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Review

# The Potential Roles of EZH2 in Regenerative Medicine

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Enhancer of zeste homolog 2 (EZH2), a catalytic component of polycomb repressive complex 2, serves as a histone methyltransferase toward histone H3K27 trimethylation and also recruits DNA methyltransferases to regulate gene expression and chromatin structure. Accumulating evidence indicates the critical roles of EZH2 in stem cell maintenance and cell fate decision in differentiation into specific cell lineages. In this article, we review the updated progress in the field and the potential application of EZH2 in regenerative medicine including nervous system, muscle, pancreas, and dental pulp regeneration.

Key words: Enhancer of zeste homolog 2 (EZH2); Stem cells; Cell lineage; Differentiation; Regenerative medicine

## INTRODUCTION

Chromatin dynamics control gene expression by the polycomb group (PcG) proteins, including two polycomb repressive complexes (PRCs), PRC1 and PRC2 (24). PRC2 binds to the promoters of its target genes and trimethylates histone H3 at lysine 27 (H3K27me3), and PRC1 maintains gene repression by recognizing the chromodomain of histone H3K27me3 to mediate ubiquitination of H2AK119 (27). Enhancer of zeste homolog 2 (EZH2), one of the core components of PRC2, contains SET domain at its carboxy-terminal region required for the methyltransferase activity toward histone H3K27me3 (2), and the stability of PRC2 is maintained by the other two core components, suppressor of zeste-12 and embryonic ectoderm development (EED) (21). In addition to the methyltransferase activity, EZH2 could also recruit DNA methyltransferases via its amino-terminal region to silence gene expression (28). Accumulating evidence demonstrates that EZH2 is critical in stem cell maintenance and lineage specification, including myogenesis, adipogenesis, osteogenesis, neurogenesis, hematopoiesis, lymphopoiesis, epidermal differentiation, and hepatogenesis (7). Here we review the updated progress in the field and the potential application of EZH2 in regenerative medicine including nervous system, muscle, pancreas, and dental pulp regeneration.

## EZH2 IN STEM CELL MAINTENANCE

Embryonic stem cells (ESCs) are pluripotent cells, which are capable of differentiation into all types of cells in adult organisms. In the embryonic stage, high levels of PcG proteins repress the early differentiation genes to maintain the pluripotency of ESCs. At the initiation of cell lineage commitment, the early differentiation marker genes are reactivated by reduction of repressive PRC2-mediated histone H3K27me3, while PcG proteins remain to occupy the late differentiation marker genes required for specific cell lineage. In the final stage, the decreased PcG proteins trigger derepression of the late differentiation marker genes in the terminally differentiated cells (23). In accordance with the high levels of PcG proteins in early embryonic stage, highly expressed EZH2 in the ESCs is required for early mouse development (18). Similarly, EZH2 is abundant in epidermal progenitor cells, but decreases upon terminal differentiation (9). The capability of EZH2

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to maintain the multipotent identity has been demonstrated in different types of adult stem cells, including muscle cell precursors (myoblasts) (3), hematopoietic stem cells (HSCs) (8), as well as neural stem cells (NSCs) (26). Overexpression of *EZH2* in HSCs keeps the repopulating potential long term to prevent HSC exhaustion after serial transplantations (16). Suppression of muscle differentiation from myoblasts by the increased EZH2 requires the histone lysine methyltransferase activity of SET domain at its carboxy-terminal region (3). While EZH2 highly expresses in undifferentiated NSCs, the expression level of EZH2 declines upon differentiation into astrocytes, which is disrupted by forced expression of *EZH2* (26). Although overexpression of *EZH2* in astrocytes induces their dedifferentiation toward NSCs, these EZH2-induced NSC-like cells are deficient in the capability of differentiation, indicating that overexpression of *EZH2* alone is insufficient for a complete dedifferentiation (25).

## THE POTENTIAL APPLICATION OF EZH2 IN REGENERATIVE MEDICINE

### *Nervous System*

The nervous system consists of different cell types, including neurons, astrocytes, oligodendrocytes, and astroglia, in which EZH2 plays different roles in their proliferation and differentiation. It has been demonstrated that knocking down of PcG protein, such as EED or EZH2, enhances neurogenesis of NSCs (10). EZH2 is required for proliferation and maintenance of polypotency in NSCs, and its expression decreases during NSC differentiation into neurons and astrocytes. However, EZH2 remains highly expressed after differentiation into an oligodendrocytic cell lineage, suggesting its role in proliferation from oligodendrocyte precursor cells to the immature (premyelinating) oligodendrocyte stage. Overexpression of *EZH2* in NSCs results in an increase in oligodendrocyte and decrease in astrocyte differentiation (26). Forced expression of *EZH2* in postnatal mouse astrocytes reduces expression of typical astrocytic genes, glial fibrillary acidic protein and S100 calcium-binding protein, but increases expression of the NSC-related genes, nestin, sex-determining region Y-box 2, musashi RNA-binding protein 1, and CD133 antigen (also known as prominin-1), leading to converting astrocytes into proliferating round neurosphere-like clusters, suggesting its role in dedifferentiation of astrocytes to NSCs (25). More recently, EZH2 has been reported to be essential for astroglial differentiation in the subventricular zone of the adult mouse through inhibition of *Ink4a* (*p16*)/*Arf* (*p19*) and *Olig2* (14). In contrast, knocking out *EZH2* results in reduction of histone H3K27me3 in cortical progenitor cells, leading to differentiation both directly into neurons and indirectly via basal progenitor cell genesis in the cerebral cortex in cerebral development of the mice (22). In addition, human mesenchymal stem cells (hMSCs) derived from bone marrow, which are easily obtained and safely expanded in vitro, can also be induced to differentiate into multiple lineages, including bone, fat, and cartilage, as well as neurons (12,13). We demonstrated that downregulated EZH2 increases the expression of type I phosphatidylinositol-4-phosphate 5-kinase- (*PIP5K1C*) gene to evoke the amounts of $PI(4,5)P_2$ and elevate intracellular $Ca^{2+}$ contents, leading to promoting neuronal differentiation from hMSCs (7). We further elucidated that Smurf2-mediated polyubiquitination at K421 on EZH2 is critical in its degradation during neuronal differentiation from hMSCs. Peroxisome proliferator-activated receptor (*PPAR*), a downstream target of EZH2, is induced in neuronal differentiation. Intracerebral implantation with *EZH2*-knocked-down hMSCs or treatment with a PPAR agonist, rosiglitazone, after implantation of hMSCs showed better improvement than those without *EZH2* knockdown or without rosiglitazone treatment after a stroke injury in the rat model (32). Taken together, these results provide the evidence for the new insight of the potential of downregulation of EZH2 in the clinical applications for neurodegenerative diseases, such as stroke. For instance, EZH2 inhibitors, such as EPZ-6438 (E7438), a selective EZH2 inhibitor in phase I/II clinical trial for advanced solid tumors or B-cell lymphomas (ClinicalTrials.gov Identifier:NCT01897571), might be used to treat stroke patients to enhance their neuron regeneration. Alternatively, intracerebral implantation of ex vivo *EZH2*-knocked down hMSCs to facilitate neuronal differentiation might be another potential strategy for treatment of stroke patients.

### *Muscle Regeneration*

EZH2 is inversely correlated to myogenesis in the development of skeletal muscle. It associates with a transcriptional regulator, YY1, and the complex recruits a histone deacetylase, HDAC1, to repress transcription of muscle-specific genes in undifferentiated myoblasts. At the induction of differentiation, the complex of YY1, EZH2, and HDAC1 dissociates from muscle loci and, subsequently, is replaced with MyoD, SRF, and histone acetyltransferases to trigger differentiation into skeletal muscle cells (SMCs) (3). In undifferentiated myoblasts, an intronic region containing the microRNA miR-214 is occupied and repressed transcription by EZH2; upon induction of differentiation, EZH2 dissociates from chromatin and recruits MyoD and myogenin, and activates miR-214 transcription, resulting in promoting differentiation into SMCs. Consequently, induced miR-214 conversely regulates *EZH2* by targeting to its 3 -UTR via a negative feedback mechanism, leading to promoting SMC differentiation (15). Abnormal expression of *EZH2* is related to muscular disorders. In Duchenne muscular dystrophy, increased amounts of TNF- from myotubes inhibits the regenerative potential of satellite cells via epigenetic silencing of the Notch-1 signaling by NF- B-stimulated

recruitment of EZH2 and DNMT3b on *Notch1* gene promoter, thereby suppressing *Notch1* expression and inhibiting SMC differentiation (1). Moreover, TNF- activates p38 kinase to phosphorylate EZH2 at threonine 372 and thus enriches the interaction between YY1 and PRC2, leading to formation of repressive chromatin on Pax7 promoter. Treatment with the antibody against TNF- stimulates proliferation of satellite cells in regenerating muscles of dystrophic or normal mice. Pharmacological inhibition or genetic knockdown of *p38α* kinase or *EZH2* might promote *Pax7* activation and expansion of satellite cells that retain their differentiation potential (20). miR-29 is a promyogenic factor that interacts with YY1 and EZH2 in PRC and directly targets to the 3 -UTR of *Ring1* and YY1-binding protein (*Rybp*), which is downregulated during myogenesis and acts as a negative regulator of skeletal myogenesis both in vitro during myoblast differentiation and in vivo in injury-induced muscle regeneration. Several myogenic loci, including miR-29 are co-occupied by Rybp and YY1 to silence their expression, thereby forming a Rybp–miR-29 feedback loop. Overexpression of Rybp enhances the enrichment or stabilization of the PRCs, including EZH2 at target myogenic loci, indicating its converse role in myogenesis (35).

*Pancreatic Regeneration*

Proliferation of -cells in pancreatic islets is an important mechanism for self-renewal and for adaptive islet expansion. EZH2 has been reported to repress *Ink4a/Arf* in -cells of pancreatic islets. Upon aging of islet -cells, declined amounts of EZH2 reduce histone H3K27me3 at *Ink4a/Arf*, leading to induction of *Ink4a/Arf* to limit -cell regeneration. Similarly, conditional deletion of *EZH2* in -cells in juvenile mice also reveals the same phenomena with increased Ink4a/Arf, leading to reduced -cell proliferation and mass, hypoinsulinemia, and mild diabetes. Streptozotocin-induced destruction of islet -cells leads to increased EZH2 expression in accordance with adaptive proliferation of -cells and reestablishment of their mass in normal mice (4). Cerulein-induced pancreatic injury also upregulates EZH2 for pancreatic tissue repair by promoting the regenerative proliferation of progenitor cells, whereas loss of EZH2 leads to impaired pancreatic regeneration (17). The inducible pancreatic -cell-specific *EZH2* transgenic mouse model reveals that transgenic expression of *EZH2* is sufficient to increase replication and regeneration of -cells in young adult mice, but not in the mice older than 8 months. The *Ink4a* locus in older mice is occupied by a trithorax group (TrxG) protein complex, which activates gene expression, and thus it prevents EZH2-mediated repression of *Ink4a*, leading to failure in adult -cell replication. Knockdown of TrxG complex components, in combination with transgenic expression of *EZH2*, overcomes the obstruction in the aged mice, leading to *Ink4a* repression and increased replication of -cells (34). Taken together, EZH2 plays an essential role in expansion and regeneration in pancreatic islets by repression of *Ink4a/Arf* in -cells.

*Dental Pulp Regeneration*

Dental pulp regeneration is limited and occurs in the early stage of pulpitis. Recently, EZH2 has been reported to be involved in regeneration of dental pulp (11). Decreased EZH2 and histone H3K27me3 and increased lysine demethylase 6B (KDM6B), a specific H3K27me3 demethylase, occurs in infected pulp tissue and human dental pulp cells (hDPCs). Inhibition of EZH2 by DZnep suppresses proliferation, inflammation response, including expression of IL-1 , IL-6, and IL-8 mRNA, and impairs adipogenic differentiation of hDPCs, and enhances alkaline phosphatase activity, osteoblast factor osterix (OSX), and bone sialoprotein (BSP) mRNA in mineralization induction of hDPCs (11).

*Osteogenesis and Adipogenesis*

Accumulating evidence indicates a reciprocal relationship between adipogenesis and osteogenesis, in which numerous molecules are involved in the switch. The osteogenic phenotype is enriched in the serum containing 1,25 dihydroxyvitamin $D_3$ [1,25$(OH)_2D_3$] but is repressed in dexamethasone-containing media, which confers osteogenic differentiation in human bone marrow cells (19). Msh homeobox 2 promotes osteogenesis by upregulation of osteoblast factor OSX but suppresses adipogenesis of multipotent mesenchymal progenitors (6). Activation of cAMP/protein kinase A promotes *PPARγ2* and lipoprotein lipase expressions to confer adipogenesis, but inhibits runt-related transcription factor 2 (*RUNX2*) and osteopontin expressions for osteogenesis by suppressing leptin levels in hMSCs (31). In contrast, melatonin promotes *RUNX2* expression to facilitate osteogenesis and simultaneously suppresses *PPARγ* expression required for adipogenesis of hMSCs (33). Inactivation of EZH2 by cyclin-dependent kinase 1-mediated phosphorylation at threonine 487 leads to osteogenesis from hMSCs (30). Dissociation of EZH2 from the promoter region of myocyte enhancer factor-2-interacting transcriptional repressor (*MITR*) gene, also named as histone deacetylase 9c (*HDAC9c*), results in induction of its expression and association with PPAR 2 in the nucleus to impair PPAR 2 activity and prevent adipogenesis and, thus, enhances osteogenic differentiation from hMSCs (5). In contrast, EZH2 promotes adipogenesis by disrupting the Wnt/ -catenin signaling through direct binding to the promoters of *Wnt* genes, such as *Wnt1*, *-6*, *-10a*, and *-10b*, to repress their expression (29).

Taken together, EZH2 inhibits osteogenic differentiation of hMSCs, whereas it promotes adipogenesis of hMSCs and inflammation, proliferation, and regeneration of pulp cells.

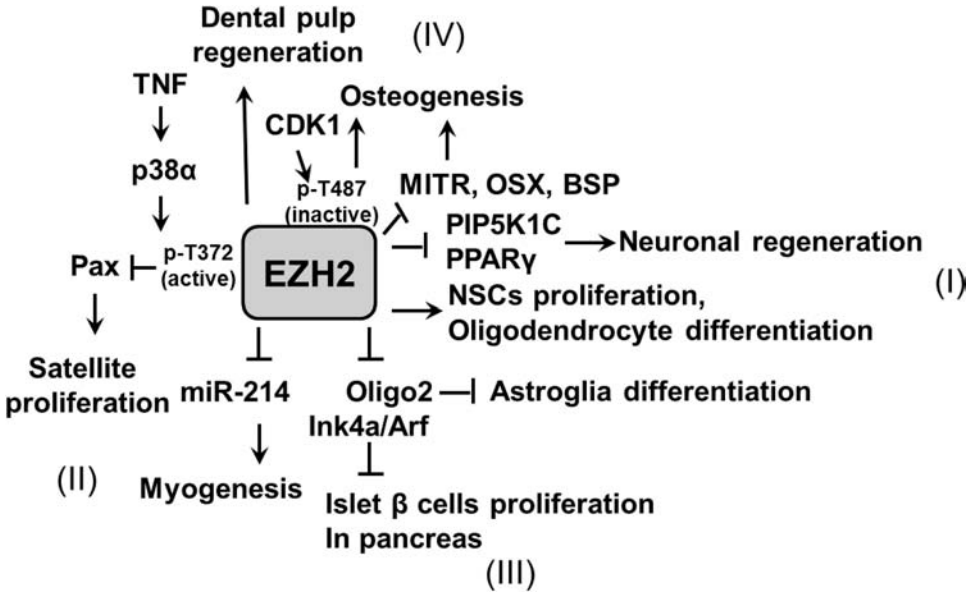


**Figure 1.** The potential roles of EZH2 in regenerative medicine. The plot illustrates the roles of EZH2 in (I) nervous system, (II) muscle, (III) pancreas, and (IV) dental pulp regeneration. The key molecules in these pathways are as indicated.

## CONCLUSION

EZH2, a catalytic component of PRC2, trimethylates histone H3K27 and also recruits DNA methyltransferases to silence specific gene expression and contributes to regulation of stem cell properties, differentiation, and regeneration. (I) EZH2 has diverse roles in the nervous system, in which EZH2 is involved in NSC proliferation and differentiation into oligodendrocytes or astroglia via suppression of *Oligo2* and *Ink4a/Arf*, whereas it negatively inhibits neuronal differentiation. (II) EZH2 prevents myogenesis via repressing the expression of miR-214. In addition, TNF- activates p38 kinase to phosphorylate EZH2 at T372, leading to inhibition of Pax7 required for proliferation of satellite cells in regenerating muscles. (III) EZH2 participates in expansion and regeneration in pancreatic islet by repression of *Ink4a/Arf* in -cells. (IV) EZH2 is also involved in dental pulp regeneration, but inhibits osteogenesis via suppression of alkaline phosphatase activity, OSX, and BSP mRNA in HDPCs (Fig. 1). To sum up, enrichment or activation of EZH2 maintains polypotency of stem cells and promotes their proliferation, and enhances islet -cells and dental pulp regeneration, and differentiation into oligodendrocytes and adipocytes. In contrast, pharmacological inhibition or genetic knockdown of EZH2 might have potential in neuronal, myogenic, and osteogenic regeneration. Therefore, modulation of EZH2 amounts or activity is critical in regenerative medicine.

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