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Molecular Mechanisms of Stem Cell Aging and Their Challenges and Applications in Regenerative Medicine

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Abstract: Stem cell aging is a complex biological process characterized by diminished self-renewal capacity and impaired differentiation potential, directly contributing to decreased tissue regeneration and age-related diseases. This review systematically examines the molecular mechanisms underlying stem cell aging, including telomere shortening, DNA damage accumulation, metabolic imbalance, mitochondrial dysfunction, epigenetic modifications, and inflammatory responses. These interconnected mechanisms form a complex regulatory network driving stem cell functional decline. The challenges posed by stem cell aging to regenerative medicine are substantial: aging reduces tissue regenerative capacity across hematopoietic, neural, and muscular systems, limits the efficacy of stem cell transplantation due to poor survival rates and altered differentiation bias, and increases the risk of malignant transformation. To address these challenges, researchers have developed various intervention strategies, including cell reprogramming technology, gene editing approaches, metabolic regulation, antioxidant therapies, exosome applications, and microenvironment optimization. While significant progress has been made, challenges remain, particularly regarding off-target effects in gene editing, dose-dependent toxicity in metabolic regulation, and standardization issues in exosome production. Future research directions include developing aging-specific biomarkers for precision intervention, analyzing tissue-specific aging mechanisms, and exploring metabolism-epigenetic-immunity regulatory networks. The advancement of stem cell aging intervention has profound implications for both regenerative medicine and anti-aging therapies, offering promising approaches to address age-related diseases and improve quality of life.

Keywords: Stem Cell Aging, Regenerative Medicine, Epigenetic Modifications, Cell Reprogramming, Mitochondrial Dysfunction

1. Introduction

Stem cells maintain tissue homeostasis and repair damage through self-renewal and multi-directional differentiation capabilities [1]. With aging, the number of stem cells decreases and their ability to proliferate and differentiate declines, directly leading to decreased tissue regeneration capacity and the development of aging-related diseases [2]. Studies show that only about 10% of the hematopoietic stem cell pool remains youthful in 70-year-old individuals [3].

Stem cell aging research importance is reflected in two levels: First, uncovering mechanisms of stem cell aging elucidates the biological nature of organismal aging; Second, from an application perspective, it offers targets for developing anti-aging therapies [4].

Stem cell aging involves multi-level regulatory mechanisms including telomere shortening, DNA damage accumulation, metabolic imbalance, mitochondrial dysfunction, epigenetic modification changes, and inflammatory responses. These mechanisms interact closely, forming a complex regulatory network driving stem cell functional decline.

Aging poses multiple challenges to regenerative medicine: reduced tissue regeneration capacity, limited therapeutic efficacy of aged stem cell transplantation, and altered tissue microenvironment unfavorable for transplanted cells. Researchers have developed various strategies to address these challenges, including cell reprogramming, gene editing technologies, metabolic regulation, antioxidant strategies, exosome applications, and microenvironment optimization.

2. Molecular Mechanisms of Stem Cell Aging

2.1. Telomere Shortening and DNA Damage

Telomere shortening is considered a central hallmark of replicative cellular senescence. Loss of telomerase activity leads to persistent activation of the DNA damage response (DDR), triggering p53/p21 pathway-dependent cell cycle arrest [5]. Studies show that telomere abnormalities in bone marrow mesenchymal stem cells (BMSCs) act synergistically with oxidative stress to accelerate mitochondrial DNA mutations [6]. Genome-wide analyses have revealed a 3-5-fold increase in γ-H2AX foci in senescent stem cells, indicating declined DNA repair capacity [7].

DNA damage extends throughout the genome, particularly affecting transcriptionally active gene regions, and promotes formation of senescence-associated secretory phenotype (SASP) by activating inflammatory signaling pathways.

2.2. Metabolic Imbalance and Mitochondrial Dysfunction

Senescent stem cells exhibit "metabolic rigidity": glycolysis is enhanced but oxidative phosphorylation is less efficient, resulting in 40-60% reduction in ATP production [8]. Defects in mitophagy lead to accumulation of damaged mitochondria, while elevated reactive oxygen species (ROS) induce mitochondrial DNA mutations [9]. Decreased SIRT3 deacetylase activity exacerbates this process, while NAD+ precursor supplementation partially restores metabolic homeostasis [10].

Mitochondrial dynamic imbalance affects stem cell energy allocation and metabolic reprogramming capacity. Metabolic imbalance also influences key epigenetic modifications, forming a metabolism-epigenetic regulatory network amplifying aging effects.

2.3. Epigenetic Modification Changes

Co-existence of genome-wide DNA hypomethylation and local hypermethylation is typical in senescent stem cells, with hypermethylation of Oct4 and Nanog promoters leading to loss of pluripotency [11]. Regarding histone modifications, upregulation of H3K27me3 in senescent MSCs inhibits pro-regenerative pathways such as Wnt/β-catenin [4].

Single-cell sequencing revealed senescent hematopoietic stem cells exhibit clonally dominant epigenetic drift, potentially associated with DNMT3A mutations [3]. Additionally, alterations in non-coding RNA expression profiles represent important features of stem cell aging, such as upregulation of lncRNA NEAT1 promoting autophagy abnormalities in aged MSCs.

2.4. Inflammation and Immune Aging

The senescence-associated secretory phenotype (SASP) releases inflammatory factors such as IL-6 and TGF-β, inducing senescence in neighboring stem cells through paracrine effects [12]. Thymic degeneration leads to reduced naïve T cells, while mitochondrial fragmentation in senescent T cells exacerbates proinflammatory cytokine storms, creating an "inflammaging" microenvironment [13].

Clinical data show plasma IL-6 levels are 2-3-fold elevated in older individuals compared to youth, positively correlating with stem cell transplant failure rates [14]. Aging of the innate immune system, including abnormal macrophage polarization and weakened natural killer cell function, aggravates the inflammatory state of the stem cell microenvironment.

3. Challenges of Stem Cell Aging for Regenerative Medicine

3.1. Decreased Tissue Regenerative Capacity

Hematopoietic stem cell aging leads to reduced erythropoiesis and immune cell dysfunction, with 4-fold increased anemia incidence in people over 60 [3]. Reduced SIRT1 expression in neural stem cells decreases hippocampal neurogenesis by 50%, correlating with cognitive decline [15].

Deletion of skeletal muscle satellite cell mitochondrial fusion protein MFN2 leads to delayed muscle regeneration, with muscle strength decreasing 30-40% in older individuals [16]. Aged satellite cells exhibit weakened activation capacity, prolonged proliferation cycles, and abnormal differentiation.

The decline in tissue regenerative capacity affects multiple systems. For example, the relationship between hematopoietic stem cells and bone marrow mesenchymal stem cells is disrupted during aging, leading to overall functional decline in the bone marrow microenvironment.

3.2. Limitations of Stem Cell Transplantation Therapy

Senescent mesenchymal stem cells have less than 10% survival rate after transplantation (compared with 60% for young cells) and tend to differentiate into adipocytes rather than osteoblast [17]. This low survival rate results from poor adaptation to hypoxic environments, abnormal expression of adhesion molecules, and altered secretory functions preventing effective microenvironment remodeling.

Hematopoietic stem cells with shortened telomeres have 5-fold increased risk of clonal hematopoiesis after transplantation, with significantly higher leukemia incidence in those carrying DNMT3A or TET2 mutations [18]. Genomic and epigenomic instability in senescent stem cells increases tumor risk. For every 10-year increase in donor age, the recipient's 5-year survival rate decreases by approximately 5%.

Proteases like MMP9 secreted by senescent cells degrade extracellular matrix, affecting transplanted cell engraftment [19]. Communication barriers between senescent stem cells and recipient tissue cells lead to poor integration, limiting long-term therapeutic effects.

Senescent stem cells exhibit increased risk of immune rejection due to altered surface antigen expression patterns and reduced immunomodulatory capacity. Clinical research shows allogeneic transplantation using elderly donors' stem cells requires stronger immunosuppressive therapy, with increased graft-versus-host disease incidence.

4. Strategies for Addressing Stem Cell Aging

4.1. Cell Reprogramming and Gene Editing

Induced Pluripotent Stem Cells (iPSCs) technology can reset epigenetic age through OSKM factors, although complete reprogramming may increase cancer risk by 20% [20]. Partial reprogramming (short-term, cyclic expression of OSKM factors) can eliminate cellular senescence markers without affecting cell identity. Preclinical studies show partially reprogrammed stem cells exhibit 45% increased tissue regenerative capacity after transplantation, with 60% reduced inflammatory response.

CRISPR-mediated activation of the TERC gene can lengthen telomeres in human MSCs by 1.5kb, restoring proliferative capacity to youthful levels [4]. Gene editing technologies target p16INK4a or p21CIP1 to break the senescence barrier and repair mitochondrial DNA mutations or abnormal epigenetic modifications [21]. New base editing and prime editing technologies have reduced off-target risks and improved precision.

Improvements in gene therapy vectors have facilitated clinical translation. Adeno-associated virus (AAV) and lipid nanoparticle (LNP) delivery systems enhance gene editing efficiency while reducing immunogenicity. Combining single-cell sequencing and AI algorithms allows prediction of individual stem cell aging trajectories and design of personalized gene editing protocols.

4.2. Metabolic Regulation and Antioxidant Strategies

Nicotinamide mononucleotide (NMN) supplementation restored NAD+ levels by 80% in aged mice hematopoietic stem cells, with 3-fold increase in post-transplantation reconstruction efficiency [10]. NAD+ regulates mitochondrial biogenesis and autophagy through activation of Sirtuins family proteins. Clinical studies indicate NMN and nicotinamide riboside (NR) supplementation improves mitochondrial function and reduces oxidative stress in elderly individuals.

SIRT1 activator SRT1720 enhances mitophagy in senescent neural stem cells, reducing ROS levels by 60% [15]. Dietary strategies like intermittent fasting and caloric restriction improve stem cell metabolic function through regulating mitochondrial dynamics and autophagy via AMPK-mTOR signaling. Second-generation mTOR inhibitors (rapalogues) selectively inhibit mTORC1 rather than mTORC2, reducing adverse reactions.

Since moderate ROS levels are crucial for maintaining stem cell self-renewal and differentiation balance, mitochondria-targeted antioxidants (MitoQ, SS-31) are superior to whole-cell antioxidants, selectively eliminating mitochondria-derived ROS while preserving cytoplasmic ROS signaling. Combined use of mitochondria-targeted antioxidants and NAD+ precursors produces synergistic effects.

4.3. Exosomes and Microenvironment Optimization

Young MSCs-derived exosomes enriched with miR-21-5p and TSG101 inhibit the p53 pathway and repair mitochondrial membrane potential, increasing proliferative capacity of senescent cells by 50% [22]. Exosomes transfer anti-aging miRNAs, proteins, functional mitochondria, and epigenetic regulatory factors. Research found miR-146a in young stem cell exosomes suppresses inflammatory responses, miR-133b promotes neural regeneration, and let-7 regulates metabolic reprogramming.

Three-dimensional hydrogel scaffolds loaded with VEGF and FGF2 mimic youthful ecological niches, promoting vascularization and colonization of grafted stem cells [17]. Modified polyethylene glycol-hyaluronic acid hydrogels significantly improve autologous stem cell transplantation efficiency in elderly patients. Pretreatment of elderly donor stem cells in biomimetic youthful microenvironments for 24-48 hours can temporarily reverse their epigenetic age.

Preclinical studies demonstrated combining exosomes with scaffolding materials improves cardiac function recovery from 25% to 65% in myocardial infarction models [22]. The latest "extracellular matrix-exosome-bioactive factor" triple delivery system shows excellent therapeutic efficacy across various disease models.

Selective clearance of senescent cells using senolytic agents (dasatinib combined with quercetin) significantly improves the tissue microenvironment, reducing inflammatory factor levels and creating favorable conditions for stem cell functional recovery.

5. Conclusion

Stem cell aging is driven by multiple factors including telomere shortening, DNA damage accumulation, metabolic imbalance, epigenetic dysregulation, and inflammatory microenvironment [18]. These mechanisms form an aging cascade effect leading to stem cell functional decline and impaired tissue regenerative capacity.

Stem cell aging poses significant challenges to regenerative medicine through reduced tissue regeneration capacity and limitations in transplantation therapy. As global population aging accelerates, understanding stem cell aging mechanisms and developing effective intervention strategies have significant scientific value and social importance.

Intervention strategies targeting stem cell aging show remarkable progress, including cell reprogramming, gene editing, metabolic regulation, antioxidant strategies, exosomes, and microenvironment optimization. However, challenges remain, including off-target effects in gene editing, dose-dependent toxicity in metabolic regulation, and standardization issues in exosome production [23].

Future research directions include developing aging-specific biomarkers for precision intervention, analyzing heterogeneous mechanisms of aging in different tissue stem cells, and exploring the "metabolism-epigenetic-immunity" inter-regulatory network [15]. Advanced technologies such as single-cell multi-omics, in vivo lineage tracing, and AI-assisted drug design will accelerate research progress.

Stem cell aging research contributes to understanding fundamental principles of organismal aging and provides new approaches for addressing aging-related diseases. Through integration of basic research and clinical applications, stem cell aging intervention will become an important intersection between regenerative medicine and anti-aging medicine, contributing to healthy aging and quality of life improvement.

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