

SENOLYTICS: EMERGING THERAPEUTICS TARGETING CELLULAR SENESCENCE AND AGE-RELATED DISEASES

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ABSTRACT:

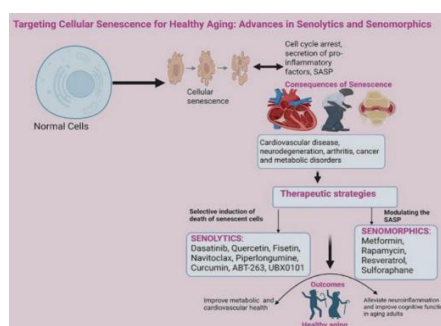
The condition in which cells are permanently stop dividing due to aging, damage of DNA is called cellular senescence(1,2). This process acts as a protective mechanism against malignancy (cancer), aggregation of senescent cells leads to chronic inflammation and dysfunction of tissue. Inflammatory factors called as senescence –associated secretory phenotype (SASP) was released by these cells, which causes aging and disease progression. Cellular senescence is related to several age related diseases which includes cardiovascular diseases, neurodegenerative disorders, diabetes, osteoporosis and cancer. Some drugs are emerged by targeting cellular senescence for improving health span(3,4). These drugs are called senolytics that act by eliminating the senescent cells, while senomorphics suppress the harmful effects of SASP without destroying the cells. Some studies have shown that removal of senescent cells can reduce inflammation and improve tissue function(3,4). Overall, targeting cellular senescence has a potential for prevention and treatment of age related diseases(4).

INTRODUCTION

Aging is a natural biological process accompanied by gradual deterioration of the functions of cellular, tissue, and organ structures leading to the increased risk of developing chronic diseases. One of the cellular features of aging is cellular senescence. It is a state when cells permanently cease to divide under influence of different kinds of stresses, such as DNA damage, oxidative stress, and shortening of telomeres (1,2).

Initially, cellular senescence is regarded as a protection strategy since it inhibits proliferations of the altered or damaged cells and thus helps to prevent tumour development (2,5). However, with the increase of age, the number of senescent cells in tissues grows, thus impairing the function of surrounding healthy cells. Despite the fact that senescent cells do not replicate normally, they are still metabolically active and produce a variety of inflammatory mediators by means of a senescence-associated secretory phenotype (SASP) (2,5).

SASP includes cytokines, chemokines, growth factors, and enzymes that cause tissue damage and inflammation. The constant secretion of these substances leads to a change in the tissue microenvironment, causing chronic inflammation and tissue dysfunction in connection with age-related disorders (3,4). It means that the accumulation of senescent cells becomes the key factor in the link between cellular aging and pathologies.



There is a greater chance of cardiovascular diseases, neurodegenerative disorders, diabetes, osteoporosis, osteoarthritis, lung diseases, kidney diseases, and cancer in older individuals. Senescent cells have been found in various tissues affected by these diseases, implying that cellular senescence plays a role in the pathogenesis and progression of such diseases (3,4). Furthermore, senescent cells can evade apoptosis through the activation of various anti-apoptotic pathways. Therefore, they can survive in tissues and constantly release harmful SASP factors (3).

In the understanding of these pathways, senolytic therapy became possible. Senolytic drugs are medications that selectively kill senescent cells by utilizing the dependency of senescent cells on certain anti-apoptotic survival pathways (3,4). Key senolytic drugs that were researched include Dasatinib, Quercetin, Fisetin, and Navitoclax. Their elimination

will help mitigate the negative impact of SASP, lower chronic inflammation and provide an optimal microenvironment for tissue repair and regeneration (3,4,7,9).

Another method is using senomorphics, which do not eliminate senescent cells but instead block their secretion of harmful products. Thus, senolytics and senomorphics are two approaches that can be used in targeting cellular senescence (3,4).

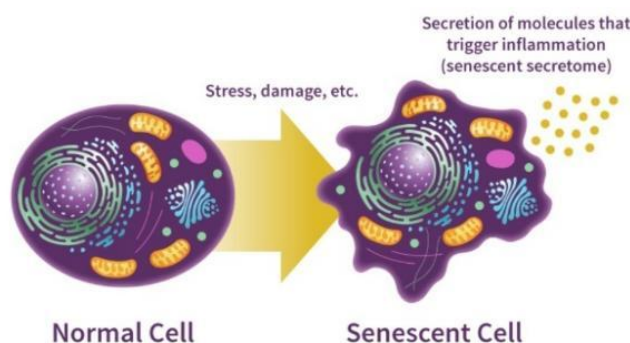
It is for this reason that current scientific studies have redirected focus to address the cellular processes associated with aging rather than the symptoms of the age-related disease. Cellular senescence has been established as one of the cellular processes that should be targeted therapeutically. In this review, the focus will be directed towards understanding the biological aspects and processes associated with cellular senescence, the mechanism of action of senolytic agents and classes of senolytic drugs, and their applications and limitations.

Cellular Senescence

Cellular senescence is an irreversible stable state of cell cycle arrest where cells are not capable of further division but retain their metabolic activity. It may result from different kinds of cellular stress such as DNA damage, oxidative stress, telomere shortening, mitochondrial malfunctioning and other kinds of cellular injuries (2,5). Cells become senescent, undergoing numerous changes in cellular characteristics and functions, while retaining their metabolic activity.

Cellular senescence serves as an important protection system in the organism. Undergoing damage, cells enter senescence and stop dividing, thus, preventing themselves from further growth and spreading of their damaged condition. It helps to prevent uncontrolled cell growth and tumorigenesis (2,5). Besides, cellular senescence plays its part in physiological processes, such as tissue remodelling and wound healing.

But with the accumulation of senescent cells in tissues, their effect starts to cause harm. Senescent cells are resistant to apoptosis and stay alive for a long time period. They secrete different kinds of inflammatory cytokines, chemokines, growth factors and matrix-degrading enzymes using senescence-associated secretory phenotype (SASP) (2,5). All those substances influence neighboring cells and form chronic inflammation.



Senescent cell accumulation and constant SASP release may result in tissue dysfunction, regeneration impairments, degradation of the extracellular matrix, and inflammation (3,4). As the individual gets older, the amount of senescent cells increases in various tissues, which indicates that cellular senescence is one of the key factors of age-related disease onset and progression.

Depending on the type of cell and the surrounding tissue microenvironment, cellular senescence might manifest in different ways and have various biological effects. Senescent cells have been linked to the development of cardiovascular diseases, neurodegenerative diseases, osteoarthritis, diabetes, pulmonary fibrosis, renal disorders, and cancer (3,4). Thus, cellular senescence has both protective and harmful functions: it prevents the growth of the damaged cells, yet, at the same time, its prolonged presence leads to inflammation and tissue damage.

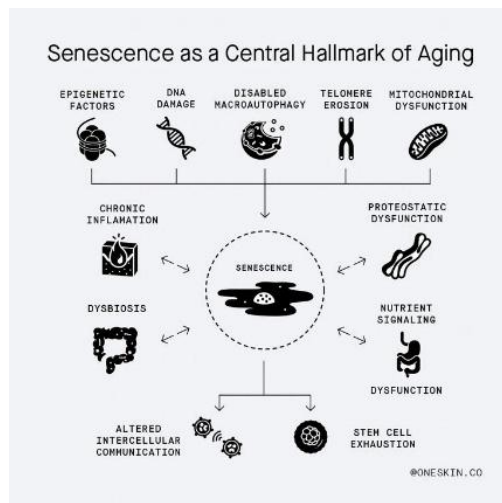
One of the key characteristics of senescent cells is their survival in spite of cellular damage. This happens due to the activation of certain anti-apoptotic/prosurvival signaling pathways like BCL-2/BCL-xL and PI3K/AKT pathways (3). This allows the senescent cells to avoid programmed cell death. Their survival dependency is one of the key features that should be considered when developing senolytics.

It is, therefore, vital to understand the mechanisms by which senescent cells form and sustain their deleterious effects. Targeted elimination of these cells through the use of senolytics will help lower the SASP-induced inflammation and create a better microenvironment within the tissues. Hence, cellular senescence has become an important area of research concerning aging, age-related conditions, and regenerative medicine (3,4).

Mechanism

Senescence is an intricate process during which cells irreversibly cease to divide but remain alive metabolically. It is caused primarily by persistent stress factors such as DNA damage, oxidative stress, telomere shortening, mitochondria dysfunction, and other types of cellular damage (2, 5). In response to such stress, cells activate intracellular signaling pathways to avoid further cell division of the damaged cell.

An important mechanism responsible for the induction of cellular senescence is the activation of DNA damage response (DDR). Persistent DNA damage leads to activation of intracellular signaling pathways that involve tumor suppressor genes such as p53. These result in increased levels of p21 protein. p53/p21 signaling pathway blocks activities of cyclin-dependent kinases (CDKs) and prevents cell cycle progression (3, 5). There is also involvement of p16INK4a/Rb signaling pathway in cellular senescence through the suppression of CDK activities. One of the important mechanisms triggering cellular senescence is the shortening of telomeres. With each cell division, telomeres become shorter. Once telomeres reach critically short length, they are detected as DNA damage, causing activation of DNA damage response. As a result, p53/p21 and p16/Rb signaling are activated, resulting in irreversible cell-cycle arrest (1, 2, 5).



Oxidative stress is also involved in the development and maintenance of cellular senescence. The excessive formation of reactive oxygen species (ROS) may cause DNA, protein, lipid, and mitochondrial damage. Thus, oxidative stress can enhance the signaling of DNA damage and maintain cellular senescence. The dysfunction of mitochondria can also increase ROS production and support cellular senescence (2,5).

After arresting the cell cycle, senescent cells experience many structural and functional changes, which involve cell enlargement and flattening, as well as metabolism and gene expression modifications. Despite that the cells no longer divide, they retain their metabolic activity and can synthesize and secrete different signaling molecules.

The formation of the senescence-associated secretory phenotype (SASP) is one of the distinctive features of senescent cells. SASP includes proinflammatory cytokines, chemokines, growth factors, and matrix metalloproteinases (MMPs). Among the SASP factors, there are IL-6, IL-8, TNF- α , and MMPs (2,5).

Furthermore, senescent cells become resistant to apoptosis due to the activation of a number of pro-survival and anti-apoptotic pathways such as BCL-2/BCL-xL and PI3K/AKT pathways (3). The activation of these pathways helps senescent cells to survive for a long time without going into programmed cell death. As a result, these senescent cells continue to produce SASP factors causing chronic inflammation and tissue damage.

Thus, the presence of senescent cells leads to a vicious circle, where cellular stress causes senescence, senescent cells produce SASP factors that lead to the inflammatory microenvironment contributing to the damage of cells and tissues. This phenomenon is related to aging and the development of many age-related diseases such as cardiovascular diseases, osteoarthritis, diabetes, pulmonary fibrosis, neurodegenerative diseases, renal diseases, and cancer (3,4).

The presence of senescent cells and their dependence on certain survival pathways form the foundation of senolytic therapy. Senolytic therapy acts against these pro-survival pathways and causes selective apoptosis of senescent cells. Various agents including Dasatinib, Quercetin, Fisetin, and Navitoclax have been studied due to their interference with certain survival pathways of senescent cells and help in removing the cells (3,7,9). The elimination of such cells may reduce the amount of SASP, decrease chronic inflammation and improve tissue functionality and regeneration (3,4).

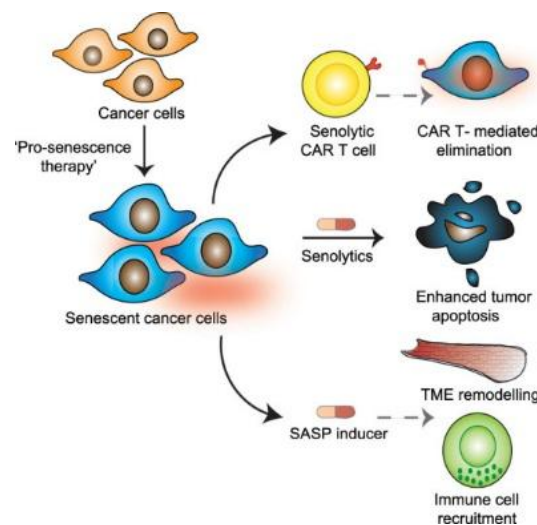
In summary, the mechanism of cellular senescence is characterized by a cell response to stress conditions, induction of cell cycle inhibitory pathways, permanent arrest of the cell cycle, formation of SASP, and activation of anti-apoptotic survival pathways. The understanding of the above mechanisms forms the biological background of the senescent cell removal as a therapeutic method.

Mechanism Of Action Of Senolytics

Senolytics are a type of drugs that selectively remove senescent cells through disrupting the survival pathways responsible for preventing the apoptotic death in these cells (3,4). Senescent cells form during aging and acquire enhanced dependency on several anti-apoptotic and survival pathways, like BCL-2/BCL-xL, PI3K/AKT, among others (3,4). Senescent cells use such pathways for surviving in spite of the damage to their structures. Senolytics affect these pathways and facilitate the process of apoptosis, leading to selective elimination of senescent cells.

One of the mechanisms includes blocking the BCL-2 family of proteins that inhibit the apoptosis through blocking pro-apoptotic signaling. Senescent cells may be dependent on these proteins for their survival. The inhibitor of BCL-2 family proteins, navitoclax, blocks the action of these proteins and facilitates the apoptotic process (7,8), which causes the mitochondrial dysfunction, release of cytochrome c, triggering downstream apoptotic signaling, and finally the cell death of senescent cells.

The second major survival pathway is the PI3K/AKT pathway, which ensures survival of the cells and their protection from apoptosis. Quercetin has been found to interfere with the PI3K/AKT-related signaling and promote elimination of senescent cells (3,5).



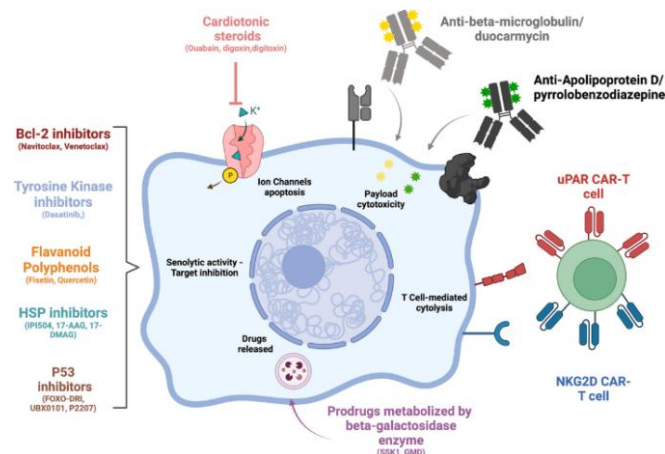
Dasatinib operates through inhibition of multiple tyrosine kinases, which are responsible for cell survival and signaling. Senolytic properties of Dasatinib can inhibit signaling pathways responsible for sustaining senescent cells (3). In combination with Quercetin, Dasatinib and Quercetin can target different survival pathways to increase senescence clearance (3,4).

Naturally occurring flavonoid Fisetin is also considered a senolytic compound capable of interfering with survival pathways and decreasing senescence. It can block survival pathways of the senescent cell and decrease SASP secretion, thus reducing inflammatory response of senescent cells (9).

Other possible strategy for senolysis is use of FOXO4-DRI peptide, which blocks interaction between FOXO4 and p53. As a result of blocking the interaction, apoptosis signaling initiated by p53 is stimulated to selectively kill senescent cells (3). Another molecule – Piperlongumine increases oxidative stress in senescent cells. Given that senescent cells have already increased levels of oxidative stress, increase in ROS leads to cellular damage and promotes apoptosis (3). HSP90 inhibitors make up yet another class of senolytic drugs. HSP90 is required for the stabilization of various proteins that promote the survival of senescent cells. As a consequence, the inhibition of HSP90 leads to the degradation of proteins involved in the promotion of survival and increases the level of cellular stress and apoptotic death of senescent cells (11).

Furthermore, cardiac glycosides such as digoxin and ouabain exhibit senolytic potential by the inhibition of Na^+/K^+ -ATPase pump. Disturbance of ion balance in cells causes stress and induces apoptosis of senescent cells. The natural polyphenol curcumin has relatively lower senolytic potential but might affect the process of cellular senescence and suppress the inflammatory activity of SASP.

After the removal of senescent cells, there will be less SASP secretion into the tissue microenvironment. Such reduction of the number of inflammatory cytokines, chemokines, growth factors, and proteases can assist in decreasing chronic inflammation and tissue dysfunction (3,4). The removal of senescent cells can create an optimal microenvironment for healthy cells.



One key aspect of senolytic therapy is that it is cell- and tissue-specific, meaning its efficacy is dependent on the type of cell and tissue in which senescent cells are present. Senescent cells are heterogeneous, and their survival could depend on different signaling mechanisms based on their source and stress factors responsible for their senescence state. In other words, it is likely that a single senolytic agent would not have the capability to clear all types of senescent cell

populations; combination therapy, such as Dasatinib with Quercetin, would allow senescent cells to be cleared more effectively because they would target multiple survival mechanisms (3,4).

In summary, the mode of action of senolytics is as follows: identification of senescent cells → blocking pro-survival/anti-apoptotic pathways of senescent cells → triggering apoptosis → selective elimination of senescent cells → decrease in SASP → lowering of chronic inflammation → improvement of tissue microenvironment and function.

Major Senolytic Agents

Senolytics are those substances, whether synthetic or natural, which selectively kill senescent cells by disrupting the pro-survival mechanisms of these cells. These substances help to reduce chronic inflammation and enhance organ/tissue functions with aging (3,4).



Dasatinib + Quercetin : Dasatinib and Quercetin are some of the well-researched senolytic agents that operate through targeting different survival pathways of senescent cells (3). Dasatinib inhibits tyrosine kinase signaling pathway, which plays a role in keeping senescent cells alive. Quercetin, a flavonoid found naturally, targets the PI3K/AKT signaling and cause reduction of oxidative stress. These both senolytics act by suppressing the anti-apoptotic pathways and trigger cell death pathways, thereby eliminating senescent cells and inflammation caused by SASP (3,5).

Navitoclax: The role of Navitoclax is elimination of senescent cells by targeting the inhibition of anti-apoptotic proteins belonging to the BCL-2 family. These proteins include BCL-2 and BCL-xL and provide protection to senescent cells from cell death. By the means of Navitoclax, the pro-apoptotic pathway is activated and cytochrome c release occurs (7,8).

Fisetin: Fisetin is an organic compound which works against damages and reduces inflammation. It comes from plants. This compound works by stopping molecules like PI3K/AKT, that help cells survive. It also stops the production of proteins that prevent cells from dying. Fisetin targets these cells. It also reduces the secretion of SASP factors, thus causing less inflammation (9).

FOXO4-DRI Peptide: This is an engineered peptide, which disrupts the FOXO4-p53 interaction in senescent cells. Normally, FOXO4 blocks the activation of p53-mediated apoptosis. The disruption of this interaction leads to p53-mediated activation of apoptosis resulting in selective clearance of senescent cells (3).

Piperlongumine: Piperlongumine is a substance found in nature which specifically increases the levels of reactive oxygen species in senescent cells. Senescent cells are already characterized by oxidative stress. Increased levels of ROS therefore increase cellular damage, mitochondrial dysfunction and apoptosis in senescent cells resulting in their clearance (3).

HSP90 Inhibitors: The inhibitory action of inhibitors of HSP90 happens through inhibition of Heat shock protein 90 which is required for the stability of survival proteins of senescent cells (11). HSP90 inhibition leads to protein degradation, cellular stress, and apoptosis.

Curcumin: Curcumin is a natural polyphenol occurring in turmeric which serves as an anti-inflammatory agent as well as an antioxidant. It alleviates oxidative stress and inhibits SASP production. Curcumin also controls certain pathways that play an important role in cellular senescence. It has relatively weak senolytic properties as compared to other agents but can promote healthy aging.

Cardiac Glycosides: Cardiac glycosides such as digoxin, ouabain and others function as senolytics due to their ability to inhibit Na⁺/K ATPase pumps. Such an action alters cell ion balance and promotes stress signaling that eventually causes apoptosis.

Therapeutic Applications of Senolytics in Age-Related Diseases

Senolytics show strong potential and may become effective treatments for various age-related diseases by the removal of senescent cells and decrease the chronic inflammation.

1. Neurodegenerative Diseases

Neurodegenerative diseases refer to progressive conditions that result from loss of neurons form and function. Some common examples include Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. The aging process, oxidative stress, mitochondrial impairment, DNA damage, and chronic inflammation are major factors associated with the pathogenesis of such conditions. (2,5)

There is an increased understanding about cellular senescence being an underlying factor that causes neurological diseases due to age. Cells undergo senescence with aging and produce inflammatory molecules called senescence-associated secretory phenotype (SASP). Senescent glial cells can also play a role in causing neurological problems, such as tau pathology (12).

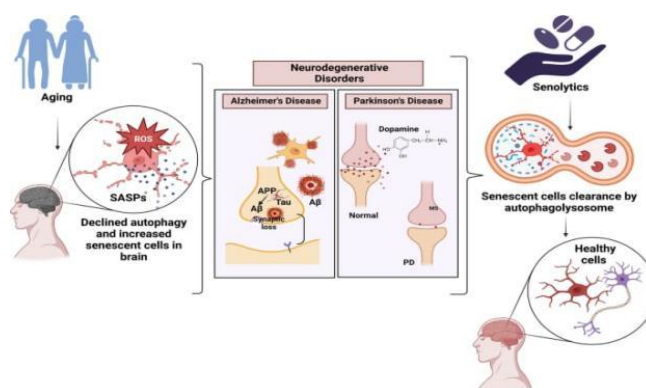
This implies that cellular senescence is a potential target for neurodegenerative diseases(12).

Mechanism

Cellular senescence in the brain is one of the sign of neurodegenerative conditions such as Alzheimer's and Parkinson's disease. In these neurodegenerative diseases, senescence of neurons, astrocytes, microglia, and other brain cells leads to neuroinflammation, oxidative stress, synaptic dysfunction, and neurodegeneration. Senescent cells of brain tissue display senescence-associated secretory phenotype (SASP) which includes IL-6, IL-8, TNF- α , chemokines, and reactive oxygen species (ROS)(2,5).

The mechanism of senolytic agents includes selective elimination of these damaging senescent cells(3). Senescent cells are able to survive because of various anti-apoptotic survival pathways such as BCL-2/BCL-xL, PI3K/AKT, and others. The drugs like Dasatinib + Quercetin (D+Q), Fisetin, and Navitoclax inhibit anti-apoptotic survival pathways and trigger apoptosis of senescent cells(3,7,9,12). This leads to the decrease of SASP release, inflammation reduction, and formation of favorable environment for neurons.

Following the removal of senescent cells, senolytic therapy may positively affect the functioning of neurons due to the reduction of oxidative stress, preservation of synapses, stimulation of tissue repair, and normalizing the interaction between brain cells(12,13).



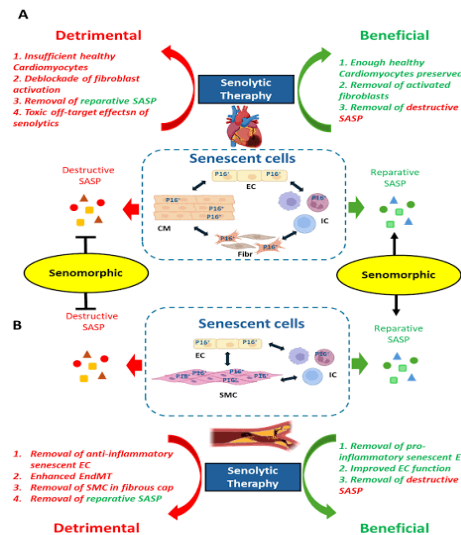
2. Cardiovascular Diseases

Cardiovascular diseases comprise a class of medical conditions which affect the heart and the blood vessels and are linked to old age. Ageing is associated with increased numbers of senescent cells in the vascular and cardiac tissue, resulting in stiffening of the vasculature and cardiovascular dysfunction. Cellular senescence has been linked to various age-related cardiovascular conditions such as endothelial dysfunction.

Senescence of the vascular cells can lead to inflammation and subsequent vascular dysfunction. This implies that targeting senescent cells using senolytic therapy may help to enhance endothelial function among other cardiovascular conditions(14).

Mechanism

During cardiovascular diseases, accumulation of senescence occurs in the blood vessels, heart, and smooth muscle cells within blood vessels because of aging, oxidative stress, DNA damage, and chronic inflammation. These senescing cells secrete senescence-associated secretory phenotype (SASP) factors, including IL-6, IL-8, TNF- α , growth factors, and matrix metalloproteinases (MMPs). These molecules trigger inflammation, endothelial dysfunction, degradation of the extracellular matrix, vascular stiffness, and development of atherosclerosis. Senolytics remove the senescent cardiovascular cells through mechanisms that involve targeting the survival pathways of these senescent cells, including the BCL-2/BCL-xL and PI3K/AKT pathways(14). The drugs used in Senolytic treatment include: Dasatinib + Quercetin, Navitoclax, and Fisetin. Senescent cells are removed via apoptosis caused by anti-apoptotic signaling pathway blockage(3,7,9,14).



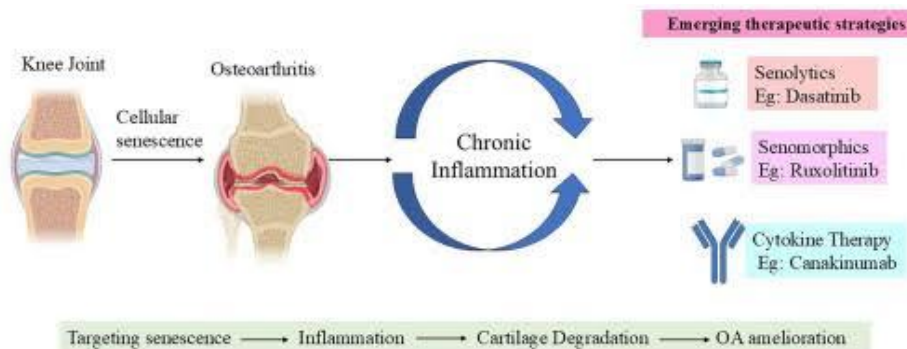
3. Osteoarthritis

Osteoarthritis (OA) is one of the most prevalent age-related degenerative diseases that affect the joints, involving cartilage damage and inflammation of the joint along with joint dysfunction. Ageing and repetitive mechanical stress are thought to stimulate the production of senescent cells in the joints, including cartilage.

The senescent cells present in the cartilage and other joint tissues can lead to inflammation of tissues and further damage to the joint tissue. In this way, senescent cell elimination using senolytic therapy is considered a promising treatment for joint degeneration and repair of joint tissues(15).

Mechanism

Osteoarthritis (OA), aging, physical stresses, and oxidative damage trigger the accumulation of senescent cells in joint tissues including chondrocytes (cells of the cartilage), synovial cells, and other joint cells. Senescent cells exhibit senescence-associated secretory phenotype (SASP) and secrete inflammatory cytokines such as IL-6, IL-8, TNF- α , as well as extracellular matrix degrading enzymes such as matrix metalloproteinases (MMPs). These factors cause the destruction of cartilage, inflammation, degradation of extracellular matrix and joint degeneration process. Senolytic therapy clears senescent cells through targeting senescent cell anti-apoptotic survival mechanisms such as BCL-2/BCL-xL and PI3K/AKT pathway(15). Senolytic drugs like Dasatinib + Quercetin and Fisetin induce apoptosis in senescent chondrocytes and reduce SASP secretion and inflammation(3,9,15).



4. Diabetes and Metabolic Disorders

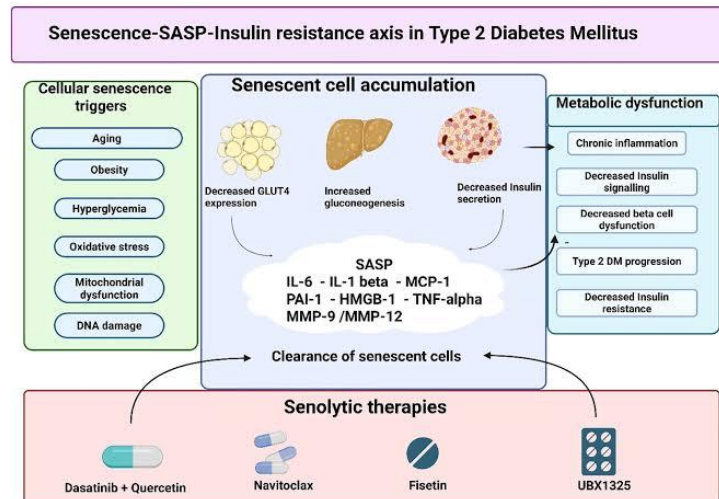
Diabetes and metabolic disorders are two common diseases associated with aging, in which there are disruptions in glucose and energy metabolism. Aging and metabolic stress can lead to the buildup of senescent cells within the adipose tissue and other metabolic organs, which might lead to metabolic dysfunction and inflammation (16).

The secreted factors from senescent cells are able to cause negative effects on other cells and tissues and could be involved in the development of insulin resistance and metabolic dysfunction. Senolytic treatment directed at senescent cells is therefore considered a therapeutic method of treating metabolic problems (16).

Mechanism

In terms of diabetes and metabolic disorders, the presence of senescent cell formation as a result of aging, obesity, oxidative stress, and metabolic stress takes place in tissues including adipose tissue, pancreatic β -cell, liver, and skeletal muscle. These senescent cells produce a secretion called SASP (senescence-associated secretory phenotype) which includes IL-6, IL-8, TNF- α , and others. This SASP causes chronic inflammation, insulin resistance, metabolic dysfunction, and organ dysfunction causing the progression of type 2 diabetes and metabolic syndrome. Senolytics eliminate the presence of senescent cells by inhibiting senescent survival mechanisms such as BCL-2/BCL-xL and PI3K/AKT(16). Some medications include Dasatinib + Quercetin, and Fisetin. They cause the apoptosis of senescent cells and reduce the inflammation caused by SASP(3,9,16). The elimination of senescent cells enhances the insulin

sensitivity, reduces the inflammation of adipose tissue, restores the function of pancreatic β -cell, and restores metabolic homeostasis(16).



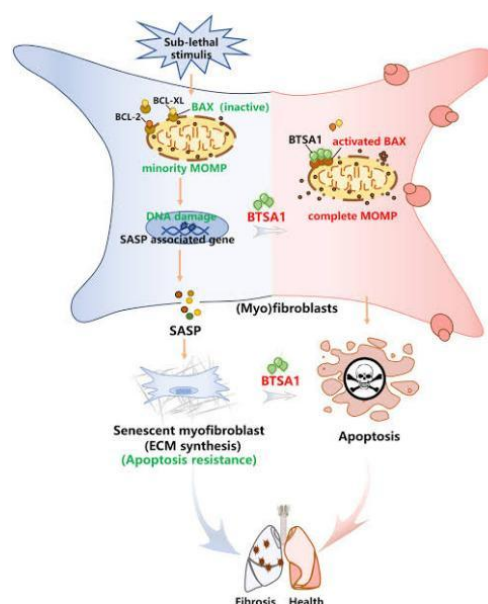
5. Pulmonary Fibrosis

Pulmonary fibrosis is a disease of the lungs that involves the development of scarring and hardening of lung tissue. Ageing is a significant risk factor and the presence of senescent cells in lung tissue contributes to inflammation and subsequent tissue damage (17).

Senescent cells produce inflammatory and fibrotic factors that lead to the production of a milieu that promotes fibrosis and tissue remodelling. Targeting of senescent cells through senolytic treatment is a strategy that could be used to reduce fibrosis(17).

Mechanism

Aging, recurrent lung injury, oxidative stress, pulmonary fibrosis, environmental factors, as well as other stimuli result in the accumulation of senescent cells in the lungs. Senescent cells include alveolar epithelial cells, fibroblasts, immune cells, and others. They secrete senescence-associated secretory phenotype (SASP) factors that consist of IL-6, IL-8, TNF- α , TGF- β , MMPs. They stimulate chronic inflammation, activate fibroblasts, promote extracellular matrix (ECM) production, and lead to increased collagen deposition. It causes scar formation in lungs and decreased lung function. Senolytic drugs destroy senescent cells through the inhibition of their survival pathways such as BCL-2/BCL-xL and PI3K/AKT pathways(17). For example, treatment with Dasatinib + Quercetin, Navitoclax, Fisetin leads to the induction of apoptosis in senescent cells(3,7,9,17). It causes the elimination of SASP factors secretion and inflammatory signaling(17).



6. Cancer

Cancer is defined as a collection of diseases which are caused due to the uncontrolled growth of cells. Senescence has an elaborate function in cancer as senescence acts as a defensive factor for preventing cell proliferation. Nevertheless, the

buildup of senescent cells and its secretory products can contribute to a tissue milieu which can impact the development of cancer (18).

Cancer therapies such as chemotherapy can cause senescence in the normal cells and cancerous cells as well; thus, senolytic therapies have been identified as one of the effective strategies to clear the senescent cells which have been developed due to therapy (18).

Mechanism

In oncology, cellular senescence plays a dual role. On the one hand, it is a protective response since senescence inhibits the development of cells with damage and prevents their uncontrolled division. On the other hand, the presence of senescent cells in the tumor microenvironment promotes cancer progression due to the secretion of factors of senescence-associated secretory phenotype (SASP), which include IL-6, IL-8, TNF- α , TGF- β , and growth factors. Such molecules are capable of promoting chronic inflammation, angiogenesis, immunosuppression, survival of tumor cells, and metastasis. Therapy-induced senescence caused by chemotherapy or radiation may lead to cancer recurrence. Senolytics act on these senescent cells and kill them through inhibition of their pro-survival signaling pathways, which include BCL-2/BCL-xL, PI3K/AKT, and other anti-apoptotic mechanisms (18). For example, Navitoclax, Dasatinib + Quercetin, and Fisetin are able to trigger apoptosis of senescent tumor-associated cells and decrease SASP secretion, thereby creating a less favorable microenvironment for tumors (3,7,9,18).

7. Kidney Diseases

Kidney diseases refer to abnormalities in the normal anatomy and physiology of the kidneys that result in poor renal function. Ageing is a key factor that affects renal dysfunction and leads to an increase in senescent cells in renal tissues with increasing age. These factors could contribute to a decline in renal function (19).

There could be an accumulation of senescent cells in various types of renal cells, such as renal tubular epithelial cells, podocytes, endothelial cells, and fibroblasts. Senescent cell accumulation results in inflammation and fibrosis of the tissues, thereby contributing to poor renal function. Consequently, senolytics have been identified as a therapeutic approach that could minimize the age-related damage of the kidneys (19).

Mechanism

Various conditions such as kidney disease, aging, oxidative stress, DNA damage, inflammation, and metabolic stress cause accumulation of senescent cells in the kidney, which is made up of tubular epithelial cells, podocytes, endothelial cells, and fibroblasts. Senescent cells secrete SASP proteins such as IL-6, IL-8, TNF- α , TGF- β , and MMPs. SASP results in chronic inflammation, immune disorders, fibrosis and deposition of extracellular matrix, causing kidney injury and reduced renal function. Senolytics promote the elimination of senescent renal cells by inhibition of the senescence survival pathways, mainly BCL-2/BCL-xL and PI3K/AKT signaling pathways (19). Agents such as Dasatinib + Quercetin, Navitoclax and Fisetin induce apoptosis in senescent renal cells causing their death and reduction of the production of SASP molecules and the inflammatory response (3,7,9,19).

8. Frailty and Physical Dysfunction

Frailty is an age-associated syndrome with poor physical strength, poor endurance, and increased susceptibility to stressors. It causes poor mobility, poor physical function, and poor ability to carry out daily activities. Senescence of cells in aging might play a role in frailty and physical dysfunction (20).

Senescence of cells might result in inflammation and dysfunction in tissues, which might adversely affect muscle function. Thus, targeting of senescent cells through senolytic treatment might be a possible strategy for mitigating age-related physical decline and improvement in physical function (20).

Mechanism

Frailty and physical dysfunction are among the conditions that often occur during aging, characterized by muscle weakness, movement disorders, and poor physical performance.

During aging, senescent cells accumulate in various tissues, including skeletal muscles, fat, bone, and connective tissues, caused by oxidative stress, DNA damage, and chronic inflammation. Senescent cells produce different SASP factors, among which IL-6, IL-8, TNF- α , and many others. The production of SASP causes chronic inflammation, muscle loss, inability for effective tissue regeneration, exhaustion of stem cells, and impaired physical performance that leads to frailty. Senolytic agents kill accumulated senescent cells through their survival signaling, mainly BCL-2/BCL-xL and PI3K/AKT (20). Dasatinib + Quercetin and Fisetin act on the cells causing cell death or apoptosis and prevent SASP-mediated inflammation (3,9,20). Senescent cells elimination enables the improvement of muscle stem cells to perform better in repairing tissues and reducing inflammation and improve muscle strength (20).

Advantages of Senolytic Therapy

1. Selectively Eliminate Senescent Cells: Senolytics are drugs that can remove senescent cells by causing little harm to the healthy cells. Senescent cells have special survival mechanisms that prevent their cell death through the process of apoptosis. Senolytics act through targeting these mechanisms in order to remove senescent cells. This may assist in decreasing the number of senescent cells in old tissues (3,4).

By removing senescent cells, senolytic treatment can decrease the negative impacts of senescent cells, such as inflammation and tissue dysfunction. Senescent cell removal may also be helpful in keeping tissue homeostasis. Thus, the removal of senescent cells can be viewed as one of the important benefits of senolytic treatment (3,4).

2. Reduction in Chronic Inflammation: One of the ways by which the build-up of senescent cells can cause chronic inflammation is the production of a variety of inflammatory molecules that occur due to the presence of SASP (senescence associated secretory phenotype). Senolytic treatment aids in the reduction of the number of senescent cells, hence reducing the levels of inflammatory molecules produced (3,4). Reducing the chronic inflammatory response can aid in protecting other healthy cells from harm and preserve the physiological functioning of tissues (3,4).

3. Promote Tissue Regeneration: Aging can lead to the accumulation of senescent cells within tissues, affecting the proper functioning of these tissues. Senolytics work to eliminate the presence of such cells that are no longer functional, thus creating an ideal environment for tissue regeneration (3,4). Senolytic therapy can be a very useful tool in ensuring the restoration of tissue functions through eliminating senescent cells (3,4).

4. Delay Age-Related Diseases: An increase in the number of senescent cells is linked to the onset and development of a variety of age-related diseases. Senolytic treatment might be able to delay the development of such diseases by selectively eliminating senescent cells. (3,4). Through reducing the number of senescent cells, senolytics can play a role in delaying aging-related diseases. The potential of senolytics to delay diseases makes it a good choice for extending the period of healthy aging (3,4).

5. Improve Organ Function: Accumulation of senescent cells can have a detrimental effect on the normal functioning of tissues and organs during aging process. Senolytic treatment can restore normal functioning of organs by elimination of such cells and decrease their damaging effect on surrounding healthy cells. Senescence cell clearance can be beneficial for restoring of tissue homeostasis and maintenance of normal function of affected organs. In consequence, senolytics can be effective for maintaining normal organ function during aging process (3,4).

6. Improves Physical Performance: One of the possible reasons for reduced physical function due to aging is the build-up of senescent cells, which may cause physical weakness and reduced endurance. Senolytics can be helpful for improving physical function by eliminating senescent cells and their negative influence on the surrounding tissue. Elimination of senescent cells might be helpful for maintaining tissue balance and, consequently, improved physical function. Thus, senolytics can help reduce age-related deterioration of physical function and preserve physical ability (20).

7. Restricts Fibrosis and Tissue Damage: The presence of senescent cells has been shown to facilitate the development of tissue injury that results in the development of fibrosis by generating an inflammatory microenvironment. This process can be prevented through senolytic treatment which targets the senescent cells. By reducing the number of senescent cells, it would result in reduced inflammation as well as less tissue remodeling and hence prevent fibrosis (17).

8. Anti Aging/ Health Span Effects: One of the key elements of biological aging is the build-up of senescent cells, which can lead to impaired tissue function and aging. Senolytic treatment can be a way of dealing with these issues, as senescent cells are selectively eliminated. Thanks to the decrease in the number of senescent cells, senolytic treatment might help in maintaining tissue balance, preserving the functioning of organs, and healthy aging (4).

9. Increases the Efficacy of Other Therapies: Senescent cells might create an unfavorable tissue environment and might also make other treatment methods less effective. Senescent cells' elimination through the use of senolytics might be able to improve the tissue environment, thus making other types of treatment more effective. Thus, the combination of senolytics with conventional treatments could lead to additional advantages by decreasing the number of senescent cells and increasing treatment efficiency (18).

10. Innovative Therapy in Regenerative Medicine: The senolytic treatment is considered an innovative way of therapy as it implies targeting the process of removal of senescent cells, which is not the case in the traditional therapies that target the symptoms of age-related diseases. Senolytic treatment targets the underlying causes of aging and can be used in various age-related diseases. It can be used in various tissues and age-related diseases. Further investigations are needed to prove the safety and efficacy of the senolytic therapy (4).

Limitations and Challenges of Senolytic Therapy

1. Lack of Clinical Research Data Over Time: Although the efficiency of senolytics has been proven in laboratory and experimental researches, the issue of safety, efficacy, and long-lasting results of such drugs in clinical human trials still remains questionable. Thus, further research in the sphere should be conducted (4,20).

2. Off-Target Effects and Toxicity: Senolytics can potentially become toxic or affect cells that are not targeted for treatment. For instance, Navitoclax has potential to cause toxicity due to the effect on BCL-2 protein family (7,8).

3. Selectivity in Targeting: Senescent cells are highly heterogeneous and differ from each other. It is challenging to create the drugs that would specifically target only detrimental cells without affecting other cells (3,4).

4. Function of the Healthy Senescent Cells: Healthy senescent cells perform certain biological tasks (wound healing, tissue regeneration, embryonic development, cancer suppression). Their excessive elimination can be harmful for biological processes (2,5).

5. Development of Biomarkers: There is no one universal biomarker for the detection of all types of senescent cells (3).

6. Appropriate Dosage and Administration: Appropriate dosage and administration of the senolytic treatment have yet to be determined. The incorrect administration could lead to ineffectiveness or even toxicity (4,20).

7. Tissue-Specific Factors: Properties and roles of senescent cells can vary from one tissue to another in the body. A drug that is effective in one tissue might not provide the same effect in another tissue (3,4).

8. Difficulty of Delivery: It is challenging to deliver senolytics into the specific tissue. Specialized techniques of delivery are required for such purpose (4).

9. Developing Resistance to Drugs: There is a risk that some senescent cells might develop resistance to the drug by switching to other mechanisms (4).

10. Cost: Creating new senolytics could be costly.

Future Perspectives of Senolytic Therapy

The future of senolytic therapy will involve the development of more safe, specific and effective ways of eliminating senescent cells using medications. Senolytic agents that currently exist present good results, but the future of research lies in developing more selective agents that will selectively target only pathological senescent cells and will leave beneficial senescent cells that play a role in normal biological processes such as healing wounds and regenerating tissues. The identification of novel signaling pathways involved in the survival of senescent cells will lead to developing the new generation of senolytics which may have less side effects than current drugs. One more important aspect of the future of senolytic therapy is personalized therapy where therapeutic approaches can be tailored taking into account age, genetic background, disease status and distribution of senescent cells throughout tissues. Diagnostic tools will allow detecting senescent cells in a body and monitoring their activity as well as response to therapy. This will lead to the improved efficiency of the treatment and reduced exposure to unnecessary drugs.

Further investigations in future are likely to look into the development of combination therapies wherein senolytics would be employed in conjunction with senomorphics that would inhibit the harmful effects of SASP without destroying the cells as well as antioxidants, anti-inflammatory agents, stem cell treatments, and regeneration. These combining approaches would lead to better results through the removal of the damaged cells coupled with the regeneration of the tissues. The development in the field of nanotechnology and the targeted delivery system of drugs is likely to enhance the efficacy of senolytic treatment through the delivery of drugs to the tissues under investigation with high effects and decreased toxicity. The senolytics may find further applications in the treatment of age-related diseases like neurodegenerative diseases, heart ailments, osteoarthritis, diabetes, pulmonary fibrosis, renal diseases, and cancerous conditions. In conclusion, senolytic treatment is considered an encouraging avenue in anti-aging and regenerative medicine.

DISCUSSION

Cellular senescence is a multi-faceted physiological phenomenon that serves both beneficial and damaging functions in terms of human well-being. In general, senescence is one of the mechanisms of protection from malignant growth because it inhibits the growth of cells that have undergone damage and become dysfunctional(2,5). Nevertheless, the accumulation of senescent cells occurs with age or due to constant stress exposure such as DNA damage, oxidative stress, and inflammation(2,5). The cells that acquire senescence do not lose their metabolic activity but start producing a range of inflammatory components due to the senescence-associated secretory phenotype (SASP), namely cytokines, chemokines, growth factors, and matrix-degrading enzymes(2,5).

The emergence of senolytic therapy has led to the development of a novel strategy for targeting the basic aging mechanisms rather than managing only the symptoms of associated diseases. These include the medications like Dasatinib, Quercetin, Fisetin, and Navitoclax(3,7,9) which are used in clearing out the senescent cells by inhibiting their capacity to survive through the activation of signaling mechanisms like BCL-2/BCL-xL and PI3K/AKT(3,4). Several pre-clinical researches have proven that the clearance of the senescent cells leads to reduction of inflammation, promotion of tissue regeneration, improvement of physical functions, and prevention from the advancement of many aging-related diseases including cardiovascular, neurodegenerative diseases, osteoarthritis, diabetes, pulmonary fibrosis, kidney diseases. Although senolytics appear to have many potentials, there are many factors which hinder their application clinically. Senescent cells are heterogeneous and differ from one another depending on tissues(4,20). Moreover, some of the senescent cells perform certain physiological functions in wound healing and repair of tissues or in the prevention of tumors(2,5); therefore, it may not always be ideal to eliminate all senescent cells.

Future advances in senolytic therapy will revolve around designing specific drugs, developing better delivery methods, discovering reliable biomarkers, and employing senolytics alongside other treatment methods including senomorphics and regenerative medicine. Generally, senolytic therapy is an innovative approach to the field of anti-aging and regenerative medicine that promises success in extending healthy life span and alleviating age-associated diseases(4,20). Nevertheless, thorough clinical trials are required to assess its safety and efficacy in humans.

There are a number of senolytic compounds which demonstrated good results in pre-clinical and early clinical studies. Some of those compounds are Dasatinib, Quercetin, Fisetin, and Navitoclax. They might be useful for improving tissue regeneration and slowing down the process of aging-related diseases. However, more research is needed to solve some issues connected with their safety and efficacy.

CONCLUSION

Cellular senescence is a complicated physiological process, which features not only positive but also negative consequences. While senescence initially protects the organism by inhibiting the growth of cells, which are damaged, senescence leads to chronic inflammation, malfunctioning of tissues, and development of age-associated diseases due to the accumulation of senescent cells during aging.

Senolytic treatment has proven to be an effective strategy to remove such unhealthy senescent cells from the organism. Such treatment is expected to control inflammation, regenerate tissues, maintain organ function, enhance physical performance, and postpone aging-related loss of functions. The broad application of senolytics in neurodegenerative diseases, cardiovascular diseases, osteoarthritis, diabetes and metabolic disorders, pulmonary fibrosis, kidney diseases, cancers, and frailty proves its great therapeutic value.

Nevertheless, there are several challenges, such as off-target toxicity, cellular heterogeneity, lack of selectivity, absence of markers, tissue specificity, and insufficient clinical experience. It should also be noted that there are some physiological functions of the senescent cells, so their elimination is not always desirable.

The areas of future investigation would be improving safety and selectivity of senolytics, devising personalized approaches for senolytic treatment, establishing biomarkers, and optimizing the delivery of these drugs. The combination of senolytics with senomorphics, regeneration therapies, and other medical approaches might further increase the efficacy of senolytic therapy.

In general, senolytic therapy is a revolutionary and promising approach that changes the focus from the treatment of aging-related consequences to the treatment of the mechanism of aging itself. In the course of further investigations and clinical trials, the effectiveness of senolytic therapy can be proven, making it an important part of healthy aging and regenerative medicine.

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