JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

Senescence-Associated Secretory Phenotype (SASP) in Diabetes

Nandini Mode*[1], Chaitanya B[2]

[1]*UG Scholar, Department of Pharmaceutics, Joginpally BR Pharmacy College, Moinabad, Telangana, India*
[2]*Assistant Professor, Department of Pharmaceutics, Joginpally BR Pharmacy College, Moinabad, Telangana, India*

Publication history: Received on 7th Jan 2025; Revised on 10th Jan 2025; Accepted on 12th Jan 2025

Article DOI: 10.69613/qjzz6g14

Abstract: Cellular senescence represents a critical biological process characterized by permanent cell cycle arrest and distinct metabolic alterations. The senescence-associated secretory phenotype (SASP) has emerged as a fundamental mediator linking cellular aging to various pathological conditions, including diabetes mellitus. Recent investigations have unveiled the intricate relationship between SASP and pancreatic β-cell dysfunction, insulin resistance, and diabetic complications. The accumulation of senescent cells in pancreatic islets correlates with diminished insulin production and secretion, while SASP factors contribute to chronic inflammation and oxidative stress. The molecular mechanisms underlying SASP in diabetes involve complex interactions between p16INK4a/p53 pathways, DNA damage responses, and inflammatory mediators. Notably, senescent β-cells exhibit altered expression of key metabolic regulators and increased production of pro-inflammatory cytokines, chemokines, and matrix-degrading proteins. The identification of these pathways has led to innovative therapeutic strategies, including senolytic drugs that selectively eliminate senescent cells. Preclinical studies demonstrate that targeting SASP can improve glucose homeostasis, enhance insulin sensitivity, and potentially reverse diabetic complications. Moreover, the interaction between SASP and metabolic dysfunction extends beyond pancreatic tissue, affecting adipose tissue, skeletal muscle, and liver function.

Keywords: Cellular Senescence; Beta-cell dysfunction; Senolytic therapy; Metabolic inflammation; Insulin resistance.

1. Introduction

Cellular senescence represents a fundamental biological process characterized by irreversible cell cycle arrest, occurring in response to various stressors including telomere erosion, DNA damage, and metabolic perturbations [1]. This complex cellular fate decision serves as a critical checkpoint mechanism that prevents the proliferation of potentially damaged or dysfunctional cells, thereby acting as a natural barrier against tumorigenesis. However, the effects of cellular senescence extend far beyond its tumour-suppressive functions.

The senescence-associated secretory phenotype (SASP) has garnered significant attention in recent years due to its profound implications in age-related diseases, particularly diabetes mellitus [2]. This distinctive secretory program encompasses a diverse array of biologically active molecules that dramatically alter the tissue microenvironment and influence neighbouring cell behaviour. The composition and intensity of SASP can vary depending on the triggering stimulus and tissue context, creating a dynamic and complex signalling network.

The progressive accumulation of senescent cells in pancreatic tissue and other metabolically active organs presents a crucial link between aging and metabolic dysfunction [3]. These senescent cells, which gradually accumulate with advancing age, create focal points of tissue dysfunction and inflammation that can disrupt normal metabolic homeostasis. Their presence in key metabolic tissues such as pancreas, adipose tissue, and skeletal muscle creates a perfect storm of cellular dysfunction that contributes to metabolic deterioration.

Recent advances in molecular biology have revealed that senescent cells, rather than being merely passive bystanders, actively contribute to tissue dysfunction through the secretion of various pro-inflammatory factors, growth factors, and proteases collectively known as the SASP [4]. This secretory phenomenon transforms senescent cells into active modulators of their tissue environment, capable of influencing the function and fate of surrounding cells through paracrine signalling mechanisms. The SASP components create a complex web of intercellular communication that can propagate and amplify the initial senescence response.

* Corresponding author: Nandini Mode

In the context of diabetes, SASP components have been shown to directly influence insulin secretion, β-cell function, and peripheral insulin sensitivity [5]. These effects manifest through multiple mechanisms, including direct interference with insulin signaling pathways, promotion of chronic inflammation, and disruption of tissue architecture. The presence of senescent cells and their SASP creates a self-perpetuating cycle of tissue dysfunction that can accelerate the progression of diabetic pathology and complicate therapeutic interventions.

2. Molecular Basis of SASP in Diabetes

2.1. DNA Damage Response and Senescence Initiation

The onset of cellular senescence in diabetic conditions involves complex molecular mechanisms initiated by various stressors. These intricate cellular responses represent a sophisticated defense mechanism that becomes paradoxically detrimental in the context of metabolic disease. The process begins at the molecular level, where the diabetic microenvironment creates conditions that challenge cellular homeostasis and genomic stability.

Table 1. Components of the Senescence-Associated Secretory Phenotype (SASP) in Diabetes

Category	Factors	Primary Effects in Diabetes
Inflammatory Cytokines	IL-1β, IL-6, IL-8, TNF-α	β-cell dysfunction, Insulin resistance
Chemokines	CCL2, CXCL1, CXCL8, CCL5	Immune cell recruitment, Islet inflammation
Growth Factors	VEGF, PDGF, FGF	Altered tissue remodeling, Vascular dysfunction
Matrix Metalloproteinases	MMP-1, MMP-3, MMP-13	ECM degradation, Tissue architecture disruption
Tissue Inhibitors	TIMP-1, TIMP-2	Fibrosis, Altered tissue repair

Chronic hyperglycemia induces DNA damage through increased oxidative stress and advanced glycation end-products (AGEs) formation [6]. This hyperglycemic environment creates a perfect storm of cellular stress, where elevated glucose levels drive the production of reactive oxygen species (ROS) while simultaneously compromising cellular repair mechanisms. The formation of AGEs further compounds this damage by modifying both cellular proteins and DNA, creating a self-perpetuating cycle of molecular damage that overwhelms cellular repair capacity.

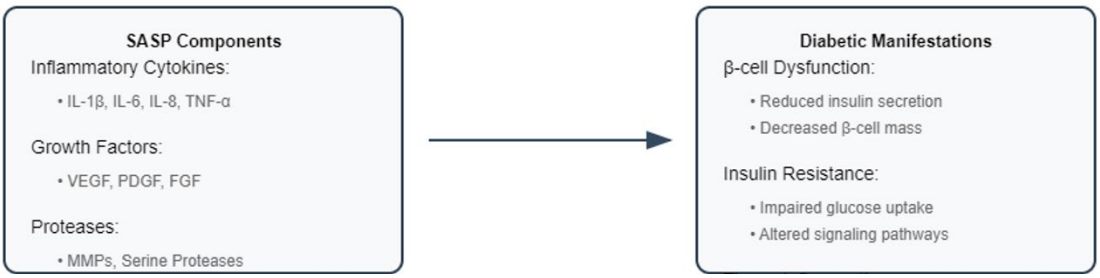

Figure 1. Cellular Senescence and SASP in Diabetes Pathogenesis

The activation of ATM/ATR kinases triggers the p53/p21 and p16INK4a/pRb pathways, leading to cell cycle arrest and subsequent development of the senescent phenotype [7]. This signaling cascade represents a highly coordinated cellular response to genomic stress. The ATM/ATR kinases act as molecular sensors, detecting DNA damage and initiating a phosphorylation cascade that ultimately enforces cell cycle arrest. The dual activation of p53/p21 and p16INK4a/pRb pathways ensures a robust and typically irreversible exit from the cell cycle, establishing the foundation of the senescent state.

In pancreatic β-cells, this process is particularly detrimental as it impairs insulin production and secretion capacity [8]. The specialized nature of β-cells makes them especially vulnerable to senescence-induced dysfunction. Unlike many other cell types, β-cells must maintain both their differentiated state and their capacity for regulated insulin secretion. The onset of senescence not only arrests their proliferative capacity but also compromises their essential endocrine functions, creating a direct link between cellular senescence and diabetic pathology.

2.2. SASP Components and Signaling Pathways

The SASP in diabetic conditions comprises a complex mixture of factors that collectively create a sophisticated network of intercellular communication. This secretory phenotype represents more than just a collection of proteins; it constitutes a highly orchestrated response that fundamentally alters the tissue microenvironment. The major components include:

2.2.1. Pro-inflammatory cytokines (IL-1β, IL-6, TNF-a)

These central mediators of inflammation serve as primary architects of the inflammatory response. IL-1β acts as an early initiator of the inflammatory cascade, while IL-6 amplifies the response and promotes chronic inflammation. TNF-α contributes to insulin resistance and cellular stress responses, creating a bridge between inflammation and metabolic dysfunction.

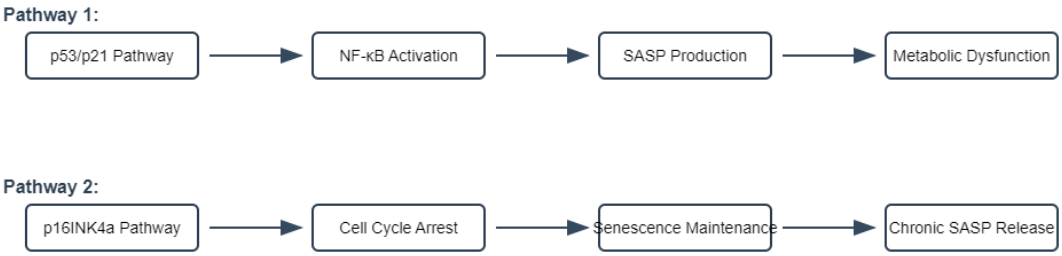

Figure 1. Signalling Pathways

2.2.2. Chemokines (CCL2, CXCL8)

These specialized signaling proteins act as cellular beacons, orchestrating the recruitment and movement of immune cells. CCL2, also known as MCP-1, specifically attracts monocytes and macrophages to sites of inflammation, while CXCL8 primarily recruits neutrophils, establishing a complex immune cell infiltration pattern in affected tissues.

2.2.3. Growth factors (VEGF, PDGF)

These potent signaling molecules modulate tissue remodeling and vascular responses. VEGF influences vascular permeability and angiogenesis, potentially affecting nutrient delivery and tissue oxygenation. PDGF contributes to tissue remodeling and fibrosis, potentially altering the structural integrity of metabolic tissues.

2.2.4. Matrix metalloproteinases (MMP-3, MMP-13)

These enzymes actively remodel the extracellular matrix, influencing tissue architecture and cell-cell communication. MMP-3 and MMP-13 can degrade various matrix components, potentially affecting tissue structure and function, while also processing bioactive molecules that influence cellular behavior.

These factors are regulated through multiple signaling cascades, primarily involving NF-ϰB and C/EBPβ transcription factors [9]. The NF-ϰB pathway serves as a master regulator of inflammatory responses, integrating various cellular stress signals and coordinating the expression of multiple SASP components. C/EBPβ works in concert with NF-ϰB, fine-tuning the expression of specific SASP factors and ensuring a sustained response. This regulatory network involves complex feedback loops and cross-talk between different signaling pathways, creating a highly coordinated but potentially destructive response. The persistent activation of these pathways creates a self-sustaining inflammatory environment that exacerbates metabolic dysfunction [10]. This chronic activation establishes a vicious cycle where initial metabolic perturbations trigger SASP production, which in turn further compromises metabolic function.

2.3. Impact on Pancreatic β-cell Function

2.3.1. Direct Effects on Insulin Production

Senescent β-cells exhibit marked alterations in glucose-stimulated insulin secretion (GSIS) machinery [11]. This dysfunction represents a fundamental breakdown in the sophisticated molecular mechanisms that normally ensure precise glucose sensing and insulin secretion. The GSIS machinery, a complex interplay of glucose transporters, metabolic coupling factors, and secretory mechanisms, becomes progressively impaired as cells enter senescence. This deterioration affects multiple steps in the insulin secretion pathway, from glucose recognition to insulin granule exocytosis. The accumulation of senescent cells in pancreatic islets correlates with reduced expression of key glucose transporters and insulin processing enzymes [12]. This reduction creates a cascading effect on β-cell function, beginning with diminished glucose sensing capacity through downregulation of GLUT2 transporters. The compromised insulin processing due to reduced prohormone convertase activity further compounds the dysfunction. The altered calcium handling affects the precise timing of insulin granule release, while disrupted mitochondrial function impacts the generation of metabolic coupling signals essential for proper insulin secretion. Additionally, SASP factors directly interfere with insulin gene expression and protein folding mechanisms [13]. This interference occurs through transcriptional

suppression of the insulin gene and disruption of the elaborate protein folding machinery in the endoplasmic reticulum. The compromised post-translational modifications essential for insulin bioactivity, coupled with impaired assembly and trafficking of insulin secretory granules, further deteriorate β-cell function. These molecular perturbations collectively contribute to a progressive decline in insulin production and secretory capacity.

Table 2. Tissue-Specific Effects of Cellular Senescence in Diabetes

Tissue	Senescence Markers	Metabolic Impact	Clinical Manifestations
Pancreatic β-cells	p16INK4a, SA-β-gal, p53	Reduced insulin secretion, β-cell mass decline	Impaired glucose tolerance
Adipose Tissue	p21, p53, SA-β-gal	Altered adipokine profile, Increased inflammation	Insulin resistance
Skeletal Muscle	p16INK4a, p21	Decreased glucose uptake, Mitochondrial dysfunction	Sarcopenia, Reduced exercise capacity
Liver	p21, SA-β-gal	Impaired gluconeogenesis, Lipid accumulation	Hepatic steatosis

2.3.2. Paracrine Effects and Islet Inflammation

The secretion of SASP components by senescent β-cells creates a hostile microenvironment within pancreatic islets. This microenvironmental transformation fundamentally alters islet physiology through the attraction of pro-inflammatory macrophages and T-cells, establishing chronic immune cell infiltration. The resulting inflammatory foci within islets amplify local inflammatory responses, creating a self-perpetuating cycle of inflammation and dysfunction.

The enhanced local inflammation manifests through elevated pro-inflammatory cytokine levels and activation of inflammatory signaling cascades. This inflammatory state generates considerable oxidative stress and disrupts normal islet cell communication patterns. The paracrine effects extend to neighboring non-senescent β-cells, suppressing their insulin secretion and inducing stress responses. The compromise of cell-cell coupling, essential for coordinated insulin release, further deteriorates islet function, potentially accelerating senescence in adjacent cells.

The disruption of islet architecture and vascularization [14] represents another critical consequence of senescence-induced inflammation. The alterations in extracellular matrix composition and compromised islet blood flow patterns disturb the carefully organized islet cellular architecture. This structural disruption impairs the delivery of nutrients and oxygen to islet cells, creating a metabolically challenged environment that further compromises β-cell function.

3. Systemic Effects of SASP in Diabetes

3.1. Adipose Tissue Dysfunction

The accumulation of senescent cells in adipose tissue significantly impacts whole-body glucose homeostasis. Senescent adipocytes exhibit altered adipokine secretion patterns and reduced insulin sensitivity [15]. The SASP factors released by these cells promote macrophage infiltration and create a pro-inflammatory environment that extends beyond the local tissue. These changes result in impaired glucose uptake and increased lipolysis, contributing to systemic insulin resistance [16]. The cross-talk between senescent adipocytes and immune cells perpetuates a cycle of inflammation and metabolic dysfunction, further exacerbating diabetic complications [17].

3.2. Skeletal Muscle Alterations

Skeletal muscle, a primary site of glucose disposal, undergoes significant changes in response to SASP factors. Senescent cells accumulating in muscle tissue secrete factors that interfere with insulin signaling pathways and glucose transporter trafficking [18]. The presence of SASP components leads to reduced mitochondrial function and decreased glucose uptake capacity in myocytes. These alterations contribute to the development of sarcopenia in diabetic patients, creating a complex relationship between muscle weakness and metabolic dysfunction [19].

3.3. Hepatic Manifestations

The liver represents another crucial target of SASP-mediated effects in diabetes. Senescent hepatocytes contribute to hepatic insulin resistance through multiple mechanisms [20]. The accumulation of these cells promotes lipid accumulation and alters glucose metabolism through disrupted gluconeogenesis and glycogen storage. Furthermore, SASP factors from senescent hepatocytes influence surrounding cells, promoting inflammation and fibrosis [21].

3.4. Therapeutic Interventions

3.4.1. Senolytic Approaches

The development of senolytic drugs represents a promising therapeutic strategy for diabetes treatment. These compounds selectively eliminate senescent cells by targeting specific survival pathways [22]. Recent clinical trials have demonstrated the potential of senolytics in improving glucose metabolism and insulin sensitivity [23]. The combination of established drugs like dasatinib and quercetin has shown particular promise in reducing SASP burden and improving metabolic parameters [24].

3.4.2. Novel Therapeutic Targets

Beyond traditional senolytics, new therapeutic approaches target specific components of the SASP pathway. Small molecule inhibitors of key SASP regulatory proteins, such as NF-κB and p38 MAPK, have demonstrated efficacy in preclinical models [25]. Additionally, emerging therapies focus on modulating the senescence-associated metabolic pathways to prevent the development of diabetic complications [26].

3.4.3. SASP Modification Strategies

Recent advances have focused on modifying rather than eliminating the SASP profile. This approach aims to maintain the beneficial aspects of senescence while mitigating its detrimental effects [27]. The development of selective SASP modulators shows promise in reducing inflammation while preserving tissue repair functions [28].

Table 3. Current Therapeutic Strategies for Targeting Senescence in Diabetes

Approach	Therapeutic Agents	Mechanism of Action	Development Stage	Benefits
Senolytics	Dasatinib + Quercetin	Selective elimination of senescent cells	Clinical trials	Improved insulin sensitivity [23,24]
SASP Inhibitors	Rapamycin, Metformin	mTOR inhibition, AMPK activation	FDA-approved for other indications	Reduced inflammation [22]
Novel Compounds	UBX0101, Navitoclax	Bcl-2 family inhibition	Preclinical/Early clinical	Promising metabolic outcomes [25]
Lifestyle Interventions	Exercise, Dietary restriction	Multiple pathways	Established	Reduced senescent cell burden [18]

4. Challenges

4.1. Biomarker Development:

The identification of reliable SASP-associated biomarkers remains crucial for monitoring disease progression and treatment efficacy [29]. This challenge encompasses multiple layers of complexity, from molecular detection to clinical interpretation. The dynamic nature of the SASP, which can vary significantly depending on cell type, tissue context, and triggering stimuli, makes the development of universal biomarkers particularly challenging. The temporal evolution of SASP components adds another layer of complexity, as the secretory profile can change dramatically over the course of disease progression. Current research focuses on developing novel detection methods for circulating SASP factors and senescent cell burden [30]. These efforts extend beyond simple protein quantification to include sophisticated approaches for detecting specific SASP signatures. Researchers are exploring various technological platforms, from advanced proteomics to novel imaging techniques, in the quest to establish reliable biomarker panels. The challenge lies not only in detecting these factors but also in distinguishing disease-specific SASP signatures from age-related background signals. The development of sensitive and specific detection methods must also consider practical aspects such as sample accessibility, stability, and the feasibility of routine clinical implementation.

4.2. Personalized Medicine Approaches

Individual variations in SASP profiles suggest the need for personalized therapeutic strategies [31]. This observation reflects the growing understanding that the senescence response and its associated secretory phenotype can vary significantly among individuals. The heterogeneity in SASP profiles may arise from multiple sources, including genetic polymorphisms, epigenetic modifications, and varying environmental exposures. These individual differences can significantly impact both disease progression and treatment response, necessitating a more nuanced approach to therapeutic intervention.

The integration of genetic, metabolic, and environmental factors may help optimize treatment outcomes for different patient populations [32]. This comprehensive approach requires sophisticated analysis of multiple data streams to create personalized disease profiles. The challenge extends to understanding how these various factors interact to influence SASP composition and its

effects on tissue function. Metabolic parameters, in particular, play a crucial role in modulating both the senescence response and the resulting secretory profile. Environmental factors, including lifestyle choices and exposure to various stressors, add another dimension to this complex picture.

The development of personalized medicine approaches must also consider practical aspects of clinical implementation. This includes the development of reliable methods for patient stratification, the identification of treatment-response predictors, and the establishment of monitoring protocols that can track individual responses to therapy. The economic implications of personalized approaches, including the cost-effectiveness of individualized testing and treatment strategies, present additional challenges that must be addressed.

5. Conclusion

The identification of specific SASP components and their roles in pancreatic β-cell dysfunction, insulin resistance, and tissue inflammation has provided valuable insights into disease progression. Therapeutic strategies targeting senescent cells and their secretory phenotype have shown promising results in preclinical and early clinical studies, offering new hope for diabetes management. The development of more selective and efficient senolytic compounds, coupled with advanced biomarker detection methods, may revolutionize the treatment approach for diabetic patients.

References

[1] van Deursen JM. The role of senescent cells in ageing. Nature. 2014;509(7501):439-46.

[2] Palmer AK, Tchkonia T, LeBrasseur NK, Chini EN, Xu M, Kirkland JL. Cellular Senescence in Type 2 Diabetes: A Therapeutic Opportunity. Diabetes. 2015;64(7):2289-98.

[3] He S, Sharpless NE. Senescence in Health and Disease. Cell. 2017;169(6):1000-1011.

[4] Tchkonia T, Zhu Y, van Deursen J, Campisi J, Kirkland JL. Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. J Clin Invest. 2013;123(3):966-72.

[5] Aguayo-Mazzucato C, van Haaren M, Mruk M, et al. β Cell Aging Markers Have Heterogeneous Distribution and Are Induced by Insulin Resistance. Cell Metab. 2017;25(4):898-910.

[6] Newsholme P, Cruzat VF, Keane KN, Carlessi R, de Bittencourt PI Jr. Molecular mechanisms of ROS production and oxidative stress in diabetes. Biochem J. 2016;473(24):4527-4550.

[7] Childs BG, Baker DJ, Kirkland JL, Campisi J, van Deursen JM. Senescence and apoptosis: dueling or complementary cell fates? EMBO Rep. 2014;15(11):1139-53.

[8] Thompson PJ, Shah A, Ntranos V, Van Gool F, Atkinson M, Bhushan A. Targeted Elimination of Senescent Beta Cells Prevents Type 1 Diabetes. Cell Metab. 2019;29(5):1045-1060.

[9] Coppe JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol. 2010;5:99-118.

[10] Prattichizzo F, De Nigris V, La Sala L, Procopio AD, Olivieri F, Ceriello A. "Inflammaging" as a Druggable Target: A Senescence-Associated Secretory Phenotype-Centered View of Type 2 Diabetes. Oxid Med Cell Longev. 2016;2016:1810327.

[11] Aguayo-Mazzucato C, Andle J, Lee TB Jr, Midha A, Talemal L, Chipashvili V, et al. Acceleration of β Cell Aging Determines Diabetes and Senolysis Improves Disease Outcomes. Cell Metab. 2019;30(1):129-142.

[12] Sone H, Kagawa Y. Pancreatic beta cell senescence contributes to the pathogenesis of type 2 diabetes in high-fat diet-induced diabetic mice. Diabetologia. 2005;48(1):58-67.

[13] Cristofalo VJ, Lorenzini A, Allen RG, Torres C, Tresini M. Replicative senescence: a critical review. Mech Ageing Dev. 2004;125(10-11):827-48.

[14] Kirkland JL, Tchkonia T. Cellular Senescence: A Translational Perspective. EBioMedicine. 2017;21:21-28.

[15] Palmer AK, Xu M, Zhu Y, Pirtskhalava T, Weivoda MM, Hachfeld CM, et al. Targeting senescent cells alleviates obesity-induced metabolic dysfunction. Aging Cell. 2019;18(3):e12950.

[16] Minamino T, Orimo M, Shimizu I, Kunieda T, Yokoyama M, Ito T, et al. A crucial role for adipose tissue p53 in the regulation of insulin resistance. Nat Med. 2009;15(9):1082-7.

[17] Xu M, Palmer AK, Ding H, Weivoda MM, Pirtskhalava T, White TA, et al. Targeting senescent cells enhances adipogenesis and metabolic function in old age. Elife. 2015;4:e12997.

[18] Schafer MJ, White TA, Evans G, Tonne JM, Verzosa GC, Stout MB, et al. Exercise Prevents Diet-Induced Cellular Senescence in Adipose Tissue. Diabetes. 2016;65(6):1606-15.

[19] Zamboni M, Rossi AP, Fantin F, Zamboni G, Chirumbolo S, Zoico E, et al. Adipose tissue, diet and aging. Mech Ageing Dev. 2014;136-137:129-37.

[20] Ogrodnik M, Miwa S, Tchkonia T, Tiniakos D, Wilson CL, Lahat A, et al. Cellular senescence drives age-dependent hepatic steatosis. Nat Commun. 2017;8:15691.

[21] Hong B, Lee S, Jin HY, Park Y, Lee KW, Jin X, et al. Elimination of Senescent Cells Prevents Hepatic Steatosis and Metabolic Dysfunction in Mice With Obesity. Aging Cell. 2022;21(4):e13580.

[22] Kirkland JL, Tchkonia T. Senolytic drugs: from discovery to translation. J Intern Med. 2020;288(5):518-536.

[23] Justice JN, Nambiar AM, Tchkonia T, LeBrasseur NK, Pascual R, Hashmi SK, et al. Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. EBioMedicine. 2019;40:554-563.

[24] Hickson LJ, Langhi Prata LGP, Bobart SA, Evans TK, Giorgadze N, Hashmi SK, et al. Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. EBioMedicine. 2019;47:446-456.

[25] Xu M, Pirtskhalava T, Farr JN, Weigand BM, Palmer AK, Weivoda MM, et al. Senolytics improve physical function and increase lifespan in old age. Nat Med. 2018;24(8):1246-1256.

[26] Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, et al. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. Nature. 2016;530(7589):184-9.

[27] Kojima H, Inoue T, Kunimoto H, Nakajima K. IL-6-STAT3 signaling and premature senescence. JAKSTAT. 2013;2(4):e25763.

[28] Prattichizzo F, De Nigris V, Mancuso E, Spiga R, Giuliani A, Matacchione G, et al. Short-term sustained hyperglycaemia fosters an archetypal senescence-associated secretory phenotype in endothelial cells and macrophages. Redox Biol. 2018;15:170-181.

[29] Hernandez-Segura A, Nehme J, Demaria M. Hallmarks of Cellular Senescence. Trends Cell Biol. 2018;28(6):436-453.

[30] Schafer MJ, Zhang X, Kumar A, Atkinson EJ, Zhu Y, Jachim S, et al. The senescence-associated secretome as an indicator of age and medical risk. JCI Insight. 2020;5(12):e133668.

[31] Basisty N, Kale A, Jeon OH, Kuehnemann C, Payne T, Rao C, et al. A proteomic atlas of senescence-associated secretomes for aging biomarker development. PLoS Biol. 2020;18(1):e3000599.

[32] Borghesan M, Fafián-Labora J, Eleftheriadou O, Carpintero-Fernández P, Paez-Ribes M, Vizcay-Barrena G, et al. Small Extracellular Vesicles Are Key Regulators of Non-cell Autonomous Intercellular Communication in Senescence via the Interferon Protein IFITM3. Cell Rep. 2019;27(13):3956-3971..