



The Epigenetic Regulation of Quiescent in Stem Cells

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Glob Med Genet 2023;10:339–344.

Abstract

This review article discusses the epigenetic regulation of quiescent stem cells. Quiescent stem cells are a rare population of stem cells that remain in a state of cell cycle arrest until activated to proliferate and differentiate. The molecular signature of quiescent stem cells is characterized by unique epigenetic modifications, including histone modifications and deoxyribonucleic acid (DNA) methylation. These modifications play critical roles in regulating stem cell behavior, including maintenance of quiescence, proliferation, and differentiation. The article specifically focuses on the role of histone modifications and DNA methylation in quiescent stem cells, and how these modifications can be dynamically regulated by environmental cues. The future perspectives of quiescent stem cell research are also discussed, including their potential for tissue repair and regeneration, their role in aging and age-related diseases, and their implications for cancer research. Overall, this review provides a comprehensive overview of the epigenetic regulation of quiescent stem cells and highlights the potential of this research for the development of new therapies in regenerative medicine, aging research, and cancer biology.

Keywords

- ▶ epigenetic regulation
- ▶ quiescent stem cells
- ▶ histone modifications
- ▶ DNA methylation
- ▶ molecular signature
- ▶ environmental cues
- ▶ tissue repair

Introducing Quiescent Stem Cells

Stem cells are cells that have the ability to self-renew and differentiate into different cell types. They are critical for the maintenance and repair of various tissues in the body. One unique characteristic of stem cells is their ability to enter a state of quiescence, or a dormant state, in which they stop actively dividing and remain in a state of inactivity until activated to differentiate.^{1–3} Quiescence is a highly regulated and reversible state, and it plays an important role in the maintenance of stem cell pools in different tissues. Quiescent stem cells have been identified in many different tissues, including the hematopoietic system, the intestinal epithelium, and the skin.^{4,5} The ability of stem cells to enter and exit quiescence is critical for their function. For example, in the hematopoietic system, quiescent hematopoietic stem cells (HSCs) are responsible for the long-term maintenance of

blood cell production. When the demand for blood cells increases, quiescent HSCs can be activated to differentiate and produce more blood cells.^{6,7} Quiescent stem cells are also thought to play a role in protecting stem cells from damage and preventing the accumulation of deoxyribonucleic acid (DNA) mutations. By entering a dormant state, stem cells can reduce the risk of acquiring DNA damage during cell division.⁸ The regulation of stem cell quiescence is a complex process that involves many different factors, including signaling pathways, epigenetic modifications, and metabolic pathways. Understanding the mechanisms that regulate quiescence in stem cells is critical for the development of strategies to manipulate stem cell behavior for therapeutic purposes.⁹

Quiescence is an important state for stem cells, which allows them to maintain their stem cell properties and respond to changing physiological demands. Further

DOI <https://doi.org/10.1055/s-0043-1777072>.
ISSN 2699-9404.

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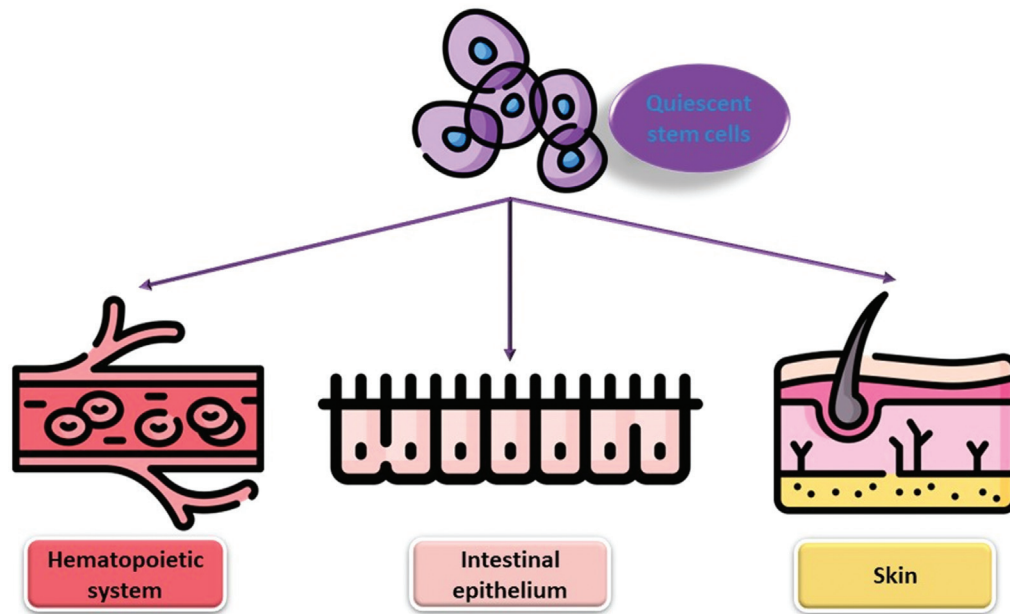


Figure 1. Presence of quiescent stem cells in many different tissues, including the hematopoietic system, the intestinal epithelium, and the skin.

research into the regulation of quiescence in stem cells will be essential for the development of new therapies for a range of diseases and conditions (► **Fig. 1**).

Molecular Signature of Quiescent Stem Cells

Quiescent stem cells are a unique and important population of cells that play a critical role in tissue maintenance and regeneration. These cells have been found to have a distinct molecular signature that sets them apart from other stem cell populations.^{10,11} One of the hallmarks of quiescent stem cells is their ability to enter a dormant state, in which they stop dividing and remain inactive until they are needed for tissue repair or regeneration. This state of quiescence is maintained by a complex network of signaling pathways, epigenetic modifications, and metabolic processes that work together to regulate stem cell behavior.^{12,13} At the molecular level, quiescent stem cells have been found to exhibit unique gene expression patterns compared with other stem cell populations. For example, a study of quiescent HSCs found that they express high levels of genes involved in cell cycle arrest and DNA repair, while genes associated with cell proliferation and differentiation were downregulated.^{11,14} In addition to gene expression changes, quiescent stem cells also exhibit epigenetic modifications that help to regulate their behavior. For example, quiescent HSCs have been found to have high levels of DNA methylation, which is thought to contribute to the maintenance of their stem cell properties.^{15,16} Another important aspect of the molecular signature of quiescent stem cells is their metabolic profile. Quiescent stem cells have been found to have lower rates of metabolism compared with proliferating cells, which may help to protect them from oxidative stress and DNA damage.¹⁷

Overall, the molecular signature of quiescent stem cells is a complex and highly regulated network of gene expression, epigenetic modifications, and metabolic processes that work together to regulate stem cell behavior. Understanding the molecular mechanisms that govern quiescence in stem cells is critical for the development of new therapies for a range of diseases and conditions (► **Fig. 2**).

Epigenetics Modifications in Quiescent Stem Cells

Epigenetic modifications play a critical role in regulating the behavior of quiescent stem cells. These modifications refer to changes in gene expression that occur without changes to the underlying DNA sequence, and they can be influenced by a variety of environmental factors.¹⁸ One of the most well-studied epigenetic modifications in quiescent stem cells is DNA methylation. This modification involves the addition of a methyl group to cytosine residues in the DNA, which can lead to changes in gene expression.¹⁹ In quiescent stem cells, DNA methylation has been found to be important for the maintenance of stem cell properties and the regulation of cell cycle progression.²⁰ For example, DNA methylation has been shown to regulate the expression of key cell cycle regulators such as cyclin D and p21, which are important for the transition from quiescence to proliferation.²¹ Another important epigenetic modification in quiescent stem cells is histone modification. Histones are proteins that help to package DNA into chromatin, and modifications to these proteins can influence gene expression.²² In quiescent stem cells, histone modifications have been found to play a critical role in the maintenance of stem cell properties and the regulation of differentiation. For example, histone acetylation has been shown to promote the expression of stem cell

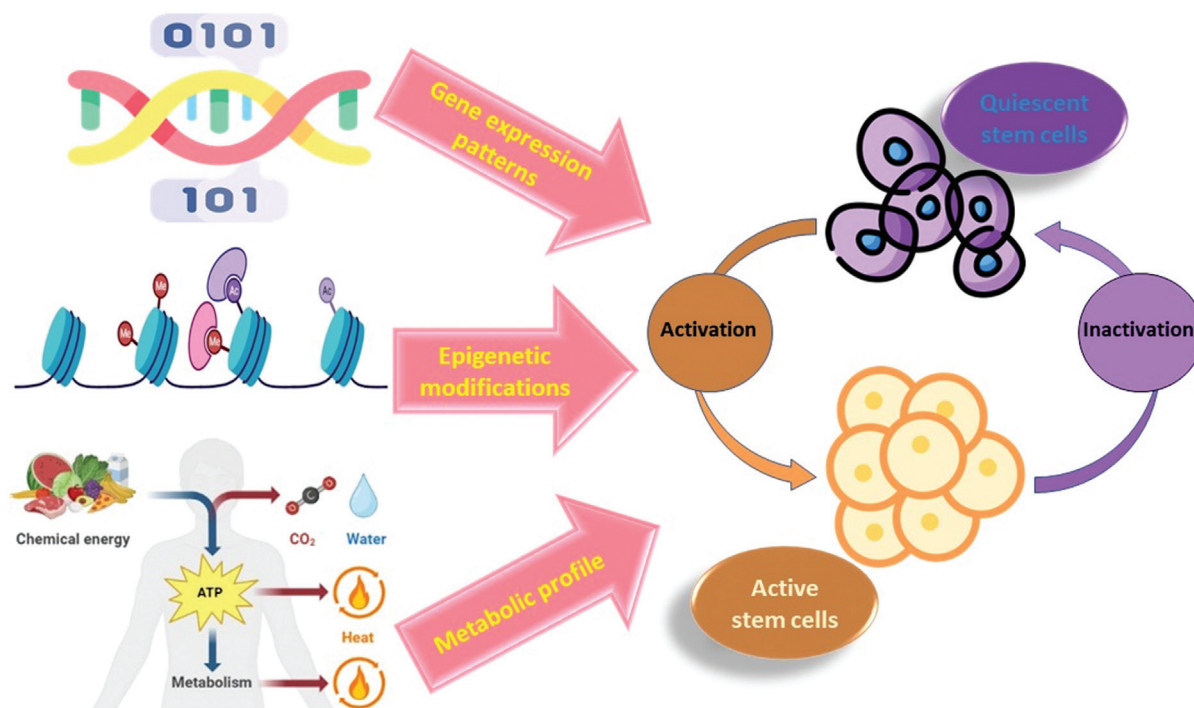


Figure 2. Molecular signature of quiescent stem cells. Quiescent stem cells have been found to exhibit unique gene expression patterns, epigenetics modifications and metabolic profile compared to other stem cell populations.

genes, while histone deacetylation can promote differentiation.^{23,24} In addition to DNA methylation and histone modification, other epigenetic modifications such as chromatin remodeling and noncoding RNA regulation have also been found to be important in regulating quiescent stem cell behavior. These modifications can influence gene expression and help to maintain stem cell properties, as well as regulate the transition from quiescence to proliferation.^{9,25}

Epigenetic modifications play a critical role in regulating the behavior of quiescent stem cells. Understanding the mechanisms that govern these modifications will be essential for the development of new therapies that target quiescent stem cells for tissue repair and regeneration (► Fig. 3).

Histone Modifications

Histone modifications are critical epigenetic regulators of gene expression in quiescent stem cells. In quiescent cells, histone modifications help to maintain stem cell properties and regulate the transition from quiescence to proliferation.^{26,27} Studies have shown that histone modifications such as acetylation, methylation, and phosphorylation play important roles in quiescent stem cells. For example, histone acetylation has been found to be important for maintaining the self-renewal capacity of HSCs.²⁸ In contrast, histone deacetylation has been shown to promote differentiation in neural stem cells.²⁹ Histone methylation has also been implicated in the regulation of quiescent stem cells. For example, the methylation of histone H3K4 has been shown to be important for maintaining the quiescent state of HSCs.³⁰ Similarly, the methylation of histone H3K27 has

been found to play a critical role in regulating the transition from quiescence to proliferation in neural stem cells.³¹ In addition to acetylation and methylation, histone phosphorylation has also been shown to play a role in quiescent stem cells. For example, the phosphorylation of histone H3 at serine 10 has been found to be important for the transition of quiescent HSCs to an active state.³²

Histone modifications are important regulators of gene expression in quiescent stem cells. Understanding the specific mechanisms by which these modifications regulate stem cell behavior will be critical for the development of new therapies for tissue repair and regeneration.

Chromatin Remodeling

Chromatin remodeling is an important process in the regulation of gene expression in quiescent stem cells. Chromatin remodeling involves the physical reorganization of chromatin structure, which can influence the accessibility of DNA to transcription factors and other regulatory proteins.³³ In quiescent stem cells, chromatin remodeling plays a critical role in maintaining stem cell properties and regulating the transition from quiescence to proliferation.³⁴ For example, studies have shown that the adenosine triphosphate-dependent chromatin remodeling complex SWI/SNF is important for the maintenance of HSC quiescence.³⁵ SWI/SNF regulates the accessibility of DNA by altering chromatin structure, which in turn affects the binding of transcription factors to DNA.³⁶ Similarly, the polycomb group (PcG) proteins have been implicated in the regulation of chromatin structure in quiescent stem cells. PcG proteins are involved in the

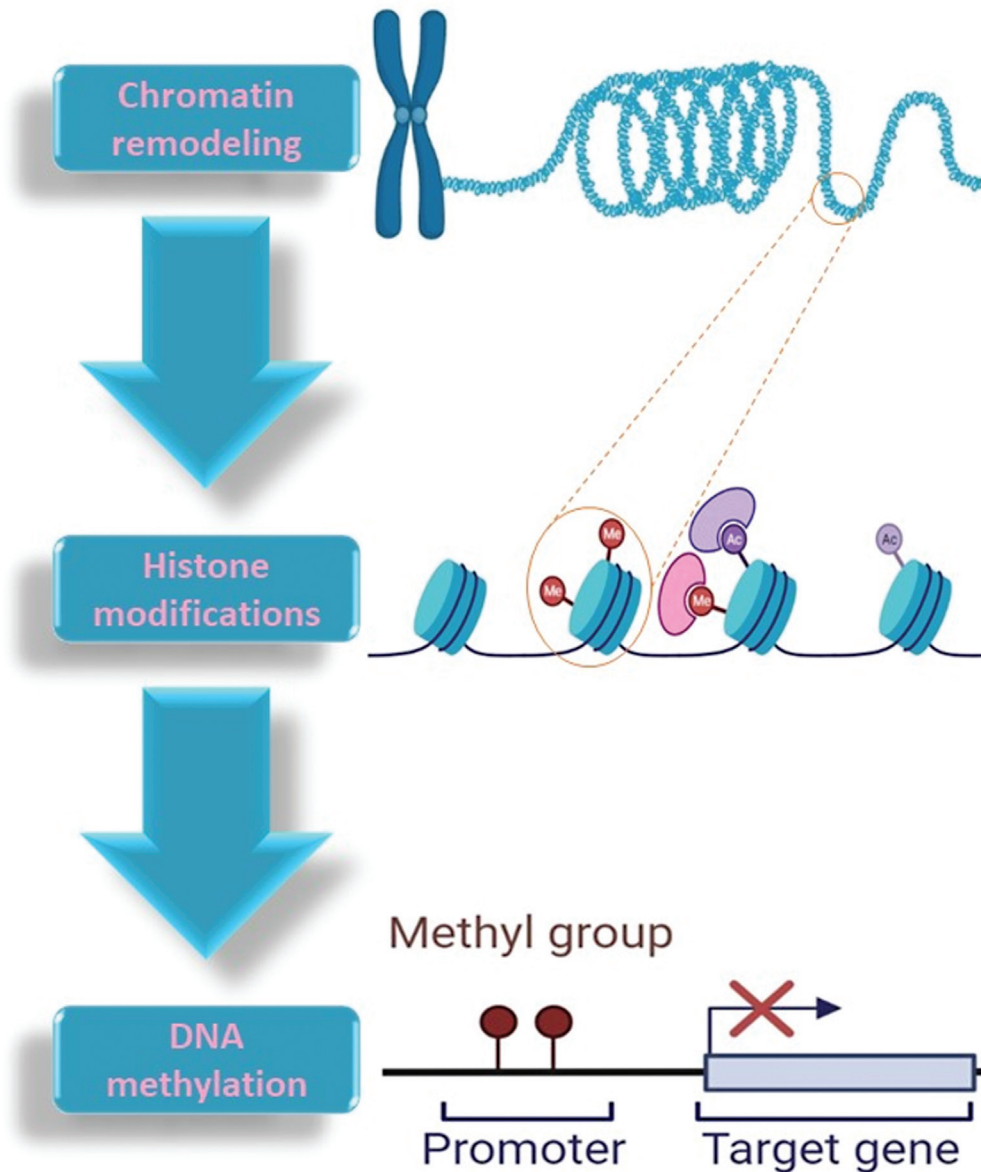


Figure 3. Epigenetic modifications play a critical role in regulating the behavior of quiescent stem cells.

formation of repressive chromatin structures, which can regulate gene expression by inhibiting the accessibility of DNA to transcription factors.³⁷ Studies have shown that PcG proteins play an important role in the maintenance of quiescence in HSCs and neural stem cells.³⁸ In addition to SWI/SNF and PcG proteins, other chromatin remodeling complexes have also been implicated in the regulation of quiescent stem cells. For example, the nucleosome remodeling and deacetylase (NuRD) complex has been found to play a role in the maintenance of quiescence in HSCs.³⁹

Chromatin remodeling is an important mechanism for regulating gene expression in quiescent stem cells. Understanding the specific mechanisms by which chromatin remodeling complexes regulate stem cell behavior will be critical for the development of new therapies for tissue repair and regeneration.

DNA Methylation

DNA methylation is a critical epigenetic modification that regulates gene expression in quiescent stem cells. DNA methylation involves the addition of a methyl group to the cytosine residues of DNA, usually in the context of a CpG dinucleotide. This modification can influence gene expression by altering the accessibility of DNA to transcription factors and other regulatory proteins.^{40,41} In quiescent stem cells, DNA methylation plays an important role in regulating stem cell properties and the transition from quiescence to proliferation.²⁷ For example, studies have shown that DNA methylation is critical for the maintenance of HSC quiescence. Loss of DNA methylation leads to the activation of genes that promote proliferation, leading to a loss of stem cell self-renewal capacity.^{20,42} To the maintenance of quiescence,

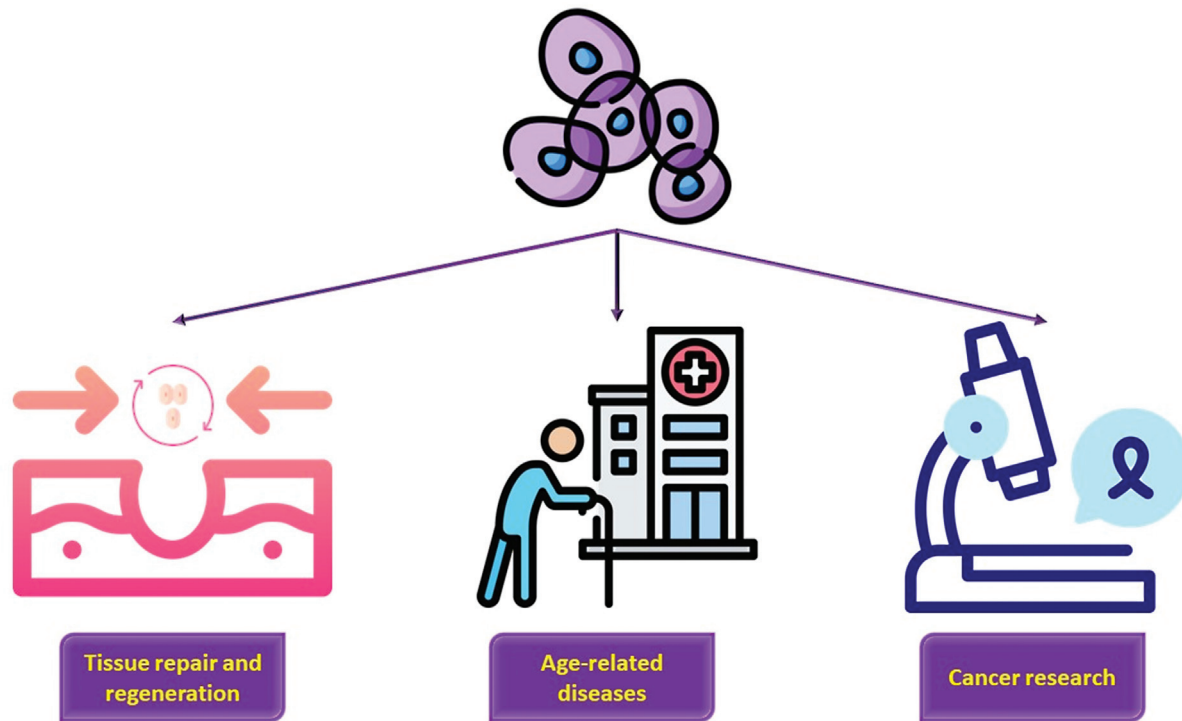


Figure 4. The study of quiescent stem cells has broad implications for regenerative medicine, aging research, and cancer biology.

DNA methylation also plays a role in regulating stem cell differentiation. Studies have shown that DNA methylation patterns are dynamically regulated during the differentiation of stem cells into different cell types.⁴³ Interestingly, recent studies have shown that DNA methylation patterns in quiescent stem cells are not static, but rather can be dynamically regulated by environmental cues. For example, changes in nutrient availability or exposure to toxins can alter DNA methylation patterns in HSCs, leading to changes in stem cell behavior.^{44,45}

Overall, DNA methylation is an important regulator of gene expression in quiescent stem cells. Understanding the specific mechanisms by which DNA methylation regulates stem cell behavior will be critical for the development of new therapies for tissue repair and regeneration.

Future Perspective

The study of quiescent stem cells is a rapidly developing field with exciting future perspectives. One area of research that holds great promise is the development of new therapies for tissue repair and regeneration. Quiescent stem cells have the potential to differentiate into a variety of cell types, making them ideal candidates for cell-based therapies to treat a wide range of diseases and injuries. One challenge in the field of quiescent stem cells is the development of methods to activate quiescent stem cells and promote their proliferation and differentiation. A better understanding of the epigenetic modifications and signaling pathways that regulate quiescence and activation will be critical for developing such methods. Another area of research with future perspectives

is the role of quiescent stem cells in aging and age-related diseases. Aging is associated with a decline in stem cell function and a decrease in the number of quiescent stem cells. Understanding the mechanisms that regulate stem cell quiescence and how these mechanisms are disrupted with age may lead to new therapies to improve stem cell function in aging populations. The study of quiescent stem cells also has implications for cancer research. Quiescent cancer stem cells have been implicated in tumor recurrence and resistance to chemotherapy. Understanding the mechanisms that regulate quiescence in cancer stem cells may lead to the development of new therapies to target these cells and improve cancer treatment outcomes.

The study of quiescent stem cells has broad implications for regenerative medicine, aging research, and cancer biology. Continued research in this field will undoubtedly lead to new insights and developments that have the potential to transform medicine and improve human health (►Fig. 4).

Conflict of Interest

None declared.

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