Hypothesis

Polycomb Repressive Complex 2: Emerging Roles in the Central Nervous System

Pei-Pei Liu[1,2,*], Ya-Jie Xu[1,2,*], Zhao-Qian Teng[1,2], and Chang-Mei Liu[1,2]

Abstract

The polycomb repressive complex 2 (PRC2) is responsible for catalyzing both di- and trimethylation of histone H3 at lysine 27 (H3K27me2/3). The subunits of PRC2 are widely expressed in the central nervous system (CNS). PRC2 as well as H3K27me2/3, play distinct roles in neuronal identity, proliferation and differentiation of neural stem/progenitor cells, neuronal morphology, and gliogenesis. Mutations or dysregulations of PRC2 subunits often cause neurological diseases. Therefore, PRC2 might represent a common target of different pathological processes that drive neurodegenerative diseases. A better understanding of the intricate and complex regulatory networks mediated by PRC2 in CNS will help to develop new therapeutic approaches and to generate specific brain cell types for treating neurological diseases.

Keywords

Introduction

Polycomb group (PcG) proteins are key epigenetic suppressors of gene expression, which maintain or change chromatin structures and modulate gene expression through histone modifications (Hirabayashi and others 2009). These proteins are highly conserved regulatory factors that are originally found as suppressors of homeobox (HOX) family genes during embryonic development in Drosophila (Margueron and Reinberg 2011). The polycomb repressive complex 1 (PRC1) and 2 (PRC2) are two distinct PcG proteins that have been identified, and the composition of these complexes is variable and context-dependent (e.g., differentiation status) (Sauvageau and Sauvageau 2010). Mounting evidence has shown that PcG proteins are broadly involved in multiple biological processes that maintain the identity of stem/progenitor cells and differentiated cells, and regulate the growth, development, and tissue homeostasis (e.g., Piunti and Shilatifard 2016; Sauvageau and Sauvageau 2010).

PRC2 plays pivotal roles in modulating chromatin modifications by catalyzing di- and trimethylation of histone H3 at lysine 27 (H3K27me2/3) within the PcG protein complex (Ciferri and others 2012; Margueron and Reinberg 2011). In mammals, the PRC2 complex is composed of four core proteins, including embryonic ectoderm development (EED), either one of enhancer of zeste homolog1

(EZH1) or EZH2, suppressor of zeste 12 (SUZ12), and retinoblastoma (Rb)-associated protein 46/48 (RbAp46/48) (Margueron and Reinberg 2011). EZH2 and EZH1 are methyltransferases that can catalyze mono-, di-, and tri-methylation of H3K27 (Di Croce and Helin 2013). Members of the PRC2 complexes have been implicated in the regulation of cell fate decisions and maintenance of cellular identity (Conway and others 2015). As early as 2006, a number of embryonic stem (ES) cells studies have demonstrated that many genes involved in neurogenesis are targets for PRC2-mediated deposition of H3K27me3 in neural differentiation (e.g., Boyer and others 2006; Lee and others 2006). Then growing evidence has shown that PRC2 has numerous functions in mammalian central nervous system (CNS) (e.g., Aldiri and others 2013; Pereira and others 2010; Vizan and others 2015).

[1]State Key Laboratory of Stem Cell and Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing, China
[2]Savaid Medical School, University of Chinese Academy of Sciences, Beijing, China
*These authors contributed equally.

Corresponding Author:
Chang-Mei Liu, State Key Laboratory of Stem Cell and Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, 1 Beichen West Road, Beijing, 100101, China.
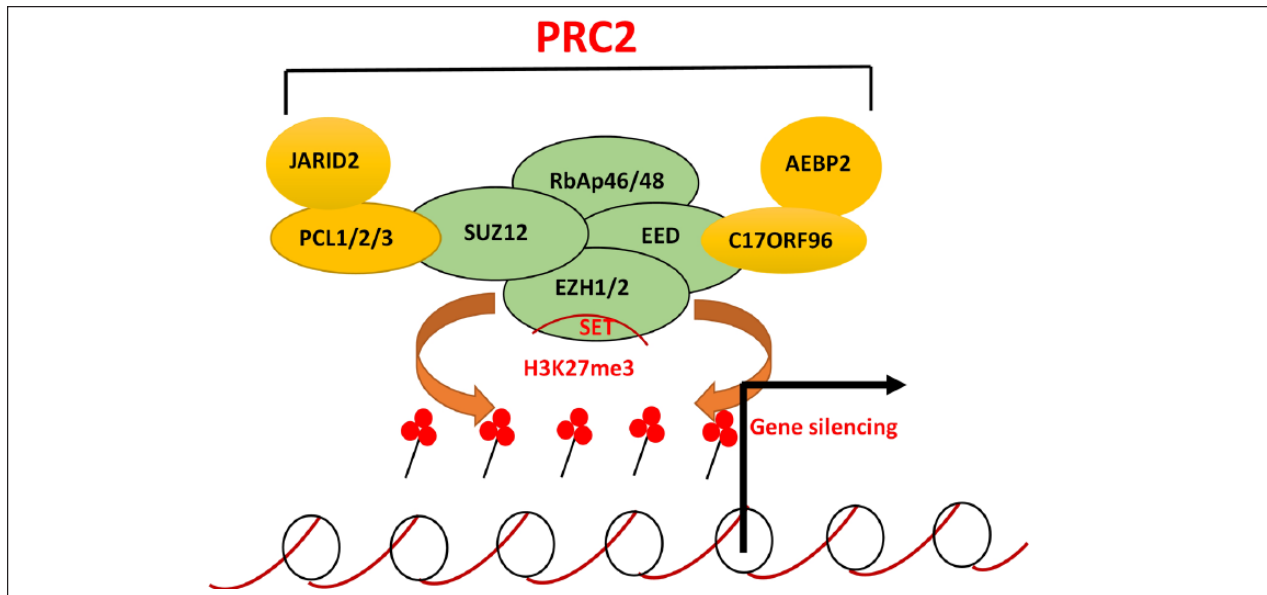Email: liuchm@ioz.ac.cn

Figure 1. An illustration of the protein composition of polycomb repressive complex 2 (PRC2) complex. PRC2 includes four core components (green ovals): EZH1/2, SUZ12, EED, and RbAp46/48. EZH1 and EZH2 have the catalytic SET domain and exhibit methyltransferase activity by adding H3K27me3 modification to target genes. SUZ12 is essential for the stability and catalytic activity of EZH2-meidated H3K27. EED plays a key role in the maintenance and propagation of EZH2-mediated H3K27me3 during cell division through binding H3K27me3 with its C-terminal domain. EZH1/2, EED, and SUZ12 form the minimal PRC2 components that are necessary for methylation catalytic activity and subsequent repression of gene transcription initiation. RbAP46/48 have important roles in chromatin-metabolizing processes. Yellow ovals show PRC2 recruitment factors Jarid2, PLC1/2/3, AEBP2, and C17ORF96. PRC2 recruitment to gene promoters leads to deposition of H3K27me3 (red dots) and gene repression.

In this review, we will discuss the studies from the protein composition of PRC2 complex, its newly discovered recruitment factors, and their distinct functions in CNS, especially in neurogenesis, gliogenesis, neuronal migration, and maturation, as well as the underlying regulatory mechanisms. We will also summarize recent findings on the pathological roles of PRC2 and H3K27 methylation in neurological diseases.

Protein Composition of the PRC2 Complex

There are four core subunits in the PRC2 complex that have been identified in CNS, namely EZH1/2, EED, SUZ12 and RbAP46/48 (Fig. 1) (Kuzmichev and others 2005). EZH1 and EZH2 have the catalytic SET domain and exhibit methyltransferase activity by controlling H3K27 methylation, a modification that can be recognized by one of the PRC1 components, the CBX family proteins (Margueron and Reinberg 2011). EZH1 and EZH2 are well-characterized transcription repressors that can silence many developmental regulators (Akizu and others 2016). EZH1 is predominantly expressed in differentiated tissues, while EZH2 is highly expressed in proliferating cells, such as embryonic and adult neural stem/progenitor cells (NSPCs) (Muller and others 2002; Su and others 2005). Although EZH1 can mediate methylation of H3K27 (Shen and others 2008), PRC2 complexes containing EZH1 have lower enzymatic activity than those containing EZH2 (Margueron and others 2008). SUZ12, another component of PRC2, is essential for the stability and catalytic activity of EZH2 in vivo (Pasini and others 2007). EED, a WD-40 repeat protein that directly interacts with EZH2, plays a key role in the maintenance and propagation of EZH2-mediated H3K27me3 during cell division through binding to H3K27me3 via its C-terminal domain (Kuzmichev and others 2005; Margueron and Reinberg 2011). EZH1/2, EED, and SUZ12 are believed to form the minimal PRC2 complex that are necessary for the catalytic activity of PRC2 and subsequent repression of transcriptional initiation (Ketel and others 2005). The fourth core subunit of PRC2 complex, histone chaperone RbAP46/48 proteins, contain conserved WD-40 repeat and have important roles in chromatin-metabolizing processes (Kuzmichev and others 2005). Although p46/p48 proteins are not required for histone methyltransferase activity of EZH2, they are required for association of PRC2 with the histone tails (Kuzmichev and others 2005).

Besides above-mentioned four core subunits, the PRC2 complex also recruits additional factors (Fig. 1), such as zinc finger protein AEBP2 (AE binding protein 2), PCLs (polycomb-likes), JARID2 (Jumonji and AT-rich interaction domain containing 2) and C17orf96 (chromosome 17 open reading frame 96), to regulate gene expression in mammalian CNS (Corley and Kroll 2015). Presence of AEBP2 in the EED-EZH2 complex significantly stimulates the histone methyltransferase activity of PRC2 (Cao and Zhang 2004). PCLs, first identified in Drosophila, are involved in recruiting the PcG homologue of EZH2 (Savla and others 2008). There are three orthologous of PCL in mammal CNS, namely PHD Finger Protein 19 (PHF19)/PCL3, PHF1/PCL1, and metal response element binding transcription factor 2 (MTF2)/PCL2. These proteins are required for the de novo recruitment of PRC2 to chromatin and the subsequent maintenance of PRC2 on chromatin (Brien and others 2012; Nekrasov and others 2007). Notably, the activity and specificity of PCL-containing complexes for H3K27 methylation is very different from that of the complexes without PCL proteins (Savla and others 2008). Mammalian PRC2-binding sites are enriched in CG content that displays a low level of DNA methylation, and recent structural and biochemical analyses of both the PHF1 and the MTF2 N-terminal cassettes establish the PCL EHWH motifs as a new family of unmethylated CpG-containing DNA binding motifs (Li and others 2017). As PCLs also have a complete Tudor domain, future studies are needed to examine whether they interact with trimethylated lysines and help to recruit PRC2 complex to regulate gene expression (Vizan and others 2015).

JARID2 is a founder member of the Jumonji family group of proteins known to have indispensable function by catalyzing demethylation of histone proteins during development, especially in liver and cardiovascular system (Mysliwiec and others 2010; Takeuchi and others 1995). As early as 2009, JARID2 was identified as a PRC2 component that enhances the activity of the PRC2 and stimulates the mono- and dimethylation of H3K27 in vitro (Peng and others 2009). The interactions between JARID2 and PRC2 were then validated by several biochemical and genome-wide studies (e.g., Landeira and others 2010; Li and others 2010; Pasini and others 2010; Peng and others 2009; Shen and others 2009). Inactivation of JARID2 results in impairment of PRC2 recruitment, but H3K27me3 levels are only modestly affected (Landeira and others 2010; Shen and others 2009). In addition to H3K27 methylation, JARID2 is also involved in the fine-tuning of gene expression that is critical for ES differentiation by coordinating gene silencing through H3K9 and H3K27 methylation (Montgomery and others 2005) JARID2 directly recognizes and binds to mono-ubiquitinated histone H2A at lysine 119, a key mechanism that links PRC1 and PRC2 in the establishment of polycomb domains through development and cellular differentiation (Cooper and others 2016). JARID2 also supports co-recruitment of PRC1 and Ser 5-phosphorylated RNA polymerase II (RNAP) to target genes, which are necessary for embryonic development (Akizu and others 2016; Landeira and others 2010). Taken together, these findings support that JARID2 is an important component of PRC2 complex by coordinately regulating targets with PRC1 complex.

Three Forms of H3K27 Methylation Exist in Mammalian CNS

Histone H3K27 exists in three methylation states, mono-methylated (H3K27me1), dimethylated (H3K27me2), and trimethylated (H3K27me3) (Fig. 2). H3K27me2 is the most abundant form, while H3K27me3 has been the well-characterized form (Papp and Muller 2006; Steiner and others 2011). In ES cells, more than 70% of histone H3 is methylated on H3K27me2, together with 7% to 10% of H3K27me3, and 4% to 10% of H3K27me1 (Di Croce and Helin 2013). PRC2 contributes to all the methylation states of H3K27 (Ferrari and others 2014; Shen and others 2008), supporting previous findings about the distribution of H3K27me1/2 (Sneeringer and others 2010). H3K27me1 accumulates within transcribed genes and promotes transcription because H3K27me1 deposition takes place in the absence of a stable association of PRC2 with these genomic regions. However, H3K27me2 has a broad distribution and is distributed in large chromatin domains (Ferrari and others 2014). Recent evidence shows that PRC2 localizes with H3K27me3; however, the conversion from H3K27me2 to H3K27me3 by the PRC2 complex is much slower than that for H3K27me1 to H3K27me2 (Di Croce and Helin 2013; Sneeringer and others 2010).

Despite being deposited by the same enzyme, the roles of H3K27me3, H3K27me2, and H3K27me1 remain somewhat elusive (Jacob and Michaels 2009). Although H3K27me1 accumulates within transcribed genes and promotes transcription (Ferrari and others 2014), variable associations of gene expression and patterns of gene enrichment for H3K27me1 have been noticed (Jacob and Michaels 2009). H3K27me1 is primarily located in the areas of pericentric heterochromatin, supporting the idea that H3K27me1 might be a gene repression marker (Baker and others 2015; Ferrari and others 2014). However, a controversial finding reports that H3K27me1 is selectively depleted near transcription start sites (Vakoc and others 2006). Moreover, H3K27me1 signals are higher at active promoters than at silent promoters, suggesting that increased enrichment for H3K27me1 at
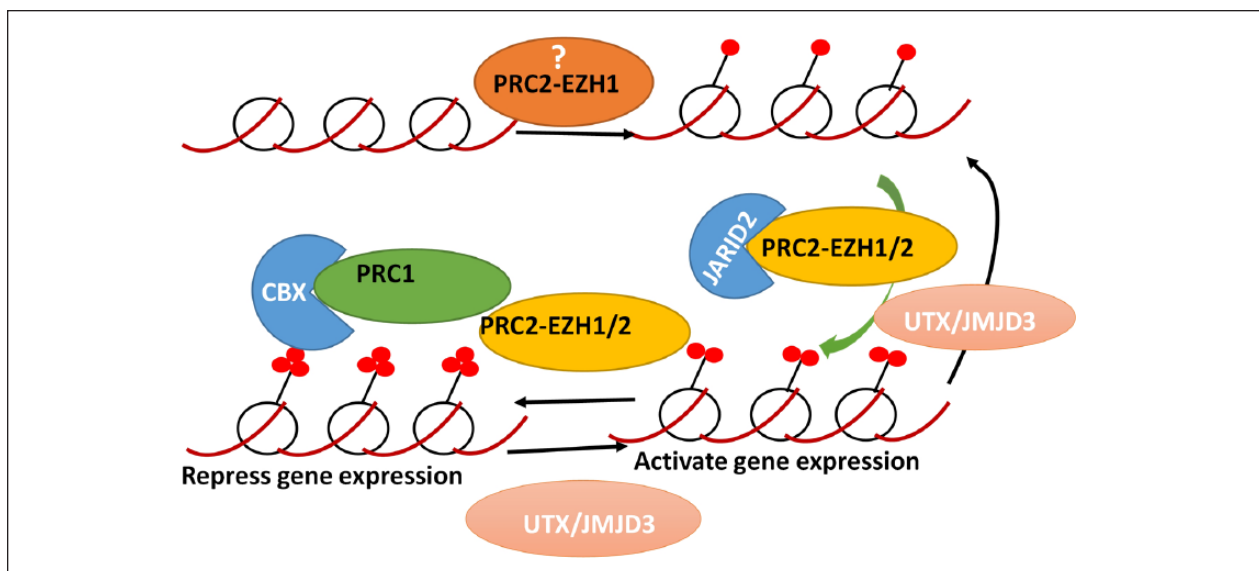
Figure 2. Roles of polycomb repressive complex 2 (PRC2) complex in mediating different H3K27 methylations. PRC2 binds to chromatin and catalyzes methylation of histone H3 at Lys27 (H3K27me2/3) (represented by red dots). UTX and JMJD3 are the only two histone demethylases that activate gene expression via demethylating H3K27me3 to H3K27me2 or H3K27me1.

promoter regions can increase mRNA expression levels (Barski and others 2007). Furthermore, the locations of H3K27me1 enrichment vary in different cell types (Cui and others 2009), and its biological functions in cellular processes and mechanisms that modulate H3K27me1 are largely unknown. Jacob's group found that arabidopsis trithorax–related proteins ATXR5 and ATXR6 are H3K27 methyltransferases (Jacob and others 2009). Specifically, ATXR5 and ATXR6 catalyze H3K27 from H3K27me0 to H3K27me1, but not H3K27me2 or H3K27me3 (Jacob and others 2009). However, homologs of ATXR5 or ATXR6 have not been identified in animals yet. In addition to EZH1/2, EED has also been demonstrated to be related with H3K27me1 (Montgomery and others 2005). Taken together, PRC2 complex is an important player for modulating H3K27me1 in mammals. Although PRC2 has been implicated in all three methylation states of H3K27, it remains to be determined how PRC2 establishes individual methylation state. Thus, identification of novel enzymes contributing to H3K27 modifications in animals would uncover potential mechanisms underlying the biological roles of PRC2 and H3K27 modifications.

Recent studies in Drosophila (Lee and others 2015) and in PRC2 (EED$^{-/-}$) knockout ESCs attribute a role of H3K27me2 in preventing inappropriate enhancer activation (Lee and others 2015). Through manipulating the H3K27me2/H3K27me3 ratio in mouse ESCs, H3K27me2 and H3K27me3 are found mainly distributed at regulatory regions, and modifying the ratio of H3K27me2/H3K27me3 is sufficient for the acquisition and repression transcriptional programs and phenotypes of defined cell lineage, as well as for induction of the ESC ground state (Juan and others 2016). This notion is supported by a follow-up study demonstrating that genome-wide distribution of H3K27me3 and H3K27me2 differs in pluripotent and differentiating ESCs, with the two degrees of H3K27 methylation being enriched at functionally distinct genomic regulatory regions of different classes of genes (Juan and others 2017). Specifically, H3K27me2 is preferentially enriched at metabolic genes in pluripotent ESCs and replaced by acetylation in differentiating ESCs, indicating that H3K27me2 may play different roles compared to H3K27me3 modification (Juan and others 2017).

Reduction of H3K27me3 can be accomplished by active H3K27me3 demethylation mediated by H3K27me2/3 demethylases in mammals. These enzymes include UTX (ubiquitously transcribed tetratricopeptide repeat, X chromosome)/KMD6A (lysine demethylase 6A) and JMJD3/KDM6B, both of which contain a JmjC (Jumonji) catalytic domain for de-methylation of H3K27me3 (Fig. 2). Although H3K27me3 enriched at promoter regions is associated with gene repression, the activation-associated H3K4me3 mark is also found at the promoters of "bivalent genes" that have larger regions of H3K27 and smaller regions of H3K4. These bivalent genes, characteristic of embryonic stem cells (ESCs) (Bernstein and others 2006), are poised for either activation or repression. Once differentiation, either H3K27me3 or H3K4me3 is lost, leading to gene activation or repression, respectively. Accordingly, EZH2 and the PRC2 complex are shown to be essential for normal differentiation of ESCs (Pasini and others 2007).
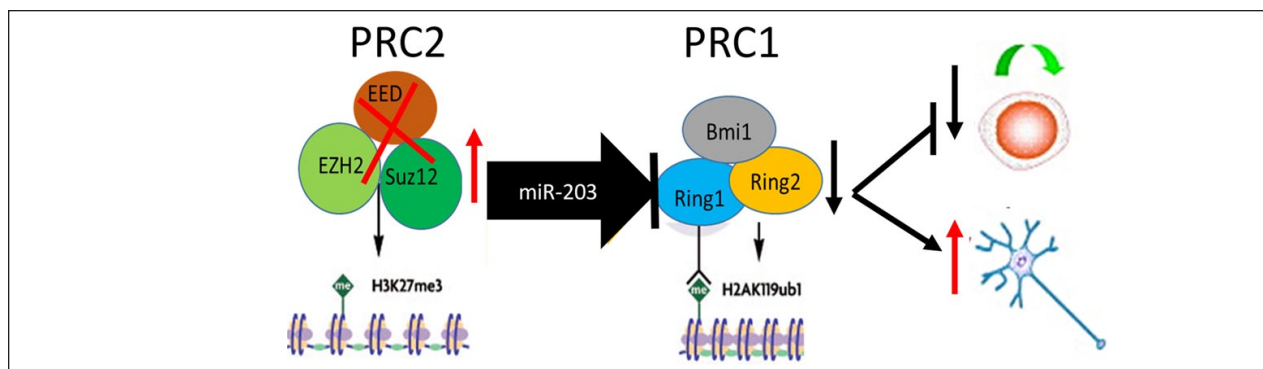
Figure 3. Coordinated function of PRC2-miR-203-PRC1 regulatory axis in regulating proliferation and differentiation of NSPCs. EZH2, a key component of PRC2, directly regulates the expression of miR-203 in both embryonic and adult NPSCs, and high levels of miR-203 negatively regulates self-renewal and proliferation of NSPCs, but promotes neuronal differentiation capacity. One of PRC1 components, Bmi1, is a direct downstream target of miR-203 in NSPCs. Hence, miR-203 interplays with polycomb repressive complexes to form a regulatory axis in proliferation and differentiation of NSPCs. PRC, polycomb repressive complex; NSPC, neural stem/progenitor cells

PRC2 Modulates Neuronal Identity, Proliferation, and Differentiation of NSPCs

Neurogenesis begins with segregation of the neural plate from the ectoderm of the trilaminar embryo and continues into and throughout adult life. Neural stem cells in CNS undergo repeated asymmetric cell divisions in a defined order, first producing neurons then glia (Sparmann and others 2013; Temple 2001; Miller and Gauthier 2007). PRC2 components are highly expressed in embryonic and adult NSPCs (Akizu and others 2016; Hirabayashi and others 2009; O'Carroll and others 2001; Piper and others 2014; Shen and others 2008; Zhang and others 2014a). Thus, it is not surprising that PRC2 has multiple functions during neurogenesis at distinct levels, such as self-renewal of neural stem cells, neuronal-glial fate specification and maturation (Guillemot 2007). Several studies demonstrate that PRC2 has an essential role in maintaining neural progenitor cell identity. In early stage of neural development, EZH2 contributes to the structure integrity and morphology of neuroepithelium to maintain survival of neural progenitor cells by directly repressing the cell cycle regulator p21WAF1/CIP in the chicken spinal cord (Akizu and others 2016; Akizu and Martinez-Balbas 2016). Moreover, conditional deletion of EZH2 in the developing midbrain not only affected proliferation and precocious cell cycle exit of neural progenitors but also promoted ectopic expression of a forebrain transcriptional program and reduced expression of midbrain markers that led to reestablishment of forebrain identity (Zemke and others 2015).

We recently found that EZH2 is an important modulator for proliferation of NSPCs. Specifically, conditional knockout of EZH2 results in decreased proliferation ability of both embryonic and adult NSPCs (Liu and others 2017). We further showed that miR-203, a negative regulator of proliferation of NSPCs, is repressed by EZH2 in both embryonic and adult NSPCs. Importantly, one of PRC1 components, Bmi1, is a downstream target of miR-203 in NSPCs. Therefore, our study provides evidence for coordinated function of the EZH2-miR-203-BMI1 axis in regulating proliferation of NSPCs (Fig. 3).

PRC2 and PRC2-mediated H3K27me3 modifications are lost or acquired at many genes in both progenitor and terminal states (Mohn and others 2008). In NSPCs, neuron-specific genes that become activated on terminal differentiation are polycomb targets, while promoters marked by H3K27me3 frequently become DNA methylated during differentiation, suggesting context-dependent crosstalk between polycomb and DNA methylation (Mohn and others 2008). Activation of neuron-specific genes are dynamically modulated by H3K27 methylation and demethylation for proper neural fate acquisition (Burgold and others 2012; Mikkelsen and others 2007). Loss of PRC2 function in the developing cortex removes the repressive mark of H3K27me3 in cortical progenitor cells and shifts the balance between self-renewal and differentiation toward differentiation (Pereira and others 2010). In line with this finding, PRC2 functions to repress the activity of a large number of neuronal genes that are involved in neuronal development (Dietrich and others 2012). Additionally, through working cooperatively with mediator CDK (cyclin dependent kinase) subunits, such as CDK8 and CDK19, PRC2 regulates the expression of retinoic acid-responsive genes in response to neural differentiation signal (Fukasawa and others 2015). PRC2 is also responsible for epigenetically inhibiting Ngn1 (neurogenin 1) and the transition of neural progenitor cell fate from neurogenic to astrogenic during late stages of
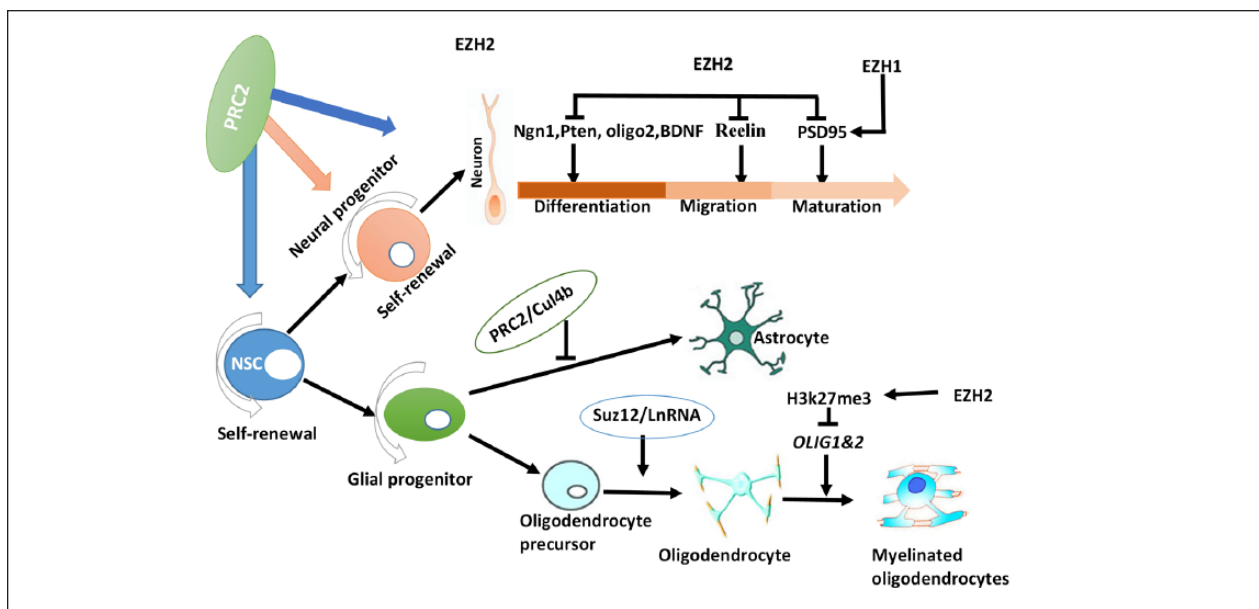
Figure 4. Regulation of neurogenesis and gliogenesis by polycomb repressive complex 2 (PRC2). EZH2 plays vital roles in modulating neuronal differentiation, migration, and maturation through targeting different downstream genes (top of the figure). PRC2/CUL4B complex represses generation of astrocytes (middle of the figure), while SUZ12/LnRNA is required for OPC maturation. EZH2 enhances the levels of H3K27me3 in nucleosomes by promoting chromatin compaction, conferring a repressive epigenetic signature at Olig1&2 sites and thereby affecting oligodendrocyte development and myelination (bottom of the figure).

neocortical development (Guillemot 2007; Hirabayashi and others 2009). Deletion or downregulation of EZH2 in cortical progenitor cells results in more rapidly cycling of neural precursors and an early increase in neurons and astrocytes in the cerebral cortex (Hirabayashi and others 2009; Pereira and others 2010; Sher and others 2008). However, the shifts from neurogenesis to astrogenesis are closed when EZH2 deletion happens at a later time point in neural precursors (Hirabayashi and others 2009). In postnatal neurogenesis, EZH2 directly targeted and repressed bHLH transcription factor Olig2 during neuronal lineage specification in the adult mouse subventricular zone (SVZ) (Hwang and others 2014) (Fig. 4). EZH2 also modulates progenitor cell proliferation by inhibiting PTEN (phosphatase and tensin homolog) expression and promoting the activation of a serine/threonine kinase Akt-mTOR (mammalian target of rapamycin) in adult hippocampus (Zhang and others 2014a). Besides forebrain neural stem cells, EZH2 also controls Purkinje cell formation and differentiation and affects cerebellar neurogenesis (Feng and others 2016).

Deficiency of PRC2 component EED in mice results in gastrulation defects and lack of a node and of neural tissue in the early development (Satijn and others 2001; Schumacher and others 1996). In the rat spina bifida, the expression levels of EED and SUZ12 are altered (Wang and others 2010), suggesting that the polycomb proteins

are essential for spinal cord development (Qi and others 2013). Furthermore, studies in the Xenopus model showed that PRC2 proteins are located primarily in the neural crest cells and modulate neural crest specification and migration (Tien and others 2015). In contrast to the observations in CNS, conditional inactivation of EZH2 in the neural crest has no effect on stem cell proliferation, neurogenesis and gliogenesis in the peripheral nervous system (Schwarz and others 2014), indicating that PRC2 may play different roles in central and peripheral nervous systems. Collectively, PRC2 functions presumably by repression of distinct sets of target genes in a cell type- and time-dependent manner during neural development.

PRC2 Modulates Neuronal Migration and Maturation

PRC2 also plays important roles in neuronal migration, differentiation, and maturation (Dietrich and others 2012; Gehani and others 2010). In the late stage of neurogenesis, PRC2 mediates appropriate gene expression patterns that are responsible for the temporal onset of neuronal migration essential for the establishment of specific neural circuits (Zhao and others 2015a). For example, Ezh2 epigenetically regulates Reelin expression pattern to fulfill proper orientation for migrating neurons (Zhao and others 2015a). In EZH2 mutants, derepression of NETRIN1

results in abnormal neuronal migration and connectivity in the cortico-ponto-cerebellar pathway (Di Meglio and others 2013). Subunits of PRC2 bind to the regulatory regions of rostral HOXA genes and control the differentiation-associated activation (Fukasawa and others 2015; Stein and others 2016). In mature hippocampal neurons, neuronal activity controls BDNF (brain-derived neurotrophic factor) expression via PRC2 that is essential for neuronal differentiation and survival (Palomer and others 2016).

It has been demonstrated that EZH2 inhibits the transcription of BDNF and restricts dendrite arborization in mammalian neurons (Qi and others 2014) (Fig. 4). Similarly, EZH1 also contributes to the maturation of post mitotic mammalian neurons through regulating the transcription of PSD-95 (Henriquez and others 2013), suggesting that neuronal development and maturation are closely related with a switch from predominantly EZH2-containing to EZH1-containing PRC2 complexes (Henriquez and others 2013) (Fig. 4). The age-dependent increase in H3K27me3 in neurons indicates the potential relevance of high levels of H3K27me3 in the maintenance of adult neuronal function (von Schimmelmann and others 2016). In our recently published paper, we found that high H3K27me3 level mediated by deletion of histone H3K27 demethylase UTX leads to deficiency of synaptic plasticity and cognitive behaviors in mice. We further demonstrated that UTX cKO mice display abnormalities of neuronal morphology, long-term potentiation, and basal synaptic transmission in area CA1 of the hippocampus (Tang and others 2017). Some genes critical for synaptic plasticity, and/or dendrite development including nitric oxide synthase 1 (NOS1), actin filament cross-linker a-actinin-2 (ACTN2), zinc finger transcription factor EGR3, transforming growth factor-b2 (TGFB2), and WNT4 are verified as the downstream targets of UTX in the hippocampus (Tang and others 2017). Taken together, these findings suggest that PRC2 plays a key role in modulating neuronal migration and maturation, and contributes to dendrite development and synaptic plasticity.

PRC2 Plays Important Roles in Regulating Gliogenesis

PRC2 is involved in the transition from neural stem cells to glial cells and regulates the production of glial cells (Liu and Casaccia 2010). In CNS, PRC2/CRL4B (cullin 4B) complexes limit the expression of prostaglandin-H2 D-isomerase (PTGDS) to restrain glial fibrillary acidic protein (GFAP) expression, illustrating the important role of PRC2 in the regulation of glial development (Zhao and others 2015b) (Fig. 4). Forced expression of EZH2 in astrocytes induces their dedifferentiation toward neural

stem cells in vitro (Sher Boddeke and Copray 2011). PRC2 directly modulates gliogenesis by regulating the transient expression of Gcm/Glide fate determinant in the Drosophila nervous system (Popkova and others 2012). Moreover, EED/PRC2 knockdown dramatically promotes neurogenic-to-gliogenic fate switching in late-stage NPCs (Hirabayashi and others 2009; Liu and Casaccia 2010).

PRC2 also has an instructive role in the differentiation of oligodendrocytes (Liu and others 2015). Recent studies have shown that the levels and activity of PRC2 complex increase on exposure to oligodendrocyte differentiation stimuli and this increase contributes to the final differentiation of oligodendrocyte progenitor cells (OPCs) into myelinating oligodendrocytes (OLs) (He and others 2017; Liu and others 2015; Sher Boddeke Olah and Copray 2012). SUZ12, together with long non-coding RNAs, is required for OPC maturation through transcriptional repression of OPC-associated genes by deposition of repressive H3K27me3 marks on their enhancers and promoters (He and others 2017). EZH2 remains at a high level in OPCs (Sher and others 2008), but is completely suppressed when NSCs differentiate into astrocytes (Liu and Casaccia 2010). In contrast, overexpression of EZH2 in cultured neural precursor cells promotes oligodendrocyte development and reduces astrocytes (Sher and others 2008). A recent study showed that EZH2 enhances the levels of H3K27me3 in nucleosomes by promoting chromatin compaction, conferring a repressive epigenetic signature at OLIG1&2 sites and thereby affecting oligodendrocyte development and myelination (Deng and others 2017) (Fig. 4). In the peripheral nervous system, PRC2 is important for myelin homeostasis. Loss of EED results in hypermyelination of smaller-diameter axons and focal myelin enfolding, revealing that PRC2-mediated H3K27me3 constitutes a novel determinant of mature myelin thickness (Ma and others 2015). Furthermore, EZH2 has recently been shown to mediate p57KIP2 activity in Schwann cells, and misregulation of EZH2 results in impaired cellular maturation and inhibition of myelin gene expression (Heinen and others 2012). Taken together, PRC2 regulates the expression of essential transcription factors during the maturation of oligodendrocytes and has key roles in myelination.

Abnormal Expressions of PRC2 Members Cause Neurological Disorders

Genome sequencing data from cancer studies reveal that PRC2 and PRC2-mediated H3K27 methylations are frequently misregulated (Conway and others 2015). EZH2

Table 1. Mutations in Genes Coding for PRC2 Subunits in Neurological Diseases.

Gene	Expression/Mutation	Disease	Reference
EZH2	Overexpression	Glioblastoma	(Lewis and others 2013)
	Overexpression	Medulloblastoma	(Alimova and others 2012)
	Deletion/mutation	Weaver syndrome	(Cohen and others 2016; Imagawa and others 2017; Usemann and others 2016)
	Knockdown	Febrile seizures	(Wang and others 2017)
	Overexpression	Ataxia-telangiectasia	(Li and others 2013; Li and Jiang 2015)
	Overexpression	Huntington's disease	(Dong and others 2015)
EED	Missense mutation	Weaver syndrome	(Cooney and others 2017; Imagawa and others 2017)
	Mutations	Glioblastoma	(De Raedt and others 2014)
SUZ12	Missense mutation	Weaver syndrome	(Imagawa and others 2017)
	Mutations	Glioblastoma	(De Raedt and others 2014)
	Overexpression	Huntington's disease	(Dong and others 2015)
	Mutations	Malignant peripheral nerve sheath tumor	(Zhang and others 2014b)
JARID2	Deficient	Chiari malformation	(Miro and others 2009)
	Deletion	Autism spectrum disorder	(Celestino-Soper and others 2012; Ramos and others 2012)

has been reported to be highly expressed in multiple cancers (Han Li and Chen 2015; Kim and Roberts 2016; Zhao and others 2016). As early as 2003, PRC2 was found to be involved in pediatric glioblastoma (GBM), the most aggressive primary brain tumor in humans (Lewis and others 2013). Recent evidence demonstrates that PRC2 components EZH2, EED, and SUZ12 are highly related to GBM (Abdouh and others 2009; De Raedt and others 2014; Dubuc and others 2013; Martinez and others 2009). EZH2 is also highly expressed in medulloblastoma, another malignant brain tumor of childhood. SUZ12 also plays a central role in malignant transformation, as somatic mutations of SUZ12 are found in malignant peripheral nerve sheath tumors (MPNSTs) (Zhang and others 2014b). More importantly, inhibition of EZH2 suppresses medulloblastoma tumor cell growth (Alimova and others 2012), supporting the notion that targeting PRC2 complexes may have therapeutic potentials for treating CNS tumors (Crea and others 2012; Dubuc and others 2013).

Both gain- and loss-of-function mutations of PRC2 subunits in humans lead to a pathogenic state and are associated with several neurological disorders (Imagawa and others 2017) (Table 1). EZH2 has been verified as a target of CHD8, an important autism gene during cortical neurogenesis (Durak and others 2016). Indeed, EZH2 mutation leads to weaver syndrome, an extremely rare congenital disorder with advanced osseous maturation, and distinctive craniofacial, skeletal, and neurological abnormalities (Gibson and others 2012; Imagawa and others 2017; Tatton-Brown and others 2011; Tatton-Brown and others 2013; Weaver and others 1974). Deregulated expression of EZH2 is also found in congenital brainstem disconnection (Barth and others 2017). Besides EZH2, loss-of-function and mutations of EED

are suggested as causes for Weaver syndrome (an extremely rare congenital disorder with intellectual disability) and Chiari malformation with neurological problems, respectively (Cooney and others 2017; Imagawa and others 2017; Miro and others 2009). In an adult mouse model of status epilepticus (SE), SE produces an early increase in the expression of EZH2 and SUZL2 in the hippocampus, implying that PcG proteins might play important roles in injury and tolerance (Reynolds and others 2015).

Accumulating evidence also suggests that PRC2 is involved in neurodegeneration. EZH2-mediated H3K27 trimethylation is thought as a crucial step leading to neurodegeneration in ataxia-telangiectasia (A-T). In A-T patients and mouse models, the physical association between EZH2 and H3K27 methylation is significantly increased, suggesting that increased trimethylation of H3K27 mediated by PRC2 is an important factor in the degeneration of neurons in A-T patients (Li and others 2013). In a Parkinsonian mouse model, dopamine signaling in terminally differentiated brain neurons induces an increase in H3K27me3S28 phosphorylation with aberrant expression of a subset of PcG repressed genes, indicating that PcGs are associated with Parkinson's disease (PD) (Sodersten and others 2014). As for Huntington's disease (HD), a comprehensive analysis of H3K4me3 ChIP-sequencing data shows that EZH2 and SUZ12 are differentially enriched in HD H3K4me3 distal peaks, and that PRC2 repressive state is substantially abolished in HD-enriched peaks, suggesting that PRC2 deletion may be related with H3K4me3 upregulation in HD (Dong and others 2015). The full-length recombinant huntingtin protein significantly increased the histone H3K27 trimethylase activity, which gives us a novel starting point for studying the role of PRC2 and molecular mechanisms in

HD (Seong and others 2010). The changes of the transcriptional program in PRC2-deleted neurons lead to "progressive and fatal neurodegeneration in mice," implying that PRC2 plays key roles in protecting neurons against degeneration (von Schimmelmann and others 2016). In addition, EED is identified as an interaction partner of neutral sphingomyelinase 2 (nSMase2), a major mediator in diseases such as Alzheimer's and ischemia/reperfusion-induced brain damage (Gu and others 2013; Philipp and others 2010). Therefore, PRC2 might represent a common target of multiple pathological processes that drive neurodegenerative diseases. However, an important question that remains unanswered is how the alterations of various PRC2 components and histone H3K27 methylation contribute to these neurological diseases. Future studies to elucidate these mechanisms will help discover novel molecule targets for treating these devastating neurological disorders.

In conclusion, as PRC2 and PRC2-mediated H3K27 methylation have numerous molecular functions, understanding the multifaceted roles of PRC2 will likely continue to be a hot topic in the coming years. Although dysregulations of several PRC2 components have been linked with neurological diseases, the underlying mechanisms have not been well defined yet. Given the fact that many mouse lines have been generated for constitutive or conditional knockout of PRC2 subunits (Li and others 2013; Pereira and others 2010; Vizan and others 2015), animal models with defined pathogenic/genetic backgrounds may provide invaluable resources for discovering the functions of PRC2 components in the process of neurological disorders. With the emergence of powerful deep-sequencing and modern biology technologies, there is no doubt that further investigations of the complete picture of the intricate and complex regulatory networks of PRC2 in nervous system, especially the dynamics of core PRC2 components and the interplay between PRC2 and other associated factors, will enable us to efficiently generate specific brain cell types and develop new therapeutic approaches for treating neurological diseases.

References

Abdouh M, Facchino S, Chatoo W, Balasingam V, Ferreira J, Bernier G. 2009. BMI1 sustains human glioblastoma multiforme stem cell renewal. J Neurosci 29(28):8884–96.

Akizu N, Garcia MA, Estaras C, Fueyo R, Badosa C, de la Cruz X, and others. 2016. EZH2 regulates neuroepithelium structure and neuroblast proliferation by repressing p21. Open Biol 6(4):150227.

Akizu N, Martinez-Balbas MA. 2016. EZH2 orchestrates apicobasal polarity and neuroepithelial cell renewal. Neurogenesis (Austin) 3(1):e1250034.

Aldiri I, Moore KB, Hutcheson DA, Zhang J, Vetter ML. 2013. Polycomb repressive complex PRC2 regulates Xenopus retina development downstream of Wnt/beta-catenin signaling. Development 140(14):2867–78.

Alimova I, Venkataraman S, Harris P, Marquez VE, Northcott PA, Dubuc A, and others. 2012. Targeting the enhancer of zeste homologue 2 in medulloblastoma. Int J Cancer 131(8):1800–9.

Baker K, Dhillon T, Colas I, Cook N, Milne I, Milne L, and others. 2015. Chromatin state analysis of the barley epigenome reveals a higher-order structure defined by H3K27me1 and H3K27me3 abundance. Plant J 84(1):111–24.

Barski A, Cuddapah S, Cui K, Roh TY, Schones DE, Wang Z, and others. 2007. High-resolution profiling of histone methylations in the human genome. Cell 129(4):823–37.

Barth PG, Aronica E, Fox S, Fluiter K, Weterman MA, Poretti A, and others. 2017. Deregulated expression of EZH2 in congenital brainstem disconnection. Neuropathol Appl Neurobiol 43(4):358–65.

Bernstein BE, Mikkelsen TS, Xie X, Kamal M, Huebert DJ, Cuff J, and others. 2006. A bivalent chromatin structure marks key developmental genes in embryonic stem cells. Cell 125(2):315–26.

Boyer LA, Plath K, Zeitlinger J, Brambrink T, Medeiros LA, Lee TI, and others. 2006. Polycomb complexes repress developmental regulators in murine embryonic stem cells. Nature 441(7091):349–53.

Brien GL, Gambero G, O'Connell DJ, Jerman E, Turner SA, Egan CM, and others. 2012. Polycomb PHF19 binds H3K36me3 and recruits PRC2 and demethylase NO66 to embryonic stem cell genes during differentiation. Nat Struct Mol Biol 19(12):1273–81.

Burgold T, Voituron N, Caganova M, Tripathi PP, Menuet C, Tusi BK, and others. 2012. The H3K27 demethylase JMJD3 is required for maintenance of the embryonic respiratory neuronal network, neonatal breathing, and survival. Cell Rep 2(5):1244–58.

Cao R, Zhang Y. 2004. SUZ12 is required for both the histone methyltransferase activity and the silencing function of the EED-EZH2 complex. Mol Cell 15(1):57–67.

Celestino-Soper PB, Skinner C, Schroer R, Eng P, Shenai J, Nowaczyk MM, and others. 2012. Deletions in chromosome 6p22.3-p24.3, including ATXN1, are associated with developmental delay and autism spectrum disorders. Mol Cytogenet 5:17.

Ciferri C, Lander GC, Maiolica A, Herzog F, Aebersold R, Nogales E. 2012. Molecular architecture of human polycomb repressive complex 2. Elife 1:e00005.

Cohen AS, Yap DB, Lewis ME, Chijiwa C, Ramos-Arroyo MA, Tkachenko N, and others. 2016. Weaver syndrome-associated EZH2 protein variants show impaired histone methyltransferase function in vitro. Hum Mutat 37(3):301–7.

Conway E, Healy E, Bracken AP. 2015. PRC2 mediated H3K27 methylations in cellular identity and cancer. Curr Opin Cell Biol 37:42–8.

Cooney E, Bi W, Schlesinger AE, Vinson S, Potocki L. 2017. Novel EED mutation in patient with Weaver syndrome. Am J Med Genet A 173(2):541–5.

Cooper S, Grijzenhout A, Underwood E, Ancelin K, Zhang TY, Nesterova TB, and others. 2016. Jarid2 binds mono-ubiquitylated H2A lysine 119 to mediate crosstalk between Polycomb complexes PRC1 and PRC2. Nat Commun 7:13661.

Corley M, Kroll KL. 2015. The roles and regulation of Polycomb complexes in neural development. Cell Tissue Res 359(1):65–85.

Crea F, Fornaro L, Bocci G, Sun L, Farrar WL, Falcone A, and others. 2012. EZH2 inhibition: targeting the crossroad of tumor invasion and angiogenesis. Cancer Metastasis Rev 31(3-4):753–61.

Cui K, Zang C, Roh TY, Schones DE, Childs RW, Peng W, and others. 2009. Chromatin signatures in multipotent human hematopoietic stem cells indicate the fate of bivalent genes during differentiation. Cell Stem Cell 4(1):80–93.

De Raedt T, Beert E, Pasmant E, Luscan A, Brems H, Ortonne N, and others. 2014. PRC2 loss amplifies Ras-driven transcription and confers sensitivity to BRD4-based therapies. Nature 514(7521):247–51.

Deng T, Postnikov Y, Zhang S, Garrett L, Becker L, Racz I, and others. 2017. Interplay between H1 and HMGN epigenetically regulates OLIG1&2 expression and oligodendrocyte differentiation. Nucleic Acids Res 45(6):3031–45.

Di Croce L, Helin K. 2013. Transcriptional regulation by Polycomb group proteins. Nat Struct Mol Biol 20(10):1147–55.

Di Meglio T, Kratochwil CF, Vilain N, Loche A, Vitobello A, Yonehara K, and others. 2013. Ezh2 orchestrates topographic migration and connectivity of mouse precerebellar neurons. Science 339(6116):204–7.

Dietrich N, Lerdrup M, Landt E, Agrawal-Singh S, Bak M, Tommerup N, and others. 2012. REST-mediated recruitment of polycomb repressor complexes in mammalian cells. PLoS Genet 8(3):e1002494.

Dong XJ, Tsuji J, Labadorf A, Roussos P, Chen JF, Myers RH, and others. 2015. The role of H3K4me3 in transcriptional regulation is altered in Huntington's disease. PLoS One 10(12):e0144398.

Dubuc AM, Remke M, Korshunov A, Northcott PA, Zhan SH, Mendez-Lago M, and others. 2013. Aberrant patterns of H3K4 and H3K27 histone lysine methylation occur across subgroups in medulloblastoma. Acta Neuropathol 125(3):373–84.

Durak O, Gao F, Kaeser-Woo YJ, Rueda R, Martorell AJ, Nott A, and others. 2016. Chd8 mediates cortical neurogenesis via transcriptional regulation of cell cycle and Wnt signaling. Nat Neurosci 19(11):1477–88.

Feng X, Juan AH, Wang HA, Ko KD, Zare H, Sartorelli V. 2016. Polycomb Ezh2 controls the fate of GABAergic neurons in the embryonic cerebellum. Development 143(11):1971–80.

Ferrari KJ, Scelfo A, Jammula S, Cuomo A, Barozzi I, Stutzer A, and others. 2014. Polycomb-dependent H3K27me1 and H3K27me2 regulate active transcription and enhancer fidelity. Mol Cell 53(1):49–62.

Fukasawa R, Iida S, Tsutsui T, Hirose Y, Ohkuma Y. 2015. Mediator complex cooperatively regulates transcription of retinoic acid target genes with Polycomb Repressive Complex 2 during neuronal differentiation. J Biochem 158(5):373–84.

Gehani SS, Agrawal-Singh S, Dietrich N, Christophersen NS, Helin K, Hansen K. 2010. Polycomb group protein displacement and gene activation through MSK-dependent H3K27me3S28 phosphorylation. Mol Cell 39(6):886–900.

Gibson WT, Hood RL, Zhan SH, Bulman DE, Fejes AP, Moore R, and others. 2012. Mutations in EZH2 cause Weaver syndrome. Am J Hum Genet 90(1):110–8.

Gu L, Huang B, Shen W, Gao L, Ding Z, Wu H, and others. 2013. Early activation of nSMase2/ceramide pathway in astrocytes is involved in ischemia-associated neuronal damage via inflammation in rat hippocampi. J Neuroinflammation 10:109.

Guillemot F. 2007. Spatial and temporal specification of neural fates by transcription factor codes. Development 134(21):3771–80.

Han Li C, Chen Y. 2015. Targeting EZH2 for cancer therapy: progress and perspective. Curr Protein Pept Sci 16(6):559–70.

He D, Wang J, Lu Y, Deng Y, Zhao C, Xu L and others. 2017. lncRNA functional networks in oligodendrocytes reveal stage-specific myelination control by an lncOL1/Suz12 complex in the CNS. Neuron 93(2):362–78.

Heinen A, Tzekova N, Graffmann N, Torres KJ, Uhrberg M, Hartung HP, and others. 2012. Histone methyltransferase enhancer of zeste homolog 2 regulates Schwann cell differentiation. Glia 60(11):1696–708.

Henriquez B, Bustos FJ, Aguilar R, Becerra A, Simon F, Montecino M, and others. 2013. Ezh1 and Ezh2 differentially regulate PSD-95 gene transcription in developing hippocampal neurons. Mol Cell Neurosci 57:130–43.

Hirabayashi Y, Suzki N, Tsuboi M, Endo TA, Toyoda T, Shinga J, and others. 2009. Polycomb limits the neurogenic competence of neural precursor cells to promote astrogenic fate transition. Neuron 63(5):600–13.

Hwang WW, Salinas RD, Siu JJ, Kelley KW, Delgado RN, Paredes MF, and others. 2014. Distinct and separable roles for EZH2 in neurogenic astroglia. Elife 3:e02439.

Imagawa E, Higashimoto K, Sakai Y, Numakura C, Okamoto N, Matsunaga S, and others. 2017. Mutations in genes

encoding polycomb repressive complex 2 subunits cause weaver syndrome. Hum Mutat 38(6):637–48.

Jacob Y, Feng S, LeBlanc CA, Bernatavichute YV, Stroud H, Cokus S, and others. 2009. ATXR5 and ATXR6 are H3K27 monomethyltransferases required for chromatin structure and gene silencing. Nat Struct Mol Biol 16(7):763–8.

Jacob Y, Michaels SD. 2009. H3K27me1 is E(z) in animals, but not in plants. Epigenetics 4(6):366–9.

Juan AH, Wang S, Ko KD, Zare H, Tsai PF, Feng X, and others. 2016. Roles of H3K27me2 and H3K27me3 examined during fate specification of embryonic stem cells. Cell Rep 17(5):1369–82.

Juan AH, Wang S, Ko KD, Zare H, Tsai PF, Feng X, and others. 2017. Roles of H3K27me2 and H3K27me3 examined during fate specification of embryonic stem cells. Cell Rep 18(1):297.

Ketel CS, Andersen EF, Vargas ML, Suh J, Strome S, Simon JA. 2005. Subunit contributions to histone methyltransferase activities of fly and worm polycomb group complexes. Mol Cell Biol 25(16):6857–68.

Kim KH, Roberts CW. 2016. Targeting EZH2 in cancer. Nat Med 22(2):128–34.

Kuzmichev A, Margueron R, Vaquero A, Preissner TS, Scher M, Kirmizis A, and others. 2005. Composition and histone substrates of polycomb repressive group complexes change during cellular differentiation. Proc Natl Acad Sci U S A 102(6):1859–64.

Landeira D, Sauer S, Poot R, Dvorkina M, Mazzarella L, Jorgensen HF, and others. 2010. Jarid2 is a PRC2 component in embryonic stem cells required for multi-lineage differentiation and recruitment of PRC1 and RNA Polymerase II to developmental regulators. Nat Cell Biol 12(6):618–24.

Lee HG, Kahn TG, Simcox A, Schwartz YB, Pirrotta V. 2015. Genome-wide activities of Polycomb complexes control pervasive transcription. Genome Res 25(8):1170–81.

Lee TI, Jenner RG, Boyer LA, Guenther MG, Levine SS, Kumar RM, and others. 2006. Control of developmental regulators by Polycomb in human embryonic stem cells. Cell 125(2):301–13.

Lewis PW, Muller MM, Koletsky MS, Cordero F, Lin S, Banaszynski LA, and others. 2013. Inhibition of PRC2 activity by a gain-of-function H3 mutation found in pediatric glioblastoma. Science 340(6134):857–61.

Li G, Margueron R, Ku M, Chambon P, Bernstein BE, Reinberg D. 2010. Jarid2 and PRC2, partners in regulating gene expression. Genes Dev 24(4):368–80.

Li H, Liefke R, Jiang J, Kurland JV, Tian W, Deng P, and others. 2017. Polycomb-like proteins link the PRC2 complex to CpG islands. Nature 549(7671):287–91.

Li J, Hart RP, Mallimo EM, Swerdel MR, Kusnecov AW, Herrup K. 2013. EZH2-mediated H3K27 trimethylation mediates neurodegeneration in ataxia-telangiectasia. Nat Neurosci 16(12):1745–53.

Li J, Jiang D. 2015. The role of epigenomics in the neurodegeneration of ataxia-telangiectasia. Epigenomics 7(2):137–41.

Liu J, Casaccia P. 2010. Epigenetic regulation of oligodendrocyte identity. Trends Neurosci 33(4):193–201.

Liu J, Magri L, Zhang F, Marsh NO, Albrecht S, Huynh JL, and others. 2015. Chromatin landscape defined by repressive histone methylation during oligodendrocyte differentiation. J Neurosci 35(1):352–65.

Liu PP, Tang GB, Xu YJ, Zeng YQ, Zhang SF, Du HZ, and others. 2017. MiR-203 interplays with polycomb repressive complexes to regulate the proliferation of neural stem/progenitor cells. Stem Cell Rep 9(1):190–202.

Ma KH, Hung HA, Srinivasan R, Xie HF, Orkin SH, Svaren J. 2015. Regulation of peripheral nerve myelin maintenance by gene repression through polycomb repressive complex 2. J Neurosci 35(22):8640–52.

Margueron R, Li G, Sarma K, Blais A, Zavadil J, Woodcock CL, and others. 2008. Ezh1 and Ezh2 maintain repressive chromatin through different mechanisms. Mol Cell 32(4):503–18.

Margueron R, Reinberg D. 2011. The Polycomb complex PRC2 and its mark in life. Nature 469(7330):343–9.

Martinez R, Martin-Subero JI, Rohde V, Kirsch M, Alaminos M, Fernandez AF, and others. 2009. A microarray-based DNA methylation study of glioblastoma multiforme. Epigenetics 4(4):255–64.

Mikkelsen TS, Ku M, Jaffe DB, Issac B, Lieberman E, Giannoukos G, and others. 2007. Genome-wide maps of chromatin state in pluripotent and lineage-committed cells. Nature 448(7153):553–60.

Miller FD, Gauthier AS. 2007. Timing is everything: making neurons versus glia in the developing cortex. Neuron 54(3):357–69.

Miro X, Zhou X, Boretius S, Michaelis T, Kubisch C, Alvarez-Bolado G, and others. 2009. Haploinsufficiency of the murine polycomb gene Suz12 results in diverse malformations of the brain and neural tube. Dis Model Mech 2(7-8):412–8.

Mohn F, Weber M, Rebhan M, Roloff TC, Richter J, Stadler MB, and others. 2008. Lineage-specific polycomb targets and de novo DNA methylation define restriction and potential of neuronal progenitors. Mol Cell 30(6):755–66.

Montgomery ND, Yee D, Chen A, Kalantry S, Chamberlain SJ, Otte AP, and others. 2005. The murine polycomb group protein Eed is required for global histone H3 lysine-27 methylation. Curr Biol 15(10):942–7.

Muller J, Hart CM, Francis NJ, Vargas ML, Sengupta A, Wild B, and others. 2002. Histone methyltransferase activity of a Drosophila polycomb group repressor complex. Cell 111(2):197–208.

Mysliwiec MR, Bresnick E, Lee Y. 2010. Jarid2/Jumonji dependent epigenetic control of Notch1 expression is required for normal cardiac development. Circulation 122(21):A21584.

Nekrasov M, Klymenko T, Fraterman S, Papp B, Oktaba K, Kocher T, and others. 2007. Pcl-PRC2 is needed to generate high levels of H3-K27 trimethylation at Polycomb target genes. EMBO J 26(18):4078–88.

O'Carroll D, Erhardt S, Pagani M, Barton SC, Surani MA, Jenuwein T. 2001. The Polycomb-group gene Ezh2 is required for early mouse development. Mol Cell Biol 21(13):4330–6.

Palomer E, Carretero J, Benvegnu S, Dotti CG, Martin MG. 2016. Neuronal activity controls Bdnf expression via Polycomb de-repression and CREB/CBP/JMJD3 activation in mature neurons. Nat Commun 7:11081.

Papp B, Muller J. 2006. Histone trimethylation and the maintenance of transcriptional ON and OFF states by trxG and PcG proteins. Genes Dev 20(15):2041–54.

Pasini D, Bracken AP, Hansen JB, Capillo M, Helin K. 2007. The polycomb group protein Suz12 is required for embryonic stem cell differentiation. Mol Cell Biol 27(10):3769–79.

Pasini D, Cloos PA, Walfridsson J, Olsson L, Bukowski JP, Johansen JV, and others. 2010. JARID2 regulates binding of the Polycomb repressive complex 2 to target genes in ES cells. Nature 464(7286):306–10.

Peng JC, Valouev A, Swigut T, Zhang J, Zhao Y, Sidow A, and others. 2009. Jarid2/Jumonji coordinates control of PRC2 enzymatic activity and target gene occupancy in pluripotent cells. Cell 139(7):1290–302.

Pereira JD, Sansom SN, Smith J, Dobenecker MW, Tarakhovsky A, Livesey FJ. 2010. Ezh2, the histone methyltransferase of PRC2, regulates the balance between self-renewal and differentiation in the cerebral cortex. Proc Natl Acad Sci U S A 107(36):15957–62.

Philipp S, Puchert M, Adam-Klages S, Tchikov V, Winoto-Morbach S, Mathieu S, and others. 2010. The Polycomb group protein EED couples TNF receptor 1 to neutral sphingomyelinase. Proc Natl Acad Sci U S A 107(3):1112–7.

Piper M, Barry G, Harvey TJ, McLeay R, Smith AG, Harris L, and others. 2014. NFIB-mediated repression of the epigenetic factor Ezh2 regulates cortical development. J Neurosci 34(8):2921–30.

Piunti A, Shilatifard A. 2016. Epigenetic balance of gene expression by Polycomb and COMPASS families. Science 352(6290):aad9780.

Popkova A, Bernardoni R, Diebold C, Van de Bor V, Schuettengruber B, Gonzalez I, and others. 2012. Polycomb controls gliogenesis by regulating the transient expression of the Gcm/Glide fate determinant. PLoS Genet 8(12):e1003159.

Qi C, Liu S, Qin R, Zhang Y, Wang G, Shang Y and others. 2014. Coordinated regulation of dendrite arborization by epigenetic factors CDYL and EZH2. J Neurosci 34(13):4494–508.

Qi L, Cao JL, Hu Y, Yang JG, Ji Y, Huang J, and others. 2013. The dynamics of polycomb group proteins in early embryonic nervous system in mouse and human. Int J Dev Neurosci 31(7):487–95.

Ramos PS, Sajuthi S, Langefeld CD, Walker SJ. 2012. Immune function genes CD99L2, JARID2 and TPO show association with autism spectrum disorder. Mol Autism 3(1):4.

Reynolds JP, Miller-Delaney SF, Jimenez-Mateos EM, Sano T, McKiernan RC, Simon RP, and others. 2015. Transcriptional response of polycomb group genes to status epilepticus in mice is modified by prior exposure to epileptic preconditioning. Front Neurol 6:46.

Satijn DPE, Hamer KM, den Blaauwen J, Otte AP. 2001. The polycomb group protein EED interacts with YY1, and both proteins induce neural tissue in Xenopus embryos. Mol Cell Biol 21(4):1360–9.

Sauvageau M, Sauvageau G. 2010. Polycomb group proteins: multi-faceted regulators of somatic stem cells and cancer. Cell Stem Cell 7(3):299–313.

Savla U, Benes J, Zhang J, Jones RS. 2008. Recruitment of Drosophila Polycomb-group proteins by Polycomblike, a component of a novel protein complex in larvae. Development 135(5):813–7.

Schumacher A, Faust C, Magnuson T. 1996. Positional cloning of a global regulator of anterior-posterior patterning in mice. Nature 384(6610):648.

Schwarz D, Varum S, Zemke M, Scholer A, Baggiolini A, Draganova K, and others. 2014. Ezh2 is required for neural crest-derived cartilage and bone formation. Development 141(4):867–77.

Seong IS, Woda JM, Song JJ, Lloret A, Abeyrathne PD, Woo CJ, and others. 2010. Huntingtin facilitates polycomb repressive complex 2. Hum Mol Genet 19(4):573–83.

Shen X, Kim W, Fujiwara Y, Simon MD, Liu Y, Mysliwiec MR, and others. 2009. Jumonji modulates polycomb activity and self-renewal versus differentiation of stem cells. Cell 139(7):1303–14.

Shen X, Liu Y, Hsu YJ, Fujiwara Y, Kim J, Mao X, and others. 2008. EZH1 mediates methylation on histone H3 lysine 27 and complements EZH2 in maintaining stem cell identity and executing pluripotency. Mol Cell 32(4):491–502.

Sher F, Boddeke E, Copray S. 2011. Ezh2 expression in astrocytes induces their dedifferentiation toward neural stem cells. Cell Reprogram 13(1):1-6.

Sher F, Boddeke E, Olah M, Copray S. 2012. Dynamic changes in Ezh2 gene occupancy underlie its involvement in neural stem cell self-renewal and differentiation towards oligodendrocytes. PLoS One 7(7):e40399.

Sher F, Rossler R, Brouwer N, Balasubramaniyan V, Boddeke E, Copray S. 2008. Differentiation of neural stem cells into oligodendrocytes: involvement of the polycomb group protein Ezh2. Stem Cells 26(11):2875–83.

Sneeringer CJ, Scott MP, Kuntz KW, Knutson SK, Pollock RM, Richon VM, and others. 2010. Coordinated activities of wild-type plus mutant EZH2 drive tumor-associated hypertrimethylation of lysine 27 on histone H3 (H3K27) in human B-cell lymphomas. Proc Natl Acad Sci U S A 107(49):20980–5.

Soderstern E, Feyder M, Lerdrup M, Gomes AL, Kryh H, Spigolon G, and others. 2014. Dopamine signaling leads to loss of Polycomb repression and aberrant gene activation in experimental parkinsonism. PLoS Genet 10(9):e1004574.

Sparmann A, Xie YL, Verhoeven E, Vermeulen M, Lancini C, Gargiulo G, and others. 2013. The chromodomain helicase Chd4 is required for Polycomb-mediated inhibition of astroglial differentiation. EMBO J 32(11):1598–612.

Stein C, Nötzold RR, Riedl S, Bouchard C, Bauer UM. 2016. The arginine methyltransferase PRMT6 cooperates with polycomb proteins in regulating HOXA gene expression. PLoS One 11(2):e0148892.

Steiner LA, Schulz VP, Maksimova Y, Wong C, Gallagher PG. 2011. Patterns of histone H3 lysine 27 monomethylation and erythroid cell type-specific gene expression. J Biol Chem 286(45):39457–65.

Su IH, Dobenecker MW, Dickinson E, Oser M, Basavaraj A, Marqueron R, and others. 2005. Polycomb group protein

ezh2 controls actin polymerization and cell signaling. Cell 121(3):425–36.

Takeuchi T, Yamazaki Y, Katoh-Fukui Y, Tsuchiya R, Kondo S, Motoyama J, and others. 1995. Gene trap capture of a novel mouse gene, jumonji, required for neural tube formation. Genes Dev 9(10):1211–22.

Tang GB, Zeng YQ, Liu PP, Mi TW, Zhang SF, Dai SK, and others. 2017. The histone H3K27 demethylase UTX regulates synaptic plasticity and cognitive behaviors in mice. Front Mol Neurosci 10:267.

Tatton-Brown K, Hanks S, Ruark E, Zachariou A, Duarte Sdel V, Ramsay E, and others. 2011. Germline mutations in the oncogene EZH2 cause Weaver syndrome and increased human height. Oncotarget 2(12):1127–33.

Tatton-Brown K, Murray A, Hanks S, Douglas J, Armstrong R, Banka S, and others. 2013. Weaver syndrome and EZH2 mutations: clarifying the clinical phenotype. Am J Med Genet A 161A(12):2972–80.

Temple S. 2001. The development of neural stem cells. Nature 414(6859):112–7.

Tien CL, Jones A, Wang HB, Gerigk M, Nozell S, Chang CB. 2015. Snail2/Slug cooperates with Polycomb repressive complex 2 (PRC2) to regulate neural crest development. Development 142(4):722–31.

Usemann J, Ernst T, Schafer V, Lehmberg K, Seeger K. 2016. EZH2 mutation in an adolescent with Weaver syndrome developing acute myeloid leukemia and secondary hemophagocytic lymphohistiocytosis. Am J Med Genet A 170A(5):1274–7.

Vakoc CR, Sachdeva MM, Wang H, Blobel GA. 2006. Profile of histone lysine methylation across transcribed mammalian chromatin. Mol Cell Biol 26(24):9185–95.

Vizan P, Beringer M, Ballare C, Di Croce L. 2015. Role of PRC2-associated factors in stem cells and disease. FEBS J 282(9):1723–35.

von Schimmelmann M, Feinberg PA, Sullivan JM, Ku SM, Badimon A, Duff MK, and others. 2016. Polycomb repressive complex 2 (PRC2) silences genes responsible for neurodegeneration. Nat Neurosci 19(10):1321–30.

Wang C, Zhao JJ, Lu CL, Han XD, An LS, Ma X. 2010. Polycomb group proteins are essential for spinal cord development. Front Biosci (Landmark Ed) 15:1018–22.

Wang Z, Zhang Y, Fang J, Yu F, Heng D, Fan Y, and others. 2017. Decreased methylation level of H3K27me3 increases seizure susceptibility. Mol Neurobiol 54(9):7343–52.

Weaver DD, Graham CB, Thomas IT, Smith DW. 1974. A new overgrowth syndrome with accelerated skeletal maturation, unusual facies, and camptodactyly. J Pediatr 84(4):547–52.

Zemke M, Draganova K, Klug A, Scholer A, Zurkirchen L, Gay MHP, and others. 2015. Loss of Ezh2 promotes a midbrain-to-forebrain identity switch by direct gene derepression and Wnt-dependent regulation. BMC Biol 13:103.

Zhang J, Ji F, Liu Y, Lei X, Li H, Ji G, and others. 2014a. Ezh2 regulates adult hippocampal neurogenesis and memory. J Neurosci 34(15):5184–99.

Zhang M, Wang Y, Jones S, Sausen M, McMahon K, Sharma R, and others. 2014b. Somatic mutations of SUZ12 in malignant peripheral nerve sheath tumors. Nat Genet 46(11):1170–2.

Zhao E, Maj T, Kryczek I, Li W, Wu K, Zhao L, and others. 2016. Cancer mediates effector T cell dysfunction by targeting microRNAs and EZH2 via glycolysis restriction. Nat Immunol 17(1):95–103.

Zhao L, Li J, Ma Y, Wang J, Pan W, Gao K, and others. 2015a. Ezh2 is involved in radial neuronal migration through regulating Reelin expression in cerebral cortex. Sci Rep 5:15484.

Zhao W, Jiang BC, Hu HL, Zhang SQ, Lv SS, Yuan JP, and others. 2015b. Lack of CUL4B leads to increased abundance of GFAP-positive cells that is mediated by PTGDS in mouse brain. Hum Mol Genet 24(16):4686–97.