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Therapeutics of Stem Cell Treatment in Anti-Aging and Rejuvenation

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Abstract

Aging populations are increasing the incidence of age-related diseases, resulting in problems at the individual and socioeconomic level. The need for effective strategies in regenerative medicine for the elderly is more important than ever. Previous studies have shown that the number and function of stem cells decline with age, thereby undermining endogenous repair processes. It has also been suggested that the aging-induced deterioration of stem cell function may play a key role in the pathophysiology of various aging-related diseases. Recent advances in our understanding of tissue regeneration and the development of methods aimed at inducing and differentiating pluripotent stem cells for cell replacement therapy which provides exciting opportunities for the treatment of degenerative diseases, such as those related to senility. In this review article, we examine several mechanisms that are believed to contribute to the aging-related dysfunction of stem cells associated with diseases of the immune system, cardiac tissue, neuronal system, articular cartilage, and skeletal muscle. We also discuss factors that affect the therapeutic potential of adult stem/progenitor cells as well as current trends in the treatment of these conditions using regenerative medicine.

Keywords

Stem Cell, Anti-Aging, Rejuvenation, Immune System, Cardiac Tissue, Central Nerve System, Articular Cartilage and Skeletal Muscle

1. Introduction

Aging-related tissue changes and stem cell depletion in mammals lead to imbalances in tissue homeostasis and decreased organ regenerative capacity [1] [2]. The mediation of aging by complex cellular and physiological processes is driven

by various acquired and genetic factors [3]. The physiological processes of aging often lead to destructive diseases, such as dementia, autoimmunity, arthritis, cardiovascular disease, cancer, tissue degeneration, neuropathy, stroke, obesity, and depression [4] [5] [6] [7]. The effects of aging are particularly noticeable in retarded eyesight, hearing, muscle strength, and bone strength [8]. Regenerative medicine can reverse or inhibit many of these health problems through the use of endogenous stem cells or exogenous replacement cells derived from stem or progenitor cells to restore or rejuvenate tissue and maintain homeostasis [9] [10] [11]. This approach is a promising strategy for rehabilitation and reducing age-related diseases [12]. In this review, we discuss several mechanisms believed to contribute to aging-related stem cell dysfunction. We also briefly discuss the neutralizing ability of stem cells and other life extension factors used to treat conditions of the immune system [13], cardiac tissue [14], central nerve system [15], articular cartilage [16], and skeletal muscle [17]. Researchers have shown that stem cell interventions could one day be used to delay senescence and prolong lifespan.

2. Impact of Stem Cell Senescence in Aging and Diseases

Tissue-specific stem cells are capable of self-renewal and differentiation to produce mature effector cells, which play a crucial role in prolonging tissue function [3] [18]. Adult stem cells, also known as somatic stem cells, serve as self-renewing cell pools to supplement senescent cells and regenerate damaged tissues throughout the body. Mesenchymal stem cells [19], cartilage progenitor [20], satellite cells [21], and adipose derived stem cells [22] are pluripotent stem cells capable of differentiating into mesenchymal tissue cells. There is ample evidence that a decline in the number of stem cells is an important factor in the initiation of several diseases associated with the aging process [23]. It has been hypothesized that the loss of stem cell populations and/or activity over time contributes to this decline. Previous research has explored key molecular pathways that are often disrupted when tissue and stem cell senescence and degradation, and experimental evidence supports these pathways themselves can reverse the aging phenotype. However, the mechanisms related to the rejuvenation of tissues have yet to be fully elucidated [24].

Epigenetic regulation is essential for establishing and maintaining stem cell function, and evidence suggests that epigenetic dysregulation leads to potential changes in stem cells during aging [18] [25] [26] [27]. The term epigenetics refers to changes in gene expression that do not involve changes in the underlying DNA sequence [28] [29]. Hereditary changes in epigenetic landscapes produced in stem cells can be passed on to offspring with functional consequences exhibited in downstream lineages. Changes in dynamic chromatin structure, including DNA methylation and histone modifications, are keys to stem cell function. Protein coding information is encoded in the genome by the nucleotide sequence, whereas epigenetic information can be encoded by chemically modify-

ing the cytosine base [30] [31] [32]. Methylated cytosine is found throughout the genome, mainly in the promoter region of housekeeping and developmental regulatory genes. The methylated cytosine is predominantly found within CpG dinucleotides [33]. Another epigenetic regulation that does not directly alter the nucleotide chemistry of DNA involves histone modification. Unlike genomic lesions that occur during aging, age-related epigenetic changes are not permanent. Appropriate epigenetic regulation of stem cells is critical to the maintenance of tissue, which is particularly important given that stem cells can genetically transmit epigenetic markers to their offspring.

Autophagy is one of the hallmarks of aging [34]. It is a constitutive pathway associated with damage to organelles and protein aggregates through a decline in the number and function of stem cells [3] [35]. Recent studies have shown that stem cells require autophagy to eliminate cellular waste generated during quiescence. Autophagy promotes cell survival by helping to maintain cell homeostasis and proper metabolic functions under conditions of stress and by maintaining bioenergetic levels and amino acid pools [36] [37]. Several studies have described the decline in autophagy activity and the expression of autophagic genes, such as ATG1, ATG5, ATG6, ATG7, ATG8, and ATG12 [38] [39] [40] [41]. Recent studies on muscle stem cells (MSCs) and hematopoietic stem cells (HSCs) have revealed impaired autophagy associated with a decline in stem cell activity [41] [42]. These findings indicate that at in advanced age, MSCs and HSCs lose their ability to regenerate and that defects in autophagy are present in aging stem cells. The effects of autophagy on maintaining cellular homeostasis open the door to novel therapies to deal with aging and age-related diseases.

It has been assumed that reactive oxygen species (ROS) may lead to a loss of differentiation [43] [44] [45]. Excessive production of ROS by environmental stresses triggers cellular senescence and the amorphous differentiation of MSCs. One member of the mitogen-activated protein kinase (MAPK) family, p38 MAPK, is an important mediator responsive to extracellular stressors [46] [47] [48]. The fact that p38 MAPK is involved in the molecular interaction during aging indicates that p53 is a major mediator of ROS-related signal transduction. The cyclin-dependent kinase inhibitor gene p16INK4a is believed to be a key factor in regulating oxidative stress-induced cell division and arresting the senescence of MSCs and tissue progenitor cells [49] [50]. It is generally believed that high levels of ROS promote senescence by inducing oxidative stress. This would mean that MSCs may contribute to organism aging by undermining tissue homeostasis.

Many types of monocytes are present in skeletal muscle, which are essential to the maintenance of stem cells, fibroblasts, and immune cells [23] [51] [52]. Age-related changes in the extracellular matrix (ECM), which can lead to pathogenicity, are associated with induced stiffness in skeletal muscle [53] [54]. These age-related changes affect stem cell behavior, and stromal cell proteins secreted by aged ECM and aged fibroblasts drive differentiation into fibroblasts

[55]. Thus, senescence is associated with intensive ECM deposition and loss of stem cell function, leading to reductions in regenerative capacity and strength. Age-related changes in the density and biophysical properties (*i.e.*, hardness) may have negative effects on the function of satellite cells. Directly or indirectly modifying ECM may provide a basis for age-related growth and insufficient strength [56] [57]. The regeneration of skeletal muscle depends on the dynamic interaction between muscle stem cells and the microenvironment or niche.

3. Stem Cells for Anti-Aging and Rejuvenation

Stem cells are characterized by their multiple-efficacy and self-renewal capabilities, resulting in progenitor or mature cells that can repair tissue and retain the characteristics of stem cells to ensure long-term maintenance of the stem cell pool [58] [59]. As stem cells age, their renewal ability deteriorates, and their ability to differentiate into various cell types is depleted. Based on current understanding of stem cells, it is feasible to design and test interventions to slow aging and improve health and longevity [8]. It is believed that stem cell failure contributes to a decline in health during aging; therefore, the development of effective methods to induce and differentiate pluripotent stem cells via cell replacement therapy provides an exciting avenue for the treatment of degenerative age-related diseases [12] [60] [61] [62]. It is believed that the regenerative potential of these cells is due to their high proliferation and differentiation capabilities, paracrine activity, and immune privilege [63]. Somatic stem cell populations differ according to the regenerative needs of the host tissue. In high turnover tissue, such as the gut or hematopoietic system, most stem cell or progenitor cell populations are active throughout life [64]. In organs lacking stem cells, inducing pluripotent stem cell (iPSC) to replace cells is a promising therapeutic approach for functional recovery [65] [66]. iPSCs restore the same developmental potential of embryonic stem cells, which means that they can then differentiate into any type of tissue. Stem cells play a key role in organogenesis and maintaining homeostasis throughout life, possess the ability to migrate long distances and target pathological conditions, express therapeutic genes, and respond to cues that redirect their differentiation into defective lineages [67]. This means that stem cells can be used for cell replacement as a therapeutic intervention aimed at mitigating the effects of aging.

4. Immune System Rejuvenation

In most species, including humans, the later stages of life see a decline in the overall maintenance of an organism and subsequent decline in health [68]. This also applies to hematopoietic systems, in which senescence is associated with increased susceptibility to hematological malignancies and other diseases. Hematopoietic stem cells are a continuous source of various lymphocytes and myeloid cells from early development through to old age [69] [70] [71]. Blood cells are responsible for the ongoing maintenance and immune protection of every cell

type. This leads to the production of billions of new blood cells by hematopoietic stem cells every hour [3] [12]. At the population level, the adaptive immune responses of elderly individuals are retarded. Studies on the process of blood cell formation have revealed that aging reduces adaptive immune responses and hemocyte components, leading to an increase in the incidence of myeloid diseases, including cancer [4] [72].

Rejuvenation is meant to reverse aging rather than simply delay it. Rejuvenation can be achieved through the reconstitution of endogenous hematopoietic stem cells or the transplantation of pluripotent hematopoietic stem cells, usually derived from bone marrow, peripheral blood, or umbilical cord blood [4] [73] [74]. The pharmacological modulation of deregulated factors is one strategy aimed at the reconstitution of endogenous HSCs. Currently, this type of intervention has achieved only partial rejuvenation. Previous proof-of-concept studies have shown that modulation of the HSC aging state can be achieved by targeting mTOR and cdc42 using exogenous agents [75] [76]. The recent use of novel compounds for the ablation of senescent cells has led to the renewal of hematopoietic stem cells and muscle stem cells in wild type aged mice, further demonstrating the efficacy of adult stem cells in overcoming the effects of aging [77]. Most research on the use of allogeneic hematopoietic stem cells for the treatment of hematological malignancies in the 1980s and early 1990s was restricted to young patients [78]. Hematopoietic stem cell transplantation is now considered a mature technology and remains an effective method for the treatment of patients presenting hematological symptoms.

5. Cardiac Rejuvenation

We are still far from a definite quantitative measure of cardiac turnover; however, it has finally been accepted that heart muscle cells can be regenerated after birth [24] [79] [80]. Nonetheless, mature cardiomyocytes are withdrawn from the cell cycle soon after birth [81] [82] [83]. The metabolism of cardiomyocytes requires the contribution of immature cells to myocyte, which are differentiation from cardiac stem cells, replacement repeatedly. However, senescent blasts and cardiomyocytes accumulate in the myocardium of elderly patients with severe systolic dysfunction. Patients with severe obstructive cardiac disease caused by the narrowing of atherosclerotic plaques present tissue retention and a reduction in the functionality of circulating vascular stem/progenitor cells to repair tissue damage [84]. This has led a number of researchers to use stem cell transplantation as a means to regenerate tissue heart in a process referred to as heart rejuvenation [24].

Researchers have recently succeeded in treating cardiovascular diseases using alternative approaches to regenerative medicine [84]. Systemic interventions involving the pharmacological removal of senescent cells inhibit pro-survival and anti-apoptotic pathways in senescent cells [85] [86]. The restoration of a juvenile microenvironment through the administration of systemic factors or the inhibi-

tion of pathways alters with age [24] [87] [88] [89]. Researchers have also investigated cell therapies involving the administration of young, healthy stem cells to a diseased heart to provide protection from cardiomyocyte senescence and promote cardiac repair [24] [90] [91]. They also investigated the *ex vivo* rejuvenation of reparative cells through the *in vitro* pharmacological pretreatment of stem cells isolated from old diseased animals followed by *in vivo* delivery. This approach was aimed at suppressing or activating modifications induced by the aging process, and epigenetic drugs were shown to at least partially restore changes associated with systemic disease [90] [92] [93]. Another approach was the genetic modification of stem cells to enhance functionality, such as the overexpression of the pro-survival kinase Pim-1 or nucelostemin to reverse cellular senescence [94] [95] [96]. Further studies have demonstrated the potential of these alternative therapeutic interventions.

6. Nerve System Rejuvenation

For decades, research proceeded on the assumption that the nervous system of adult mammals is unable to produce new neurons. However, the identification of neurogenic regions in the adult brain has prompted intense activity in the field of adult neurogenesis [97]. Most neurons are mitotic, and slow-cycle neural stem cells (NSC) maintain neural regeneration in specific areas of the mammalian brain during adulthood [98] [99]. Age-induced reduction in the number of satellite cells and neural stem cells undermines nerve regeneration [100]. Aging of the central nervous system is associated with the progressive loss of function, which can be exacerbated by neurodegenerative diseases, such as Alzheimer's disease, dementia, stroke, and Parkinson's disease [97] [101] [102] [103]. At the cellular level, senescence of the central nervous system is accompanied by a number of changes that impair cell function, including elevated levels of oxidative stress and oxidative damage associated with proteins and DNA [104]. It has also been linked to impaired cellular metabolism, lipid and protein by-products, and the accumulation of advanced glycation end products [97] [105]. The most notable age-related changes in the brain are associated with cognition and plasticity. Even in the absence of disease, aging can negatively affect nerve function. Recent data suggest that age-related defects in neural stem cells can be reversed through the reactivation of telomerase, suggesting that aged oligodendrocyte precursor cells can theoretically be used to preserve the regeneration of myelin sheaths [106]. In the adult central nervous system, remyelination is a spontaneous regenerative process that restores skip conduction, prevents axonal degeneration, and promotes functional recovery [107].

Most previous studies reported that cell therapy may be able to replenish lost cells and promote neuronal regeneration, protect neuron survival as well as play a role in overcoming permanent paralysis and sensory loss and restoring neurological function [108] [109]. Unfortunately, mechanisms for determining treatment capacity have yet to be identified [101] [110]. Previously researches im-

plied that possible mechanisms may include the following: 1) the promotion of angiogenesis, 2) induced neuronal differentiation and neurogenesis, 3) reduced reactive gliosis, 4) the inhibition of apoptosis, 5) the expression of neurotrophic factors, 6) immunomodulatory functions, and 7) the promotion of neuronal integration [101]. The two primary cell replacement strategies involve 1) the transplantation of exogenous tissue and 2) the endogenous activation of cell proliferation. Tissue can be transplanted directly in order to replace lost tissue. Genetically engineered cells can also be implanted for the secretion of factors that promote survival and/or proliferation [97] [111] [112]. The specialized microenvironment of the neural niche ensures that neural stem cells (NSCs) self-renew and differentiate but mainly enter the neurons [108] [113]. Thus, understanding the physiological characteristics of NSCs and how they are affected by changes in pathological conditions could open the door to exploiting the plasticity of NSCs for the prevention and/or treatment of degenerative diseases.

7. Articular Cartilage Rejuvenation

Articular cartilage injury is a debilitating disease that can result in fibrillation and the subsequent deterioration of the peripheral articular surface and may also involve the subchondral bone, thereby facilitating the development of osteoarthritis [114]. The special composition of the ECM gives it viscoelastic properties, which facilitate the normal function of the ECM. Collagen is hyaline cartilage composed of 60% (by dry weight) chondrocytes. Fibrocartilage and elastic cartilage are two other types of cartilage differing in ECM and cell components [115]. Age-induced changes in articular cartilage include chondrocytes acquiring a secretory phenotype, chondrocyte sensitivity to growth factors, the destructive effects of chronic ROS, and glycosylation of end products [116]. This disturbs the balance between anabolic activity and the destructive processes of chondrocytes. As the matrix decreases, articular cartilage becomes increasingly thin, the hydration of cartilage decreases, and the number of cartilage cells also decreases [115]. It appears that the bioactive paracrine factors secreted by mesenchymal stem cells (MSC) can have beneficial effects in regulating the microenvironment of damaged tissue, leading to more favorable conditions for tissue regeneration [117]. MSCs secrete a range of paracrine factors, collectively referred to as secreted proteomes, which perform a variety of biological functions, including immune regulation, angiogenesis, anti-apoptosis, anti-oxidation, cell homing, and the promotion of cell differentiation. Most previous studies have focused on the clinical benefits of MSC treatment, regardless of the source of the cells, the indications, or the mode of administration [114]. MSCs have been used in cell therapy to promote the repair of cartilage, muscle, or bone [115]. These cells are typically harvested from bone marrow and are characterized according to the stimulatory factors they provide [118]. Elucidating the mechanism that promotes the aging of articular cartilage could lead to treatments aimed at slowing aging-related changes or promoting the regeneration of articular cartilage.

8. Skeletal Muscle Rejuvenation

The extraordinary regenerative capacity of skeletal muscle can be attributed to a reserve pool of muscle-resident satellite cells located in the niche between muscles. These cells are essential to the repair and regeneration of muscle throughout life [62]. Recent studies have shown that cellular and extracellular factors are dysregulated during aging [55] [119] [120]. Aging is associated with a progressive loss of tissue function associated with a decrease in the functionality of muscle satellite cells and the total size of the muscle stem cell pool [121]. The aging of muscle is characterized by a decrease in repair capacity. Aging satellite cells show evidence of several intrinsic cellular changes associated with genomic instability, DNA damage, oxidative damage, and the deterioration of mitochondrial function [122]. Changes in homeostasis may explain the reduction in antioxidant activity, changes in protein folding, decreased myogenic differentiation, and tendency of these cells to adopt fibroblastic and adipogenic fates [123]. Another intrinsic change observed in the satellite cells of the elderly is an imbalance in protein homeostasis [35]. Satellite cells are also affected by the local microenvironment and systemic circulation, both of which are affected by aging. This means that changes in intrinsic cellular function and regenerative environmental cues tend to impair stem cell activity and reduce the regenerative capacity of aging muscle.

Interventions aimed at reversing age-related changes in satellite cells or their niche have been shown to partially restore the ability of aging muscle stem cells to regenerate. Current attempts to recover aged satellite cells include the genetic and pharmacological inhibition of p16INK4a [62] [124], STAT3 and p38 MAPK [125] [126] [127], autophagic flux [35], and NAD^+ recruitment [128] as well as the administration of hormones to revitalize oxytocin [129]. Satellite cells are essential to the maintenance and repair of many types of adult tissue during normal physiological processes as well as to the response to injury or aging [130]. Recent advances in the isolation of muscle satellite cells and the elucidation of the cellular and molecular media that control their activity have indicated that these cells are a promising therapeutic target [131]. Satellite cell-based therapy could involve the direct replacement of cells or the development of drugs that enhance endogenous muscle repair mechanisms. Satellite cells are a population of major regenerative cell in adult skeletal muscle that is capable of supporting multiple rounds of mature myofiber regeneration. These cells are attractive candidates for Duchenne muscular dystrophy, is a severe type of muscular dystrophy, and related disorders [132] [133] [134]. Previous studies have shown that at least some of the muscle satellite cells exhibit the characteristics of stem cells, such as self-renewal and differentiation. Transplanting these cells into damaged or malnourished muscle could produce permanent disease-resistant wild-type copies of genes that can incorporate into existing muscle fibers [132].

9. Conclusion

Over the past decade, researchers have made tremendous progress in under-

standing stem cell aging and the molecular mechanisms underlying this process [34]. Previous studies have also confirmed the extrinsic ingredients, and transplantation trials have identified the intrinsic components that cause an age-dependent decline in the number and function of stem cells [130]. This impairment can be attributed to changes in the intrinsic pathway of cells and the surrounding environment. Regenerative therapies focus on stem cells and other life-prolonging factors in an attempt to reverse aging. Clinical trials must also be conducted to determine whether genetically reprogramming stem cells delay senescence and enhance regeneration and whether the application of stem cells in aging individuals is ultimately approved. The *ex vivo* genetic modification of stem cells may also provide an effective strategy for rejuvenating older stem cells and diseased organs. Improved protocols for the rejuvenation of aging stem cells could help to improve the preparation and clinical application of stem cells harvested from aging tissues as well as their products.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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