

Review

EZH2 in Neurogenesis: An Epigenetic Conductor of Neural Fate

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Abstract

Enhancer of Zeste Homolog 2 (EZH2), the catalytic component of Polycomb Repressive Complex 2 (PRC2), is a key epigenetic regulator of neural development through its ability to catalyze histone H3 lysine 27 trimethylation (H3K27me3). Emerging evidence demonstrates that EZH2 plays essential roles in neural stem cell maintenance, lineage specification, neuronal differentiation, and gliogenesis by orchestrating dynamic chromatin states and transcriptional programs. Beyond its canonical gene-silencing function, EZH2 interacts with major developmental signaling pathways, including Notch, Wntless/Integrated signaling pathway (Wnt)/ β -catenin, bone morphogenetic protein (BMP)/transforming growth factor beta (TGF- β), and Phosphoinositide 3-kinase (PI3K)/Protein kinase B (AKT), enabling the integration of environmental and developmental cues into epigenetic regulation. In this review, we synthesize current knowledge regarding the molecular mechanisms by which EZH2 regulates neurogenesis during embryonic development and in adult neurogenic niches. We further discuss emerging evidence for non-canonical EZH2 activities, its role in neurological disorders and brain tumorigenesis, and its potential as a therapeutic target in regenerative medicine. Collectively, the available evidence supports a model in which EZH2 functions as a dynamic epigenetic gatekeeper that coordinates neural cell-state transitions by balancing stem cell self-renewal and differentiation. Understanding these context-dependent functions of EZH2 will provide new insights into neural development and facilitate the development of targeted epigenetic therapies for neurological diseases and brain cancers.

Keywords: EZH2, neurogenesis, epigenetics, histone methylation, neural stem cells, PRC2.

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Introduction

The mammalian brain is one of the most remarkable and complex biological organs, which develops out of a minimal number of neuroepithelial stem cells during its early stages of development. It is a series of cellular events, involving widespread proliferation, fate specification, migration, and terminal differentiation, that these neural progenitors undergo to produce the diverse repertoire of neuronal and glial cell types that are required for the brain structure and brain function [1,2]. This cascade of development is no longer a simple manifestation of an already extant genetic program but is itself dynamically controlled by complicated epigenetic processes that reorganize the chromatin environment. This kind of remodeling guarantees a stringent regulation of spatiotemporal levels of expression of genes that are essential to a lineage commitment and neural maturation, and therefore, the shaping of the functional architecture of the nervous system [3,4].

Epigenetics involves a continuum of regulatory mech-

anisms such as DNA methylation, histone modification, and non-coding RNAs, which have a role in regulating gene expression without any change to the underlying DNA sequence. Of these, the histone methylation has become one of the crucial determinants of cell identity and cell fate determination, as a molecular switch, activating or silencing genetic programs during development [5,6]. Polycomb group (PcG) proteins are a set of evolutionarily conserved epigenetic regulators discovered in *Drosophila* to silence homeotic (Hox) genes that have become prominent as the master controllers of stem cell pluripotency, lineage restriction, and differentiation [7,8]. Enhancer of Zeste Homolog 2 (EZH2) is the enzymatic domain of Polycomb Repressive Complex 2 (PRC2), which is a histone methyltransferase (HMT) with a SET domain catalyzing histone H3 lysine 27 trimethylation (H3K27me3). This histone mark is a characteristic of facultative heterochromatin, which suppresses transcription of specific loci in the genome, effectively silencing lineage-specific genes until they are activated in the

process of differentiation [9–11].

A central issue in terms of neural development is the maintenance of proliferative potential of neural stem and progenitor cells together with the ability to differentiate into various neural lineages. The key to resolving this paradox is EZH2. It creates a repressive chromatin state, which keeps the differentiation programs in their inactive state, hence securing an insurance preventive factor against premature draining of the stem cell pool [12,13]. This repression is not an irreversible lock but a finely adjustable brake. In response to developmental cues, the activation of neurogenic and gliogenic gene networks is precisely timed, allowing for rapid adaptation to changes in the cellular environment. Besides, the regulatory effect of EZH2 is not confined to the embryonic levels but has been observed to regulate neurogenesis even in adult life, including in the subventricular zone (SVZ) and within the hippocampal dentate gyrus of the hippocampus [14,15].

In addition to its physiologically relevant functions, the dysregulation of the EZH2 and PRC2 functions has also been recognized in various neurological diseases and tumor malignancies, making the homeostasis of the epigenetic regulation in the brain one of the key areas. The knowledge of the complex functions of EZH2 in neurogenesis and neural plasticity has several therapeutic implications in the treatment of neurodevelopmental disorders, neurodegenerative disorders, and brain cancers [16]. The purpose of the review is to synthesize the existing knowledge on the role of EZH2 during neural development and in adult neurogenic processes, to provide mechanistic insights into the role of EZH2 in neural development, its interaction with other regulatory pathways, and its role in homeostasis processes and pathogenesis of the brain [17,18]. We will attempt to clarify the pivotal role of EZH2-mediated chromatin modifications in shaping the mammalian nervous system through an integrative analysis of the latest developments.

EZH2 and the PRC2

Structure and Function

The catalytic part of PRC2 is called EZH2, and it jointly determines repressive chromatin domains via the methylation of histone H3 lysine 27, which silences gene expression in development, stem cell maintenance, and disease conditions such as cancer [19]. EZH2 functional activity in assembling the multi-subunit PRC2 core (containing enhancer of zeste homolog 1 (EZH1) or EZH2, suppressor of zeste 12 homolog (SUZ12), embryonic ectoderm development (EED), and retinoblastoma-binding proteins 46/48 (RbAp46/48) (or RBBP4/7) cannot be completely independent of assembly during the multi-subunit core assembly; an interaction of recruitment, allosteric activation, and substrate recognition is the means by which locus-specific repression programs are sculpted [20,21]. The C-terminal SET domain of EZH2 is a catalyst of mono-, di-, and tri-methylation of H3K27, which uses S-

adenosylmethionine as the natural methyl donor. This H3K27me3 pre-existing peptide recognition by EED offers an allosteric feed-forward switch to increase catalyst turnover and promote Langevin diffusion of H3K27me3 between chromatin domains [22,23]. The accessory proteins, DNA characteristics like CpG islands, contacts with transcription factors, existing histone marks, and long non-coding RNAs are recruited in a combinatoric manner to bring PRC2 to developmental genes and an RNA polymerase II-refractory state of chromatin [24,25].

The PRC2 core consists of two functional lobes: a catalytic lobe comprising EZH2, EED, and the VEFS domain of SUZ12, and a targeting lobe that engages with nucleosomes and auxiliary factors, which forms a stable, four-lobed structure when RbAp46/48 is present [26]. EZH2 is catalytically inactive as its post-SET segment blocks the lysine-binding channel; however, the active site is reconfigured by EZH2 assembly with SUZ12 and EED to allow access to the histone tail and release auto-inhibition, facilitating methyl transfer at H3K27 [27]. The CXC domain and the bridge helix of EZH2 are also involved in contacting nucleosomal DNA and positioning the H3 tail into the active site so that the ϵ -amino group of K27 can be adequately oriented concerning the SAM methyl group to be catalyzed efficiently [28]. The SET domain features a hydrophobic tunnel that holds the lysine side chain and an adjacent cofactor pocket containing SAM, which is crucial for product specificity. Specific cancer-associated mutations in this pocket cause gain-of-function phenotypes in malignancy [29]. SUZ12 stabilizes the complex and folds the catalytic geometry. In contrast, the EED, a WD40-repeat propeller, identifies trimethyl-lysine ligands, most prominently H3K27me3, to induce allosteric stimulation of EZH2 by folding of the stimulatory response motif (SRM) and linking it to the SET domain, which is the basis of the positive-feedback spreading mechanism of PRC2 domains [30].

Functionally, PRC2 triggers H3K27 mono-, di-, and tri-methylation with H3K27me3 acting as a signal of facultative heterochromatin and stable transcriptional repression at developmental choice decision or off genes [31]. The repressive chromatin structure brought about by H3K27me3 does not favor recruitment and transcriptional initiation of RNA polymerase II. It serves to preserve lineage boundaries and to counteract aberrant expression of different genes [32]. Accessory factors partition PRC2 into complementary assemblies: PRC2.2 carries jumonji and AT-rich interaction domain containing 2 (JARID2) and adipocyte enhancer-binding protein 2 (AEBP2), which can interact with chromatin bearing histone H2A lysine 119 monoubiquitination (H2AK119ub) placed by EED at its aromatic cage and themselves modulate (JARID2 K116me3) to replicate H3K27me3 at the aromatic cage of EED, catalyzing activation in cis [33,34]. PRC2.1 has Polycomb-like (PCL) proteins (PHD finger protein 1 (PHF1), PHD finger protein 19 (PHF19), MTF2) that harbor Tudor domains ca-

pable of sensing histone H3 lysine 36 di-/trimethylation (H3K36me_{2/3}) and may work together with K36 demethylases to deactivate active chromatin to repress domains during developmental transitions [35]. Although these recruitment modes are possible, it is possible to maintain H3K27me₃ patterns throughout the genome-wide during accessory factor depletion, indicating that the read-write circuitry of the core complex (through EED allostery) can maintain established domains once they have been established [36,37].

Another form of control arises from PRC2's ability to read chromatin context: EZH2 detects inactive H3K36 by pockets in the CXC/SET region, which stimulates catalysis, and H3K36 methylation and some acetylation marks inhibit PRC2 activity, thus limiting H3K27me₃ deposition on transcriptionally active chromatin [38]. This crosstalk describes the PRC2 repression in active transcription regions, which is consistent with the structural study results indicating that the characteristics of active chromatin conformation are antagonistic to PRC2 binding and action [26,39]. However, allosteric stimulation of EED by methylated peptides of H3K27me₃, along with the methylated peptides of other accessory factors (e.g., JARID2 and PALI1), transforms existing repression into local catalysis, extending the H3K27me₃ along the nucleosomal arrays, or silencing states [40–42]. RbAp46/48 is involved in stabilizing histone H3/H4 as well as uncovering the rounded histone tails, thus facilitating the binding of their catalytic lobe with this preference to the specific geometries of the nucleosome [43,44]. Genomic recruitment of PRC2 is multifactorial, involving cell state, DNA sequence features (notably CpG islands), transcription factor interactions, RNA-mediated guidance, and crosstalk with histone marks [45,46]. Long non-coding RNAs may serve as molecular scaffolds and guides to PRC2, and a body of research has established direct RNA PRC2 binding and sequence preferences that support the ubiquitous lncRNA-mediated tethering; these RNAs have been shown to target PRC2 to specific chromosome neighborhoods, including HOX transcript antisense intergenic RNA (HOTAIR) and transcripts of stem cell loci such as Sox2ot [47,48]. Basic patches and domains on the RNA-binding surfaces of PRC2 that favor high-affinity, but promiscuous interactions provide a flexible recruitment platform, which is optimized by the cis-context inputs of DNA, as well as accessory modules [24]. Transcription factors can recruit or repel PRC2 depending on the situation, and chromatin marks, including H2AK119ub placed by Polycomb repressive complex 1 (PRC1), give recognition sites to the PRC2.2 axis, unifying the hierarchical Polycomb system in which PRC1 and PRC2 mutually induce repression [39,49]. This stratified logic of recruitment seems to be consistent with the finding that PRC2 catalytic stimulation and recruitment can be decoupled: core components detect chromatin to regulate catalysis, but locus-specific tethering required by developmental regulation of

H3K27me₃ is achieved by incorporating accessory subunits differently [20,50]. EZH1, an EZH2 paralog, can partially replace EZH2 in some tissues and dormant cells, but EZH2 prevails in growing cell populations, which is consistent with the increase in catalytic throughputs of cell division and lineage remodelling [51–53]. Both paralogs constitute PRC2 cores comprising SUZ12, EED, and RbAp46/48, though with different sensitivities to allosteric cues and accessory factors, indicating paralog-specific regulation of chromatin programs [39,54]. The biological impact of dominant overexpression of EZH2 in cycling cells is reinforced by the overall oncogenic selection of EZH2 mutation rewiring product specificity and augmenting H3K27me₃ production in B-cell lymphomas and other tumors, which alters transcriptional correction toward malignant identities. Such mutations tend to be clustered in residues that frame the lysine/SAM pockets in the SET domain, and in the interfaces that transmit allosteric signals with EED and lead to massive effects on gene repression landscapes [27,55]. Active transcription activates PRC2 in several different ways: antagonism of changes in histone state, nucleosome remodelling state, and steric hindrance, which restricts effective docking of the catalytic lobe onto nucleosomes in open chromatin [56]. Structural analyses demonstrate that the association of PRC2 with nucleosomal DNA and the H3 tail is highly sensitive to the chromatin context, and the properties of active chromatin make it less likely to form SRM folds and interact with the SET-domain to catalyze effectively. This is the reason why H3K27 methylation and acetylation at the adjacent residues are mutually antagonistic, and PRC2 is preferentially reactive to compacted chromatin templates, as further supported by the segregation of active and repressed domains [26,56,57]. Notably, when H3K27me₃ domains are formed, the subsequent recognition of the mark by EED keeps PRC2 in an active form locally, which enables the silencing to be maintained during cell divisions, as expected of the heritable nature of Polycomb repression [58]. Taken together, both EZH2 and PRC2 have formed a comprehensive, allosterically wired repressor capable of assembling both nucleosome geometry, histone mark crosstalk, RNA guidance, as well as accessory subunit structures to depose and spread H3K27me₃ upon the genome to stabilize developmental programs and limit transcriptional programs of malignancy. The requirement of SUZ12 and EED to stabilize and promote the switch, and RbAp46/48 to interact with histone, significantly highlights the importance of EZH2 functionality coupled with the holocomplex in PRC2. This is because only partial EZH1 compensation is sufficient, leading to strict assembly-state-gated decisions during catalysis. The recruitment inputs mentioned: CpG island-containing promoters, interaction with transcription factors, installation of H2AK119ub by PRC2, and long non-coding RNAs (lncRNAs) like HOTAIR or Sox2ot create a strong combinatoric code, which places PRC2 where repression is required, and

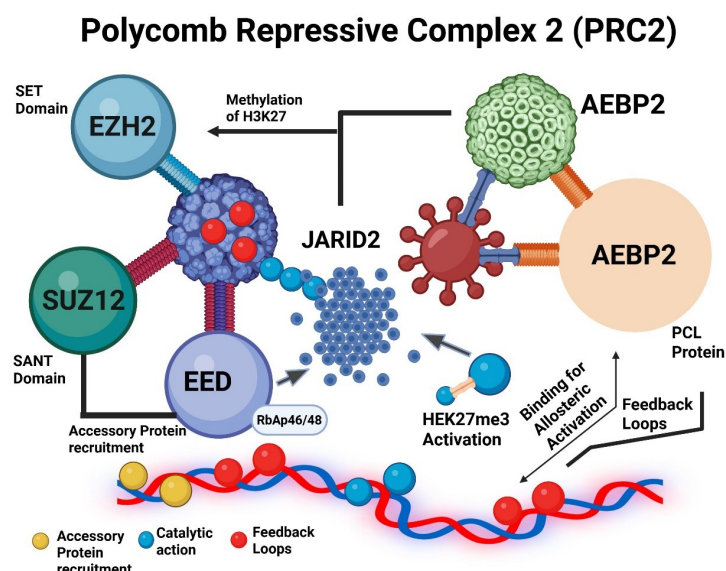


Fig. 1. Structure and regulatory mechanisms of the PRC2 complex. The core components of PRC2 are displayed, such as the catalytic subunit EZH2, including the SET domain that is involved in the H3K27 methylation. Recognition of H3K27me3 stabilizes the complex and allosteric activation of EZH2 by SUZ12 and EED. RbAp46/48 aids in the attachment of histone. Recruitment and target specificity are facilitated by accessory factors like JARID2, AEBP2, and PCL proteins (PHF1, PHF19, MTF2). The process of recruitment includes interactions with the CpG islands in the DNA and can be directed by long non-coding RNAs (e.g., HOTAIR, Sox2ot). Arrows represent the enzymatic methylation, recruitment pathways, as well as EED-mediated activation of feedback. Created in BioRender. Liu, M. (2026) <https://BioRender.com/rqcemhlg>.

the feed-forward read-write loop of EED ensures that once bound, the domains of H3K27me3 are extended and maintained. Such specificity and stability during gene silencing of PRC2 in a wide variety of biological settings is the result of these structural and mechanistic principles, and the maladaptation of EZH2 activities, recruitment, or allosteric regulation through unease is EZH2 reprogramming of cell identity and illness [42,59,60] (Fig. 1).

Developmental Expression Patterns

EZH2 is a catalytic subunit of PRC2, which has significantly regulated developmental expression that is core to neural stem and progenitor cell biology. Its patterns of expression in embryonic development and in normal neurogenic niches indicate its key functions in neural proliferation, lineage regulation, and differentiation regulation (Fig. 2).

Early and Embryonic Developmental Expression

In embryogenesis, EZH2 is highly expressed in the neuroepithelium and the ventricular areas, which contain actively dividing neural stem cells (NSCs) and progenitor cells. It is an essential phrase to preserve the undifferentiated nature and a high proliferation rate of such progenitors [61]. EZH2 is a mechanistic part of the PRC2, which places the tri-methylation mark on H3K27me3, one of the most significant repressive epigenetic marks, and silences differentiation-promoting genes. These si-

lencing preserves progenitor proliferation by keeping the differentiation-related genes off. EZH2 conditional ablation of embryonic NSCs leads to early neuronal differentiation, loss of apical (Pax6 positive) as well as basal (Tbr2 positive) progenitor pool, and cortical developmental defects. The EZH2 downregulation time course is consistent with developmental transitions of differentiation, and this suggests its critical role in regulating progenitor proliferation and cell fate commitment [13,62]. Recent research indicates that EZH2 postpones differentiation genes in the development of cerebellar granule neuron precursors and plays a pivotal role in the pathogenesis of medulloblastoma, by preserving transcriptional repression of neuronal differentiation pathways [63]. Moreover, the postnatal expression of EZH2 exhibits a temporal gradient, becoming suppressed in the nervous system. Still, upon injury to adult peripheral neurons, it reactivates and favors axonal regeneration, featuring a dynamic equilibrium regulated by development [64]. Non-redundant functions of EZH2 and related EZH1 in the development of the nervous system have been identified using gain and loss-of-function experiments, where EZH2 played a significant role in generating progenitor proliferation, and EZH1 played a major role in terminal differentiation [63]. Besides the neural stem and progenitor cells, EZH2 plays an essential role in the oligodendrocyte lineage differentiation, where the protein suppresses the alternative fate decisions and controls the time of differentiation [65,66]. Moreover, EZH2 controls

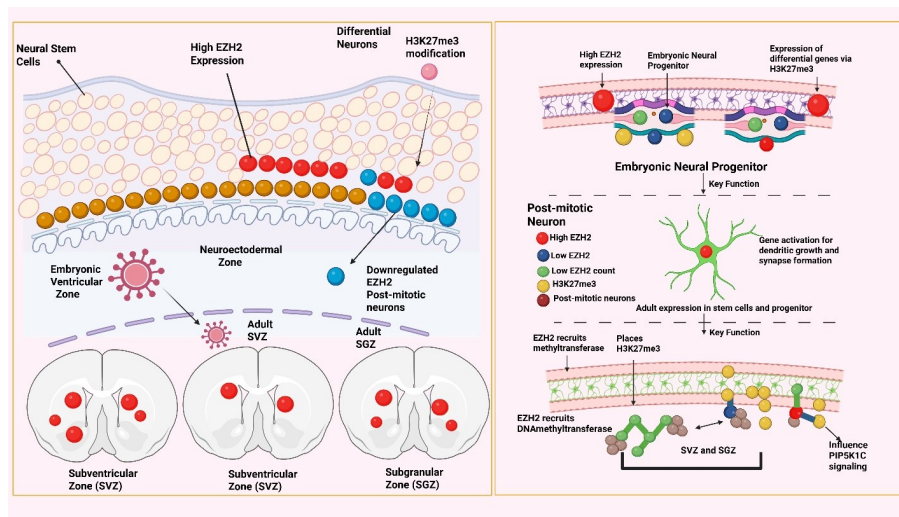


Fig. 2. Multifaceted roles of EZH2 in embryonic neurogenesis. Multifaceted functions of EZH2 in embryonic neurogenesis, this schematic viewpoint demonstrates the significant functions of the HMT EZH2 in controlling neural development during embryogenesis that falls into three major domains: Maintenance of neural stem cells (NSCs): EZH2 preserves the NSC pool by H3K27me3 of cell cycle suppressor promoters, which includes cyclin-dependent kinase inhibitor 2A (CDKN2A) (p16Ink4a), This suppression inhibits the untimely exit and differentiation of the cell cycle, thus retaining self-renewal and multipotency of NSCs in the early brain development. Superego of Neuronal Fate Specification: The Hox gene combats the switching on of an inappropriate transcriptional program by silencing the lineage-inappropriate fate determinants, such as Hox genes, and the fate of the region, notably in the forebrain, is preserved through EZH2. Further, Sox2 and EZH2 combine to place H3K27me3 marks on proneural basic helix-loop-helix (bHLH) genes such as Neurogenin2 and Mash1 to balance between NSC stemness and differentiation until neurogenic signals relieve repression. Temporal Regulation of the Switch between Neurogenesis and Gliogenesis: At early neurogenic stages, EZH2 suppresses glial genes like the astrocyte marker glial fibrillary acidic protein (GFAP) as well as the oligodendrocyte lineage glial precursor activator Olig2 through H3K27me3 to suppress the early onset of gliogenesis. With continued growth, the repression of EZH2 at these loci is released by means of chromatin remodeling, which allows the neuron production to turn over into astrocyte and oligodendrocyte generation, which are required to take the place of neurons in central nervous system (CNS) maturation. Created in BioRender. Liu, M. (2026) <https://BioRender.com/30r5tlw>.

the neurogenesis in adult neurogenic niches, including the dentate gyrus in the hippocampus, during physiological and ischemic states, by maintaining the balance between neural progenitor proliferation and differentiation [67]. Putting together these results, EZH2 is a key epigenomic master regulator that coordinates nerve precursor maintenance, differentiation timing, and lineage specification during embryonic growth and well into adulthood.

Post-Mitotic Neurons Downregulation

EZH2 has been so critical in regulating the identity of the neural progenitor cells by placing the repressive histone mark H3K27me3 on genes of differentiation. With the transition of the neural progenitors out of the cell cycle and through terminal differentiation, EZH2 expression is increasingly suppressed, which results in a considerable loss of H3K27me3 levels at neuronal gene loci and allows neurons to activate gene programs necessary to mature and develop dendrites and synapses. Mice, e.g., conditional knockout studies have shown that the reduction of EZH2 in post-mitotic neurons leads to increased dendritic branching and increased spine density, but with a higher percentage of immature spines, which is indicative of disordered synap-

tic maturation. This is a developmentally regulated process that depends on transcriptional and post-translational regulation, and partial mitigation by the corresponding methyltransferase EZH1 to preserve locus-specific epigenetic alterations [68,69]. However, as further explained by recent studies, EZH2 is a developmental timer that delays expression of late differentiation genes (and therefore accurately timing the maturation program); impairment of this time program causes morphological and functional abnormalities in neurons [63,70,71]. Furthermore, the repression by EZH2 is also found to extend to the activity-regulated genes associated with synaptic plasticity and cognition, which ties the involvement of epigenetic regulation with the higher-order brain functions. Notably, neural-origin cancers as well as neurodevelopmental disorders have been linked to the dysregulation of EZH2 downregulation processes, which highlights the importance of the latter in developmental neurobiology and cancer pathogenesis [72]. Taken together, these results support EZH2 downregulation as a basic epigenetic process that enables the conversion of the neural progenitors into full-fledged and functional neurons.

EZH2 Adult Neurogenic Niches: SVZ and Subgranular Zone (SGZ)

The expression of EZH2 is remarkably preserved in adult brain primary neurogenic niches: SVZ along the lateral ventricles and SGZ of the hippocampal dentate gyrus. However, it is widely lost in mature non-neurogenic regions. In these niches next to NSCs, EZH2 has also been detected in transit-amplifying progenitors, but not in differentiated neurons, providing evidence of an EZH2 role in maintaining the stem cell identity as well as neurogenerative potential during adulthood. EZH2 has been demonstrated to play a vital role in adult NSC proliferation and lineage fate, such as silencing of gene expression, mainly by inhibition of OLIG2 in the SVZ. This transcription factor should remain silent to allow differentiation into neurons [73–75]. Knockout or knockdown of EZH2 in adult NSCs in these niches results in an inability to generate neurogenesis, decreased production of progenitor cells, and a disproportionate production of neurons versus glial lineage [76,77]. Mechanistically, EZH2 has been reported to mediate adult neurogenesis by modulating pathways such as phosphatase and tensin homolog (PTEN)-protein kinase B (AKT)-mechanistic target of rapamycin (mTOR), which allows the proliferation and survival of progenitor cells and maintains a state of differentiation-repressing activity to suppress early lineage commitment [78,79]. Recent studies also indicate that EZH2 activity can tune the epigenetic environment in adult NSCs, by acting at both promoter regions and distal regulatory elements, to tune gene expression programs that are critical to maintaining and differentiating the state of stem cells [80]. Moreover, EZH2 is co-regulatory of cell fate choices with various other chromatin modifiers, including Suv4-20h1, in adult neurogenic niches. Extrinsic signals of the niche environment, including growth factors, stress signals, etc., are also included in the dynamic regulation of EZH2 levels throughout the cell cycle of adult NSCs and enable adaptation of neurogenesis rates to physiological requirements [81]. Moreover, disruption of EZH2 in adult SVZ and SGZ has been suggested in cognitive dysfunction, as well as being studied as a possible cause in age-related neurodegeneration and brain tumorigenesis. Therefore, EZH2 is an essential epigenetic controller that maintains adult neural progenitor-proliferative and differentiation potentials, eventually guaranteeing neurogenic plasticity and brain well-being throughout the course of life.

Molecular Processes of EZH2 Function

As has been outlined above, EZH2 acts on multifaceted molecular pathways that lie beyond its classical activity of tri-methylation of H3K27me3 position. It constitutes the catalytic center of PRC2 and performs gene silencing through the development of repressive chromatin conditions. Significantly, EZH2 also brings together DNA methyltransferase to the CpG islets in promoters of target genes, which strengthens stable repression of transcrip-

tional repression dependent on DNA methylation and histone modification crosstalk. Non-histone EZH2 targets further broaden the regulatory program of EZH2; an example is EZH2 silencing phosphatidylinositol-4-phosphate 5-kinase type 1 gamma (PIP5K1C), a kinase that regulates intracellular calcium signalling pathways essential in neuronal differentiation, in mesenchymal stem cells [24]. Competition of EZH2 at clusters of genes regulating cell cycle progression, stemness, and lineage commitment is dynamic in NSCs and in differentiating brain cells by chromatin immunoprecipitation and sequencing (ChIP-seq) studies [82–84]. EZH2 target genes are deregulated during the lineage-specific differentiation of neurons and astrocytes, which allows the activation of neuronal and astrocytic programs of transcription. Conversely, during oligodendrocyte lineage cell survival, EZH2 functions and H3K27me3 marks are maintained longer to stabilize the oligodendrocyte identity and maturation [85,86]. Recent studies also indicate that non-enzymatic functions of EZH2 in cell cycle regulation and transcriptional regulation in neural progenitors, as well as its scaffold functions in protein complexes without methyltransferase activity, are involved in gene expression regulation [87,88]. In addition, new indications suggest that EZH2 integrates external signaling to dynamically organize epigenomic landscapes in response to neurogenesis, thereby allowing adaptability to developmental stimuli. The role of EZH2 in DNA damage response and chromatin remodeling in neural cells has also been investigated, and its association with genome stability throughout neurodevelopment has been found. Combined, these results highlight the multifaceted nature of the molecular activities of EZH2, which makes it a strategic crossroad in epigenetic and signaling regulation that are crucial to developing and differentiating the nervous system. In addition to the normal development of the brain, the regulation of EZH2 expression and activity is also critical to the plasticity and repair of the brain. EZH2 dysregulation is associated with different pathologies. The oncogenic effect of EZH2 overexpression or mutation in brain tumors, including glioblastoma, promotes proliferation and inhibits differentiation [89,90]. On the other hand, a lack of proper EZH2 activity may impair neurogenesis and neural repair mechanisms and further deteriorate neurodegenerative disorders. This preference in EZH2 expression during adult neurogenic niches is an attractive target for regenerative medicine approaches that can be used to improve brain repair following injury. The expression of EZH2 is very dynamic during brain development, reaching its highest level in the proliferative embryonic neural progenitors, where it keeps the cells in a stem condition and suppresses premature differentiation. It gradually diminishes in the post-mitotic neurons, leading to their maturation. It is also the only model that is active in adult neurogenic niches and maintains neural stem cell identity and neurogenic competence. Its many-sided epigenetic and signaling functions knowingly balance

proliferation and differentiation among the neural proliferation, which is the foundation of normal development and adult brain plasticity.

Role of EZH2 in Embryogenesis, Neurogenesis

Neural Stem Cell Maintenance

EZH2 plays a key role in maintaining neural stem cell (NSC) maintenance during embryonic neurogenesis to facilitate the self-renewing pool of NSCs underlying the differentiation of the embryonic central nervous system into a variety of neuronal lineages. Stemness is maintained through a high level of fine-tuning between the intrinsic and extrinsic developmental signals, with EZH2 playing the key role in the execution of Polycomb-mediated gene silencing. Another key role played by EZH2 is the inhibition of cell-cycle inhibitors and pro-differentiation factors, which otherwise could push NSCs out of the mitotic cycle. This occurs by depositing the trimethyl mark onto H3K27me3, which causes a strong and inheritable transcriptional state silenced at genes associated with cell-cycle arrest and differentiation [91,92]. A significant target is the cyclin-dependent kinase inhibitor 2A (CDKN2A) locus, a potent cell cycle inhibitor, p16Ink4a. The EZH2 silencing of Cdkn2a allows NSCs to advance their cell cycle and to have a proliferative potential that is needed to grow the brain in the early stages of development [93,94]. The control of stem cell identity is not only a role of EZH2, but also plays a role in cell cycle control. In the highly dynamic embryonic environment, NSCs are exposed to diverse instructive signals that lead to differentiation into either a neuronal or glial fate. EZH2 is a protective response to these differentiation signals that it maintains through organizing a repressive chromatin environment. It suppresses transcription of differentiation-related genes, thus ensuring the multipotent condition of NSCs. It is vital that when rapid brain development and regional differentiation occur, and loss of stemness occurs prematurely, this may lead to severe developmental impairment, such as cortical hypoplasia and disorganized brain architecture [95–97]. Notably, the control provided by EZH2 is not entirely fixed. The fine entrainment of the protein abundance, chromatin binding affinity, and gene-specific activities occurs during embryonic stages when Polycomb group factors interact with other epigenetic or transcriptional regulators. It could be controlled responsively: during periods when NSC expansion is a priority, EZH2 activity is increased to maintain stemness and inhibit differentiation pathways. The required changes can alter the presence or activity of EZH2 at critical loci in response to changes in development and the requirement of new neurons, allowing the programmable transition between stem cell maintenance and lineage commitment [98–100]. This delicate balance is disrupted by the loss of EZH2 activity in the developing brain, resulting in the rapid extinction of NSCs and causing a surge of premature neuronal differentiation. NSCs exit the cell cy-

cle, increase differentiation markers, and lose the ability to maintain a pool of self-renewing cells, which is crucial for whole-brain development. An extreme EZH2 activity, on the other hand, can preserve the stemness at the expense of the required neuronal production, which demonstrates the necessity of the controlled expression and activity of this vital enzyme [101,102]. Therefore, EZH2 creates a molecular environment that is favorable to the maintenance of NSCs by inhibiting undesired differentiation and cell-cycle exit, thereby preserving the self-renewal capacity and developmental competence of the NSC pool.

Neuronal Fate Specification Regulation

EZH2 has a long-range impact on neuronal fate determination in embryonic development, which in turn determines future neuronal diversity and functional circuitry that are critical to the brain. The problem of neuronal subtype specification is fundamentally based on the interactions of extrinsic developmental cues with the chromatin organization that EZH2 supports [103–105]. Silencing of lineage-inappropriate transcriptional programs is a key aspect of EZH2's impact. At the initial stages of neural evolution, NSCs and neural progenitors are multipotent in that they can form a wide range of neuronal types. The fate decisions made by these cells heavily rely on the suppression of other fate determinants, so that regional identity and proper differentiation into neuronal subtypes are observed. EZH2 does so by acting on genes, including some members of the Hox family, which encode transcription factors that determine regional or posterior identity. EZH2 maintains the anterior identity of these forebrain progenitors by selectively silencing Hox genes, thereby facilitating proper neuronal patterning and inhibiting abnormal fate choices [106–108]. Together with the contribution to regional identity, EZH2 also liaises with other master regulators like Sox2 in the regulation of the transition between NSC multipotency and neuronal lineage commitment. Sox2 is a transcription factor essential to stemness, which hires EZH2 at essential neurogenic loci, including those encoding proneural basic helix-loop-helix (bHLH) transcription factors like Neurogenin2 and Mash1. At low levels, H3K27 methylation of these loci by EZH2 suppresses expression and maintains the stem cell fate, as well as prevents spontaneous neuronal differentiation. Later in development, pro-differentiation cues change the dynamics of interaction between Sox2, EZH2, and these target genes. Repressive marks can be removed by changing extrinsic signals or intrinsic maturation conditions, which causes the activation of the bHLH cascade that drives NSCs into differentiated neuronal progenitors [109–111]. These transitions are unique, time-dependent, and essential for proper brain development. Mistiming may cause either loss of NSCs by premature differentiation or generation of the wrong type of neurons, which interferes with regular cortical stratification, interneuron variety, and brain connections. The role of EZH2 in regulating chro-

matin accessibility is central in eliminating these errors, which is a form of spatial and temporal fidelity during the process of defining neuronal fate [112]. Moreover, EZH2 does not act independently in fate specification. It is connected to a greater web of epigenetic regulators, transcription factors, and signaling pathways, such as Notch, Wntless/Integrated signaling pathway (Wnt), and bone morphogenetic protein (BMP), which together form the fate landscape in neurogenesis. Dynamically responding to these inputs such that EZH2 can tightly regulate the time and place of differentiation events enables the selective generation of the many distinct populations of neurons that constitute the brain structure and function [76,113–115]. Altogether, EZH2 is a symphonist in the program of neuronal specification, silencing of improper programs, and cooperation with the key regulatory factors, and enables timely neurogenic cascades. It is the selective and reversible repression brought about by EZH2 that plays a significant role in the development of specific neuronal subtypes and maintenance of regional brain identity (Fig. 3).

Timing of Switch Between Neurogenesis and Gliogenesis

Neurons and glial cells are sequentially developed in the mammalian brain, and EZH2 plays a pivotal role in the timing of this neurogenesis-gliogenesis transition. This temporal order is needed not just in the formation of neuronal networks, but also in the formation of supportive glial networks that are involved in brain maturation, synaptic plasticity, and continuing functioning [105,116,117]. During early development, neural stem and progenitor cells are skewed towards producing neurons, a process supported by EZH2 through the active downregulation of glial-like lineage genes. EZH2 suppresses major determinants of astrocytes and oligodendrocytes, including the glial fibrillary acidic protein (GFAP) and transcription factor Olig2, connected with the deposition of H3K27me3. The presence of this chromatin makes an epigenetic barrier, which prevents the early beginning of glial differentiation and maintains the neuronal output as the dominant one in the early development of the brain [118–120]. When neurogenesis is blocked, developmental signals, which are intrinsic to the progenitor cells and extrinsic to the environment in which the cell is located, come together to de-repress glial gene loci by EZH2. Such cues can involve rearrangement of complexes of chromatin remodeling, the presence of transcription factors, and morphogen gradients that change the epigenomic landscape. The intrinsic maturation signals reduce the EZH2 binding or increase the recruitment of the demethylases and other chromatin modifiers that eliminate the repressive H3K27me3 marks. Meanwhile, EZH2 also decreases and stimulates the opening of glial chromatin domains by extrinsic signaling molecules, including cytokines and growth factors. The lifting of the epigenetic barrier exposes the glial determinant genes to transcription factors that initiate the differentiation of oligodendrocytes and as-

trocytes [121,122]. This will enable neural progenitor cells (NPCs) and NSCs to traverse the stem cell to neuron developmental interface, yielding the much-needed support cells that structure and streamline brain activity. The glial gene expression is released at the correct time to guarantee the presence of a coordinated switch as neurons are prevalent during the early stages of the central nervous system (CNS) development, and glia in the subsequent stages [123–125]. EZH2 may become dysregulated or untimed, which may significantly impact this process. In case EZH2 is prematurely lost, the effect can be inappropriate activation of glial genes, which leads to premature gliogenesis and failure to generate the appropriate type and quantity of neurons. On the other hand, continued EZH2 activity after it has passed its developmental window may repress glial gene expression and prevent normal glial maturation that can have adverse effects on brain health and function [126]. Neurogenesis-gliogenesis switching is not a switch, not an on-off process, but a gradual, well-coordinated cascade. EZH2, along with other chromatin controllers, provides the opportunity for the transition to take place in phase with developmental milestones, enabling brain development, cell type differentiation, and functional maturation. The finesse and specificity that EZH2 brings are key to the acquisition of proper sequencing and balance of neurons and glia, which consequently is the key to healthy brain development and brain functions.

Role of EZH2 in Postnatal/Adult Neurogenesis

SVZ

One of the most characterized neurogenic niches in the adult mammalian brain is the SVZ, where NSCs reside and maintain the process of neurogenesis throughout life. Such NSCs in the SVZ produce transient amplifying progenitors and then neuroblasts that travel rostrally along the rostral migratory stream (RMS) to the olfactory bulb, where they develop into inhibitory interneurons, which are essential to the olfactory process [127–129]. A delicate balance between NSC quiescence, activation, proliferation, and differentiation in the SVZ niche is the only required factor to support long-term neurogenesis. It requires tightly regulated epigenetic pathways. EZH2, the HMT subunit of PRC2, is among the epigenetic factors that have been identified to play a critical role in balancing NSCs' quiescence, activation, proliferation, and differentiation [130,131].

EZH2 activates the process of H3K27me3, which is a repressive epigenetic mark that suppresses the expression of gene programs incompatible with stem cell maintenance. EZH2 is very active in adult SVZ in active NSCs and transient amplifying progenitors, with no or significantly lower levels in quiescent NSCs, indicating its involvement in the control of dormancy-activation transition [132]. Deletion of EZH2 in adult mice with EZH2 conditionally expressed in the SVZ NSCs results in aberrant and transient hyper-

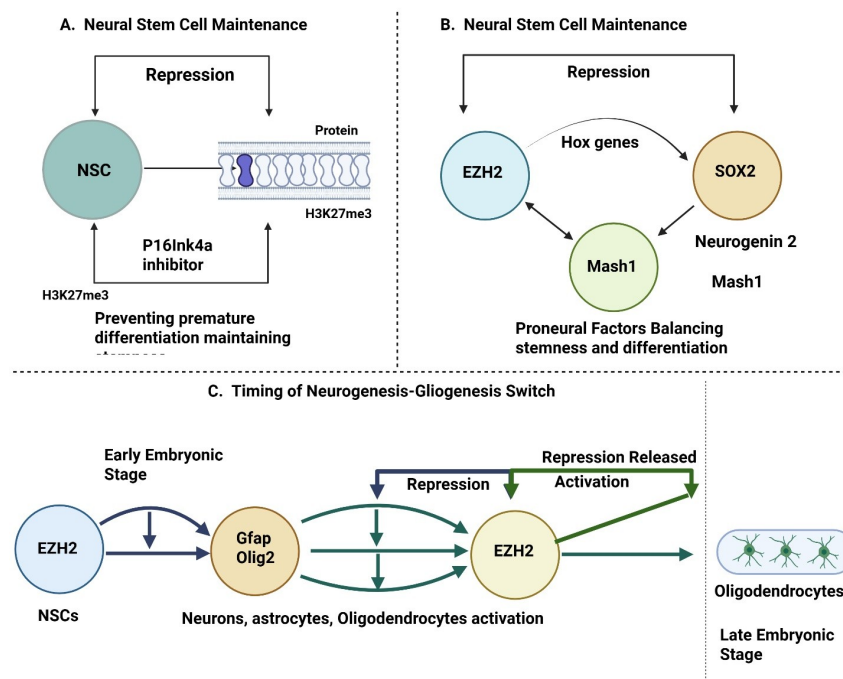


Fig. 3. Mechanisms of EZH2-mediated embryonic neurogenesis. Complex roles in EZH2-mediated embryonic neurogenesis, this schematic perspective shows the significant roles of the HMT EZH2 in regulating neural development during embryogenesis that can be subdivided into three key areas: (A) NSCs Maintenance EZH2 maintains the pool of NSCs by H3K27me3 of cell cycle suppressor promoters, which encompass CDKN2A (p16Ink4a), this suppression prevents the premature cell cycle exit and differentiation, thus retaining self-renewal and multipotency. (B) The Hox gene opposes the activation of an improper transcriptional program by inactivating the lineage-inappropriate fate determinants, including Hox genes, and the fate of the area, particularly the forebrain, is maintained via EZH2. Moreover, Sox2 and EZH2 interact to add H3K27me3 marks to proneural basic helix-loop-helix (bHLH) genes like Neurogenin2 and Mash1 to maintain NSC stemness versus differentiation until neurogenic signals remove the repression. (C) Temporal Control of the Choice between Neurogenesis and Gliogenesis: EZH2 represses glial genes such as the astrocyte marker glial fibrillary acidic protein (GFAP) and the glial precursor marker Olig2 transcriptional activator of the oligodendrocyte line in early neurogenesis by H3K27me3. As the process further develops, the repression of EZH2 at these loci is relieved through the process of chromatin remodeling that consequently enables the development of neuron production to be replaced by astrocyte and oligodendrocyte production, as needed to substitute the neurons during central nervous system (CNS) maturation. A gatekeeper that synchronizes the departure from stemness to developmental demands. It is a very fine-tuning of the stem cell fate that is imperative to the production of a correctly structured and functionally variable central nervous system. Created in BioRender. Liu, M. (2026) <https://BioRender.com/5hyqg8u>.

activation of the quiescent stem cells, as evidenced by an increase in proliferation markers. Still, the hyperactivation is short-lived, and rapid depletion of the stem cell pool occurs, impairing the long-term regenerative potential of the SVZ niche [133,134]. EZH2-depleting loss of EZH2 derepresses the Ink4a/Arf locus, which encodes the cell cycle inhibitors p16Ink4a and p19Arf, causing premature cell cycle exit and depletion of the stem cell pool; yet, even in EZH2-deficient NSCs that have been deleted Ink4a/Arf, loss of EZH2 promotes neurogenesis, suggesting that there are other, Ink4a/Arf-independent EZH2 targets [135]. Additional data indicate that EZH2 is not only necessary in SVZ neurogenesis through the control of NSC proliferation; however, it is also essential in the process of neuronal lineage choice. The H3K27me3 silenced by EZH2 is used to silence genes that are not suitable in the SVZ-derived neuronal subtypes, which provides the fidelity in specifying

ing neuronal subtypes [136,137].

The loss of EZH2 results in impaired neuroblast differentiation of SVZ NSCs and a parallel increase of astrocytic markers, which is an effect of lineage skewing. This is an epigenetic regulation that is cell-autonomous, as demonstrated by *in vitro* monolayer culture experiments in which EZH2-deficient SVZ NSCs become unable to form neurons despite the presence of wild-type cells, highlighting the activities of EZH2 in lineage commitment [138]. The long-term effect of the deletion of EZH2 in the SVZ is a significant decrease in the production of new interneurons in the olfactory bulbs that are required to mediate olfactory activity and plasticity to discriminate between odors. This associates EZH2's pathophysiological impact with functional results in sensory information processing pathways. The importance of EZH2 in maintaining the NSC pool and continuous neurogenesis indicates its relevance to neurological

well-being. It proposes sites for enhancing regeneration or inhibiting NSC depletion in aging or disease [139,140].

Hippocampal Dentate Gyrus

The major adult neurogenic niche is the hippocampal dentate gyrus (DG), where neural stem and progenitor cells continually produce granule neurons that are crucial to various cognitive processes, including learning, memory formation, pattern separation, and mood regulation. In this case, epigenetic control via EZH2 plays an important role, ensuring the maintenance of the balance between progenitor proliferation, differentiation, and maturation [141–143]. The expression of EZH2 is favored in progenitor populations in the active state, in the SGZ of the DG. Still, it is significantly down-regulated in quiescent NSCs, indicating a dynamic involvement in progenitor cell cycle regulation and lineage progression conditional deletion of EZH2 in the hippocampal progenitor cells results in a reduction of progenitor proliferation, EZH2 silenced the tumor suppressor gene PTEN, which negatively regulates the phosphoinositide 3-kinase (PI3K)/AKT/mTOR signaling. The deletion of EZH2 leads to the increase of the PTEN level, the reduction of PI3K/AKT/mTOR signaling, and, as a result, loss of progenitor pool expansion [67,144,145].

This impairment in the growth of progenitor cells is then transferred into a reduced number of newly born granule neurons joining the preexisting circuitry of the hippocampus. Biochemically, mice with the EZH2 gene deleted in DG progenitors exhibit impairment in hippocampus cognitive functions, such as poor spatial learning, fear memory, and poor pattern separation, and demonstrate the behavioral effects of epigenetic dysregulation in adult neurogenesis [146,147]. Molecularly, H3K27 trimethylation by EZH2 plays a dual role, both repressive and modulatory, fine-tuning the expression of genes linked to synaptic plasticity. As an example, EZH2 controls the expression of N-methyl-D-aspartate (NMDA) receptor subunits (Grin2a, Grin2b) and neurotrophic factors (brain-derived neurotrophic factor (BDNF)) that are key to long-term potentiation (LTP) and synaptic plasticity, which support learning and memory. EZH2 conditional knockout leads to reduced LTP and inhibits the nucleotide changes in the genome associated with long-term synaptic changes [148–150].

Further, EZH2 will influence the fate choice and timing of neurogenesis and astrogenesis, as well as neuronal differentiation. Deletion of EZH2 in neural progenitors alters the balance between pro- and anti-astrocytic genes, specifically Ngn1, affecting both the number and quality of neurons in the DG. Epigenetic silencing of neurogenic signaling pathways integrates EZH2 into a vital node that links intrinsic transcriptional programs and external signals to regulate adult hippocampal neurogenesis [82]. Besides progenitor proliferation and differentiation, other new findings indicate functions of EZH2 in adult neurons, possibly

requiring EZH2 to regulate the activity-dependent expression of genes associated with synaptic plasticity and memory reconsolidation. This cognitive plasticity depends on this epigenetic plasticity to form neuronal ensembles that help in mental flexibility. Overall, it can be stated that EZH2 in the hippocampal dentate gyrus coordinates a coordinated program of epigenetics that regulates the survival and renewal of the progenitor pool, fate determination of newborn neurons, and plasticity of mature neurons. This complex interrelation provides molecular epigenetic processes and higher-order brain functions and behavior, with EZH2 at the center of adult hippocampal neurogenesis and cognitive well-being regulation.

EZH2 Interaction With Signaling Pathways

The catalytic subunit of PRC2, EZH2, is essential in the regulation of gene expression and H3K27me₃, by which transcriptional repression of the target genes is facilitated. Nevertheless, EZH2 operates in a very complex web of signaling pathways that control cellular activities, including differentiation, proliferation, apoptosis, and tumor development. These signaling pathways modulate EZH2 activity, recruitment, and specificity to substrate and combine epigenetic regulation, developmental, and oncogenic signaling. In this section, interactions of EZH2 with central signaling cascades are examined with a particular focus on the role of such interactions in cellular plasticity, lineage specification, and disease progression (Fig. 4).

Notch Signaling

Notch signaling plays a critical role in determining the neural progenitor states by inhibiting early neuronal differentiation. The cleavage and nuclear translocation of the Notch intracellular domain (NICD) occur in response to activation of Notch receptors and form a complex with transcription factor recombination signal binding protein for immunoglobulin kappa J region (RBPJ) [151]. Another essential element of Notch activity is that it collaborates with EZH2 to induce repression of proneural genes. When activated by Notch, EZH2 is then recruited to the promoters of genes like achaete-scute family BHLH transcription factor 1 (ASCL1), neurogenin 2 (NEUROG2), and doublecortin (DCX), which are known to induce differentiation of the neurons. EZH2 promotes the H3K27me₃ changes at these loci, which strengthens the process of chromatin compaction and silencing of genes [152,153]. The given epigenetic repression of progenitor identity maintains the progenitors' identity and regulates neurogenesis timing, thereby inhibiting neurogenic signs. It has been shown that either genetic knockdown or chemical inhibition of EZH2 disrupts the repression of Notch and facilitates differentiation, showing a synergistic interaction. This partnership maintains cancer stem cell subsets by repressing differentiation programs in pathological settings, such as glioblastoma, making EZH2 and Notch co-targeting a promising

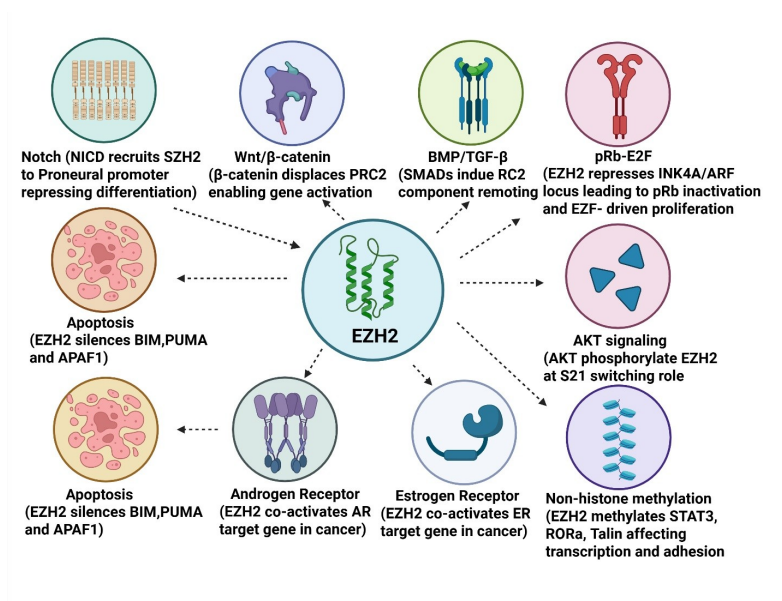


Fig. 4. EZH2 signaling networks in development and cancer. The figure shows that EZH2 is a key epigenetic controller that is incorporated in several critical signaling pathways that define cellular differentiation, proliferation, and survivability. Arrows represent forging or recruiting interactions (in that regard), in which signaling molecules like the Notch intracellular domain (NICD) recruit EZH2 to promote progenitor genes to enforce transcriptional repression and stabilize progenitor states. Wnt/ β -catenin signaling inhibits EZH2 by making PRC2 vacuolar off the chromatin, thus de-repressing neuronal differentiation. BMP/transforming growth factor beta ($\text{TGF-}\beta$) signaling stimulates EZH2 gene expression with the help of suppressor of mothers against decapentaplegic (SMAD) transcription factors to stimulate astrocyte differentiation due to integrated EZH2-mediated silencing of other lineage genes. The tumor suppressive Ink4a/Arf locus in the Retinoblastoma protein–E2F transcription factor family (E2F) transcription factor (pRb-E2F) pathway is suppressed by EZH2 to promote cell cycle progression through activation of E2F. Apoptotic pathways are also controlled through EZH2 silencing, leading to the expression of significantly pro-apoptotic genes (BCL2-like protein 11/BCL-2-interacting mediator of cell death (BIM), p53 upregulated modulator of apoptosis (PUMA), apoptotic protease-activating factor 1 (APAF1)), which play a crucial role in the survival of cancer cells by conferring resistance to apoptosis. Through the AKT signaling pathway, the post-translational modification responsible for EZH2 functioning is a phosphorylated serine 21, which activates a functional switch between canonical HMT activity and non-canonical roles of transcriptional co-activator. An example can be found in hormone-based cancers as a non-canonical activity where EZH2 interacts with androgen and estrogen receptors as a co-activator, which promotes oncogenic transcriptional programs. Lastly, EZH2 also regulates non-histone proteins, including signal transducer and activator of transcription 3 (STAT3), ROR2, and Talin, after methylation, which affect transcriptional activity, circadian regulation, metabolism, and cell adhesion. Taken together, the roles played by EZH2 in developmental biology and tumorigenesis make this diagram a crucial component in any major signaling network. Created in BioRender. Liu, M. (2026) <https://BioRender.com/ae96cq6>.

treatment option [154,155].

Wnt/ β -Catenin Pathway

The Wnt/ β -catenin pathway frequently has antigenic effects on those of EZH2 in the case of neurogenesis. Wnt signaling stabilizes cytoplasmic β -catenin, which is then able to translocate to the nucleus and interact with T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factors to stimulate neurogenic gene expression [156,157]. Wnt signaling, using a mechanical mechanism, facilitated the displacement of PRC2 protein on the primary neurogenic locus, reducing H3K27me3 levels and facilitating the process of transcriptional activation. Indicatively, in the hippocampus, Wnt stimulation increases neuronal signature expression and breaks EZH2 occupancy, which shows a functional counteraction between the two path-

ways. Here, however, the interaction is situational in cancer [158]. Wnt/EZH2 is suppressed by Wnt inhibitors, such as Dickkopf Wnt signaling pathway inhibitor 1 (DKK1), thereby indirectly maintaining Wnt signaling, which in turn enhances tumor proliferation and stemness. Therefore, the Wnt/EZH2 axis is a complex, two-way interaction that changes, dependent upon cell context and differentiation condition [159,160].

BMP/Transforming Growth Factor Beta ($\text{TGF-}\beta$) Pathway

During development, including gliogenesis, BMP and $\text{TGF-}\beta$ signaling pathways play critical roles in regulating neural stem and progenitor cell fate decisions. BMP signaling promotes transcription factors suppressor of mothers against decapentaplegic (SMAD)1/5/8 that contribute to increased PRC2 components, such as EZH2. The en-

hancement of PRC2 expression enhances the repression of neuronal genes and allows transcriptional activation of astrocyte markers such as GFAP and S100b [161–164]. The interactions between BMP signaling and EZH2, therefore, enable astrocyte differentiation by silencing alternative neuronal programs and specific lineage gene regulation. Similarly, EZH2 is recruited to silence epithelial gene transcription by SMAD complexes mediated by TGF- β to induce mesenchymal and invasive phenotypes in cancer cells through epithelial–mesenchymal transition (EMT) [165]. This is one of the ways EZH2 incorporates external cues to remodel chromatin landscapes to facilitate physiological differentiation as well as pathological development [166,167].

pRb-E2F Transcription Factor Family (E2F) Pathway

The pRb-E2F axis plays a critical part in regulating cell cycle progression, where pRb represses transcription factors of the E2F family to suppress G1/S transition [168]. EZH2 is a direct suppressor of the Inhibitor of Cyclin-Dependent Kinase 4A/Alternative Reading Frame (Ink4a/Arf) locus, encoding tumor suppressors p16Ink4a and p14Arf, which are required to activate pRb and stabilize p53, respectively [169]. EZH2-mediated silencing of this locus results in E2F-liberated hyperphosphorylation and inactivation of pRb to stimulate genes of the DNA replication and cell cycle [170]. This repression is a feed-forward mechanism in cancer cells, which causes an unchecked increase in high levels of EZH2. The EZH2-pRb-E2F pathway plays a central role in regulating the replicative ability of both stem and tumor cells and is a canonical pathway through which EZH2 promotes oncogenesis [171].

Apoptosis Pathways

The ability to resist apoptosis or programmed cell death is a key hallmark of cancer cells, enabling them to survive in adverse environments such as DNA damage, oxidative stress, or cytotoxic therapies. EZH2 plays a significant role in apoptotic evasion by maintaining a group of key pro-apoptotic genes inactive through epigenetic silence in the intrinsic mitochondrial program of apoptosis. Some of these genes include BCL2-like protein 11/BCL-2-interacting mediator of cell death (BIM), p53 upregulated modulator of apoptosis (PUMA), and apoptotic protease-activating factor 1 (APAF1), which are essential to trigger the cell death cascade after a cell experiences stress [172–175]. EZH2 is responsible for the trimethylation of H3K27me3 at the promoters of these genes, thereby establishing a repressive chromatin context inhibiting the expression of these genes. Reduced BIM and PUMA expression destabilizes mitochondrial outer membrane permeabilization, which is a conclusive event in cytochrome c release and caspase activation, with APAF1 repression further destabilizing the assembly of the apoptosome required to initiate the caspase cascades. As a result, the cancer

cells have a strong survival signaling pathway, and as a result, they become less susceptible to chemotherapy, radiation, or targeted therapy-induced apoptosis [176–179]. Interestingly, genetic silence or pharmacological inhibition of EZH2 removes this epigenetic block, resulting in the return of expression of these effector apoptotic cell types [180,181]. The reactivation restores competence of mitochondrial apoptosis, sensitizing tumor cells to anticancer agents. EZH2 inhibitors in preclinical models were shown to combine with chemotherapeutics to increase cancer cell death, indicating that EZH2 is a promising therapeutic target to surmount apoptosis resistance.

AKT Signaling Pathway

The serine/threonine kinase AKT coordinates several survival and growth signals, such as direct post-translational control of EZH2. AKT also phosphorylates EZH2 on serine 21 (S21), which significantly inhibits the canonical activity of EZH2 as a HMT in H3K27 [182,183]. This phosphorylation causes the global level of H3K27me3 to decrease, releasing the repression of EZH2 target genes and altering transcriptional landscapes.

In addition to losing enzymatic activity, S21-phosphorylated EZH2 switches functions, acquiring non-canonical capacities as a transcriptional co-activator. The change of paradigm is best illustrated in prostate cancer, where the interaction of phosphorylated EZH2 with the androgen receptor (AR) activates AR-mediated transcription with or without PRC2 and H3K27 trimethylation [184,185]. This co-activation facilitates the expression of genes that stimulate tumor cell growth and survival, especially in the face of androgen deprivation therapy resistance. In this way, AKT is a molecular switch that regulates dual-functioning EZH2, which incorporates external growth signals to dynamically regulate epigenetic repression and transcriptional activation programs, ultimately facilitating tumor progression and resistance to therapy [186].

Androgen Receptor Signaling

Androgen receptor signaling is frequently administered together with atropine or triptorelin, which inhibits the activation of these receptors. In castration-resistant prostate cancer (CRPC), EZH2 has an additional role in epigenetic silencing, but also direct interaction with the androgen receptor (AR) [187,188]. EZH2 physically interacts with AR to form a co-activator complex that enhances AR-mediated transcription of oncogenic target genes. Such interaction is largely achieved on EZH2 phosphorylation by AKT, which inactivates its canonical repressive function but allows it to boost AR transcriptional output [106,189].

This non-canonical role of EZH2 facilitates androgen-independent tumor progression, which is one of the primary mechanisms that lead to CRPC recurrence even in the condition of hormone deprivation treatment [190]. The EZH2-AR complex activates proliferation, survival, and metas-

tasis gene expression by passing conventional epigenetic pathways. This plasticity of EZH2 during adaptation to the oncogenic signaling environment turns it into an essential therapeutic target in metastatic prostate cancer [191].

Estrogen Receptor Signaling

It could be crucial to note that the estrogen receptor promotes cell proliferation, which explains why cancer cells are recognized as strongly expressing estrogen receptors. This is executed in a parallel fashion in breast cancer, in which EZH2 collaborates with the estrogen receptor (ER) to advocate tumorigenic transcriptional programs [192]. EZH2 is also recruited to ER-promoters and ER-responsive enhancers in ER-positive breast cancer cells as a transcriptional co-activator [107]. Such co-activation often entails the recruitment of other cofactors and may involve the EZH2-mediated methylation of ER per se or other transcription factors it associates with, stabilized or active it [193]. High EZH2 levels are associated with increased proliferation, tumor aggressiveness, and poor prognosis of breast cancer. These data extend the notion of EZH2 non-canonical functions by showing that the protein is involved in the area of hormone receptor signaling rather than chromatin-level repression, which led to hormone-mediated oncogenesis and possible failure of hormone therapy [194].

Transient Receptor Potential Melastatin 7 (TRPM7) Signaling

TRPM7 is a distinct channel-converting protein that regulates intracellular Mg^{2+} and Ca^{2+} homeostasis, playing a critical role in cell proliferation, migration, and survival signals [195]. TRPM7 also has an intrinsic serine/threonine kinase domain, enabling it to directly couple ionic homeostasis to intracellular signaling pathways [196]. TRPM7 is a unique “chanzyme” (channel + enzyme) that acts primarily at the plasma membrane. However, it can be proteolytically cleaved to release its C-terminal kinase domain, known as TRPM7 cleaved kinase (M7CK). Once released, this kinase translocates to the nucleus where it interacts with several key protein complexes and transcription factors [197,198]. EZH2 is one of the most critical nuclear binding partners of TRPM7. This interaction is a cornerstone of how TRPM7 functions as an epigenetic regulator rather than just an ion channel. The relationship between TRPM7 and EZH2 is primarily mediated by the M7CK.

Despite the mechanistic understanding of the association between EZH2 and TRPM7 currently being an active area of research, there is an evolving body of literature indicating that EZH2 can control the expression of TRPM7 or can mediate downstream signaling pathways that are dependent on TRPM7 activity [199]. Dysregulated TRPM7 activity in glioblastoma and other malignant tumors influences calcium-dependent signaling in regulating cytoskeletal dynamics and aggressive migration of cancerous stem cells.

Repression or stimulation of genes of these pathways by EZH2 can modify those of TRPM7 that control tumor progression and microenvironmental responses [197,200,201]. Crosstalk is a new field of study that provides new possible therapeutic options that involve epigenetic regulation and ion channel signaling in cancer.

Direct Methylation of Non-Histone Proteins

In addition to histones, EZH2 also evokes one of its roles by epigenetically modifying non-histone proteins to regulate the activities of various cell processes. EZH2 methylation of signal transducer and activator of transcription 3 (STAT3) increases the transcriptional activity of STAT3, which is oncogenic [202]. Likewise, transcription factor RORA methylation also changes the expression of circadian genes and metabolic activity, and attributes EZH2 activity to systemic physiological rhythms and tumor metabolic activity [203]. Integrin signaling and cell adhesion are altered by methylation of Talin, which impacts the capacity to migrate cells and their ability to invade during metastasis [204]. Altogether, these methylation dynamics broaden the functional range of EZH2 to demonstrate that this protein qualifies as a highly adaptable regulator that can modulate the dynamics of the chromatin, as well as signaling transduction, transcriptional regulation, and post-translational remodeling, which are essential factors of cellular homeostasis and disease [205].

Relevance of EZH2-Regulated Circadian Genes in Neurogenesis

EZH2 has a complex function in regulating neurogenesis through epigenetic control of circadian rhythm genes, which play a crucial role in coordinating the proliferation, differentiation, and maturation of NSCs in the brain. The key circadian regulators (period circadian regulator 1 (PER1) and period circadian regulator 2 (PER2)) are negative constituents of the transcription-translation feedback loop (TTFL) that regulates circadian timing by suppressing the brain and muscle ARNT-like 1 (BMAL1)-circadian locomotor output cycles kaput (CLOCK) complex. These PER proteins are found in the neural stem and progenitor cells, with PER2 playing a role in the timing of neurogenesis and maturation of the neurons [206,207]. In the hippocampus, PER2 regulates cell cycle dynamics and the fate choice of NSC cells, and dysregulated PER expression leads to a loss of this regulation. Similarly, the neuronal progenitors are also involved in the expression of cryptochrome circadian regulator 1 (CRY1) and cryptochrome circadian regulator 2 (CRY2), which stabilize the circadian phase by inhibiting the activity of BMAL1-CLOCK. CRY1 loss prevents NSCs and cortical layering homeostasis, which may rely indirectly on developmental signatures of Notch and Wnt, and highlights a circadian regulation of these major differentiation cues [208,209] (Table 1).

BMAL1 (aryl hydrocarbon receptor nuclear

Table 1. Relevance of EZH2-regulated circadian genes in neurodevelopment.

Genes	Role in circadian regulation	Evidence in neurogenesis/NSCs	Mechanism	References
PER1/PER2	Negative regulates the TTFL, further repressing the BMAL1-CLOCK activity.	In NSCs where they differentiate into neurons, PER2 modulates neurogenic time and maturation of neurons.	PER2 regulates events in the cell cycle and fate choice of NSC cells; manipulation of cellular PER expression has an impact on the timing of proliferation and differentiation in the hippocampal neurogenesis.	[206,207]
CRY1/CRY2	Repress the BMAL1/CLOCK phase stabilization.	CRY1/2 are fabricated in the neural progenitor; CRY1 knockout obstructs the NSCs' proliferation and cortical layering.	CRY1 has a more indirect impact on Notch and Wnt signaling by circadian cascade, loss of CRY crowdsources differentiation time.	[208,209]
BMAL1 (ARNTL)	Circadian activator	BMAL1 deletion in NSCs decreases the hippocampal and cortical proliferation and neurogenesis. Strong evidence: BMAL1 deletion in NSCs reduces neural progenitor proliferation and neurogenesis in the hippocampus and cortex.	Spanning the spectrum scope to provide insights into MSC self-renewal (both redox regulation via the Nrf2 pathway and Notch signaling) and gliogenesis, the BMAL1 protein demonstrates involvement with NSC self-renewal.	[210,211]
DBP	Output of Circadian transcription factor involvement in the regulation of detox genes	Manifested in the growing brain; less first-hand evidence.	DBP can control neuronal excitations and synaptic gene activity during differentiation steps; it is also associated with the rhythms of astrocytes.	[212,213]
REV-ERB α (NR1D1)	Downregulation of BMAL1 transcription stabilizes the Secondary loop	Expressed in neuronal progenitors, it regulates the differentiation of cells into neurons and the remodeling of the spine.	REV-ERB α governs neuronal maturation and synaptic plasticity; it affects the differentiation of the NSCs to neurons or glia.	[214,215]
SIRT1	nicotinamide adenine dinucleotide (NAD ⁺)-dependent deacetylase; modulates BMAL1 and PER1	Firm connection—SIRT1 regulates self-renewal, differentiation, and NSC aging.	SIRT1 controls circadian and developmental timing, Notch signaling, mitochondrial metabolism, and chromatin state in NSCs.	[216,217]
PGC-1 α	Co-activator involved in metabolic and circadian programming	Governs neuronal differentiation and mitochondrial biogenesis	PGC-1 α not only regulates neuronal differentiation and oxidative metabolic processes but also synaptic activity; maturation timing is associated.	[218,219]

translocator-like protein 1 (ARNTL)) plays a significant role in the self-renewal and neurogenesis of NSCs because its deletion significantly decreases the proliferation of NSCs in the hippocampal and cortical areas. BMAL1 facilitates neural stem cell survival through nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated redox homeostasis regulation and facilitation of endodermally essential Notch signaling, which subsequently controls progenitor fate in addition to playing a role in glial cell fate [210]. Other transcription factors controlled by the circadian system, such as D-box binding PAR bZIP transcription

factor (DBP), also may control neuronal excitability as well as synaptic gene expression during differentiation. Still, their functions are not well defined [212,213].

Moreover, nuclear receptor subfamily 1 group D member 1 (REV-ERB α , NR1D1) nuclear receptor silences the transcription of BMAL1, thereby stabilizing the secondary circadian feedback loop. It plays a role in controlling neuronal maturation and synaptic plasticity and is required for the differentiation of NSCs into neuronal or glial lineages. With its control of networks linked to REV-ERB α , EZH2 plays a role in the developmen-

tal timing fine-tuning of the nervous system [214,215]. Additionally, nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylase Sirtuin 1 (SIRT1) regulates circadian proteins BMAL1 and PER2, playing a remarkable role in NSC aging, self-renewal, and differentiation. SIRT1 links the day-neutral metabolic signals to messengers of circadian and developmental timing during neurogenesis via mitochondrial metabolic regulation, Notch-mediated, and chromatin regulation [216,217].

Additionally, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) coactivator combines both metabolic and circadian regulation programs to enhance neuronal, mitochondrial, and synaptic roles, and energy metabolism and neural maturation timing are connected. All this network of circadian genes governed by EZH2 coordinated the relationship between proliferation, differentiation, and maturation of the neural populations, bringing together the epigenetic regulation and inherent biological rhythms. This organization provides the accurate temporal sequence of brain development and focuses on the central role of EZH2 in aligning molecular clocks with neurogenic events [218,219].

Mechanistic Insights: EZH2 in Chromatin Dynamics

Bivalent Domains

EZH2, as the catalytic subunit of PRC2, plays a vital role in maintaining the epigenetic plasticity of NSCs through its influence on bivalent chromatin domains [220]. These unique domains are defined by the co-occurrence of two mutually exclusive histone modifications at gene promoters: the repressive trimethylation of H3K27me3, catalyzed by EZH2, and the activating trimethylation at lysine 4 (histone H3 lysine 4 trimethylation (H3K4me3)), mediated by the mixed-lineage leukemia/lysine methyltransferase 2 family (MLL)/SET1 family of methyltransferases [221]. The simultaneous presence of these epigenetic marks creates a “poised” chromatin state in which genes, typically those involved in developmental fate decisions, remain transcriptionally silent but are primed for rapid activation when differentiation cues are received [222]. In NSCs, this poised configuration ensures that the cells retain a multipotent character, preserving the ability to differentiate into various neural lineages in response to environmental and developmental stimuli. Recent single-cell mapping studies using cleavage under targets and tagmentation (CUT & Tag) and single-cell ChIP-seq have revealed that the bivalent configuration is dynamically remodeled during neurogenesis—developmental genes lose H3K27me3 and transition into a fully active state marked solely by H3K4me3. In contrast, pluripotency-associated genes acquire additional repressive modifications and become stably silenced [222–224]. This transition highlights how EZH2-dependent methylation acts as a molecular checkpoint that must be resolved to permit lineage commitment.

Mechanistically, the formation of bivalents requires the interplay of PRC2 with other chromatin-associated complexes. PRC2 recruitment to CpG-rich promoters is facilitated by accessory subunits such as JARID2 and AEBP2, which enhance its binding specificity. Additionally, PRC1-mediated H2A ubiquitination acts synergistically with H3K27me3 to strengthen chromatin compaction at bivalent promoters [26,33,225]. Recent evidence suggests that chromatin accessibility and transcriptional pausing at these promoters are regulated not only by histone modifications but also by the occupancy of RNA polymerase II in a paused configuration [226,227]. Loss-of-function experiments demonstrate that EZH2 ablation leads to premature derepression of differentiation genes such as *Pax6*, *Sox1*, and *Neurogenin2*, resulting in precocious neuronal differentiation at the expense of stem cell self-renewal. Thus, EZH2-mediated bivalency ensures temporal precision in gene activation during neural lineage specification [63,228].

Moreover, dysregulation of bivalent domain resolution has been linked to neurodevelopmental disorders and tumorigenesis. In glioblastoma stem cells, persistent bivalency at key differentiation genes contributes to the maintenance of stem-like properties and therapeutic resistance [229,230]. Therefore, pharmacological targeting of EZH2 or its accessory cofactors represents an attractive approach to induce differentiation in these malignancies. Collectively, EZH2-dependent bivalent domains act as dynamic epigenetic switches, integrating intrinsic developmental programs with extrinsic signaling to fine-tune neural fate transitions.

Interaction With Non-coding RNAs

The functional spectrum of EZH2 extends far beyond its canonical role as a HMT. Recent research has unveiled a pivotal role for non-coding RNAs (ncRNAs), including lncRNAs, microRNAs (miRNAs), and circular RNAs (circRNAs), in modulating EZH2 activity and genomic targeting [231–234]. Initially, EZH2 was presumed to be recruited primarily by transcription factors or DNA sequence motifs; however, it is now clear that RNA-mediated interactions provide an essential layer of regulation, influencing both its localization and catalytic function. lncRNAs such as HOTAIR, antisense non-coding RNA in the INK4 locus (ANRIL), and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) serve as molecular scaffolds that tether EZH2 to specific genomic loci [235,236]. These interactions enable PRC2 to establish repressive H3K27me3 marks at target promoters, often leading to silencing of tumor suppressor genes such as CDKN2A or breast cancer type 1 susceptibility protein (BRCA1), thus promoting oncogenesis. Conversely, specific ncRNAs, including GAS5 and maternally expressed gene 3 (MEG3), act as decoys that sequester EZH2 away from chromatin, attenuating its silencing effects [237,238] (Table 2).

Table 2. Interaction with non-coding RNAs.

Type of interaction	Example involved	Mechanism	Significance/Outcomes
LncRNA recruits the EZH2	ANRIL, HOTAIR	Guiding/scaffolding	Tumor suppressor
miRNA downregulates the EZH2	miR-101 and miR-26a	Silenced the EZH2 mRNA	Downregulate the EZH2 target
EZH2-based silencing of miRNA	EZH2 silenced miR-31	H3K27me3 at the promoter of miRNA	Decreased the Tumor suppression
circRNA sponges the miRNA	circRNA sponge miR-26a	Prohibited miR-26a from inhibiting EZH2	Indirect EZH2 up-regulation

MicroRNAs also exert fine-tuned post-transcriptional control over EZH2 expression. miR-101, miR-26a, and miR-214 have been identified as potent negative regulators of EZH2 translation by binding to complementary sequences within its 3'-UTR, leading to decreased EZH2 protein levels [239–241]. The downregulation of these miRNAs in various cancers results in EZH2 overexpression and aberrant repression of differentiation genes. Intriguingly, EZH2 itself can silence tumor-suppressive miRNAs such as miR-31 through direct H3K27me3 deposition on their promoter regions, creating a feed-forward regulatory loop that perpetuates oncogenic epigenetic states [92,242]. Furthermore, emerging evidence indicates that circRNAs can act as sponges for EZH2-targeting miRNAs, thereby indirectly upregulating EZH2 and enhancing its downstream repressive functions. For instance, circRNA CDR1as, by sponging miR-26a, prevents EZH2 suppression in glioblastoma cells, contributing to increased proliferation and stemness [243,244].

These multilayered interactions illustrate that EZH2 does not operate in isolation but rather as part of a dense RNA–protein regulatory network that integrates chromatin state with RNA metabolism. Beyond cancer, similar EZH2–ncRNA interactions modulate neural differentiation, synaptic plasticity, and response to injury. Studies in neural progenitor cells have revealed that lncRNA taurine upregulated gene 1 (TUG1) guides EZH2 to neurodevelopmental loci to repress differentiation genes, maintaining stemness [88,245]. Thus, ncRNAs provide specificity and versatility to EZH2's chromatin functions, enabling context-dependent outcomes depending on developmental or pathological cues.

Interaction With Other Epigenetic Modifiers

EZH2 acts as part of a complex epigenetic environment, interacting with several chromatin-modifying enzymes and regulatory proteins to repress or activate transcription in a context-specific manner. In addition to its direct interaction with PRC2 as the catalytic subunit of trimethylating H3K27me3, EZH2 interacts dynamically with other epigenetic repressors such as histone deacetylases (HDACs), DNA methyltransferases (DNMTs), and histone demethylases. These synergistic and antagonistic interactions ensure a multilayer regulation of chromatin structure and gene expression during key developmental and pathological events [246,247].

HDACs also tend to work together with EZH2 to con-

dense repressive chromatin states. Histone tails deacetylated after PRC2 recruitment and H3K27me3 deposition are often deacetylated by the action of HDAC1 and HDAC2, which cause chromatin compaction and reduction of transcriptional accessibility. Some research has shown that PRC2 can physically associate with HDAC-containing complexes, including nucleosome remodeling and deacetylase complex (NuRD), which functions to enhance the suppression of differentiation genes in stem cells. Such a collaboration between EZH2 and HDACs not only inhibits the improper activation of developmental genes but also causes long-term silencing of genes that remain silent even after several cell divisions. The histone methylation and deacetylation, when combined in a combinatoric manner, therefore present a dual-layer repression of transcription [248–251].

EZH2 is also found to interact with DNA methyltransferases, especially DNMT1, DNMT3A, and DNMT3B, to stabilize DNA-level gene silencing. Promoters or enhancers containing Methylated CpG islands may recruit PRC2 complexes, or PRC2 may direct DNMTs to loci. This two-way connection plays a significant role in the maintenance of epigenetic stability in lineage commitment [252,253]. One example is during neurodevelopment, astroglia genes repressed by EZH2 are commonly maintained in transcriptional silence by downstream promoter DNA stamps and only overcome when cells differentiate. It is this cellular interaction that highlights the importance of a coordinated effect of histone and DNA methylation systems to create long-lasting transcriptional memory. At the other end of this regulatory balance, there are Trithorax group (TrxG) proteins that are the functional antagonists of Polycomb-mediated repression [254,255]. Transcriptional initiation is connected to the site of transcription that is marked by activation through the portion of the histone protein TrxG complex, especially the MLL family of methyltransferases [256,257]. The hostility between H3K4me3 and H3K27me3 states of bivalently chromatinized domains is a state of poise that enables developmental genes to be silent but ready to be rapidly activated upon differentiation cues.

This mechanism varies during neurogenic states in which TrxG function supersedes EZH2 inhibition, allowing the neurons to express the necessary genes; they can specify their lineage. Lysine demethylase 6A (KDM6A/UTX) and lysine demethylase 6B (KDM6B/JMJD3), which are the main demethylases that remove the H3K27me3 mark, also play a role in antagonizing EZH2-dependent repression.

These enzymes facilitate transcriptional activation and access to the chromatin by erasing the methylation mark. The spatiotemporal expression control of KDM6A/B enables the EZH2-repression to be reversible, enabling adaptable regulation of genes that are necessary in dynamic developmental processes like neuronal differentiation, synaptic plasticity, and responses to stress [258,259].

Altogether, the summary shows that EZH2 functions in a highly interactive epigenetic system where reciprocal support and antagonism between various chromatin modifiers establish the specificity of transcriptional consequences required to generate cell identity. The stable repression is made possible by the collaborative activities with HDACs and DNMTs, and antagonist relationships provide the responsive balance between silencing and activation with TrxG proteins and KDM6A/B/B. This exquisitely sensitive crosstalk is a pointer to the significance of EZH2 as a central regulator as well as a sensitive member of the larger epigenetic system of gene expression during neurodevelopment.

The EZH2 in Neurodevelopmental Disorders and Diseases

Intellectual Disability and Developmental

Weaver syndrome is an autosomal dominant overgrowth syndrome caused by heterozygous germline defects in EZH2, which is characterized by tall stature, macrocephaly, bone aging, facial morphology, and impaired cognitive ability. Most of these mutations cause the partial deactivation of or a change in the catalytic activity of the EZH2 methyltransferase domain, which disrupts the global H3K27me3 during an initial stage of maturation. The neurological symptoms of the disease in individuals affected are indicative of EZH2 regulating critical transcriptional networks controlling EZH2 NSC proliferation, neuronal differentiation, and cortical patterning [260–262].

EZH2 deletion in the animal neural progenitors causes premature cell cycle withdrawal, migration defects, and abnormal layering of the cerebral cortex that are highly similar to structural and functional defects in human syndromic diseases. Further, transcriptomic data indicate gene alterations of processes involved with synaptogenesis, axon guidance, and neurogenesis, which supports the idea that EZH2-mediated suppression guarantees appropriate timing of neurodevelopmental programs [70,263]. Patients with Weaver syndrome regularly show brain MRI evidence of findings related to ventriculomegaly, corpus callosum malformation, and cerebellar hypoplasia—evidence that demonstrates the malfunction

The EZH2 interferes with neuronal and glial lineage development in the early brain morphogenesis. Therefore, the neuropathology phenotypes of the Weaver syndrome highlight the essential function of EZH2 as a global controller of neurodevelopmental chromatin structure [264, 265].

Neuropsychiatric Disorders

Abnormal EZH2 activity and H3K27me3 homeostasis have been suggested in the pathogenesis of several neuropsychiatric disorders, such as schizophrenia, autism spectrum disorders (ASD), and depression. The postmortem gene results of schizophrenic brains have demonstrated EZH2 and its target gene dysregulation of genes that play a role in the function of synapses, neuronal differentiation, and cortical maturation. Alteration of these regulatory pathways can cause dysfunction of dendritic spine morphology and neuroplasticity, which can add to cognitive and behavioral impairments. On the same note, animal models of ASD indicate that increased EZH2 activity disrupts the process of excitatory and inhibitory synapse formation, resulting in unusual social and communication behaviors [266,267].

Activation of stress on EZH2 in the hippocampal dentate gyrus in depression models suppresses neurogenic factors via BDNF and DCX and causes decreased adult neurogenesis. Chronic silencing of neurogenesis is linked to anhedonia and cognitive impairment, indicating EZH2 transcriptional suppression has a mechanistic part in mood regulation. Interestingly, EZH2 pharmacological or genetic inhibition has been revealed to reestablish hippocampal neurogenesis and to ameliorate depressive-like behaviors in rodents, which makes it a promising therapeutic target in affective disorders. Together, these results indicate that EZH2 is an epigenetic integrator of environmental stress and developmental cues as well as neuronal plasticity, determining long-term neural function and susceptibility to psychiatric disease [268–270] (Fig. 5).

Brain Tumors

EZH2 is significantly overexpressed in various aggressive brain tumors, such as glioblastoma (GBM) and medulloblastoma, which promotes malignant redesign and tumor quality by epigenetic reprogramming. In GBMs, EZH2 maintains self-renewal and an undifferentiated cancer stem cell (CSC) state that has enhanced tumor heterogeneity and resistance to radiochemotherapy. Mechanically, EZH2 suppresses the tumor suppressor genes, including PTEN, CDKN2A, and p21, and concurrently suppresses the differentiation-linked transcription factors. With this large web of silenced genes, unregulated proliferation and invasive capacity are encouraged. Similarly, oncogenic (Sonic Hedgehog (SHH) and Wnt) cascades are amplified by EZH2, which boosts tumor growth and metastatic potential in medulloblastoma [271–273].

Considering its key position in tumor behavior, EZH2, in turn, has turned out to be a convenient therapeutic target. The clinical trials on malignant gliomas and medulloblastomas evaluate EZH2 inhibitors, such as tazemetostat, which has been approved so far in epithelioid sarcoma and follicular lymphoma. There is preclinical evidence that the inhibition of EZH2 causes tumor cells to differentiate,

reduces their clonogenic potential, and makes CSCs more sensitive to conventional therapies. Nevertheless, the problem of therapeutic resistance and context effect is persistent, which highlights the importance of combinatorial treatment options. In general, EZH2 represents an epigenetic center connecting developmental control and cancerous change in the central nervous system [274,275].

EZH2 has emerged as a critical epigenetic regulator of cancer immunity [181]. By controlling tumor antigen presentation, immune cell function, immune checkpoint signaling, and the tumor microenvironment, EZH2 contributes significantly to immune evasion and therapeutic resistance [276]. Pharmacological inhibition of EZH2 offers a promising strategy to enhance antitumor immunity and improve responses to immune checkpoint blockade [277]. As our understanding of EZH2-mediated immune regulation continues to expand, EZH2-targeted therapies are expected to become increasingly important components of next-generation cancer immunotherapy.

Clinical Implications and Prospects

The dualistic nature of EZH2, as both an overall controller of developmental events and a disease-causing agent in cancers and neurological disorders, is a paradoxical therapeutic environment. Its irreplaceable contribution to neural progenitor maintenance and differentiation makes the design of interventions that can discriminate against its physiological and pathological effects extremely complex. Therefore, the application of EZH2 should be context-specific to identify the right balance between accuracy and safety so that the therapeutic effects of the treatments can be achieved, while avoiding the occurrence of unintended epigenetic disturbances (Fig. 6).

EZH2 Inhibitors

Pharmacological inhibition of EZH2 has spurred great interest in cancer biology, especially in cancer types where functional EZH2 gain-of-function mutations or PRC2 dependence on transcriptional repression exist. Several small-molecule inhibitors with high potency have shown clinical activity in lymphoma as well as in selected solid tumors by rejuvenating silenced tumor suppressor genes via H3K27 trimethylation. Application of this success to brain tumors, especially glioma and medulloblastoma, is very promising because EZH2 has been reported to play a role in sustaining the tumor-initiating stem-like cells and resistance to therapy. Nevertheless, when EZH2 is systemically inhibited in the central nervous system, there is a high-risk factor. With EZH2 playing a significant role in the maintenance of neural stem and progenitor cell stocks, prolonged/systemic inhibition could cause neurodevelopmental trianarchy, or decline in regeneration ability. Thus, treatment plans should seek to achieve local or time-limited drug delivery, possibly through nanoparticle carriers, or convection-enhanced intrathecal delivery, to achieve optimal on-target tumorici-

dal effect without disrupting normal neurogenesis and cognitive function [278,279].

Topical Editing of Epigenetics

New technologies in programmable epigenomic editing will revolutionize the therapeutic control of all chromatin states regulated by EZH2. The mammalian gene-specific regulation of gene expression by catalytically inactive clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (dCas9) fused with epigenetic effector domains opens a new era of locus-specific regulation of gene expression. As an example, combining dCas9 with the catalytic domain of EZH2 is capable of targeting promoters with H3K27me3 repressive marks, which can be removed with ease by fusing it to the demethylase JMJD3 [280]. The attractive epigenetic signatures at the disease-relevant locus can be fine-tuned using this modular design without disrupting chromatin-wide activity of this PR during disease progression. There are no known examples of conventional types of wholesale inhibitors that demonstrate this kind of precision editing, but only at levels of high risk to the cell or tissue, because of collateral damage to non-target EZH2 proteins. In addition to this, CRISPR/dCas9-based systems can be reversibly changed, which provides temporal manipulation of the cellular identity or state. A combination of these tools and the single-cell epigenomic profiling would further trim down therapeutic interventions to provide a more personalized correction of the dysregulated chromatin landscape for patients.

Regenerative Medicine

Regulation of EZH2 in regenerative neuroscience is a key interface for improving endogenous brain recovery. EZH2 has close control over the self-renewal-differentiation balance of neural stem cells, and therefore, it is a significant switch in neurogenesis. What might have happened is controlled modulation, not wholesale inhibition, to activate the quiescent neural progenitors in such settings as Alzheimer's disease, traumatic injury, or ischemic stroke. It is preclinical models that temporary downregulation of EZH2 could be beneficial to the differentiation of neurons and synaptic integration, but to maintain a proper lineage commitment and maturation, its activity needs to be restored later [281]. Such narrow and optimal control is likely based on advances in inducible systems, including optogenetic or nanomaterial-based delivery, which enables spatiotemporal control of EZH2 activity. The result is that, to translate these results into clinical therapies, it will be necessary to consider the ethical and safety concerns of long-term epigenetic reprogramming, but with the potential benefits of restoring cognitive and motor function via endogenous regenerative pathways, it is an interesting subject of future neurotherapeutic studies.

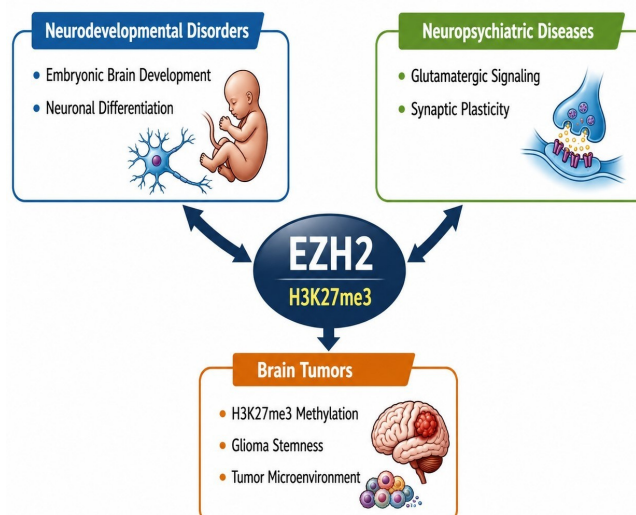


Fig. 5. Roles of EZH2 in neurological disorders and brain tumors. This schematic figure demonstrates the complex functions of EZH2 in neuropsychiatric diseases and neurodevelopmental disorders, as well as brain tumors. EZH2, the HMT responsible for H3K27me3, does not appear to be regulated by the modifications represented by the moieties studied. Nevertheless, it is crucial to recognize it as an essential, central nitrogen-carrying regulatory component that influences the observed changes. EZH2 in neurodevelopmental disorders regulates embryonic brain development and neuronal differentiation. In the neuropsychiatric disease, EZH2 is shown to mediate glutamatergic signaling and synaptic plasticity. The figure further depicts the role of EZH2 in brain tumors, involving the stimulation of histone H3K27me3 methylation, the influence of glioma stemness, and the influence on the tumor microenvironment. Arrows represent the relationships between EZH2 and every one of the pathological or developmental domains. Created by ChatGPT (GPT-5.6 Sol; OpenAI, San Francisco, CA, USA; accessed September 2026) and verified by all authors.

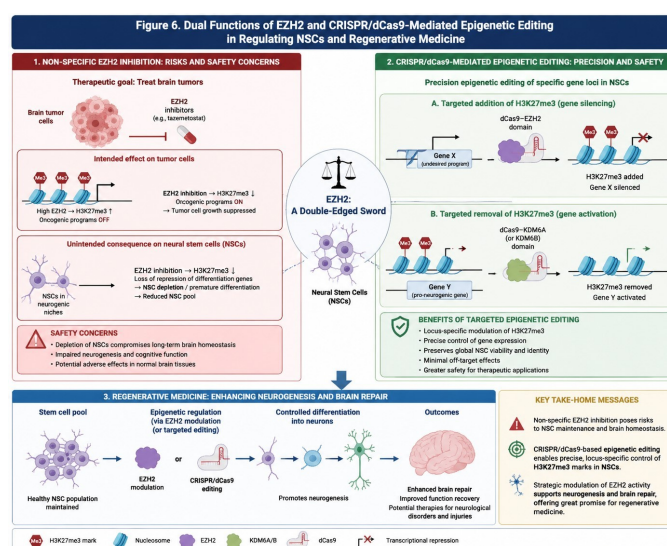


Fig. 6. EZH2-targeted epigenetic therapy and neural regeneration. This figure provides a schematic summary of the two functions of EZH2 and clustered regularly interspaced short palindromic repeats (CRISPR)/catalytically inactive CRISPR-associated protein 9 (dCas9)-mediated epigenetic editing in regulating NSCs and regenerative medicine. When considering the treatment of brain tumors, EZH2 inhibitors will be engineered to cause cancer cells, but, unintentionally, might cause depletion of the population of NSCs, thus leading to safety concerns regarding brain homeostasis in the long-term. CRISPR/dCas9-based technologies provide a remedy by making it feasible to add or remove gene locus-specific H3K27me3 epigenetic marks on NSCs, which is a precise modulation of gene expression without affecting stem cell viability globally. Within a regenerative medicine paradigm, regulating EZH2 activity in stem cell groups enhances neurogenesis and brain repair by increasing the controlled differentiation of stem cells into neurons. Therefore, the figure demonstrates the dangers of non-specific EZH2 inhibition as well as the therapeutic possibilities of targeted epigenetic editing to develop further neural regeneration and targeted brain repair plans. Created by ChatGPT and verified by all authors.

Conclusions

Collectively, the evidence reviewed here supports a unifying mechanistic model in which EZH2 functions as an epigenetic gatekeeper of neurogenesis. Through PRC2-dependent H3K27me3 deposition, EZH2 establishes reversible repressive chromatin states that preserve neural stem cell identity, suppress lineage-inappropriate transcriptional programs, and coordinate the temporal progression of neural development. Rather than acting as a static transcriptional silencer, EZH2 dynamically integrates intrinsic transcription factor networks and extrinsic developmental signals to regulate the transition from stem cell maintenance to neuronal differentiation, and subsequently from neurogenesis to gliogenesis.

A central concept emerging from recent studies is that EZH2 operates in a highly context-dependent manner. During embryonic development, EZH2 preserves neural progenitor pools by repressing differentiation-associated genes; in adult neurogenic niches, it maintains the balance between stem cell self-renewal and lineage commitment; and in mature neurons, its progressive downregulation permits neuronal maturation and synaptic plasticity. These stage-specific functions position EZH2 as a molecular timer that coordinates developmental transitions while ensuring cellular identity and tissue homeostasis.

An additional conceptual advance highlighted in this review is the recognition that EZH2 functions beyond canonical histone methylation. Interactions with signaling pathways, including Notch, Wnt/ β -catenin, BMP/TGF- β , and PI3K/AKT, reveal that EZH2 serves as a signaling-responsive epigenetic hub capable of integrating environmental cues into chromatin-based regulatory programs. Furthermore, emerging evidence suggests that non-canonical and methyltransferase-independent activities of EZH2 contribute to neural development and disease progression.

From a translational perspective, dysregulation of EZH2 disrupts the delicate balance between stemness and differentiation, contributing to neurodevelopmental disorders, impaired regeneration, and brain tumorigenesis. Future studies combining single-cell multi-omics, spatial epigenomics, and CRISPR-based epigenetic editing will be essential to define cell-type-specific EZH2 functions and therapeutic windows. Understanding how EZH2 coordinates chromatin architecture across developmental stages may ultimately enable precise manipulation of neural stem cell fate for regenerative medicine while minimizing the oncogenic risks associated with aberrant EZH2 activity.

Thus, the conceptual framework emerging from current evidence is that EZH2 acts not merely as a repressor of gene expression but as a master regulator of neural cell-state transitions, integrating epigenetic memory, developmental signaling, and lineage specification throughout neurogenesis.

List of Abbreviations

AEBP2, adipocyte enhancer-binding protein 2; AKT, protein kinase B; ANRIL, antisense non-coding RNA in the INK4 locus; APAF1, apoptotic protease-activating factor 1; AR, androgen receptor; ARNTL, aryl hydrocarbon receptor nuclear translocator-like protein 1; ASCL1, achaete-scute family BHLH transcription factor 1; ASD, autism spectrum disorder; BDNF, brain-derived neurotrophic factor; bHLH, basic helix-loop-helix; BIM, BCL2-like protein 11/BCL-2-interacting mediator of cell death; BMAL1, brain and muscle ARNT-like 1; BMP, bone morphogenetic protein; BRCA1, breast cancer type 1 susceptibility protein; CDKN2A, cyclin-dependent kinase inhibitor 2A; ChIP-seq, chromatin immunoprecipitation sequencing; circRNAs, circular RNAs; CLOCK, circadian locomotor output cycles kaput; CNS, central nervous system; CRISPR, clustered regularly interspaced short palindromic repeats; CRPC, castration-resistant prostate cancer; CRY1, cryptochrome circadian regulator 1; CRY2, cryptochrome circadian regulator 2; CSC, cancer stem cell; CUT & Tag, cleavage under targets and tagmentation; dCas9, catalytically inactive CRISPR-associated protein 9; DBP, D-box binding PAR bZIP transcription factor; DCX, doublecortin; DG, dentate gyrus; DKK1, Dickkopf Wnt signaling pathway inhibitor 1; DNMTs, DNA methyltransferases; E2F, E2F transcription factor family; EED, embryonic ectoderm development; EMT, epithelial–mesenchymal transition; ER, estrogen receptor; EZH1, enhancer of zeste homolog 1; EZH2, enhancer of zeste homolog 2; GBM, glioblastoma; GFAP, glial fibrillary acidic protein; H2AK119ub, histone H2A lysine 119 monoubiquitination; H3K4me3, histone H3 lysine 4 trimethylation; H3K27me3, histone H3 lysine 27 trimethylation; H3K36me2/3, histone H3 lysine 36 di-/trimethylation; HDACs, histone deacetylases; HMT, histone methyltransferase; HOTAIR, HOX transcript antisense intergenic RNA; JARID2, jumonji and AT-rich interaction domain containing 2; KDM6A/UTX, lysine demethylase 6A; KDM6B/JMJD3, lysine demethylase 6B; lncRNAs, long non-coding RNAs; LTP, long-term potentiation; M7CK, TRPM7 cleaved kinase; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MEG3, maternally expressed gene 3; miRNAs, microRNAs; MLL, mixed-lineage leukemia/lysine methyltransferase 2 family; mTOR, mechanistic target of rapamycin; NAD⁺, nicotinamide adenine dinucleotide; ncRNAs, non-coding RNAs; NEUROG2, neurogenin 2; NICD, Notch intracellular domain; NMDA, N-methyl-D-aspartate; NPCs, neural progenitor cells; NR1D1, nuclear receptor subfamily 1 group D member 1/REV-ERB α ; Nrf2, nuclear factor erythroid 2-related factor 2; NSCs, neural stem cells; NuRD, nucleosome remodeling and deacetylase complex; PcG, Polycomb group; PCL, Polycomb-like; PER1, period circadian regulator 1; PER2, period circadian regulator 2; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PHF1, PHD finger protein

1; PHF19, PHD finger protein 19; PI3K, phosphoinositide 3-kinase; PIP5K1C, phosphatidylinositol-4-phosphate 5-kinase type 1 gamma; PRC1, Polycomb repressive complex 1; PRC2, Polycomb repressive complex 2; PTEN, phosphatase and tensin homolog; PUMA, p53 upregulated modulator of apoptosis; RbAp46/48, retinoblastoma-binding proteins 46/48; RBPJ, recombination signal binding protein for immunoglobulin kappa J region; REV-ERB α , nuclear receptor subfamily 1 group D member 1; RMS, rostral migratory stream; SGZ, subgranular zone; SHH, Sonic Hedgehog; SIRT1, sirtuin 1; SMAD, suppressor of mothers against decapentaplegic; SRM, stimulatory response motif; STAT3, signal transducer and activator of transcription 3; SUZ12, suppressor of zeste 12 homolog; SVZ, subventricular zone; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; TGF- β , transforming growth factor beta; TRPM7, transient receptor potential melastatin 7; TrxG, Trithorax group; TTFL, transcription–translation feedback loop; TUG1, taurine upregulated gene 1; Wnt, Wingless/Integrated signaling pathway.

Declaration of AI and AI-assisted Technologies in the Writing Process

We have used ChatGPT in preparing the Graphical Abstract.

Availability of Data and Materials

The data produced during the study are governed by a data-sharing requirement and are accessible in a public repository that does not assign DOIs to datasets.

Author Contributions

Conceptualization: GDW, MLL; methodology, investigation, data curation, writing—original draft preparation: RSS, SCG; writing—review and editing: RSS, SCG, GDW, MLL; supervision, funding acquisition: GDW, MLL; project administration: MLL. All authors have read and agreed to the published version of the manuscript. All authors participated fully in the work, took public responsibility for appropriate portions of the content, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or completeness of any part of the work were appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors assert that they possess no identifiable competing financial interests or personal affiliations that may have seemingly influenced the work presented in this study.

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