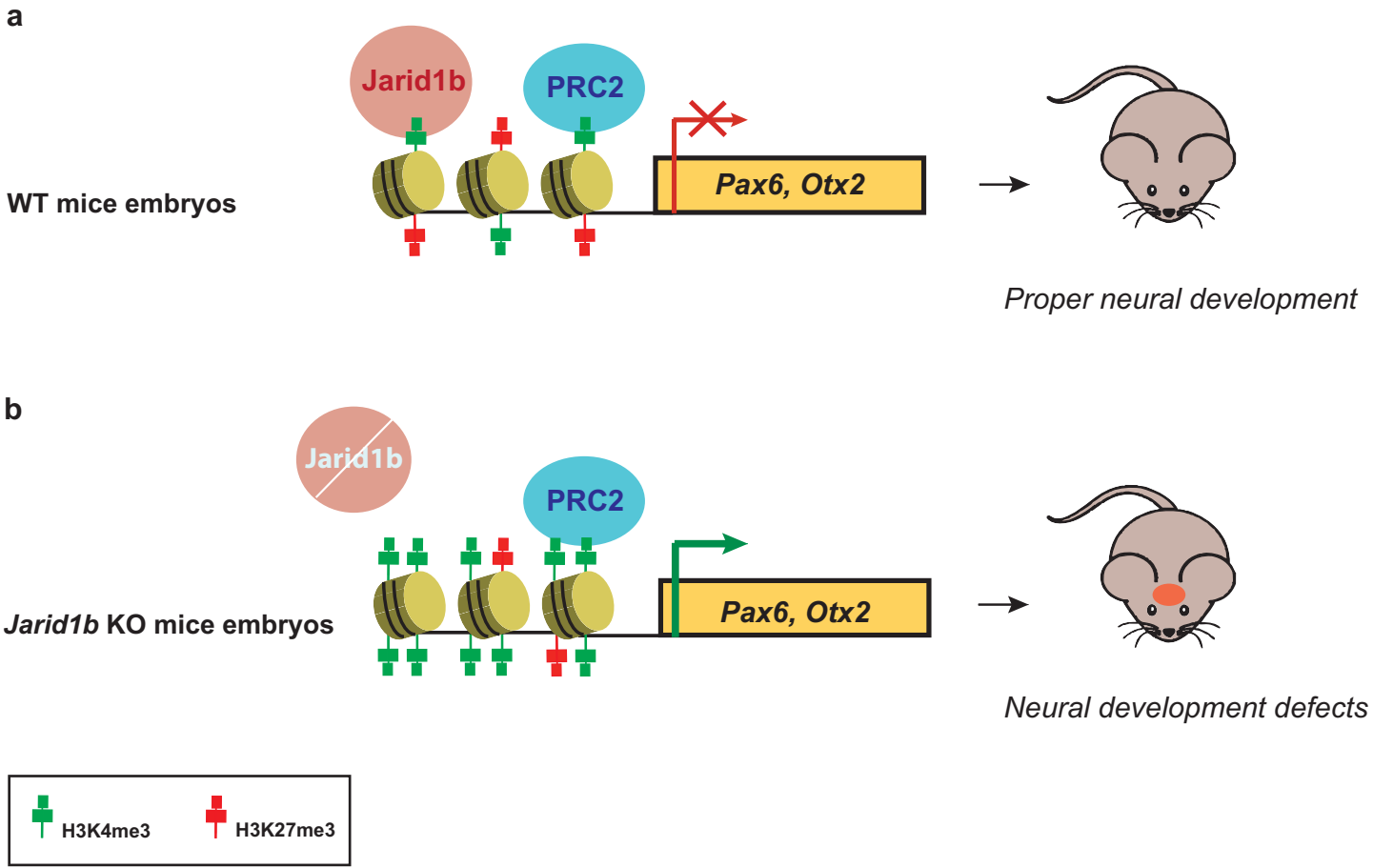
a
Jarid1b
PRC2
WT mice embryos
Pax6, Otx2
Proper neural development
b
Jarid1b
PRC2
Jarid1b KO mice embryos
Pax6, Otx2
Neural development defects
H3K4me3
H3K27me3

Figure 2

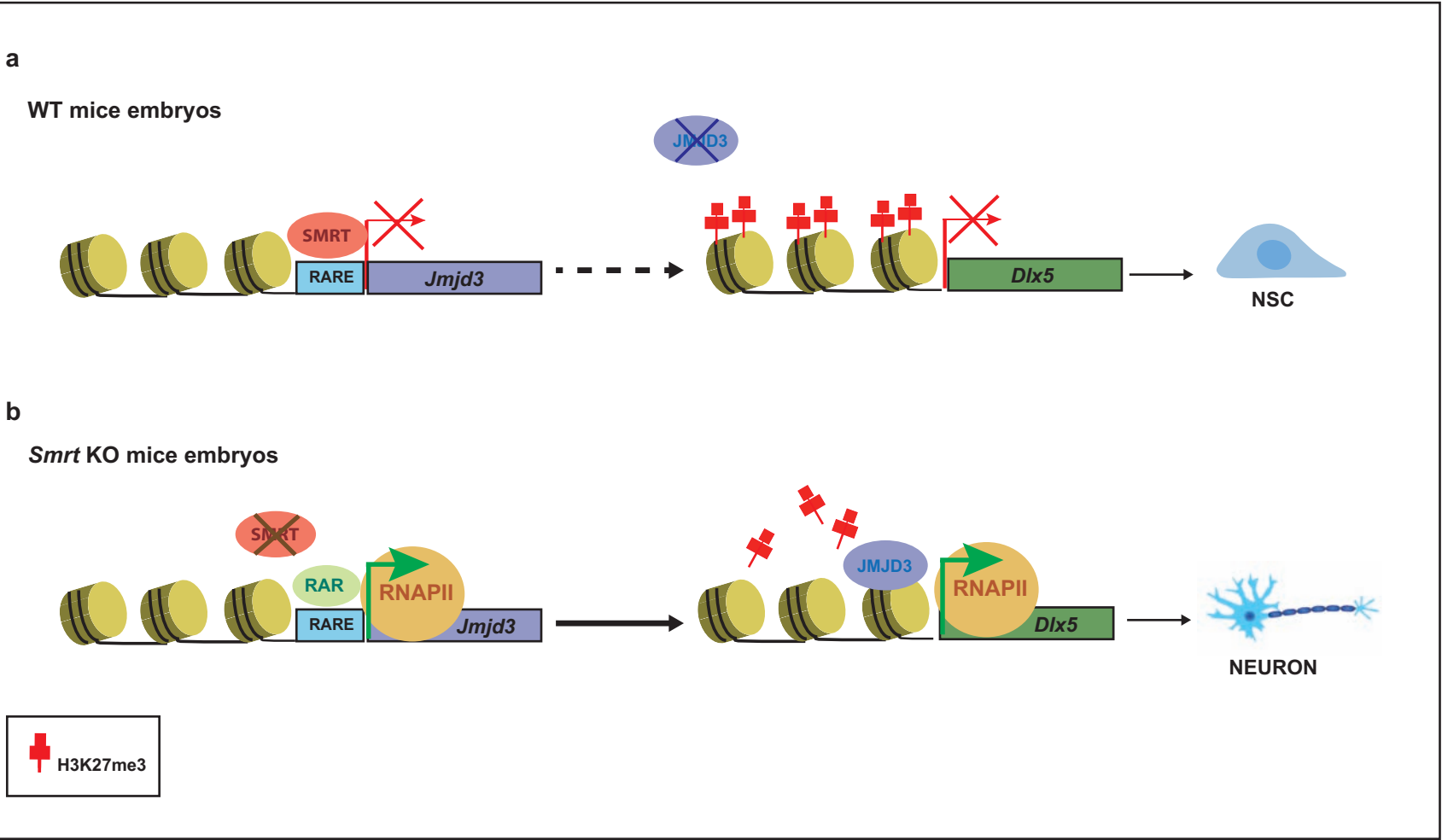
a
WT mice embryos
JMJD3
SMRT
RARE
Jmjd3
Dlx5
NSC
b
Smrt KO mice embryos
SMRT
RAR
RARE
RNAPII
Jmjd3
JMJD3
RNAPII
Dlx5
NEURON
H3K27me3

Figure 3

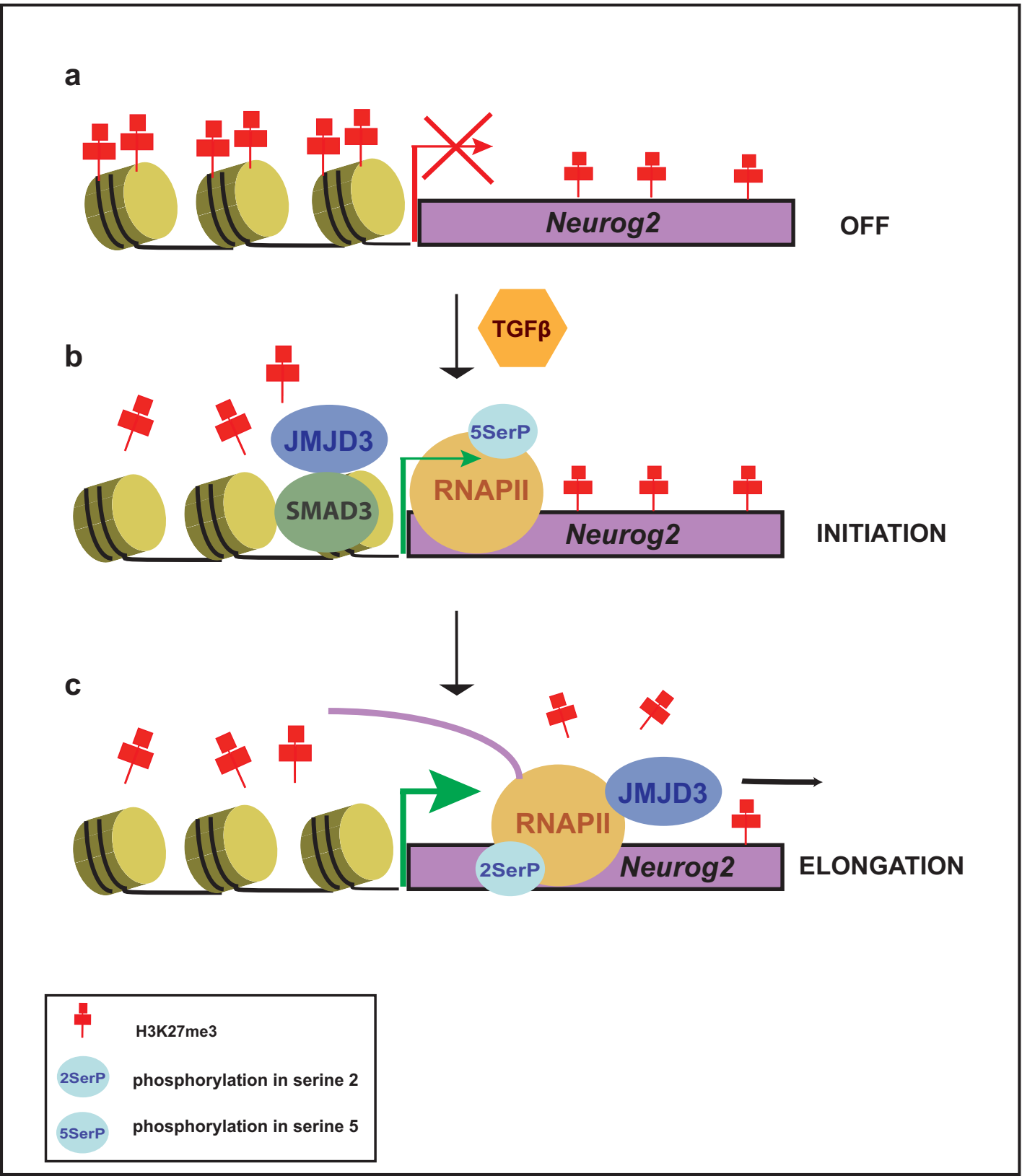
a
Neurog2
OFF
TGFβ
b
JMJD3
SMAD3
5SerP
RNAPII
Neurog2
INITIATION
c
RNAPII
JMJD3
2SerP
Neurog2
ELONGATION
H3K27me3
2SerP
phosphorylation in serine 2
5SerP
phosphorylation in serine 5

Figure 4

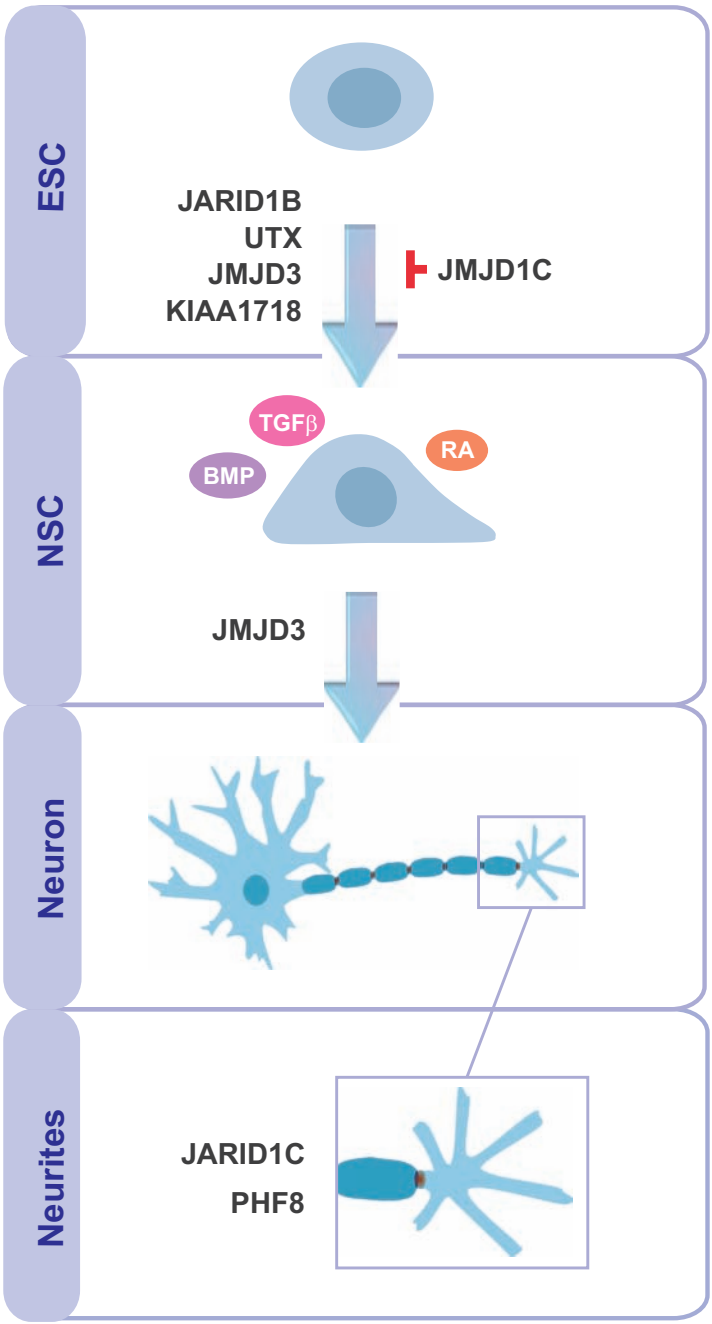
ESC
JARID1B
UTX
JMJD3
KIAA1718
JMJD1C
NSC
TGFβ
BMP
RA
JMJD3
Neuron
Neurites
JARID1C
PHF8

Table 1. Human histone demethylases

FAMILY	HDM	OTHER NAMES	HISTONE SUBSTRATE	REFERENCES	RELATED HUMAN HMT
LSD	**KDM1A**	KDM1, KIAA0601, LSD1, AOF2	H3K4me2/me1, H3K9me2/me1	Shi et al. 2004, Metzger et al. 2005	**H3K4me2/me1**: SETD1A-B, KMT2A-D, KMT2E*; **H3K4me1**: ASH1L, SETD7; **H3K9me2:** SUV39H1-2; **H3K9me2/me1:** SETDB1, EHMT1-2, PRDM2.
	KDM1B	LSD2, AOF1, C6orf193	H3K4me2/me1, H3K9me2/me1	Ciccone et al. 2009	
JMJC	**KDM2A**	JHDM1A, KIAA1004, CXXC8, FBL7, FBXL11	H3K36me2/me1	Tsukada et al. 2006	**H3K4me3**: KMT2A-D, SETD1A-B, SMYD3, ASH1L, PRMD9; **H3K36me2**: SMYD2; **H3K36me2/me1**: SETD2, SETMAR, NSD1-3, ASH1L.
	KDM2B	JHDM1B, CXXC2, FBL10, FBXL10, PCCX2	H3K4me3, H3K36me2	Frescas et al. 2007, He et al. 2008	
	KDM3A	JHDM2A, JMJD1, JMJD1A, KIAA0742, TSGA	H3K9me2/me1	Yamane et al. 2006	**H3K9me2:** SUV39H1-2; **H3K9me2/me1**: SETDB1, EHMT1-2, PRDM2.
	KDM3B	JHDM2B, JMJD1B, KIAA1082, C5orf7	H3K9me2/me1	Kim et al. 2012	
	JMJD1C	JHDM2C, KIAA1380, TRIP8	H3K9me2/me1	Kim et al. 2010	
	KDM4A	JHDM3A, JMJD2A, KIAA0677	H3K9me3/me2, H3K36me3/me2, H1.4K26me3	Whetstine et al. 2006, Klose et al. 2006, Trojer et al. 2009	**H3K9me3:** SETD2; **H3K9me3/me2**: SUV39H1-2, SETDB1, PRDM2; **H3K9me2**: EHMT1-2; **H3K36me3/me2**: SETD2, NSD1-3, ASH1L, SMYD2; **H3K36me2**: SETMAR; **H1.4K26me3/me2**: EZH2, EHMT1-2.
	KDM4B	JHDM3B, JMJD2B, KIAA0876	H3K9me3/me2, H3K36me3/me2, H1.4K26me3	Whetstine et al. 2006, Fodor et al. 2006, Trojer et al. 2009	
	KDM4C	JHDM3C, JMJD2C, KIAA0780, GASC1	H3K9me3/me2, H3K36me3/me2, H1.4K26me3	Whetstine et al. 2006, Cloos et al. 2006, Trojer et al. 2009	
	KDM4D	JHDM3D, JMJD2D, FLJ10251	H3K9me3/me2, H1.4K26me3/me2	Whetstine et al. 2006, Trojer et al. 2009	
	KDM5A	JARID1A, RBP2	H3K4me3/me2	Christensen et al. 2007, Klose et al. 2007	**H3K4me3:** ASH1L, PRDM9; **H3K4me3/me2**: KMT2A-D, SETD1A-B, SMYD3.
	KDM5B	JARID1B, PLU1	H3K4me3/me2	Christensen et al. 2007	
	KDM5C	JARID1C, SMCX	H3K4me3/me2	Christensen et al. 2007, Iwase et al. 2007	
	KDM5D	JARID1D, SMCY	H3K4me3/me2	Lee et al. 2007a	
	KDM6A	UTX	H3K27me3/me2	Agger et al. 2007, Lan et. Al 2007	**H3K27me3/me2**: EZH1-2.
	KDM6B	JMJD3, KIAA0346	H3K27me3/me2	Agger et al. 2007, Lan et. Al 2007	
	UTY				
	KDM7A	JHDM1D, KIAA1718, KDM7	H3K9me2/me1, H3K27me2/me1	Tsukada et al. 2010, Horton et al. 2010, Huang et al. 2010b	**H3K9me2**: SUV39H1-2; **H3K9me2/me1**: SETDB1, EHMT1-2, PRDM2; **H3K27me2/me1**: EZH1-2; **H4K20me3**: SMYD5, SUV420H2; **H4K20me1**: SETD8.
	PHF8	JHDM1F, KIAA1111, ZNF422	H3K9me2/me1, H4K20me1	Loenarz et al. 2010, Liu et al. 2010, Qi et al. 2010	
	PHF2	JHDM1E, KIAA0662	H3K9me2/me1, H4K20me3	Wen et al. 2010, Baba et al. 2011, Stender et al. 2012	

* after GlcNAcylation

Table2. JMJC demethylases and their role in neural development and disease

HDM	Function in Neural Development	Associated pathologies	References
KDM2B	Embryonic neural tube development and neurulation in mice.		Fukuda et al. 2011
JMJD1C	Inhibition of neural differentiation in hESC.		Wang et al. 2014
KDM4A	Neural crest specification in chick embryo.		Strobl-Mazzulla et al. 2010
KDM4C		Autism spectrum disorders.	Kantojarvi et al. 2010
KDM5B	Repression of stem cell genes to allow ESC differentiation into neurons.		Schmitz et al. 2011, Albert et al. 2013
KDM5C	Repression of neuronal genes in non-neuronal cells. Neuronal survival and dendritic development.	X-linked mental retardation, autism spectrum disorders, epilepsy.	Jensen et al. 2005, Tahiliani et al. 2007, Iwase et al. 2007, Adegbola et al. 2008
KDM6A	Induction of neural differentiation in hESC.	Kabuki syndrome.	Lederer et al. 2012, Shahhoseini et al. 2013
KDM6B	Forebrain development antagonized by SMRT in isolated cortical progenitors. Neuronal differentiation in P19 cells. Neural commitment of ESC. BMP-induced dorsal interneurons generation in chick embryo neural tube. TGFβ-induced neuronal differentiation in mNSC.		Jepsen et al. 2007, Burgold et al. 2008, Dai et al. 2010, Akizu et al. 2010, Estaras et al. 2012
KDM7A	Neural differentiation in mESCs. Neural induction on early chick embryos.		Huang et al. 2010a, Huang et al. 2010b
PHF8	Tectum development and neural survival in zebrafish embryos. Interaction with ZNF711 and regulation of JARID1C. Regulation of cytoskeleton-related genes neccesary for proper neurite formation.	X linked mental retardation, cleft lip/palate.	Laumonnier et al. 2005, Qi et al. 2010, Tsukada et al. 2010, Kleine-Kohlbrecher et al. 2010, Asensio-Juan et al. 2012