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Review

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Age-related declines in stem cell function: Molecular insights and future therapies

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Abstract

Stem cells are fundamental units that support tissue homeostasis throughout life, thus, progressive loss of function with aging would result in defective maintenance and regeneration of tissues, which in turn increases vulnerability to age-associated diseases. This review summarizes the potential contributors such as telomere shortening, DNA damage accumulation, epigenetic changes and mitochondrial dysfunction to age-associated defects in stem cell function. We discuss the interactions of these intrinsic factors with changes in the stem cell niche, including blood-derived inflammatory signals and changes in the extracellular matrix that contribute to stem cell exhaustion. Despite this local accessibility and its known role in regeneration, our knowledge about the age-related loss of tissue-specific regenerative potential is limited largely to age-related changes in specific stem cell populations, including hematopoietic, mesenchymal, neural, muscle satellite and intestinal stem cells, and highlights the potential for tissue-specific regenerative impediments. Further, new therapeutic strategies against stem cell exhaustion are discussed, such as caloric restriction, genetic and epigenetic reprogramming, senolytics, stem cell transplantation, and mitochondrial-targeted therapies. It also discusses challenges in tumorigenesis, immune rejection, and long-term efficacy. The review then ends with a reminder of the importance of ongoing studies for generating applicable treatments to prolong healthy life and promote regenerative responses. The present extensive synthesis is intended to assist further regenerative medicine efforts by presenting the most promising therapies to counteract aging effects on stem cells.

Keywords: stem cells, cell aging, mitochondrial dysfunction, epigenetics

1. Introduction

1.1. Overview of stem cells

Stem cells are specialized cells found in most adult mammalian tissues that play a crucial role in maintaining tissue homeostasis and facilitating tissue repair and regeneration in response to damage (1). These cells are characterized by their ability to self-renew and differentiate into various cell types, although they make up only a small fraction of the total cells within any tissue (2). Their identification and study have been a challenge, but recent advances have led to the discovery of molecular markers that allow for the isolation of tissue-specific stem cells (3). This has opened new avenues for research into the molecular mechanisms governing stem cell behavior, including multipotentiality and self-renewal. Additionally, the development of stem cell–based therapies hold significant promise for regenerative medicine. Stem cells reside within specialized microenvironments, or niches, which regulate their activity (4). These niches are composed of various elements such as the extracellular matrix, neighboring cells, and locally secreted soluble factors. Importantly, these niches, and the systemic milieu that influences them, dynamically adapt to regulate stem cell function, especially with regard to aging(5). This review explores what is known about the aging process in several key stem cell populations, including hematopoietic stem cells (HSCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), intestinal stem cells (ISCs), satellite cells (Muscle stem cells), EpSCs and neural stem cells (NSCs) (Fig. 1) (6). We examine the changes that occur in stem cell number and function with age, explore the factors that make stem cells susceptible or resistant to aging, and evaluate the extent to which stem cell dysfunction contributes to overall aging processes (7). Stem cell aging reveals age-related declines in stem cell populations. Studies on serial transplantations show that while stem cells can pass through multiple recipients, their regenerative capacity diminishes after a few passages (8). Donor stem cells become less competitive over time, and even in primary transplants, stem cells recover to only a fraction of their original numbers (9). This decline might be influenced by extrinsic factors such as the bone marrow environment, but still points to limitations in stem cell self-renewal with age (10).

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Age-related changes in stem cell populations significantly affect their function and regenerative capacity (11). HSCs, while capable of serial transplantation, exhibit limitations in longevity, typically sustaining only five passages (12). Over time, host stem cells gain a competitive advantage over transplanted donor cells, leading to diminished hematopoietic function (13). This limitation may arise from transplant-related manipulations, not reduced stem cell potency. Aged stem cells show higher apoptosis rates due to accumulated cellular damage, which hampers their self-renewal and differentiation (14). The efficiency of stem cells homing to their marrow environment also declines with age. Despite apoptosis being a crucial regulatory mechanism for stem cell populations, targeting it might improve aging outcomes (15). Studies involving genetically modified mice show that preventing apoptosis can increase stem cell numbers and enhance engraftment. Stem cell migration plays a role in normal hematopoiesis, as evidenced by cross-engraftment in conjoined mice (16).

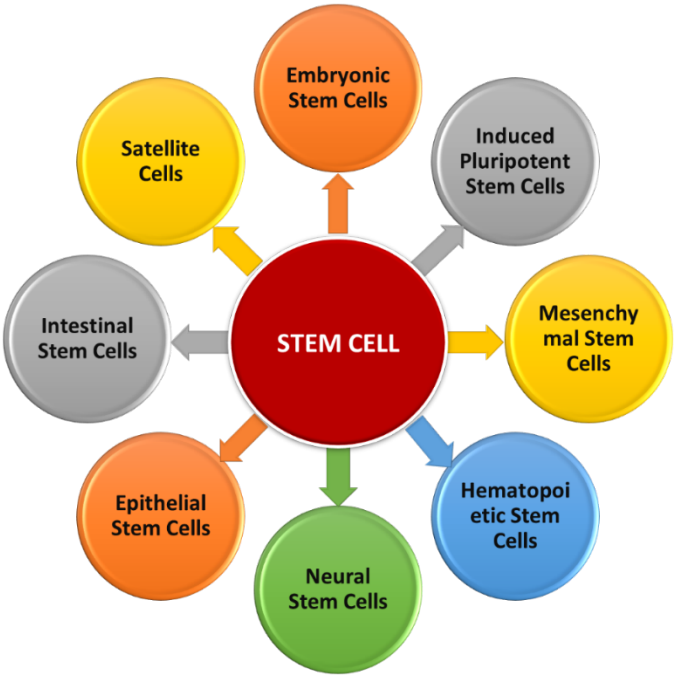

Fig. 1. Different types of stem cells

ESCs, derived from the inner cell mass of blastocysts, serve as a gold standard for pluripotency and self-renewal. While their direct therapeutic application remains limited due to ethical concerns and risks of teratoma formation, ESCs provide invaluable models for studying the molecular pathways governing cellular aging (17). Comparative studies between ESCs and aged somatic cells have revealed critical differences in DNA repair mechanisms, epigenetic regulation, and mitochondrial function that contribute to age-related cellular deterioration (18).

iPSCs have emerged as a revolutionary alternative, offering patient-specific models of aging and regeneration. By reprogramming somatic cells using Yamanaka factors (OCT4, SOX2, KLF4, c-MYC), iPSCs reset the aging clock, providing insights into cellular rejuvenation (19). However, recent studies show that iPSCs derived from aged donors may retain epigenetic memories of aging, limiting their functionality. Current research focuses on optimizing reprogramming techniques to generate "younger" iPSCs for autologous therapies in age-related diseases, such as Parkinson's and cardiovascular disorders (20).

MSCs found in bone marrow, adipose tissue, and umbilical cord, play a pivotal role in tissue maintenance and immune modulation. With advancing age, MSCs exhibit reduced proliferative capacity, increased senescence-associated secretory phenotype (SASP), and skewed differentiation potential—often favoring adipogenesis over osteogenesis (21). This shift contributes to age-related conditions like osteoporosis and sarcopenia. Strategies to rejuvenate aged MSCs, including mitochondrial transfer, senolytic drugs, and exosome-based therapies, are under investigation to restore their regenerative potential (22).

In the nervous system, NSCs residing in the subventricular zone and hippocampus sustain neurogenesis throughout life. Aging leads to a dramatic decline in NSC proliferation and differentiation, resulting in diminished cognitive plasticity and increased vulnerability to neurodegenerative diseases like Alzheimer's (23). Key factors implicated in NSC aging include accumulated DNA damage, dysregulated Wnt/β-catenin signaling, and chronic inflammation. Interventions such as exercise, caloric restriction, and pharmacological activation of neurogenic pathways show promise in mitigating these declines (24).

EpSCs are critical for maintaining the skin and other barrier tissues, undergo functional attrition with age. Reduced self-renewal capacity, coupled with impaired wound healing, leads to thinning epidermis, chronic ulcers, and increased susceptibility to infections (25). Similarly, ISCs located in the crypts of Lieberkühn experience age-related declines in regenerative activity, contributing to leaky gut syndrome, malabsorption, and systemic inflammation. The Wnt and Notch signaling pathways, essential for ISC maintenance, become dysregulated with age, offering potential therapeutic targets for preserving gut homeostasis in the elderly (26).

Satellite Cells (Muscle Stem Cells) are indispensable for skeletal muscle repair and regeneration. During aging, these cells enter a state of quiescence or senescence due to niche alterations, oxidative stress, and chronic inflammation, leading to sarcopenia—the progressive loss of muscle mass and strength. Emerging therapies, including stem cell transplantation, myostatin inhibition, and NAD+ boosters, aim to reactivate satellite cell function and restore muscle integrity in aged individuals (27).

1.2. The impact of aging on stem cells

Aging is a complex biological process characterized by the progressive decline in physiological function and increased

susceptibility to diseases, particularly those associated with impaired tissue repair and regeneration (28). One of the hallmarks of aging is the deterioration of stem cell function, a phenomenon commonly referred to as "stem cell aging." As organisms age, stem cells exhibit reduced regenerative capacity, increased senescence, and altered differentiation patterns (29). These changes compromise the ability of tissues to recover from injury and maintain homeostasis, contributing to the development of age-related disorders such as osteoporosis, neurodegenerative diseases, cardiovascular conditions, and sarcopenia (30). Several factors contribute to the decline in stem cell function with age, including genetic and epigenetic alterations, oxidative stress, mitochondrial dysfunction, telomere shortening, and changes in the stem cell microenvironment (niche) (31). The molecular pathways driving these changes are diverse, involving DNA damage accumulation, cellular senescence, disrupted signaling pathways, and a shift towards a pro-inflammatory systemic environment (32). Understanding the molecular mechanisms behind these processes is essential for developing therapeutic interventions aimed at rejuvenating aged stem cells and restoring regenerative potential (33).

1.3. Purpose of the review

This review aims to provide a comprehensive overview of the current understanding of stem cell aging, focusing on the molecular insights that drive the age-related decline in stem cell function. We will explore the general mechanisms underlying stem cell aging, such as telomere attrition, DNA damage accumulation, and mitochondrial dysfunction, as well as the specific effects on various stem cell populations, including HSCs, MSCs, NSCs, satellite cells, and ISCs. Additionally, we will discuss how changes in the stem cell niche and systemic factors influence stem cell aging. Finally, we will examine potential therapeutic strategies to counteract age-related declines in stem cell function, including caloric restriction, genetic and epigenetic reprogramming, senolytics, stem cell transplantation, and mitochondrial-targeted therapies. The review concludes with a discussion on the challenges and future directions for translating these insights into clinical applications aimed at improving healthy aging and regenerative outcomes. Fig.2 representing the stem cell aging and their mechanism.

2. Stem cell function and aging: general mechanisms

One of the hallmarks of aging is stem cell exhaustion, characterized by a gradual decline in the number and function of stem cells (34). Stem cell exhaustion manifests as a reduced ability to maintain tissue homeostasis, repair damaged tissues, and support the regenerative processes required for normal functioning (35). This decline is observed across various stem cell types, including HSCs, MSCs, NSCs, and muscle satellite cells, leading to age-related pathologies such as immune senescence, osteoporosis, neurodegeneration, and muscle wasting (36).

2.1. Factors causıng stem cell depletıon

Several intrinsic and extrinsic factors contribute to stem cell exhaustion (37). Intrinsic factors include DNA damage accumulation, telomere attrition, and metabolic changes, while extrinsic factors involve alterations in the stem cell niche, systemic inflammation, and age-related shifts in circulating factors (28). Stem cell exhaustion results in a reduced pool of functional stem cells, a decline in self-renewal potential, and aberrant differentiation patterns, which collectively contribute to impaired tissue regeneration and increased vulnerability to age-related diseases (38).

Telomere shortening and its role in stem cell aging

Telomeres are repetitive nucleotide sequences located at the ends of chromosomes, serving to protect genomic integrity during cell division (39). With each cell division, telomeres gradually shorten due to the "end-replication problem (40)." In stem cells, the enzyme telomerase counteracts this shortening by adding telomeric repeats to the ends of chromosomes, thus maintaining replicative capacity (41). However, as stem cells age, telomerase activity decreases, leading to progressive telomere shortening and an eventual loss of telomere integrity (42). Telomere attrition limits the replicative lifespan of stem cells, triggering cellular senescence or apoptosis when telomeres reach a critically short length (43). This phenomenon is particularly evident in tissues that require frequent cell turnover, such as the hematopoietic and intestinal systems (44). For example, in HSCs, telomere shortening impairs the ability to generate adequate immune cells, contributing to immune senescence (45). In 888NSCs, reduced telomerase activity and telomere shortening are associated with diminished neurogenesis and cognitive decline (46). The molecular mechanisms linking telomere shortening to stem cell dysfunction involve DNA damage response pathways (47). Critically short telomeres are recognized as DNA double-strand breaks, activating pathways such as p53, which induces cell cycle arrest and senescence. The accumulation of senescent stem cells further disrupts tissue function and propagates age-related degeneration (48).

DNA Damage Accumulation and Cellular Senescence

DNA damage is a key factor driving cellular aging, with stem cells being particularly susceptible due to their potential for long-term self-renewal (49). Accumulation of DNA damage occurs as a result of various factors, including endogenous metabolic processes, reactive oxygen species (ROS), and environmental insults (50). With age, the ability of stem cells to repair DNA damage diminishes, leading to the accumulation of genetic lesions and chromosomal instability (51).

One consequence of unresolved DNA damage in stem cells is the activation of cellular senescence, a state of permanent cell cycle arrest characterized by changes in gene expression, secretion of pro-inflammatory factors, and altered metabolic activity (52). Senescent stem cells contribute to the aging process by impairing tissue regeneration and creating a pro-inflammatory environment through the secretion of a distinct

set of factors known as the senescence-associated secretory, phenotype (SASP) (53). SASP factors include cytokines, chemokines, proteases, and growth factors that can disrupt the local stem cell niche and promote chronic inflammation (54).

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Oxidative stress is a significant contributor to DNA damage and cellular senescence in aging stem cells (55). The increased production of ROS, coupled with a decline in antioxidant defenses, leads to oxidative damage to DNA, proteins, and lipids (56). This is especially detrimental in stem cells, where maintaining genomic integrity is crucial for their regenerative function (57).

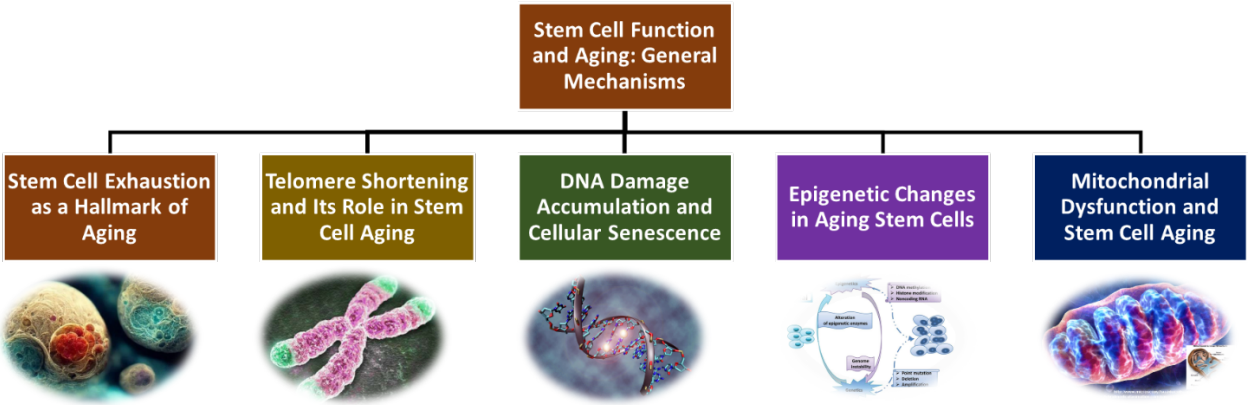

Fig. 2. Diagrammatic representation of stem cell aging and their mechanism

Epigenetic changes in aging stem cells

Epigenetic regulation, which includes DNA methylation, histone modifications, and non-coding RNA activity, plays a vital role in maintaining stem cell identity and function (58). However, aging leads to changes in the epigenetic landscape of stem cells, a phenomenon often referred to as "epigenetic drift (59)." This drift results in altered gene expression profiles, loss of stem cell identity, and compromised self-renewal and differentiation capacity (60). In aged stem cells, DNA methylation patterns become more heterogeneous, with regions of hypermethylation and hypomethylation (61). These changes can disrupt the expression of genes involved in stem cell maintenance, leading to impaired regenerative function (62). For example, hypermethylation of promoter regions associated with key self-renewal genes can reduce stem cell activity, while hypomethylation of repetitive elements may contribute to genomic instability (63). Histone modifications also change with age, affecting chromatin structure and gene accessibility (64). For instance, a reduction in histone acetylation may decrease the expression of genes essential for maintaining a stem cell's undifferentiated state, while increased histone methylation can contribute to the repression of genes involved in cell cycle regulation (65). Collectively, these epigenetic alterations limit the ability of aged stem cells to respond to regenerative signals effectively (66).

Mitochondrial dysfunction and stem cell aging

Mitochondria play a central role in cellular energy production, metabolism, and regulation of apoptosis (67). In stem cells, mitochondrial function is crucial for maintaining the balance between self-renewal and differentiation (68). However, mitochondrial dysfunction becomes more pronounced with age, leading to a decline in stem cell regenerative potential (69). The mechanisms underlying mitochondrial dysfunction in aging stem cells involve alterations in mitochondrial biogenesis, dynamics (fusion and fission), and mitophagy (selective autophagy of damaged mitochondria) (70). Age-related changes in these processes can lead to the accumulation of dysfunctional mitochondria, impaired energy production, and increased ROS generation (71). The resulting oxidative stress exacerbates DNA damage and cellular senescence, further compromising stem cell function (72). In addition to oxidative damage, shifts in stem cell metabolism from glycolysis to oxidative phosphorylation can contribute to aging-related declines (73). Young stem cells typically rely on glycolysis for energy production, a metabolic state that supports quiescence and reduces ROS generation. However, aged stem cells exhibit increased oxidative phosphorylation, which is associated with higher ROS levels and oxidative damage (74). This metabolic shift can also influence differentiation patterns, as certain lineage commitments may require specific metabolic states (75).

3. Age-related changes in specific stem cell populations

Aging impacts stem cell populations differently depending on the tissue type and functional requirements. The following subsections explore how specific stem cell types—hematopoietic, mesenchymal, neural, muscle satellite, and (ISCs)—experience age-related declines in function and the implications for tissue maintenance and repair.

3.1. Hematopoietic stem cells (HSCs)

HSCs are specialized cells found in the bone marrow that are essential for the continuous production of all blood cells throughout an individual's life (76). These cells are responsible for generating a diverse range of blood components, including oxygen-carrying red blood cells, infection-fighting white blood cells, and platelets, which are crucial for blood clotting and wound healing (77). Functionality of HSCs declines as individual age. Aging affects their regenerative capacity, making them less efficient at replenishing the blood system (78). Their self-renewable ability decreases over time, leading to a gradual depletion of the stem cell pool (79). One of the significant changes associated with aging is lineage skewing, where HSCs show a preference for producing specific types of blood cells, often favoring myeloid cells over lymphoid cells (80). This imbalance contributes to an increased risk of age-related hematopoietic disorders, such as anemia, reduced immune function, and an elevated likelihood of developing blood-related cancers (81).

Impact of aging on HSC Function

As individuals age, HSCs experience a significant shift in their blood cell production, moving from generating lymphoid cells, such as T cells and B cells, to favoring myeloid cell lineages like macrophages and granulocytes (82). This phenomenon, called "myeloid skewing," is a hallmark of aging and contributes to immune senescence—a decline in the immune system's efficiency (83). As a result, older adults face diminished adaptive immune responses, making them more vulnerable to infections and reducing the effectiveness of vaccines. Additionally, the decreased regenerative capacity of aged HSCs limits their ability to adequately replenish blood cells after injuries or physiological stress, increasing the risks of anemia, excessive bleeding, and other blood-related disorders (84).

Molecular mechanisms underlying HSC Aging

Several molecular mechanisms drive the age-related decline in HSC functions are mentioned below (Fig. 3):

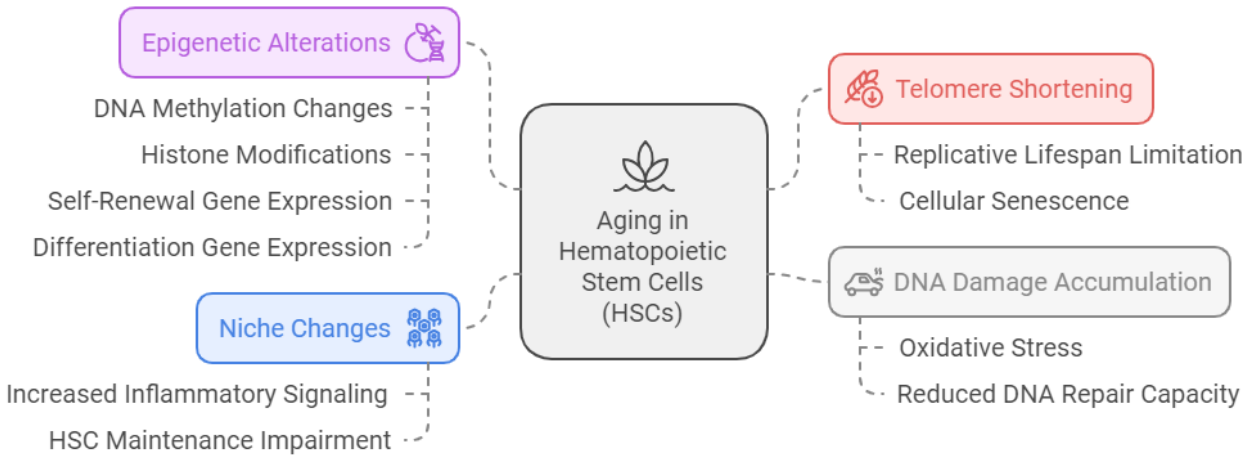

Fig. 3. Mechanism of age-related decline in hematopoietic stem cell

Telomere Shortening: HSCs undergo progressive telomere shortening as they age, which limits their ability to replicate over time (85). This gradual loss of telomere length leads to a reduction in the cells' regenerative capacity, ultimately contributing to cellular senescence (86). The resulting decline in HSC function is linked to aging and the reduced ability to maintain tissue homeostasis (87).

DNA damage accumulation: In aged HSCs, increased DNA damage occurs due to heightened oxidative stress and a diminished capacity for DNA repair (88). This accumulation of damage impairs the cells' normal functions, reducing their ability to regenerate and maintain healthy blood and immune systems, which contributes to age-related cellular dysfunction and disease (89).

Epigenetic alterations: Aging causes alterations in DNA methylation and histone modifications within HSCs, leading to changes in the regulation of genes essential for self-renewal and differentiation (90). These epigenetic changes disrupt the normal function of HSCs, impairing their ability to regenerate and differentiate, ultimately contributing to age-related functional decline (88).

Niche changes: As the bone marrow microenvironment, or niche, ages, it experiences increased inflammatory signaling and other alterations that impair its ability to support HSCs (91). These changes negatively affect HSC maintenance, reducing their regenerative capacity and function, which contributes to the overall decline in blood and immune system health with age (92).

3.2. Mesenchymal stem cells (MSCs)

MSCs are multipotent stem cells present in several tissues, including bone marrow, adipose tissue, and the umbilical cord (93). They possess the unique ability to differentiate into various cell types, such as osteoblasts (bone cells), chondrocytes (cartilage cells), and adipocytes (fat cells), making them essential for the repair and maintenance of bone,

cartilage, and fat tissues (94). As individuals age, MSCs experience a decline in their regenerative abilities, differentiation potential, and responsiveness to tissue damage (95). This reduced function contributes to age-related tissue degeneration, impaired healing processes, and diminished capacity for tissue regeneration and repair in aging individuals (96).

Aging-related changes in MSC Function

Age-related changes in MSCs include a shift in differentiation potential, favoring adipogenesis over osteogenesis, which contributes to conditions such as osteoporosis (97). The decline in the ability to form new bone cells and cartilage impacts the integrity of the skeletal system, leading to an increased risk of fractures, osteoarthritis, and other degenerative joint disorders (98).

Molecular mechanisms underlying MSC Aging

***Mitochondrial dysfunction*:** Aging MSCs exhibit diminished mitochondrial function and heightened production of reactive oxygen species (ROS) (99). This increase in ROS leads to oxidative stress, causing cellular damage and impairing MSC functionality (100). Consequently, the reduced ability to maintain and repair tissues contributes to age-related degeneration and diminished regenerative capacity (101).

***Senescence and SASP*:** As MSCs accumulate senescence in aging tissues, they release pro-inflammatory factors through the senescence-associated secretory phenotype (SASP) (102). This release disrupts the local tissue microenvironment, promoting inflammation and impairing the regenerative capacity of tissues, thereby contributing to age-related tissue degeneration and reduced healing and repair processes (103).

***Epigenetic modifications*:** Age-related changes in DNA methylation and histone modifications alter the expression of key genes involved in MSC differentiation (104). These epigenetic changes reduce the cells' ability to undergo osteogenesis (bone formation) and chondrogenesis (cartilage formation), leading to a diminished regenerative capacity in aging tissues and impaired skeletal health (105).

***Altered niche interactions*:** As the bone marrow and other MSC niches age, they undergo inflammatory changes that disrupt the local environment (106). This inflammation impairs the ability of MSCs to effectively respond to signals for tissue repair, reducing their regenerative function and contributing to age-related tissue degeneration and delayed healing (107).

3.3. Neural stem cells (NSCs)

NSCs are specialized cells located in specific areas of the adult brain, primarily in the subventricular zone and the hippocampus (108). These regions are key to neurogenesis, the generation of new neurons and glial cells, which are essential for brain function (109). NSCs are crucial for maintaining cognitive abilities, supporting learning and memory, and aiding in the brain's recovery from neurological damage (110). Unfortunately, as individuals age, the activity of NSCs decreases significantly, leading to a decline in neurogenesis (111). This reduction is a major factor contributing to age-related cognitive decline, impairments in memory, and an increased susceptibility to neurodegenerative conditions such as Alzheimer's and Parkinson's diseases (112). Understanding NSC dynamics is therefore vital for developing therapies to combat these age-associated neurological issues (113).

Decline in neurogenesis and cognitive function

As individuals age, the rate of neurogenesis declines due to reduced NSC proliferation, increased cellular senescence, and shifts in differentiation that favor the production of glial cells over neurons (114). This decline is associated with impairments in cognitive functions such as learning and memory. Additionally, age-related neuroinflammation, marked by the activation of microglia and elevated cytokine levels, further exacerbates the reduction in NSC function and neurogenesis (115). These factors contribute to diminished brain plasticity and may increase the risk of cognitive decline and neurodegenerative diseases in older individuals (116).

Molecular mechanisms contributing to NSC aging

***Telomere Shortening*:** Like other stem cells, NSCs undergo telomere shortening as they age, which limits their ability to proliferate (117). Telomeres, protective caps at the ends of chromosomes, gradually shorten with each cell division (118). In NSCs, this telomere erosion reduces their regenerative capacity, impairing their ability to generate new neurons and glial cells (119). As a result, the brain's ability to repair and maintain itself diminishes over time, contributing to cognitive decline and an increased risk of neurodegenerative diseases (120). Telomere shortening is thus a key factor in the aging of NSCs and the overall decline in brain plasticity (121).

***DNA damage and senescence*:** The accumulation of DNA damage and the onset of cellular senescence in NSCs significantly impede their regenerative capacity, contributing to brain aging (122). Over time, NSCs experience increased DNA damage due to oxidative stress and other age-related factors (123). This damage triggers cellular senescence, a state in which cells lose their ability to divide and function properly (124). Senescent NSCs not only fail to regenerate neurons and glial cells but also release pro-inflammatory factors that promote a neurodegenerative environment (125). This shift exacerbates age-related cognitive decline and increases the risk of neurodegenerative diseases, such as Alzheimer's and Parkinson's (126).

***Epigenetic dysregulation*:** Changes in histone modifications and DNA methylation in aging NSCs) can influence the expression of key genes involved in neurogenesis and neuronal differentiation (127). These epigenetic alterations may disrupt normal gene regulation, leading to impaired brain cell development and reduced neuroplasticity, contributing to cognitive decline and age-related neurological conditions (128). Understanding these changes is crucial for developing potential interventions to support healthy brain aging (129).

***Mitochondrial dysfunction*:** Aging NSCs show impaired mitochondrial function, resulting in decreased energy production and heightened oxidative stress (130). This dysfunction negatively impacts neurogenesis, reducing the ability to generate new neurons and maintain brain health (131). Understanding these changes in mitochondrial efficiency is essential for developing strategies to mitigate age-related declines in cognitive function and support neural regeneration (132).

3.4. Satellite cells

Satellite cells are a type of adult stem cell located between the basal lamina and sarcolemma of skeletal muscle fibers (133). These cells are essential for the repair, regeneration, and maintenance of skeletal muscle, especially after injury or damage (134). When muscles are injured, satellite cells become activated, proliferate, and differentiate into myoblasts, which fuse with damaged muscle fibers to aid in repair (135). However, as satellite cells age, their regenerative potential diminishes, leading to impaired muscle repair and regeneration (136). This decline contributes significantly to sarcopenia, the age-related loss of muscle mass and strength, which is a major cause of reduced muscle function in the elderly (137). The reduced efficiency of satellite cells in aging muscles is linked to cellular senescence, alterations in the stem cell niche, and changes in signaling pathways, all of which reduce their ability to respond to muscle damage (138). Understanding these mechanisms is the key to developing interventions for age-related muscle loss (139).

Decreased in satellite cell activity

With age, the number of quiescent satellite cells decreases, and their capacity to activate and proliferate in response to muscle injury declines (140). This reduced responsiveness leads to a weakened muscle repair process. Moreover, aged satellite cells often show an impaired ability to differentiate into mature myofibers, which further hinders muscle regeneration (141). As a result, muscle healing becomes delayed and incomplete, contributing to a decline in muscle function over time (142). These age-related changes in satellite cell behavior are key factors in the development of sarcopenia, the progressive loss of muscle mass and strength in the elderly (143).

Molecular pathways involved in the decline of muscle regeneration

***Cellular Senescence*:** The increased senescence of satellite cells reduces their ability to effectively participate in muscle repair, weakening the regeneration process (144). Additionally, the senescence-associated secretory phenotype (SASP) released by these aging cells disrupts the muscle microenvironment, promoting inflammation and further impairing muscle regeneration (145). This dual impact of cellular aging contributes to delayed healing and reduced muscle function, exacerbating age-related conditions like sarcopenia (146).

***Notch and Wnt Signaling dysregulation*:** Age-related changes in signaling pathways, such as Notch and Wnt, negatively impact the activation and differentiation of satellite cells, impairing their ability to regenerate muscle tissue. The Notch pathway, essential for satellite cell activation, becomes less efficient with age, while increased Wnt signaling promotes differentiation into fibrotic tissue instead of healthy muscle. These imbalances disrupt the muscle repair process, contributing to weakened muscle regeneration and increasing the risk of sarcopenia and muscle function decline in aging individuals.

Mitochondrial dysfunction and metabolic shifts: Aged satellite cells exhibit reduced mitochondrial function and altered metabolic profiles, which significantly limit their capacity for effective muscle regeneration (78). Mitochondria, the powerhouse of the cell, play a crucial role in energy production required for cell proliferation and repair (147). With aging, mitochondrial dysfunction leads to decreased energy availability, impairing satellite cell activation and their ability to undergo proper differentiation (148). Additionally, metabolic shifts in aged satellite cells contribute to reduced efficiency in muscle regeneration, further slowing the repair process and promoting muscle degeneration, which exacerbates age-related conditions like sarcopenia (149).

***Inflammatory environment*:** Chronic low-grade inflammation, known as "Inflammaging," occurs in aged muscle tissues and has a detrimental impact on satellite cell function and muscle regeneration (150). This persistent inflammatory state is characterized by elevated levels of pro-inflammatory cytokines, which disrupt the muscle microenvironment (151). Inflammaging impairs the activation, proliferation, and differentiation of satellite cells, limiting their ability to effectively repair muscle damage (152). Over time, this inflammation-induced dysfunction accelerates muscle degeneration, contributing to age-related muscle loss (sarcopenia) and reduced muscle strength (153). Managing chronic inflammation may be key to improving muscle regeneration and mitigating the effects of aging on skeletal muscle (154).

3.5. Intestinal stem cells (ISCs)

ISCs reside at the base of the intestinal crypts and play a vital role in maintaining the integrity of the gut lining (155). They continuously replenish the epithelial cells, ensuring efficient nutrient absorption and acting as a barrier against pathogens. However, as individuals age, the regenerative capacity of ISCs declines (156). This reduced functionality contributes to a weakening of the intestinal barrier, slower cell turnover, and compromised epithelial repair (157). Consequently, the aging gut becomes more susceptible to inflammation, infections, and gastrointestinal disorders, such as inflammatory bowel disease and colorectal cancer (158). Diminished ISC activity also affects nutrient absorption efficiency, potentially leading to

nutrient deficiencies (159). Understanding the age-related changes in ISCs is crucial for developing targeted therapies to preserve gut health, enhance intestinal regeneration, and reduce the risk of age-associated gastrointestinal conditions, thereby improving overall well-being in the aging population (160).

Impact of aging on ISC turnover and gut health

As ISCs age, their function declines, leading to slower renewal of the intestinal epithelium and increased permeability of the gut barrier (161). This deterioration raises the risk of gastrointestinal disorders, including inflammatory bowel disease (IBD) and colorectal cancer (162). Additionally, aging impacts the differentiation potential of ISCs, causing a shift in cell fate decisions. There's a tendency for aged ISCs to favor the production of secretory cells—like goblet and Paneth cells—over absorptive cells, which can compromise nutrient uptake and overall gut function (163). This imbalance in cell types contributes to a less efficient and more vulnerable intestinal lining. Understanding these age-related shifts in ISC behavior is essential for developing strategies to maintain gut health, prevent gastrointestinal diseases, and optimize nutrient absorption in older adults, thereby supporting better overall health and quality of life as the population ages (164).

Molecular mechanisms of ISC Aging

***Telomere attrition and DNA damage*:** Aging ISCs undergo telomere shortening and accumulate DNA damage, reducing their ability to proliferate effectively (165). This decline in regenerative capacity impacts the maintenance of the intestinal lining, leading to compromised gut function (166). Understanding the mechanisms of telomere attrition and DNA damage accumulation in ISCs is crucial for developing interventions to support gut health and counteract age-related gastrointestinal issues (167).

***Mitochondrial dysfunction*:** In aged ISCs, the buildup of dysfunctional mitochondria hampers energy production and elevates reactive oxygen species (ROS) levels (168). This oxidative stress reduces the cells' regenerative potential, compromising the maintenance of a healthy intestinal lining (169). Addressing mitochondrial dysfunction in aging ISCs is key to enhancing their regenerative capacity and supporting overall gut health (170).

***Niche changes*:** With age, the ISC niche experiences alterations, including shifts in key signaling pathways like Wnt, Notch, and BMP (171). These changes disrupt the delicate balance of ISC self-renewal and differentiation, leading to impaired gut regeneration and altered cell fate decisions (172). Understanding how aging impacts these signaling molecules is crucial for developing strategies to maintain ISC function and promote healthy gut aging (173).

3.6. Embryonic stem cells (ESCs)

ESCs are pluripotent cells derived from the inner cell mass of blastocysts, capable of differentiating into any cell type in the body. Their remarkable self-renewal and differentiation potential make them invaluable for regenerative medicine, disease modeling, and developmental biology research (174). However, despite their inherent plasticity, ESCs are not entirely immune to aging-related changes, particularly when maintained in long-term culture. Over time, ESCs may experience a decline in functionality, including reduced proliferation capacity, altered differentiation potential, and epigenetic instability. Understanding these age-related changes is crucial for optimizing their use in clinical applications, ensuring that ESC-derived therapies remain effective and safe for regenerative treatments (175).

Impact of aging on embryonic stem cell potency and differentiation

As ESCs age, either *in vivo* (in early developmental stages) or in vitro (during prolonged culture), their ability to self-renew and differentiate efficiently can diminish. One of the key observations is that aged ESCs exhibit slower proliferation rates, possibly due to accumulated cellular stress or epigenetic modifications (176). Additionally, their differentiation potential may become skewed, leading to a preference for certain cell lineages over others. This bias could compromise their utility in generating specific tissues for regenerative therapies. Another critical factor is epigenetic drift—changes in DNA methylation and histone modifications that alter gene expression patterns, potentially leading to loss of pluripotency or abnormal differentiation. These age-related shifts highlight the need for improved culture techniques and interventions to maintain ESC quality over extended periods (177).

Molecular mechanisms underlying ESC aging

***Telomere attrition and genomic instability*:** ESCs normally maintain their telomeres through high telomerase activity, which prevents the shortening typically seen in somatic cells during replication. However, prolonged in vitro culture or exposure to cellular stress can lead to gradual telomere erosion and DNA damage accumulation (178). When telomeres become critically short, cells enter senescence or apoptosis, impairing their regenerative potential. Additionally, genomic instability from DNA damage further compromises ESC function, reducing their ability to self-renew and differentiate efficiently. Understanding and mitigating telomere attrition in ESCs is crucial for maintaining their long-term therapeutic potential (179).

***Mitochondrial dysfunction and oxidative stress*:** While ESCs primarily rely on glycolysis for energy production, mitochondria play a vital role during differentiation. As ESCs age, mitochondrial efficiency declines, leading to the accumulation of defective mitochondria (179). This dysfunction results in increased production of reactive oxygen species (ROS), causing oxidative damage to proteins, lipids, and DNA. Elevated ROS levels not only impair ESC pluripotency but also disrupt differentiation capacity. Strategies to enhance mitochondrial quality control, such as antioxidant supplementation or mitophagy activation, could

help preserve ESC functionality in regenerative applications (180).

***Epigenetic alterations*:** Aging ESCs undergo significant epigenetic changes, including DNA methylation shifts and histone modifications, which alter gene expression patterns. These changes can lead to the silencing of pluripotency genes (e.g., *Oct4*, *Nanog*) or aberrant activation of differentiation pathways (181). Epigenetic drift contributes to reduced stem cell stability and increases the risk of uncontrolled differentiation or senescence. Epigenetic reprogramming techniques, such as transient exposure to Yamanaka factors, may help reset these modifications and restore youthful gene expression profiles in aged ESCs (182).

***Niche signaling pathway disruptions*:** The stem cell niche provides critical signals that regulate ESC self-renewal and differentiation. With aging, changes in key signaling pathways—such as Wnt, BMP, and FGF—can disrupt the balance between stemness and differentiation (183). For example, altered Wnt signaling may promote spontaneous differentiation, while dysregulated BMP activity could bias lineage specification. Optimizing culture conditions to mimic a youthful niche, including the use of growth factor cocktails or 3D scaffolds, may help maintain ESC potency and function over extended periods (184).

3.7. Induced pluripotent stem cells (iPSCs)

iPSCs are reprogrammed somatic cells that regain pluripotency through the introduction of key transcription factors (Oct4, Sox2, Klf4, c-Myc). While iPSCs share many characteristics with ESCs, including self-renewal and differentiation potential, they also exhibit unique aging-related challenges (185). Over time, both the original somatic cell age and the reprogramming process can influence iPSC functionality. Understanding these age-associated changes is critical for ensuring the reliability of iPSCs in regenerative medicine, disease modeling, and drug discovery (186).

Impact of aging on iPSC reprogramming efficiency and function

Aging significantly affects iPSC generation and function. Older donor cells carry epigenetic changes and DNA damage that reduce reprogramming efficiency and often leave residual age-related markers in resulting iPSCs. These aged iPSCs show three main limitations: (1) lower reprogramming success due to epigenetic barriers and cellular senescence, (2) inconsistent differentiation potential across cell lineages, and (3) increased genomic instability raising safety concerns (187). These challenges are particularly problematic for developing therapies for age-related diseases, where patient-specific iPSCs would ideally come from elderly donors. Current research focuses on improving reprogramming techniques, enhancing epigenetic resetting, and implementing stricter quality controls to overcome these age-related limitations in iPSC technology (188).

Molecular mechanisms underlying iPSC aging

***Epigenetic memory and incomplete reprogramming*:** iPSCs often retain epigenetic marks from their original somatic cell type, a phenomenon known as "epigenetic memory." This residual memory can bias differentiation toward the donor cell's lineage, limiting their plasticity (189). Incomplete reprogramming is more common in aged cells due to accumulated DNA methylation and histone modifications. Advanced reprogramming techniques, such as prolonged factor expression or small molecule treatments, may help erase these aging signatures (186).

***Mitochondrial dysfunction and metabolic shifts*:** Reprogramming resets cellular metabolism from oxidative phosphorylation to glycolysis, but aged iPSCs may retain mitochondrial abnormalities. Dysfunctional mitochondria can increase reactive oxygen species (ROS), contributing to oxidative stress and impairing iPSC self-renewal. Strategies to enhance mitochondrial clearance (mitophagy) or provide metabolic support could improve iPSC quality (190).

***Genomic instability and DNA damage accumulation*:** Aged somatic cells often harbor pre-existing DNA damage, which can persist after reprogramming. Additionally, the reprogramming process itself can induce genomic stress, leading to mutations or chromosomal abnormalities. Monitoring and selecting high-quality iPSC clones is crucial for clinical applications, particularly in aging research (190).

***Telomere dynamics and replicative senescence*:** While reprogramming extends telomeres through telomerase reactivation, iPSCs derived from aged cells may have shorter initial telomeres, potentially affecting long-term culture stability. Ensuring proper telomere maintenance is vital for sustaining iPSC proliferation and differentiation capacity (190).

3.8. Epithelial stem cells (EpSCs)

EpSCs are tissue-specific adult stem cells responsible for the continuous renewal and repair of epithelial tissues, which form critical barriers between the body and its external environment. Found in the skin, gastrointestinal tract, respiratory system, mammary glands, and other epithelial-rich organs, these stem cells maintain tissue homeostasis by balancing self-renewal and differentiation (26). Their primary role is to replace damaged or dying epithelial cells, ensuring proper barrier function, nutrient absorption (in the gut), pathogen defense (in the skin and airways), and wound healing (191).

Impact of Aging on EpSC function

Aging profoundly disrupts the regenerative capacity of EpSCs, leading to progressive tissue dysfunction across multiple organ systems. The decline in EpSC activity manifests through both cell-intrinsic changes and alterations in the stem cell niche, ultimately compromising tissue integrity and repair mechanisms (192).

Molecular mechanisms underlying EpSC aging genomic instability

Aged EpSCs accumulate DNA damage from telomere shortening and oxidative stress. Declining repair mechanisms lead to persistent DNA damage, triggering senescence or apoptosis. This depletes functional stem cells while increasing cancer risk (193).

Epigenetic dysregulation: Aging alters DNA methylation and histone marks, silencing stemness genes (e.g., *Lgr5*, *p63*) and disrupting chromatin accessibility. Non-coding RNA imbalances further impair regeneration, locking EpSCs in dysfunctional states (194).

Mitochondrial dysfunction: Damaged mitochondria accumulate due to failed quality control, increasing ROS and reducing ATP production. NAD+ depletion worsens this metabolic crisis, impairing EpSC proliferation and tissue repair (195).

Proteostasis collapse: Aged EpSCs lose protein-folding capacity as chaperone systems decline. Impaired autophagy and proteasome function allow toxic protein aggregates to accumulate, triggering chronic ER stress and senescence (195).

Niche degradation: The stem cell microenvironment stiffens with cross-linked ECM proteins while growth factor signaling (Wnt, BMP) becomes imbalanced. Senescent niche cells secrete inflammatory factors (IL-6, TGF-β) that suppress EpSC function (196).

Table 1. Different types, source, characteristics and role in aging of stem cells

Stem Cell Type	Source	Characteristics	Role in Aging	References
Embryonic Stem Cells	Blastocyst (early-stage embryo)	Pluripotent, unlimited self-renewal, can differentiate into any cell type	Declines with age; potential for regenerative medicine to counteract aging effects	(197)
Induced Pluripotent Stem Cells	Reprogrammed somatic cells (e.g., skin cells)	Pluripotent, genetically reprogrammed, avoid ethical concerns of ESCs	Used to model aging diseases; potential for autologous cell therapy in aging	(198)
Mesenchymal Stem Cells	Bone marrow, adipose tissue, umbilical cord	Multipotent, support tissue repair, immunomodulatory properties	Reduced regenerative capacity contributes to osteoporosis, arthritis, and frailty	(199)
Hematopoietic Stem Cells	Bone marrow, umbilical cord blood	Multipotent, give rise to blood and immune cells	Decline in function leads to anemia, immune senescence, and increased cancer risk	(200)
Neural Stem Cells	Brain (subventricular zone, hippocampus)	Multipotent, generate neurons and glial cells	Decline leads to cognitive impairment, neurodegenerative diseases (e.g., Alzheimer's)	(201)
Epithelial Stem Cells	Skin, gut lining, other epithelial tissues	Maintain and repair epithelial barriers, high turnover	Dysfunction leads to thinning skin, poor wound healing, and gastrointestinal decline	(202)
Intestinal Stem Cells	Crypts of Lieberkühn (small intestine)	Rapidly dividing, maintain gut epithelium, Lgr5+ marker	Decline leads to impaired gut barrier, reduced nutrient absorption, and increased susceptibility to infections	(203)
Satellite Cells (Muscle Stem Cells)	Skeletal muscle (under basal lamina)	Unipotent, repair and regenerate muscle fibers	Reduced activity causes sarcopenia (age-related muscle loss) and impaired recovery	(204)
Cardiac Stem Cells	Heart tissue (niche-dependent)	Limited regenerative capacity, can form cardiomyocytes and vascular cells	Insufficient repair contributes to heart failure and age-related cardiac decline	(205)

4. The stem cell niche and its role in aging

The stem cell niche is a unique microenvironment that plays a critical role in regulating stem cell behavior by providing structural support, essential nutrients, and biochemical signals (206). This niche controls key processes such as self-renewal, differentiation, and overall maintenance of stem cells (207). However, as stem cells age, the niche undergoes significant changes that can adversely affect stem cell function (208). These age-related alterations in the niche, including shifts in extracellular matrix composition, changes in signaling molecules, and increased inflammation, contribute to the decline in the regenerative capacity of stem cells (209). Additionally, systemic factors such as circulating hormones, immune cell activity, and metabolic signals also influence the aging of stem cells (210). Together, these local and systemic changes impact the stem cells' ability to repair and regenerate tissues, accelerating age-related degeneration (211). Understanding these dynamics is crucial for developing targeted interventions to slow down stem cell aging and promote healthy tissue maintenance (212).

4.1. Changes in the stem cell microenvironment (Niche)

The stem cell niche consists of diverse cellular and acellular elements that work together to support stem cell function (211). These include the extracellular matrix (ECM), niche cells,

signaling molecules, and mechanical cues—all of which create a dynamic environment influencing stem cell behavior (213). As the body ages, significant alterations occur in these niche components (214). The ECM may stiffen or degrade, niche cells can change in number or function, signaling molecules may become imbalanced, and mechanical properties of the tissue can shift (215). These changes can disrupt the communication between stem cells and their microenvironment, leading to a decline in stem cell maintenance and regenerative capacity (216). The cumulative impact of these age-related modifications in the niche contributes to diminished tissue repair and increased susceptibility to age-associated diseases, highlighting the importance of preserving niche integrity to support healthy aging (211).

Extracellular matrix alterations

The extracellular matrix (ECM) plays a critical role in supporting the stem cell niche, influencing stem cell behavior through its biochemical signals and mechanical properties (217). As aging progresses, the ECM undergoes changes in composition and stiffness, often linked to increased collagen cross-linking and the buildup of advanced glycation end products (AGEs) (218). These modifications can significantly alter the mechanical environment of the niche, impacting stem cell function (219). For example, a stiffer ECM has been found to drive MSCs towards a senescent state, reducing their ability to self-renew and differentiate effectively (220). This age-related shift in ECM properties can lead to impaired tissue regeneration and increased susceptibility to age-related conditions (221). Understanding the impact of ECM alterations on stem cell health is crucial for developing strategies to counteract the negative effects of aging and maintain tissue functionality (222).

Changes in niche cell populations

The stem cell niche is composed of various supporting cells, including fibroblasts, endothelial cells, and immune cells, which release signaling molecules that regulate stem cell behavior and maintenance (210). These niche cells create a microenvironment that is crucial for the proper functioning of stem cells (223). However, with aging, significant changes occur within the niche (224). The populations of these supporting cells shift, and their secretory profiles are altered, leading to disruptions in the regulation of stem cell activity (213). For instance, in the bone marrow niche, aging affects two key cell types, osteoblasts, which form bone, and adipocytes, which store fat (225). Changes in these cells negatively impact HSCs), the stem cells responsible for generating blood and immune cells (226). As a result, aged HSCs exhibit reduced regenerative capacity and altered differentiation patterns, contributing to a decline in immune function and the body's ability to repair tissues (156). These age-related changes in the niche play a critical role in the overall decline of tissue homeostasis and regeneration observed in older individuals, linking the aging process to impaired stem cell function and increased vulnerability to diseases associated with aging (227).

4.1.3 Inflammatory signals and "Inflammaging"

Chronic low-grade inflammation, or "inflammaging," is a hallmark of aging that disrupts the stem cell niche (228). Pro-inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) accumulate in aged tissues, disturbing the signaling balance needed for proper stem cell function (229, 230). This pro-inflammatory environment contributes to cellular senescence, impaired tissue regeneration, and altered stem cell differentiation. Inflammaging thus creates conditions that undermine the regenerative capacity of tissues (231). For example, increased levels of TNF-α in the aging muscle niche are linked to reduced satellite cell activity, which impairs muscle repair (232). This illustrates how chronic inflammation in aged tissues negatively impacts stem cell activity, accelerating tissue decline and contributing to age-related functional deterioration (233). Inflammaging is therefore a key factor in the reduced regenerative ability of tissues and organs commonly observed with aging (234).

4.2. Systemic factors and their influence on stem cell aging

The aging process affects not only the local environment of the stem cell niche but also systemic factors that regulate stem cell function across the entire body (235). Circulating factors, such as hormones, growth factors, and cytokines, play an essential role in maintaining stem cell activity, mediating repair, and supporting tissue regeneration (236). With age, these systemic factors become imbalanced, leading to a decline in stem cell function and regenerative capacity (237). Hormones like growth hormone and insulin-like growth factor-1 (IGF-1), which support tissue repair, decrease with age, negatively influencing stem cell maintenance and differentiation (238). Similarly, pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) accumulate in the bloodstream, further disrupting stem cell function across various tissues (239). This systemic shift in circulating factors contributes to the overall decline in tissue regeneration and the increased susceptibility to age-related diseases (240). For example, the decline in muscle repair seen in aging individuals is linked not only to local changes in the muscle niche but also to reduced levels of circulating regenerative factors (241). These systemic changes, combined with local niche deterioration, create a multi-faceted challenge for stem cell function, leading to impaired tissue maintenance and repair during aging (237, 238).

The Role of circulating factors in stem cell aging

Systemic factors in the blood, through endocrine signaling, play a crucial role in regulating stem cell function, and their decline with age significantly impacts tissue regeneration (242). Hormones like insulin-like growth factor-1 (IGF-1) and growth hormone (GH) decrease as we age, impairing the regenerative potential of stem cells in various tissues, including

muscle and bone (243). These hormones are vital for maintaining stem cell activity and tissue repair, and their reduced levels directly contribute to the body's diminished ability to heal (244). Additionally, age-related declines in estrogen and testosterone negatively affect MSCs and muscle satellite cells, leading to decreased bone density and impaired muscle regeneration (245). Estrogen plays a key role in bone health, and its reduction contributes to osteoporosis, while lower testosterone levels hinder muscle repair (246). Together, the decline in these systemic factors compromises stem cell function, driving tissue deterioration and contributing to age-related health issues (247).

Parabiosis experiments and implications for systemic regulation of aging

Parabiosis, a technique where the circulatory systems of two animals are surgically joined, has been used to study the effects of systemic factors on aging and stem cell function (248). Experiments involving heterochronic parabiosis (pairing of young and old animals) have shown that exposure to a young circulatory environment can rejuvenate aged stem cells and improve tissue function (249). For example, in heterochronic parabiosis studies, aged muscle satellite cells exposed to young systemic factors exhibited increased regenerative capacity and a reversal of age-related decline (250). Conversely, young stem cells exposed to an old circulatory environment showed signs of premature aging (251). These findings suggest that systemic factors play a significant role in regulating stem cell aging and that modifying these factors could be a potential therapeutic approach to rejuvenate aged stem cells (252).

Age-related changes in the hematopoietic and NSC niches

Specific stem cell niches, such as those for hematopoietic and neural stem cells, undergo distinct age-related changes that affect stem cell function (12, 88, 253).

Hematopoietic stem cell niche: The bone marrow niche for HSCs experiences structural and functional changes with age, including increased adipogenesis and altered osteoblastic activity (254, 255). These changes contribute to a decline in HSC function, leading to myeloid skewing and immune senescence (256). The aged HSC niche also exhibits increased inflammation and oxidative stress, further impairing stem cell function (92, 254).

Neural stem cell niche: The neurogenic niches in the aged brain show decreased levels of growth factors such as brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF), which are essential for NSC maintenance and neurogenesis (257). In addition, increased neuroinflammation and activation of microglia in the aging brain negatively impact NSC function, contributing to cognitive decline and an increased risk of neurodegenerative diseases (258).

Extracellular vesicles and their role in stem cell aging

Extracellular vesicles (EVs), including exosomes and microvesicles, are released by cells and serve as carriers of signaling molecules like proteins, lipids, and RNA, playing a vital role in intercellular communication (259). They can influence stem cell function by transferring these bioactive molecules between cells (260). However, with aging, the composition and function of EVs change, potentially contributing to stem cell dysfunction (261). For instance, aged EVs may carry pro-inflammatory signals that promote cellular senescence and impair tissue regeneration. This shift can exacerbate the decline in regenerative capacity seen in aging tissues (262). In contrast, EVs derived from younger organisms have shown promise in rejuvenating aged stem cells by delivering regenerative factors that enhance their function (263). These findings highlight the dual role of EVs in either promoting or mitigating age-related stem cell decline, depending on their source and molecular content (264).

5. Therapeutic approaches to combat stem cell aging

As research into age-related stem cell decline advances, a range of therapeutic strategies have been developed to combat aging impact on stem cells (265). These methods aim to restore the regenerative abilities of aging stem cells, rejuvenate tissues, and promote healthier, extended lifespan (266). Key approaches include dietary interventions, which leverage nutrition to enhance stem cell function; genetic and epigenetic reprogramming, which modifies DNA and gene expression to reverse aging markers; and therapies targeting cellular senescence to remove or alter dysfunctional cells (267). Other strategies involve stem cell transplantation to replace damaged cells, tissue engineering to repair or regenerate organs, and mitochondrial-targeted therapies, focusing on improving cellular energy production (268). Collectively, these innovative approaches aim to slow or reverse the detrimental effects of aging, offering potential pathways to healthier aging (269).

5.1. Caloric restriction and dietary interventions

Caloric restriction (CR) and other dietary interventions have been widely researched for their potential anti-aging effects (269-271). CR entails reducing calorie intake without causing malnutrition and has been shown to extend lifespan and delay the onset of age-related diseases in various organisms, including mammals (272). The anti-aging benefits of CR on stem cells are mediated through its influence on key cellular pathways involved in metabolism, stress response, and nutrient sensing (271, 273). These pathways help regulate how cells respond to energy levels, environmental stressors, and nutrient availability, all of which play critical roles in aging (274). By activating these mechanisms, CR enhances cellular repair processes, reduces oxidative damage, and improves the regenerative capacity of stem cells (275). This maintenance of stem cell function is crucial for tissue homeostasis and slowing the decline associated with aging (272, 276). As a result, CR offers a promising approach to promoting healthy aging, not only by extending lifespan but also by preserving the regenerative potential of stem cells, delaying the onset of age-

related dysfunction (277).

Influence of caloric restriction on stem cell aging

Caloric restriction (CR) has been shown to improve the function of several stem cell populations, including HSCs, neural stem cells (NSCs), and MSCs (271). In HSCs, CR enhances function by reducing oxidative stress and preventing the accumulation of DNA damage, both of which are key contributors to stem cell aging (270). This preservation of HSC function supports blood and immune system regeneration, which typically declines with age. For NSCs, CR has been found to increase neurogenesis—the production of new neurons—and improve cognitive functions, including learning and memory (272, 273). These effects are mediated through the modulation of key signaling pathways, such as the insulin/IGF-1 and AMP-activated protein kinase (AMPK) pathways, both of which play critical roles in cellular metabolism and stress response (274). By influencing these pathways, CR helps maintain NSC activity, which is essential for brain health and function during aging. Similarly, CR also benefits MSCs by promoting their regenerative potential, aiding in the maintenance of bone, cartilage, and muscle tissues (275, 276). Collectively, these effects of CR on stem cell populations highlight its broad potential in preserving tissue homeostasis and combating the detrimental effects of aging (272).

Role of nutrient-sensing pathways

Key nutrient-sensing pathways, such as AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), and sirtuins, play crucial roles in mediating the effects of CR on stem cell aging.

AMPK: Activation of AMP-activated protein kinase (AMPK) during caloric restriction (CR) boosts mitochondrial biogenesis and reduces oxidative stress, both of which contribute to improved stem cell function (278). By promoting the formation of new mitochondria, AMPK helps enhance energy production and cellular health, while lowering oxidative stress protects cells from damage and aging. This dual effect supports the maintenance and regenerative capacity of stem cells, enabling better tissue repair and overall function, which are key factors in healthy aging (278, 279). AMPK activation through CR thus plays a crucial role in sustaining stem cell vitality (280, 281).

mTOR: Inhibition of the mTOR (mechanistic target of rapamycin) pathway has been linked to increased stem cell self-renewal and delayed stem cell aging (282). The mTOR pathway plays a key role in regulating cell growth and metabolism, and its suppression helps reduce cellular stress and aging-related damage (283). Rapamycin, a well-known mTOR inhibitor, has demonstrated potential in enhancing the regenerative capacity of aging stem cells. By inhibiting mTOR, rapamycin promotes stem cell maintenance and improves their ability to regenerate tissues, which is crucial for maintaining tissue health during aging (284). This has made mTOR inhibition an attractive therapeutic target for promoting longevity and mitigating age-related decline in stem cell function (285, 286).

Sirtuins: NAD+-dependent deacetylases, known as sirtuins, are activated by caloric restriction (CR) and play a vital role in regulating cellular metabolism, stress response, and longevity (287). Sirtuin activation enhances mitochondrial function, improving energy production and cellular health, while also reducing inflammation in aging stem cells. This dual action is crucial for preserving stem cell function and delaying age-related decline (288). By boosting mitochondrial efficiency and limiting chronic inflammation, sirtuins help maintain stem cells' regenerative potential, supporting tissue repair and overall health during aging. This makes sirtuin activation an important mechanism in CR's anti-aging effects (289).

Potential of dietary interventions

In addition to caloric restriction, other dietary approaches such as intermittent fasting, ketogenic diets, and supplementation with specific nutrients have shown potential in delaying stem cell aging and improving tissue regeneration (278, 279). Intermittent fasting and ketogenic diets influence nutrient-sensing pathways, promoting cellular repair processes and enhancing the regenerative capacity of stem cells. Supplementing with nutrients like nicotinamide riboside, which boosts NAD+ levels, further supports these effects by activating sirtuins and improving mitochondrial function. These dietary strategies help modulate key pathways involved in metabolism and stress response, offering a non-invasive method to rejuvenate aging stem cells and improve tissue repair (280). By targeting the fundamental mechanisms of cellular aging, such approaches may provide effective means to promote healthy aging and combat age-related tissue degeneration (270).

5.2. Genetic and epigenetic reprogramming

Genetic and epigenetic reprogramming strategies aim to reverse age-related changes in gene expression, restoring a more youthful state in aging stem cells. By resetting the epigenetic landscape, these approaches can rejuvenate stem cells, enhancing their ability to regenerate tissues and maintain tissue homeostasis (256). A groundbreaking development in this field is the reprogramming of somatic cells into iPSCs, which has transformed regenerative medicine. iPSCs can differentiate into various cell types, offering the potential to replace damaged or aged tissues (126). This technology has opened new possibilities for treating age-related diseases by providing patient-specific cells for repair and regeneration. By reversing cellular aging markers and restoring stem cell function, genetic and epigenetic reprogramming represents a promising approach to combat aging and improve longevity in therapeutic settings (65).

Induced pluripotent stem cells (iPSCs)

iPSCs are created by reprogramming somatic cells through the introduction of specific transcription factors, such as Oct4,

Sox2, Klf4, and c-Myc. This process resets the cells' epigenetic landscape, effectively rejuvenating them and restoring their ability to differentiate into any cell type, a property known as pluripotency (118). iPSC technology holds great promise for generating patient-specific stem cells, offering new possibilities for personalized regenerative therapies. However, several challenges must be overcome for its clinical application. Issues such as the risk of tumorigenesis, genetic instability, and immune rejection pose significant hurdles (225). Tumor formation can result from the reprogramming process, while genetic instability might affect cell safety. Additionally, immune rejection could occur despite the patient-specific nature of iPSCs. Addressing these challenges is crucial for safely harnessing the full potential of iPSCs in treating diseases and promoting tissue regeneration (118).

Partial reprogramming to rejuvenate aging cells

An emerging strategy in regenerative medicine is "partial reprogramming," which involves the transient expression of reprogramming factors to rejuvenate aging cells without reverting them to a pluripotent state (90). This approach has shown promise in reversing cellular senescence, improving mitochondrial function, and restoring the regenerative potential of various stem cell types. For instance, the application of partial reprogramming using the Yamanaka factors—Oct4, Sox2, Klf4, and c-Myc—has successfully rejuvenated aged muscle and NSCs, significantly enhancing their regenerative capabilities (244). By inducing a temporary state of reprogramming, this method can restore cellular health and function while avoiding the risks associated with full pluripotency, such as tumorigenesis (58). As research continues to unfold, partial reprogramming may emerge as a powerful tool for combating age-related decline and improving tissue regeneration, paving the way for innovative therapies in age-related diseases (237).

Epigenetic therapies

Epigenetic therapies aim to target age-associated changes in DNA methylation and histone modifications, restoring youthful gene expression patterns. These therapies involve the use of inhibitors of histone deacetylases (HDACs) and DNA methyltransferases (DNMTs), which have shown potential in reversing age-related epigenetic alterations and improving stem cell function (125). By modifying the epigenetic landscape, these inhibitors can enhance the ability of stem cells to regenerate tissues and maintain homeostasis. Additionally, compounds like resveratrol, known for their ability to activate sirtuins, also play a role in modulating the epigenetic environment. Sirtuin activation can improve mitochondrial function and reduce inflammation, further supporting stem cell maintenance (237). Together, these epigenetic therapies offer a promising avenue for addressing age-related decline in stem cell functionality and may contribute to healthier aging and enhanced tissue repair. As research progresses, these approaches could lead to innovative treatments for age-related diseases (105, 146).

5.3. Senolytics and senescence-targeting therapies

The accumulation of senescent cells in aging tissues significantly contributes to tissue dysfunction and impaired regeneration. These cells, while no longer dividing, can adversely affect their environment through the senescence-associated secretory phenotype (SASP), which releases inflammatory factors and disrupts neighboring cell function (267). Senolytics are a class of drugs designed to selectively eliminate senescent cells, effectively reducing their detrimental effects on tissue health. By removing these cells, senolytics can enhance tissue function and promote regeneration. Additionally, senescence-targeting therapies aim to modulate the SASP, mitigating its harmful impact without necessarily eliminating the senescent cells (290). By addressing the underlying mechanisms of cellular senescence, both senolytics and SASP-modulating therapies hold promise for improving tissue health, restoring regenerative capacity, and potentially extending healthy lifespan. Continued research into these strategies could lead to innovative treatments for age-related diseases and enhance the overall quality of life in aging populations (291, 292).

Development of senolytic drugs

Several senolytic agents, including dasatinib, quercetin, and fisetin, have demonstrated effectiveness in reducing the burden of senescent cells in animal models of aging. These drugs specifically target key survival pathways in senescent cells, promoting their selective elimination while sparing healthy cells (291). The removal of these dysfunctional cells is linked to significant improvements in tissue function, reduced inflammation, and enhanced stem cell activity. By clearing senescent cells, senolytics can help restore the regenerative capacity of tissues and improve overall health. In preclinical studies, treatments with these agents have shown promise in mitigating age-related decline, suggesting potential applications in clinical settings for age-related diseases (290). As research continues, the development and optimization of senolytic therapies may offer a novel approach to promote healthy aging and enhance the quality of life for aging populations. Further studies will be crucial to determine the long-term effects and safety of these therapies in humans (292).

Targeting the SASP to improve regenerative capacity

The senescence-associated secretory phenotype (SASP) is marked by the secretion of pro-inflammatory cytokines, growth factors, and proteases that disrupt the tissue microenvironment and impair stem cell function. This inflammatory milieu negatively impacts neighboring cells and can lead to further aging-related decline (290). Therapies designed to modulate the SASP, such as JAK/STAT inhibitors and NF-κB blockers, have shown promise in reducing inflammation and enhancing the regenerative potential of aging tissues. By targeting the SASP, these therapies may improve the niche environment for stem cells, facilitating better tissue repair and regeneration. Consequently, modifying the SASP could restore normal tissue function and promote

healthier aging (291). This approach highlights the importance of addressing the underlying mechanisms of cellular senescence to improve stem cell activity and overall tissue health, potentially leading to innovative strategies for treating age-related diseases and enhancing quality of life in older individuals. Continued research in this area is essential for clinical applications (292).

5.4. Stem cell transplantation and tissue engineering

Stem cell transplantation and tissue engineering present promising strategies for rejuvenating aging tissues and addressing age-related degenerative diseases. By harnessing the regenerative capabilities of stem cells, these approaches aim to restore tissue function and improve patient outcomes (293). Advances in stem cell biology have deepened our understanding of stem cell properties, enabling the development of more effective therapies. Innovations in biomaterials have significantly enhanced the delivery and integration of stem cells into damaged tissues, improving the overall efficacy of stem cell-based interventions (106). Tissue engineering combines scaffolding materials with stem cells to create artificial tissues that can replace damaged ones, supporting cell survival and providing the necessary microenvironment for stem cell differentiation and function. Additionally, 3D bioprinting technologies allow for the precise construction of complex tissue structures that mimic natural tissues (211). Together, these advancements offer exciting possibilities for developing effective therapies to combat the effects of aging, potentially making stem cell transplantation and tissue engineering integral components of regenerative medicine and improving the quality of life for older adults (100).

Autologous stem cell transplantation

Autologous stem cell transplantation involves utilizing a patient's own stem cells to regenerate damaged or aged tissues, which significantly reduces the risk of immune rejection and other complications associated with allogeneic transplants (244). This approach capitalizes on the patient's natural regenerative capacity, making it a safer and more personalized treatment option. Techniques for autologous transplantation typically include the isolation and expansion of various types of stem cells, such as MSCs, HSCs, or iPSCs derived from the patient's own tissues (237). Following the expansion process, these stem cells can be transplanted back into the patient to promote tissue repair and regeneration. This method has shown promising potential in treating a range of conditions, including osteoarthritis, cardiovascular diseases, and neurodegenerative disorders, where conventional therapies may fall short (243). By harnessing the body's own stem cells, autologous transplantation not only enhances the likelihood of successful integration and regeneration but also paves the way for personalized medicine approaches that cater to individual patient needs, ultimately improving clinical outcomes and quality of life (202).

Tissue engineering and creation of rejuvenated niches

Tissue engineering integrates stem cells, scaffolds, and growth factors to develop functional tissue constructs capable of replacing or repairing damaged tissues. This interdisciplinary approach utilizes biomaterials designed to mimic the natural extracellular matrix, which plays a crucial role in supporting cell attachment, proliferation, and differentiation (220). By closely resembling the physiological environment, these biomaterials enhance the integration and function of transplanted stem cells, thereby improving tissue regeneration outcomes. Moreover, engineering rejuvenated niches by incorporating young systemic factors or anti-inflammatory agents into the scaffolds can significantly augment the regenerative capacity of aged stem cells. These factors help create a more favorable microenvironment that mitigates age-related decline, promoting better cell survival and functionality (212). As a result, engineered tissues not only support the healing of damaged areas but also potentially restore the overall health of aging tissues. This innovative approach holds great promise for treating various degenerative diseases, enabling the development of personalized therapies that harness the body's regenerative potential and improve the quality of life for patients with age-related conditions (199). With ongoing research and technological advancements, tissue engineering is poised to revolutionize regenerative medicine and offer effective solutions for tissue repair and replacement (294).

5.5. Mitochondrial-targeted therapies

Mitochondrial dysfunction is a hallmark of aging that significantly contributes to the decline in stem cell function. As mitochondria play a crucial role in energy production and cellular metabolism, their impairment can lead to reduced ATP levels, increased oxidative stress, and compromised cellular health (71). Strategies focused on improving mitochondrial function, such as the use of antioxidants or compounds that enhance mitochondrial biogenesis, hold promise for restoring the regenerative capacity of aging stem cells. By mitigating oxidative stress and enhancing energy production, these approaches can rejuvenate stem cells, promoting their ability to repair and regenerate tissues effectively (92). Additionally, interventions that target mitochondrial health may also improve the overall function of aged tissues, contributing to healthier aging. As research advances in this area, enhancing mitochondrial function in aging stem cells could become a key therapeutic strategy for combating age-related decline and promoting tissue regeneration in various degenerative diseases (253).

Enhancing mitochondrial function

Several approaches have been explored to improve mitochondrial function in aging stem cells:

Mitochondrial biogenesis: Activating pathways that promote mitochondrial biogenesis, such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated

receptor gamma coactivator 1-alpha (PGC-1α), can significantly enhance mitochondrial function and energy production in aging stem cells (237). AMPK serves as an energy sensor that, when activated, initiates process to boost mitochondrial mass and efficiency. Similarly, PGC-1α is a key regulator of mitochondrial biogenesis, driving the expression of genes involved in energy metabolism (70). By stimulating these pathways, it is possible to rejuvenate aging stem cells, improve their regenerative capacity, and enhance overall cellular health, ultimately contributing to healthier aging and tissue repair (61).

Antioxidant therapies: The use of antioxidants, such as N-acetylcysteine (NAC) and mitochondrial-targeted antioxidants like MitoQ, can effectively reduce oxidative damage and enhance stem cell maintenance. NAC acts as a precursor to glutathione, a powerful antioxidant that helps neutralize reactive oxygen species (ROS) and mitigate oxidative stress within cells (295). This reduction in oxidative damage is crucial for maintaining the health and functionality of stem cells, particularly as they age. MitoQ, on the other hand, is specifically designed to target mitochondria, delivering antioxidant protection directly where it is most needed. By reducing oxidative stress in these organelles, MitoQ can help preserve mitochondrial function and support energy production in aging stem cells (296). Together, these antioxidants offer promising strategies for improving stem cell viability and regenerative capacity, ultimately contributing to better tissue repair and healthier aging. Continued research into their effects may lead to innovative therapies for age-related degenerative diseases (297).

NAD+ restoration: NAD+ levels decline with age, significantly impacting mitochondrial function and cellular metabolism. This reduction in NAD+ is associated with various age-related health issues, including diminished stem cell activity. Supplementation with NAD+ precursors, such as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), has demonstrated the ability to restore mitochondrial function and enhance stem cell activity in animal models of aging (298). These precursors facilitate the biosynthesis of NAD+, which plays a crucial role in energy production and the regulation of cellular processes. By replenishing NAD+ levels, NR and NMN can improve mitochondrial health, boost metabolic efficiency, and enhance the overall regenerative capacity of aging stem cells (299). This approach highlights the potential of NAD+ supplementation as a therapeutic strategy to combat age-related decline, offering promising avenues for improving tissue repair and promoting healthier aging in humans. Continued research is essential to fully understand the benefits and mechanisms of these NAD+ precursors in stem cell biology and aging (288).

Mitochondrial replacement therapy: Mitochondrial replacement therapy (MRT) is an innovative approach that involves replacing dysfunctional mitochondria in aging cells with healthy mitochondria. This technique has shown promise in enhancing mitochondrial function and reversing age-related decline in stem cell activity (300). By providing healthy mitochondria, MRT can help restore energy production and reduce oxidative stress, which are crucial for maintaining cellular health and function. Although MRT is still in the experimental stages, preliminary research suggests it could serve as a potential future strategy for rejuvenating aged stem cells and improving tissue regeneration (301). This could have significant implications for treating age-related diseases and promoting healthier aging. As the understanding of mitochondrial dynamics and their role in cellular aging continues to evolve, MRT may emerge as a transformative therapeutic option. Continued research and clinical trials will be essential to evaluate the safety and efficacy of this approach, paving the way for its potential application in regenerative medicine and anti-aging therapies (302).

6. Challenges and future directions

The development of therapeutic approaches aimed at counteracting age-related declines in stem cell function holds great promise for regenerative medicine; however, several significant challenges must be addressed to translate these strategies into clinical practice (92). One major hurdle is ensuring the safety and efficacy of treatments, particularly when dealing with stem cell manipulation and transplantation, as concerns about tumorigenesis, genetic instability, and immune rejection must be thoroughly evaluated to minimize risks. Additionally, the complexities of the aging process complicate the identification of effective therapeutic targets, given that age-related changes are multifaceted and involve numerous cellular pathways (303). Another challenge lies in the scalability and reproducibility of stem cell therapies, making the development of standardized protocols for stem cell isolation, expansion, and differentiation crucial for consistent outcomes. Furthermore, effectively delivering these therapies to the appropriate tissue sites in a controlled manner remains a significant obstacle (247). Future directions to overcome these challenges include advancing technologies such as gene editing, improved biomaterials for stem cell delivery, and refined methods for assessing treatment safety (303). Collaborative research efforts among scientists, clinicians, and regulatory bodies will be essential to foster innovation and ensure the successful translation of stem cell rejuvenation therapies into clinical practice for aging populations (301).

6.1. Overcoming hurdles in stem cell rejuvenation

Despite the promising results of various interventions aimed at rejuvenating aging stem cells, several technical and biological challenges remain.

Tumorigenesis and safety concerns

The potential for tumorigenesis is a significant concern in stem cell-based therapies, especially with genetic and epigenetic reprogramming techniques. Introducing pluripotency factors to

reprogram somatic cells carries the risk of inducing uncontrolled cell proliferation and malignant transformation (155). This risk is compounded by the possibility of generating teratomas, which are tumors that can arise from pluripotent stem cells. Similarly, the use of senolytic drugs, which aim to eliminate senescent cells, may inadvertently promote the survival of pre-cancerous cells that could evade treatment (53). Such outcomes highlight the need for a careful assessment of the risks and benefits associated with these therapies. Developing safer reprogramming methods, including more targeted approaches that minimize the potential for malignancy, is essential for advancing stem cell research (119). Ongoing studies should focus on identifying biomarkers for early detection of tumorigenesis and implementing rigorous safety protocols to ensure the long-term safety and efficacy of stem cell-based therapies (28).

***Immune rejection and allogeneic* transplants**

Stem cell therapies frequently involve the transplantation of cells derived from donors, known as allogeneic transplants, which can lead to immune rejection and other immune-related complications. While autologous stem cell therapies, which utilize the patient's own cells, may reduce the risk of rejection, they are often time-consuming and costly (106). Additionally, the age-related decline in the function of autologous stem cells can limit their therapeutic potential. These challenges underscore the need for innovative solutions in stem cell therapy. Developing immunomodulatory strategies could help create a more favorable environment for transplant acceptance, minimizing the risk of rejection (304). Furthermore, employing gene-editing techniques to reduce the immunogenicity of allogeneic stem cells may enhance their compatibility and effectiveness in diverse patient populations (305). By addressing these immunological challenges, researchers can improve the feasibility and outcomes of stem cell therapies, ultimately advancing the field of regenerative medicine and expanding treatment options for various degenerative diseases (306).

Stem cell survival and integration in aged tissues

The effectiveness of stem cell-based therapies relies heavily on the ability of transplanted cells to survive, integrate, and function within the aged tissue environment. However, the aged niche is often characterized by chronic inflammation, oxidative stress, and impaired signaling, which can significantly hinder the survival and regenerative potential of transplanted stem cells. These adverse conditions create a challenging environment that diminishes the effectiveness of stem cell therapies (305). To improve therapeutic outcomes, enhancing the local microenvironment through niche engineering is crucial. This can involve creating a supportive scaffold that mimics the natural extracellular matrix or delivering factors that promote a healthier environment. Additionally, implementing anti-inflammatory treatments can help reduce chronic inflammation, allowing transplanted cells to thrive (269). Preconditioning of stem cells prior to transplantation, such as exposing them to mild stressors or specific growth factors, may also enhance their resilience and functionality once integrated into the aged tissue (307). By addressing the challenges posed by the aged niche, these strategies could significantly improve the success of stem cell therapies in regenerative medicine (308).

Long-term efficacy and sustainability

While several interventions show promise in reversing age-related declines in stem cell function, the long-term efficacy and sustainability of these approaches remain uncertain. It is crucial to determine whether these therapies can provide lasting benefits or if repeated treatments will be necessary to maintain their effects (309). Understanding the duration of the therapeutic impact is essential for evaluating the overall feasibility and practicality of these interventions in clinical settings. Furthermore, it is vital to investigate the potential side effects and unintended consequences associated with long-term use of these therapies (310). Prolonged interventions could lead to unforeseen complications, such as altered cellular behavior, immune responses, or even the promotion of tumorigenesis (311). Thorough research and long-term studies are needed to assess the safety profiles of these treatments and ensure they do not compromise patient health. By addressing these critical questions, researchers can work towards developing safe, effective, and sustainable therapies that genuinely enhance stem cell function and promote healthy aging (312).

6.2. Personalized medicine and stem cell therapies

The future of regenerative medicine lies in personalized approaches that take into account individual variations in genetics, lifestyle, and environmental factors. Tailoring stem cell therapies to the unique needs of each patient could significantly improve therapeutic outcomes and minimize adverse effects.

Patient-specific stem cells

The use of patient-specific stem cells, particularly iPSCs derived from an individual's somatic cells, presents a significant advancement in personalized regenerative therapies. This approach enables the generation of autologous transplants that are less likely to be rejected by the immune system, thereby reducing complications associated with immune rejection often seen in allogeneic transplants (313). Moreover, iPSCs hold immense potential for correcting disease-causing mutations through genetic modification, offering a potential cure for genetic disorders. By reprogramming somatic cells into a pluripotent state, iPSCs can be differentiated into various cell types needed for therapy, tailored specifically to the patient's requirements (314). This not only enhances the likelihood of successful integration and function within the recipient's tissue but also empowers patients with personalized treatment options that target the underlying causes of their conditions. As research progresses, the application of patient-specific iPSCs could revolutionize

the field of regenerative medicine, paving the way for innovative therapies that improve patient outcomes and quality of life (315).

Targeting individual aging pathways

Aging is a complex and multifactorial process, and the rate of stem cell decline can vary significantly among individuals. This variability highlights the need for personalized medicine approaches that target specific aging pathways, such as telomere maintenance, epigenetic alterations, and mitochondrial dysfunction (225). By focusing on these individual factors, tailored interventions can be developed to more effectively address age-related diseases. Furthermore, the advancement of biomarkers to assess the biological age of stem cells and predict their regenerative potential could greatly enhance the design of individualized therapies (316). These biomarkers would enable clinicians to evaluate the functional capacity of a patient's stem cells, guiding treatment decisions and optimizing therapeutic outcomes. By integrating personalized approaches with biomarker assessments, healthcare providers can create targeted strategies that enhance stem cell function, improve tissue regeneration, and ultimately promote healthier aging (317). As research continues to uncover the intricacies of aging and stem cell biology, the potential for personalized interventions in regenerative medicine will become increasingly feasible and impactful (318).

6.3. Ethical and clinical considerations

The application of stem cell-based therapies for aging raises several ethical and clinical challenges that must be carefully considered to ensure responsible and equitable use.

Ethical challenges in stem cell research

Ethical concerns surrounding the use of stem cells, particularly ESCs, have been a longstanding issue in regenerative medicine. The derivation of ESCs involves the destruction of human embryos, raising significant questions about the moral status of the embryo and the implications of such actions (319). While iPSCs and adult stem cells provide alternative sources that circumvent these ethical dilemmas, they are not without their own set of concerns. Issues regarding the long-term safety of these technologies remain a critical topic of discussion, particularly in light of potential risks associated with genetic modifications or unforeseen side effects (320). Additionally, the possibility of misuse of stem cell technologies, such as genetic enhancement or anti-aging treatments aimed at life extension, raises ethical questions about the implications for societal inequality and the definition of a "normal" human lifespan (321). As the field of stem cell research continues to advance, it is essential to engage in ongoing ethical deliberation and establish robust regulatory frameworks to ensure responsible use of these powerful technologies, balancing innovation with moral considerations (322).

Access to stem cell therapies

As stem cell therapies become more advanced, ensuring equitable access to these treatments will present a significant challenge. The high costs associated with developing and delivering personalized regenerative therapies may restrict availability to a limited subset of the population, raising concerns about equity in healthcare (301). If these therapies remain accessible only to those who can afford them, they could exacerbate existing health disparities and create a divide between socioeconomic groups. Policymakers and healthcare systems must prioritize strategies that promote inclusive access to these innovations, ensuring that advances in stem cell research benefit a broad range of patients, regardless of their financial situation (322). This may involve developing funding models, subsidizing treatment costs, and fostering partnerships between public and private sectors to support research and delivery. Additionally, efforts should be made to raise awareness and educate communities about available treatments (237). By addressing these challenges proactively, the healthcare system can strive to provide equitable access to stem cell therapies, promoting justice and fairness in the evolving landscape of regenerative medicine (322).

Regulatory and Clinical Trial Challenges

Bringing stem cell therapies to market necessitates rigorous regulatory oversight to ensure their safety and efficacy. Clinical trials for stem cell-based treatments encounter several challenges, including patient heterogeneity, the complexity of stem cell biology, and the requirement for long-term follow-up to assess outcomes and potential side effects (323). The diverse responses among individuals can complicate the evaluation of treatment effectiveness and safety. Additionally, the intricate mechanisms governing stem cell behavior and their interactions with the host environment require careful consideration in trial design. As such, regulatory agencies must adapt to the unique characteristics of stem cell therapies, moving beyond traditional frameworks to establish appropriate guidelines for their evaluation and approval (324). This may involve developing specialized protocols that account for the specific risks and benefits associated with stem cell interventions, as well as facilitating adaptive trial designs that allow for modifications based on emerging data (325). By ensuring that regulatory processes are tailored to the distinct nature of stem cell therapies, agencies can help expedite the development of safe and effective treatments while maintaining high standards of patient safety (326).

6.4. Emerging technologies in stem cell research

The field of stem cell research is rapidly advancing, with new technologies offering the potential to overcome current limitations and open new avenues for rejuvenation and regenerative medicine.

CRISPR and genome editing

CRISPR-Cas9 and other genome-editing technologies have revolutionized the field of genetic engineering by providing precise tools for editing the genome. These advanced technologies enable researchers to correct genetic mutations,

enhance stem cell function, and mitigate the risk of tumorigenesis associated with stem cell therapies (141). The ability to perform targeted genome editing in stem cells holds immense promise for personalized medicine, allowing for the customization of treatments tailored to the unique genetic profiles of individual patients. This can be particularly beneficial in treating genetic disorders, where specific mutations can be corrected at the genomic level, potentially offering a cure rather than merely managing symptoms (302). Furthermore, genome editing can enhance the safety and efficacy of stem cell therapies by ensuring that cells used in treatment are genetically optimized for better integration and function within the host environment. As research progresses, the integration of CRISPR-Cas9 and similar technologies into stem cell therapies could lead to groundbreaking advancements in regenerative medicine, transforming the landscape of treatment options available for various diseases and conditions (293).

Single-cell RNA sequencing

Single-cell RNA sequencing (scRNA-seq) has emerged as a powerful tool that allows researchers to examine gene expression at the level of individual cells. This technology provides critical insights into the heterogeneity of stem cell populations and the molecular mechanisms underlying aging (109). By analyzing the gene expression profiles of individual stem cells, scRNA-seq can identify specific subpopulations that are more susceptible to age-related decline, revealing the distinct biological pathways and stress responses that characterize these cells (90). This detailed understanding can guide the development of targeted therapies aimed at rejuvenating these vulnerable stem cell populations, potentially improving tissue regeneration and restoring functionality in aged tissues (110). Moreover, scRNA-seq can help uncover biomarkers associated with stem cell aging, facilitating the design of personalized treatment strategies tailored to the unique characteristics of an individual's stem cell landscape (262). As researchers continue to explore the implications of scRNA-seq in stem cell biology, its potential to inform therapeutic interventions for age-related diseases becomes increasingly evident, paving the way for advancements in regenerative medicine (92).

Organoids and 3D bioprinting

Organoids, which are miniature, self-organizing tissue structures derived from stem cells, have emerged as invaluable tools for studying tissue development, disease modeling, and drug testing. These "mini-organs" can effectively recapitulate the cellular architecture and function of human tissues, providing a robust platform for personalized medicine applications (208). Their ability to mimic the in vivo environment makes organoids particularly useful for understanding disease mechanisms and testing therapeutic interventions in a controlled setting. Additionally, advancements in 3D bioprinting technology enable the fabrication of complex tissue constructs, further enhancing their application in tissue engineering and regenerative therapies (327). By integrating stem cells, biomaterials, and bioengineering techniques, researchers can create functional tissues and organs that can be used for transplantation or to model human diseases more accurately. This innovative approach holds great promise for addressing the challenges of organ shortages and developing personalized therapeutic strategies, ultimately contributing to the future of regenerative medicine and improving patient outcomes (328). The combination of organoids and bioprinting is poised to revolutionize our understanding of human biology and the development of effective treatments for a range of conditions (329).

6.5. Potential breakthroughs in reversing age-related stem cell decline

Future research may lead to breakthroughs that can effectively reverse age-related declines in stem cell function, potentially extending healthy lifespan and improving regenerative outcomes.

Discovery of new molecular targets

Ongoing research is poised to uncover new molecular targets involved in stem cell aging and tissue regeneration. By identifying key regulators of stem cell function, including transcription factors, signaling pathways, and metabolic enzymes, scientists can gain deeper insights into the mechanisms driving stem cell behavior and aging (76). These discoveries may pave the way for the development of novel therapeutic agents specifically designed to target these pathways, aiming to rejuvenate aging stem cells and enhance their regenerative capacity. For instance, targeting specific signaling pathways that influence cell fate decisions could improve stem cell viability and functionality in aged tissues (66). Additionally, understanding the metabolic shifts that occur during stem cell aging could inform strategies to optimize energy production and reduce oxidative stress in these cells. As researchers continue to explore the intricate molecular landscape of stem cells, the potential for innovative therapies that harness these insights grows, offering promising avenues for improving tissue regeneration and combating age-related decline (28). Such advancements could ultimately transform the field of regenerative medicine, leading to effective interventions for a range of age-associated diseases (128).

Combining multiple therapeutic approaches

Combining different therapeutic approaches, such as caloric restriction, senolytics, mitochondrial-targeted therapies, and genetic reprogramming, may yield synergistic effects that significantly enhance stem cell rejuvenation and tissue repair. A multi-faceted strategy that simultaneously targets various aspects of aging could prove more effective than single interventions alone (53). For instance, caloric restriction can improve cellular metabolism and reduce oxidative stress, while senolytics can eliminate senescent cells that hinder tissue regeneration. Mitochondrial-targeted therapies can enhance energy production and reduce damage from reactive oxygen

species, and genetic reprogramming can restore youthful gene expression patterns in aging stem cells (330). By integrating these approaches, researchers may be able to create a comprehensive therapeutic regimen that not only rejuvenates stem cells but also creates a more favorable microenvironment for tissue repair. This holistic strategy acknowledges the complexity of aging and aims to address it from multiple angles, ultimately leading to improved outcomes in regenerative medicine and potentially extending healthy lifespan (331). As research advances, the development of combination therapies could represent a significant leap forward in our ability to combat age-related decline and enhance the body's regenerative capabilities (332).

Development of "Youth Factors" for rejuvenation

The identification of "youth factors" present in young organisms that promote tissue regeneration could pave the way for developing rejuvenating therapies. For instance, proteins or extracellular vesicles derived from young plasma may hold the potential to reverse age-related decline in stem cell function and improve tissue health (333). Parabiosis experiments, which involve connecting the circulatory systems of young and aged animals, have demonstrated that young systemic factors can rejuvenate aged tissues, highlighting the role of these factors in enhancing regenerative processes. However, while these findings are promising, the isolation and clinical application of specific youth factors require further investigation to understand their mechanisms and therapeutic potential fully (334). Researchers must work to identify the precise molecules responsible for these rejuvenating effects and explore how they can be effectively delivered in clinical settings. Additionally, addressing challenges related to safety, dosage, and long-term effects will be essential for translating these discoveries into viable therapeutic strategies (335). As research progresses, the development of therapies based on youth factors could revolutionize approaches to combatting age-related decline and promoting healthier aging (336).

7. Conclusion

The decline in stem cell function with age plays a central role in the progressive deterioration of tissue homeostasis, repair, and regeneration. Understanding the molecular mechanisms underlying age-related changes in stem cells and their niches is crucial for developing effective strategies to combat age-related diseases and promote healthy aging. This review highlights the complex interplay between intrinsic factors, such as telomere shortening, DNA damage, epigenetic changes, and mitochondrial dysfunction, and extrinsic factors, including alterations in the stem cell niche and systemic signals, that drive stem cell aging. Intrinsic factors contribute to the cellular aging process by compromising stem cell viability and functionality, while extrinsic factors can create an unfavorable microenvironment that hinders stem cell activity. By elucidating these interconnected mechanisms, researchers can identify potential therapeutic targets and devise interventions aimed at rejuvenating aging stem cells and restoring tissue regeneration. Ultimately, advancing our understanding of stem cell aging is essential for developing innovative approaches to enhance health span and mitigate the impact of aging on overall well-being. This knowledge could lead to transformative therapies that address the root causes of age-related decline and improve the quality of life for aging populations. Stem cell biology has the potential to transform the landscape of aging medicine and pave the way for a future where regenerative therapies extend not just lifespan but health span.

Conflict of interest

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