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Aging, Cellular Senescence, and Type 2 Diabetes: Unraveling the Links for Novel Therapeutic Approaches

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ABSTRACT

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), is an escalating global health crisis, with projections indicating a rise from 537 million to 783 million affected individuals by 2045. Central to the progression of T2DM is the intricate interplay between insulin resistance, aging, and cellular senescence, especially in peripheral adipose tissues and pancreatic β-cells. This review highlights pathophysiological mechanisms underlying T2DM, emphasizing how aging exacerbates insulin resistance and impairs insulin secretion. We present evidence linking cellular senescence with increased adiposity and dysfunction in β-cells, illustrating how age-related changes foster a chronic inflammatory milieu that worsens metabolic dysregulation. Cellular senescence, characterized by the accumulation of dysfunctional cells producing the senescence-associated secretory phenotype (SASP), contributes significantly to the development and complications of diabetes. Notably, emerging therapies targeting senescent cells, such as senolytics and senomorphics, offer innovative strategies to mitigate diabetes-related decline. These therapeutic approaches aim to enhance insulin sensitivity and improve β-cell function, potentially reshaping diabetes management. This review underscores the importance of a nuanced understanding of cellular senescence in devising targeted senotherapies, advocating for a dual organ-oriented strategy to optimize treatment outcomes for diabetes and associated comorbidities.

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1. INTRODUCTION

Diabetes mellitus is becoming an increasingly prevalent issue worldwide. In 2021, it was estimated that 537 million people were living with diabetes mellitus, which was also linked to 6.7 million deaths. Projections suggest that the number of individuals affected by this disease will rise to 643 million by 2030 and 783 million by 2045 [1]. Additionally, the majority of those with type 2 diabetes mellitus (T2DM) are over 65 years old. Nearly 1 in 4 people suffer from T2DM, and this number continues to grow. To address this challenge, it is crucial to gain a thorough understanding of the detailed pathogenesis of diabetes and to develop new treatment strategies focused on both clinical and molecular aspects of aging [2-5].

Intensified insulin resistance and weakened insulin secretion play key roles in the causes, mechanisms and patterns of T2DM. Insulin resistance occurs due to impaired responses to insulin signaling in peripheral tissues such as muscle, liver, and fat. This resistance is further exacerbated by obesity, which leads to the accumulation of dysfunctional adipose tissues and a compensatory increase in insulin secretion [6-8]. Eventually, a decline in pancreatic β-cell function can lead to the development of diabetes mellitus in susceptible individuals. The quantity and function of adipose tissue are influenced by aging, as well as by factors like calorie intake, physical activity, and overall health. Consequently, aging is well known to be associated with increased insulin resistance, highlighting the significant role of cellular senescence in adipose tissue in

the onset and progression of the disease [9-11].

Insulin generation is known to decrease with age. This decline is influenced not only by the secretory capacity of individual β cells but also by the overall β-cell mass (BCM). Researches involving isolated human islets have shown an age-related reduction in insulin secretion [12]. While it is generally believed that BCM is not solely impacted by aging, significant changes in BCM can occur with the development and progression of obesity and diabetes. A reduction in BCM can have a substantial effect on diabetes management, including glycemic control and the effectiveness of anti-diabetic treatments. In response to increased insulin resistance, BCM may expand to compensate for lack of insulin generation [13,14]. However, this compensatory expansion may be restricted in part due to a decrease in β-cell multiplication as a result of aging. The age-related changes in β-cell function and multiplication highlight the role of cellular aging in the disease caution of type 2 diabetes mellitus (T2DM). That's why, a better knowledge of cellular senescence in β cells and adipose tissue could lead to new curative strategies for the illness [15-18].

Aging in humans is associated with a range of complicated symptoms and diseases, such as diabetes and obesity, which arise from the gradual decrease in the function of different tissues and organs over time [19-21]. Strehler identified four key characteristics of aging in organisms: totality, entity, progressiveness, and harmfulness [22]. In line with the concept of totality, it is widely recognized that aging cells collect in the tissues and organs of aged individuals. As aging progresses or diseases develop, normal cells and tissues in the body are exposed to various stresses, leading to cellular damage that requires recovery, adjustment, programmed cell death, or other protection mechanisms [23-25]. Cellular aging refers to a state where cells undergo irreversible cell cycle capture and experience functional decline due to telomere shortening or stressors that provoke aging, such as DNA damage, oncogenic stress, and oxidative stress. Senescent cells differ from non-senescent ones, exhibiting unique characteristics like an enlarged, flattened shape, altered nuclear structure, formation of H2Aγ foci, enhanced expression of cell cycle blockers (p16Ink4 and p21Cip1), and more [26-29].

The INK4/ARF site encrypts the neoplasm cancellers, p16Ink4 and p19Arf, both of which function as inhibitors of the cell cycle. p16Ink4 inhibits cyclin-dependent kinase (CDK)4/6, while p19Arf prevents the degradation of p53. Additionally, p21Cip1, another CDK inhibitor, is a transcriptional target of p53 [30-32]. In normal cells, the INK4/ARF site is regulated epigenetically. In young cells, it is kept quiet by polycomb repressive complexes PRC1 and PRC2, which contain chromobox protein homolog (CBX)7, B cell-specific Moloney murine leukemia virus integration site (BMI)1, and enhancer of zeste homolog 2. These complexes

maintain repressive epigenetic marks, such as trimethylation of histone H3K27 on the locus. However, in senescent cells, epigenetic activation of the INK4/ARF locus leads to unchangeable cell cycle capture [33-35]. Interestingly, the ectopic expression of CBX7 or BMI1 can beglect aging in basic cells. Furthermore, several other epigenetic factors, including Mixed lineage leukemia protein-1, Jumonji domain-containing protein-3, and Zuotin-related factor 1, also play roles in the regulation of this locus [36,37].

The idea that aging is an entirely irreversible process has been partially challenged. For instance, telomere length, a notorious marker of cellular aging in vitro, is one area of focus. Telomeres reduce as a result of replicative depletion. Recent advancements in technology have made it possible to measure telomere length in leukocytes, revealing a strong correlation between telomere length and the health status of individuals, particularly in relation to conditions such as cancer, atherosclerosis, heart failure, diabetes, depression, and chronic inflammation [38-41]. Interestingly, telomere reduction can be partially revoked through lifestyle modifications, including regular physical activity, a balanced diet without excess calories, and stress reduction. These findings indicate that certain aspects of the aging process may be correctable.

The negative aspects of aging have become a topic of debate due to the complex, dual nature of senescent cells [42-44]. Even adolescent cells with undamaged telomeres can enter a senescent state when exposed to oncogenic stress, such as the activation of oncogenic Ras, a process known as oncogene-induced senescence (OIS). OIS cells are also observed in vivo and are believed to act as a protective mechanism against the harmful development of neoplasms. However, senescent cells also exhibit increased secretion of proinflammatory cytokines and chemokines through the activation of the nuclear factor-kappa B (NF-kB) pathway, leading to what is termed a senescence-associated secretory phenotype (SASP) [45-47]. Additionally, the activation of the NF-kB pathway makes senescent cells more impervious to apoptotic incentives by amplification of anti-apoptotic factors like X-linked inhibitor of apoptosis protein and Bcl-2. The SASP contributes to chronic inflammation, which in turn fosters the development of age-related diseases. Consequently, senescent cells not only accumulate in aged tissues but also contribute to organ dysfunction associated with various lifestyle diseases, playing a key role in their illness formation [48-50].

According to these concepts, targeting chronic inflammation or removing senescent cells is becoming a promising therapeutic strategy for diseases associated with aging. Antibody therapies targeting inflammatory cytokines like interleukin (IL)-6 and tumor necrosis factor (TNF)-α are already in clinical use through molecularly aimed pharmaceuticals [51,52]. Lately, an anti-IL-1 antibody drug, canakinumab, was produced for the cure of certain autoimmune conditions. Notably, the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) demonstrated that canakinumab could impede atherosclerosis and lung cancer in approximately 10,000 elderly individuals [53-56]. This represents a groundbreaking example of the effective reduction of chronic inflammation. Additionally, last improvements in aging

research have indicated that eliminating senescent cells, a process known as senolysis, is an encouraging strategy (senotherapy) for minimizing chronic inflammation and cure age-associated illnesses [57-60].

Fundamental ageing mechanisms contribute to diabetes pathogenesis

The mechanisms underlying aging are numerous and interconnected. A few models have been proposed to categorize age-related processes, superposing with abnormalities observed in obesity and diabetes. This overlap has been particularly well-documented in the situation with adipose tissue. Generally, the fundamental mechanisms of aging can be grouped into the next categories: (1) macromolecular dysfunction, which includes the loss of proteostasis, impaired DNA damage repair, and abnormal mRNA processing; (2) sterile inflammation, characterized by the infiltration of immune cells and the emission of proinflammatory cytokines without the presence of a specific pathogen, along with fibrosis; (3) progenitor cell dysfunction, which encompasses the depletion of progenitor cell pools, reduced differentiation capacity, or abnormal lineage distribution; and (4) cellular aging [61-64]. These groups are explored more thoroughly below, particularly in relation to their roles in the pathogenesis and development of diabetes. Special attention is given to adipose tissue due to its significant role in the progression of inflammation, insulin impedance, and related maladies, and because several mechanistic studies on senescent cells within adipose tissue have been conducted [65-67].

Senescent cell burden is increased in diabetes

The primary risk factors for progression type 2 diabetes are age and adiposity, both of which are linked to a higher accumulation of aging cells. While cellular senescence is thought to play a role in the onset of diabetes, as mentioned earlier, the diabetic microhabitat also appears to contribute to the increased charge of senescent cells [68,69]. For instance, heightened glucose and lipid levels, similar to inflammation, can trigger cellular aging. Either type 1 or type 2 diabetes are connected to a higher risk of glucose-related microvascular intricacies affecting the eyes, nerves, and kidneys. However, the role of cellular aging in the evolution of these intricacies remains poorly understood [70].

While most of the current researches on the consequences of cellular senescence has been performed using animal models, several studies have also examined senescence in human cells from both diabetic and non-diabetic individuals. The following is a summary of the latest data on cellular senescence in key tissues linked to the development and clinical manifestations of type 2 diabetes [71-74].

Beta cells

The onset of insulin resistance requires a compensatory growth in insulin secretion to maintain normal glucose levels. Type 2 diabetes develops when this compensatory insulin secretion becomes insufficient to counteract the level of insulin resistance. A few investigations have demonstrated that the gene expression profile in beta cells changes with age, with an upregulation of genes associated with cellular senescence, such as **Cdkn2a** and **Cdkn2b [75-77]**. While this typically results in a reduced capacity for cell proliferation, an unexpected discovery was that insulin secretion was actually enhanced in **p16Ink4a**-induced senescent cells, rather than diminished. The extent to which this finding explains the age-related increase in basal insulin secretion, generally attributed to the concurrent rise in obesity and insulin resistance, remains unclear but presents an intriguing hypothesis [78-81]. More recently, research has shown that eliminating senescent beta cells in a mouse model of type 1 diabetes improved insulin secretion and preserved the cells' insulin-producing ability, suggesting a novel connection between cellular senescence and serious insulin lack [82-86].

Abdominal/visceral obesity

Inflammation in adipose tissue increases as a result of adipocyte hypertrophy, which in turn can lead to the aggregation of aging cells. Fatness, particularly when linked to hypertrophic expansion, is associated with elevated indicators of cellular senescence. These markers include increased β-galactosidase activity in adipose tissue, which indicates high lysosomal activity and content, as well as elevated levels of plasminogen activator inhibitor 1 (PAI-1), p53, and cyclin-dependent kinase inhibitors like p16Ink4a [87-91]. Senescent ancestry cells impede adipogenesis, leading to ectopic lipid collection, increased visceral fat, and abdominal fatness. Correspondingly, ageing is connected with the buildup of non-dividing senescent cells in adipose tissue. Additionally, age-related increases in visceral fat have been observed independently of BMI [92-96].

Fatty liver disease

Type 2 diabetes is linked to a higher risk of developing non-alcoholic fatty liver disease (NAFLD). Recent studies have demonstrated that the burden of senescent cells in the liver is elevated in individuals with NAFLD, with the degree of steatosis corresponding to indicators of senescence. In mouse models, inducing senescence specifically in hepatocytes led to increased fat accumulation, suggesting that senescent hepatocytes play a direct role in the development of NAFLD. Furthermore, treatment with senolytics (D+Q) was found to reduce steatosis [97-100].

Cardiovascular disease

Cells in the aortic media and atherosclerotic plaques of hypercholesterolaemic (ApoE−/−) and ageing mice exhibit elevated pointers of senescence. Research has shown that the removal of senescent cells improves vascular smooth muscle sensitivity to nitric oxide donors and reduces plaque calcium deposits, suggesting that senescent cells contribute to endothelial dysfunction in atherosclerosis [101-103]. Additionally, clearing senescent cells in obese mice improved cardiac diastolic function, a finding with potential relevance for diabetic patients, who often experience heart failure with preserved ejection fraction. During aging, senescent cardiac ancestry cells develop a hypertrophic, pro-fibrotic phenotype and lose their ability to replicate. Removing these senescent cells in mice reduced age-related dysfunction in cardiac ancestry cells and reduced fibrotic area formation following myocardial infarction [104-107].

Renal dysfunction

Cellular senescence is more prevalent in kidney cells from individuals with type 2 diabetes and also enlargers with age in non-diabetic individuals. The clinical significance of this observation is underscored by recent findings that senolytic treatment (D+Q) reduced proteinuria in obese, insulin-resistant mice [108-110].

Cognitive dysfunction and Alzheimer's disease

Cellular senescence has been implicated in mental disability in both obese, insulin-resistant mice and aged mice. Senolytic therapy (D+Q) decreased the abundance of senescent cells in the brain, restored neurogenesis, and alleviated neuropsychiatric defect in obese animals. In aged mice with an Alzheimer's-like condition induced by Tau protein overexpression, these agents also reduced neuroinflammation, restored neurogenesis, and partially reversed brain atrophy [111-113].

Collectively, these findings from both human and animal studies strongly support the role of cellular senescence in the development of diabetes and its associated complications. Moreover, they suggest that reducing the burden of senescent cells could be a promising new therapeutic approach for managing diabetes and its related difficulties [114-116].

Senotherapy: Senolytics and Senomorphics

Table 1. Senotherapeutic Strategies for Managing Type 2 Diabetes Mellitus (T2DM)

Therapy Type	Examples	Mechanism of Action	Clinical Benefits	Research Status
Senolytics	Dasatinib, Quercetin (D+Q)	Induces apoptosis in senescent cells	Reduces senescent cell burden, enhances tissue function	Clinical trials ongoing
	ABT263, ABT199	Targets BCL-2 to promote β-cell apoptosis	Improves insulin secretion, lowers blood sugar	Preclinical and clinical data available
Senomorphics	Metformin	Modulates SASP without eliminating senescent cells	Improves insulin sensitivity, decreases inflammation	Widely used in clinical practice
	Curcumin	Activates autophagic pathways, counters oxidative stress	Protects against β-cell dysfunction	Emerging evidence, clinical studies ongoing
Antibody Therapies	Anti-IL-6, Anti-TNF-α	Neutralizes inflammatory cytokines	Reduces chronic inflammation, improves insulin sensitivity	Under investigation in clinical trials

Therapy Type	Examples	Mechanism of Action	Clinical Benefits	Research Status
Lifestyle Interventions	Diet, Exercise	Promotes metabolic health and reduces adiposity	Enhances overall metabolic function	Well-established; recommended for all T2DM patients
Combination Therapies	Metformin + Senolytics	Synergistic effects targeting multiple pathways	Potentially greater improvements in glycemic control	Research ongoing; promising preliminary results
Nutraceuticals	Omega-3 Fatty Acids	Modulates inflammatory pathways	Reduces inflammation, supports cardiovascular health	Some evidence supports efficacy
Gene Therapy	Gene editing approaches	Targets senescence-related genes	Potential to delay or reverse age-related dysfunction	Experimental; requires further validation

Senotherapies, which include senolytics and senomorphics, have the potential to reduce the onset of age-related pathologies. Senolytics work by selectively eliminating senescent cells through the targeting of SCAP (Senescence-Associated Anti-apoptotic Pathways). RNA interference techniques have identified drugs that target critical nodes within SCAP pathways, such as BCL-2/BCL-XL, PI3K/AKT, and p53/p21/serpins [117-119]. This approach has led to the discovery of several senolytics that induce apoptosis in senescent cells. On the other hand, senomorphics modulate SASP (Senescence-Associated Secretory Phenotype) pathways without killing the senescent cells [120,121].

This part will concentrate on the senolytics and senomorphics that have been used in clinical tests and animal studies, particularly in the context of type 2 diabetes (T2DM) and its intricacies. Senolytics such as D, Q, fisetin, and ABT263 have been investigated, while metformin has been explored as a senomorphic.

2. DASATINIB AND QUERCETIN

D is a tyrosine kinase inhibitor used in the treatment of chronic myeloid leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia that is firm or prejudiced to other treatments. Q is an innate flavonoid that hinders PI3K [122,123]. The first clinical use of a senolytic involved the combination of D+Q, which was reported in 2015. In studies involving insulin resistance using S961, an insulin receptor antagonist, D+Q was shown to reduce the number of β-gal-positive dispersed islet cells both in vitro and in vivo, and to lower blood glucose levels in a mouse model of insulin resistance [124-126].

The D+Q combination also diminished the number of naturally occurring senescent cells and their SASP emission in human adipose obese extracts. This research utilized omental adipose tissue obtained from eight obese subjects undergoing gastric bypass surgery. Notably, D+Q has potential adverse reactions including hematologic dysfunction, fluid retention, skin rash, and QT prolongation. Further clinical studies are required to assess its potential efficacy in treating type 2 diabetes (T2DM) [127-129].

BCL-2 Inhibitors: ABT263 (NAVITOCLAX), ABT199 (VENETOCLAX), and ABT737

ABT263 (Navitoclax) aims the BCL-2 course. The studies found that ABT263 effectively eliminated a significant portion of β-gal-positive dispersed islet cells in vitro. Additionally, ABT263 reduced blood glucose grades and p16Ink4a emission in a medication-associated insulin-repellent mouse model [130-132]. It also reduced p16Ink4a levels in peripheral tissues in a high-fat diet (HFD)-induced insulin resistance example. When used in combination with D+Q, Navitoclax selectively aimed and eliminated senescent cells, and improved outcomes in SARS-CoV-2-infected hamsters and mice with reduced lung disease. Despite its potential, common side effects such as diarrhea, nausea, and thrombocytopenia restrict its clinical

applicability [133-135].

ABT199 (Venetoclax) optionally hinders BCL-2, an apoptosis-suppressing protein. Venetoclax is an oral BCL-2 hinder endorsed for use in relapsed/refractory chronic lymphocytic leukemia and acute myeloid leukemia. In studies, administration of ABT199 to normoglycemic non-obese diabetic (NOD) mice suppressed the development of diabetes in contradiction of controls in a type 1 diabetes mellitus (T1DM) example [136,137].

ABT737, another BCL-2 inhibitor, has demonstrated productive antitumor activity in cancerous lymphoma and small-cell lung cancer. Treatment with ABT737 in NOD mice resulted in a 30% reduction in β-cells emitting cyclin-dependent kinase inhibitor 2A (Cdkn2a) and a diminished incidence of T1DM [138-141].

Senomorphic: Metformin

Metformin has been used for decennaries to cure type 2 diabetes (T2DM) by reducing circulating glucose levels through the restraint of hepatic gluconeogenesis. Beyond its glucose-lowering effects, metformin may also possess anti-aging characteristics by avoiding DNA damage and inflammation and has been shown to exhibit senomorphic effects. In a mouse model of kidney disease, a brief course of metformin inhibited acute senescence in bone marrow mesenchymal stem cells (MSCs) [142,143]. Other studies have demonstrated that metformin reduces ROS levels and delays the onset of senescence in mouse adipose-derived MSCs. Additionally, treating human adipose stem cells with metformin at therapeutic concentrations for 6 weeks led to a decline in β-galactosidase activity. Measuring circulating SASP levels before and after metformin control could help to define patients who might profit most from its senomorphic consequences [144-146].

Others: Curcumin

Curcumin, a phytocompound found in turmeric, has been investigated in numerous clinical tests for type 2 diabetes (T2DM). Research has shown that a combination of curcumin and hesperetin, two antioxidant polyphenolic compounds, can enhance cellular senescence outcomes. This combination has been reported to reduce β-galactosidase staining, p16Ink4a, and p21Cip1 in neurons and rats induced with D-galactose. Additionally, curcumin has been shown to mitigate D-galactose-induced senescence in cardiomyocytes by promoting autophagy through the SIRT1/AMPK/mTOR pathway [147-149].

While numerous clinical studies have explored the effects of curcumin on type 2 diabetes (T2DM), there is currently no evidence directly demonstrating its impact on senescent pancreatic β-cells. Many trials have shown that curcumin significantly reduces T2DM incidence among individuals with prediabetes. In diabetic mouse models, curcumin treatment has improved β-cell function, as indicated by higher homeostasis model assessment of β-cell function (HOMA-β) and lower homeostasis model assessment of insulin resistance (HOMA-IR) in contradiction of placebo [150,151]. Additionally, curcumin has been reported to protect against diabetes-induced pathological changes in the aorta, primarily by inhibiting JNK2 and upregulating nuclear factor erythroid 2-related factor 2 (Nrf2) expression and function. Furthermore, a combination of metformin and curcumin provided greater myocardial protection in diabetic rats than metformin alone, seems to indicate that inhibition of the JAK/STAT pathway and activation of the Nrf2/heme oxygenase 1 (HO-1) pathway may negotiate these effects. Notably, the JAK/STAT pathway is also a known regulator of SASP secretion, highlighting a possible healing mechanism. Although there are no clinical studies yet examining curcumin's role in elimination of senescent cells in diabetic patients, further research is warranted [152-154].

3. FUTURE PERSPECTIVES

Over the past twenty years, research has significantly advanced our knowledge of cellular senescence in adipose tissue and pancreatic β cells related to diabetes, involving its morbid effect and impact on the growth and progression of the disease. Recent studies on senolysis have introduced the concept of senotherapy as a potential new treatment for diabetes. Since both aging and metabolic stress—such as insulin resistance—affect the onset, progression, and potential reversal of cellular senescence, individuals may experience varying degrees of senescence even at the same age [155-158]. Additionally, distinct indicators and molecular mechanisms of senescence have been identified in adipose tissue and pancreatic β cells, suggesting that the extent and impact of senescence on diabetes can vary between these two critical components of diabetes pathology. In adipose tissue, p21Cip1 serves as a marker of early-stage senescence and a primary target for senolysis to reduce insulin resistance. Conversely, targeting p16INK4a can enhance β cell function in pancreatic β cells, while targeting p21high cells has shown limited effects [159,160]. Therefore, a targeted approach that addresses both organs with specific molecular targets and therapeutic strategies could be a promising senotherapeutic method for diabetes. Further research into the molecular mechanisms of senescence in diabetes and the clinical efficacy and safety of senolytic agents is needed to make this concept a viable clinical treatment.

4. CONCLUSION

In conclusion, the intricate relationship between aging, cellular senescence, and type 2 diabetes mellitus (T2DM) reveals

the critical roles that these biological processes play in the pathogenesis of this widespread condition. As the prevalence of T2DM continues to rise globally, a deeper understanding of how aging influences insulin resistance and β-cell dysfunction is essential for developing effective therapeutic strategies. The accumulation of senescent cells in adipose tissue and pancreatic β-cells not only exacerbates metabolic dysregulation but also highlights the potential for senotherapy as a groundbreaking approach in diabetes management.

Emerging evidence supports the efficacy of senolytics and senomorphics in reducing the burden of senescent cells and mitigating the inflammatory responses they invoke. By targeting specific molecular pathways, these therapies have the potential to restore insulin sensitivity and enhance β-cell function, offering hope for improved outcomes in individuals with T2DM. This review emphasizes the need for continued research to elucidate the underlying mechanisms of cellular senescence and to evaluate the clinical efficacy and safety of these novel therapies. A targeted approach that addresses the unique senescence markers and mechanisms in both adipose tissue and pancreatic β-cells could significantly advance our ability to manage diabetes and its associated complications.

Ultimately, integrating insights from aging research with diabetes treatment strategies holds the promise of not only alleviating the immediate challenges posed by the disease but also improving long-term health outcomes for millions worldwide. As we move forward, a concerted effort to understand and leverage the biology of aging will be essential in shaping the future landscape of diabetes management.

REFERENCES

[1] Magliano DJ, Boyko EJ; IDF Diabetes Atlas 10th edition scientific committee. IDF DIABETES ATLAS [Internet]. 10th ed. Brussels: International Diabetes Federation; 2021. PMID: 35914061.

[2] Reed J, Bain S, Kanamarlapudi V. A Review of Current Trends with Type 2 Diabetes Epidemiology, Aetiology, Pathogenesis, Treatments and Future Perspectives. Diabetes Metab Syndr Obes. 2021 Aug 10;14:3567-3602. doi: 10.2147/DMSO.S319895. PMID: 34413662; PMCID: PMC8369920.

[3] Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C. Pathophysiology of Type 2 Diabetes Mellitus. Int J Mol Sci. 2020 Aug 30;21(17):6275. doi: 10.3390/ijms21176275. PMID: 32872570; PMCID: PMC7503727.

[4] Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022 Nov 1;45(11):2753-2786. doi: 10.2337/dci22-0034. PMID: 36148880; PMCID: PMC10008140.

[5] Chandrasekaran P, Weiskirchen R. The Role of Obesity in Type 2 Diabetes Mellitus-An Overview. Int J Mol Sci. 2024 Feb 4;25(3):1882. doi: 10.3390/ijms25031882. PMID: 38339160; PMCID: PMC10855901.

[6] Ruze R, Liu T, Zou X, Song J, Chen Y, Xu R, Yin X, Xu Q. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. Front Endocrinol (Lausanne). 2023 Apr 21;14:1161521. doi: 10.3389/fendo.2023.1161521. PMID: 37152942; PMCID: PMC10161731.

[7] Sadeghi, A., Niknam, M., Momeni-Moghaddam, M.A. *et al.* Crosstalk between autophagy and insulin resistance: evidence from different tissues. *Eur J Med Res* **28**, 456 (2023). https://doi.org/10.1186/s40001-023-01424-9

[8] Janssen JAMJL. Overnutrition, Hyperinsulinemia and Ectopic Fat: It Is Time for A Paradigm Shift in the Management of Type 2 Diabetes. Int J Mol Sci. 2024 May 17;25(10):5488. doi: 10.3390/ijms25105488. PMID: 38791525; PMCID: PMC11121669.

[9] Murakami T, Inagaki N, Kondoh H. Cellular Senescence in Diabetes Mellitus: Distinct Senotherapeutic Strategies for Adipose Tissue and Pancreatic β Cells. Front Endocrinol (Lausanne). 2022 Mar 31;13:869414. doi: 10.3389/fendo.2022.869414. PMID: 35432205; PMCID: PMC9009089.

[10] Biondi G, Marrano N, Borrelli A, Rella M, Palma G, Calderoni I, Siciliano E, Lops P, Giorgino F, Natalicchio A. Adipose Tissue Secretion Pattern Influences β-Cell Wellness in the Transition from Obesity to Type 2 Diabetes. Int J Mol Sci. 2022 May 15;23(10):5522. doi: 10.3390/ijms23105522. PMID: 35628332; PMCID: PMC9143684.

[11] Antar SA, Ashour NA, Sharaky M, Khattab M, Ashour NA, Zaid RT, Roh EJ, Elkamhawy A, Al-Karmalawy AA. Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments. Biomed Pharmacother. 2023 Dec;168:115734. doi: 10.1016/j.biopha.2023.115734. Epub 2023 Oct 17. PMID: 37857245.

[12] Sasaki H, Saisho Y, Inaishi J, Itoh H. Revisiting Regulators of Human β-cell Mass to Achieve β-cell-centric Approach Toward Type 2 Diabetes. J Endocr Soc. 2021 Jul 19;5(10):bvab128. doi: 10.1210/jendso/bvab128.

PMID: 34405128; PMCID: PMC8361804.

[13] De Tata V. Age-related impairment of pancreatic Beta-cell function: pathophysiological and cellular mechanisms. Front Endocrinol (Lausanne). 2014 Sep 3;5:138. doi: 10.3389/fendo.2014.00138. PMID: 25232350; PMCID: PMC4153315.

[14] Sridhar A, Khan D, Babu G, Irwin N, Gault VA, Flatt PR, Moffett CR. Chronic exposure to incretin metabolites GLP-1(9-36) and GIP(3-42) affect islet morphology and beta cell health in high fat fed mice. Peptides. 2024 Aug;178:171254. doi: 10.1016/j.peptides.2024.171254. Epub 2024 May 28. PMID: 38815655.

[15] Tudurí E, Soriano S, Almagro L, Montanya E, Alonso-Magdalena P, Nadal Á, Quesada I. The pancreatic β-cell in ageing: Implications in age-related diabetes. Ageing Res Rev. 2022 Sep;80:101674. doi: 10.1016/j.arr.2022.101674. Epub 2022 Jun 17. PMID: 35724861.

[16] Diane A, Allouch A, Mu-U-Min RBA, Al-Siddiqi HH. Endoplasmic reticulum stress in pancreatic β-cell dysfunctionality and diabetes mellitus: a promising target for generation of functional hPSC-derived β-cells *in vitro*. Front Endocrinol (Lausanne). 2024 Jun 20;15:1386471. doi: 10.3389/fendo.2024.1386471. PMID: 38966213; PMCID: PMC11222326.

[17] Salinno C, Cota P, Bastidas-Ponce A, Tarquis-Medina M, Lickert H, Bakhti M. β-Cell Maturation and Identity in Health and Disease. Int J Mol Sci. 2019 Oct 30;20(21):5417. doi: 10.3390/ijms20215417. PMID: 31671683; PMCID: PMC6861993.

[18] Sudhakar, M., Winfred, S.B., Meiyazhagan, G. *et al.* Mechanisms contributing to adverse outcomes of COVID-19 in obesity. *Mol Cell Biochem* **477**, 1155–1193 (2022). https://doi.org/10.1007/s11010-022-04356-w

[19] Zhu M, Liu X, Liu W, Lu Y, Cheng J, Chen Y. β cell aging and age-related diabetes. Aging (Albany NY). 2021 Mar 3;13(5):7691-7706. doi: 10.18632/aging.202593. Epub 2021 Mar 3. PMID: 33686020; PMCID: PMC7993693.

[20] Zhang K, Ma Y, Luo Y, Song Y, Xiong G, Ma Y, Sun X, Kan C. Metabolic diseases and healthy aging: identifying environmental and behavioral risk factors and promoting public health. Front Public Health. 2023 Oct 13;11:1253506. doi: 10.3389/fpubh.2023.1253506. PMID: 37900047; PMCID: PMC10603303.

[21] Chowdhury SG, Misra S, Karmakar P. Understanding the Impact of Obesity on Ageing in the Radiance of DNA Metabolism. J Nutr Health Aging. 2023;27(5):314-328. doi: 10.1007/s12603-023-1912-1. PMID: 37248755.

[22] Strehler BL. Understanding aging. Methods Mol Med. 2000;38:1-19. doi: 10.1385/1-59259-070-5:1. PMID: 22351262.

[23] Li Z, Zhang Z, Ren Y, Wang Y, Fang J, Yue H, Ma S, Guan F. Aging and age-related diseases: from mechanisms to therapeutic strategies. Biogerontology. 2021 Apr;22(2):165-187. doi: 10.1007/s10522-021-09910-5. Epub 2021 Jan 27. PMID: 33502634; PMCID: PMC7838467.

[24] Liochev SI. Which Is the Most Significant Cause of Aging? Antioxidants (Basel). 2015 Dec 17;4(4):793-810. doi: 10.3390/antiox4040793. PMID: 26783959; PMCID: PMC4712935.

[25] Wissler Gerdes EO, Zhu Y, Weigand BM, Tripathi U, Burns TC, Tchkonia T, Kirkland JL. Cellular senescence in aging and age-related diseases: Implications for neurodegenerative diseases. Int Rev Neurobiol. 2020;155:203-234. doi: 10.1016/bs.irn.2020.03.019. Epub 2020 Aug 11. PMID: 32854855; PMCID: PMC7656525.

[26] Sacco A, Belloni L, Latella L. From Development to Aging: The Path to Cellular Senescence. Antioxid Redox Signal. 2021 Feb 1;34(4):294-307. doi: 10.1089/ars.2020.8071. Epub 2020 May 5. PMID: 32228062; PMCID: PMC7821433.

[27] Rocha A, Dalgarno A, Neretti N. The functional impact of nuclear reorganization in cellular senescence. Brief Funct Genomics. 2022 Jan 25;21(1):24-34. doi: 10.1093/bfgp/elab012. PMID: 33755107; PMCID: PMC8789270.

[28] Kumari R, Jat P. Mechanisms of Cellular Senescence: Cell Cycle Arrest and Senescence Associated Secretory Phenotype. Front Cell Dev Biol. 2021 Mar 29;9:645593. doi: 10.3389/fcell.2021.645593. PMID: 33855023; PMCID: PMC8039141.

[29] Poznyak AV, Orekhova VA, Sukhorukov VN, Khotina VA, Popov MA, Orekhov AN. Atheroprotective Aspects of Heat Shock Proteins. Int J Mol Sci. 2023 Jul 21;24(14):11750. doi: 10.3390/ijms241411750. PMID: 37511509; PMCID: PMC10380699.

[30] Fontana R, Ranieri M, La Mantia G, Vivo M. Dual Role of the Alternative Reading Frame ARF Protein in Cancer. Biomolecules. 2019 Mar 4;9(3):87. doi: 10.3390/biom9030087. PMID: 30836703; PMCID:

PMC6468759.

[31] Nikiforov NG, Kirichenko TV, Kubekina MV, Chegodaev YS, Zhuravlev AD, Ilchuk LA, Nikolaeva MA, Arefieva AS, Popov MA, Verkhova SS, Bagheri Ekta M, Orekhov AN. Macrophages derived from LPS-stimulated monocytes from individuals with subclinical atherosclerosis were characterized by increased pro-inflammatory activity. Cytokine. 2023 Dec;172:156411. doi: 10.1016/j.cyto.2023.156411. Epub 2023 Oct 31. PMID: 37918051

[32] Finn, R.S., Aleshin, A. & Slamon, D.J. Targeting the cyclin-dependent kinases (CDK) 4/6 in estrogen receptor-positive breast cancers. *Breast Cancer Res* **18**, 17 (2016). https://doi.org/10.1186/s13058-015-0661-5

[33] Roger L, Tomas F, Gire V. Mechanisms and Regulation of Cellular Senescence. Int J Mol Sci. 2021 Dec 6;22(23):13173. doi: 10.3390/ijms222313173. PMID: 34884978; PMCID: PMC8658264.

[34] Gahan JM, Rentzsch F, Schnitzler CE. The genetic basis for PRC1 complex diversity emerged early in animal evolution. Proc Natl Acad Sci U S A. 2020 Sep 15;117(37):22880-22889. doi: 10.1073/pnas.2005136117. Epub 2020 Aug 31. PMID: 32868440; PMCID: PMC7502728.

[35] Wang W, Qin JJ, Voruganti S, Nag S, Zhou J, Zhang R. Polycomb Group (PcG) Proteins and Human Cancers: Multifaceted Functions and Therapeutic Implications. Med Res Rev. 2015 Nov;35(6):1220-67. doi: 10.1002/med.21358. Epub 2015 Jul 30. PMID: 26227500; PMCID: PMC4718713.

[36] de Groot AP, de Haan G. How CBX proteins regulate normal and leukemic blood cells. FEBS Lett. 2024 Mar 1. doi: 10.1002/1873-3468.14839. Epub ahead of print. PMID: 38426219.

[37] Kraus, L., Bryan, C., Wagner, M., Kino, T., Gunchenko, M., Jalal, W., Khan, M., & Mohsin, S. (2021). Bmi1 Augments Proliferation and Survival of Cortical Bone-Derived Stem Cells after Injury through Novel Epigenetic Signaling via Histone 3 Regulation. *International journal of molecular sciences*, *22*(15), 7813. https://doi.org/10.3390/ijms22157813

[38] Daios S, Anogeianaki A, Kaiafa G, Kontana A, Veneti S, Gogou C, Karlafti E, Pilalas D, Kanellos I, Savopoulos C. Telomere Length as a Marker of Biological Aging: A Critical Review of Recent Literature. Curr Med Chem. 2022;29(34):5478-5495. doi: 10.2174/0929867329666220713123750. PMID: 35838223.

[39] Schellnegger M, Lin AC, Hammer N, Kamolz LP. Physical Activity on Telomere Length as a Biomarker for Aging: A Systematic Review. Sports Med Open. 2022 Sep 4;8(1):111. doi: 10.1186/s40798-022-00503-1. PMID: 36057868; PMCID: PMC9441412.

[40] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. Cell. 2023 Jan 19;186(2):243-278. doi: 10.1016/j.cell.2022.11.001. Epub 2023 Jan 3. PMID: 36599349.

[41] Vaiserman A, Krasnienkov D. Telomere Length as a Marker of Biological Age: State-of-the-Art, Open Issues, and Future Perspectives. Front Genet. 2021 Jan 21;11:630186. doi: 10.3389/fgene.2020.630186. PMID: 33552142; PMCID: PMC7859450.

[42] Boccardi V, Paolisso G, Mecocci P. Nutrition and lifestyle in healthy aging: the telomerase challenge. Aging (Albany NY). 2016 Jan;8(1):12-5. doi: 10.18632/aging.100886. PMID: 26826704; PMCID: PMC4761710.

[43] Malek Rivan NF, Shahar S, Rajab NF, Singh DKA, Din NC, Hazlina M, Hamid TATA. Cognitive frailty among Malaysian older adults: baseline findings from the LRGS TUA cohort study. Clin Interv Aging. 2019 Jul 25;14:1343-1352. doi: 10.2147/CIA.S211027. PMID: 31413555; PMCID: PMC6663036.

[44] Poznyak AV, Sukhorukov VN, Popov MA, Chegodaev YS, Postnov AY, Orekhov AN. Mechanisms of the Wnt Pathways as a Potential Target Pathway in Atherosclerosis. J Lipid Atheroscler. 2023 Sep;12(3):223-236. doi: 10.12997/jla.2023.12.3.223. Epub 2023 Sep 7. PMID: 37800111; PMCID: PMC10548192.

[45] Baker DJ, Alimirah F, van Deursen JM, Campisi J, Hildesheim J. Oncogenic senescence: a multi-functional perspective. Oncotarget. 2017 Apr 18;8(16):27661-27672. doi: 10.18632/oncotarget.15742. PMID: 28416761; PMCID: PMC5432366.

[46] Schmitt CA, Wang B, Demaria M. Senescence and cancer - role and therapeutic opportunities. Nat Rev Clin Oncol. 2022 Oct;19(10):619-636. doi: 10.1038/s41571-022-00668-4. Epub 2022 Aug 31. PMID: 36045302; PMCID: PMC9428886.

[47] Roger L, Tomas F, Gire V. Mechanisms and Regulation of Cellular Senescence. Int J Mol Sci. 2021 Dec 6;22(23):13173. doi: 10.3390/ijms222313173. PMID: 34884978; PMCID: PMC8658264.

[48] Hu L, Li H, Zi M, Li W, Liu J, Yang Y, Zhou D, Kong QP, Zhang Y, He Y. Why Senescent Cells Are Resistant to Apoptosis: An Insight for Senolytic Development. Front Cell Dev Biol. 2022 Feb 16;10:822816. doi: 10.3389/fcell.2022.822816. PMID: 35252191; PMCID: PMC8890612.

[49] Liu Y, Lomeli I, Kron SJ. Therapy-Induced Cellular Senescence: Potentiating Tumor Elimination or Driving

Cancer Resistance and Recurrence? Cells. 2024 Jul 30;13(15):1281. doi: 10.3390/cells13151281. PMID: 39120312; PMCID: PMC11312217.

[50] Saito, Y., Yamamoto, S. & Chikenji, T.S. Role of cellular senescence in inflammation and regeneration. *Inflamm Regener* **44**, 28 (2024). https://doi.org/10.1186/s41232-024-00342-5

[51] Jiang B, Zhang W, Zhang X, Sun Y. Targeting senescent cells to reshape the tumor microenvironment and improve anticancer efficacy. Semin Cancer Biol. 2024 Jun;101:58-73. doi: 10.1016/j.semcancer.2024.05.002. Epub 2024 May 27. PMID: 38810814.

[52] Suda M, Paul KH, Minamino T, Miller JD, Lerman A, Ellison-Hughes GM, Tchkonia T, Kirkland JL. Senescent Cells: A Therapeutic Target in Cardiovascular Diseases. Cells. 2023 May 2;12(9):1296. doi: 10.3390/cells12091296. PMID: 37174697; PMCID: PMC10177324.

[53] Poznyak AV, Kashirskikh DA, Postnov AY, Popov MA, Sukhorukov VN, Orekhov AN. Sialic acid as the potential link between lipid metabolism and inflammation in the pathogenesis of atherosclerosis. Braz J Med Biol Res. 2023 Dec 11;56:e12972. doi: 10.1590/1414-431X2023e12972. PMID: 38088673; PMCID: PMC10712282.

[54] Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ; CANTOS Trial Group. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet. 2017 Oct 21;390(10105):1833-1842. doi: 10.1016/S0140-6736(17)32247-X. Epub 2017 Aug 27. PMID: 28855077.

[55] Gluba-Brzózka A, Franczyk B, Rysz-Górzyńska M, Ławiński J, Rysz J. Emerging Anti-Atherosclerotic Therapies. Int J Mol Sci. 2021 Nov 9;22(22):12109. doi: 10.3390/ijms222212109. PMID: 34829992; PMCID: PMC8624828.

[56] Libby P. Interleukin-1 Beta as a Target for Atherosclerosis Therapy: Biological Basis of CANTOS and Beyond. J Am Coll Cardiol. 2017 Oct 31;70(18):2278-2289. doi: 10.1016/j.jacc.2017.09.028. PMID: 29073957; PMCID: PMC5687846.

[57] Lorenzo EC, Torrance BL, Haynes L. Impact of senolytic treatment on immunity, aging, and disease. Front Aging. 2023 Oct 10;4:1161799. doi: 10.3389/fragi.2023.1161799. PMID: 37886012; PMCID: PMC10598643.

[58] Pignolo RJ, Passos JF, Khosla S, Tchkonia T, Kirkland JL. Reducing Senescent Cell Burden in Aging and Disease. Trends Mol Med. 2020 Jul;26(7):630-638. doi: 10.1016/j.molmed.2020.03.005. Epub 2020 Apr 17. PMID: 32589933; PMCID: PMC7857028.

[59] Cai, Y., Zhou, H., Zhu, Y. *et al.* Elimination of senescent cells by β-galactosidase-targeted prodrug attenuates inflammation and restores physical function in aged mice. *Cell Res***30**, 574–589 (2020). https://doi.org/10.1038/s41422-020-0314-9

[60] Khalil R, Diab-Assaf M, Lemaitre JM. Emerging Therapeutic Approaches to Target the Dark Side of Senescent Cells: New Hopes to Treat Aging as a Disease and to Delay Age-Related Pathologies. Cells. 2023 Mar 16;12(6):915. doi: 10.3390/cells12060915. PMID: 36980256; PMCID: PMC10047596.

[61] Ou MY, Zhang H, Tan PC, Zhou SB, Li QF. Adipose tissue aging: mechanisms and therapeutic implications. Cell Death Dis. 2022 Apr 4;13(4):300. doi: 10.1038/s41419-022-04752-6. PMID: 35379822; PMCID: PMC8980023.

[62] Franceschi C, Garagnani P, Morsiani C, Conte M, Santoro A, Grignolio A, Monti D, Capri M, Salvioli S. The Continuum of Aging and Age-Related Diseases: Common Mechanisms but Different Rates. Front Med (Lausanne). 2018 Mar 12;5:61. doi: 10.3389/fmed.2018.00061. PMID: 29662881; PMCID: PMC5890129.

[63] Wang X, Xu M, Li Y. Adipose Tissue Aging and Metabolic Disorder, and the Impact of Nutritional Interventions. Nutrients. 2022 Jul 29;14(15):3134. doi: 10.3390/nu14153134. PMID: 35956309; PMCID: PMC9370499.

[64] Jia D, Zhang H, Liu T, Wang R. Exercise Alleviates Aging of Adipose Tissue through Adipokine Regulation. Metabolites. 2024 Feb 22;14(3):135. doi: 10.3390/metabo14030135. PMID: 38535295; PMCID: PMC10972279.

[65] Palmer AK, Tchkonia T, LeBrasseur NK, Chini EN, Xu M, Kirkland JL. Cellular Senescence in Type 2 Diabetes: A Therapeutic Opportunity. Diabetes. 2015 Jul;64(7):2289-98. doi: 10.2337/db14-1820. PMID: 26106186; PMCID: PMC4477358.

[66] Jimenez-Gutierrez GE, Martínez-Gómez LE, Martínez-Armenta C, Pineda C, Martínez-Nava GA, Lopez-Reyes A. Molecular Mechanisms of Inflammation in Sarcopenia: Diagnosis and Therapeutic Update. Cells. 2022 Aug 1;11(15):2359. doi: 10.3390/cells11152359. PMID: 35954203; PMCID: PMC9367570.

[67] Rossing P, Baeres FMM, Bakris G, Bosch-Traberg H, Gislum M, Gough SCL, Idorn T, Lawson J, Mahaffey KW, Mann JFE, Mersebach H, Perkovic V, Tuttle K, Pratley R. The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease. Nephrol Dial Transplant. 2023 Aug 31;38(9):2041-2051. doi: 10.1093/ndt/gfad009. Erratum in: Nephrol Dial Transplant. 2024 Mar 27;39(4):724. doi: 10.1093/ndt/gfad252. PMID: 36651820; PMCID: PMC10469096.

[68] Novoselova EG, Lunin SM, Khrenov MO, Glushkova OV, Novoselova TV, Parfenyuk SB. The Possible Role of B-Cell Senescence in the Development of Type 2 Diabetes Mellitus. Cell Physiol Biochem. 2023 Feb 15;57(1):34-48. doi: 10.33594/000000606. PMID: 37161897.

[69] Narasimhan A, Flores RR, Robbins PD, Niedernhofer LJ. Role of Cellular Senescence in Type II Diabetes. Endocrinology. 2021 Oct 1;162(10):bqab136. doi: 10.1210/endocr/bqab136. PMID: 34363464; PMCID: PMC8386762.

[70] Lee J, Yun JS, Ko SH. Advanced Glycation End Products and Their Effect on Vascular Complications in Type 2 Diabetes Mellitus. Nutrients. 2022 Jul 27;14(15):3086. doi: 10.3390/nu14153086. PMID: 35956261; PMCID: PMC9370094.

[71] Kudlova N, De Sanctis JB, Hajduch M. Cellular Senescence: Molecular Targets, Biomarkers, and Senolytic Drugs. Int J Mol Sci. 2022 Apr 10;23(8):4168. doi: 10.3390/ijms23084168. PMID: 35456986; PMCID: PMC9028163.

[72] Chaib, S., Tchkonia, T. & Kirkland, J.L. Cellular senescence and senolytics: the path to the clinic. *Nat Med* **28**, 1556–1568 (2022). https://doi.org/10.1038/s41591-022-01923-y

[73] Raffaele M, Vinciguerra M. The costs and benefits of senotherapeutics for human health. Lancet Healthy Longev. 2022 Jan;3(1):e67-e77. doi: 10.1016/S2666-7568(21)00300-7. PMID: 36098323.

[74] Varghese SS, Dhawan S. Senescence: a double-edged sword in beta-cell health and failure? Front Endocrinol (Lausanne). 2023 May 9;14:1196460. doi: 10.3389/fendo.2023.1196460. PMID: 37229454; PMCID: PMC10203573.

[75] Weir GC, Bonner-Weir S. Reduced glucose-induced first-phase insulin release is a danger signal that predicts diabetes. J Clin Invest. 2021 Jun 15;131(12):e150022. doi: 10.1172/JCI150022. PMID: 34128470; PMCID: PMC8203449.

[76] Zhao X, An X, Yang C, Sun W, Ji H, Lian F. The crucial role and mechanism of insulin resistance in metabolic disease. Front Endocrinol (Lausanne). 2023 Mar 28;14:1149239. doi: 10.3389/fendo.2023.1149239. PMID: 37056675; PMCID: PMC10086443.

[77] Li, M., Chi, X., Wang, Y. *et al.* Trends in insulin resistance: insights into mechanisms and therapeutic strategy. *Sig Transduct Target Ther* **7**, 216 (2022). https://doi.org/10.1038/s41392-022-01073-0

[78] Helman A, Klochendler A, Azazmeh N, Gabai Y, Horwitz E, Anzi S, Swisa A, Condiotti R, Granit RZ, Nevo Y, Fixler Y, Shreibman D, Zamir A, Tornovsky-Babeay S, Dai C, Glaser B, Powers AC, Shapiro AM, Magnuson MA, Dor Y, Ben-Porath I. p16(Ink4a)-induced senescence of pancreatic beta cells enhances insulin secretion. Nat Med. 2016 Apr;22(4):412-20. doi: 10.1038/nm.4054. Epub 2016 Mar 7. PMID: 26950362; PMCID: PMC5546206.

[79] Melo Dos Santos LS, Trombetta-Lima M, Eggen B, Demaria M. Cellular senescence in brain aging and neurodegeneration. Ageing Res Rev. 2024 Jan;93:102141. doi: 10.1016/j.arr.2023.102141. Epub 2023 Nov 27. PMID: 38030088.

[80] Safwan-Zaiter H, Wagner N, Wagner KD. P16INK4A-More Than a Senescence Marker. Life (Basel). 2022 Aug 28;12(9):1332. doi: 10.3390/life12091332. PMID: 36143369; PMCID: PMC9501954.

[81] Tenchov R, Sasso JM, Wang X, Zhou QA. Antiaging Strategies and Remedies: A Landscape of Research Progress and Promise. ACS Chem Neurosci. 2024 Feb 7;15(3):408-446. doi: 10.1021/acschemneuro.3c00532. Epub 2024 Jan 12. PMID: 38214973; PMCID: PMC10853939.

[82] 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 May 7;29(5):1045-1060.e10. doi: 10.1016/j.cmet.2019.01.021. Epub 2019 Feb 21. PMID: 30799288.

[83] Rubin de Celis MF, Bonner-Weir S. Reversing and modulating cellular senescence in beta cells, a new field of opportunities to treat diabetes. Front Endocrinol (Lausanne). 2023 Sep 26;14:1217729. doi: 10.3389/fendo.2023.1217729. PMID: 37822597; PMCID: PMC10562723.

[84] Cha J, Aguayo-Mazzucato C, Thompson PJ. Pancreatic β-cell senescence in diabetes: mechanisms, markers and therapies. Front Endocrinol (Lausanne). 2023 Aug 31;14:1212716. doi: 10.3389/fendo.2023.1212716.

PMID: 37720527; PMCID: PMC10501801.

[85] Blagov AV, Sukhorukov VN, Guo S, Zhang D, Popov MA, Orekhov AN. Impaired Mitochondrial Function in T-Lymphocytes as a Result of Exposure to HIV and ART. Cells. 2023 Apr 2;12(7):1072. doi: 10.3390/cells12071072. PMID: 37048145; PMCID: PMC10093108.

[86] Wiley, C.D., Campisi, J. The metabolic roots of senescence: mechanisms and opportunities for intervention. *Nat Metab* **3**, 1290–1301 (2021). https://doi.org/10.1038/s42255-021-00483-8

[87] Ou HL, Hoffmann R, González-López C, Doherty GJ, Korkola JE, Muñoz-Espín D. Cellular senescence in cancer: from mechanisms to detection. Mol Oncol. 2021 Oct;15(10):2634-2671. doi: 10.1002/1878-0261.12807. Epub 2020 Oct 22. PMID: 32981205; PMCID: PMC8486596.

[88] Tan H, Xu J, Liu Y. Ageing, cellular senescence and chronic kidney disease: experimental evidence. Curr Opin Nephrol Hypertens. 2022 May 1;31(3):235-243. doi: 10.1097/MNH.0000000000000782. Epub 2022 Feb 9. PMID: 35142744; PMCID: PMC9035037.

[89] Moiseeva V, Cisneros A, Cobos AC, Tarrega AB, Oñate CS, Perdiguero E, Serrano AL, Muñoz-Cánoves P. Context-dependent roles of cellular senescence in normal, aged, and disease states. FEBS J. 2023 Mar;290(5):1161-1185. doi: 10.1111/febs.16573. Epub 2022 Aug 2. PMID: 35811491.

[90] Sorokina AG, Orlova YA, Grigorieva OA, Novoseletskaya ES, Basalova NA, Alexandrushkina NA, Vigovskiy MA, Kirillova KI, Balatsky AV, Samokhodskaya LM, Danilova NV, Dyachkova UD, Kakotkin VV, Asratyan DA, Akopyan ZA, Efimenko AY. Correlations between biomarkers of senescent cell accumulation at the systemic, tissue and cellular levels in elderly patients. Exp Gerontol. 2023 Jun 15;177:112176. doi: 10.1016/j.exger.2023.112176. Epub 2023 Apr 24. PMID: 37080342.

[91] Hamsanathan S, Gurkar AU. Lipids as Regulators of Cellular Senescence. Front Physiol. 2022 Mar 4;13:796850. doi: 10.3389/fphys.2022.796850. PMID: 35370799; PMCID: PMC8965560.

[92] Nerstedt A, Smith U. The impact of cellular senescence in human adipose tissue. J Cell Commun Signal. 2023 Sep;17(3):563-573. doi: 10.1007/s12079-023-00769-4. Epub 2023 May 17. PMID: 37195383; PMCID: PMC10409694.

[93] Iacobini C, Vitale M, Haxhi J, Menini S, Pugliese G. Impaired Remodeling of White Adipose Tissue in Obesity and Aging: From Defective Adipogenesis to Adipose Organ Dysfunction. Cells. 2024 Apr 30;13(9):763. doi: 10.3390/cells13090763. PMID: 38727299; PMCID: PMC11083890.

[94] Arias, C., Álvarez-Indo, J., Cifuentes, M. *et al.* Enhancing adipose tissue functionality in obesity: senotherapeutics, autophagy and cellular senescence as a target. *Biol Res* **57**, 51 (2024). https://doi.org/10.1186/s40659-024-00531-z

[95] Pan XX, Yao KL, Yang YF, Ge Q, Zhang R, Gao PJ, Ruan CC, Wu F. Senescent T Cell Induces Brown Adipose Tissue "Whitening" *Via* Secreting IFN-γ. Front Cell Dev Biol. 2021 Mar 4;9:637424. doi: 10.3389/fcell.2021.637424. PMID: 33748126; PMCID: PMC7969812.

[96] De Fano M, Bartolini D, Tortoioli C, Vermigli C, Malara M, Galli F, Murdolo G. Adipose Tissue Plasticity in Response to Pathophysiological Cues: A Connecting Link between Obesity and Its Associated Comorbidities. Int J Mol Sci. 2022 May 14;23(10):5511. doi: 10.3390/ijms23105511. PMID: 35628322; PMCID: PMC9141504.

[97] Engelmann C, Tacke F. The Potential Role of Cellular Senescence in Non-Alcoholic Fatty Liver Disease. Int J Mol Sci. 2022 Jan 7;23(2):652. doi: 10.3390/ijms23020652. PMID: 35054837; PMCID: PMC8775400.

[98] Lee CH, Lui DT, Lam KS. Non-alcoholic fatty liver disease and type 2 diabetes: An update. J Diabetes Investig. 2022 Jun;13(6):930-940. doi: 10.1111/jdi.13756. Epub 2022 Feb 14. PMID: 35080136; PMCID: PMC9153839.

[99] Ogrodnik, M., Miwa, S., Tchkonia, T. *et al.* Cellular senescence drives age-dependent hepatic steatosis. *Nat Commun* **8**, 15691 (2017). https://doi.org/10.1038/ncomms15691

[100] Vetrano E, Rinaldi L, Mormone A, Giorgione C, Galiero R, Caturano A, Nevola R, Marfella R, Sasso FC. Non-alcoholic Fatty Liver Disease (NAFLD), Type 2 Diabetes, and Non-viral Hepatocarcinoma: Pathophysiological Mechanisms and New Therapeutic Strategies. Biomedicines. 2023 Feb 6;11(2):468. doi: 10.3390/biomedicines11020468. PMID: 36831004; PMCID: PMC9953066.

[101] Zha Y, Zhuang W, Yang Y, Zhou Y, Li H, Liang J. Senescence in Vascular Smooth Muscle Cells and Atherosclerosis. Front Cardiovasc Med. 2022 Jun 1;9:910580. doi: 10.3389/fcvm.2022.910580. PMID: 35722104; PMCID: PMC9198250.

[102] Shimizu I, Minamino T. Cellular Senescence in Arterial Diseases. J Lipid Atheroscler. 2020 Jan;9(1):79-91. doi: 10.12997/jla.2020.9.1.79. Epub 2020 Jan 8. PMID: 32821723; PMCID: PMC7379072.

[103] Greenberg HZE, Zhao G, Shah AM, Zhang M. Role of oxidative stress in calcific aortic valve disease and its therapeutic implications. Cardiovasc Res. 2022 May 6;118(6):1433-1451. doi: 10.1093/cvr/cvab142. PMID: 33881501; PMCID: PMC9074995.

[104] Gevaert AB, Shakeri H, Leloup AJ, Van Hove CE, De Meyer GRY, Vrints CJ, Lemmens K, Van Craenenbroeck EM. Endothelial Senescence Contributes to Heart Failure With Preserved Ejection Fraction in an Aging Mouse Model. Circ Heart Fail. 2017 Jun;10(6):e003806. doi: 10.1161/CIRCHEARTFAILURE.116.003806. PMID: 28611124.

[105] Walaszczyk A, Dookun E, Redgrave R, Tual-Chalot S, Victorelli S, Spyridopoulos I, Owens A, Arthur HM, Passos JF, Richardson GD. Pharmacological clearance of senescent cells improves survival and recovery in aged mice following acute myocardial infarction. Aging Cell. 2019 Jun;18(3):e12945. doi: 10.1111/acel.12945. Epub 2019 Mar 28. PMID: 30920115; PMCID: PMC6516151.

[106] Lin, H., Chen, X., Pan, J. *et al.* Secretion of miRNA-326-3p by senescent adipose exacerbates myocardial metabolism in diabetic mice. *J Transl Med* **20**, 278 (2022). https://doi.org/10.1186/s12967-022-03484-7

[107] Zhang YX, Ou MY, Yang ZH, Sun Y, Li QF, Zhou SB. Adipose tissue aging is regulated by an altered immune system. Front Immunol. 2023 Feb 17;14:1125395. doi: 10.3389/fimmu.2023.1125395. PMID: 36875140; PMCID: PMC9981968.

[108] Farr JN. Skeletal Senescence with Aging and Type 2 Diabetes. Endocrinol Metab (Seoul). 2023 Jun;38(3):295-301. doi: 10.3803/EnM.2023.1727. Epub 2023 Jun 14. PMID: 37312256; PMCID: PMC10323162.

[109] Gong X, Zeng X, Fu P. The impact of weight loss on renal function in individuals with obesity and type 2 diabetes: a comprehensive review. Front Endocrinol (Lausanne). 2024 Jan 31;15:1320627. doi: 10.3389/fendo.2024.1320627. PMID: 38362272; PMCID: PMC10867247.

[110] Eckhardt BA, Rowsey JL, Thicke BS, Fraser DG, O'Grady KL, Bondar OP, Hines JM, Singh RJ, Thoreson AR, Rakshit K, Lagnado AB, Passos JF, Vella A, Matveyenko AV, Khosla S, Monroe DG, Farr JN. Accelerated osteocyte senescence and skeletal fragility in mice with type 2 diabetes. JCI Insight. 2020 May 7;5(9):e135236. doi: 10.1172/jci.insight.135236. PMID: 32267250; PMCID: PMC7253018.

[111] Sikora E, Bielak-Zmijewska A, Dudkowska M, Krzystyniak A, Mosieniak G, Wesierska M, Wlodarczyk J. Cellular Senescence in Brain Aging. Front Aging Neurosci. 2021 Feb 25;13:646924. doi: 10.3389/fnagi.2021.646924. PMID: 33732142; PMCID: PMC7959760.

[112] Ogrodnik M, Zhu Y, Langhi LGP, Tchkonia T, Krüger P, Fielder E, Victorelli S, Ruswhandi RA, Giorgadze N, Pirtskhalava T, Podgorni O, Enikolopov G, Johnson KO, Xu M, Inman C, Palmer AK, Schafer M, Weigl M, Ikeno Y, Burns TC, Passos JF, von Zglinicki T, Kirkland JL, Jurk D. Obesity-Induced Cellular Senescence Drives Anxiety and Impairs Neurogenesis. Cell Metab. 2019 May 7;29(5):1061-1077.e8. doi: 10.1016/j.cmet.2018.12.008. Epub 2019 Jan 3. Erratum in: Cell Metab. 2019 May 7;29(5):1233. doi: 10.1016/j.cmet.2019.01.013. PMID: 30612898; PMCID: PMC6509403.

[113] Shafqat A, Khan S, Omer MH, Niaz M, Albalkhi I, AlKattan K, Yaqinuddin A, Tchkonia T, Kirkland JL, Hashmi SK. Cellular senescence in brain aging and cognitive decline. Front Aging Neurosci. 2023 Nov 23;15:1281581. doi: 10.3389/fnagi.2023.1281581. PMID: 38076538; PMCID: PMC10702235.

[114] Khosla S, Farr JN, Monroe DG. Cellular senescence and the skeleton: pathophysiology and therapeutic implications. J Clin Invest. 2022 Feb 1;132(3):e154888. doi: 10.1172/JCI154888. PMID: 35104801; PMCID: PMC8803328.

[115] Wang, Y., Kuca, K., You, L. *et al.* The role of cellular senescence in neurodegenerative diseases. *Arch Toxicol* **98**, 2393–2408 (2024). https://doi.org/10.1007/s00204-024-03768-5

[116] Alexander N. Orekhov1,* , Volha I. Summerhill1,* , Victoria A. Khotina2, Mikhail A. Popov3, Jamol K. Uzokov4 and Vasily N. Sukhorukov1. Role of Mitochondria in the Chronification of Inflammation: Focus on Dysfunctional Mitophagy and Mitochondrial DNA Mutations. Gene Expression 2023;22(4):329-344. doi: 10.14218/GE.2023.00061

[117] Robbins PD, Jurk D, Khosla S, Kirkland JL, LeBrasseur NK, Miller JD, Passos JF, Pignolo RJ, Tchkonia T, Niedernhofer LJ. Senolytic Drugs: Reducing Senescent Cell Viability to Extend Health Span. Annu Rev Pharmacol Toxicol. 2021 Jan 6;61:779-803. doi: 10.1146/annurev-pharmtox-050120-105018. Epub 2020 Sep 30. PMID: 32997601; PMCID: PMC7790861.

[118] Joma N, Bielawski PB, Saini A, Kakkar A, Maysinger D. Nanocarriers for natural polyphenol senotherapeutics. Aging Cell. 2024 May;23(5):e14178. doi: 10.1111/acel.14178. Epub 2024 Apr 29. PMID: 38685568; PMCID: PMC11113259.

[119] Gasek, N.S., Kuchel, G.A., Kirkland, J.L. *et al.* Strategies for targeting senescent cells in human disease. *Nat*

Aging **1**, 870–879 (2021). https://doi.org/10.1038/s43587-021-00121-8

[120] Thompson EL, Pitcher LE, Niedernhofer LJ, Robbins PD. Targeting Cellular Senescence with Senotherapeutics: Development of New Approaches for Skin Care. Plast Reconstr Surg. 2022 Oct 1;150:12S-19S. doi: 10.1097/PRS.0000000000009668. Epub 2021 Sep 28. PMID: 36170431; PMCID: PMC9529240.

[121] Park J, Shin DW. Senotherapeutics and Their Molecular Mechanism for Improving Aging. Biomol Ther (Seoul). 2022 Nov 1;30(6):490-500. doi: 10.4062/biomolther.2022.114. Epub 2022 Oct 13. PMID: 36226551; PMCID: PMC9622307.

[122] Soverini, S., Mancini, M., Bavaro, L. *et al.* Chronic myeloid leukemia: the paradigm of targeting oncogenic tyrosine kinase signaling and counteracting resistance for successful cancer therapy. *Mol Cancer* **17**, 49 (2018). https://doi.org/10.1186/s12943-018-0780-6

[123] Dai X, Tian F, Xu Z, Kong X, Jiang P, Xia W, Zhu X. Philadelphia chromosome-positive acute lymphoblastic leukemia: a case report. Ann Palliat Med. 2021 Jan;10(1):742-748. doi: 10.21037/apm-20-469. Epub 2020 Sep 17. PMID: 32954738.

[124] Aguayo-Mazzucato C, Andle J, Lee TB Jr, Midha A, Talemal L, Chipashvili V, Hollister-Lock J, van Deursen J, Weir G, Bonner-Weir S. Acceleration of β Cell Aging Determines Diabetes and Senolysis Improves Disease Outcomes. Cell Metab. 2019 Jul 2;30(1):129-142.e4. doi: 10.1016/j.cmet.2019.05.006. Epub 2019 May 30. PMID: 31155496; PMCID: PMC6610720.

[125] Cha J, Aguayo-Mazzucato C, Thompson PJ. Pancreatic β-cell senescence in diabetes: mechanisms, markers and therapies. Front Endocrinol (Lausanne). 2023 Aug 31;14:1212716. doi: 10.3389/fendo.2023.1212716. PMID: 37720527; PMCID: PMC10501801.

[126] Rubin de Celis MF, Bonner-Weir S. Reversing and modulating cellular senescence in beta cells, a new field of opportunities to treat diabetes. Front Endocrinol (Lausanne). 2023 Sep 26;14:1217729. doi: 10.3389/fendo.2023.1217729. PMID: 37822597; PMCID: PMC10562723.

[127] Arias C, Álvarez-Indo J, Cifuentes M, Morselli E, Kerr B, Burgos PV. Enhancing adipose tissue functionality in obesity: senotherapeutics, autophagy and cellular senescence as a target. Biol Res. 2024 Aug 8;57(1):51. doi: 10.1186/s40659-024-00531-z. PMID: 39118171; PMCID: PMC11312694.

[128] Conley SM, Hickson LJ, Kellogg TA, McKenzie T, Heimbach JK, Taner T, Tang H, Jordan KL, Saadiq IM, Woollard JR, Isik B, Afarideh M, Tchkonia T, Kirkland JL, Lerman LO. Human Obesity Induces Dysfunction and Early Senescence in Adipose Tissue-Derived Mesenchymal Stromal/Stem Cells. Front Cell Dev Biol. 2020 Mar 26;8:197. doi: 10.3389/fcell.2020.00197. PMID: 32274385; PMCID: PMC7113401.

[129] An SM, Cho SH, Yoon JC. Adipose Tissue and Metabolic Health. Diabetes Metab J. 2023 Sep;47(5):595-611. doi: 10.4093/dmj.2023.0011. Epub 2023 Jul 24. PMID: 37482656; PMCID: PMC10555533.

[130] Yang H, Chen C, Chen H, Duan X, Li J, Zhou Y, Zeng W, Yang L. Navitoclax (ABT263) reduces inflammation and promotes chondrogenic phenotype by clearing senescent osteoarthritic chondrocytes in osteoarthritis. Aging (Albany NY). 2020 Jul 1;12(13):12750-12770. doi: 10.18632/aging.103177. Epub 2020 Jul 1. PMID: 32611834; PMCID: PMC7377880.

[131] Gulej R, Nyúl-Tóth Á, Ahire C, DelFavero J, Balasubramanian P, Kiss T, Tarantini S, Benyo Z, Pacher P, Csik B, Yabluchanskiy A, Mukli P, Kuan-Celarier A, Krizbai IA, Campisi J, Sonntag WE, Csiszar A, Ungvari Z. Elimination of senescent cells by treatment with Navitoclax/ABT263 reverses whole brain irradiation-induced blood-brain barrier disruption in the mouse brain. Geroscience. 2023 Oct;45(5):2983-3002. doi: 10.1007/s11357-023-00870-x. Epub 2023 Aug 29. PMID: 37642933; PMCID: PMC10643778.

[132] Sharma AK, Roberts RL, Benson RD Jr, Pierce JL, Yu K, Hamrick MW, McGee-Lawrence ME. The Senolytic Drug Navitoclax (ABT-263) Causes Trabecular Bone Loss and Impaired Osteoprogenitor Function in Aged Mice. Front Cell Dev Biol. 2020 May 20;8:354. doi: 10.3389/fcell.2020.00354. PMID: 32509782; PMCID: PMC7252306.

[133] Lorenzo EC, Torrance BL, Haynes L. Impact of senolytic treatment on immunity, aging, and disease. Front Aging. 2023 Oct 10;4:1161799. doi: 10.3389/fragi.2023.1161799. PMID: 37886012; PMCID: PMC10598643.

[134] de Lange P, Lombardi A, Silvestri E, Cioffi F, Giacco A, Iervolino S, Petito G, Senese R, Lanni A, Moreno M. Physiological Approaches Targeting Cellular and Mitochondrial Pathways Underlying Adipose Organ Senescence. Int J Mol Sci. 2023 Jul 19;24(14):11676. doi: 10.3390/ijms241411676. PMID: 37511435; PMCID: PMC10380998.

[135] Arabi T, Shafqat A, Sabbah BN, Fawzy NA, Shah H, Abdulkader H, Razak A, Sabbah AN, Arabi Z. Obesity-related kidney disease: Beyond hypertension and insulin-resistance. Front Endocrinol (Lausanne). 2023 Jan 16;13:1095211. doi: 10.3389/fendo.2022.1095211. PMID: 36726470; PMCID: PMC9884830.

[136] Cang S, Iragavarapu C, Savooji J, Song Y, Liu D. ABT-199 (venetoclax) and BCL-2 inhibitors in clinical development. J Hematol Oncol. 2015 Nov 20;8:129. doi: 10.1186/s13045-015-0224-3. PMID: 26589495; PMCID: PMC4654800.

[137] Lehmann, C., Friess, T., Birzele, F. *et al.* Superior anti-tumor activity of the MDM2 antagonist idasanutlin and the Bcl-2 inhibitor venetoclax in p53 wild-type acute myeloid leukemia models. *J Hematol Oncol* **9**, 50 (2016). https://doi.org/10.1186/s13045-016-0280-3

[138] Wang, B., Ni, Z., Dai, X. *et al.* The Bcl-2/xL inhibitor ABT-263 increases the stability of Mcl-1 mRNA and protein in hepatocellular carcinoma cells. *Mol Cancer* **13**, 98 (2014). https://doi.org/10.1186/1476-4598-13-98

[139] Gardner EE, Connis N, Poirier JT, Cope L, Dobromilskaya I, Gallia GL, Rudin CM, Hann CL. Rapamycin rescues ABT-737 efficacy in small cell lung cancer. Cancer Res. 2014 May 15;74(10):2846-56. doi: 10.1158/0008-5472.CAN-13-3460. Epub 2014 Mar 10. PMID: 24614082; PMCID: PMC4510983.

[140] Kim YJ, Witwit H, Cubitt B, de la Torre JC. Inhibitors of Anti-apoptotic Bcl-2 Family Proteins Exhibit Potent and Broad-Spectrum Anti-mammarenavirus Activity via Cell Cycle Arrest at G0/G1 Phase. J Virol. 2021 Nov 23;95(24):e0139921. doi: 10.1128/JVI.01399-21. Epub 2021 Sep 29. PMID: 34586865; PMCID: PMC8610586.

[141] Gorombei P, Guidez F, Ganesan S, Chiquet M, Pellagatti A, Goursaud L, Tekin N, Beurlet S, Patel S, Guerenne L, Le Pogam C, Setterblad N, de la Grange P, LeBoeuf C, Janin A, Noguera ME, Sarda-Mantel L, Merlet P, Boultwood J, Konopleva M, Andreeff M, West R, Pla M, Adès L, Fenaux P, Krief P, Chomienne C, Omidvar N, Padua RA. BCL-2 Inhibitor ABT-737 Effectively Targets Leukemia-Initiating Cells with Differential Regulation of Relevant Genes Leading to Extended Survival in a NRAS/BCL-2 Mouse Model of High Risk-Myelodysplastic Syndrome. Int J Mol Sci. 2021 Sep 30;22(19):10658. doi: 10.3390/ijms221910658. PMID: 34638998; PMCID: PMC8508829.

[142] Madiraju AK, Qiu Y, Perry RJ, Rahimi Y, Zhang XM, Zhang D, Camporez JG, Cline GW, Butrico GM, Kemp BE, Casals G, Steinberg GR, Vatner DF, Petersen KF, Shulman GI. Metformin inhibits gluconeogenesis via a redox-dependent mechanism in vivo. Nat Med. 2018 Sep;24(9):1384-1394. doi: 10.1038/s41591-018-0125-4. Epub 2018 Jul 23. Erratum in: Nat Med. 2019 Mar;25(3):526-528. doi: 10.1038/s41591-018-0220-6. PMID: 30038219; PMCID: PMC6129196.

[143] Chang W, Li W, Li P. The anti-diabetic effects of metformin are mediated by regulating long non-coding RNA. Front Pharmacol. 2023 Nov 20;14:1256705. doi: 10.3389/fphar.2023.1256705. PMID: 38053839; PMCID: PMC10694297.

[144] Acar MB, Ayaz-Güner Ş, Gunaydin Z, Karakukcu M, Peluso G, Di Bernardo G, Özcan S, Galderisi U. Proteomic and Biological Analysis of the Effects of Metformin Senomorphics on the Mesenchymal Stromal Cells. Front Bioeng Biotechnol. 2021 Oct 5;9:730813. doi: 10.3389/fbioe.2021.730813. PMID: 34676202; PMCID: PMC8524175.

[145] Al-Azab, M., Safi, M., Idiiatullina, E. *et al.* Aging of mesenchymal stem cell: machinery, markers, and strategies of fighting. *Cell Mol Biol Lett* **27**, 69 (2022). https://doi.org/10.1186/s11658-022-00366-0

[146] Mullen M, Nelson AL, Goff A, Billings J, Kloser H, Huard C, Mitchell J, Hambright WS, Ravuri S, Huard J. Fisetin Attenuates Cellular Senescence Accumulation During Culture Expansion of Human Adipose-Derived Stem Cells. Stem Cells. 2023 Jul 14;41(7):698-710. doi: 10.1093/stmcls/sxad036. PMID: 37279940; PMCID: PMC10346405.

[147] Stefanska B. Curcumin ameliorates hepatic fibrosis in type 2 diabetes mellitus - insights into its mechanisms of action. Br J Pharmacol. 2012 Aug;166(8):2209-11. doi: 10.1111/j.1476-5381.2012.01959.x. PMID: 22452372; PMCID: PMC3448887.

[148] Rahman MM, Dhar PS, Sumaia, Anika F, Ahmed L, Islam MR, Sultana NA, Cavalu S, Pop O, Rauf A. Exploring the plant-derived bioactive substances as antidiabetic agent: An extensive review. Biomed Pharmacother. 2022 Aug;152:113217. doi: 10.1016/j.biopha.2022.113217. Epub 2022 Jun 6. PMID: 35679719.

[149] Pivari F, Mingione A, Brasacchio C, Soldati L. Curcumin and Type 2 Diabetes Mellitus: Prevention and Treatment. Nutrients. 2019 Aug 8;11(8):1837. doi: 10.3390/nu11081837. PMID: 31398884; PMCID: PMC6723242.

[150] Hussain Y, Khan H, Alotaibi G, Khan F, Alam W, Aschner M, Jeandet P, Saso L. How Curcumin Targets Inflammatory Mediators in Diabetes: Therapeutic Insights and Possible Solutions. Molecules. 2022 Jun 24;27(13):4058. doi: 10.3390/molecules27134058. PMID: 35807304; PMCID: PMC9268477.

[151] Marton LT, Pescinini-E-Salzedas LM, Camargo MEC, Barbalho SM, Haber JFDS, Sinatora RV, Detregiachi

CRP, Girio RJS, Buchaim DV, Cincotto Dos Santos Bueno P. The Effects of Curcumin on Diabetes Mellitus: A Systematic Review. Front Endocrinol (Lausanne). 2021 May 3;12:669448. doi: 10.3389/fendo.2021.669448. PMID: 34012421; PMCID: PMC8126655.

[152] Li C, Miao X, Wang S, Adhikari BK, Wang X, Sun J, Liu Q, Tong Q, Wang Y. Novel Curcumin C66 That Protects Diabetes-Induced Aortic Damage Was Associated with Suppressing JNK2 and Upregulating Nrf2 Expression and Function. Oxid Med Cell Longev. 2018 Nov 28;2018:5783239. doi: 10.1155/2018/5783239. PMID: 30622669; PMCID: PMC6304198.

[153] Pourbagher-Shahri AM, Farkhondeh T, Ashrafizadeh M, Talebi M, Samargahndian S. Curcumin and cardiovascular diseases: Focus on cellular targets and cascades. Biomed Pharmacother. 2021 Apr;136:111214. doi: 10.1016/j.biopha.2020.111214. Epub 2021 Jan 12. PMID: 33450488.

[154] Shahcheraghi SH, Salemi F, Peirovi N, Ayatollahi J, Alam W, Khan H, Saso L. Nrf2 Regulation by Curcumin: Molecular Aspects for Therapeutic Prospects. Molecules. 2021 Dec 28;27(1):167. doi: 10.3390/molecules27010167. PMID: 35011412; PMCID: PMC8746993.

[155] Aguayo-Mazzucato C, Cha J, Thompson PJ. Editorial: Cellular senescence in diabetes: from markers to mechanisms and therapies. Front Endocrinol (Lausanne). 2023 Dec 18;14:1345529. doi: 10.3389/fendo.2023.1345529. PMID: 38164496; PMCID: PMC10757974.

[156] Suda M, Paul KH, Tripathi U, Minamino T, Tchkonia T, Kirkland JL. Targeting Cell Senescence and Senolytics: Novel Interventions for Age-Related Endocrine Dysfunction. Endocr Rev. 2024 Sep 12;45(5):655-675. doi: 10.1210/endrev/bnae010. PMID: 38500373; PMCID: PMC11405506.

[157] Kulkarni AS, Gubbi S, Barzilai N. Benefits of Metformin in Attenuating the Hallmarks of Aging. Cell Metab. 2020 Jul 7;32(1):15-30. doi: 10.1016/j.cmet.2020.04.001. Epub 2020 Apr 24. PMID: 32333835; PMCID: PMC7347426.

[158] Hela F, Aguayo-Mazzucato C. Interaction between Autophagy and Senescence in Pancreatic Beta Cells. Biology (Basel). 2023 Sep 4;12(9):1205. doi: 10.3390/biology12091205. PMID: 37759604; PMCID: PMC10525299.

[159] Dilworth L, Facey A, Omoruyi F. Diabetes Mellitus and Its Metabolic Complications: The Role of Adipose Tissues. Int J Mol Sci. 2021 Jul 16;22(14):7644. doi: 10.3390/ijms22147644. PMID: 34299261; PMCID: PMC8305176.

[160] Iwasaki K, Abarca C, Aguayo-Mazzucato C. Regulation of Cellular Senescence in Type 2 Diabetes Mellitus: From Mechanisms to Clinical Applications. Diabetes Metab J. 2023 Jul;47(4):441-453. doi: 10.4093/dmj.2022.0416. Epub 2023 Mar 6. PMID: 36872059; PMCID: PMC10404529..

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