The Dynamic Partnership of Polycomb and Trithorax in Brain Development and Diseases

Janise N. Kuehner, Bing Yao*
Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA;

Abstract

Epigenetic mechanisms, including DNA and histone modifications, are pivotal for normal brain development and functions by modulating spatial and temporal gene expression. Dysregulation of the epigenetic machinery can serve as a causal role in numerous brain disorders. Proper mammalian brain development and functions depend on the precise expression of neuronal-specific genes, transcription factors and epigenetic modifications. Antagonistic polycomb and trithorax proteins form multimeric complexes and play important roles in these processes by epigenetically controlling gene repression or activation through various molecular mechanisms. Aberrant expression or disruption of either protein group can contribute to neurodegenerative diseases. This review focus on the current progress of Polycomb and Trithorax complexes in brain development and disease, and provides a future outlook of the field.

Keywords
epigenetics; polycomb; trithorax; brain development; neurodegeneration; Alzheimer’s Disease; Huntington’s Disease; Parkinson’s Disease

1. Introduction

Originally discovered in Drosophila melanogaster as antagonistic regulators of the developmental Hox genes [1], Polycomb and Trithorax proteins have taken center stage in being some of the most dynamic multimeric complexes involved in development. As organisms advance through development, stem cells progressively lose their pluripotent potential in part because of chromatin reorganization. Cells acquire and maintain tissue and cell type-specific genetic patterns, promoting their differentiation and development of all the body systems. Polycomb group (PcG) and trithorax group (TrxG) proteins regulate the surrounding chromatin environment by co-occupying the same genomic regions [2].

Demonstrating the absolute necessity PcGs and TrxGs for proper development, deletion of some of these proteins results in embryonic lethality, as observed in mouse models [3]. Recently, the importance of the delicate balance between PcG and TrxG proteins throughout
brain development—particularly embryonic and adult neurogenesis, aging, neuroprotection and neurodegeneration—is being recognized [4–6]. The aberrant expression of either PcG or TrxG proteins is beginning to be associated with neurodegenerative disease, such as Alzheimer’s, Huntington’s and Parkinson’s disease [7–9]. The current challenge lies in determining the extent to which PcG and TrxG proteins play in the development and progression of these diseases, and if unique complexes exist that could act as early detection biomarkers.

2. Polycomb Group Proteins

Polycomb group (PcG) and trithorax group (TrxG) proteins exhibit profound conservation between plants, worms and mammals [10,11], indicative of their indispensable functions. The antagonistic relationship between PcG and TrxG proteins adds dimension to the epigenome, creating a dualistic epigenetic switch allowing genes to cycle between activation, inactivation, reactivation and even an intermediate state. PcG and TrxG are best known for their roles in regulating gene expression by forming large, multimeric complexes that maintain the local chromatin environment in either a repressed or active state, respectively [12,13]. For example, PcG and TrxG complexes dynamically modulate genes critical for development and cellular differentiation pathways [14]. In the following sections, we discuss the core and accessory proteins that make up these complexes, as well as their roles in the central nervous system (CNS).

2.1. Polycomb Repressive Complex 2

Two multimeric protein complexes comprise the PcG proteins: polycomb repressive complex 1 (PRC1) and polycomb repressive complex 2 (PRC2), collectively working together to generate a repressive chromatin environment [15] (Figure 1A). The basic function of each complex is attributed to the core proteins found in all PRC1s or PRC2s. There are four Drosophila core proteins for PRC2: enhancer of zeste (E(z)) protein, extra sex combs (Esc) protein, suppressor of zeste 12 (Su(z)12) and the histone binding protein p55 [16–18]. Each Drosophila core protein has one or more conserved homologs making up the mammalian PRC2, including enhancer of zeste homologs 1 and 2 (EZH1 and EZH2), embryonic ectoderm development (EED), suppressor of zeste 12 (SU(Z)12) and histone binding proteins RBAP48 and RBAP46. The lysine methyltransferase activity of PRC2, specifically on histone 3 at lysine 27 (H3K27), depends on the catalytic activity of the SET domain within either EZH1 or EZH2 [19] (Figure 1B). For E(z) to have complete catalytic activity to generate the H3K27me3 mark, E(z) requires the presence of both Esc and Su(z)12 [20]. Interestingly, mutations in EZH2, EED and SU(z)12 have all been found in patients with Weaver syndrome, a rare congenital disorder characterized by intellectual disabilities, accelerated bone age and general overgrowth of the head and facial features [21–23]. In vitro assays demonstrate that several of the identified mutations in these core proteins reduce the histone methyltransferase ability of PRC2 [24,25].

How mammalian PRC2 is recruited to chromatin is not well understood. In Drosophila, there are DNA sequences called polycomb response elements (PREs) that recruit PcG proteins; however, PREs are not conserved between fly and mammals [26]. For example, the
Drosophila polycomb proteins pleiohomeotic (Pho) and pleiohomeotic-like (Pho-l) contain a DNA binding domain and interact with PcG proteins [27]. However, the mammalian homolog of Pho—YY1—does not colocalize with PRC2 in mammalian embryonic stem cells (ESCs) [28], suggesting that YY1 does not recruit PRC2 to DNA in mammals. In 2009 and 2010, the first promising PREs were identified in mammals, PRE-kr in the mouse and D11.12 (a 1.8 kb region between HOXD11 and HOXD12) in human cells [29–31]. PRE-kr regulates the Ma flowering gene’s spatial expression during hindbrain formation in mouse and flies by stably recruiting PRC1 in the anterior and TrxG proteins in the posterior hindbrain [29]. D11.12 was discovered in human ESCs based on its similar properties to Drosophila PREs, such as nuclease sensitivity and YY1 binding sites within GC-rich regions [30,31]. The enigmatic quest to identify and characterize PREs in the human genome remains a challenge due to the likelihood that PRC2 protein recruitment depends on multiple components and not just a sequence motif. Furthermore, mammalian PRC1 and PRC2 have multiple isoforms of their subunits, allowing them to function at different developmental stages and at different genetic loci, further complicating the understanding of PREs in mammals [3]. One such example is the mammalian versions of E(z), EZH1 and EZH2. PRC2 complexes that contain EZH2 are most commonly found in embryonic stem cells and in highly proliferative cells. On the other hand, those with EZH1 are predominately found in differentiated and non-dividing cells [32].

The function of PRC2 depends on the numerous combinations of cofactors that associate with it, such as AEBP2, JmjC-domain proteins and chromodomain helicase DNA-binding protein 5 (CHD5) [33], enhancing its ability to function spatiotemporally. Immunoprecipitation experiments repeatedly show that the zinc finger, AEBP2, frequently associates with PRC2 and is required to optimize the methyltransferase activity of PRC2 [34,35]. Evidence suggests that PRC2 complexes containing AEBP2 can promote cell migration and contribute to neural crest development [36,37]. The JmjC-domain protein, Jmjd3, specifically removes H3K27me3 marks at genes highly expressed in neural progenitor cells (NPCs), such as Pax6, Nestin and Sox1, and is required for neural lineage commitment [38]. CHD5 is a neuron-specific chromatin remodeler that is required for terminal neuronal differentiation [39]. Small hairpin knockdown of CHD5 in SH-SY5Y cells mitigate the activation of critical neuronal genes such as PHOX2A, RARA and TBX2. Interestingly, the chromodomain of CHD5 binds to H3K27me3 modifications and assists PRC2 in depositing more H3K27me3 marks to maintain the repression of PRC2 target genes during adult neurogenesis.

2.2. Polycomb Repressive Complex 1

PRC1 is also composed of a set of four core proteins, including polycomb (Pc), polyhomeotic (Ph), posterior sex combs (Psc) and sex combs extra/ring finger protein 1 (Sce/dRing 1) [15] (Figure 1A). In vertebrates, each of the core proteins has numerous paralogs that can have either redundant or unique functions [26]. The chromodomain in Pc is responsible for recognizing and binding H3K27me3, facilitating the recruitment of PRC1 to induce structural changes in the chromatin [19,40,41] (Figure 1B). There are five mammalian isoforms of Pc (Chromobox Homologs: CBX2, CBX4, CBX6, CBX7 and CBX8) that bind H3K27me3 [42], as well as other methylated histones, non-PcG proteins
and even RNA [43,44]. Notably, Cbx4 (Pc2) is unique among the five isoforms, as it is the only one involved in sumoylation [45]. The many combinations of core protein isoforms comprising PRC1 can affect where in the genome different PRC1 complexes bind. Interestingly, different CBX proteins bind to nucleosomes in distinct subnuclear regions [42].

The RING1A/B proteins in PRC1 are responsible for the monoubiquitination of lysines on histone H2A, especially at lysine 119 to generate the H2AK119ub1 mark [46,47] (Figure 1B). Knockout of just Ring1B is sufficient to deplete global H2A ubiquitination in ESCs; however, knockout of both Ring1A/B is required to deplete H2A ubiquitination on the inactive X chromosome [46]. H2AK119ub1 can be regulated in an H3K27me3-independent mechanism. Tavares et al. identified two distinct PRC1 complexes in mouse ESCs composed of different PRC1 catalytic subunits and the protein RING1 and YY1 Binding Protein (RYBP) [48]. The first complex, CBX-PRC1, is recruited in the canonical fashion by H3K27me3 interactions; however, the second complex, RYBP-PRC1, is recruited by an unknown mechanism independent of H3K27me3. Knockdown experiments of RYBP show a significant loss of H2AK119ub1 levels, demonstrating the critical role of RYBP in maintaining H2AK119ub1 levels. Furthermore, proteomic and genomic studies have distinguished six PRC1 complex groups that are composed of unique subunits that localize to different genomic regions [49]. All six PRC1 complexes contain a RING1A/B protein and one of the six human Psc homologs, the polycomb group finger (PCGF) subunits. Notably, each unique PRC1 complex has minimal overlapping binding patterns. The remarkable diversity found in PRC1 composition and its variance in genomic localization expands the possible biological function of PRC1 further than the field initially expected.

3. Trithorax Group Proteins

TrxG complexes deposit histone 3 lysine 4 trimethyl (H3K4me3)-activating histone marks as opposed to the H3K27me3 repressive histone marks deposited by PcG complexes. TrxG proteins modify histones to remodel and bind chromatin to promote an active environment. Similar to the polycomb proteins, trithorax proteins are evolutionarily conserved and function in large multimeric protein complexes. In general, the function and localization of trithorax protein complexes are influenced by the binding targets of accessory proteins [50]. We will briefly discuss the three different groups of TrxG proteins, as they have been thoroughly reviewed elsewhere [51].

3.1. Trithorax SET Domain Histone Methyltransferases

Initially discovered in yeast, mono-, di- and tri-methylation on H3K4 is catalyzed by a complex of proteins associated with Set1 or Complex of Proteins Associated with Set1 (COMPASS) [52,53] (Figure 1A,B). There are six COMPASS-like complexes in mammals comprised of one of the following catalytic domains: SET1A, SET1B or Mixed Lineage Leukemia 1–4 (MLL1–4) [54,55]. In addition to their catalytic subunit, COMPASS complexes are also composed of a core group of proteins: WD Repeat Domain 5 (WDR5), ASH2, Retinoblastoma-Binding Protein 5 (RBBP5) and DPY30 [56,57]. As a complex, these proteins are responsible for most of the H3K4me3 present globally, and thus global
gene activation [54,55]. Lentiviral infection of shRNAs targeting either Dpy30 or RbBP5 in mouse ESCs results in a significant reduction in H3K4me3, causing defects in ESC differentiation into neuronal lineages, but not self-proliferation [54]. The MLL complexes are best known for their proto-oncogenic roles in leukemia; however, mutations in these genes also cause neurodevelopmental disorders such as Kabuki syndrome and Wiedemann–Steiner syndrome. Kabuki syndrome is a rare disorder characterized by numerous skeletal deformities and moderate intellectual disabilities [58]. Interestingly, in a screening of 110 families with Kabuki syndrome, 74% had frame shift mutations in MLL2, resulting in haploinsufficiency. Whole exome sequencing identified de novo mutations in MLL1 in individuals diagnosed with Wiedemann–Steiner syndrome, another extremely rare neurodevelopmental disease [59]. Like polycomb proteins, the function of trithorax proteins vary based on what accessory proteins they are in contact with, permitting their spatiotemporal regulation. For example, the zinc finger protein ZNF335 (a known causal gene for microcephaly and essential for NPC self-renewal, neurogenesis and neural differentiation) is a component of a COMPASS-like complex containing MLL and SETD1A [60]. Together, this complex modulates the master neural gene regulator RE1-Silencing Transcription Factor/Neuron-Restrictive Silencer Factor (REST/NRSF), which promotes NPC proliferation by inhibiting genes required for neural differentiation [61].

3.2. ATP-Dependent Chromatin Remodelers

As their name implies, ATP-dependent chromatin remodelers use energy derived from ATP to physically slide/evict nucleosomes and rearrange the chromatin environment. The ability of these proteins to remodel the chromatin is modulated by histone post-translational modifications, histone variants and the length of the linker DNA sequence between two nucleosomes [62]. Trithorax ATP-dependent chromatin remodelers are categorized into four groups based on their ATPase domains: the switch/sucrose non-fermentable (SWI/SNF) complexes, the imitation switch (ISWI) complexes, the chromodomain helicase DNA-binding/nucleosome remodeling deacetylase (CHD/NuRD) complexes and the inositol auxotroph 80 (INO80/SWR) complexes [50,63] (Figure 1A). In the mammalian brain, these chromatin remodelers have essential roles in proper brain development and function. For example, in the CNS, the SWI/SNF complexes, also known as BRG1/brahma (BRM)-associated factor (BAF) complexes, exist in a regimented spatiotemporal manner. The transition from ESCs to neural progenitor cells (NPCs) to mature neurons is modulated by the specific BAF complexes esBAF, npBAF and nBAF, respectively [64,65]. Mutations in the core components or accessory proteins of these complexes are increasingly being reported in neurological disorders, such as intellectual disabilities, schizophrenia and microcephaly [66,67]. Additionally, the mammalian ISWI proteins SNF2L and SNF2H (encoded by SMARCA1 and SMARCA5) are also involved in NPC differentiation, as deletions within either gene results in abnormal brain growth and attenuated proliferation [68,69]. Using whole exome sequencing, mutations in SMARCA1 have been identified in patients with microcephaly, Rett syndrome and schizophrenia [67,70,71]. However, each of these cases are isolated examples, prompting further work to be done in exploring the role of SMARCA1 in neurological disorders. The Chd7 gene, the encoding part of the CHD/NuRD complexes, shows specific and dynamic spatiotemporal expression patterning in the developing mouse brain, and is essential during neuronal differentiation [72–76].
Interestingly, de novo mutations that result in haploinsufficiency of *CHD7* are the major contributor in CHARGE syndrome, a rare congenital disease where patients have abnormal brain structure formation [77,78]. Finally, functional roles for the INO80/SWR complexes are the least explored chromatin remodelers in the brain. Recent work suggests several unique roles for INO80 in transcription regulation and DNA replication and repair [79]. In summary, ATP-dependent chromatin remodelers can have very broad or very specific roles in the mammalian brain.

### 3.3. TrxG Response Elements (TREs)

As with polycomb recruitment, trithorax recruitment in mammals also does not appear to be conserved. In the attempts to determine how TrxG proteins are recruited in the mammalian systems, several hypotheses have been proposed. One such hypothesis is that regions dense in CG dinucleotides, such as CpG islands, could recruit them [28,80,81]. Supporting this, the mammalian versions of the trithorax proteins, MLL1 and MLL2, both have a CXXC domain that recognizes and binds to unmethylated CpG regions, which is not conserved in flies [82]. However, several other publications found conflicting evidence, where CG density failed to predict or was not sufficient to recruit polycomb and trithorax response elements [29,31]. These experiments only analyzed a single locus compared to the genome-wide approach taken in the previous studies, suggesting that other mechanisms in addition to CG content may be required for polycomb and trithorax recruitment in mammals. Recent work paired bioinformatics with the reporter luciferase assay to predict candidate PREs and TREs in the human genome [83]. Five putative PREs and four TREs characterized by either enrichment of H3K27me3 and strong signals for EZH2 and EED, or enrichment of H3K4me3 and strong signals for MLL1 and WDR5, respectively, were identified. Notably, CG content was also not found to be directly coupled to PcG or TrxG proteins; however, CpG islands appeared to correlate more strongly with TREs compared to PREs. Another hypothesis suggests that noncoding RNA molecules, such as long noncoding RNAs (lncRNAs), could have recruitment function. For example, the lncRNA *HOTTIP* activates *HOXA* genes by directly targeting the WDR5/MLL complex, allowing for H3K4me3 marks to be dispersed [84]. Furthermore, *HOTAIR* acts as a scaffold to bring PRC2 and the H3K4 demethylase LSD1 into close enough proximity to help resolve bivalent promoters to retain H3K27me3 marks [85]. The most recent hypothesis proposes that DNA modifications may be important for PcG and TrxG target recognition. In flies, the repressive DNA modification, N<sup>6</sup>-methyladenosine (6mA), epigenetically regulates genes involved in neurodevelopment and neuronal functions by recruiting PcG and TrxG proteins [86]. Co-immunoprecipitation experiments determined that the demethylase for 6mA, DMAD, interacts with the TrxG protein Wds (WDR5 in mammals) to coordinately remove 6mA marks, promoting an active chromatin environment. Conversely, depletion of DMAD results in the failure of Wds recruitment, an accumulation in 6mA and consequently recruitment of the PcG to repress these regions. Likewise, in mammals, 6mA expression is correlated with an increase in PRC1 ubiquitination of H2A and to a lesser extent H3K27me3, preserving silenced gene regions [87]. Both pieces of evidence suggest that 6mA is correlated with PcG binding and could potentially serve as an interesting mechanism for PcG–TrxG commitment. Overall, there are many proposed mechanisms that could contribute to polycomb and trithorax recruitment in mammals. Individually, each hypothesis may be supported by individual
situations; however, it is far more likely that these mechanisms act cooperatively to recruit polycomb and trithorax complexes.

4. PcG and TrxG Proteins in the CNS

From the above discussion, it is evident that polycomb and trithorax complexes have numerous roles in development that are influenced by the co-factors with which they interact. Since identifying these various accessory proteins, researchers have begun elucidating their copious functions in the nervous system. In the following sections, we discuss the functional roles of Polycomb and Trithorax complexes in a variety of neural processes, including neurogenesis, CNS development, gliogenesis and neuronal migration.

Mammalian neurogenesis is the process by which NPCs differentiate to form new neurons, and have been thoroughly reviewed elsewhere [88]. This process occurs during embryonic development and in several regions of the adult brain: the subventricular zone of the lateral ventricles and subgranular zones of the dentate gyrus [89]. NPCs generate fate-restricted radial glia cells that give rise to intermediate progenitor cells, neurons, astrocytes and oligodendrocytes, which then migrate outward to form the outer layers of the brain [90]. Part of this differentiation process requires that bivalent domains, silenced regions that simultaneously contain H3K27me3 and H3K4me3 marks, in ESCs to commit to either a repressed or active state (Figure 1B). These regions are considered “poised” because of their potential to be activated. In mouse ESCs, many bivalent domains are found near transcription start sites (TSSs) encoding transcription factor genes critical for proliferation (Sox, Fox, Pax, etc.) [91]. In addition, bivalent domains are also found near genes critical for development (Pax2 and Wnt8b) and neural development (Fgf8 and Prok1). In mice, as ESCs differentiate into either NPCs or mouse embryonic fibroblast (MEF), their bivalent promoters start to commit to either a repressive or active state [92]. As expected, housekeeping genes maintain their H3K4me3 mark in all cell types, but genes specific to either NPCs (Olig1, Neurog1 and Fabp7) or MEFs (Pparg) lose their H3K27me3 mark, but maintain their H3K4me3 mark or maintain a bivalent state during differentiation. PcG and TrxG proteins undoubtedly have essential roles in the early stages of neurogenesis, as ESCs differentiate into NPCs to initiate the development of the CNS.

4.1. PRC1 in Neurogenesis and CNS Development

Mammalian PRC1 complexes are far more diverse compared to PRC2 because each core component has numerous paralogs that have non-overlapping functions. Vogel et al. revealed spatiotemporal expression patterns of PRC1 members during both neurogenesis and brain development using in situ hybridization in mouse brain [93]. In general, PRC1 complexes composed of Ring1a, Rnf2, M33 and Ph2 show the greatest expression in the ventricular zone in highly proliferative cell populations, whereas Cbx4, Cbx7, Bmi1 and Mel18 are more highly expressed in differentiated neurons in the outer layers of the developing brain. All PRC1 complexes contain RING1A/B [49] and knockout studies demonstrate that Ring1B has critical roles in mouse neocortical development [94]. The Ring1B catalytic unit of PRC1 controls the transition from the neurogenic phase to the astrogenic phase in NPCs by suppressing the transcription factor neurogenin 1 (Ngn1). In vertebrates, the Psc proteins
are known as polycomb group finger (PCGF) and PCGF4, or Bmi1 [95], and are required for NPCs’ self-renewal by repressing the cyclin-dependent kinase inhibitor genes p16\(^{ink4a}\), p19\(^{Arf}\) and p21 in mouse [96–98]. When Bmi1 is mutated, there is a significant reduction of NPCs in the subventricular zone (SVZ) of adult mice. PRC1 complexes take on a broad range of specialized functions depending on which core proteins associate with each other. It is surprising that additional work has not yet been done to elucidate novel functions of PRC1 in brain development. Further investigation is warranted to determine the existence of spatiotemporal PRC1 complexes and what unique contributions they could have towards brain development.

4.2. PRC2 in Neurogenesis and CNS Development

Members of PRC2 have been implicated in numerous roles including, but not limited to: neuronal identity, proliferation, differentiation and neuronal morphology [99]. Here, we discuss the roles of the core proteins (EZH2, EED, SUZ12 and RBAP46/48) and their unique involvement in neurogenesis. For ESCs to maintain their pluripotent state, PcG proteins target and repress key developmental regulators, such as Hox genes and transcription factors such as Fox and Sox genes, to prevent differentiation [100–103]. EZH2 is predominately expressed in proliferating cells such as ESCs and NPCs. Several studies have reported that deletion of Ezh2 in mouse NPCs disrupts the timing and number of neurons during neurogenesis and cortical plate thickness [94,104,105]. Conditional knockout of Ezh2 in the forebrain or midbrain of mice before the onset of neurogenesis shifts the balance of NPC self-proliferation towards NPC differentiation, and prevents expansion of the cortex [104,105]. Ezh2 also promotes the development of brain region identities, as loss of Ezh2 in the midbrain results in ectopic expression of forebrain-specific genes Foxg1 and Pax6 and repression of midbrain markers Pax3 and Pax7 [105].

Interestingly, genes that inhibit cellular proliferation (Cdkn2a and Cdkn2c) and Wnt signaling (Wif1 and Dkk2) are de-repressed upon Ezh2 loss. In addition to inappropriate expression of mature neurons, mice null for Ezh2 have significantly reduced levels of H3K27me3 in both their NPCs and the neurons that are generated from them [104]. Consequently, genes only expressed in differentiated neurons of the cortex, such as Bcl11b, Myt1l, Met2c and Neurod6, are upregulated during early cortical development. Additionally, loss of H3K27me3 profoundly disrupt the regulation of key transcription factors implicated in ventricular zone neurogenesis [106]. Mice with a conditional knockout of Ezh2 show an upregulation of GABAergic interneuron markers (Pax2, Pax5 and Pax8), and a downregulation of Purkinje cell gene markers (Rora, Olig2 and Olig1). Consequently, the increase of GABAergic interneurons and decrease of Purkinje cells results in an underdeveloped cerebellum early in development. Interestingly, in the subventricular zone, there is a unique population of astrocytes termed neurogenic astrocytes, that retain a “stem cell like” state and continue to produce neurons into adulthood [107]. What distinguishes neurogenic astrocytes from non-neurogenic astrocytes is the robust expression of Ezh2. In neurogenic astrocytes, Ezh2 has two distinct functions. The first function is to maintain the self-renewal production of more astrocytes by repressing the cell cycle inhibitor Ink4a/Arf or Cdkn2a. The second function is to promote neuronal lineage differentiation where neurogenic astrocytes produce neurons via inhibition of transcription factor Olig2. It would
be interesting to determine if neurogenesis could be reinstated in the non-neurogenic astrocytes by expressing \textit{Ezh2}, which could be a model for regenerative medicine.

Less work has been done to determine functional roles of EED, SUZ12 and RBAP46/48 in neurodevelopment. A recent study determined that dormant and actively proliferating NSCs in the SVZ express Eed \cite{108}. Eed is required for NSC proliferation and neurogenesis, as conditional deletion of \textit{Eed} results in NSC differentiation and a reduction in new neuronal numbers, respectively. The \textit{Hox} homeotic genes are established targets of PcG that encode transcription factors that help to regulate anterior–posterior body planning \cite{109,110}. Interestingly, in the embryonic CNS of bilateria animals, there is no \textit{Hox} gene expression in the anterior/brain region of the embryo due to PcG repression of these \textit{Hox} genes \cite{110,111}. Mutations or knockouts of the PRC2 protein, Esc in \textit{Drosophila} or Eed in mammals, results in the loss of H3K27me3 marks in the developing CNS \cite{112}. Furthermore, the anterior/brain region of both species exhibit an increase and extended period of NPC proliferation, whereas the posterior/nerve/spinal cord regions are unaffected by PRC2 loss. In addition to repressing \textit{Hox} gene expression in the brain, PRC2 also promotes the expression of transcription factors (Hbn, Rx, Dpn, etc.) unique to the developing embryonic brain \cite{113}. Ectopic expression these brain transcription factors in the \textit{Drosophila} nerve cord or wing disc is sufficient to reprogram the spinal cord to exhibit a more brain/CNS-like structure. Rescue experiments conducted in \textit{Esc} mutant embryos demonstrate that expression of Tll, Erm or Tetra transcription factors can ameliorate the reduced proliferation phenotype \cite{113}. These findings suggest that PRC2 specifically promotes the expansion and development of the anterior/brain regions by repressing \textit{Hox} gene expression in the brain and driving the expression of brain transcription factors \cite{112–114}. During early embryonic nervous system development of both mice and humans, Eed and Suz12 proteins are continuously expressed from embryonic days 9–14 in multiple brain regions \cite{115}. Homozygous knockout mice of either \textit{Eed} or \textit{Suz12} do not develop past the gastrulation phase \cite{116,117}; however, mice heterozygous for \textit{Suz12} can survive, but display a wide range of brain and neural tube defects \cite{118}. The fourth core protein, RBAP46/48 is best known for its general role as a histone chaperone that helps to maintain chromosome stability \cite{119}. Very little is known about how RBAP46/48 affects neurogenesis or brain development. One could speculate that even though RBAP46/48 is not required for the enzymatic activity of PRC2 \cite{120}, its chromatin remodeling ability could aid in repression of NSC-specific genes by condensing the chromatin during differentiation.

4.3. TrxG in Neurogenesis and CNS Development

Comparatively, much more work has been done to elucidate the molecular mechanisms of PcG functions in neurogenesis and CNS development than TrxG proteins. ATP-dependent chromatin remodeler, CHD7, is known to have essential roles in early cerebellar development and adult neurogenesis. Cre inactivation of \textit{Chd7} at embryonic day 8.5 in mouse granule cells of the cerebellum results in cerebellar differentiation defects and mis-localization of Purkinje cells \cite{73}. During adult neurogenesis, loss of \textit{Chd7} abrogates neuronal differentiation by preventing the remodeling and activation of the promoters \textit{Sox4} and \textit{Sox11}, essential genes for proper neuronal differentiation \cite{74,121}. Furthermore, TrxG member Mll1 is essential for neurogenesis to occur in the SVZ of mouse postnatal brains.
Neural stem cells deficient for Mll1 display normal cell survival, proliferation and glial cell differentiation; however, differentiation into neural lineages is severely hindered. As neural stem cells differentiate, ChIP analysis has revealed that the bivalent promoters of Mash1, Olig2 and Dlx2 shift so that they become enriched for H3K4me3 activating marks. Interestingly, in cells deficient for Mll1, the Dlx2 promoter retains a strong H3K27me3-repressive mark that spreads further upstream. This suggests that the H3K4me3 catalytic activity of Mll1 regulates Dlx2 to promote neurogenesis.

4.4. PcG and TrxG in Astrogliogenesis and Oligodendrogenesis

Aside from neurogenesis, PcG and TrxG proteins are essential for the development of glial cells, such as astrocytes and oligodendrocytes. During early neocortical development (embryonic day 11.5), there is rapid and symmetric division of NSCs, followed by asymmetric NSC division to initiate neurogenesis [123,124]. By late embryonic development (embryonic day 17.5), neurogenesis concludes and switches to gliogenesis, as reviewed elsewhere [5]. During the termination of neurogenesis, both PRC1 and PRC2 are necessary to promote astrogliogenesis [94]. In fact, deletion of the core subunits Ring1B, Ezh2, or Eed in mouse neocortical NPCs prolong neurogenesis and delay entry into the astrogenic phase. Notably, PcG proteins repress the transcription factor neurogenin 1 (Ngn1), a known suppressor of astrogliogenesis [125]. Silencing of Ngn1 is a key prerequisite in the transition of NPCs to glial fate. An interesting observation is that as expected—when NPCs differentiate into neurons and astrocytes, Ezh2 decreases; however, the NPCs that differentiate into oligodendrocyte-lineage retain high levels of Ezh2 from precursors to mature oligodendrocytes (OLs) [126]. When Ezh2 is overexpressed in embryonic day 14 mouse NSCs, there is an overproduction of OLs and a reduction in astrocyte production. The dynamic epigenetic regulation involved in oligodendrogenesis has been recently reviewed [127]. The SWI/SNF member Brg1 is necessary and sufficient for oligodendrogenesis [128]. Interestingly, Brg1 is directed to oligodendrocyte-specific enhancer elements by the transcription factor Olig2, thus promoting OL lineage differentiation and subsequently CNS myelination. Furthermore, Brg1 and Olig2 directly target the gene that encodes Chd7, promoting its activation [76]. Chd7 co-immunoprecipitation identified Sox10, a critical transcription factor in the development of OLs, to associate together and functionally regulate myelination and remyelination of the CNS.

4.5. PcG and TrxG in Neuronal Migration

The majority of studies have focused on the involvement of polycomb and trithorax proteins in the neurogenic aspect of brain development. Another key aspect of proper brain development is the migration of neuronal cells to the outermost layers of the brain. In the developing mouse hindbrain, Ezh2 controls dorsal–ventral pontine neuron migration by regulating netrin 1 (an axon guidance molecule) and restricting various Hox gene expressions through the anterior extramural stream (AES) [129,130]. Similar to how the BAF complexes switch out subunits during NPC differentiation, the CHD/NuRD complex also exchanges the CHD ATPase subunit during mouse cortical development [131]. Deletions of Chd3, Chd4 or Chd5, followed by rescue experiments, demonstrate the non-overlapping functions of each CHD/NuRD complex. Subsequently, CHD4-containing
complexes promote NPC proliferation in the deep cortical layers. CHD5 complexes regulate early neural migration, and CHD3 complexes facilitate late migration, as well as the establishment of features that distinguish mature neurons. Additionally, the brahma (Brm) subunit of the BAF complexes is critical for cortical neuron migration in mice, as Brm−/− mice have less neurons that reach the cortical plate relative to wild type mice [132]. Brm expression is orchestrated by the histone deacetylase HDAC2 when it is nitrosylated. Nitric oxide (NO) acts as an external stimulus that affects the localization, interaction and function of proteins that it modifies (S-nitrosylation), such as HDAC2 [133]. Importantly, NO signaling is critical in regulating NPC proliferation and adult neurogenesis [134], as well as cerebellar cell migration [135]. Furthermore, when neuronal nitric oxide synthase (nNOS) is embryonically deleted in mice, cortical migration is disrupted [132].

4.6. PcG and TrxG in Neuroprotection and Aging

Brain injury induced by impaired blood flow, otherwise known as ischemia or stroke, is the second leading cause of death in the United States [136]. A neuroprotective response to ischemia occurs when the brain has been subjected to brief, non-damaging ischemic events to build a protective tolerance known as ischemic tolerance [137]. Studies have shown that ischemic tolerant brains have an increased abundance of PcG proteins, particularly SCHM1, BMI1 and RING2 (members of PRC1), as well as repressor histone variants H2A and H2B [138]. PcG proteins bind at the promoters of Kcna5 and Kchab2 (two potassium ion channels in the brain known to be down regulated in ischemic tolerant brains), repressing them, and essentially protecting neural cells from injury. Interestingly, potassium channel blockers improve stroke recovery in animals as well as protect neurons from apoptosis [139,140]. Targeting polycomb complexes to increase their abundance after a stroke has recently been proposed as a putative treatment option [141]. The involvement of polycomb proteins in aging and neural stem cell proliferation are also thought to protect and promote recovery of the brain after an ischemic injury [141].

Neurodegeneration is an inevitable part of aging, whose molecular mechanism is poorly understood. Experiments performed in Drosophila have begun to elucidate this mechanism. Flies that are heterozygous for mutations in either E(z) or Esc have a longer life span, are resistant to oxidative stress and have reduced levels of H3K27me3 [6]. Antagonistically, when flies are heterozygous for Trx, the opposite phenotypes are observed, suggesting that lifespan and oxidative resistance are dependent on H3K27me3 levels. Notably, genome-wide mapping of polycomb proteins have failed to target canonical genes associated with longevity, such as Sir2, Rpd3, Foxo and InR. However, a putative target of E(z), Odc1, is involved in the enzymatic processing of polyamines, which have been linked to oxidative stress resistance [142] and increased lifespan [143].

During aging, there is an imbalance of molecular damage caused, in part, by reactive oxygen species (ROS) that is combated by antioxidant defenses [144]. Most intracellular ROS are generated by the mitochondria [145–147]. Mouse studies demonstrate that the polycomb group protein, Bmi1, modulates aging by repressing p53 signaling to promote neuron survival and antioxidant defenses [144]. The function of p53 in aging and cellular oxidative metabolism is ambiguous, as p53 has both pro- and anti-aging/oxidant properties in
proliferative cells [148–151]. Mice deficient for Bmi1 show signs of premature aging (e.g., presence of cataracts in the eyes) and have shorter lifespans compared to wild type littermates [144]. In addition, Brtr−/− neurons have augmented apoptosis due to neurotoxic reagents, such as camptothecin, β-amyloid plaques and ROS. ChIP experiments demonstrate enrichment of p53 at the promoters of antioxidant defense genes, such as xCT and Sod2, in Brtr−/− neurons. This evidence suggests that, in the context of postmitotic neurons in the adult CNS, p53 has both pro-aging and pro-oxidant properties.

5. PcG and TrxG in Neurodegenerative Diseases

As described in the sections above, polycomb and trithorax proteins are essential during brain development and are responsible for establishing early developmental features that are carried into the adult brain. Maintenance of proper chromatin environments to control gene expression is critical to neuron function and survival. Recent work has made apparent the critical role of PcG and TrxG proteins in preventing neurodegeneration. When PRC2 is conditionally depleted in adult mouse projection neurons, there is ectopic de-repression of genes encoding transcriptional regulators of non-neural (Pax6 and Tbx20), non-projection neuron (Eomes and Pou4f1) and death-promoting genes (Pmaip1, Cdkn2al/b and Igfbp3) [152]. Furthermore, neurons with increased expression of death-promoting genes exhibit a known neurodegenerative phenotype known as dark cell degeneration, demonstrating the importance of PRC2 to suppress neurodegeneration. In the following sections, we discuss known roles of PcG and TrxG proteins in various neurodegenerative diseases.

5.1. Huntington’s Disease

Huntington’s Disease (HD) is an autosomal dominant, genetic disease caused by a 40 or more trinucleotide repeat expansion (CAG) in the huntingtin gene (HTT) [153]. The age of onset is typically in the 40s and individuals with this disease suffer from motor, cognitive and psychiatric symptoms [154]. Work in the field has uncovered putative roles of PcG and TrxG proteins and how they may contribute to HD.

Before we can understand the dynamic interaction of PcG proteins with mutant HTT, it is important to understand the essential molecular interactions PcG proteins have with wildtype HTT. PcG proteins were initially thought to interact with Htt as mouse embryos null for either Htt or PRC2 displayed similar phenotypes (i.e., failure to repress growth factors, Nodal and Fgf8 and transcription factors, Evx1) [155]. When comparing wild type Htt to null Htt in embryonic day 7.5 mouse embryos, the null embryos show ectopic expression of Hoxb1, Hoxb2 and Hoxb9, all of which are regulated by PRC2 [156]. This finding suggests that a normal function of Htt could be to facilitate PRC2’s repressive function of Hox genes during development. Co-IP experiments on day 4 embryoid bodies (EBs) generated from either wild type or null Htt animals demonstrate that wild type Htt associates with Ezh2 and Suz12 [156]. Also, ChIP experiments on these EBs show that only full length Htt protein and H3K27me3 marks are at the Hoxb9 sequence. When comparing wild type Htt to mutant Htt, both proteins stimulate PRC2 activity; however, more PRC2 activity correlate with increasing polyglutamine length in mutant Htt. The role that PRC2’s association with mutant Htt might play in the pathology of HD remains to be explored.
ESCs null for Htt, show a loss of H3K27me3, specifically at bivalent promoters destined have H3K4me3 enrichment in NPCs [157]. This is a startling finding because it suggests that a normal biological function of huntingtin is to remove H3K27me3 marks. Whereas null Htt is mainly associated with loss of H3K27me3, mutant Htt mainly affects H3K4me3 levels. For example, in Htt mutant NPCs, the vast majority of TSSs show decreasing levels of H3K4me3, which is correlated with decreased transcription at these sites [157]. Similar results were found in human HD postmortem brains, where of the 720 genes identified with differential H3K4me3 levels, 616 genes had reduced H3K4me3 in HD brains relative to control healthy brains [158].

Recent studies have started to explore how non-protein coding genes, such as long non-coding RNAs (lncRNAs), contribute to HD, which has been discussed elsewhere [159]. Several studies demonstrate that lncRNAs interact with PRC2 and sequester it to their target genes, although the mechanism behind this is unknown [160,161]. For example, the lncRNA HOTAIR is required for PRC2 to deposit H3K27me3 marks throughout the HOXD locus for its repression [161]. One possible reason for the absence of PREs in the mammalian genome is that PRCs are brought to target genes by various noncoding RNAs. Microarrays have identified seven lncRNA that are dysregulated in HD brains compared to healthy brains [159]. Of the seven lncRNA, TUG1 and MEG3 have previously been found to associate with PRC2 [160,162]. To what end the interaction of lncRNAs with PRC2 has in HD pathogenesis remains to be discovered.

5.2. Alzheimer’s Disease

Alzheimer’s disease (AD) is considered one of the most common neurodegenerative diseases worldwide, and is characterized by memory loss and impairments in cognitive function [163]. These phenotypes are accompanied by β-amyloid plaques, phosphorylated Tau and neurofibrillary tangles that accumulate in the brain [164]. Typically, onset does not occur until 60 years of age and is strongly associated with the risk gene apolipoprotein-E (APOE) “ε4” [165]. However, there is a rare early onset form known as familial AD that is linked to mutations in the key AD risk genes amyloid beta precursor (APP), presenilin 1 (PSEN1) or presenilin 2 (PSEN2) [166]. Research has mainly focused on risk gene discovery, cognitive function, neurodegeneration pathologies and epigenetic modifications. The dynamics of the chromatin environment and the extent to which chromatin remodelers participate in AD are poorly characterized.

There are a handful of studies that observe some association of aberrant PcG and TrxG protein regulation in AD. For example, both lysine methyltransferases Kmt2a and Kmt2b (Mll1 and Mll2, respectively) are involved in memory formation [167], which is impaired in AD patients. In mouse hippocampal neurons, loss of Kmt2a partially recapitulates a down-regulated gene list similar to that observed in the mouse AD model. Another study identified that deficiency of PRC1 components responsible for the monoubiquitination of H2A, Bmi1/Ring1, are associated with late-onset AD [7]. This study observed that, in AD brains and induced pluripotent stem cell-differentiated neurons derived from late-onset individuals, Bmi1 is silenced. Notably, Bmi1 silencing is not seen in brains of familial AD patients or other dementia-like diseases. Finally, loss of the brain-specific, ATPase chromatin remodeler
CHD5 in primary neurons augments genes with known roles in aging and AD [168,169]. An interesting area for new research would be to identify more brain-specific, chromatin-remodeling proteins and elucidate any roles they could have in neurological diseases. Given that most remodelers are ubiquitously expressed, finding remodelers that are brain-specific could lead to the development of biomarkers.

To characterize and compare the human AD epigenome to the mouse AD epigenome, ChIP experiments on various histone marks, including H3K4me3 and H3K27me3, were computationally profiled [170]. Overall, human and mouse AD models show similar peak overlaps, especially at H3K27me3 peaks, demonstrating conservation of the epigenome between mice and humans. Promoters with increased H3K4me3 correspond to immune genes, whereas decreased H3K4me3 promoters correspond to neuronal genes. This work supports the current hypothesis that AD development could be attributed to an immune response provoked from environmental factors (chronic diseases, obesity and type 2 diabetes) experienced during aging, and genetic factors (gene mutations and epigenetic dysregulations) contributing to cognitive impairments [170,171].

5.3. Parkinson’s Disease

Parkinson’s Disease (PD) is believed to be caused by dopaminergic neuron death in the substantia nigra [172], a region of the brain that helps control movement, cognition and motivational reward [173]. Following neuron death, α-synuclein containing protein aggregates, known as Lewy bodies [174], begin to form and impair nerve cell communication, and this is thought to spread to healthy neurons [175]. Individuals with PD suffer from tremors and impaired posture and movement [172,176]. Genetic risk factors have been identified, such as mutations and/or duplication events in the α-synuclein (SNCA) gene [177]. Of all the neurodegenerative diseases discussed, how dysregulation of PcG and TrxG proteins might contribute to PD pathology is the least studied and understood.

Patients with PD were initially treated with a compound called L-DOPA, a precursor of dopamine that, once across the blood–brain barrier, is easily converted to dopamine [178]. However, chronic treatment with L-DOPA causes dyskinesia or involuntary muscle movements [179,180] due to increased D1 dopamine receptor signaling [181]. Acute treatment of L-DOPA in terminally differentiated neurons, based on a parkinsonism mouse model, increases the presence of the H3K27me3S28 phosphorylation (H3K27me3S28p) double-mark [8]. Interestingly, H3K27me3S28p reduces the binding abilities of PcG proteins, de-repressing target genes such as Atf3, Npas4 and Hoxa2. This effect was found to uniquely occur in dopamine-expressing, medium spiny neurons of the striatum, the primary brain region affected in PD [182].

6. Future Outlook and Conclusions

Epigenetic regulation of the chromatin environment through polycomb and trithorax proteins requires a delicate balance to promote healthy and proper brain development, and to prevent the development of neurodegenerative diseases. There has been insufficient work done to identify any clear contributing roles of PcG and TrxG proteins in neurodegenerative disorders, despite their clear necessity in brain development. Drug targeting of PcG or TrxG
complexes can be challenging because of these complexes’ diverse association with many
gene targets; however, this could be beneficial as many neurological disorders consequently
arise because of epigenetic disruption of several genes. Additionally, further research is
warranted in identifying PcG or TrxG brain/disease-specific complexes that could serve as
biomarkers or specific treatment targets. Given that PcG and TrxG have such essential roles
early in development, it would be worthwhile to investigate familial cases of
neurodegenerative diseases, and to determine if an altered chromatin environment could be
detected before disease onset. Such research could initiate the development of preventative
treatments.

Increased efforts are being made to better elucidate epigenetic changes involved in stem cell
reprogramming to cultivate cell-replacement therapy for neurodegenerative diseases [183].
Before stem cell therapy can become beneficial, understanding how epigenetic mechanisms,
such as chromatin remodeling, promote cell fate by restricting cell plasticity is critical.
Currently, bone marrow-derived mesenchymal stem cells (BM-MSCs) are one type of stem
cell that is being used to treat HD, AD and PD by genetically overexpressing proteins that
are downregulated in each disease, such as brain-derived neurotrophic factor (BDNF), nerve
growth factor (NGF) and glial-derived neurotrophic factor (GDNF), respectively [184–186].
In their undifferentiated state, mesenchymal stem cells (MSCs) have H3K4me3 and
H3K27me3 marks on promoters that control lineage-specifications [187]. Depending on
which mark persists during differentiation, the downstream lineage of undifferentiated
MSCs is affected. Additionally, alterations in histone modifications are associated with the
number of passages MSCs undergo in culture. In early passages of MSCs, there is less
H3K27me3 at promoters, but with further passaging, promoters start to maintain H3K27me3
and there is an upregulation of PRC2 [188]. This suggests that there could be an optimal
time in which cultured stem cells are best fit to be used for cell-replacement therapy.

The use of in vitro studies on polycomb and trithorax complexes has benefitted the scientific
field in that they have permitted the discovery of their core subunits, their direct targets and
their molecular function, as discussed in this review. However, one of the most critical roles
of PcGs and TrxGs is to control anterior–posterior patterning during embryonic development
[189], which cannot be readily studied in an in vitro system as it requires signaling and cell
communication, both of which are lost in single cell 2D cultures. 3D culturing of brain
organoids could overcome the single cell limitations of 2D culture methods because they
have been developed to contain multiple neuronal cell types, including NPCs, mature
neurons and microglia [190–195]. Up until very recently, organoids did not develop
anterior–posterior and dorsal–ventral axes [196]. Cederquist et al. developed an inducible
human pluripotent cell line that expresses the sonic hedgehog (SHH) signaling factor [197].
When these cells are embedded into a pole of a developing organoid, upon doxycycline
induction, they will express SHH, generating topographically-patterned organoids. Research
is underway to generate more sophisticated organoid models that better recapitulate
organogenesis. These improvements include developing methods to further drive anterior–
posterior and dorsal–ventral axes, as well as vascular systems to improve oxygen and
nutrient distribution for better growth [198].
An important area of polycomb and trithorax research not discussed in this review are the critical roles these complexes have in cancer. Altered expression of PcG proteins, such as EZH2, SUZ12 and BMI1, are found in numerous cancer types, such as prostate, breast, liver and neuroblastomas, to name a few [199]. Mutations in TrxG complexes, such as SWI/SNF subunits SMARCA/B or COMPASS member MLL, are also found in ovarian cancer, lung cancer and leukemia [200]. In cancer, the polycomb protein BMI1, in cooperation with MYC, promotes tumor development by repressing tumor-suppressor genes, such as INK4A and ARF[97,201–203]. With regards to cancer prognosis, PcG expression levels could serve as predictive marks for cancer severity. For example, overexpression of EZH2 is highly correlated with a poor prognosis of prostate [204], breast [205], kidney [206] and lung cancer [207]. Given that EZH2 overexpression is a reliable predictor of various cancer progressions, several small molecule inhibitors have been developed for therapeutic treatments and are currently in clinical trials [208].

In conclusion, we have discussed a spectrum of functions of PcG and TrxG complexes in the mammalian CNS. Further studies are merited to define clear molecular contributions of these diverse and dynamic multimeric complexes in neurodegenerative diseases.

Acknowledgments:

We would like to thank Emily Bruggeman for discussing and helping with revisions of the material in the manuscript.

Funding: J.N.K. is supported by the National Institutes of Health T32 training grant in Genetics and Molecular Biology graduate program at Emory University (NIGMS GM008490). B.Y. is supported by National Institutes of Health (R01-MH117122 and R01-AG062577).

References

1. Schuettengruber B; Chourrout D; Vervoort M; Leblanc B; Cavalli G Genome regulation by polycomb and trithorax proteins. Cell 2007, 128, 735–745. [PubMed: 17320510]
2. Chinwalla V; Jane EP; Harte PJ The Drosophila trithorax protein binds to specific chromosomal sites and is co-localized with Polycomb at many sites. EMBO J. 1995, 14, 2056–2065. [PubMed: 7744011]
3. Margueron R; Reinberg D The Polycomb complex PRC2 and its mark in life. Nature 2011, 469, 343–349. [PubMed: 21248841]
4. Hwang JY; Aromolaran KA; Zukin RS Author Correction: The emerging field of epigenetics in neurodegeneration and neuroprotection. Nat. Rev. Neurosci 2018, 19, 771. [PubMed: 30291299]
5. Ohtsuka T; Kageyama R Regulation of temporal properties of neural stem cells and transition timing of neurogenesis and gliogenesis during mammalian neocortical development. Semin. Cell Dev. Biol 2019.
6. Siebold AP; Banerjee R; Tie F; Kiss DL; Moskowitz J; Harte PJ Polycomb Repressive Complex 2 and Trithorax modulate Drosophila longevity and stress resistance. Proc. Natl. Acad. Sci. USA 2010, 107, 169–174. [PubMed: 20018689]
7. Flamier A; El Hajjar J; Adjaye J; Fernandes KJ; Abdouh M; Bernier G Modeling Late-Onset Sporadic Alzheimer’s Disease through BMI1 Deficiency. Cell Rep. 2018, 23, 2653–2666. [PubMed: 29847796]
8. Sodersten E; Feyder M; Lerdrup M; Gomes AL; Kryh H; Spigolon G; Caboche J; Fisone G; Hansen K Dopamine signaling leads to loss of Polycomb repression and aberrant gene activation in experimental parkinsonism. PLoS Genet. 2014, 10, e1004574. [PubMed: 25254549]
9. Bassi S; Tripathi T; Monziani A; Di Leva F; Biagioli M Epigenetics of Huntington’s Disease. Adv. Exp. Med. Biol 2017, 978, 277–299. [PubMed: 28523552]
10. Kohler C; Hennig L Regulation of cell identity by plant Polycomb and trithorax group proteins. Curr. Opin. Genet. Dev 2010, 20, 541–547. [PubMed: 20684877]

11. Whitcomb SJ; Basu A; Allis CD; Bernstein E Polycomb Group proteins: An evolutionary perspective. Trends Genet. 2007, 23, 494–502. [PubMed: 17825942]

12. Franke A; DeCamillis M; Zink D; Cheng N; Brock HW; Paro R Polycomb and polyhomeotic are constituents of a multimeric protein complex in chromatin of Drosophila melanogaster. EMBO J. 1992, 11, 2941–2950. [PubMed: 1353445]

13. Locke J; Kotarski MA; Tartof KD Dosage-dependent modifiers of position effect variegation in Drosophila and a mass action model that explains their effect. Genetics 1988, 120, 181–198. [PubMed: 3146523]

14. Schwartz YB; Pirrotta V Polycomb complexes and epigenetic states. Curr. Opin. Cell Biol. 2008, 20, 266–273. [PubMed: 18439810]

15. Shao Z; Raible F; Mollaahababa R; Guyon JR; Wu CT; Bender W; Kingston RE Stabilization of chromatin structure by PRC1, a Polycomb complex. Cell 1999, 98, 37–46. [PubMed: 10412979]

16. Ng J; Hart CM; Morgan K; Simon JA A Drosophila ESC-E(Z) protein complex is distinct from other polycomb group complexes and contains covalently modified ESC. Mol. Cell Biol. 2000, 20, 3069–3078. [PubMed: 10757791]

17. Tie F; Furuyama T; Prasad-Sinha J; Jane E; Harte PJ The Drosophila Polycomb Group proteins ESC and E(Z) are present in a complex containing the histone-binding protein p55 and the histone deacetylase RPD3. Development 2001, 128, 275–286. [PubMed: 11124122]

18. Kuzmichev A; Nishioka K; Erdjument-Bromage H; Tempst P; Reinberg D Histone methyltransferase activity associated with a human multiprotein complex containing the Enhancer of Zeste protein. Genes Dev. 2002, 16, 2893–2905. [PubMed: 12435631]

19. Cao R; Wang L; Wang H; Xia L; Erdjument-Bromage H; Tempst P; Jones RS; Zhang Y Role of histone H3 lysine 27 methylation in Polycomb-group silencing. Science 2002, 298, 1039–1043. [PubMed: 12351676]

20. Ketel CS; Andersen EF; Vargas ML; Suh J; Strome S; Simon JA Subunit contributions to histone methyltransferase activities of fly and worm polycomb group complexes. Mol. Cell Biol. 2005, 25, 6857–6868. [PubMed: 16055700]

21. Cooney E; Bi W; Schlesinger AE; Vinson S; Potocki L Novel EED mutation in patient with Weaver syndrome. Am. J. Med. Genet. A 2017, 173, 541–545. [PubMed: 27868325]

22. Imagawa E; Albuquerque EVA; Isidor B; Mitsuhashi S; Mizuguchi T; Miyatake S; Takata A; Miyake N; Boguszewski MCS; Boguszewski CL; et al. Novel SUZ12 mutations in Weaver-like syndrome. Clin. Genet. 2018, 94, 461–466. [PubMed: 30019515]

23. Tatton-Brown K; Hanks S; Ruark E; Zachariou A; Duarte Sdel V; Ramsay E; Snape K; Murray A; Perdeaux ER; Seal S; et al. Germline mutations in the oncogene EZH2 cause Weaver syndrome and increased human height. Oncotarget 2011, 2, 1127–1133. [PubMed: 22190405]

24. Cohen AS; Yap DB; Lewis ME; Chijiwa C; Ramos-Arroyo MA; Tkachenko N; Milano V; Fradin M; McKinnon ML; Townsend KN; et al. Weaver Syndrome-Associated EZH2 Protein Variants Show Impaired Histone Methyltransferase Function In Vitro. Hum. Mutat 2016, 37, 301–307. [PubMed: 26694085]

25. Imagawa E; Higashimoto K; Sakai Y; Numakura C; Okamoto N; Matsunaga S; Ryo A; Sato Y; Sanefuji M; Ihara K; et al. Mutations in genes encoding polycomb repressive complex 2 subunits cause Weaver syndrome. Hum. Mutat 2017, 38, 637–648. [PubMed: 28229514]

26. Bauer M; Trupke J; Ringrose I. The quest for mammalian Polycomb response elements: Are we there yet? Chromosoma 2016, 125, 471–496. [PubMed: 26453572]

27. Mohd-Sarip A; Venturini F; Chalkley GE; Verrijzer CP Pleiohomeotic can link polycomb to DNA and mediate transcriptional repression. Mol. Cell Biol. 2002, 22, 7473–7483. [PubMed: 12370294]

28. Mendenhall EM; Koche RP; Truong T; Zhou VW; Issac B; Chi AS; Ku M; Bernstein BE GC-rich sequence elements recruit PRC2 in mammalian ES cells. PLoS Genet. 2010, 6, e1001244. [PubMed: 21170310]

29. Sing A; Pannell D; Karaiskakis A; Sturgeon K; Djabali M; Ellis J; Lipshitz HD; Cordes SP A vertebrate Polycomb response element governs segmentation of the posterior hindbrain. Cell 2009, 138, 885–897. [PubMed: 19737517]
30. Woo CJ; Kharchenko PV; Daheron L; Park PJ; Kingston RE. A region of the human HOXD cluster that confers polycomb-group responsiveness. Cell 2010, 140, 99–110. [PubMed: 20085705]
31. Schorderet P; Lonfat N; Darbellay F; Tschopp P; Gatto S; Soshnikova N; Duboule D. A genetic approach to the recruitment of PRC2 at the HoxD locus. PLoS Genet. 2013, 9, e1003951. [PubMed: 24244202]
32. Margueron R; Li G; Sarma K; Blais A; Zavladil J; Woodcock CL; Dynlacht BD; Reinberg D. Ezh1 and Ezh2 maintain repressive chromatin through different mechanisms. Mol. Cell 2008, 32, 503–518. [PubMed: 19026781]
33. Corley M; Kroll KL. The roles and regulation of Polycomb complexes in neural development. Cell Tissue Res. 2015, 359, 65–85. [PubMed: 25367430]
34. Ciferri C; Lander GC; Maiolica A; Herzog F; Aebersold R; Nogales E. Molecular architecture of human polycomb repressive complex 2. Elife 2012, 1, e00005. [PubMed: 23110252]
35. Cao R; Zhang Y. SUZ12 is required for both the histone methyltransferase activity and the silencing function of the EED-EZH2 complex. Mol. Cell 2004, 15, 57–67. [PubMed: 15225548]
36. Kim H; Ekram MB; Bakshi A; Kim J. AEBP2 as a transcriptional activator and its role in cell migration. Genomics 2015, 105, 108–115. [PubMed: 25451679]
37. Kim H; Kang K; Ekram MB; Roh TY; Kim J. Aebp2 as an epigenetic regulator for neural crest cells. PLoS ONE 2011, 6, e25174. [PubMed: 21949878]
38. Burgold T; Spreafico F; De Santa F; Totaro MG; Prosperini E; Natoli G; Testa G. The histone H3 lysine 27-specific demethylase Jmjd3 is required for neural commitment. PLoS ONE 2008, 3, e3034. [PubMed: 18716661]
39. Egan CM; Nyman U; Skotte J; Streubel G; Turner S; O’Connell DJ; Rraklli V; Dolan MJ; Chadderton N; Hansen K; et al. CHD5 is required for neurogenesis and has a dual role in facilitating gene expression and polycomb gene repression. Dev. Cell 2013, 26, 223–236. [PubMed: 23948251]
40. Fischle W; Wang Y; Jacobs SA; Kim Y; Allis CD. Khorasanizadeh S. Molecular basis for the discrimination of repressive methyl-lysine marks in histone H3 by Polycomb and HP1 chromodomains. Genes Dev. 2003, 17, 1870–1881. [PubMed: 12897054]
41. Min J; Zhang Y; Xu RM. Structural basis for specific binding of Polycomb chromodomain to histone H3 methylated at Lys 27. Genes Dev. 2003, 17, 1823–1828. [PubMed: 12897052]
42. Vincenz C; Kerppola TK. Different polycomb group CBX family proteins associate with distinct regions of chromatin using nonhomologous protein sequences. Proc. Natl. Acad. Sci. USA 2008, 105, 16572–16577. [PubMed: 18927235]
43. Bernstein E; Duncan EM; Masui O; Gil J; Heard E; Allis CD. Mouse polycomb proteins bind differentially to methylated histone H3 and RNA and are enriched in facultative heterochromatin. Mol. Cell Biol. 2006, 26, 2560–2569. [PubMed: 16537902]
44. Sewalt RG; Gunster MJ; van der Vlag J; Satijn DP; Otte AP. C-Terminal binding protein is a transcriptional repressor that interacts with a specific class of vertebrate Polycomb proteins. Mol. Cell Biol. 1999, 19, 777–787. [PubMed: 9858600]
45. Kagey MH; Melhuish TA; Wotton D. The polycomb protein Pc2 is a SUMO E3. Cell 2003, 113, 127–137. [PubMed: 12679040]
46. de Napoles M; Mermoud JE; Wakao R; Tang YA; Endoh M; Appanaad R; Nesterova TB; Silva J; Otte AP; Vidal M; et al. Polycomb group proteins Ring1A/B link ubiquitylation of histone H2A to heritable gene silencing and X inactivation. Dev. Cell 2004, 7, 663–676. [PubMed: 15525528]
47. Wang H; Wang L; Erdjument-Bromage H; Vidal M; Tempst P; Jones RS; Zhang Y. Role of histone H2A ubiquitination in Polycomb silencing. Nature 2004, 431, 873–878. [PubMed: 15386022]
48. Tavares L; Dimitrova E; Oxley D; Webster J; Poot R; Demmers J; Bezstarosti K; Taylor S; Ura H; Koide H; et al. RYBP-PRC1 complexes mediate H2A ubiquitylation at polycomb target sites independently of PRC2 and H3K27me3. Cell 2012, 148, 664–678. [PubMed: 22325148]
49. Gao Z; Zhang J; Bonasio R; Strino F; Sawai A; Parisi F; Kluger Y; Reinberg D. PCGF homologs, CBX proteins, and RYBP define functionally distinct PRC1 family complexes. Mol. Cell 2012, 45, 344–356. [PubMed: 22325352]
50. Moccia A; Martin DM. Nervous system development and disease: A focus on trithorax related proteins and chromatin remodelers. Mol. Cell Neurosci. 2018, 87, 46–54. [PubMed: 29196188]
51. Schuettengruber B; Martinez AM; Ioivino N; Cavalli G Trithorax group proteins: Switching genes on and keeping them active. Nat. Rev. Mol. Cell Biol 2011, 12, 799–814. [PubMed: 22108599]
52. Miller T; Kroga NJ; Dover J; Erdjument-Bromage H; Tempst P; Johnston M; Greenblatt JF; Shilatifard A COMPASS: A complex of proteins associated with a trithorax-related SET domain protein. Proc. Natl. Acad. Sci. USA 2001, 98, 12902–12907. [PubMed: 11687631]
53. Roguev A; Schaft D; Shevchenko A; Pijnappel WW; Wilm M; Aasland R; Stewart AF The Saccharomyces cerevisiae Set1 complex includes an Ash2 homologue and methylates histone 3 lysine4. EMBO J. 2001, 20, 7137–7148. [PubMed: 11742990]
54. Jiang H; Shukla A; Wang X; Chen WY; Bernstein BE; Roeder RG Role for Dpy-30 in ES cell-fate specification by regulation of H3K4 methylation within bivalent domains. Cell 2011, 144, 513–525. [PubMed: 21335234]
55. Wu M; Wang PF; Lee JS; Martin-Brown S; Florens L; Washburn M; Shilatifard A Molecular regulation of H3K4 trimethylation by Wdr82, a component of human Set1/COMPASS. Mol. Cell Biol. 2008, 28, 7337–7344. [PubMed: 18838538]
56. Steward MM; Lee JS; O’Donovan A; Wyatt M; Bernstein BE; Shilatifard A Molecular regulation of H3K4 trimethylation by ASH2L, a shared subunit of MLL complexes. Nat. Struct. Mol. Biol 2006, 13, 852–854. [PubMed: 16892064]
57. Dong Y; Milne TA; Ruthenburg AJ; Lee S; Lee JW; Verdin E; Allis CD; Roeder RG Regulation of MLL1 H3K4 methyltransferase activity by its core components. Nat. Struct. Mol. Biol 2006, 13, 713–719. [PubMed: 16878130]
58. Hannibal MC; Buckingham KJ; Ng SB; Ming JE; Beck AE; McMillin MJ; Gildersleeve HI; Bigham AW; Tabor HK; Mefford HC; et al. Spectrum of MLL2 (ALR) mutations in 110 cases of Kabuki syndrome. Am. J. Med. Genet. A 2011, 155, 1511–1516.
59. Jones WD; Dafou D; McEntagart M; Woollard WJ; Elmslie FW; Holder-Espinasse M; Irving M; Sagar AK; Smithson S; Trembath RC; et al. De novo mutations in MLL cause Wiedemann-Steiner syndrome. Am. J. Hum. Genet 2012, 91, 358–364. [PubMed: 22795537]
60. Yang Y; Baltus AE; Mathew RS; Murphy EA; Evrony GD; Gonzalez DM; Wang EP; Marshall-Walker CA; Barry BJ; Murn J; et al. Microcephaly gene links trithorax and REST/NRSF to control neural stem cell proliferation and differentiation. Cell 2012, 151, 1097–1112. [PubMed: 23178126]
61. Sun YM; Greenway DJ; Johnson R; Street M; Belyaev ND; Deuchars J; Bee T; Wilde S; Buckley NJ Distinct profiles of REST interactions with its target genes at different stages of neuronal development. Mol. Biol. Cell 2005, 16, 5630–5638. [PubMed: 16195345]
62. Paul S; Bartholomew B Regulation of ATP-dependent chromatin remodelers: Accelerators/brakes, anchors and sensors. Biochem. Soc. Trans 2018, 46, 1423–1430. [PubMed: 30467122]
63. Sokpor G; Castro-Hernandez R; Rosenbusch J; Staiger JF; Tuoc T ATP-Dependent Chromatin Remodeling During Cortical Neurogenesis. Front. Neurosci 2018, 12, 226. [PubMed: 29686607]
64. Kaeser MD; Aslanian A; Dong MQ; Yates JR 3rd; Emerson BM BRD7, a novel PBAF-specific SWI/SNF subunit, is required for target gene activation and repression in embryonic stem cells. J. Biol.Chem 2008, 283, 32254–32263. [PubMed: 18809673]
65. Lessard J; Wu JI; Ranish JA; Wan M; Winslow MM; Staahl BT; Wu H; Aebersold R; Graef IA; Crabtree GR An essential switch in subunit composition of a chromatin remodeling complex during neural development. Neuron 2007, 55, 201–215. [PubMed: 17640523]
66. Yip DJ; Corcoran CP; Alvarez-Saavedra M; DeMaria A; Rennick S; Mears AJ; Rudnicki MA; Messier C; Picketts DJ Snfl2 regulates Foxgl1-dependent progenitor cell expansion in the developing brain. Dev. Cell 2012, 22, 871–878. [PubMed: 22516202]
69. Alvarez-Saavedra M; De Repentigny Y; Lagali PS; Raghu Ram EV; Yan K; Hashem E; Ivanochko D; Huh MS; Yang D; Mears AJ; et al. Snf2h-mediated chromatin organization and histone H1 dynamics govern cerebellar morphogenesis and neural maturation. Nat. Commun 2014, 5, 4181. [PubMed: 24946904]

70. Lopes F; Barbosa M; Ameur A; Soares G; de Sa J; Dias AI; Oliveira G; Cabral P; Temudo T; Calado E; et al. Identification of novel genetic causes of Rett syndrome-like phenotypes. J. Med. Genet 2016, 53, 190–199. [PubMed: 26740508]

71. Homann OR; Misura K; Lamas E; Sandrock RW; Nelson P; McDonough SI; DeLisi LE Whole-genome sequencing in multiplex families with psychoses reveals mutations in the SHANK2 and SMARCA1 genes segregating with illness. Mol. Psychiatry 2016, 21, 1690–1695. [PubMed: 27001614]

72. Bosman EA; Penn AC; Ambrose JC; Kettleborough R; Stemple DL; Steel KP Multiple mutations in mouse Chd7 provide models for CHARGE syndrome. Hum. Genet. 2005, 114, 3463–3476. [PubMed: 16207732]

73. Feng W; Kawauchi D; Korkel-Qu H; Deng H; Serger E; Sieber L; Lieberman JA; Jineno-Gonzalez S; Lambo S; Hanna BS; et al. Chd7 is indispensable for mammalian brain development through activation of a neuronal differentiation programme. Nat. Commun 2017, 8, 14758. [PubMed: 28317875]

74. Feng W; Khan MA; Bellvis P; Zhu Z; Bernhardt O; Herold-Mende C; Liu HK The chromatin remodeler CHD7 regulates adult neurogenesis via activation of Sox transcription factors. Cell Stem Cell 2013, 13, 62–72. [PubMed: 23827709]

75. Jiang X; Zhou Y; Xian L; Chen W; Wu H; Gao X The mutation in Chd7 causes misexpression of Bmp4 and developmental defects in telencephalic midline. Am. J. Pathol 2012, 181, 626–641. [PubMed: 22658483]

76. He D; Marie C; Zhao C; Kim B; Wang J; Deng Y; Clavairoloy A; Frah M; Wang H; He X; et al. Chd7 cooperates with Sox10 and regulates the onset of CNS myelination and remyelination. Nat. Neurosci 2016, 19, 678–689. [PubMed: 26928066]

77. Vissers LE; van Ravenswaaij CM; Admiraal R; Hurst JA; de Vries BB; Janssen IM; van der Vliet WA; Huys EH; de Jong PJ; Hamel BC; et al. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. Nat. Genet 2004, 36, 955–957. [PubMed: 15300250]

78. Feng W; Shao C; Liu HK Versatile Roles of the Chromatin Remodeler CHD7 during Brain Development and Disease. Front. Mol. Neurosci 2017, 10, 309. [PubMed: 29033785]

79. Poli J; Gasser SM; Papamichos-Chronakis M The INO80 remodeler in transcription, replication and repair. Philos. Trans. R Soc. Lond. B Biol.Sci. 2017, 372, 20160290. [PubMed: 28847827]

80. Ku M; Koche RP; Rheinbay E; Mendenhall EM; Endoh M; Mikkelsen TS; Presser A; Nusbaum C; Xie X; Chi AS; et al. Genomewide analysis of PRC1 and PRC2 occupancy identifies two classes of bivalent domains. PLoS Genet. 2008, 4, e1000242. [PubMed: 18974828]

81. Lynch MD; Smith AJ; De Gobbi M; Flenley M; Hughes JR; Vernimmen D; Ayyub H; Sharpe JA; Sloane-Stanley JA; Sutherland L; et al. An interspecies analysis reveals a key role for unmethylated CpG dinucleotides in vertebrate Polycomb complex recruitment. EMBO J. 2012, 31, 317–329. [PubMed: 22056776]

82. Dillon SC; Zhang X; Trievel RC; Cheng X The SET-domain protein superfamily: Protein lysine methyltransferases. Genome Biol. 2005, 6, 227. [PubMed: 16086857]

83. Du J; Kirk B; Zeng J; Ma J; Wang Q Three classes of response elements for human PRC2 and MLL1/2-Trithorax complexes. Nucleic Acids Res. 2018, 46, 8848–8864. [PubMed: 29992232]

84. WANG KC; Yang YW; Liu B; Sanyal A; Corces-Zimmerman R; Chen Y; Lajoie BR; Protacio A; Flynn RA; Gupta RA; et al. A long noncoding RNA maintains active chromatin to coordinate homeotic gene expression. Nature 2011, 472, 120–124. [PubMed: 21423168]

85. Tsai MC; Manor O; Wan Y; Mosammaparast N; Wang JK; Lan F; Shi Y; Segal E; Chang HY Long noncoding RNA as modular scaffold of histone modification complexes. Science 2010, 329, 689–693. [PubMed: 20616235]

86. Yao B; Li Y; Wang Z; Chen L; Poidevin M; Zhang C; Lin L; Wang F; Bao H; Jiao B; et al. Active N(6)-Methyladenine Demethylation by DMAD Regulates Gene Expression by Coordinating with Polycomb Protein in Neurons. Mol. Cell 2018, 71, 848–857.e6. [PubMed: 30078725]
87. Kweon SM; Chen Y; Moon E; Kvaredaviciute K; Klimasauskas S; Feldman DE. An Adversarial DNA N(6)-Methyladenine-Sensor Network Preserves Polycomb Silencing. Mol. Cell 2019, 74, 1138–1147.e6. [PubMed: 30982744]

88. Yao B; Christian KM; He C; Jin P; Ming GL; Song H. Epigenetic mechanisms in neurogenesis. Nat. Rev. Neurosci 2016, 17, 537–549. [PubMed: 27334043]

89. Kaplan MS; Hinds JW. Neurogenesis in the adult rat: Electron microscopic analysis of light radioautographs. Science 1977, 197, 1092–1094. [PubMed: 887941]

90. Gotz M; Huttner WB. The cell biology of neurogenesis. Nat. Rev. Mol. Cell Biol. 2005, 6, 777–788. [PubMed: 16314867]

91. Bernstein BE; Mikkelsen TS; Xie X; Kamal M; Huebert DJ; Cuff J; Fry B; Meissner A; Wernig M; Plath K; et al. A bivalent chromatin structure marks key developmental genes in embryonic stem cells. Cell 2006, 125, 315–326. [PubMed: 16630819]

92. Mikkelsen TS; Ku M; Jaffe DB; Issac B; Lieberman E; Giannoukos G; Alvarez P; Brockman W; Kim TK; Koche RP; et al. Genome-wide maps of chromatin state in pluripotent and lineage-committed cells. Nature 2007, 448, 553–560. [PubMed: 17603471]

93. Vogel T; Stoykova A; Gruss P. Differential expression of polycomb repression complex 1 (PRC1) members in the developing mouse brain reveals multiple complexes. Dev. Dyn 2006, 235, 2574–2585. [PubMed: 16786585]

94. Hirabayashi Y; Suzuki N; Tsuboi M; Endo TA; Toyoda T; Shinga J; Koseki H; Vidal M; Gotoh Y. Polycomb limits the neurogenic competence of neural precursor cells to promote astroglial fate transition. Neuron 2009, 63, 600–613. [PubMed: 19755104]

95. Connelly KE; Dykhuizen EC. Compositional and functional diversity of canonical PRC1 complexes in mammals. Biochim. Biophys. Acta Gene Regul. Mech 2017, 1860, 233–245. [PubMed: 28007606]

96. Molofsky AV; Pardal R; Iwashita T; Park IK; Clarke MF; Morrison SJ. Bmi-1 dependence distinguishes neural stem cell self-renewal from progenitor proliferation. Nature 2003, 425, 962–967. [PubMed: 14574365]

97. Jacobs JJ; Kieboom K; Marino S; DePinho RA; van Lohuizen M. The oncogene and Polycomb-group gene bmi-1 regulates cell proliferation and senescence through the ink4a locus. Nature 1999, 397, 164–168. [PubMed: 9923679]

98. Fasano CA; Phoenix TN; Kokovay E; Lowry N; Elkabetz Y; Dimos JT; Lemischka IR; Studer L; Temple S. Bmi-1 cooperates with Foxg1 to maintain neural stem cell self-renewal in the forebrain. Genes Dev. 2009, 23, 561–574. [PubMed: 19270157]

99. Liu PP; Xu YJ; Teng QZ; Liu CM. Polycomb Repressive Complex 2: Emerging Roles in the Central Nervous System. Neuroscientist 2018, 24, 208–220. [PubMed: 29283025]

100. Lehmann OJ; Sawden JC; Carlsson P; Jordan T; Bhattacharya SS. Fox’s in development and disease. Trends Genet. 2003, 19, 339–344. [PubMed: 12801727]

101. O’Carroll D; Erhardt S; Pagani M; Barton SC; Surani MA; Jenuwein T. The polycomb-group gene Ezh2 is required for early mouse development. Mol. Cell Biol. 2001, 21, 4330–4336. [PubMed: 11390661]

102. Schepers GE; Teasdale RD; Koopman P. Twenty pairs of Sox: Extent, homology, and nomenclature of the mouse and human Sox transcription factor gene families. Dev. Cell 2002, 3, 167–170. [PubMed: 12194848]

103. Boyer LA; Plath K; Zeitlinger J; Brambrink T; Medeiros LA; Lee TI; Levine SS; Wernig M; Tajonar A; Ray MK; et al. Polycomb complexes repress developmental regulators in murine embryonic stem cells. Nature 2006, 441, 349–353. [PubMed: 16625203]

104. Pereira JD; Sansom SN; Smith J; Dobenecker MW; Tarakhovsky A; Livesey FJ. Ezh2, the histone methyltransferase of PRC2, regulates the balance between self-renewal and differentiation in the cerebral cortex. Proc. Natl. Acad. Sci. USA 2010, 107, 15957–15962. [PubMed: 20798045]

105. Zemke M; Draganova K; Klug A; Scholer A; Zurkirchen L; Gay MH; Cheng P; Koseki H; Valenta T; Schubeler D; et al. Loss of Ezh2 promotes a midbrain-to-forebrain identity switch by direct gene derepression and Wnt-dependent regulation. BMC Biol. 2015, 13, 103. [PubMed: 26621269]
106. Feng X; Juan AH; Wang HA; Ko KD; Sartorelli V Polycomb Ezh2 controls the fate of GABAergic neurons in the embryonic cerebellum. Development 2016, 143, 1971–1980. [PubMed: 27068104]

107. Hwang WW; Salinas RD; Siu JJ; Kelley KW; Delgado RN; Paredes MF; Alvarez-Buylla A; Oldham MC; Lim DA Distinct and separable roles for EZH2 in neurogenic astroglia. Elife 2014, 3, e02439. [PubMed: 24867641]

108. Sun B; Chang E; Gerhartl A; Szele FG Polycomb Protein Eed is Required for Neurogenesis and Cortical Injury Activation in the Subventricular Zone. Cereb. Cortex 2018, 28, 1369–1382. [PubMed: 29415247]

109. Kassis JA; Kennison JA; Tamkun JW Polycomb and Trithorax Group Genes in Drosophila. Genetics 2017, 206, 1699–1725. [PubMed: 28778878]

110. Philippidou P; Dasen JS Hox genes: Choreographers in neural development, architects of circuit organization. Neuron 2013, 80, 12–34. [PubMed: 24094100]

111. Holland LZ; Carvalho JE; Escriva H; Laudet V; Shimeld SM; Yu JK Evolution of bilaterian central nervous systems: A single origin? Evodevo 2013, 4, 27. [PubMed: 24098981]

112. Yaghmaeian Salmani B; Monedero Cobeta I; Rakar J; Bauer S; Curt JR; Starkenberg A; Thor S Evolutionarily conserved anterior expansion of the central nervous system promoted by a common PcG-Hox program. Development 2018, 145, dev160747.

113. Curt JR; Yaghmaeian Salmani B; Thor S Anterior CNS expansion driven by brain transcription factors. Elife 2019, 8, e45274. [PubMed: 31271353]

114. Monedero Cobeta I; Salmani BY; Thor S Anterior-Posterior Gradient in Neural Stem and Daughter Cell Proliferation Governed by Spatial and Temporal Hox Control. Curr. Biol 2017, 27, 1161–1172. [PubMed: 28392108]

115. Qi L; Cao J; Hu Y; Yang JG; Ji Y; Huang J; Zhang Y; Sun DG; Xia HF; Ma X The dynamics of polycomb group proteins in early embryonic nervous system in mouse and human. Int. J. Dev. Neurosci 2013, 31, 487–495. [PubMed: 23727134]

116. Faust C; Lawson KA; Schork NJ; Thiel B; Magnuson T The Polycomb-group gene eed is required for normal morphogenetic movements during gastrulation in the mouse embryo. Development 1998, 125, 4495–4506. [PubMed: 9778508]

117. Pasini D; Bracken AP; Jensen MR; Lazzerini Denchi E; Helin K Suz12 is essential for mouse development and for EZH2 histone methyltransferase activity. EMBO J. 2004, 23, 4061–4071. [PubMed: 15385962]

118. Miro X; Zhou X; Boretius S; Michaelis T; Kubisch C; Alvarez-Bolado G; Gruss P Haploinsufficiency of the murine polycomb gene Suz12 results in diverse malformations of the brain and neural tube. Dis. Model. Mech 2009, 2, 412–418. [PubMed: 19535498]

119. Satrimafitrah P; Barman HK; Ahmad A; Nishitoh H; Nakayama T; Fukagawa T; Takami Y RbAp48 is essential for viability of vertebrate cells and plays a role in chromosome stability. Chromosome Res. 2016, 24, 161–173. [PubMed: 26667624]

120. Kuzmichev A; Margueron R; Vaquero A; Preisnner TS; Scher M; Kirmizis A; Ouyang X; Brockdorff N; Abate-Shen C; Farnham P; et al. Composition and histone substrates of polycomb repressive group complexes change during cellular differentiation. Proc. Natl. Acad. Sci. USA 2005, 102, 1859–1864. [PubMed: 15684044]

121. Bergslund M; Werme M; Malewicz M; Perllmann T; Muhr J The establishment of neuronal properties is controlled by Sox4 and Sox11. Genes Dev. 2006, 20, 3475–3486. [PubMed: 17182872]

122. Lim DA; Huang YC; Swigut T; Mirick AL; Garcia-Verdugo JM; Wysocka J; Ernst P; Alvarez-Buylla A Chromatin remodelling factor Mll1 is essential for neurogenesis from postnatal neural stem cells. Nature 2009, 458, 529–533. [PubMed: 19212323]

123. Takahashi T; Nowakowski RS; Caviness VS Jr. Mode of cell proliferation in the developing mouse neocortex. Proc. Natl. Acad. Sci. USA 1994, 91, 375–379. [PubMed: 8278397]

124. Chenn A; McConnell SK Cleavage orientation and the asymmetric inheritance of Notch1 immunoreactivity in mammalian neurogenesis. Cell 1995, 82, 631–641. [PubMed: 7664342]
125. Sun Y; Nadal-Vicens M; Misono S; Lin MZ; Zubiaga A; Hua X; Fan G; Greenberg ME. Neurogenin promotes neurogenesis and inhibits glial differentiation by independent mechanisms. Cell 2001, 104, 365–376. [PubMed: 11239394]

126. Sher F; Rossler R; Brouwer N; Balasubramaniyan V; Boddeke E; Copray S. Differentiation of neural stem cells into oligodendrocytes: Involvement of the polycomb group protein Ezh2. Stem Cells 2008, 26, 2875–2883. [PubMed: 18687996]

127. Koreman E; Sun X; Lu QR. Chromatin remodeling and epigenetic regulation of oligodendrocyte myelination and myelin repair. Mol. Cell Neurosci. 2018, 87, 18–26. [PubMed: 29254827]

128. Yu Y; Chen Y; Kim B; Wang H; Zhao C; He X; Liu L; Liu W; Wu LM; Mao M; et al. Olig2 targets chromatin remodelers to enhancers to initiate oligodendrocyte differentiation. Cell 2013, 152, 248–261. [PubMed: 23323759]

129. Di Meglio T; Kratochwil CF; Vilain N; Loche A; Vitobello A; Yonehara K; Hrycaj SM; Roska B; Peters AH; Eichmann A; et al. Ezh2 orchestrates topographic migration and connectivity of mouse precerebellar neurons. Science 2013, 339, 204–207. [PubMed: 23307742]

130. Kratochwil CF; Maheshwari U; Rijli FM. The Long Journey of Pontine Nuclei Neurons: From Rhombic Lip to Cortico-Ponto-Cerebellar Circuitry. Front. Neural Circuits 2017, 11, 33. [PubMed: 28567005]

131. Nott A; Watson PM; Robinson JD; Crepaldi L; Riccio A. S-Nitrosylation of histone deacetylase 2 induces chromatin remodelling in neurons. Nature 2008, 455, 411–415. [PubMed: 18754010]

132. Packer MA; Stasiv Y; Benraiss A; Chmielnicki E; Grinberg A; Westphal H; Goldman SA; Enikolopov G. Nitric oxide negatively regulates mammalian adult neurogenesis. Proc. Natl. Acad. Sci. USA 2003, 100, 9566–9571. [PubMed: 12886012]

133. Tanaka M; Yoshida S; Yano M; Hanaoka F. Roles of endogenous nitric oxide in cerebellar cortical development in slice cultures. Neuroreport 1994, 5, 2049–2052. [PubMed: 7865742]

134. Mozaffarian D; Benjamin EJ; Go AS; Arnett DK; Blaha MJ; Cushman M; Das SR; De Ferranti S; Despres JP; Fullerton HJ; et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation 2016, 133, e38–e48. [PubMed: 26673558]

135. Stenzel-Poore MP; Stevens SL; Xiong Z; Lessov NS; Harrington CA; Mort I; Meller R; Rosenzweig HL; Tobar E; Shaw TE. Effect of ischaemic preconditioning on genomic response to cerebral ischaemia: Similarity to neuroprotective strategies in hibernation and hypoxia-tolerant states. Lancet 2003, 362, 1028–1037. [PubMed: 14522533]

136. Stapels M; Piper C; Yang T; Li M; Stowell C; Xiong ZG; Saugstad J; Simon RP; Geromanos S; Langridge J; et al. Polycomb group proteins as epigenetic mediators of neuroprotection in ischemic tolerance. Sci. Signal 2010, 3, ra15. [PubMed: 20197544]

137. Wei L; Yu SP; Gottron F; Snider BJ; Zipfel GJ; Choi DW. Potassium channel blockers attenuate hypoxia- and ischemia-induced neuronal death in vitro and in vivo. Stroke 2003, 34, 1281–1286. [PubMed: 12677023]

138. Iaci JF; Parry TJ; Huang Z; Finklestein SP; Ren J; Barrile DK; Davenport MD; Wu R; Blight AR; Caggiano AO. Dalfampridine improves sensorimotor function in rats with chronic deficits after middle cerebral artery occlusion. Stroke 2013, 44, 1942–1950. [PubMed: 23652269]

139. Elder J; Cortes M; Rykman A; Hill J; Karuppagounder S; Edwards D; Ratan RR. The epigenetics of stroke recovery and rehabilitation: From polycomb to histone deacetylases. Neurotherapeutics 2013, 10, 808–816. [PubMed: 24092615]

140. Chattopadhyay MK; Tabor CW; Tabor H. Polyamine deficiency leads to accumulation of reactive oxygen species in a spe2Delta mutant of Saccharomyces cerevisiae. Yeast 2006, 23, 751–761. [PubMed: 16862607]
143. Soda K; Dobashi Y; Kano Y; Tsujimaka S; Konishi F Polyamine-rich food decreases age-associated pathology and mortality in aged mice. Exp. Gerontol 2009, 44, 727–732. [PubMed: 19735716]

144. Chatoo W; Abdouh M; David J; Champagne MP; Ferreira J; Rodier F; Bernier G The polycomb group gene Bmi1 regulates antioxidant defenses in neurons by repressing p53 pro-oxidant activity. J. Neurosci 2009, 29, 529–542. [PubMed: 19144853]

145. Balaban RS; Nemoto S; Finkel T Mitochondria, oxidants, and aging. Cell 2005, 120, 483–495. [PubMed: 15734681]

146. Halliwell B Oxidative stress and neurodegeneration: Where are we now? J. Neurochem 2006, 97, 1634–1658. [PubMed: 16805774]

147. Lin MT; Beal MF Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 2006, 443, 787–795. [PubMed: 17051205]

148. Bauer JH; Poon PC; Glatt-Deeley H; Abrams JM; Helfand SL Neuronal expression of p53 dominant-negative proteins in adult Drosophila melanogaster extends life span. Curr. Biol 2005, 15, 2063–2068. [PubMed: 16303568]

149. Faragno R; Vergara P; Di Marzo D; Pierantoni MG; Napolitano M; Russo T; Cimino F p53 suppresses the Nrf2-dependent transcription of antioxidant response genes. J. Biol. Chem 2006, 281, 39776–39784. [PubMed: 17070087]

150. Matheu A; Maraver A; Klatt P; Flores I; Garcia-Cao I; Borras C; Flores JM; Vina J; Blasco MA; Serrano M Delayed ageing through damage protection by the Arf/p53 pathway. Nature 2007, 448, 375–379. [PubMed: 17637672]

151. Tyner SD; Venkatachalam S; Choi J; Jones S; Ghebranious N; Igelmann H; Lu X; Soron G; Cooper B; Brayton C; et al. p53 mutant mice that display early ageing-associated phenotypes. Nature 2002, 415, 45–53. [PubMed: 11780111]

152. von Schimmelmann M; Feinberg PA; Sullivan JM; Ku SM; Badimon A; Duff MK; Wang Z; Lachmann A; Dewell S; Ma’ayan A; et al. Polycomb repressive complex 2 (PRC2) silences genes responsible for neurodegeneration. Nat. Neurosci 2016, 19, 1321–1330. [PubMed: 27526204]

153. MacDonald ME; Ambrose CM; Duyao MP; Myers RH; Lin C; Srinidhi L; Barnes G; Taylor SA; James M; Groot N A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington’s disease chromosomes. Cell 1993, 72, 971–983. [PubMed: 8458085]

154. Martin JB; Gusella JF Huntington’s disease. Pathogenesis and management. N. Engl. J. Med 1986, 315, 1267–1276. [PubMed: 2877396]

155. Woda JM; Calzonetti T; Hilditch-Maguire P; Duyao MP; Conlon RA; MacDonald ME Inactivation of the Huntington’s disease gene (Hdh) impairs anterior streak formation and early patterning of the mouse embryo. BMC Dev. Biol 2005, 5, 17. [PubMed: 16109169]

156. Seong IS; Woda JM; Song JJ; Lloret A; Abevatne PD; Woo CJ; Gregory G; Lee JM; Wheeler VC; Walz T; et al. Huntington facilitates polycomb repressive complex 2. Hum. Mol. Genet 2010, 19, 573–583. [PubMed: 19933700]

157. Biagioli M; Ferrari F; Mendenhall EM; Zhang Y; Erdin S; Vijayvargia R; Vallabha SM; Solomos N; Manavalan P; Ragavendran A; et al. Htt CAG repeat expansion confers pleiotropic gains of mutant huntingtin function in chromatin regulation. Hum. Mol. Genet 2015, 24, 2442–2457. [PubMed: 25574027]

158. Dong X; Tsujii J; Labadof G; Roussos P; Chen JF; Myers RH; Akbarian S; Weng Z The Role of H3K4me3 in Transcriptional Regulation Is Altered in Huntington’s Disease. PLoS ONE 2015, 10, e0144398. [PubMed: 26636336]

159. Johnson R Long non-coding RNAs in Huntington’s disease neurodegeneration. Neurobiol. Dis 2012, 46, 245–254. [PubMed: 22202438]

160. Khalil AM; Guttman M; Huarte M; Garber M; Raj A; Rivea Morales D; Thomas K; Presser A; Bernstein BE; van Oudenaarden A; et al. Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. Proc. Natl. Acad. Sci. USA 2009, 106, 11667–11672. [PubMed: 19571010]
161. Rinn JL; Kertesz M; Wang JK; Squazzo SL; Xu X; Brugmann SA; Goodnough LH; Helms JA; Farnham PJ; Segal E; et al. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell 2007, 129, 1311–1323. [PubMed: 17604720]

162. Zhao J; Ohsumi TK; Kung JT; Ogawa Y; Grau DJ; Sarma K; Song JJ; Kingston RE; Borowsky M; Lee JT Genome-wide identification of polycomb-associated RNAs by RIP-seq. Mol. Cell 2010, 40, 939–953. [PubMed: 21172659]

163. Anand R; Gill KD; Mahdi AA Therapeutics of Alzheimer’s disease: Past, present and future. Neuropharmacology 2014, 76, 27–50. [PubMed: 23891641]

164. Ramirez-Bermudez J Alzheimer’s disease: Critical notes on the history of a medical concept. Arch. Med. Res 2012, 43, 595–599. [PubMed: 23178566]

165. Bertram L; Tanzi RE The genetics of Alzheimer’s disease. Prog. Mol. Biol. Transl. Sci 2012, 107, 79–100. [PubMed: 22482448]

166. Blennow K; de Leon MJ; Zetterberg H Alzheimer’s disease. Lancet 2006, 368, 387–403. [PubMed: 16876668]

167. Kerimoglu C; Sakib MS; Jain G; Benito E; Burkhardt S; Capece V; Kaurani L; Halder R; Agis-Balboa RC; Stilling R; et al. KMT2A and KMT2B Mediate Memory Function by Affecting Distinct Genomic Regions. Cell Rep. 2017, 20, 538–548. [PubMed: 28723559]

168. Potts RC; Zhang P; Wurster AL; Precht P; Mughal MR; Wood WH 3rd; Zhang Y; Becker KG; Mattson MP; Pazin MJ CHD5, a brain-specific paralog of Mi2 chromatin remodeling enzymes, regulates expression of neuronal genes. PLoS ONE 2011, 6, e24515. [PubMed: 21931736]

169. Thompson PM; Gotoh T; Kok M; White PS; Brodeur GM CHD5, a new member of the chromodomain gene family, is preferentially expressed in the nervous system. Oncogene 2003, 22, 1002–1011. [PubMed: 12592387]

170. Gjoneska E; Pfenning AR; Mathys H; Quon G; Kundaje A; Tsai LH; Kellis M Conserved epigenomic signals in mice and humans reveal immune basis of Alzheimer’s disease. Nature 2015, 518, 365–369. [PubMed: 25693568]

171. Heppner FL; Ransohoff RM; Becher B Immune attack: The role of inflammation in Alzheimer disease. Nat. Rev. Neurosci 2015, 16, 358–372. [PubMed: 25991443]

172. Forno LS Neuropathology of Parkinson’s disease. J. Neuropathol. Exp. Neurol 1996, 55, 259–272. [PubMed: 8786384]

173. Groenewegen HJ The basal ganglia and motor control. Neural. Plast 2003, 10, 107–120. [PubMed: 14603112]

174. Spillantini MG; Crowther RA; Jakes R; Hasegawa M; Goedert M alpha-synuclein in filamentous inclusions of Lewy bodies from Parkinson’s disease and dementia with lewy bodies. Proc. Natl. Acad. Sci. USA 1998, 95, 6469–6473. [PubMed: 9600990]

175. Burke WJ; Kumar VB; Pandey N; Panneton WM; Gan Q; Franko MW; O’Dell M; Li SW; Pan Y; Chung HD; et al. Aggregation of alpha-synuclein by DOPAL, the monoamine oxidase metabolite of dopamine. Acta Neuropathol. 2008, 115, 193–203. [PubMed: 17965867]

176. Jankovic J Parkinson’s disease: Clinical features and diagnosis. J. Neurol. Neurosurg. Psychiatry 2008, 79, 368–376. [PubMed: 18344392]

177. Riederer P; Berg D; Casadei N; Cheng F; Classen J; Dresel C; Jost W; Kruger R; Muller T; Reichmann H; et al. alpha-synuclein in Parkinson’s disease: Causal or bystander? J. Neural Transm. 2019, 126, 815–840. [PubMed: 31240402]

178. Birkmayer W; Hornykiewicz O The effect of L-3,4-dihydroxyphenylalanine (=DOPA) on akinesia in parkinsonism. Parkinsonism Relat. Disord. 1998, 4, 59–60. [PubMed: 18591089]

179. Birkmayer W; Hornykiewicz O The L-dihydroxyphenylalanine (L-DOPA) effect in Parkinson’s syndrome in man: On the pathogenesis and treatment of Parkinson akinesis. Arch. Psychiat. Nervenkr. Z Gesamte. Neurol. Psychiatr 1962, 203, 560–574. [PubMed: 13971142]

180. Birkmayer W; Hornykiewicz O The L-3,4-dihydroxyphenylalanine (DOPA)-effect in Parkinson-akinesia. Wien. Klin. Wochenschr 1961, 73, 787–788. [PubMed: 13869404]

181. Aubert I; Guigoni C; Häkansson K; Li Q; Dovero S; Barthe N; Bioulac BH; Gross CE; Fisone G; Bloch B Increased D1 dopamine receptor signaling in levodopa-induced dyskinesia. Ann. Neurol 2005, 57, 17–26. [PubMed: 15514976]
182. Zhai S; Tanimura A; Graves SM; Shen W; Surmeier DJ Striatal synapses, circuits, and Parkinson’s disease. Curr. Opin. Neurobiol 2018, 48, 9–16. [PubMed: 28843800]
183. Srinageshwar B; Maiti P; Dunbar GL; Rossignol J Role of Epigenetics in Stem Cell Proliferation and Differentiation: Implications for Treating Neurodegenerative Diseases. Int. J. Mol. Sci 2016, 17, 199.
184. Blurton-Jones M; Spencer B; Michael S; Castello NA; Agazaryan AA; Davis JL; Muller FJ; Loring JF; Masliah E; LaFerla FM Neural stem cells genetically-modified to express neprilysin reduce pathology in Alzheimer transgenic models. Stem Cell Res. 2014, 5, 46.
185. Crane AT; Rossignol J; Dunbar GL Use of Genetically Altered Stem Cells for the Treatment of Huntington’s Disease. Brain Sci. 2014, 4, 202–219. [PubMed: 24961705]
186. d’Anglemont de Tassigny X; Pascual A; Lopez-Barneo J GDNF-based therapies, GDNF-producing interneurons, and trophic support of the dopaminergic nigrostriatal pathway. Implications for Parkinson’s disease. Front. Neuroanat 2015, 9, 10. [PubMed: 25762899]
187. Collas P; Noer A; Sorensen AL Epigenetic Basis for the Differentiation Potential of Mesenchymal and Embryonic Stem Cells. Transfus Med. Hemother 2008, 35, 205–215. [PubMed: 21547118]
188. Noer A; Lindeman LC; Collas P Histone H3 modifications associated with differentiation and long-term culture of mesenchymal adipose stem cells. Stem Cells Dev. 2009, 18, 725–736. [PubMed: 18771397]
189. McGinnis W; Krumlauf R Homeobox genes and axial patterning. Cell 1992, 68, 283–302. [PubMed: 1346368]
190. Abreu CM; Gama L; Krasemann S; Chesnut M; Odwin-Dacosta S; Hogberg HT; Hartung T; Pamies D Microglia Increase Inflammatory Responses in iPSC-Derived Human BrainSpheres. Front. Microbiol 2018, 9, 2766. [PubMed: 30619100]
191. Ormel PR; Vieira de Sa R; van Bodegraven EJ; Karst H; Harschnitz O; Sneebomer MAM; Johansen LE; van Dijk RE; Scheefhals N; Berdenis van Berlekom A; et al. Microglia innately develop within cerebral organoids. Brain Commun 2018, 2, 4167. [PubMed: 30301888]
192. Qian X; Nguyen HN; Song MM; Hadjono C; Ogden SC; Hammack C; Yao B; Hamersky GR; Jacob F; Zhong C; et al. Brain-Region-Specific Organoids Using Mini-bioreactors for Modeling ZIKV Exposure. Cell 2016, 165, 1238–1254. [PubMed: 27118425]
193. Xiang Y; Tanaka Y; Patterson B; Kang YJ; Govindaiah G; Roselaar N; Cakir B; Kim KY; Lombroso AP; Hwang SM; et al. Fusion of Regionally Specified hPSC-Derived Organoids Models Human Brain Development and Interneuron Migration. Cell Stem Cell 2017, 21, 373–398.e7. [PubMed: 28757360]
194. Bagley JA; Reumann D; Bian S; Levi-Strauss J; Knoblich JA Fused cerebral organoids model interactions between brain regions. Nat. Methods 2017, 14, 743–751. [PubMed: 28504681]
195. Lancaster MA; Renner M; Martin CA; Wenzel D; Bicknell LS; Hurles ME; Homfray T; Penninger JM; Jackson AP; Knoblich JA Cerebral organoids model human brain development and microcephaly. Nature 2013, 501, 373–379. [PubMed: 23995685]
196. Kelava I; Lancaster MA Stem Cell Models of Human Brain Development. Cell Stem Cell 2016, 18, 736–748. [PubMed: 27257762]
197. Cederquist GY; Asciolla JJ; Tchieu J; Walsh RM; Cornacchia D; Resh MD; Studer L Specification of positional identity in forebrain organoids. Nat. Biotechnol 2019, 37, 436–444. [PubMed: 30936566]
198. Takebe T; Wells JM Organoids by design. Science 2019, 364, 956–959. [PubMed: 31171692]
199. Sparmann A; van Lohuizen M Polycomb silencers control cell fate, development and cancer. Nat. Rev. Cancer 2006, 6, 846–856. [PubMed: 17060944]
200. Schuettengruber B; Bourbon HM; Di Croce L; Cavalli G Genome Regulation by Polycomb and Trithorax: 70 Years and Counting. Cell 2017, 171, 34–57. [PubMed: 28938122]
201. Haupt Y; Alexander WS; Barri G; Klinken SP; Adams JM Novel zinc finger gene implicated as myc collaborator by retrovirally accelerated lymphomagenesis in E mu-myc transgenic mice. Cell 1991, 65, 753–763. [PubMed: 1904009]
202. van Lohuizen M; Verbeek S; Scheijen B; Wientjens E; van der Gulden H; Berns A Identification of cooperating oncogenes in E mu-myc transgenic mice by provirus tagging. Cell 1991, 65, 737–752. [PubMed: 1904008]

203. Jacobs JJ; Scheijen B; Voncken JW; Kieboom K; Berns A; van Lohuizen M Bmi-1 collaborates with c-Myc in tumorigenesis by inhibiting c-Myc-induced apoptosis via INK4a/ARF. Genes Dev. 1999, 13, 2678–2690. [PubMed: 10541554]

204. Varambally S; Dhanasekaran SM; Zhou M; Barrette TR; Kumar-Sinha C; Sanda MG; Ghosh D; Pienta KJ; Sewalt RG; Otte AP; et al. The polycomb group protein EZH2 is involved in progression of prostate cancer. Nature 2002, 419, 624–629. [PubMed: 12374981]

205. Kleer CG; Cao Q; Varambally S; Shen R; Otta I; Tomlins SA; Ghosh D; Sewalt RG; Otte AP; Hayes DF; et al. EZH2 is a marker of aggressive breast cancer and promotes neoplastic transformation of breast epithelial cells. Proc. Natl. Acad. Sci. USA 2003, 100, 11606–11611. [PubMed: 14500907]

206. Wagener N; Macher-Goeppinger S; Pritsch M; Husing J; Hoppe-Seyler K; Schirmacher P; Pfitzenmaier J; Haerkamp A; Hoppe-Seyler F; Hohenfellner M Enhancer of zeste homolog 2 (EZH2) expression is an independent prognostic factor in renal cell carcinoma. BMC Cancer 2010, 10, 524. [PubMed: 20920340]

207. Takawa M; Masuda K; Kunizaki M; Daigo Y; Takagi K; Iwai Y; Cho HS; Toyokawa G; Yamane Y; Maejima K; et al. Validation of the histone methyltransferase EZH2 as a therapeutic target for various types of human cancer and as a prognostic marker. Cancer Sci. 2011, 102, 1298–1305. [PubMed: 21539681]

208. Yamagishi M; Uchimaru K Targeting EZH2 in cancer therapy. Curr. Opin. Oncol 2017, 29, 375–381. [PubMed: 28665819]
Figure 1.
Polycomb and trithorax group protein subunits and complexes: (a) polycomb repressive complex 1 (PRC1) and polycomb repressive complex 2 (PRC2) are multimeric complexes composed of core proteins that are responsible for their catalytic activity. Trithorax group (TrxG) complexes: there are six COMPASS-like SET domain histone methyltransferases (HMTs) and four ATP-dependent chromatin remodelers in mammals; arrow with red cross: no transcription (b) Embryonic stem cells give rise to differentiated cells over the course of development. Part of this differentiation process requires that bivalent promoters commit to either a repressed or active state. Abbreviations: Pc: polycomb, CBX: Chromobox homolog, Ph: polyhomeotic, PH: polyhomeotic, Psc: posterior sex combs, PCGF: polycomb group finger, BMI1: polycomb complex protein BMI1, Sce/dRing 1: sex combs extra/ring finger protein 1, RING1A/B: ring finger protein 1A or ring finger protein 1B, E(z): enhancer of zeste protein, EZH1/EZH2: enhancer of zeste homolog 1 and 2, Esc: extra sex combs protein, EED: embryonic ectoderm development, Su(z)12: suppressor of zeste 12, SU(Z)12: suppressor of zeste 12, p55: histone binding protein, RBAP48 and RBAP46: histone binding proteins, COMPASS: Complex of Proteins Associated with Set1, SET: Sur3–9 Enhancer-of-zeste and Trithorax, MLL1–4: mixed lineage leukemia 1–4, SWI/SNF: switch/sucrose non-fermentable complexes, ISWI: imitation switch complexes, CHD/NuRD: the chromodomain helicase DNA-binding/nucleosome remodeling deacetylase complexes, INO80/SWR:

| Subunit | Molecular Function | Subunit | Molecular Function | Complexes | Catalytic Subunit |
|---------|-------------------|---------|-------------------|-----------|-------------------|
| Pc (CBX) | Recognize and bind H3K27me3 | E(z) (EZH1/EZH2) | SET Domain methylates H3K27 | SET1A | SET1A |
| Ph (PH1) | Facilitates DNA and protein interactions | Ess (EED) | Enhances E(z) catalytic activity | SET1B | SET1B |
| Pac (PCGF/BMI1) | Aids in the compaction of chromatin | Su(z)12 (SU(Z)12) | Enhances E(z) catalytic activity | MLL1-4 | MLL1-4 |
| Sce/dRing 1 | Ubiquitinate H2A | p55 (RBAP48/46) | Histone binding properties | ATP-Dependent Chromatin Remodelers | ATP-Dependent Chromatin Remodelers |

**Epigenomes. Author manuscript; available in PMC 2021 April 27.**
inositol auxotroph 80 complexes, BRG1/BRM: BRG1/brahma (BRM)-associated factor (BAF) complexes.