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Perspective

Rejuvenation of Tissue Stem Cells by Intrinsic and Extrinsic Factors

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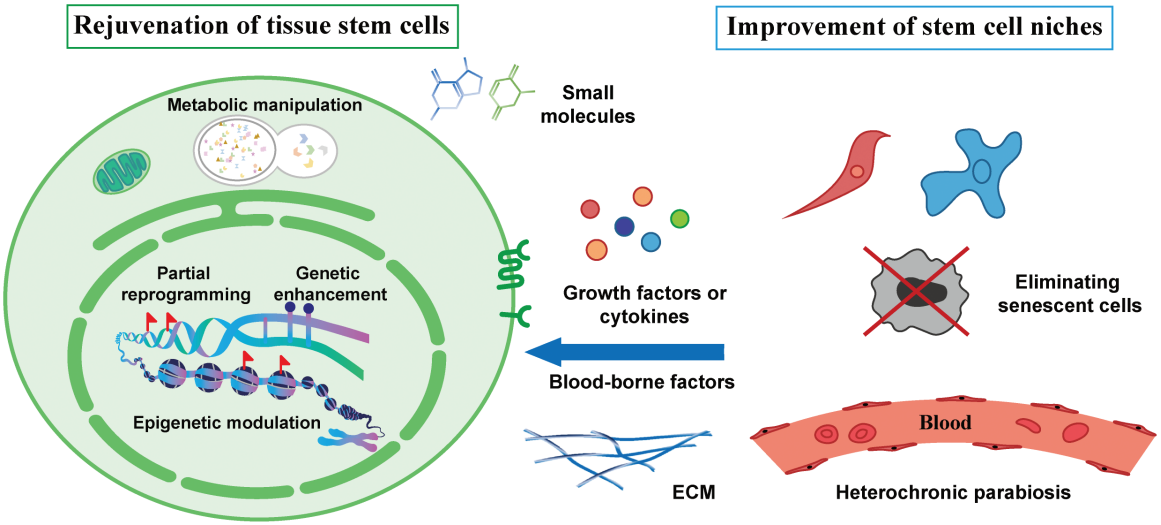
Abstract

Stem cell therapies, including stem cell transplantation and rejuvenation of stem cells in situ, are promising avenues for tackling a broad range of diseases. Stem cells can both self-renew and differentiate into other cell types, and play a significant role in the regulation of tissue homeostasis and regeneration after cell degeneration or injury. However, stem cell exhaustion or dysfunction increases with age and impedes the normal function of multiple tissues and systems. Thus, stem cell therapies could provide a solution to aging and age-associated diseases. Here, we discuss recent advances in understanding the mechanisms that regulate stem cell regeneration. We also summarize potential strategies for rejuvenating stem cells that leverage intrinsic and extrinsic factors. These approaches may pave the way toward therapeutic interventions aiming at extending both health and life span.

Key words: stem cell; rejuvenation; regeneration; aging.

Graphical Abstract



Potential strategies are developed for rejuvenating stem cells that leverage intrinsic and extrinsic factors including targeting signaling pathways, small molecules, epigenetic modulation, genetic enhancement, in vivo partial reprogramming, and metabolic manipulation. In addition, paracrine factors, extracellular matrix, heterochronic parabioses, or elimination of senescent cells may also rejuvenate stem cells through modulation of stem cell niches.

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Introduction

Stem cell exhaustion or dysfunction is a major characteristic of aging and the driving force behind the age-related decline in tissue regeneration.[1,2] Tissue stem cells exist in small numbers but are found across tissues and organs and play a critical role in homeostasis and tissue regeneration.[2,3] These stem cells are multipotent or unipotent and include hematopoietic stem cells (HSCs), neural stem cells (NSCs), muscle stem cells (MuSCs), mesenchymal stem cells (MSCs), hair follicle stem cells (HFSCs), and intestinal stem cells (ISCs).[2,4] Tissue stem cells reside in specific local tissue microenvironments, known as "stem cell niches", that facilitate stem cell maintenance.[4] Upon cell loss or injury, resident tissue stem cells show remarkable proliferative capacity and can differentiate to replace different mature cell types, allowing tissues to recover from damage.[2,5] However, tissue stem cells exhibit a profound decline in function during aging, that includes dysregulated proliferative capacity, skewed differentiation bias, and an impaired response to tissue injury.[6,7] The resulting impairments in tissue homeostasis and regeneration lead to tissue aging and age-related diseases.[1,5,8,9]

Understanding the molecular mechanisms underlying stem cell aging might help to develop therapies that greatly relieve the societal and personal burden of age-related diseases, including neurodegenerative diseases (Alzheimer's disease, etc), sarcopenia and muscular dystrophy, osteoporosis, and lung fibrosis.[5,10] In this review, we summarize several signaling pathways, which are responsible for the maintenance and function modulation of multiple tissue stem cells, serving as potential targets to revive stem cells. We further discuss potential strategies to improve stem cell functions, including targeting signaling pathways, small-molecule treatment, epigenetic modulation, genetic enhancement, in vivo reprogramming, and metabolic manipulation, which we termed intrinsic factors. Finally, we present some prospective strategies, including the modulation of the extrinsic environmental milieu by using paracrine factors, modification of extracellular matrix (ECM), heterochronic parabioses (the circulatory system connection of young and old individuals), or elimination of senescent cells to rejuvenate stem cells.

Rejuvenation of Adult Stem Cells

Signaling Pathways

Signaling pathways, including Wnt, Notch, p38 MAPK, and Cdc42, have been reported to regulate the proliferation and function of multiple adult stem cells (Fig. 1). Age-related dysregulation of these signaling pathways compromises tissue homeostasis and regeneration.[11] Consequently, modulation of these signaling pathways may serve as a potential strategy to revive tissue stem cells thus contributing to organismal rejuvenation.

Wnt Signaling Pathway

The Wnt family are key signaling factors that play a crucial role in embryonic development and tissue homeostasis through the maintenance of stem cell pools.[12] Activation of Wnt signaling stimulates the long-term expansion of naïve pluripotent cells, including mouse embryonic stem cells (mESCs) and mouse induced pluripotent stem cells (iPSCs).[13] For tissue stem cells, canonical Wnt signaling decreases in aged ISCs and their niches.[14] Activation of Wnt signaling by treatment of Wnt3a improves proliferation and function of aged ISCs during growth of intestinal organoid cultures (a particular type of 3D cell culture system).[14] Overexpression of β-catenin, an important downstream component of the Wnt signaling pathway, also facilitates the maintenance of stemness in HSCs. β-Catenin expression also promotes the long-term growth of HSCs in vitro by upregulation of genes involved in HSC self-renewal, including *Notch1* and *HoxB4*.[15] In addition, aged HFSCs exhibit compromised canonical Wnt signaling, which is critical for the onset of the active phase of hair growth, anagen, in HFSCs.[16] Importantly, Wnt signaling also induces other stem cells to self-renew and fuels regeneration in diverse organs including the brain and mammary glands.[17]

Notch Signaling Pathway

Notch signaling plays a conserved role in embryonic development and controls tissue stem cell self-renewal and activity.[18] For example, Notch signaling plays a critical role in the activation and subsequent proliferation of muscle stem cells (also known as satellite cells), thereby promoting muscle regeneration upon injury.[19] Notch activation also restores the regeneration capacity of aged muscle. In contrast, Notch inhibition impairs the regeneration of young muscle.[19] In addition, activation of Notch signaling by one of its ligands Delta1 improves the ex vivo expansion of human $CD34^+$ cord blood progenitors. Delta1-mediated activation of Notch also promotes multilineage reconstitution of the hematopoietic system after in vivo transplantation.[18,20] The Notch pathway

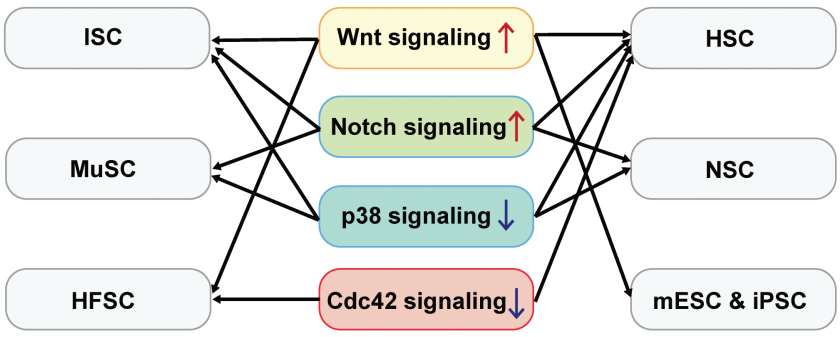

Figure 1. Rejuvenation of different stem cells by modulation of signaling pathways. Modulation of signaling pathways, including the activation of Wnt and Notch pathways (red arrows), and the inhibition of p38 MAPK and Cdc42 (blue arrows), could facilitate the maintenance and self-renewal of multiple stem cell systems (gray boxes). ISC, intestinal stem cell; MuSC, muscle stem cell; HFSC, hair follicle stem cell; HSC, hematopoietic stem cell; NSC, neural stem cell; mESC, mouse embryonic stem cell; iPSC, induced pluripotent stem cell.

also promotes proliferation of ISCs and binary cell fate decisions.[21] Recent work indicates that *Notch2* deletion leads to NSC exhaustion and impaired neurogenesis, contributing to an aging-like phenotype.[22]

p38 Signaling

The p38 mitogen-activated protein kinases (MAPKs) are activated by a variety of environmental stresses and inflammatory cytokines and can stimulate a range of cellular responses, including cellular proliferation, differentiation, apoptosis, and autophagy.[23,24] MuSCs from aged mice show the elevated activity of p38 MAPK and a failure to proliferate.[25] Inhibition of p38 MAPK with the small molecule SB203580 increased self-renewal of aged MuSCs and rescued the engraftment of these aged cells.[25] These results suggest an avenue to ameliorating aging-related defects in stem cell self-renewal and restoring satellite cell homeostasis.[25] In addition, p38 MAPK activates in response to increased reactive oxygen species (ROS) levels, resulting in HSC exhaustion and limiting their reconstitution capacity.[26] Conversely, p38 MAPK inactivation increased HSC life span during serial transplantations.[26] p38 MAPK inhibition with SB203580 also prevented secretory differentiation and facilitated the long-term expansion of human ISCs.[27,28] Increased p38 MAPK activity was also observed in aged NSCs from the subventricular zone of the brain. This signaling activity reduces NSC proliferation.[29,30] Indeed, pharmacological inhibition of p38 MAPK signaling pathway revived the activity of NSCs in vitro.[29]

Cdc42 Signaling

Cdc42 (cell division control protein 42) is a small GTPase in the Rho family and regulates diverse cellular functions, including cell cycle progression, cell migration, and reorganization of the actin cytoskeleton.[31] Cdc42 activity is increased in aged HSCs and other cell types compared to their young counterparts.[16] Increasing Cdc42 activity using genetic approaches induced aging-associated phenotypes in young HSCs and led to depolarization of long-term HSCs (LT-HSCs). Conversely, specific inhibition of Cdc42 activity with CASIN, restored polarization of aged LT-HSCs and reduced myeloid lineage differentiation. CASIN treatment also improved homing to the bone marrow (BM) after transplantation, thus recovering LT-HSC function. Cdc42 inhibition restored decreased histone H4 lysine 16 acetylation levels and spatial distribution of this histone modification in aged HSCs.[32] These data together argue that Cdc42 is an intrinsic modulator of stem cell aging. Aged HFCSs (alpha-6 integrin^{high} CD34^{+} cells, HFSC) also exhibit elevated Cdc42 activity.[16] CASIN treatment-induced "young" phenotypes in aged HFSCs and facilitated the onset of anagen in aged mice.[16] Interestingly, systemic administration of CASIN significantly extends average and maximum life span, decreases serum levels of the age-related cytokines IL-1β, IL-1α, and INF-γ, and induces a younger epigenetic clock (an epigenetic estimator of age based on DNA methylation) in blood cells.[33]

Tissue stem cells have characteristics specific to their host tissues. For example, ISCs and HSCs continuously proliferate for the ongoing production of differentiated cells. This feature sustains tissue stability in the face of high cell turnover in the intestine and blood, respectively.[5] In contrast, NSCs and MuSCs rarely proliferate under normal conditions, and only become activated upon extreme tissue injury.[34] Despite these variations in stem cell properties, increasing data suggest that common signaling pathways differentially regulate tissue stem cell function. As outlined above, these include Wnt, Notch, p38 MAPK, and Cdc42 signaling (Fig. 1). Indeed, modulation of these signaling pathways systemically may have a positive effect across tissues and organ systems, suggesting a promising strategy in regenerative medicine.

Pharmacological Approaches

Small-molecule compounds targeting specific signaling pathways may act to alleviate stem cell senescence and stimulate the expansion of different stem cells both ex vivo and in vivo.[35] Pharmacological approaches could therefore improve tissue homeostasis, repair, and regeneration.[36] HSCs account for less than 0.01% of BM cells, which limits the widespread use of human HSC transplantation, the only therapy for multiple hematologic malignancies.[37] Unbiased screening using primary human HSCs recently identified a purine derivative, StemRegenin 1 (SR1), that promotes the ex vivo expansion of HSCs. StemRegenin 1 facilitates human HSC expansion by directly interacting with and inhibiting the aryl hydrocarbon receptor (AHR).[38] Aryl hydrocarbon receptor was reported to regulate hematopoiesis by modulation of β-catenin, c-MYC, C/EBP, HES-1, and PU.1 pathways.[39] Another screen found that the pyrimidoindole derivatives, UM729 and UM171, stimulated ex vivo expansion of human cord blood cells, providing a potential resource for long-term in vivo repopulation.[37] UM171 promotes HSC expansion by targeting lysine-specific histone demethylase 1A instead of aryl hydrocarbon.[40] Screening has also been conducted in WRN-deficient human mesenchymal stem cells (WS-hMSCs), a cellular model of Werner syndrome (WS), an adult progeria characterized by premature aging.[41] Werner syndrome pathogenesis is associated with genome and epigenomic instability due to mutations in the *WRN* gene, which encodes a DNA helicase responsible for DNA repair, replication, transcription, and recombination.[42,43] In the cellular premature aging model, WS-hMSCs exhibit decreased proliferation and premature cellular senescence.[41] Screening a natural product library and FDA-approved drugs revealed that quercetin, Vitamin C, and gallic acid can improve WS-hMSC proliferation and alleviate premature aging phenotypes in these cells.[44-47] Furthermore, an in vivo screen of 1000 selected compounds found that P7C3 enhances neurogenesis in the sub-granular zone of the dentate gyrus in the hippocampus of the mouse brain, likely through stimulation of NSC proliferation.[48] Similarly, treatment with P7C3 facilitates neurogenesis in the dentate gyrus and preserves cognitive capacity in aged rats.[48]

Genetic Enhancement

Stromal stem cells, such as hMSCs, are an attractive option for personalized cell-based therapy.[49] These cells have promising characteristics including multi-lineage potential and the ability to modulate immune cells. However, after serial passaging, hMSCs tend to have reduced proliferation capacity and senescence phenotypes. Genetic enhancement has been explored as a method for improving the regenerative capacity of hMSCs, as well as reducing the risk of tumorigenesis.[50] *Nuclear factor erythroid-2-like 2* (*NRF2*) mediates the antioxidative response, and could potentially promote rejuvenation of hMSCs. Leveraging gene editing, a single-nucleotide variation (A245G) was introduced into *NRF2*. *NRF2*-engineered human ESC-derived hMSCs exhibit robust self-renewal and decreased expression levels of senescence-associated genes

(*p16Ink4a* and *p21Waf1*) in the late passages.[51] Consistent with the anti-oxidation role of NRF2, *NRF2*$^{AG/AG}$ hMSCs have lower levels of ROS and oxidative byproducts. These genetically enhanced stem cells were transplanted into the hind-limb of an ischemia murine model and showed better cell retention and improved regenerative ability compared to the wild type controls.[51] Recoding 2 nucleotides of *FOXO3* (causing 2 substitutions at the amino acid level: S253A, S315A), a longevity factor, also endows hMSCs with increased proliferation and decreased senescence-associated (SA)-β-gal activity compared to wild type hMSCs.[52] Transplantation of *FOXO3*$^{2SA/2SA}$ hMSCs into the hind limb ischemia mouse model promoted revascularization and the recovery of blood flow.[52] In addition, delivery of *FOXO3* genetic enhanced hMSCs into the myocardial ischemia mouse model reversed increased pro-inflammatory factor levels, reduced cardiac fibrosis, and improved heart function.[50] Collectively, genetic enhancement of certain functional genes in adult stem cells protects stem cells from aging and improves regeneration capacity.

Epigenetic Regulation

Major changes occur in the aging epigenome.[53,54] DNA methylation, post–translational histone modifications, chromatin remodeling, and non–coding RNAs are all altered in aged tissue stem cells, impeding normal function and homeostasis.[54] Senescent hMSCs exhibit dysregulated heterochromatin architecture and impaired proliferation. Overexpression of heterochromatin stabilizing factors could potentially consolidate heterochromatin and alleviate hMSC aging.[55-57] WRN protein, is a helicase that regulates genome integrity and interacts with the heterochromatin proteins SUV39H1 and HP1α.[41,43] Consistently, WRN-deficient hMSCs show accelerated loss of heterochromatin.[41] A number of factors have the potential to alleviate hMSC aging through stabilization of heterochromatin, including ZKSCAN3, a newly identified epigenetic modulator, and the heterochromatin-interacting factors DGCR8, CLOCK, and CBX4.[55-58] The SIRT family, encoding NAD-dependent histone deacetylases, has a well-established link to metabolic regulation and aging. Interestingly, both SIRT7 and nuclear-localized SIRT3 can also interact with heterochromatin-associated proteins and consolidate heterochromatin, alleviating hMSC aging.[59,60] In addition, SIRT6 regulates Wnt signaling through H3K56 deacetylation and facilitates HSC self-renewal, as well as safeguarding hMSCs from oxidative stress.[61]

Partial Reprogramming

Somatic cells can be induced into a pluripotent stem cell state through overexpression of the Yamanaka transcription factors, OCT4, SOX2, KLF4, and c-MYC (OSKM).[62] This reprogramming resets a number of senescence phenotypes. For example, OSKM treatment reduces expression of the senescence factors p16INK4A and p21CIP1, resets shortened telomeres, and reverses changes in mitochondrial metabolism associated with senescent cells.[63] Partial reprogramming by short-term expression of OSKM also reverses cellular senescence and resets the aging epigenome without erasing cell identity.[64] Importantly, in vivo partial reprogramming induced the expansion of MuSCs (Pax7-positive cells) in skeletal muscle of both *Lmna* mutant (LAKI) progeria mice and 12-month-old mice thus improving muscle regeneration after injury. Furthermore, partial reprogramming in myofibers via OSKM could remodel stem cell niche, stimulate the activation of satellite cells and promote muscle regeneration.[65] Of note, partial reprogramming also extended the life span of progeria mice and ameliorated a panel of aging hallmarks in 12-month-old wild-type mice.[64] Recently, researchers found that ectopic expression of *Oct4*, *Sox2*, and *Klf4* genes (OSK) recovered youthful DNA methylation patterns (also known as the Epigenetic Clock) and promoted axon regeneration after optic nerve injury.[66] OSK induction using the adeno-associated virus system reversed vision loss in glaucoma mice and aged mice. More importantly, transient, heart-specific expression of OSKM-induced the dedifferentiation of cardiomyocytes (CMs) and reset the gene expression profile to a state resembling that of fetal CMs.[67] Short-term expression of OSKM also attenuated the heart damage and improved the cardiac function in a myocardial infarction mouse model, which indicated an enhanced regenerative capacity after partial reprogramming.[67] Taken together, partial programming is a potential avenue to rejuvenating aged cells and improving regeneration of different tissues.

Metabolic Manipulation

Autophagy, is a conserved intracellular degradation and recycling pathway, and is critical to metabolic regulation and maintaining stem cell homeostasis, which is associated with health and longevity.[68,69] Impaired autophagy in satellite cells induces senescence and increases oxidative stress, resulting in a decline in the number and function of stem cells.[70] Restoration of autophagy rescues senescence and improves regeneration in geriatric satellite cells.[70] In addition, autophagy in HSCs removes activated mitochondria and controls oxidative metabolism, thereby promoting HSC stemness and regeneration capacity.[69] At the organismal level, prolonged fasting promotes self-renewal of HSCs and lineage-balance in hematopoietic regeneration by decreasing IGF-PKA signaling.[71] A periodic diet that mimics fasting also increases hematopoietic and mesenchymal stem/progenitor cells in the BM and promotes neurogenesis, thereby resulting in the enhanced tissue regeneration and increased health span and median life span.[72]

Modulation of Stem Cell Niches

Stem cell niches are specialized local tissue microenvironments that directly interact with resident stem cells and regulate their maintenance and functions.[73,74] Supporting cells in the niche include endothelial cells, osteoblasts, osteoclasts, fibroblasts, and other stromal cells. Stem cell niche cells can secret key factors to sustain stemness and regeneration.[4,75] In addition, stem cells and their niches are markedly affected by ECM microenvironment,[76] and long-range factors produced by donors in heterochronic parabiosis experiments in which young and old mice are connected.[77] Elimination of senescent cells also improves the microenvironment and regeneration of tissues by reducing levels of senescence-associated secretory phenotype (SASP)-related cytokines and alleviation of chronic sterile inflammation (Fig. 2).[78,79]

Growth Factors or Cytokines

Secreted growth factors or cytokines exert important roles in the regulation of tissue stem cells, and their dysregulation may contribute to a hostile microenvironment for stem cell maintenance.[80] For instance, the environment where MuSCs

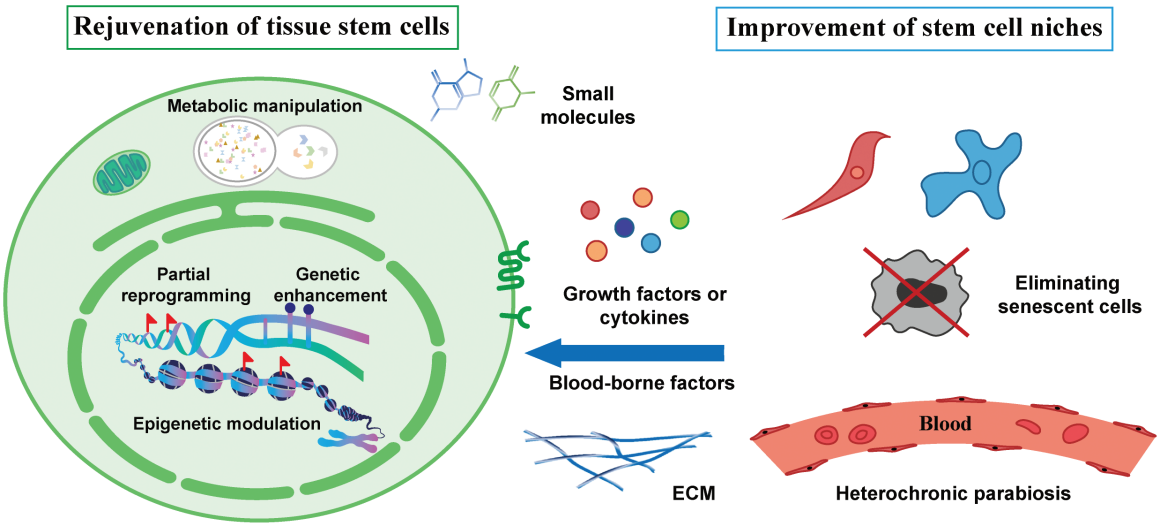

Figure 2. Strategies of rejuvenating tissue stem cells. To regulate intrinsic factors and improve the functions of tissue stem cells, several approaches including targeting signaling pathways, small molecules, epigenetic modulation, genetic enhancement, in vivo partial reprogramming, and metabolic manipulation are developed. In addition, paracrine factors, extracellular matrix (ECM), heterochronic parabioses or elimination of senescent cells may also rejuvenate stem cells through modulation of stem cell niches.

reside is a major contributor to muscle regeneration. T cells facilitate MuSC proliferation and tissue regeneration through the secretion of inflammatory factors.[81] A combination of inflammation-related cytokines including IL-1α, IL-13, TNF-α, and IFN-γ was able to stimulate long-term cultured MuSC proliferation and improve MuSC expansion in vivo. In addition, injection of the 4 cytokines facilitates muscle regeneration in *Rag1*$^{-/-}$ mice.[81] Tissue inhibitor of metalloproteinases 2 (TIMP2), which is enriched in human cord blood plasma and young mouse plasma, has been shown to enhance plasticity, induce hippocampal neurogenesis, and improve cognitive functions in aged mice.[82] Tissue inhibitor of metalloproteinases 2 serves as a key rejuvenating factor to alleviate aging-associated dysfunction of neurogenesis.[82] Hematopoietic stem cells reside in perivascular niches where secreted niche factors regulate hematopoiesis.[73] For instance, endothelial cells and other stromal cells in the BM are crucial sources of HSC niche factors responsible for HSC maintenance, including stem cell factor (SCF) and CXC chemokine ligand 12.[83,84] Finally, SCF from adipocytes in BM is also required for the proliferation and hematopoiesis of HSCs after irradiation.[85]

Extracellular Matrix Microenvironment

The extracellular matrix is a multifunctional macromolecular network, encompassing collagens, glycoproteins, proteoglycans, and glycosaminoglycans, that supports the structural integrity and biochemical function of all tissues.[76] The ECM has a profound impact on stem cell self-renewal and differentiation as well as tissue repair and regeneration.[86,87] Among ECM proteins, tenascin-C (TN-C) is primarily expressed by BM niche cells, such as endothelial cells and stromal cells, and supports normal HSC function.[88] In vitro, TN-C coating facilitates HSC proliferation and increases cyclin expression (*cyclinD1* and *cyclinE1*) in an integrin 9-dependent manner, indicating that TN-C, by virtue of being a critical ECM component, is significant for hematopoietic regeneration.[88] Similarly, the ECM glycoprotein fibronectin, which is transiently increased after muscle injury to remodel the stem cell niche, stimulates the symmetric expansion of MuSCs.[89] In the skin, the ECM protein nephronectin, which is produced by bulge stem cells, interacts with the α8β1 integrin receptor to regulate the function of HFSCs.[90] In addition, soft substrates of 0.6 kPa polyacrylamide gels coated with type-1 collagen (collagen-1) promote mESC self-renewal and the maintenance of pluripotency via the biophysical mechanism of promoting low cell-matrix tractions.[91] Collectively, these findings suggest that the ECM, as a key component of stem cell niches, can be manipulated to modulate stem cell rejuvenation through different sensing mechanisms and activated downstream pathways.[92]

Heterochronic Parabiosis

Heterochronic parabiosis is a model in which the circulation system is shared between surgically joined young and old mice, providing a unique platform to examine the influence of systemic factors on stem cells and their niches.[77] Previous work showed that systemic factors in young mice could restore molecular signaling, including the activity of that Notch ligand Delta, and thus promote muscle regeneration through the proliferation of resident aged satellite cells. These results indicate that the reduced regeneration potential in aged stem cells can be reversed by the young, but not old, systemic factors.[77] Furthermore, exposure to the youthful systemic milieu also promoted the proliferation of oligodendrocyte precursor cells and angiogenesis, potentially facilitating regeneration in the aging central nervous system.[93] For instance, blood-borne factors including TIMP2 and colony-stimulating factor 2 were found to enhance neurogenesis and improve memory.[82,94] In contrast, CCL11 (also known as eotaxin 1), an eosinophil-recruiting chemokine, was identified as a pro-aging factor that impairs cognitive functions in young mice after heterochronic parabiosis.[95]

Elimination of Senescent Cells

Stem cell senescence, a persistent state of cell cycle arrest, impairs the normal function of stem cells including proliferation

or differentiation, and induces chronic, low-degree inflammation, thus inhibiting tissue regeneration.[5] In both aged and sublethal total body irradiation induced long-term BM injury mice, senescent cells accumulated and the SASP response was elevated, associated with impaired HSC self-renewal and hematopoietic function.[96] Recently, the elimination of senescent cells using a senolytic drug improved the BM microenvironment and reinvigorated the hematopoietic system of injured mice and aged mice, probably through the regulation of the SASP.[96] In addition, a newly designed prodrug targeting the increased activity of lysosomal β-galactosidase and chimeric antigen receptor T cells targeting the urokinase-type plasminogen activator receptor eliminate senescent cells in vivo, thus restoring tissue homeostasis and improving lung and liver regeneration through modulation of the stem/progenitor cell niche.[78,97]

Perspectives and Conclusions

Novel approaches to tissue culture are further facilitating analysis of tissue stem cells and the development of strategies for regenerative medicine. Recent advances in stem cell-derived organoid culture provide an unparalleled platform to explore the self-organization of stem cells and interactions between cells and their environment.[98] In addition, 3D culture of hMSCs increases the expression of anti-inflammatory (TSG-6, STC-1, and LIF) and antitumorigenic (IL-24 and TRAIL) genes suggesting that spheroid hMSCs could be applied to treat sterile tissue injury and unresolved inflammation.[99] Single-cell assays including transposase-accessible chromatin sequencing and single-cell RNA-sequencing, etc, together with spatial transcriptomics are also building comprehensive pictures of tissue stem cell systems.[100-102] These techniques are allowing us to analyze chromatin accessibility and gene expression at the single-cell level, decipher spatial distribution of stem cells, and uncover heterogeneous cell populations and regulatory mechanisms as well as local networks of intercellular communication.[102-104] Other promising emerging technologies include effective gene-editing tools and lineage tracing that will facilitate the identification of new stem/progenitor cell subpopulations and further clarify the origin, development, and molecular mechanisms functioning in different stem cells.[105,106] Notwithstanding all these advances, further interdisciplinary studies are needed to develop novel strategies for tissue stem cell rejuvenation.

Tissue stem cells are highly relevant to the health and life span of organisms.[6] Stem cell dysfunction is regarded as a major hallmark of aging, and drives age-associated disorders.[1,2,107] In this review, we have outlined how targeting intrinsic or extrinsic factors, eg, revitalization of stem cells or improvement of the stem cell niche, can facilitate tissue regeneration. In the future, to rejuvenate stem cells more effectively, a more comprehensive understanding of molecular networks regulating the maintenance of stem cells and their interaction with niches is required. Taken together, these rejuvenation strategies hold great promise for regenerative medicine and the treatment of multiple age-associated disorders and diseases.

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Conflict of Interest

The authors declared no competing interest.

Author Contributions

Y.C., S.W., J.Q., J.C.I.B., and G.-H.L. wrote the manuscript.

Data Availability

No new data were generated or analyzed in support of this research.

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