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Recent Advancement in Elimination Strategies and Potential Rejuvenation Targets of Senescence

Sanjay Kumar Kureel, Brandon Blair, and Michael P. Sheetz*

Cellular senescence is a state of exiting the cell cycle, resisting apoptosis, and changing phenotype. Senescent cells (SCs) can be identified by large, distorted morphology and irreversible inability to replicate. In early development, senescence has beneficial roles like tissue patterning and wound healing, where SCs are cleared by the immune system. However, there is a steep rise in SC number as organisms age. The issue with SC accumulation stems from the loss of cellular function, alterations of the microenvironment, and secretions of pro-inflammatory molecules, consisting of cytokines, chemokines, matrix metalloproteinases (MMPs), interleukins, and extracellular matrix (ECM)-associated molecules. This secreted cocktail is referred to as the senescence-associated secretory phenotype (SASP), a hallmark of cellular senescence. The SASP promotes inflammation and displays a bystander effect where paracrine signaling turns proliferating cells into senescent states. To alleviate age-associated diseases, researchers have developed novel methods and techniques to selectively eliminate SCs in aged individuals. Although studies demonstrated that selectively killing SCs improves age-related disorders, there are drawbacks to SC removal. Considering favorable aspects of senescence in the body, this paper reviews recent advancements in elimination strategies and potential rejuvenation targets of senescence to bring researchers in the field up to date.

1. Introduction

1.1. Aging

Aging can be defined as the progressive deterioration of physiological and cognitive capabilities, caused by an alteration of the state of equilibrium, in conjunction with the impairment of homeostasis.[1] Elderly individuals frequently experience a decline in auditory and visual acuity, as well as a decrease in physical activity and other physiological impairments when compared to their younger counterparts.[2] The acceleration of the aging process also operates as a green light signal for many diseases, including cancer,[3] cardiovascular,[4] osteoporosis,[5] and neurodegenerative disorders.[6]Within the field, there have been 12 cellular characteristics established as the hallmarks of aging.[7] These features are genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, disabled macro-autophagy, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis. Although cellular senescence is considered one of the hallmarks,[8] each of these characteristics contributes to a cell displaying the senescence phenotype and may have a role in maintaining it. As individuals progress in age, they become increasingly susceptible to various factors such as radiation exposure, DNA damage,[9] exposure to carcinogens, epigenetic modifications,[10] and telomere shortening.[11] These factors contribute to the development of cellular characteristics associated with the aging process. In response to these various environmental stresses, cells can exit the cell cycle via the process of differentiation and undergo either reversible arresting of the cell cycle (quiescence) or irreversible arresting of the cell cycle (senescence).[12] To prevent these harmful manifestations from spreading and transferring to future generations, cells may cease dividing and become senescent.[13,14]

1.2. Cellular Senescence

Senescence represents a cellular process characterized by a stable cessation of the cell cycle, leading to the loss of cell proliferation. Senescent cells (SCs) also release pro-inflammatory molecules which involve a variety of molecules such as messenger Ribonucleic acid (mRNA), interleukins, cytokines, chemokines, growth factors, proteases, and extracellular vesicles (EVs). Collectively, these molecules are known as the senescence-associated secretory phenotype (SASP). Additionally, SASP molecules impede the replication of neighboring cells.[12,15] These secretions include mRNA, interleukins, cytokines, growth factors, proteases, extracellular vesicles (EVs), and chemokines, which together are referred to as the SASP (**Figure 1**). This phenotype adversely influences neighboring cells and thus tissue phenotype, which in turn enhances both epithelial to mesenchymal transition (EMT)[16]

S. K. Kureel, B. Blair, M. P. Sheetz
Department of Biochemistry and Molecular Biology
University of Texas Medical Branch
Galveston, TX 77555, USA
E-mail: sakureel@utmb.edu

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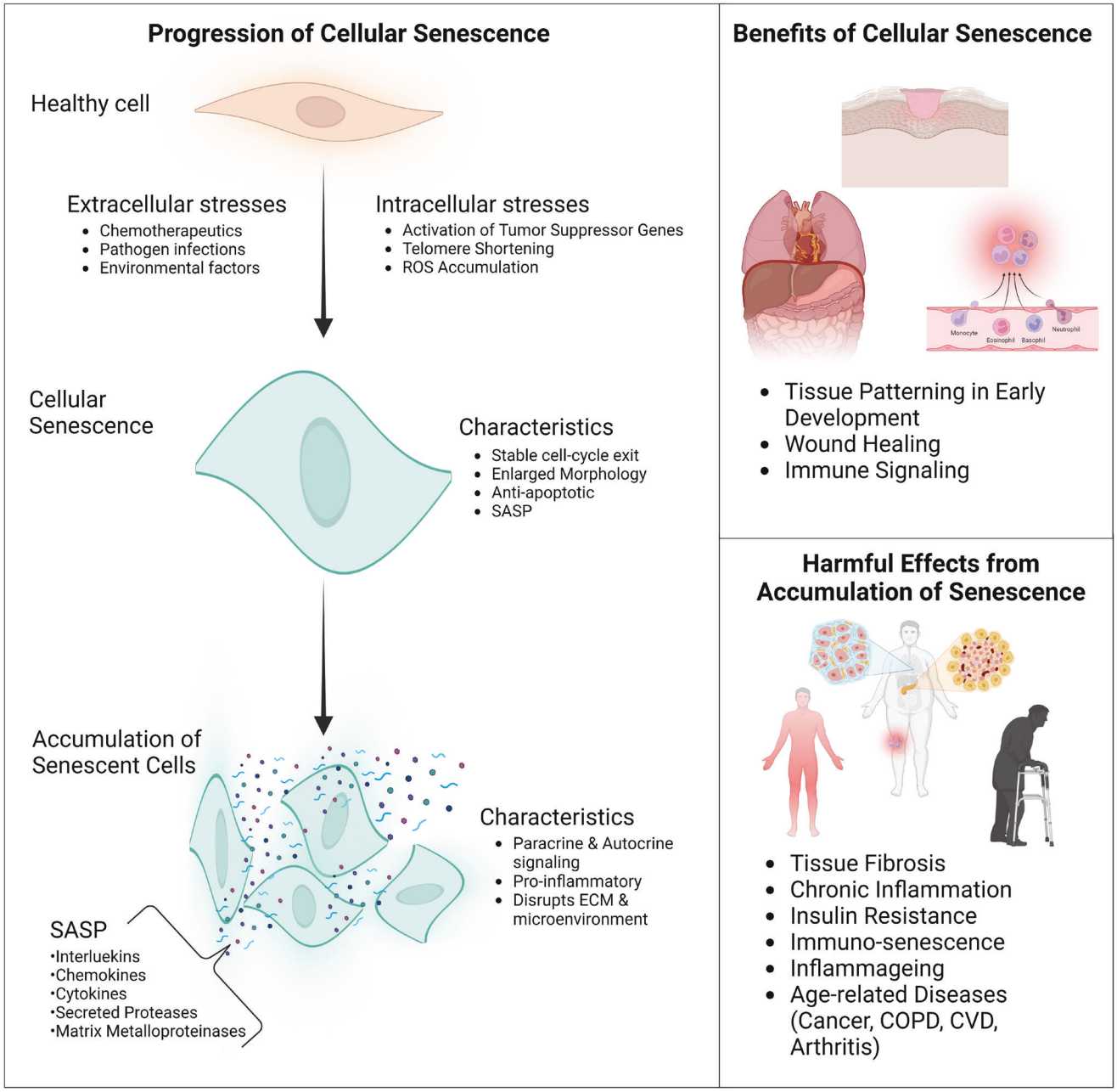

Figure 1. Brief overview of senescence. (Left) Factors affecting induction of senescence. (Top Right) Beneficial characteristics of senescence. (Bottom Right) Deleterious effects of senescence. This figure was prepared with Bio render.

and the aggressiveness of cancer cells.[17] The SASP phenotype relies on paracrine signaling, which both prevents transformation into cancer cells,[18] by inducing senescence, and also encourages tumor development.[19] Although the SASP has some benefits, such as the regulation of tissue and organ patterning during early developmental stages,[20] prevention of tumor metastasis,[21] and aiding in tissue repair,[22,23] it is also a main driver in the acceleration of senescence expansion,[24] cancer progression, and aging[25] (see Figure 1).

1.3. Key Features of Senescence

In general, cellular senescence can be distinguished by five main principles, those being: 1) stable cell cycle arrest, 2) enlarged cellular morphology, 3) increased resistance to apoptosis, 4) acquisition of the SASP, and 5) over-expression of the lysosomal enzyme, senescence-associated β-galactosidase (Figure 1).[26,27] In addition, many studies have established that senescent cells display an altered metabolism[28] compared to proliferating cells.

This is thought to contribute to their enlarged size.[29] Senescent cells have an increased ratio of AMP:ATP and ADP:ATP, which leads to higher rates of glycolysis as well as elevated (AMP-activated protein kinase (AMPK) activity.[30] AMPK is a master regulator of cellular responses to energetic stresses, and it activates fatty acid oxidation, inhibition of fatty acid synthesis, increased mitochondrial biogenesis, and stimulation of glucose uptake,[31] which are all key features associated with the senescent phenotype. Furthermore, AMPK directly phosphorylates p53,[32] which is upregulated in senescent cells and results in the arrest of proliferation. Although senescent cells utilize a glycolytic state, there is also an increase in mitochondrial respiration,[33,34] as p53 promotes oxidative phosphorylation and antagonizes glycolytic activity in senescent cells. Elevated levels of mitochondrial biogenesis and respiration contribute to the production of intracellular reactive oxygen species (ROS), lead to cellular stress, and play an important function in the development of the senescent phenotype.[35]

1.4. Markers of Senescence

Recently, many new markers have been reported including, increased Mamalian target of rapamycin (mTOR) kinase activity, mitochondrial dysfunction, decreased autophagy, low NAD+/NADH ratio, increased lamin A and decreased lamin B, telomere shortening, upregulation of p53, increased DNA damage response (DDR) activity, γH2X foci, and unfolded protein response (UPR) inhibition of the E2F protein[36,37] (Figure 1). Still, there remains a need to establish a comprehensive blueprint of senescent cells within human tissue and organs.[38] While their presence provokes tumor advancement, their absence escalates cancer transformation. Therefore, senescent cells can be viewed as a double-edged sword. These cells can also form 3D aggregates in the 2D confluent layer.[39] So far, the focus has been on trying to eliminate these stagnant cells from the microenvironment by the use of intervening drugs known as senolytics.[40] Furthermore, it is important to understand the molecular functions of senolytics' role against senescent cells.[41] In a recent study, it has been demonstrated that senescent cells incite tumor growth; therefore, senolytic-based elimination tactics may prevent tumor progression.[42] The accumulation of pro-inflammatory molecules in the bloodstream or tissues, referred to as inflammageing[43] along with a dysfunctional immune system,[44] leads to the inadequate clearance of senescent cells. Consequently, these cells begin to accumulate in various tissues and organs. The accumulation of certain factors leads to the development of various age-related pathologies.[45] Senescence is also a significant factor in the development of lung disease, as it impairs the repair of airway injury and contributes to various lung pathologies.[46–48] Therefore, the elimination of SCs shows a beneficial effect, and their eradication can help to enhance health and lifespan.[49]

1.5. Senescent Cells: Beneficial and Detrimental Effects

Senescent cells are not necessarily harmful, but their excessive accumulation causes problems. It is important to keep in mind that SCs have both beneficial and detrimental traits.[50] Senescent cells are beneficial in early development, wound healing, tumor suppression, and host immunity (see Figure 1). In early developmental stages, senescent cells are destroyed by the immune system, and thus, their progressive expansion is prevented.[51] However, during the later stages of life, there are dysfunctional clearance processes, such as immunosenescence and inflammageing, which result in the excessive accumulation of SCs within tissue environments.

Studies have repeatedly shown that the conglomeration of senescent cells causes many age-related diseases and pathologies,[52] including diabetes, metabolic syndrome, osteoarthritis, atherosclerosis, and pulmonary fibrosis. In some recent studies, the removal of SCs results in many beneficial effects on tissues and organs. Pre-clinical trials have shown that the abolition of senescent cells positively affects a multitude of age-related pathologies, along with frailty. This includes osteoarthritis, osteoporosis, sarcopenia, fibrotic diseases, neurodegeneration, diabetes type-2, cardiovascular disease, and cancer.[36] In severe obesity, adipose senescence is associated with glycemic conditions, prompting defects in glucose metabolism. The overdevelopment of SCs in adipose tissue can cause obesity-induced metabolic complications and contribute to diabetes type-2.[53]

1.6. Generation of Senescent Cells for Study

There are four working models for generating senescent cells. There is therapy-induced senescence (TIS), oncogene-induced senescence (OIS), replication-induced senescence (RIS), and the isolation of senescent cells from old individuals. Therapy-induced senescence is performed using chemotherapeutics or a form of radiation, such as gamma radiation. This technique is common and is very effective in turning proliferating cells into the senescent state. Oncogene-induced senescence is done by activating the tumor-suppressing mechanism to produce an anti-proliferation response.[54] Replication-induced senescence is as simple as continually passaging cells until they no longer divide and enter senescence.[55] This is thought to occur due to telomere shortening and reaching the Hayflick limit.[56] Methods for the generation of senescent cells can be used for senescence study.[57]

2. Strategies for Elimination of Senescent cells

We have mentioned that the accumulation of senescent cells in tissue and organs leads to an overall decline in function and can cause the progression of many age-associated diseases. Most clinical research on improving these conditions and deterring age-related deterioration has been focused on selectively killing these senescent cells. The elimination strategies include pharmacological drug intervention, immune cells, nanotechnology-based methods (**Table 1**), and activation and deactivation of senescence-associated pathways (see **Figure 2**).

2.1. Inhibiting the Anti-Apoptotic Pathway

One strategic approach is targeting the pathway resulting in SC's resistance to apoptosis. Some significant members of the BCL

Table 1. List of drugs for the elimination/removal of senescent cells and their mode of actions.

Senolytics	Implications	Mode of action	Dose	Duration	Model	References
Chiral gold nanoparticles	Elimination of SCs for alleviation of age-related ailments	Induction of apoptosis via selective antibody binding and targeting near-infrared probe	800–2000 μg mL^{-1}, 120 nM, 10 μM	6 h	Microglia, IMR90, and mouse	Xu et al.,[81] Qu et al.,[82] and Yang et al.[83]
Methylene blue beta-gal probe	Detection and elimination of SCs	Probe activated by SA-β-Gal releases Marina Blue (MB) fluorophore	10–50 μM	4–8 h	HeLa and MEF	Lee et al.[84]
Ganciclovir	Elimination of senescence for alleviation of osteoarthritis	Targeting high expressions of p16 in SCs	1100–200 μM	2 weeks	Human OA chondrocytes and mouse	Jeon et al.[85]
Navitoclax	Improving survival and recovery of acute myocardial infarction (MI)	NA	50 mg $kg^{-1}day^{-1}$	2 weeks	Mouse	Walaszczyk et al.[86] and Salerno et al.[87]
Quercetin	Localized elimination of SCs to restore bone and aid in chemotherapy-induced senescence	SASP components hydrolyzed ester bond of Hydrogel and release Quercetin	10 μM	48 h	BMSCs, MDA-MB-231, HeLa, HUVEC, U2OS, U251, MG HMEC	Xing et al.[88]
Dasatinib	Elimination of SCs to alleviate glaucoma by progressive optic neuropathies	Selective tyrosine kinase receptor inhibition	5 mg kg^{-1}	4 days	NBFs, MEFs, HEFs, HUVECs, human preadipocytes, and mouse	Rocha et al.[89]
Prodrug SSK1	Elimination of SCs to improve intervertebral disc regeneration and aid inflammation and physical function	Activates through interaction with β-Gal regardless of cell type	0.5 μM	3 days	Mouse	Cai et al.[60]
ES2 peptide	Elimination of SCs to alleviate aging and cancer recurrence	Disrupts FOX04-TP53 interaction to induce apoptosis	8 μM	0–4 h	Mouse	Le et al.[90]
ABT-199, 262, 263, and 737	Elimination and targeting of SCs for alleviation of osteoarthritis, diabetes type-1, and pancreatic lesions	Inhibits anti-apoptotic proteins (BCL2 and BXL); targets YAP1 and p21 to result in elimination by BET inhibitor JQ1	(ABT-263) 20 μM, (ABT-737) 25 mg kg^{-1}, (ABT-737 and 199), 10 μM/ 100 μM	24 h-48 h	Synovial MSCs, CHON-001, SW-1353, Hs-819T, UO2S, and mouse	Kolodkin-Gal et al.,[42] Yosef et al.,[58] Miura et al.,[91] and Zhang et al.[92]
Mitochondria-targeted tamoxifen (Mito Tam)	Elimination of SCs induced by chemotherapeutics and kills cancer cells without induction of senescence	Specific to SCs due to low levels of ANT2 expression	8 cell: 1 μM Mouse: 0.25–0.54 μmol/mouse/dose	Cell: 3 days Mouse: 2 times a week for 2 weeks	MCF7, 4T1, RPE-1, mouse	Hubackova et al.[80,93]
FOXO4-D-retro-inverso peptide (DRI-isoform)	Elimination and select targeting of senescence to alleviate age-related degeneration and chemotherapy-induced senescence	Interferes with FOX04 signaling pathway of PML/DNA-SCARS to exclude p53	6.25–25 μM	More than 3 days	Mouse and BJ, IMR90, BMK, HEK293LTV, NIH-3T3, WI-38	Baar et al.[94] and Krimpenfort and Berns[95]
Carnosine	Promotes phagocytosis of SCs in the skin, by recruitment of immune cells	Activation of AKT signaling by Carnosine	5–30 mM	24 h	Keratinocytes and HFF-1	Li et al.[77]
Rapamycin	Reduces senescence by conversion of cell state to quiescence	Inhibition of mTOR activity, mainly in MTORC1	500 nM	3 days	HT1080-p21-9 and MCF7 cells	Leontieva et al.[96]

SSK1, Senescence-Specific Killing compound 1; ES2, Endostatin 2; SA-B-Gal, Senescence Associated-Beta-Galactosidase; YAP1, Yes Assocaited Protein 1; BET, Bromodomain and Extra Terminal-domain proteins ; JQ1, BET inhibitor; ANT2, Adenine Nucleotide Translocase 2; PML/DNA-SCARS, Promyelocytic Leukemia protein/DNA-Segments with Chromatin Alterations Reinforcing Senescence; AKT, Protein Kinase B; mTOR, mammilian Target of Rapamycin; mTORC1, mammilian Target of Rapamycin Complex 1 Cell Lines: IMR90, HeLa, MEF, OA, BMSCs, MDA-MB-231, HUVEC, U2OS, U251, MG, HMC, NBFs, HEF, MSC, CHON, SW-1353, Hs-819T, MCF7, 4T1, RPE-1,BJ, BMK, HEK293LTV, NIH,3T3, WI-38, HFF-1, HT108.

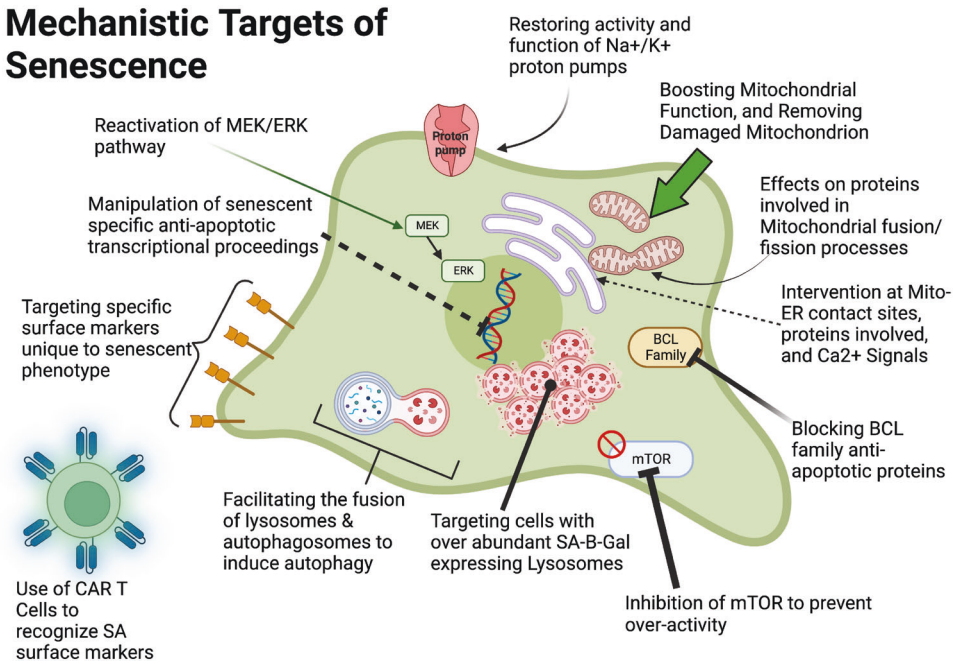

Figure 2. Illustration showing the potential mechanistic targets of senescence.

anti-apoptotic protein family are BCL-XL and BCL-WAX. The up-regulation of these proteins cultivates the persistence of senescent cells. By blocking these proteins, using the ABT molecule, apoptosis is induced, and therefore, the SCs are terminated.[58] Elimination of senescence also aids in the proliferation of hair follicle stem cells, as seen in the mouse model.[58] The downside of this strategy is that certain clinical trials, which have progressed past phase II, have demonstrated that Navitoclax (ABT-263)-treated mice develop transient thrombocytopenia and neutropenia.[59]

2.2. Prodrugs

Prodrugs are a class of drugs that remain in the inactive form and are only activated once administered and metabolized by the body. This class of drug was first developed as a replacement for encapsulated drugs in an attempt to improve specificity. The mechanism for this treatment is dependent upon the escalated number of lysosomes in senescent cells. Senescence-specific killing compound 1 (SSK1) was designed to kill senescent cells by the targeting of Senescence associated (SA)-β-galactosidase-expressing lysosome moiety, which is a lysosomal enzyme specific to senescence.[60] Gemcitabine is another prodrug used to kill senescent cells, also by reacting with SA-β-gal-expressing lysosomes. This is a highly specific and effective method used to target β -gal-positive SCs and has the potential to ameliorate age-associated disorders and diseases. At lower concentrations, these prodrugs exhibit greater selectivity in eliminating senescent cells. However, their overall efficacy is diminished, resulting in the persistence of a subset of these cells. When used at high concentrations in a co-culture of senescent and normal cells, the effect became less selective and exerted a harmful effect on healthy cells.[61,62]

2.3. Metabolic Inhibition

It has been shown that altered metabolism exerts an influence on cells displaying the senescence phenotype. Studies have implicated that glutamine metabolism has an important contribution in the viability of senescent cells through interaction with the enzyme, glutaminase-1(GL1-1). Inhibition of GL1-1 activates the apoptotic pathways in senescent cells. This approach is another means to extinguish senescent cells from aged tissue and hence improves age-related diseases.[63] However, the exact link between metabolism and senescence is still somewhat unclear, thus requiring further research to fully understand this method. Furthermore, it was found that supplementation of ammonia can ablate the senolytic activity of GL1-1 inhibition altogether.[63]

2.4. Senolytics

Senolytic drugs are simply used to kill senescent cells. One bromodomain and extra-terminal domain (BET) family protein degrader (BETd) is used to promote senolytics in SCs. BETd uses two pathways, with one causing an upregulation of autophagy and the other a reduction of non-homogeneous end joining (NHEJ).[64] Other senolytic drugs, such as dasatinib and quercetin, have been used for the removal of SCs. This class of senolytics is often used to help mitigate radiation ulcers.[65] However, this group is limited by imprecise cell specificity.[66] Other senolytics like ABT-263,[67] a BCL inhibitor, UBX0101, and

UBX1967[68] have also been used to target senescent cells. The specificity, selectivity, dosage, duration, and frequency involving senolytic administration are all very critical considerations. Dasatinib is an Receptor Tyrosine Kinase (RTK) inhibitor, and its non-specificity affects the surrounding cells. Likewise, BCL-XL inhibitors foster the deterioration of blood platelet activity. Last, cardiac glycosides are another class of senolytics that can be used to target senescent cells. Although the senolytics mechanism is not yet fully understood, it has been hypothesized that they may bind to ion channel pumps and block the flow of K^+ and Na^+ ions. This procedure would cause the depolarization of the membrane, which could potentially activate apoptotic pathways.[69] A problem with this approach is that the destruction of senescent cells may promote cancer growth.

2.5. Nanoparticles

Chiral nanoparticles (NP) have also been used to induce apoptosis in SCs. D-CuxCoyS, a NP, was used by alternating magnetic fields and near-infrared photon illumination.[70] Synergistically, these two methods induce apoptosis by both the activation of caspase-3 and by damaging the cytoskeleton.

2.6. BH3 Mimetics

B-cell lymphoma homology expresses a BH3 protein that uses a specific BH3 domain to inhibit anti-apoptotic proteins, and thus target senescent cells.[71] Drugs like ABT-199 (venetoclax) and ABT-263 (navitoclax) are BH3 mimetics, meaning that they mimic the domain of BH3. By doing so, they suppress BCL-2, BCL-X, and BCL-W in cancer treatment.[72] These drugs can also be used in targeting the unique metabolism of senescent cells.[73]

2.7. CAR T-Cell Therapy

Senescent cells can be prepared through various induction methods, which broadly display a common surface marker protein known as urokinase-type plasminogen activator receptor (uPAR). Chimeric antigen receptor (CAR) T cells can be used to clear senescent cells by selectively attacking the uPAR surface antigen.[74] These specialized CAR-T cells are developed by introducing mouse uPAR into the CD38 regions of human T-cells.[75] However, to ensure the safety of this therapy, progressive development of this approach through clinical application is necessary.

2.8. Immune Cells

Senescent cells are present throughout our bodies in diverse amounts. These cells are normally removed naturally by immune cells. For this reason, the disablement of immune function can allow for the proliferation of senescent cells which can result in age-related pathologies. Natural killer (NK) cells and macrophages are two types of functional immune cells that destroy SCs. NK cells have the ability to kill cells that have been damaged by cancer treatment. In the process of erasing pro-inflammatory senescent cells, some may escape from the NKs due to the over-expression of matrix metalloproteinase-3 (MMP3). The reason MMP3 cannot simply be inhibited is because its inhibition presents severe side effects. On the other hand, macrophages are another innate exterminator of damaged cells. However, NF-kB signaling upregulates CD47 expression, which acts as an inhibitory receptor on the surface of senescent cells. Upregulation of CD47 may assist senescence in escaping macrophage-based killing.[76] Carnosine is an anti-aging skin drug used to maintain the elasticity and dryness of skin. Carnosine promotes macrophage phagocytosis and hence improves the destruction of senescent cells.[77] Carnosine-mediated clearance is carried out by the activation of the serine/theonine protein kinase 2 (AKT2) pathway.

2.9. Plasmonic Core–Shell Spiky Nanorods

Plasmonic core–shell spiky nanorods (CSNRs) are modified with antibodies to target the mitochondria and specific receptors of senescent cells. Near-infrared irradiation-induced senescent cells were treated with these nanorods to bolster levels of ROS and cause deterioration to the cellular skeleton, thereby inducing apoptosis. This also resulted in the destruction of SCs, without harming any normal cells.[78] The only problem associated with this method is that it requires illumination and the process is yet to be demonstrated in vivo.

2.10. Ubiquitin-Specific Peptidase 7

Inhibition, or depletion, of ubiquitin-specific peptidase 7 (USP7) selectively causes apoptosis in senescent cells. This feature of USP7 is attributed to cellular degradation, which increases the level of p53 and thus induction of apoptotic proteins. Furthermore, p53 activation blocks the interaction of BCL-2 and BAK proteins[79] and generates both apoptosis and suppression of the SASP from senescent cells. Thus, USP7 has become a novel target for the elimination of senescence; however, there is some controversy as to what exactly the mechanism is. Two pathways have been hypothesized: one utilizing p53; the other is proposed to be p53-independent.

2.11. Mitochondria-Targeted Tamoxifen

Mitochondria-targeted tamoxifen (MitoTam) is a mitochondria-specific anticancer drug that is used to kill cancer cells. It is also used to dispatch both malignant and senescent cancer cells. The activity of MitoFam in SCs is regulated by the presence of low-level adenine nucleotide translocase-2 (ANT2). Restoration of ANT2 hinders the functional activity of MitoFam in SCs, while conversely, its downregulation in non-senescent cells advances their elimination.[80] Although MitoTam is a highly selective killer of senescent cells, it does have minor drawbacks. When normal cells were treated with MitoTam for 2 days, roughly 50% of the cells ceased proliferation, despite not entering senescence.

2.12. FOXO4

Forkhead Box O4 (FOX04) belongs to a transcription factor family that is associated with the process of aging. The expression of

this gene is increased in cells undergoing senescence; however, inhibiting this gene results in the activation of programmed cell death in senescent cells. Downregulation of FOXO4 in normal growing cells leads to apoptosis instead of senescence. Furthermore, the suppression of this protein in senescent cells leads to an increase in apoptosis.[95] The interaction between FOXO4 and p53 is significant in the elimination of senescent cells. A D-retro-inverto peptide (DRI) interferes with the interaction between p53 and FOXO4. Disruption of FOXO4-p53 by FOXO4-DRI caused apoptosis. FOXO4-DRI has the potential to be a drug candidate for eliminating senescent cells. However, the selectivity and efficacy of the assay in humans have not been tested yet.[94]

2.13. Inhibition of MEK/ERK Pathway

The Mitogen-activated kinase/ Extracellular Signal-regulated kinase (MEK/ERK) pathway plays an important role in cancer development. The inhibition of the MEK pathway is harmful to mitochondria. When these damaged mitochondria are not degraded by autophagy, it results in the accumulation of ROS. ROS aggregation activates the apoptotic pathway in senescent cells. Evidently, activation of the MAPK pathway restores mitochondrial health and viability. The mechanism of senescent cell death by the inhibition of the MEK/ERK pathway is due to the disruption of lysosomes, as well as auto-phagolysosomes.[97] Also, the loss of yes-associated protein (YAP1) induces cellular senescence and negatively regulates p21. Thus, sequential targeting of the YAP1 and p21 might be a novel approach to removing senescent cells.[92]

3. Drawbacks of Senescent Cell Elimination

Here, we will discuss why the elimination of SCs may not be a good choice. The discussion will include the abnormalities that occur due to their absence, along with the limitations of the senolytical approach. Senescent cells assist in wound closure, and their elimination can hamper wound healing dynamics.[22] While cellular senescence has critical involvement in early embryonic development, we will not include this area in the review, since our focus is on the accumulation of senescence associated with aging. We will explore the complex relationship between cancer and senescence and address conflicting studies on their interactions. Senescent cells also limit the degree of tissue fibrosis[98,99] and assist in immune system recruitment.

3.1. Detrimental Effect of SC Removal on Tissue Physiology

In a recent study, it has been reported that the elimination of senescent cells interferes with the native tissue environment and confers both liver and perivascular fibrosis. Moreover, demolished SCs were not replaced by normal cells, which led to harmful morphological and functional changes within the tissue.[100]Endothelial cells are one such class where clearance of senescent cells tarnishes the surrounding normal cells; for instance, the elimination of SCs caused pulmonary hypertension[101] in mice. This may be why all types of senescent cells are not eligible for termination. For example, senescent T-cells are not eliminated because they cannot be regenerated at advanced ages. Considering the beneficial properties of senescent cells, it may be better to keep them rather than delete them completely. In vivo elimination of SC studies have been performed on mice, but it became evident that senescent cells were not completely removed. This was presented by the analysis of treated mice liver and T lymphocytes. The complete or partial removal of senescent cells can cause fibrosis of tissue and organs, impairment of the blood–tissue barrier, and a reduction in health span. Over an organisms lifespan, many organs including the heart may accumulate up to 30–50% of senescent cells.[102] Therefore, the removal of SCs would leave an empty space, which would significantly hinder organ function. It is possible that the remaining proliferative cells may compensate for their removal. However, the filling process does not take place in experimental practices. For instance, the elimination of satellite cells contributes to the myopathy of skeletal muscles.[103] In addition, the loss of skin cells is not compensated by the surrounding cells, rather they leave an empty void only filled by the stretching of membranes.[104] Transplantation of stem cells has not yet been a feasible approach due to the large number of cell deaths.[105] Altogether, the replacement of 15 senescent cells with normal growing cells is a bottleneck of trial and error.

3.2. Limitations of Senolytic Drugs

A tissue is made up of a variety of cell types; therefore, there is a heterogeneous population of different forms of senescent cells. This heterogeneity present within the tissue limits the efficacy of senescent cell targeting. The specificity, dose, and duration, as well as the failure to distinguish between quiescent and senescent cells, are all problems associated with the selective elimination of senescent cells.[52,106] An approach with high selectivity may leave some SCs behind, while approaches with low selectivity may harm healthy cells. Even though in vitro studies have shown that certain drugs are capable of selectively targeting and killing senescent cells, in vivo studies have shown that harmful side effects can accompany this process. For example, many senolytics, like navitoclax and dasatinib, diminish the function of osteoblasts and bring about bone loss, as well as endothelial dysfunction.[107,108] In addition, the use of senolytics results in hypertension.[101] Complications such as these are another issue with the use of senolytics and senescence elimination in the clinical setting.

3.3. Beneficial Effect of Senescence: Wound Healing

The ability of SCs to reorganize the ECM by secreting collagen in conjunction with their strong signaling system gives them a key role in aiding wound healing.[109] Senescent cells release a specific molecule called Platelet-derived growth factor- AA (PDGF-AA), which is a component of the SASP. PDGF-AA promotes myofibroblast differentiation, which is necessary for the wound closure process.[110] Studies have revealed that the duration of senescence is a key factor in the instance of transient, or temporary, senescence. The transient dynamics of senescence is beneficial in tissue repair because it allows for the recognition of damaged tissue by the immune system.[109]

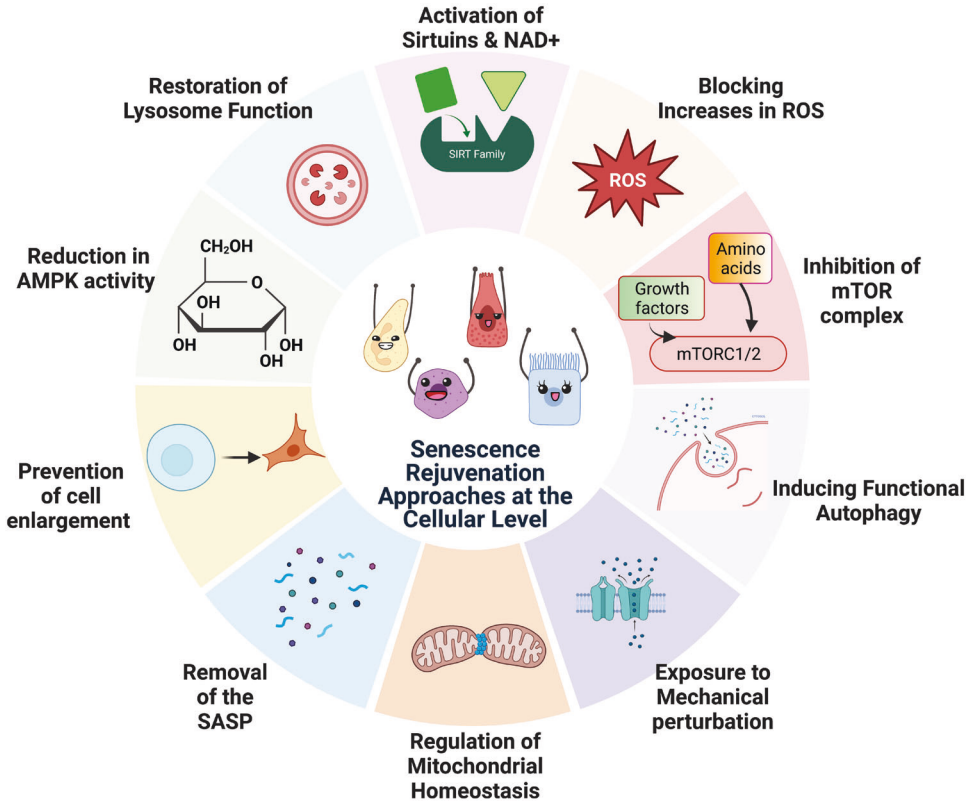

Figure 3. Potential Strategies for the rejuvenation of senescent cells.

3.4. Paradoxical Relationship between Senescence and Cancer

It has long been thought that cellular senescence is a defensive strategy to act as a tumor suppressor mechanism. This is because, senescent cells stop their proliferation and secrete the SASP, which halts the division of other cells via paracrine signaling and recruits the immune system, which attacks the transformed cells.[111,112] Therefore, expunging senescent cells may support an increase in cancer progression. One study[113] showed this by using a metallopeptidase inhibitor 1, (TIMP1). SCs have been recognized for their ability to inhibit the advancement of tumors. Nevertheless, the depletion of TIMP1 exacerbates the process of cancer metastasis. As a consequence, a significant number of individuals diagnosed with prostate cancer exhibited resistance to chemotherapeutic agents. The findings presented in this study demonstrate the dual function of senescence in the context of both the presence and absence of TIMP1.[113] When co-cultured with senescent cells, normal cells displayed increased DNA and oxidative damage and activation of many senescence-associated markers showing that paracrine signaling influences multiple cell types.[114] This explains how the presence of senescence and the SASP can prevent cells from transforming into cancer and slow tumor initiation.

Despite this evidence, many other studies have demonstrated that accumulation of senescence benefits tumor progression through certain molecules of the SASP. Vascular endothelial growth factor (VEGF) is one component of the SASP that aids in tumor vascularization and progression. Senescent fibroblasts have also been implicated in favoring tumor development shown in a study demonstrating that pre-malignant breast epithelial cells lose their differentiation characteristics, gain invasiveness, and undergo transformation when co-cultured with senescent fibroblasts.[115,116] These findings make it difficult to pinpoint how exactly senescence influences cancer and altogether show that eliminating senescent cells may give rise to a series of other problems.

4. Potential Strategies for Senescence Rejuvenation

The elimination of senescent cells has quite a few limitations which can weaken tissue structure and function. In the last 2 years, many studies have been conducted to rejuvenate senescent cells, instead of eliminating them. For example, the surgical conjoining of old and young mice, a process called parabiosis, is a method of replacing SCs. In parabiosis, both the young and old mice share circulatory systems.[117] Theoretically, the youthful immune system and blood cells from the young mouse can revamp the senescence-riddled circulatory system of the aged mouse. This study shows the promise of new strategies that are being developed as a new outlook of rejuvenating senescent cells rather than eliminating them. In this section, we will discuss various approaches used in attempts to rejuvenate senescent cells (**Figure 3**). Considering the positive implications of senescent cells, complete elimination may not be the ideal choice. Therefore, research of the rejuvenation or reversal of senescence calls for a more thorough understanding.

4.1. Extracellular Vesicles (EVs)

EVs are small lipid-bound vesicles secreted by cells into the extracellular space that influence cell–cell interactions, contribute to tissue homeostasis, and aid in local tissue development.[118,119] The content, or cargo, of EVs consists of lipids, nucleic acids, and proteins—specifically, proteins associated with the plasma membrane, cytosol, and those involved in lipid metabolism.[118,120] There are different subtypes of EVs depending upon the circumstance of their biogenesis, and their contents can vary.[121] EVs are even some of the constituents of the SASP, including both small EVs and large EVs. Additionally, small EVs isolated from old individuals have no effect on aging markers. Meanwhile, there is no evidence of large EVs having any effect on senescence and aging, regardless of donor age.[122] Small extracellular vesicles that have been isolated from the fibroblasts of young humans reduced the amount of the senescence phenotype present in cells from old donors and in old mice.[123] Authors show that small EVs can reverse ROS activity and inhibit lipid peroxidation.[124] Anti-aging features of small EVs are thought to be due to the high level of glutathione-S-transferase activity. Still, many more experiments are required to establish accurate EV isolation techniques and the therapeutic role of small EVs on aging.

4.2. Exercise and Blood-Borne Factors

It is well known that physical exercise improves age-related cognitive functions including memory and brain health.[125,126] Daily exercise, or environment enrichment, improves learning,[127] minimizes senescence physiology,[128] enhances memory and immune functions,[129] and repairs neurovascular dysfunction.[130] In animal models, blood plasma from exercise-performed mice was administered to relatively inactive aged mice. Subsequently, the blood transfusion ameliorated many age-associated cognitive defects.[131] Exercise also caused an increase in the levels of glycosylphosphatidylinositol (GPI)–specific phospholipase D1 (Gpld1), a liver-derived enzyme, in circulating blood plasma. In addition, Gpld1 levels were also found to be high in active adult humans. In parabiosis, blood from a young mouse is transferred to an old mouse by conjoining their circulatory systems,[132] and hence, the blood plasma was transferred from the immature to the mature mouse. This technique improved cognitive functions and regenerative potential within the brain of the aged mouse.[133,134]

4.3. Epigenetic Reprogramming

Epigenetic reprogramming is the process by which an organism's genotype interacts with the environment to produce its phenotype and provides a framework for explaining individual variations and the uniqueness of cells, tissues, or organs despite identical genetic information.[135] Many of these epigenetic alterations occur via processes of small-interfering RNAs, DNA methylation, or histone modifications.[136–138] These epigenetic changes could have a big influence in determining a cell's state, specifically in encoding for the senescence phenotype. In a seminal study, the David Sinclair group demonstrated that adding Sox2, Klf4, and Oct4 in ganglion cells of aged mice promoted axon regeneration and restored vision loss.[139] Thus, epigenetic reprogramming can mediate vision restoration and is thought to be caused by DNA methylation. This provides insight into how rejuvenation can occur by inducing manipulations in cellular epigenetics.

4.4. mTOR Inhibitors

The mammalian target of rapamycin (mTOR), a serine/threonine kinase, is a cell nutrient sensor and is an important regulator of metabolism. This enzyme has a vast number of roles, including regulation of autophagy, mitochondrial biogenesis, lipid and nucleotide synthesis, and increasing protein translation.[140] One marker of cellular senescence is the hyperactivation of mTOR, which sustains the cell in an anabolic (growth) state. This hyperactivity is thought to contribute to the increase in senescent cell size, as well as in intracellular crowding caused by the blocking of autophagy. Inhibitors of mTOR, including rapamycin and resveratrol, have shown the ability to reverse senescence and aging in vitro.[141] Similarly, metformin activates AMPK, another metabolic controller, and is shown to have an impact on senescence rejuvenation.

4.5. Hyperbaric Oxygen Therapy

Another recent study, published in 2020, indicated that hyperbaric oxygen therapy (HBOT) was used to investigate whether an intermittent supply of pure oxygen at high pressures affects the aging process. The authors used two key markers, telomere length and cellular senescence of mono-nuclear cells in peripheral blood, to assess the impact of intermittent exposure to HBOT in aged humans. It became evident that the HBOT significantly decreased the percentage of senescence in T cells. Interestingly, the telomere lengths of B-cells, T-cells, and natural killer cells were all increased significantly.[142] Many other studies have also shown that HBOT benefits cognitive functions[143] in adult humans. In conjunction, hyperoxia affects mitochondrial biogenesis, stem cell proliferation and migration, hyperoxia-induced factor (HIF-α), sirtuins, and VEGFs.[144]

4.6. Balance of NAD+ and NADH Ratio

The in vitro expansion of human mesenchymal stem cells (hMSCs) is shown to lead to replicative senescence and a decline in the proliferation and differentiation potential. The NAD+ to NADH ratio regulates senescence in hMSCs. When hMSCs were treated with a NAD+ precursor, nicotinamide, it increased NAD levels and maintained the NAD+/NADH ratio, as well as increased sirtuins' activity. Thus, NAD+ can maintain mitochondrial function and rejuvenate late passage senescent cells.[145]

4.7. Modulation in ROS Gene

The compilation of oxidative damages caused by high levels of ROS is one of the bases of aging among mammals. P66Shc is

one gene, member of Src homologous-collagen homologue adaptor protein that has been shown to incite a high production of ROS and oxidative damage in triple-negative cancer cells. ROS production sensitizes Poly (ADP-ribose) polymerase inhibitor (PARPi), which initiates the apoptotic pathway.[146] The P66Shc protein is shown to be colocalized in mitochondria and other organelles,[147] which are dysregulated in the senescent state. Deleterious mutation in the gene P66Shc can produce stress resistance and prolong life & health span. P66Shc is an adaptor protein and is involved in mitogenic signal transduction from an activated receptor to RAS. P66Shc is activated by an abundance of ROS, which leads to apoptosis and is thus indicative of involvement in the apoptotic signal pathway. The deletion of P66hc[148] results in an increased resistance to apoptosis and increased dysfunction of p53 and p21 responses, resemblant of the senescent phenotype. P66Shc is a downstream regulator of p53, as it distinguishes between the tumor suppressor and aging activities of p53.[149] Furthermore, cases of increased levels of ROS and oxidative damages can be determined genetically via the stress-induced pathway involving p53 and P66Shc. We must keep in mind that aging is a multifaceted process encompassing many molecular pathways; therefore, delaying the aging process requires a combination of interventions and the targeting of many different genes.

4.8. Immune Response

Earlier, we discussed that senescent cells have an important function in directing the body's immune response. After all, the immune system requires proper indication of damaged or malfunctioning tissue, to exert its effect on the specific target. The accumulation of senescence cells and secretion of the SASP may aid in recruiting the immune system and initiating a response. This contributes to the pro-inflammatory effect secretion of the SASP displays. Once the immune system recognizes the necrotic tissue by the presence of accumulated senescence, it can remove the aged cells, repair the tissue, and restore its function. This is the natural way that the body can clear the senescent cells.[150] This is assuming a fully functioning immune system. However, the problem is when the immune cells themselves start becoming senescent. Immune cell senescence leads to the gradual decline of immune capabilities and allows for SCs in tissue to build up. This is why we see diminished immunity in elderly individuals. While senolytic elimination approaches may be a plausible concept within many tissue types, it would be a disastrous tactic in targeting senescent immune cells. The difference is that if senescent cells are eliminated from an organ, many other cells may accommodate their removal. In contrast, the immune system cannot replenish its cells at advanced stages; therefore, eliminating senescent immune cells may destroy an individual's overall immunity. By considering this, rejuvenation is the desired approach in targeting immune system senescence and would be beneficial in boosting the body's natural method of senescence removal.[151]

5. Mechanobiology of Rejuvenation

Cells reside in a 3D microenvironment where they interact with other neighboring cells, components of the ECM, and respond to a multitude of biochemical and mechanical stimuli. As we age, many mechanical changes occur within the cell and tissue microenvironment.[152] Senescent cells are constantly altering the ECM by laying down collagen and other fibrous tissue, which can account for the increase in rigidity as tissue becomes aged. Many studies have shown that mechanical property, particularly rigidity, measured by Young's elastic modulus, regulates cell proliferation and cell differentiation.[153] Higher stiffness in the ECM leads to a multitude of cellular changes. Looking further into detail, mechanical stimuli that encompass many physical factors such as compliance of surface rigidity, solid stress, fluidic stress, stretch/compression, and the geometry of the microstructure, all influence cell function and state.[154,155] Mechanical stimulation has been demonstrated in some studies to enhance cellular function while also reducing markers of cellular senescence, suggesting that it may have rejuvenated effects on senescent cells (**Table 2**). For instance, much research has demonstrated that applied mechanical stresses can both decrease the expression of senescence-associated markers and increase the survival and proliferation of senescent cells.

The reports indicate that mechanical forces have a big effect on cellular functions through specific processes of mechanotransduction, that is, the conversion of biomechanical signals to biochemical signals. Mechanical forces impose regulation of a cell's metabolic operations by altering the activity of mTOR complex 1 (mTORC1), autophagy, lysosomal functions, fusion of autophagosomes and lysosomes, cell cycle, apoptosis, morphology, migration, viability, proliferation, gene expression, and immune response. These effects can also be observed in mitochondrial dynamics, cytoskeletal arrangements, and epigenetic modifications. For example, low shear stress impairs mitochondrial[156] homeostasis and blocks mitophagy in endothelial cells,[157] whereas laminar shear stress blocks inflammation through autophagy in aortic cells.[158]

Dysfunction in mitochondria regulation and inhibition of autophagy can allow for intracellular ROS and protein debris to accumulate, respectively. Furthermore, it has also been demonstrated that a cell's nuclear architecture and chromatin arrangements are also modified by exposure to mechanical forces. These types of cell stresses direct a cell into transforming into the senescent state, explaining how the mechanical properties of the environment are highly integral in maintaining a cell's state. Emerging evidence is showing how different mechanical stimuli can affect various aspects of a cell's physiology and behavior. It is now known that mitochondria respond to shear stress,[159] while cyclic stretching enhances mitochondrial oxidative phosphorylation (OXPHOS) and biogenesis.[160]

Mechanical stretching alters the cell cycle, mitochondria-mediated apoptosis, and induces cytoskeletal-mediated ROS.[156,161,162] Cyclic stretching induces oxidative stress in various cell types.[163,164] Mechanical pressure applied by atomic force microscopy induces mitochondrial fission.[165] In addition, actin-cytoskeletal contractility contributes to mitochondrial constriction.[166] Even the matrix rigidity and a cell's overall shape can influence mitochondria.[167] These examples signify how mitochondria and other cellular organelles respond to various mechanical forces.[164,166,168]

Certain biophysical cues such as rigidity, fluid flow, stretch, and contraction influence cellular functions, primarily those re-

Table 2. Key players and pathways involved in the mechano-rejuvenation process.

Drug/pathways	Activator	Inhibitors	References
Integrins	Mechanical stress, Insulin growth factors (IGF-I), and Platelet-derived growth factor (PGDF)	Cytochalasin D	Zhen et al.[173]
Rho	Mechanical stress	RhoGAPS and C3 toxins	Sah et al.[174]
ROCK	LPA and thrombin	Y27632, Fasudil, and H-1152	Knipe et al.[175]
Lamins A and B	IGF-1 and phosphorylation of lamin A and B	Lonafarnib HDAC inhibitors such as valproic acid	Zhavoronkov et al.[176]
YAP and TAZ	Mechanical stress and Hippo signaling	Verteporfin	Islam et al.[177]
Src Kinases	Mechanical stress and growth factors	Imatinib and PP2	Schernthaner et al.[178]
MAPK	Mechanical stress, growth factors, and cytokines	U0126 and SP600125	Yanoshita et al.[179]
AMPK	Metformin, AICAR, Berberine, and resveratrol	Compound C and Dorsomorphin	Hardie et al.[31] and Day et al.[180]
Sirtuins	Resveratrol, SRT1720, SRT2104, NMN, NR, and NAD+	Nicotinamide, sirtinol, cambinol, EX-527, and tenovin-6	Gertz et al.[181]
P38 pathway	TNF-alpha and IL-1 beta	SB203580 and BIRB796	Shah et al.[182]
ERK pathway	EGF and NGF	U0126 and PD184352	Slack et al.[183]
AKT pathway	Insulin, IGF-1, and PDGF	LY294002 and wortmannin	Adi et al.[184]
FOXO	ROS, IGF, CR, physical exercise, resveratrol, and curcumin	RNAi, NSC-207895, AS1842856, DMACL	Pardo et al.[185]
NF-kB	TNF-alpha, LPS, berberine, IL-1, and pathogens	Curcumin, IKK inhibitors, corticosteroids, and NSAIDs	Buhrmann et al.[186]
ATM pathway	Chemotherapeutic agents, ionization radiation, vitamin D, caffeine, and exercise	KU60019, KU-55933, RNAi, nivolumab, ipilimumab, and curcumin	Stagni et al.[187]
MicroRNA 21 and MiR-146a	Resveratrol, curcumin, PPAR gamma agonist	Luteolin, EGCG, LNAs, ASOs, SiRNA	Li et al.[188]
Telomerase activity	Meditation, exercise, TAT2 and TA-65, and Astragalus	Antisense oligonucleotides, imetelstat GRN163L, bibr1532, and EGCG	Harley et al.[189]

NF-kB, Nuclear factor kappa B; IGF-I, Insulin-like growth factor; LA, Lysophosphatic acid; AICAR, 5-Aminoimidazole-4-carboxamide ribonucleotide; NMN, Nicotinamide mononucleotide; NR, Nicotinamide riboside; EGF, Epidermal growth factor; NGF, Nerve growth factor; TNF-alpha, Tumor necrosis factor alpha; IL-1 beta, Interleukin-1 beta; IGF, Insulin-like growth factor; CR, Calorific restriction; LPS, Lipopolysaccharide; PPAR-gamma, Peroxisome proliferator-activated receptor gamma; YAP, Yes associated protein; TAZ, Transcriptional co-activator with PDZ-binding motif; ROCK, Rho associated protein kinase; MAPK, Mitogen activated protein kinase; ATM, Ataxia-telangiectasia mutated; NAD+, Nicotinamide adenine dinucleotide; HDAC, HIstone deacetylases.

lating to migration, replication, morphology, and viability. Normal growing cells have rigidity-sensing modules which are composed of actin filament, paxillin, talin, myosin, tropomyosin, and actinin proteins. Senescent cells apply more traction forces, have more focal adhesion sites, and have more actin stress filaments throughout.[169] In general, a cell's state can be characterized based on its rigidity-sensing capabilities and growth potential. Normal growing cells have intact sensing machinery, where they grow on stiff surfaces, but undergo cell death on soft surfaces.[170] In contrast, while in a transformed state, the rigidity- sensing machinery is dysfunctional, and they can grow on soft and stiff surfaces alike.[171] Recent data show that transformed cells lack rigidity-sensing abilities due to the absence of tropomyosin 2.1.[172] When Tpm 2.1 is generated in transformed cells, they begin behaving like normal cells and undergo anoikis when cultured on soft surfaces. This suggests that cells in a transformed state obtain a faulty apoptotic pathway, which may be linked to rigidity sensing.

The extent to which mechanical forces can be employed to rejuvenate senescent cells should be explored to adequately understand the mechanisms through which they may modify cellular senescence. Further research is required to determine the optimal conditions for the utilization of mechanical forces in rejuvenating senescent cells since their effects on cellular activity can be subtle and complex.

6. Outlook and Future Implications

It is important to keep in mind that cellular actions are all highly dynamic and constantly changing. However, this dynamic nature is required for a cell to adjust its physiology accordingly, to enable proper response to mechanical cues presented in the environment. By making these modifications, cells are able to maintain homeostatic equilibrium and avoid mishaps like mutation and death. While many of the adjustments in cellular processes may act transiently, chronic exposure to specific stimuli could

Outstanding questions in the field of senescence and anti-aging

In- vitro

1. Normal cell size enlarges in response to senescence inducing drugs and replicative senescence. How are chemical cues converted into the physical form?
2. How are the size of senescent cells regulated by nutrients and growth factors?
3. What is the threshold size of a cell, in which that cell becomes irreversibly senescent?
4. How are the functions of intracellular organelle altered with an enlarged size?
5. What regulates the lysosome and autophagosome fusion process?
6. What is the role of extracellular pH in the induction of senescence?
7. What determines the formation and stability of lysosome, phagophores....?
8. How are senescent cells different from diseased cells?
9. What determines whether cells enter the apoptotic or anti-apoptotic state?
10. What factors affect the migration of a single versus an aggregation of senescent cells?

In-vivo

1. Even if senescent cells are rejuvenated, the degraded microenvironment may not be rectified by the rejuvenation strategies. For cells that reside in the niche, the deterioration of the niche may be toxic for remaining cells.
2. Is it possible that the reversal and induction of senescence are competing processes? In an aged body, senescence might outcompete reversal.
3. If the SASP is already present in the tissue microenvironments, reversal may be unstable or transient. Therefore, removal of the SASP from organs and the tissue environment is yet to be performed.
4. Organs and tissues are made of several types of cells including immune cells, stem cells, and differentiated cells, but we do not yet know how rejuvenation will affect the overall variety of senescent cell types.
5. How long can rejuvenated cells survive in the body. and does the migratory potential affect tissue integrity?

Figure 4. List of outstanding questions.

enforce more permanent alterations in cellular organization. Field of senescence and ageing is growing rapidly and it is a need to answer many unresolved questions (**Figure 4**). When the balance of homeostasis is tilted too far to one side or the other, it may result in disease or abnormalities. It is now understood that the senescent state may act as a buffer to counteract harmful manifestations within the cell and its prodigy, which may be why we age.[190] Cellular senescence can be characterized as a stubborn cell state with both beneficial and detrimental roles in tissue and organ function.

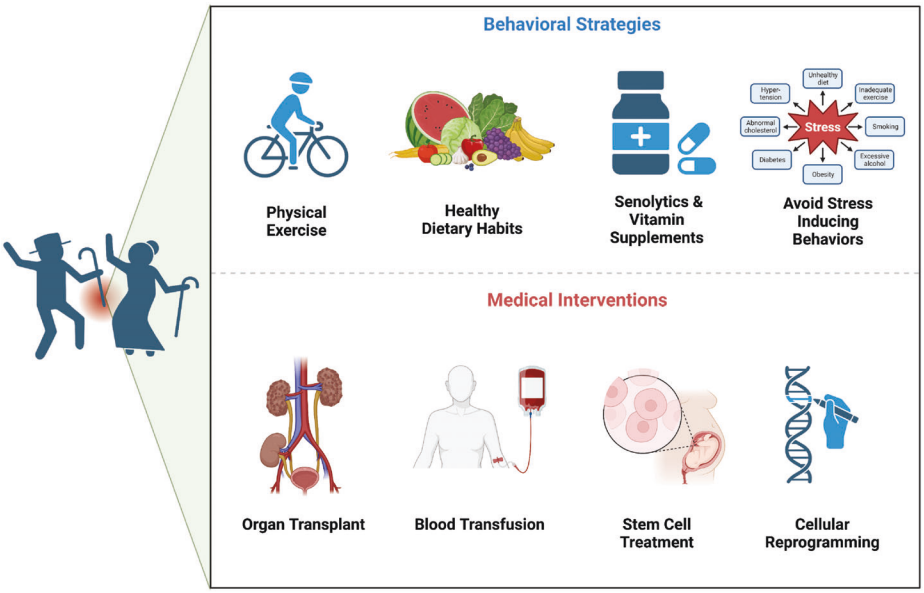

Figure 5. Illustration showing the potential age-reversal approaches.

It has been shown that damaged tissue accumulates senescence to express overall defect and act as a target for the immune system.[109] However, the senescence phenotype is very robust, and the cells become cunning in their ability to avoid death. SCs have reduced function and big implications for their surroundings.[50,152,171,191,192] Altering the mechanics of a cell's physical environment may help to understand the aging process and act as a potential strategy to revert the senescent cells to their proliferative state, thus delaying senescence-associated features. The limiting step of a mechanical-based intervention strategy is the development of a new tool to specifically target senescent cells and tissues directly or indirectly. Physical exercise is becoming established as a non-invasive strategy used to expose cells to mechanical forces. Studies have shown that physical exercise, specifically weight resistance training,[193] can simulate the action of senolytics.[130,194] Further, exercise can ameliorate some of the hallmarks of aging and improve a person's quality of health and lifespan.[195,196] However, a disadvantage of the exercise-based approach is that ill or impaired individuals may be unable to perform the required activities and movements.

In the future, it is probable that mechanical-based techniques will be more extensively utilized in combination with other available strategies. A multi-variable approach should be considered including pharmacological, dietary, and physical activity levels to rejuvenate senescent cells and slow organismal aging. Deploying pressure pulses, also a noninvasive procedure, is another mechanical cue that can influence many cellular aspects. As mentioned, low-frequency ultrasound is a new technique creating numerous new possibilities.[197] This strategy may have therapeutic potential to rejuvenate aged cells and tissue and further promote the field of anti-aging research. The advantage of using this strategy is that it is non-invasive and clinically safe. In addition, these mechanical effects could be specific only to senescent cells and have no interference with normal biological processes.

Despite several studies on the role of senolytics along with other anti-aging and longevity approaches, the use of mechanical forces as an approach remains underdeveloped. As discussed, cells sense their microenvironment and remodel many facets via mechano-signaling and mechanotransduction processes, resulting from present mechanical stimuli.[198–202] Early studies show that substrate mechanics regulate the rejuvenation of induced pluripotent stem cells (iPSCs).[38,203,204] In the absence of biochemical cues, fibroblast cells cultured on a patterned surface transform into PSCs.[38] Kureel et al.[205] show that mesenchymal stem cells cultured on soft polyacrylamide gels delay the onset of senescence and regulate cell-cycle dynamics.[206] Surface stiffness also manages the quiescence of MSCs.[207] Gilbert and Chaudhary groups have shown that substrate stiffness controls proliferation and maintains differentiation potential in muscle stem cells.[208,209] These limited but promising findings indicate a strong need for a more in-depth analysis of mechanical forces as an approach to rejuvenation (see **Figure 5**).

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

S.K.K. conceived, prepared, wrote, and prepared the figures and tables of the manuscript. B.B. edited the manuscript and prepared and edited the figures and tables. M.P.S. provided resources and funding acquisition.

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Sanjay Kureel is a postdoctoral researcher in the Department of Biochemistry and Molecular Biology at the University of Texas, in Galveston, Texas. He has an academic background in the field of chemical engineering and focuses on research to integrate the fields of mechanobiology, metabolic processes, and the biology of aging. In his previous research, he exhibited the benefit of using soft substrates in slowing down the aging process and maintaining the regenerative capabilities of human stem cells. At present, he is engaged in research into the impact of junction proteins on cellular health and diseases.

Brandon Blair is a Research Associate at the University of Texas Medical Branch at Galveston. He is currently working with Prof. Michael Sheetz, where their team is studying the role of senescence in aging and the associated dynamics of cellular metabolism. In 2021, Brandon received a Bachelor of Science in Biology from West Texas A&M University, graduating Summa Cum Laude. He is continuing his education working toward a master's in business administration with an emphasis on management and aiming to matriculate into medical school in 2024.