

Review

Regulatory networks between Polycomb complexes and non-coding RNAs in the central nervous system

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High-throughput sequencing has facilitated the identification of many types of non-coding RNAs (ncRNAs) involved in diverse cellular processes. NcRNAs as epigenetic mediators play key roles in neuronal development, maintenance, and dysfunction by controlling gene expression at multiple levels. NcRNAs may not only target specific DNA or RNA for gene silencing but may also directly interact with chromatin-modifying proteins like Polycomb group (PcG) proteins to drive orchestrated transcriptional programs. Recent significant progress has been made in characterizing ncRNAs and PcG proteins involved in transcriptional, post-transcriptional, and epigenetic regulation. More importantly, dysregulation of ncRNAs, PcG proteins, and interplay among them is closely associated with the pathogenesis of central nervous system (CNS) disorders. In this review, we focus on the interplay between ncRNAs and PcG proteins in the CNS and highlight the functional roles of the partnership during neural development and diseases.

Keywords: epigenetics, Polycomb complexes, non-coding RNAs, central nervous system, neurological diseases

Introduction

Due to the rapid development of next-generation sequencing techniques, it is well known that only ~2% of mammalian genome encodes for functional proteins, while the majority of transcripts are non-coding RNAs (ncRNAs) without protein-coding capacity. In general, ncRNAs act as vital mediators to regulate gene expression involved in biological processes, such as proliferation, differentiation, cell cycle, and apoptosis (Li et al., 2017b). In addition to binding specific DNA or RNA sequence to silence genes, ncRNAs can directly interact with epigenetic regulatory proteins, such as Polycomb group (PcG) proteins, to trigger coordinated changes in gene networks (Yaghmaeian Salmani et al., 2018; Ntini and Marsico, 2019; Täuber et al., 2019). Recent studies have suggested that ncRNAs and PcG

proteins play important roles in the central nervous system (CNS) development and functions (Wang and Bao, 2017; Gao et al., 2018). Moreover, dysregulation of ncRNAs, PcG proteins, and ncRNA–PcG interactions is implicated in the pathogenesis of CNS disorders. In this review, we summarize an overview of the functional roles of ncRNAs and PcG proteins in the CNS and discuss recent advances in our understanding of the neural mechanisms by which ncRNAs and their interplay with PcG proteins are related to the development and progress of neurological disorders.

NcRNAs serving as important epigenetic regulators

Generally, ncRNAs are divided into two main types based on their function: housekeeping and regulatory ncRNAs. Housekeeping ncRNAs such as ribosomal (rRNA), transfer (tRNA), 4.5S, RNase P, and transfer-messenger 3 (tmRNA; a small percent of these are coding) RNAs have fundamental roles in translation and slicing (Arnvig et al., 2014). Regulatory ncRNAs, as epigenetic mediators that function to regulate gene expression and chromatin remodeling, have attracted increasing attention (Wang, 2018). Based on the transcript size, regulatory ncRNAs

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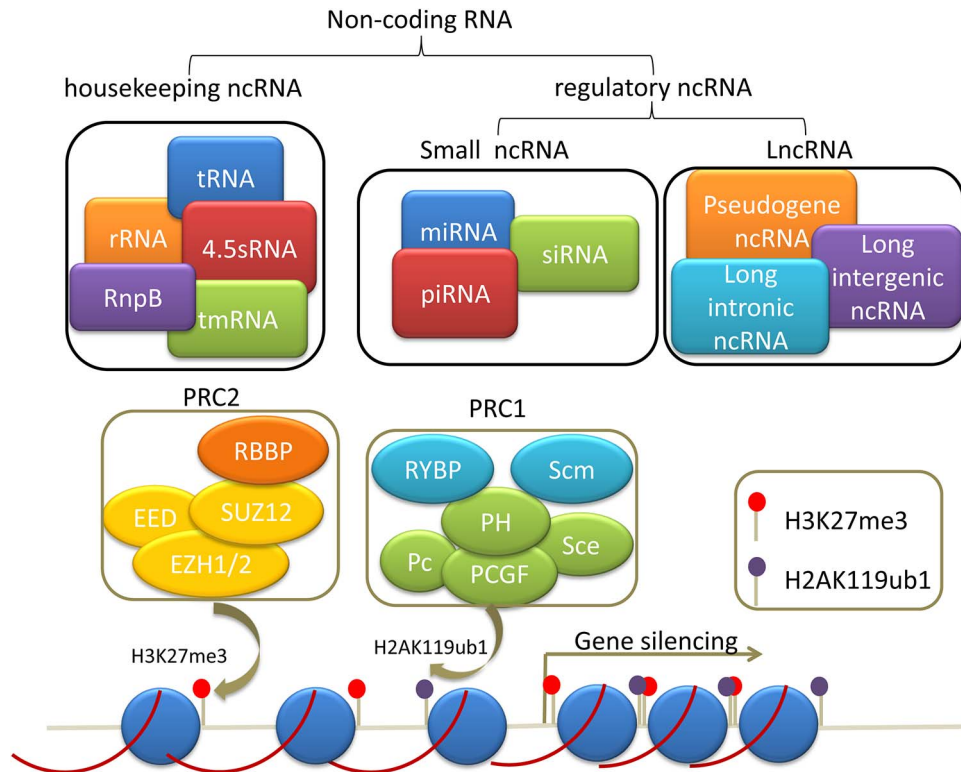


Figure 1 ncRNAs and PcG components. The upper: schematic overview of the classification of ncRNAs. NcRNAs are divided into housekeeping and regulatory ncRNAs. Housekeeping ncRNAs include rRNA, tRNA, 4.5S, RNase P, and tmRNA. Regulatory ncRNAs are further divided into small ncRNAs and lncRNAs. Small ncRNAs include miRNAs, siRNAs, and piRNAs. LncRNAs include long intergenic and long intronic ncRNAs, as well as pseudogene RNAs. Below: an illustration of PcG protein components and silencing mechanism. Polycomb repressor complex 1 (PRC1) includes four core components (green ovals): Polycomb (Pc), Sex combs extra (Sce; RING1/RING1A and RING2/RING1B), Polyhomeiotic (PH), and PCGF. Pc contains a chromo domain that binds to trimethylated lysine 27 of histone H3 (H3K27me3) with varying affinity, essential in recruiting PRC1 to the target. RING1A/B contains E3 ubiquitin ligase activity, which can mono-ubiquitylate histone H2AK119 (H2AK119ub1). Apart from the canonical subunits listed above, RYBP (RING1/YY1-binding protein) and Scm (sex comb on midleg) are supporting factors of PRC1. PRC2 also includes three core components (yellow ovals): enhancer of zeste (EZH1/2), suppressor of zeste (SUZ12), embryonic ectoderm development (EED), and additional components such as retinoblastoma binding protein (RBBP) can also regulate the activity of PRC2. PRC2 is recruited to genomic loci, and EZH2 catalyzes H3K27me3, thereby initiating the repression. Subsequently, CBX proteins bind to H3K27me3, then recruit PRC1 to chromatin, resulting in the deposition of the H2AK119ub1. The formation of repression complexes leads to chromatin compaction.

can further be classified into short and long ncRNAs. Short ncRNAs are a class of <200 nucleotides (nt) transcripts, including microRNAs (miRNAs), small interfering RNAs (siRNAs), and PIWI-associated RNAs (piRNAs). The other class named as long ncRNAs (lncRNAs) have >200 nt length, such as intergenic ncRNAs (lincRNAs), intronic ncRNAs, and pseudogene RNAs (Martens-Uzunova et al., 2014; Figure 1). Recently, significant evidence clearly shows that enhancer and circular RNAs (eRNAs and circRNAs) are identified as two novel subtypes of lncRNAs (Rinn and Chang, 2012; Kopp and Mendell, 2018). Among different regulatory ncRNAs, lncRNAs and miRNAs are well studied in regard to transcriptional, post-transcriptional, and epigenetic regulation.

lncRNAs interact with DNA, RNA, or proteins, which function to regulate gene transcription *in cis* or *in trans*, organize nuclear domains, or modulate protein translation, etc. It is well known that lncRNAs can regulate splicing, cell survival, proliferation,

and differentiation, while their dysfunctions are involved in the pathogenesis of many types of cancer (Yamada, 2017; Han et al., 2018). Usually, lncRNAs modulate epigenetic silencing by chromatin remodeling (Dey et al., 2014). Accumulating evidence supports that lncRNAs interact with transcription factors and chromatin regulators to affect the expression pattern of specific genes (Martens-Uzunova et al., 2014; Guo et al., 2018; Militello et al., 2018). lncRNAs can also function as signals, scaffolds, or antisense decoys and are implicated in transcriptional interference (Geisler and Collier, 2013; Ulitsky and Bartel, 2013). Scaffold lncRNAs bind to proteins and other RNAs to form larger functional complexes, such as the PcG complexes involved in histone modifications (McAninch et al., 2017; Guo et al., 2018). Previous studies suggested that lncRNAs do not encode proteins, whereas a recent key study reveals that many transcripts belonging to the lncRNAs class can actually be translated into proteins

in a tissue-specific fashion (Zhu et al., 2018). Although the number of identified lncRNAs continues to grow, their functional roles, as well as their biological significance, remain mysterious (McAninch et al., 2017).

In the past decade, the study of ncRNA biology, especially miRNAs, has attracted remarkable attention, resulting in rapid advances (Bianchi et al., 2017). MiRNAs are a large cluster of conserved endogenous single-stranded small ncRNAs derived from the human genome, which are ~22 nucleotides long (Du et al., 2016). MiRNAs were first discovered in 1993, and to date, >1400 miRNAs have been identified in humans (Li et al., 2017b). MiRNAs act as important regulators of gene expression through binding 3'-untranslated regions (UTRs) of target genes to inhibit their translation or stability. Each miRNA may target multiple messenger RNAs (mRNAs), and each gene can be targeted by numerous miRNAs, resulting in complex regulatory networks with profound effects on gene expression patterns (O'Loughlen et al., 2015). Therefore, the miRNA pathway has emerged as a fundamental gene regulatory pathway, with important roles in development, senescence, survival, and cancer (Wu et al., 2017; Biggar and Storey, 2018; Zhu et al., 2019).

Mounting evidence suggests that lncRNAs can also act as miRNA sponges via competing endogenous RNA (ceRNA) activity (Thomson and Dinger, 2016). Most of the studies related to lncRNA-mediated sponge interactions are found in various cancers including the hepatocellular carcinoma (HCC). For example, lncRNA colon cancer-associated transcript-1 (CCAT1) regulates cell proliferation of HCC by acting as a miR-30c-2-3p sponge by ceRNA activity (Zhang et al., 2019). In addition, lncRNA plasmacytoma variant translocation 1 (PVT1) could facilitate autophagy by acting as a sponge of miR-365, which downregulated ATG3 protein level by targeting 3'-UTR of ATG3 mRNA (Yang et al., 2019). lncRNA tumor suppressor taurine upregulated gene 1 (TUG1) is known for regulating PRC2-mediated transcription (Du et al., 2016; Lin et al., 2016). The evidence shows that TUG1, a miRNA sponge, can regulate phosphatase and tension homolog (PTEN) expression in a miRNA-dependent manner in prostate cancer (Du et al., 2016). lncRNA TUG1 promotes proliferation of vascular smooth muscle cell via targeting miR-21 to decrease PTEN activity in atherosclerosis patients (Li et al., 2018). What's more, in human glioma cells, lncRNA TUG1 can also act as a miR-26a sponge to regulate PTEN expression (Li et al., 2016a). Based on ceRNA theory, recently, multiple computational methods have been proposed to study the competitive relationships between lncRNAs and miRNA-targeted mRNAs (Zhang et al., 2018). The novel crosstalk will bring about significant insights into gene regulatory networks and have implications in development and cancer (Liu et al., 2018).

PcG protein components

The evolutionarily conserved PcG proteins are prominent epigenetic regulators that repress gene transcription. It has been demonstrated that PcG proteins regulate target gene expression during development by modulating higher-order chromatin structures (Lu et al., 2016). PcG proteins have been widely found

in all metazoans and carry out various biological functions, including cell cycle control, chromosome X-inactivation, stem cell maintenance, cell fate decisions, and developmental control (Simhadri et al., 2014; Lv et al., 2018a, b). In mammals, PcG proteins play pivotal roles in regulating early embryogenesis and disease pathogenesis (Yang et al., 2016). Mounting evidence reveals that PcG-dependent epigenetic dysregulation is closely associated with many diseases, including epilepsy and glioma tumorigenicity (Chen et al., 2017b). The components of the PcG complexes are frequently mutated in diseases, and blocking of PcG complexes interactions can impinge on tumor proliferation, immortalization, and metastasis (Zhen et al., 2016). Due to the potential clinical implications of PcG complexes, massive efforts have been devoted to exploring the mechanisms underlying the association between these complexes and diseases.

Most PcG proteins form two major protein complexes, PRC1 and PRC2, which have different enzymatic activities (Yang et al., 2016). In mammals, PRC1 has several homologs for each subunit. There are five Polycomb (CBX2, CBX4, CBX6, CBX7, and CBX8), two Sex combs extra (RING1/RING1A and RING2/RING1B), three Polyhomeotic (PHC1, PHC2, and PHC3), and six Posterior sex combs; the latter are collectively known as PcG ring fingers (PCGFs), including BMI1, NSPC1, MEL18, PCGF3, PCGF5, and MBLR (Vandamme et al., 2011; Gao et al., 2012). Additionally, there are still many other PRC1 uncanonical components and supporting factors, including the RING1/YY1-binding protein and its homolog YAF2 and the mammalian orthologs of the *Drosophila* Sex comb on midleg (Ma et al., 2014). The PRC1 complex catalyzes the mono-ubiquitination of histone H2A at lysine 119 (H2AK119ub1) by its associated E3 ligase RING1A/B, in spite of its repressive function may be independent of this enzymatic activity (Srivastava et al., 2017). While BMI1 and MEL18 promote activities of RING1A/B, PcG proteins specifically recognize tri-methylation of histone 3 at lysine 27 (H3K27me3) via their chromo domains to stabilize the interactions between PRC1 and chromatin (Morey et al., 2012).

PRC2 modulates chromatin dynamics via di- or tri-methylation of H3K27 (H3K27me2/3) for transcriptional repression. The core components of mammalian PRC2 comprise a homolog of enhancer of zeste (EZ; EZH1 or EZH2), a homolog of suppressor of zeste (SUZ; SUZ12), and an extra sex combs homolog (embryonic ectoderm development, EED). Among them, EZH2 is the catalytic subunit of PRC2 that can methylate H3K27, serving as a histone methyltransferases (HMTs; Ma et al., 2014). EZH1 is the homolog of EZH2, partially complements EZH2 in regulating H3K27me3 and maintaining stem cell identity. EED regulates the substrate specificity of the EZH2 complex, while SUZ12 critically modulates the HMT activity of PRC2, leading to differential targeting of its HMT activity toward H3K27 (Wang et al., 2015). Additional components such as chromatin assembly factor 1 (Caf1) homologues histone-binding proteins RBBP4 and RBBP7 can also regulate the activity of PRC2 through binding to SUZ12 (Schwartz and Pirrotta, 2013; Figure 1). In addition, Polycomb-like (PCL) proteins, such as PHF1 (PCL1), MTF2 (PCL2), PHF19 (PCL3), C17ORF96 (EPOP), JARID2, and

AEBP2, are a class of novel regulatory factors of PRC2 that form sub-complexes with PRC2 core components and modulate the recruitment and enzymatic activity of PRC2 (Hauri et al., 2016). Among them, MTF2 controls PRC2 recruitment via binding to specific DNA sequence or regulates PRC2 enzymatic activity, leading to X chromosome inactivation (XCI) and pluripotency (Li et al., 2017a; Perino et al., 2018). It has been reported that JARID2 is involved in PRC2-dependent inactivation of X chromosome in embryonic stem (ES) cells (da Rocha et al., 2014). EPOP stimulates the HMT activity of PRC2 in mouse ES cells (Vizan et al., 2015). Several studies have suggested that PRC2 is responsible for PRC1 recruitment, then PRC1 carries out stable repression via H2AK119ub1 or forming compact chromatin structures (Blackledge et al., 2015). However, one recent study supported the opposite view that PRC1 is sufficient to recruit PRC2 via H2AK119ub1 (Holoch and Margueron, 2017).

X-inactive specific transcript (*Xist*) is one of the most well-studied lncRNA involved in XCI (Portoso et al., 2017). PRC2 can directly bind to *Xist* and tether to the inactive X chromosome *in cis* (Chaumeil, 2006; Brockdorff, 2013; Yamada, 2017). Genetic and biochemical analyses have demonstrated that the 5'-end of *Xist* consists of a stretch of 8.5 repeats of ~28 nt sequence, called A-repeat domain (RepA) that targets PRC2 for XCI (Betancur and Tomari, 2015). Previous studies have shown that RepA can recruit PRC2, but the mechanism by which RepA attracts PRC2 is currently unknown (Zhao et al., 2008; Davidovich et al., 2015; Sunwoo et al., 2015). Genetic disruption of EED and Tsix, an antisense transcript of *Xist*, causes the loss of *Xist* repression, in spite of the existence of other *Xist* regulators, such as RNF12, NANOG, and OCT4 (Ohhata et al., 2015). Using stochastic optical reconstruction microscopy, a key study shows that only 50–100 *Xist* molecules and ~50 PRC2 foci are observed per inactive X (Xi), differing from the chromosome-wide 'coat' in deep sequencing and conventional microscopy (Sunwoo et al., 2015).

PcG proteins and lncRNA interactions in the CNS development

lncRNAs are profusely present in the brain and have important roles in brain development and neuronal function. More than 5000 of a total of 9747 identified lncRNAs are detected in the brain and involved in neurodevelopment and neurodevelopmental disorders (Wahlestedt et al., 2015). Moreover, lncRNAs, as key regulators of neurogenesis, interact with several proteins in regulating various biological processes. For instance, endogenous RNA immunoprecipitation experiments in human ES cells show that lncRNAs interact with the transcription factor SOX2 and SUZ12 to maintain pluripotency (Ng et al., 2012). The lncRNA SOX2 overlapping transcript (Sox2OT) that overlaps SOX2 gene is expressed in the mouse brain and is enriched in areas involved in neurogenesis (Tang et al., 2017). The lncRNAs rhabdo-myosarcoma 2-associated transcript (RMST) and lncRNA-N1/2/3 are physically associated with SUZ12, a core component of PRC2, to trigger a gene expression program related to neurogenesis (Ng et al., 2012). Another novel lncRNA, chromatin-associated transcripts 7 (CAT7), is essential for repression of the nearby PcG target gene motor neuron and pancreas

home box 1 (MNX1) during early neuronal differentiation (Ray et al., 2016). Particularly, CAT71 is an analog of CAT7 which interacts with BMI1 to regulate zebrafish brain development (Ray et al., 2016). In cultured primary neurons, PRC2 interacts with the lncRNA survival motor neuron-antisense 1 (SMN-AS1), transcribed within the SMN2 promoter, thereby repressing SMN2 expression by PRC2-associated epigenetic changes (d'Ydewalle et al., 2017). The lncRNA Gomafu interacts with BMI1, a key component of PRC1 that modulates schizophrenia-related gene beta crystalline (CRYBB1) expression, contributing to fear-induced anxiety-like behavior (Spadaro et al., 2015). The lncRNA six3 opposite strand (Six3OS) as a transcriptional scaffold directly binds to the PRC2 subunit EZH2 and the eyes absent gene (Eya) family members to modulate retinal cell specification and differentiation (Rapicavoli et al., 2011). lncOL1, an oligodendrocyte-restricted lncRNA, interacts with SUZ12 in control of stage-specific CNS myelination and myelin repair and is both crucial and enough for the timely initiation of oligodendrocyte differentiation and myelination in the CNS. Upregulation of lncOL1 can induce oligodendrocyte differentiation in the developing brain, whereas inactivation of lncOL1 leads to defects in the CNS myelination and remyelination following injury (He et al., 2017; Figure 2). Taken together, these findings reveal a significant role of lncRNAs–PcG complexes in regulating mammalian gene expression associated with the development and function of CNS.

PRC2 can bind to thousands of RNAs in different cells, but the mechanisms of RNA in maintaining repressed chromatin remains unclear. By quantitative electrophoretic mobility shift assays, the promiscuously binding of PRC2 and RNA was found size dependent and with lower affinity for shorter RNAs. They proposed a model that promiscuous RNA binding is likely to promote the repression mediated by PcG proteins and serve as a checkpoint to prevent escape from silencing (Davidovich et al., 2013). PRC2 can also be found in active promoters in mouse ES cells, whereas it binds to nascent transcripts (Kaneko et al., 2013). Taken together, it may support a model for the maintenance of the chromatin repression by PRC2, directed by binding to nascent RNA transcripts promiscuously.

Interplay between PcG proteins and miRNAs in the CNS development

Around 70% of the identified miRNAs have been tracked in the brain and function to regulate neurogenesis, neuroprotection, synaptic plasticity, and secretion of neurotransmitters in the CNS (Song and Kim, 2017). Accumulating evidence indicates that PcG proteins and miRNAs are co-expressed in many cell types, including neural stem cells (NSCs; Liu et al., 2017). It has been reported that, in neural tissues, miR-30b interacts with the 3'-UTR of EED and regulates the expression level of endogenous EED, a core subunit of PRC2 (Song et al., 2011). In addition, the HMT EZH2 regulates stem cell proliferation by repressing miRNA expression. For example, in both embryonic and adult neural stem/progenitor cells (NSPCs), EZH2 represses miR-203, which in turn mediates PRC2 and PRC1 interactions, thereby

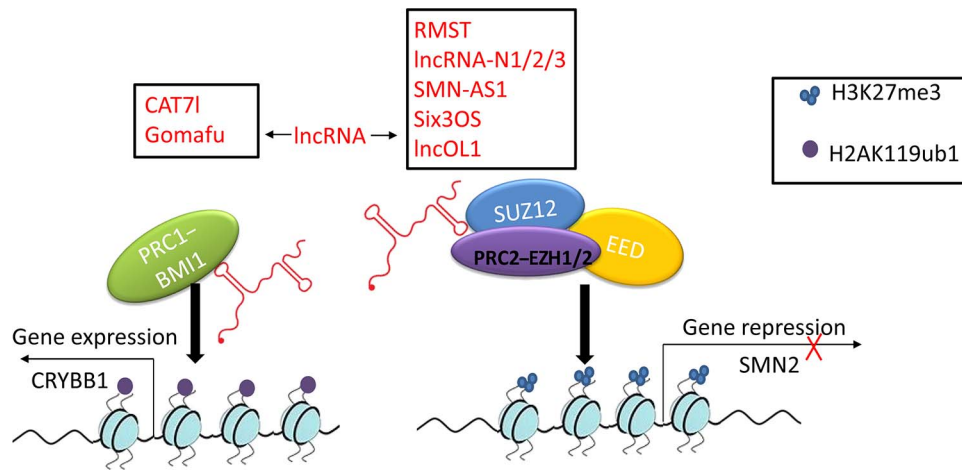


Figure 2 Interactions between lncRNAs and PcG proteins. Left: two lncRNAs, CAT71 and Gomaflu interact with BMI1, a key member of the PRC1, which epigenetically regulates specific genes expression during neural development, such as CRYBB1. Right: a subset of lncRNAs associated with PRC2 components, such as SUZ12 and EZH2. lncRNAs represses specific genes expression, such as SMN2, through PRC2-associated epigenetic changes. H3K27me3, histone H3 lysine 27 trimethylation; H2AK119ub1, histone H2A lysine 119 mono-ubiquitination; RMST, rhabdo-myosarcoma 2-associated transcript; SMN-AS1, survival motor neuron 1-antisense 1; Six3OS, Six3 opposite strand.

regulating NSPC proliferation (Liu et al., 2017). Moreover, miR-137-dependent EZH2 silencing at post-transcriptional level results in decreased global H3K27me3, thereby promoting adult NSC proliferation and inhibiting neuronal differentiation (Szulwach et al., 2010). Also, miR-137 and its downstream target, EZH2, are enriched at cortical and hippocampal neuron synapses, suggesting its role in modulating the local synaptic protein synthesis machinery (Willemsen et al., 2011). Furthermore, miR-124 promotes neuronal and hampers astrocyte-specific differentiation by directly downregulating the expression of EZH2 (Neo et al., 2014). miR-27b-dependent repression of BMI1 is required for the developmental transition of NSCs into mature, synaptic-competent neurons and the shape of neural activity in rodent cortical networks (Poon et al., 2016; Figure 3). These results suggest that interplay between the miRNA and PcG proteins could play key roles in the modulation of neurodevelopment. Thus, it will be interesting to explore the complicated partnership on how to regulate neurodevelopment and balance cell fate in future.

PcG proteins and ncRNAs abnormalities in neurological disorders

Epigenetic dysregulation has a significant role in neurological disorders, including CNS tumor and monogenic disease, etc. Thus, epigenetic mechanism will lead to a potential new therapeutic strategy or biomarker discovery for several neurological disorders. For instance, recent studies have suggested that miRNAs may be promising potential targets for gene therapy of neurological disorders (Santa-Maria et al., 2015; Chen et al., 2017a). ncRNAs or their interplay with epigenetic modifiers have been implicated in the pathogenesis of neurological disorders, while it is essential to further understand ncRNA-associated modifications in specific cellular events for potential therapeutic application.

PcG proteins and ncRNAs in glioblastoma multiforme

Glioblastoma multiforme (GBM) is the most common malignant and aggressive brain tumor in adults. It grows invasively in the CNS, causes discernible neurological symptoms and is characterized by remarkable cellular heterogeneity (Soubannier and Stifani, 2017). It accounts for 12%–15% of all intracranial tumors and ~50% of astrocytic tumors (Szopa et al., 2017). GBM mainly occurs in the elderly, and survival usually does not exceed 15 months, even after standard treatments (Soubannier and Stifani, 2017).

Hox transcript antisense intergenic RNA (HOTAIR), a 2.2-kb lncRNA transcribed from the home box C (HOXC) locus, promotes malignant progression and poor prognosis in GBM patients (Zhang et al., 2015; Zhou et al., 2015). HOTAIR binds to PRC2 through its 5'-end domain *in trans* and recruits the PRC2 complex to the HOXD locus for gene silencing (Li et al., 2013). Several significant studies have shown that HOTAIR accelerates cell cycle progression in GBM via binding to the PRC2 complex (Zhang et al., 2015; Zhou et al., 2015). In glioma stem cells, HOTAIR mediates the tri-methylation of H3K27 and the demethylation of H3K4me2 via the recruitment of the EZH2 and LSD1 proteins, respectively. And the synergistic effect of EZH2 and LSD1 results in the transcriptional inhibition of the programmed cell death gene (PDCD) and ultimately reduces proliferation, invasion, and tumorigenicity of glioma stem cells (Fang et al., 2016). Interestingly, another study has presented that HOTAIR has no significant effect on HOXD expression and is dispensable for mammalian development *in vivo* (Amandio et al., 2016). Moreover, the enrichment of HOTAIR to chromatin in cancer cells leads to transcriptional repression in PRC2-independent fashion (Portoso et al., 2017). In spite of the controversy about the effect of HOTAIR, in future an important challenge is to figure out what happens *in vivo* (Li et al., 2016b; Selleri et al., 2016). Together,

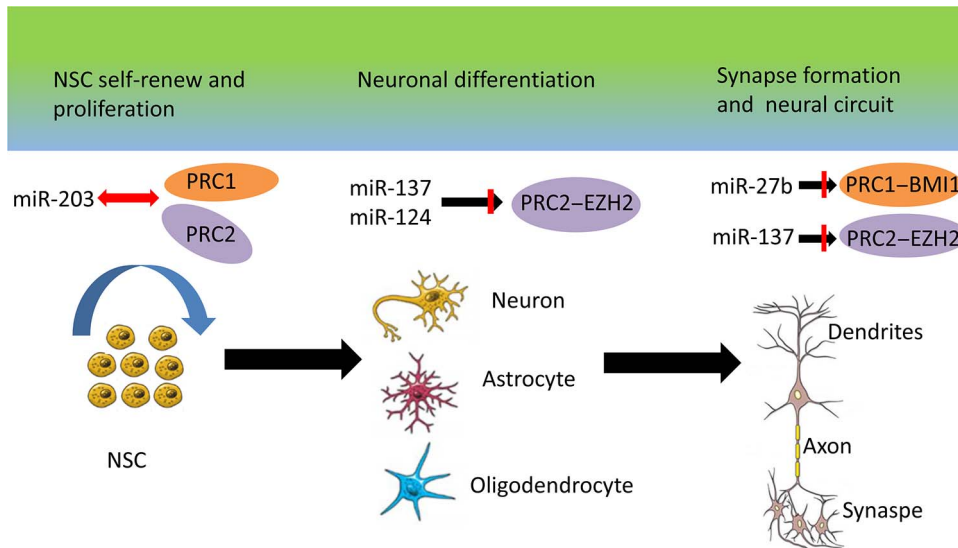


Figure 3 Interplay between PcG proteins and miRNAs in the CNS development. Regulatory loop between miRNAs and PcG proteins modulate multiple steps of neurogenesis and fate determination. Left: miR-203 is transcriptionally silenced by PRC2 and can repress PRC1 genes in NSCs. A well-characterized regulatory loop involving the PRC2–miR203–PRC1 circuit regulates NSC self-renewal and proliferation. Middle: miR-137 and miR-124 modulate neuronal differentiation by directly downregulating the expression of EZH2. Right: during synapse formation in developing neural circuits, miRNAs such as miR-27b and miR-137 interact with PcG genes, thereby regulating local synaptic protein synthesis and shaping neural activity in rodent cortical networks.

these findings suggest that in GBM cells, both HOTAIR and PRC2 are closely associated with tumor progression.

Several miRNAs including miR-130a, miR-155, miR-328, and miR-210 are downregulated in GBM, while some are upregulated, such as miR-323, miR-326, miR-21, and miR-329 (Qiu et al., 2013). miR-196 is markedly upregulated in GBM, suggesting that it may have a key role in the malignant progression and be a diagnostic and prognostic biomarker (Guan et al., 2010). miR-101 is downregulated in GBM, thereby causing EZH2-induced proliferation, migration, angiogenesis, and viability (Smits et al., 2010). In addition to miR-101, the other predicted miRNAs targeting EZH2, such as miR-98, miR-137, and miR-139, are also downregulated in GBM cells (Smits et al., 2010; Natsume et al., 2011). For example, miR-137 is decreased in GBM cell lines and associated with poor prognosis in GBM patients (Alfardus et al., 2017). Overexpression of EZH2, a direct target of miR-137, can rescue the inhibitory effect of miR-137 on GBM cell proliferation and angiogenesis (Sun et al., 2015). miR-340 as a glioma killer, extends the survival time of GBM patients (Fiore et al., 2016). Mechanically, miR-340 inhibits glioma cell growth and induces terminal differentiation via suppressing the expression level of EZH2 and BMI1 (Huang et al., 2015). Previous studies have displayed that EZH2 and BMI1 are correlated with the development, progression, and poor prognosis of GBM (Abdoun et al., 2009; Suva et al., 2009). The tumor suppressor miR-138 also controls the growth of glioma cell by targeting the EZH2-mediated signaling pathway (Huang et al., 2015). Furthermore, miR-128 in NSCs and glioma-initiating cells dramatically decreased the volume of neurospheres following the loss of BMI1 (Natsume et al., 2011). miR-128 inhibits PRC1/2

activity by directly targeting BMI1 or SUZ12 to control glioma stem cell self-renewal and maintenance (Peruzzi et al., 2013). The expression of miR-194 is significantly reduced in glioma specimens and cell lines, and the dysregulation of miR-194 has a key role in cell migration and invasion of glioma cells (Zhang et al., 2017). Moreover, bioinformatics analysis reveals that BMI1 is a functional target of miR-194 in glioma cells, and the recovery of BMI1 expression significantly abrogates the inhibitory effect of miR-194 on the epithelial–mesenchymal transition (EMT) of glioma cells (Zhang et al., 2017). Similar to miR-194, miR-429 as a tumor suppressor gene functions to negatively regulate the expression of BMI1 (Peng et al., 2017). Taken together, these significant findings reveal the important regulatory roles of miRNA and PRC1/2 complexes in GBM, and the regulation of their activity may provide a new therapeutic strategy for GBM treatment.

PcG proteins and ncRNAs in medulloblastoma

Medulloblastoma (MB), the most common malignant pediatric brain tumor, has four molecular subgroups: WNT, SHH, Group 3, and Group 4. MB is an aggressive tumor arising in the cerebellum, accounting for ~20% of all childhood CNS tumors (Mir et al., 2017; Khatua et al., 2018). Despite the high cure of MB in children, the survivors suffer from severe permanent treatment-related morbidities. Besides, toxic effects to combat the diseases result in neurocognitive impairment, endocrinopathies, and early mortality (Robinson et al., 2017). The advances of basic research and therapeutic strategies in MB will significantly improve long-term outcomes and minimize the risk of adverse late effects.

Short hairpin RNA-mediated knockdown of BMI1 or MEL18 in DAOY cells of human MB leads to the suppression of proliferation and tumor formation in 'nude' mice (Wiederschain et al., 2007). miR-128a exerts a growth suppressive activity in MB, which is partially mediated by targeting BMI1 (Blagosklonny et al., 2010). Additionally, EZH2 is highly expressed in MB and important for the transformation of NSCs, meanwhile the inhibition of EZH2 suppresses MB cell growth and tumor sphere formation partially by inducing apoptosis (Alimova et al., 2012). It was also demonstrated that H3K27me3 levels differ among MB subgroups. Moreover, the H3K27me3 modifiers EZH2, KDM6A, and KDM6B are strongly associated with MB (Mir et al., 2017).

PcG proteins and ncRNAs in spinal muscular atrophy

Spinal muscular atrophy (SMA) is a debilitating and fatal neuromuscular disorder with loss of spinal cord motor neurons and substantial muscle atrophy, owing to the homozygous mutation or deletion of SMN1 gene at position 5q13 on chromosome 5 (Wood et al., 2017). SMN2, a homolog of SMN1, is unique to humans and was shown to modify the severity of SMA disease, thus representing a promising therapeutic target (Rodriguez-Muela et al., 2018). SMA I, the most severe type of SMA disease, is characterized by serious respiratory distress owing to diaphragmatic palsy and distal muscular weakness (Ikeda et al., 2017). To date, no effective treatments for SMA are available.

Nusinersen is a steric block antisense oligonucleotide that binds to the SMN2 mRNA and promotes exon 7 inclusion, thereby increasing functional SMN protein expression (Wood et al., 2017). SMN-AS1, an lncRNA that stems from the SMN2 antisense strand, inhibits SMN2 expression at the transcriptional level via recruiting PRC2 to SMN2 promoter in neurons (d'Ydewalle et al., 2017). Furthermore, targeted regulation of SMN-AS1 or the interaction between SMN-AS1 and PRC2 leads to the increased expression of SMN2 in a mouse model of severe SMA (d'Ydewalle et al., 2017; Woo et al., 2017). These findings provide a potential novel therapeutic strategy for SMA.

PcG proteins and ncRNAs regulatory network in other types of cancer

In addition, accumulating evidence has shown that dysregulation of ncRNAs, PcG proteins, and ncRNA–PcG interactions is often related to aggressive clinic pathological features and poor prognosis in various kinds of cancer (Griffith et al., 2017). ncRNAs targeting EZH2, such as miR-143 and miR-98, play an important role in cancer migration and invasion (Mei et al., 2017). lncRNA MEG3 drives the epigenetic regulation of EMT in lung cancer cell lines by modulating EZH2 recruitment, H3K27 methylation, and the transcriptional repression of genes (Terashima et al., 2017). In most gynecological types of cancer, the interplay of PcG complexes and ncRNAs has been identified. For example, a study using luciferase reporter assays confirmed the significant reduction of BMI1, along with miR-15a and miR-16, in breast cancer cells (Patel et al., 2016). Moreover, BMI1 is a direct target of miR-376c and mediates the effect of miR-376c on the proliferation and invasion of cervical cancer cell (Deng et al., 2016).

miR-139-5p directly bind to the 3'-UTR of BMI1 mRNA to suppress BMI1 translation, suggesting that they are potential therapeutic targets for bladder cancer treatment (Luo et al., 2017). miR-203 is involved in leukemia and HCC by targeting EZH2 and BMI1 (Zhang et al., 2016). In addition, miR-101 exerts a putative tumor suppressor function and modulates the cancer epigenome by repressing EZH2 (Han Li and Chen, 2015).

lncRNAs are also involved in a variety of cancers. For instance, the endogenous expression of the tumor suppressor gene ANRASSF1 is higher in breast and prostate tumors. ANRASSF1 can recruit PRC2 to the promoter of RASSF1A, decreasing RASSF1A expression and increasing the cell proliferation (Beckedorff et al., 2013; Iranpour et al., 2016). Additionally, lncRNA-HEIH expression is also upregulated in HCC tissues and is essential for the repression of EZH2 target genes (p15, p16, p21, p57; He et al., 2014). lncRNA β -catenin methylation (lnc- β -Catm) has the same expression pattern in human HCC tumors and liver cancer stem cells (CSCs). lnc- β -Catm interacts with β -catenin and EZH2 and is essential for self-renewal of liver CSCs and tumor propagation in mice, suggesting that their expression levels are positively correlated with cancer severity and prognosis of HCC patients (Zhu et al., 2016). In proliferating cells, p21-associated ncRNA DNA damage activated (PANDA) recruit PRC complexes to suppress senescence-promoting genes transcription level. Moreover, lncRNA PANDA is significantly downregulated in HCC, which is correlated with increased expression levels of BMI1 and EZH2 (Puvvula et al., 2014). lncRNA ANRIL is increased in prostate carcinomas and selectively binds with PRC1 and PRC2 to regulate histone modifications at specific loci (Aguilo et al., 2011). Although these findings originate from cancer research, they can still provide novel insights to further explore the roles of ncRNAs–PcG interactions in the CNS.

Concluding remarks

The dynamic and reversible nature of epigenetic regulation by ncRNAs is emblematic of its ubiquitous importance in modifying gene expression. As an important part of epigenetic regulation, ncRNAs function to regulate biological processes, such as cell cycle, proliferation, differentiation, and apoptosis (Roche et al., 2017). Similar to ncRNAs, PcG proteins act as transcriptional repressors to control target gene expression at epigenetic level during development (Entrevan et al., 2016; Lu et al., 2016). CNS development, plasticity, stress responses, and homeostasis are precisely controlled by several epigenetic regulators, which drive selective deployment of functional gene networks (Qureshi et al., 2010). Given the numerous lncRNA genes, and the variety of mechanisms by which they may have effect on cell physiology, it is not surprising that many lncRNA genes have been associated with CNS diseases (Hart and Goff, 2016). Thus, it is obvious that PcG complexes and ncRNAs play vital roles in the CNS development and function, and their dysregulation is implicated in neurodegenerative, neurodevelopmental, neuroimmunological, and neurological diseases (Knauss and Sun, 2013; de Nigris, 2016). Although several key advances have been made in characterizing ncRNA–PcG interactions involved in the CNS function

and dysfunction, the underlying molecular mechanisms is still very limited. Based on our current understanding of the roles of PcG complexes or ncRNAs in the nervous system, we summarize an overview of significant progress and hypothesize a proof of concept to evaluate the potential of ncRNAs–PcG regulation as prospective novel therapeutic targets in the CNS diseases. Future efforts are required for expanding the landscape of current knowledge on the mechanisms of PcG complexes and ncRNAs in the CNS diseases and repair.

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