Am J Physiol Heart Circ Physiol 315: H448–H462, 2018.
First published May 11, 2018; doi:10.1152/ajpheart.00287.2018.

REVIEW | *Signaling and Stress Response*

Cellular senescence links aging and diabetes in cardiovascular disease

Hadis Shakeri,[1] Katrien Lemmens,[1] Andreas B. Gevaert,[1,2] Guido R. Y. De Meyer,[1] and Vincent F. M. Segers[1,3]

[1]*Laboratory of Physiopharmacology, University of Antwerp, Antwerp, Belgium;* [2]*Laboratory for Cellular and Molecular Cardiology, Department of Cardiology, University Hospital Antwerp, Edegem, Belgium; and* [3]*Department of Cardiology, University Hospital Antwerp, Edegem, Belgium*

Submitted 8 May 2018; accepted in final form 8 May 2018

Shakeri H, Lemmens K, Gevaert AB, De Meyer GR, Segers VF. Cellular senescence links aging and diabetes in cardiovascular disease. *Am J Physiol Heart Circ Physiol* 315: H448–H462, 2018. First published May 11, 2018; doi:10.1152/ajpheart.00287.2018.—Aging is a powerful independent risk factor for cardiovascular diseases such as atherosclerosis and heart failure. Concomitant diabetes mellitus strongly reinforces this effect of aging on cardiovascular disease. Cellular senescence is a fundamental mechanism of aging and appears to play a crucial role in the onset and prognosis of cardiovascular disease in the context of both aging and diabetes. Senescent cells are in a state of cell cycle arrest but remain metabolically active by secreting inflammatory factors. This senescence-associated secretory phenotype is a trigger of chronic inflammation, oxidative stress, and decreased nitric oxide bioavailability. A complex interplay between these three mechanisms results in age- and diabetes-associated cardiovascular damage. In this review, we summarize current knowledge on cellular senescence and its secretory phenotype, which might be the missing link between aging and diabetes contributing to cardiovascular disease.

aging; cardiovascular diseases; cellular senescence, diabetes; senescence-associated secretory phenotype

INTRODUCTION

Aging is a major risk factor for the occurrence of several diseases, including stroke, myocardial infarction, Alzheimer's disease, and several types of cancer. Therefore, the global rise in life expectancy will lead to a dramatic increase in age-related diseases in the coming decades. In this context, cardiovascular diseases including atherosclerosis and heart failure (HF) increase exponentially with age. Moreover, type 2 diabetes mellitus (T2DM) is closely linked to aging and is a major risk factor for age-associated diseases such as atherosclerosis and HF (12). This epidemiological connection between aging, T2DM, and cardiovascular diseases indicates that there could also be a pathophysiological link.

The aging process itself and how it interacts with diseases is incompletely understood. Aging has been associated with a change in metabolic pathways. For instance, insulin resistance and changes in body composition are important age-related mechanisms causing diabetes (130). In addition, aging has also been associated with systemic inflammation (53), which can be a cause as well as a consequence of diabetes.

Cellular senescence can be defined as a permanent arrest of cellular growth. Although senescent cells do not proliferate, they have the capacity to produce and secrete soluble factors that can influence neighboring cells and tissues (197). Secretion of these soluble factors by senescent cells has been called the senescence-associated secretory phenotype (SASP) (29). Since chronic inflammation is an important pathophysiological factor of both aging and diabetes, the SASP could be a pathophysiological link between aging and diabetes in cardiovascular diseases (Fig. 1).

Cellular senescence is conserved among species during evolution, indicating its crucial role in embryological development and in physiology of the adult organism (1). Senescence has been studied in many different organisms, including *Caenorhabditis elegans*, flies, fishes, rodents, nonhuman primates, and humans (104). Cellular senescence can be considered part of the cellular stress response, which is a complex set of mechanisms that ensure survival of healthy cells and removal of damaged cells during environmental stress (101). In the last four decades, there has been a great deal of effort to extend lifespan using gene manipulation in model systems such as *C. elegans*, *Drosophila*, and mice (123). Collectively, these studies fall under the term "geroscience," which describes scientific endeavors to better understand the biology of aging (123). The ultimate goal is to increase lifespan and improve the health of the elderly (164). In recent years, pharmacological approaches are being developed based on these genetic experiments to extend lifespan (123).

Address for reprint requests and other correspondence: V. F. Segers, Laboratory of Physiopharmacology, Univ. of Antwerp, Universiteitsplein 1, Antwerp 2610, Belgium (e-mail: Vincent.segers@uantwerpen.be).

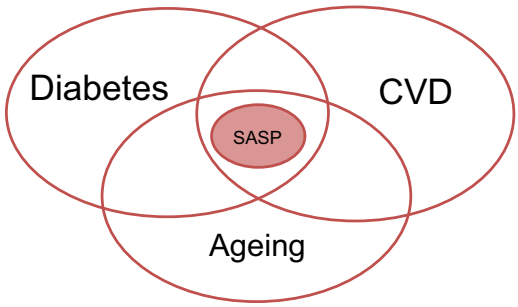

Fig. 1. Aging is a risk factor for both diabetes and cardiovascular disease, and cellular senescence is also a link between diabetes and many cardiovascular diseases including atherosclerosis and heart failure. CVD, cardiovascular disease; SASP, senescence-associated secretory phenotype.

In this review, we summarize current knowledge on the role of cellular senescence and the SASP in aging, diabetes, and cardiovascular diseases such as atherosclerosis and HF. First, we describe senescence and its associated secretory phenotype as a fundamental mechanism of aging and of diabetes. Next, we connect cellular senescence in both aging and diabetes and, finally, the link between cellular senescence and the cardiovascular complications of aging and diabetes are explored. On the basis of emerging evidence, we aim to explain how cellular senescence and the SASP may represent an important driver in the interaction of aging and diabetes in the pathophysiology of atherosclerosis and HF.

CELLULAR SENESCENCE AND AGING

Hayflick and colleagues (75, 76) initially described cellular senescence in 1961 as a permanent state of cell cycle arrest in response to DNA-damage. Cellular senescence is a fundamental feature of aging, but it was originally described as an important mechanism that prevents tumorigenesis by limiting proliferation of potential cancer cells (21, 158). To date, the causes of cellular senescence are relatively well defined, but the underlying molecular mechanisms and pathophysiological relevance remain incompletely understood.

How Do Cells Become Senescent?

Cellular senescence is in part due to telomere erosion after each cell cycle. DNA at the ends of chromosomes, telomeric DNA, is gradually lost because DNA polymerase has a limited capacity to initiate DNA synthesis at the ends of chromosomes (99). In addition, many cells have reduced or absent expression of telomerase, an enzyme that restores telomeric DNA (64, 73). Cellular senescence caused by telomere erosion and telomerase dysfunction or proliferative exhaustion (decreased proliferative capacity due to telomere shortening) is known as replicative senescence (119). When telomeres become critically short and can no longer protect the DNA structure, a DNA damage response will be initiated. The DNA damage response leads to cell cycle arrest caused by posttranslational changes in several cell cycle proteins such as p53, p16, and p21 (99).

Replicative senescence is not the only cause of cellular senescence. Senescence can be induced by different stress stimuli in the absence of telomere shortening. For instance, chronic exposure to oxidative stress, toxins, hyperglycemia, inflammation, and ultraviolet radiation can cause stress-induced premature senescence (SIPS) (103, 110, 124). When oxidative stress, toxins, or other stress stimuli cause DNA damage, cells produce a DNA damage response, which also results in arrest of cell-proliferation. If cells have been exposed to long-term stress, they lose their ability to repair DNA and enter a permanent cell cycle arrest before they reach the critically shortened telomeres. DNA damage is involved in the induction of cellular senescence either by telomere attrition (replicative senescence) or DNA-damaging agents (SIPS) (34, 157).

Senescent cells also show alterations in subcellular signaling pathways and expression levels of specific genes. Two major pathways, the p53/p21 and p16INK4a/retinoblastoma (Rb) pathways, orchestrate the development of cellular senescence (96). Inactivation of either p53 or p16 has been shown to increase the lifespan of different cell types regardless of telomere shortening (72). Senescent cells are also resistant to apoptosis, and inhibition of autophagy accelerates senescence (66). We (67) recently proposed the concept in which autophagy equals a fighting reaction, senescence equals an adaptation reaction, and apoptosis equals a surrendering reaction. Activation of intercellular signaling pathways in cellular senescence is complex and involves more pathways than will be discussed in this review; for a more in depth review of this subject, we refer the reader to excellent papers (42, 195). An interesting pathway regarding cellular senescence is the mammalian target of rapamycin (mTOR) pathway, which has been shown to promote aging in various models; e.g., in mice, inhibition of mTOR at an older age can significantly extend lifespan and mitigate age-related diseases (195). Inhibition of mTOR with rapamycin has also been shown to attenuate cellular senescence in many cultured cells (195).

The most important organelle for cellular senescence after the nucleus is the mitochondrion, as a major source of reactive oxygen species (ROS) in cells. Mitochondria produce more ROS when cells become senescent, leading to the accumulation of oxidant products such as carbonyls and lipofuscin (83). Although mitochondrial function in cellular senescence is largely associated with generation of oxidative stress and stress-induced senescence, there is also evidence showing the role of mitochondrial dysfunction and mitochondrial DNA damage in telomere shortening, causing replicative senescence. Furthermore, the telomerase enzyme, which is mainly responsible for telomere elongation, has protective effects against oxidative stress (128, 146).

Altered gene expression induces other changes in senescent cells and their neighboring microenvironment, which can be used to identify cellular senescence. The most important feature of senescent cells is their secretory phenotype. Indeed, senescent cells are nondividing but secrete a myriad of factors associated with inflammation, proliferation, and modulation of the extracellular matrix (3). Importantly, this SASP is not merely a marker of senescent cells but is also of pathophysiological relevance.

Secretory Phenotype of Senescent Cells: a Double-Edged Sword

As explained, senescent cells are nondividing with an active secretory phenotype. The secretome of senescent cells is complex, consisting of inflammatory and immune-modulatory cytokines and chemokines, including IL-1α, IL-1β, IL-6, and

IL-8 (100, 116, 118). Among these, IL-6 has been associated with DNA damage and stress-induced senescence in different cell types (100). IL-6 secretion by senescent cells directly affects all neighboring cells expressing the IL-6 receptor, including endothelial and epithelial cells (29). IL-1α and IL-1β trigger activation of the NF-κB pathway, which plays a key role in inflammation (25, 160). Both IL-1α and IL-1β also modulate cell proliferation, differentiation, and apoptosis (116). In addition, IL-1α regulates activation of the two other powerful inflammatory cytokines, IL-6 and IL-8, in senescent cells (141). This amplifying effect of SASP factors means that senescent cells can cause more cellular senescence. For instance, it has been shown that IL-6 (68), IL-1 (2), ROS (65), VEGF (2), chemokine (C-C motif) ligand 2 (CCL2) (2), and transforming growth factor-β (2) can induce senescence.

Senescent cells use the SASP as an ancient smoke signal to make themselves visible to the immune system to be eliminated (132, 196). In this way, cellular senescence prevents tumorigenesis. Cellular senescence is also considered to be beneficial in a number of other processes, including wound healing (40, 89), embryogenesis (131), cancer prevention (99), tissue regeneration (97), and the promotion of insulin secretion by pancreatic β-cells during aging (Table 1) (78).

Table 1. *Important SASP factors and their pathophysiological relevance in aging and diabetes*

SASP Factor	Mechanisms in Cellular Senescence	Pathology in Aging	Pathology in Diabetes	Beneficial Effects
Interleukin-6	● Proinflammatory cytokine ● Development, maintenance, and paracrine effect of cellular senescence (29, 100) ● Associated with DNA damage and stress-induced premature senescence (29)	● Atherosclerosis (111) ● Diabetes ● Cardiac dysfunction (153) ● Secreted by aged VSMCs in atherosclerotic plaques (111)	● Atherosclerosis (111) ● Diabetes ● Cardiac dysfunction (153) ● Insulin resistance (161)	● Embryogenesis (49) ● Cancer growth inhibition (97, 99, 109)
Interleukin-1α and interleukin-1β	● Upstream effectors of inflammatory pathways (80) ● Paracrine effects of cellular senescence ● Regulation of SASP	● Cause senescence via oxidative stress (2) ● Atherosclerosis (95)	● Insulin resistance (71)	● Cancer growth inhibition (109, 148)
Interleukin-8	● Paracrine effect of cellular senescence (30, 100)	● Atherosclerosis (173)	● Overexpression in diabetic conditions (127)	● Cancer growth inhibition (191) ● Wound healing (107)
NF-κB	● Direct cause of senescence (90) ● SASP regulation (160) ● Reinforces senescence (25, 87)	● Chronic inflammation ● Atherosclerosis (33)	● Diabetic cardiomyopathy (115, 202) ● Chronic inflammation	● Cancer growth inhibition (148, 191) ● Wound healing (156) ● Tissue regeneration (156)
Interferon-γ	● Important pathway of cellular senescence (56)	● Associated with inflammation during aging (31) ● Atherosclerosis (95)	● Cytotoxic for pancreatic β-cells by inducing reactive oxygen species (151) ● Causes disease progression (163)	● Cancer growth inhibition (81, 109)
Intracellular adhesion molecule 1	● Inflammatory factor	● Development of atherosclerosis (174)	● Biomarker of diabetes (69) ● Associated with higher cardiovascular mortality in patients with diabetes (188)	● Embryogenesis (35)
Vasclular endothelial growth factor	● Paracrine effect of cellular senescence (2)	● Atherosclerosis (174)		● Embryogenesis (169) ● Wound healing (172) ● Tissue regeneration (112)
Reactive oxygen species	● Causes of cellular senescence ● SASP factors	● Plaque formation in atherosclerosis (46) ● Endothelial dysfunction (98)	● Insulin resistance (43) ● Endothelial dysfunction (171) ● Atherosclerotic plaque instability (182)	● Embryogenesis (15) ● Cancer growth inhibition (191) ● Wound healing (89) ● Tissue regeneration (184)
Tumor necrosis factor-α	● Inflammatory mediator ● Regulation of SASP (150)	● Atherosclerosis (16) ● Related to telomere shortening (152)	● Diabetic cardiomyopathy (181) ● Atherosclerosis (139) ● Endothelial dysfunction (59) ● Insulitis (151)	● Cancer growth inhibition (109) ● Wound healing (62) ● Tissue regeneration (133)
Chemokine (C-C motif) ligand 2	● Inflammatory mediator	● Increases in aged vascular smooth muscle cells without another aging stimulus (174)	● Endothelial dysfunction ● Higher mortality caused by cardiovascular disease in patients with diabetes (188) ● Insulin resistance (44)	● Wound healing (62) ● Tissue regeneration (178)
Transforming growth factor-β	● Regulation of SASP via p21 cell cycle arrest (2) ● Paracrine effect of cellular senescence	● Related to some cancers	● Insulitis (151)	● Embryogenesis (131) ● Cancer growth inhibition (99) ● Wound healing (82)

SASP, senescence-associated secretory phenotype.

On the down side, however, the same SASP factors can locally cause tissue damage (Fig. 2). It has been shown that coculture of senescent cells with young cells causes premature cellular senescence in young cells via secreted SASP factors and via gap junction-mediated cell-cell contact (136). This paracrine effect of senescent cells is also present in vivo, as senescent cells induce p16 expression in their neighboring cells, and senescent fibroblasts alter differentiation of neighboring epithelial cells (19, 144). There is also a growth-inhibiting effect of the SASP on progenitor cells that compromises tissue renewal and repair (9).

Another important issue is that senescent cells accumulate in tissues because of their resistance to apoptosis, providing a continuous source of secreted SASP factors (26). There is evidence in the literature that cellular senescence and apoptosis are alternative cell fates, indicating that cells that become senescent could be more resistant to apoptosis. One example is the resistance of senescent fibroblasts to apoptosis by maintaining high levels of Bcl-2 (26). However, senescent endothelial cells seem to be more sensitive to apoptosis, demonstrating the heterogeneity of cellular senescence responses in different cell types (26, 200). For an in depth review of apoptosis resistance, we refer the reader to Ref. 26.

Thus, the SASP causes a persistent, self-reinforcing inflammatory microenvironment. Therefore, the SASP provides a potential explanation of how cellular senescence prevents tumorigenesis but causes aging and age-associated pathology. Recent evidence supports the idea that senescent cells drive age-related pathology (135). Accumulation of senescent cells coincides with the onset of age-associated diseases such as diabetes, hypertension, and atherosclerosis (125, 193). This has been demonstrated in an elegant study by Baker and colleagues (8, 10), in which they showed that removal of senescent cells attenuated the aging phenotype in human and mouse cells.

Markers of Cellular Senescence

Currently, there are no direct markers of cellular senescence, but a number of biological markers are used to detect senescent cells indirectly, among which senescence-associated β-galactosidase (SA-β-gal) activity is the most common. Lysosomal β-galactosidase activity is detectable only at a low pH (around pH 4) in normal cells but becomes detectable at a higher pH (pH 6) in senescent cells due to expansion of the lysosomal compartment (91). Other markers that are often used to detect cellular senescence are expressions of p16, p21, p38 MAPK, p53, and γH2AX, all associated with activation of the DNA damage response (24, 91). Also, high-mobility group A proteins or heterochromatin markers, including HP1 and trimethylated lysine 9 histone H3 (H3K9me3), are used as molecular markers of senescence-associated heterochromatin foci (91).

Cellular Senescence in the Cardiovascular System in Response to Aging

In a recent study using the senescence-accelerated mouse (SAM) model, cellular senescence in the heart and aorta was observed almost exclusively in endothelial cells but not in vascular smooth muscle cells (VSMCs) (61). These SAM mice develop cardiac fibrosis, diastolic dysfunction, and HF with preserved ejection fraction (HFpEF) when fed a Western-type diet (61, 154). HFpEF is the most common form of HF observed in the elderly (108). Interestingly, occurrence of cellular senescence in endothelial cells of SAM mice was independent of their diet (61). These data indicate that endothelial senescence is an obligatory factor in the development of HFpEF during aging but that it might be insufficient for induction of overt cardiac dysfunction in the absence of metabolic abnormalities. These data also highlight the importance of the endothelial system in normal cardiac physiology and during development of HFpEF (147, 168).

Markers of cellular senescence are activated not only in response to accelerated aging but also in response to hemody-

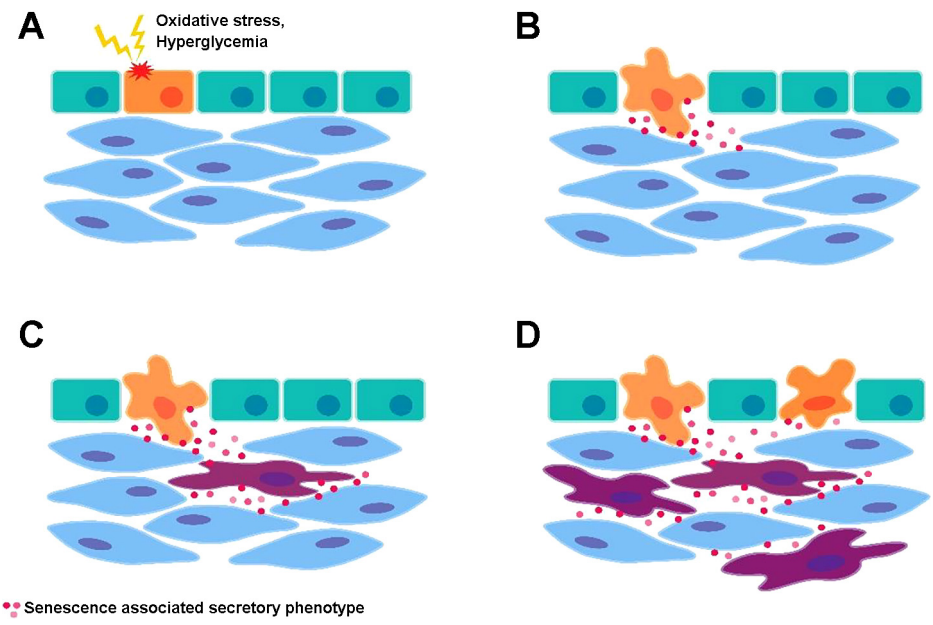

Fig. 2. *A*: cells enter a state of cell cycle arrest when oxidative stress, toxins, or proliferative exhaustion cause DNA damage. *B*: these cells then produce inflammatory factors to signal the immune system to remove them from tissue. These inflammatory factors include IL-1, IL-6, TNF-α, interferon-γ, reactive oxygen species (ROS), and chemokine (C-C motif) ligand 2 (CCL2). *C*: the inflammatory environment causes damage to neighboring cells, causing cellular senescence. *D*: senescent cells accumulate and cause further tissue damage.

namic stress. For instance, it has been shown that p53 signaling is activated in cardiac microvascular endothelial cells in response to left ventricular (LV) pressure overload (198). Increased expression of p53 in cardiac microvascular endothelial cells is accompanied by increased expression of ICAM-1, promoting infiltration of macrophages and cardiac inflammation. Consistently, depletion of p53 from cardiac microvascular endothelial cells results in suppression of ICAM-1 expression and inflammation in the myocardium (198). Inhibition of p53 in endothelial cells might be the basis for novel treatments of HFpEF.

CELLULAR SENESCENCE AND DIABETES

Diabetes mellitus is commonly divided into two types based on pathophysiology and clinical presentation (199). Type 1 diabetes mellitus (T1DM) is characterized by a loss of pancreatic β-cells and insulin production and commonly has its onset in the early decades of life. T2DM is characterized by normal plasma insulin levels and by resistance to insulin in peripheral organs. The incidence of T2DM increases with age, whereas T1DM is not necessarily an age-related disease but is rather an autoimmune disorder (199). However, because of hyperglycemia, long-standing T1DM commonly leads to an early onset of age-related diseases such as atherosclerosis and HF (199).

The interaction between cellular senescence and diabetes is complex (Fig. 3). Cellular senescence plays a role in T2DM pathophysiology through a direct impact on pancreatic β-cell function, SASP-mediated tissue damage, and involvement in adipose tissue dysfunction. On the other hand, pathological changes seen in both T1DM and T2DM, including high circulating glucose and altered lipid metabolism, can promote senescent cell formation (143).

The diabetic microenvironment promotes cellular senescence by high glucose levels, alterations in the growth hormone/insulin-like growth factor I signaling pathway, and upregulated ceramide synthesis, which, in turn, cause lipotoxicity (143). Both T1DM and T2DM have been shown to be associated with telomere shortening in different cell types (94, 113). In addition, aging and increased levels of oxidative stress cause telomere shortening in both types of diabetes (113). Furthermore, diabetic nephropathy appears to be associated with telomere length in both types of diabetes (58, 187). Currently, it remains hard to predict differences in cellular senescence between both types of diabetes. Because T2DM generally occurs in older patients compared with T1DM, the frequency of cellular senescence might be higher. On the other hand, in two patients of the same age, the one with longstanding T1DM probably has more senescent cells than the one with recent-onset T2DM.

CELLULAR SENESCENCE IS THE COMMON CELLULAR EVENT TO BOTH AGING AND DIABETES

Inflammation, oxidative stress, and subsequent impaired NO production are three commonly observed features of cellular

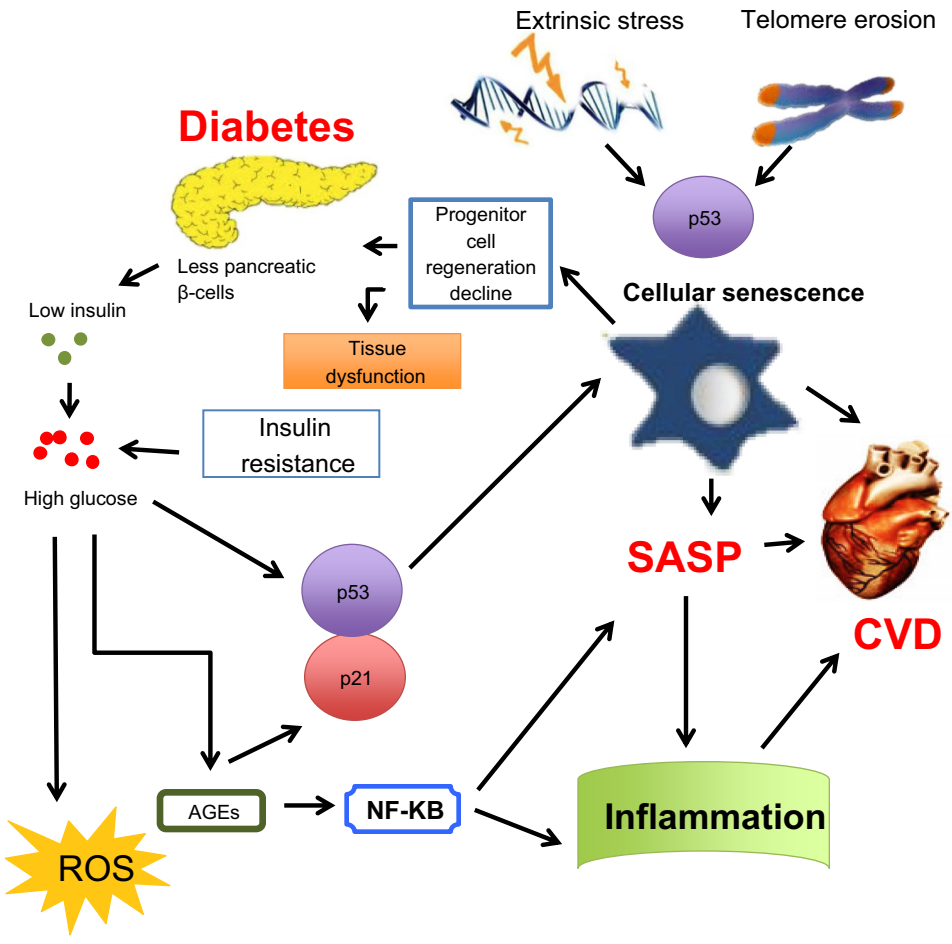

Fig. 3. Cellular senescence can take part in the onset and progression of diabetes with an important role for the inflammatory environment caused by the senescence-associated secretory phenotype (SASP). AGEs, advanced glycation end products; CVD, cardiovascular disease; ROS, reactive oxygen species.

senescence present in both aging and diabetes. Therefore, we give an overview of these three factors to explore the link between cellular senescence in aging and diabetes in the onset and prognosis of atherosclerosis and HF.

Senescent Cells Are Inflammatory Secretory Cells

As discussed above, cellular senescence is a process of cell cycle arrest in response to cellular and extracellular stimuli. However, when a cell becomes senescent and develops the SASP, it will also become an inflammatory secretory cell and influence the extracellular environment by secreting proinflammatory factors (Table 1). Proinflammatory SASP factors such as IL-1, IL-8, and IL-6 are considered to be premature markers of diabetes and its chronic complications (52, 189). Increasing evidence shows that the SASP contributes to impaired insulin signaling and glucose homeostasis. For example, IL-6 plays a crucial role in the development of insulin resistance, and its expression is elevated significantly in patients with T2DM (161). Therefore, increased levels of IL-6 are used as a robust predictor of the progression to T2DM. Other SASP factors, including IL-1β and monocyte chemoattractant protein-1, also correlate to insulin resistance (71). TNF-α, an important inflammatory marker and a strong SASP regulatory factor, has recently been associated with a higher incidence and mortality of cardiovascular diseases in diabetic patients (188). Although inflammatory factors constitute a large fraction of the SASP, not all inflammatory factors present in the circulation or even in local tissues will be derived from senescent cells. It is currently not clear to what extent the inflammatory factors that play a role in development of insulin resistance are derived from the SASP and thus senescent cells.

The underlying mechanism of several chronic diseases can, at least partially, be explained by chronic inflammation. It is already known that an inflammatory state of the arterial wall, initiated by aging, is a leading cause of atherosclerosis (77). In addition, inflammatory cytokines not only stimulate proliferation of VSMCs in the intima but also have multiple effects on endothelial function and influence deposition of extracellular matrix molecules like collagen and elastin (88, 175). Chronic inflammation is a pathophysiological hallmark of both diabetes and atherosclerosis.

Similarly, the SASP, with its inflammatory and oxidative stress characteristics, can be an underlying driver of age-associated HF. Senescent cardiac stem cells express high amounts of the inflammatory factor IL-1β (7). Increased levels of proinflammatory cytokines IL-6, IL-1β, TNF-α, and their downstream signaling pathway NF-κB are strongly associated with the onset and prognosis of HF (4). IL-6 expression has been demonstrated to cause cardiomyocyte hypertrophy and impaired LV function (153).

The link between the SASP, diabetes, and cardiovascular disease can partially be explained by the NF-κB pathway. Besides being a master modulator of inflammation, NF-κB is also a shared pathway in both diabetes and cellular senescence (33). Multiple SASP factors amplify the response of cellular senescence and are regulated by the NF-κB signaling pathway (36, 50, 160). Interestingly, an analysis of kinases regulating pro-senescence pathways shows that these are the same pathways triggered in T2DM. These data also support the role of p16 in T2DM susceptibility. Expression of p16 is increased significantly in tissue derived from patients with T2DM (50). Interestingly, although evidence points to cellular senescence as a source of chronic inflammation, it can also be an outcome of chronic inflammation. Chronic inflammation in genetically modified mice lacking a subunit of NF-κB leads to cellular senescence (90).

Accelerated Oxidative Stress: a Common Factor in Aging and Diabetes

An association between oxidative stress, cellular senescence, and age-related diseases has long been proposed. Plasma of elderly people displays increased markers of oxidative stress compared with young individuals (55). In addition to altered gene expression mentioned above, the mitochondrion is another focus point in the context of aging and cellular senescence. Oxidative stress generated by mitochondrial dysfunction has been established as an important cause of cellular senescence but also a consequence. Although the mechanisms by which mitochondrial dysfunction leads to cellular senescence are not fully explored, there is evidence that some mitochondrial signaling pathways contribute to cell cycle arrest and cellular senescence, including excessive ROS production, electron transport chain dysfunction, bioenergetics imbalance, and increased AMP-activated protein kinase activity, altered mitochondrial metabolism, and mitochondrial Ca^{2+} accumulation. Mitochondria of older people have increased ROS production, decreased ATP production, and decreased antioxidative capacity (122).

Atherosclerosis as a multifactorial disease is also associated with a long-term exposure to oxidative stress. Increased ROS generation is seen in vessel regions prone to atherosclerosis and in atherosclerotic plaques (46). Hyperglycemia is associated with an overproduction of ROS and a decrease in nitric oxide (NO) synthesis (17). This elevated ROS generation in diabetic conditions leads to an increased production of matrix metalloproteinases (MMPs) in endothelial cells, which is considered to be an important factor in development of vascular lesions and plaque instability (182). ROS accumulation in a transgenic mouse model leads to endothelial cell senescence and consequently to endothelial dysfunction (98).

The development and progression of diabetic cardiomyopathy has also been strongly associated with accelerated oxidative stress and mitochondrial dysfunction (92). The heart has relatively low endogenous antioxidant capacity, making it more susceptible to oxidative stress caused by any mitochondrial dysfunction. Increased ROS production in the heart has been associated with ventricular hypertrophy, impaired systolic and diastolic function, and altered insulin signaling (137, 194). Analysis of myocardial tissue in insulin-resistant rodents by transmission electron microscopy showed a great number of morphologically abnormal mitochondria (45, 137). Hyperglycemia-induced oxidative stress alters cardiac progenitor cell function, resulting in impaired cardiomyocyte formation and growth (159). This imbalance between cardiomyocyte formation and death in diabetic patients leads to premature myocardial aging and HF. Beyond this effect of high glucose levels, myocardial insulin resistance in T2DM, which is associated with altered mito-

chondrial dysfunction, is also an important underlying cause of diabetic cardiomyopathy (93, 192).

Impaired NO Signaling Pathway: Links Cellular Senescence to Diabetic Pathology

The endothelium is not only a mere mechanical barrier between the blood and vascular wall but is recognized as the most important active regulator of vascular homeostasis and is regarded as a very complex endocrine and paracrine organ (18, 168). NO synthase expressed in endothelial cells [endothelial NO synthase (eNOS)] is a crucial factor in vascular function, and the role of NO in endothelial cell function has been well established (18). Advanced age leads to reduced NO bioavailability, which contributes to age-related endothelial dysfunction. Endothelial senescence may be involved in this phenomenon because senescent endothelial cells have lower levels of eNOS activity and produce less NO (Fig. 4) (79, 120).

In addition, several studies have demonstrated that hyperglycemia and diabetes lead to impaired NO production and reduced vasodilatory capacity of the endothelium (114). The impaired NO production in diabetes is caused by lack of L-arginine availability, an important substrate for eNOS to produce NO. This shortage causes uncoupling of eNOS, which consequently leads to superoxide formation at the site of diabetic complications (11, 162). Both ROS and reduced NO production lead to endothelial dysfunction, an early feature of diabetic vascular disease (17). Interestingly, decreased NO production is related to the onset of chronic inflammation (74). Also, a study in porcine pulmonary artery endothelial cells showed that proinflammatory cytokines downregulate gene expression and activity of eNOS (201).

Endothelial dysfunction is considered a precursor of atherosclerotic disease. Again, NO is a central mediator, exerting several beneficial effects beyond vasodilation. NO inhibits oxidation of low-density lipoprotein, platelet aggregation, and VSMC proliferation, which all contribute to the atherosclerotic process (37). In patients with HF, endothelial dysfunction is very common and independently predicts mortality (38, 108). In HFpEF, reduced NO bioavailability has even been hypothesized to play a central role in its pathogenesis, inducing maladaptive changes in adjacent cardiomyocytes (hypertrophy, passive stiffness) and fibroblasts (increased collagen secretion), leading to diastolic dysfunction and HF (147).

ROLE OF DIABETES-ASSOCIATED SENESCENCE IN ACCELERATED AGING

In the arterial system, streptozotocin-induced T1DM in mice leads to cellular senescence in both endothelial cells and VSMCs (170). Cellular senescence in both cell types could be prevented by treatment with neuregulin-1, a member of the epidermal growth factor family (170, 185, 186). These findings indicate that neuregulin-1 might be a novel factor attenuating cellular senescence. Exposure of human aortic endothelial cells to high glucose levels leads to increased β-galactosidase expression and decreased telomerase activity, both markers of cellular senescence (120).

In myocardial tissue of rodents with T1DM and diabetic cardiomyopathy, abundant cellular senescence is observed in cardiomyocytes and cardiac microvascular endothelial cells (70, 91). Hyperglycemia leads to p53 activation in cardiomyocytes, which upregulates the renin-angiotensin system (51). Increased angiotensin II production leads to an increase in ROS formation and an increase in intracellular Ca^{2+} current, which both initiate telomere shortening, cellular senescence, and cell death (51). It has also been shown in these models that cardiomyocyte senescence can be prevented by inhibition of p53 (70). Moreover, data indicate that ROS production in diabetes induces cellular senescence in cardiac progenitor cells, raising the possibility that diabetic cardiomyopathy is in part a stem cell disease (159). However, more research is needed to determine to what extent cellular senescence contributes to the pathophysiology of diabetic cardiomyopathy.

Cellular senescence in the cardiovascular system seems to have different phenotypes depending on the causative factor being aging or diabetes. For instance, as indicated above, cellular senescence when induced by aging in both heart and vessels is mostly limited to endothelial cells (61), whereas when induced by diabetes it occurs in endothelial cells, VSMCs, and cardiomyocytes (170). Furthermore, the SASP has been shown to differ depending on the senescence-initiating stimulus being aging or disease (28).

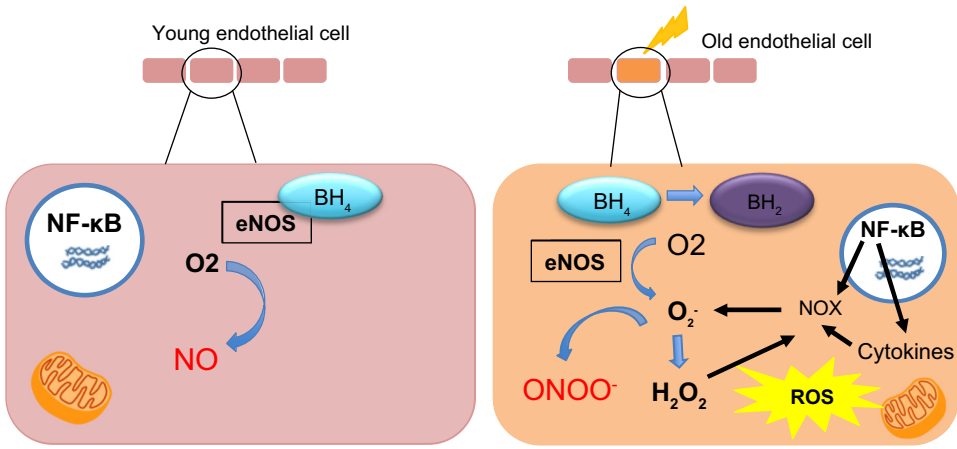

Fig. 4. Oxidative stress and inflammation reduce nitric oxide (NO) bioavailability in aged endothelial cells. Lack of tetrahydrobiopterin (BH4), a crucial cofactor of endothelial NO synthase (eNOS), leads to impaired NO bioavailability. In aged endothelial cells, high reactive oxygen species (ROS) production in mitochondria causes the conversion of NO to $ONOO^-$ mediated by NADPH oxidase (NOX), which leads to more ROS production. ROS cause further activation of the proinflammatory transcription factor NF-κB, which, in turn, activates NOX. BH_2, dihydrobiopterin; O_2^-, superoxide anion; $ONOO^-$, peroxynitrite.

ROLE OF AGE-ASSOCIATED SENESCENCE IN THE DEVELOPMENT OF DIABETES MELLITUS

Pancreatic Cellular Senescence

As discussed above, loss of pancreatic β-cells leading to loss of insulin production is the hallmark of T1DM. However, T1DM is not an age-related disorder, whereas T2DM clearly is. The hallmark of T2DM is insulin resistance in peripheral tissues such as skeletal muscles, but in advanced stages of the disease insulin production can be impaired as well (86). As a result of insulin resistance, pancreatic β-cell hyperplasia has been observed, which can lead to proliferative exhaustion and senescence of β-cells (140, 177). Furthermore, the number of pancreatic β-cells decreases with age because of a decline in turnover in elderly people (179). Besides a lower number of β-cells, senescence of β-cells can also lead to a decrease in insulin production in T2DM (180). However, the pathophysiology of pancreatic β-cell senescence appears to be complex, as it has been shown recently that induction of senescence in β-cells could also lead to increased insulin production (78).

Cellular Senescence Leading to Insulin Resistance

Chronic low-grade inflammation is thought to be an important factor for the development of insulin resistance (48, 143). Several components of the SASP, such as IL-8, IL-6, and monocyte chemoattractant protein-1, are increased in obese individuals and could contribute to a proinflammatory state. It has been shown in patients that that elevated IL-6 and the combined elevations of IL-6 and IL-1β are independent predictors of diabetes (143, 149, 176). It has been speculated that senescent cells, which accumulate in obesity and aging, may be the source of some of the inflammatory factors inducing insulin resistance and T2DM (143). However, more research is necessary to demonstrate the extent to which senescent cells contribute to this inflammatory state.

Other features of cellular senescence besides the SASP can contribute to the pathophysiology of diabetes. For instance, changes in senescence-associated genes such as p16 and p21 are correlated with the onset and prognosis of T2DM (117). Moreover, multiple lines of evidence support the hypothesis that age-associated mitochondrial dysfunction is linked to the pathophysiology of T2DM (93) and that accelerated oxidative stress caused by mitochondrial dysfunction in diabetes is one of the primary events leading to diabetic complications (32, 171). Several studies have also suggested the existence of an impaired antioxidant system in diabetic organs (22, 41). Also, the upregulated renin-angiotensin system in diabetes leads to increased oxidative damage and subsequently to cell death (57).

ROLE OF THE INTERACTION OF AGING AND DIABETES IN THE INCIDENCE OF CARDIOVASCULAR DISEASES

In the cardiovascular system, the secretory phenotype of senescent cardiovascular cells might promote structural and functional changes through chronic inflammation and extracellular matrix degradation. In this regard, atherosclerosis and HF are two major examples showing the pathophysiological role of cellular senescence in cardiovascular diseases.

Atherosclerosis is known to be an age-associated inflammatory disease (190). Senescence of endothelial cells, VSMCs, and their progenitor cells has been implicated to play a key role in the development of atherosclerosis (47, 134). Human coronary endothelial cells found on the surface of atherosclerotic plaques display morphological features of premature senescence (126). Likewise, VSMCs isolated from atherosclerotic vessels show an earlier growth arrest in vitro compared with cells derived from healthy vessels (47). Advanced atherosclerotic lesions consist of a necrotic core covered by a fibrous cap. VSMCs play multiple roles in atherosclerosis, including stabilization of the fibrous cap (67). Loss of VSMCs leads to thinning of the fibrous cap, promotes growth of the necrotic core, and could eventually lead to plaque rupture (67). VSMCs in atherosclerotic plaques show signs of cellular senescence, such as increased SA-β-Gal activity, upregulation of cell cycle regulators (p16 and p21), decreased telomerase activity, and telomere shortening (63, 121, 129). Telomere shortening in atherosclerotic plaques is strongly associated with severity of atherosclerosis (121). A recent study by Childs et al. (27) elegantly demonstrated that senescent cells increase atheroma formation at different stages of disease in a transgenic mouse model of atherosclerosis. More specifically, foamy macrophages showing cellular senescence are drivers of atheroma formation and plaque instability (27). Deletion of senescence cells in this mouse model of atherosclerosis increases plaque thickness and VSMC multiplicity while reducing inflammation (27). In general, VSMC proliferation in atherosclerotic plaques seems to be beneficial and VSMC senescence seems to be detrimental. However, VSMC biology in atherosclerosis is complex, with many unanswered questions (13).

The SASP of senescent cells in atherosclerotic plaques also plays important roles in disease progression (13). For instance, microarray analysis of genes expressed by senescent VSMCs showed that upregulated genes in these cells play a role in either inflammation (IL-1β, IL-8, ICAM-1, and CCL2) or tissue remodeling (VEGF and MMPs) (20). Furthermore, aged VSMCs may represent a major source of inflammatory cytokines during atherosclerosis (44). As shown in Table 1, many of the inflammatory cytokines of the SASP accelerate the progression of atherosclerosis by attracting inflammatory cells (44).

Furthermore, increased oxidative stress and decreased NO bioavailability are also hallmarks of atherosclerosis (74). Reduced NO bioavailability, which leads to endothelial dysfunction, has been shown to precede plaque formation in atherosclerosis (54). These two factors play a crucial role in the pathogenesis of cellular senescence as well.

HF is a common health condition with an increasing prevalence in the older population. HF is characterized by functional and structural alterations in the heart (38, 165). These changes can be partially explained by cardiac aging at a cellular level. Cardiomyocytes generally do not proliferate, and this low renewal capacity leads to a continuous loss of myocytes during aging (166). This reduction is usually compensated for by reactive hypertrophy of the remaining cells and expansion of the extracellular matrix. Thus, with age, the heart typically displays cardiomyocyte hypertrophy and increased interstitial collagen deposition, leading to diastolic dysfunction (5).

Increasing evidence shows a paramount role of senescent cardiomyocytes in the pathophysiology of age-related HF at a cellular level (23). First, cardiac stem cells isolated from failing hearts demonstrate features of cellular senescence in vitro (7).

Table 2. *Experimental rodent models to study senescence in cardiovascular disease*

	Model Description	Reference
Transgenic models		
INK-ATTAC	Selective ablation of senescent cells	8
p16-3MR	Ablation and tracking of senescent cells	40
p16(INK4a)-luciferase	In vivo tracking of senescent cells	19
Models of atherosclerosis		
apoE$^{-/-}$C1039G$^{+/-}$	Vulnerable plaque model	183
apoE$^{-/-}$	Atherosclerosis	60
LDLR$^{-/-}$	Atherosclerosis	60
Heart failure models		
Left anterior descending coronary artery ligation	Ischemic cardiomyopathy model	167
Aortic banding	Hypertrophic cardiac remodeling	105
Doxorubicin	Toxic cardiomyopathy model	84
Senescence-accelerated mice	Heart failure with preserved ejection fraction	61

ATTAC, apoptosis through targeted activation; apoE. apolipoportien E; LDLR, low-density lipoprotein receptor.

Also, telomere shortening and high p53 expression in cardiomyocytes of telomerase knockout (Terc$^{-/-}$) mice result in severe LV failure and premature death (106). It has also been shown that deletion of senescent p16(Ink4a)-positive cells in mice increases their lifespan but also delays the onset of age-related cardiac histopathological findings (8). Deletion of p16(Ink4a)-positive cells does not change overall cardiac mass but results in smaller and probably more numerous cardiomyocytes, indicating that p16(Ink4a)-positive senescent cells play a driving role in development of age-related cardiac pathology (8).

As stated above, diabetes is associated with increased cardiovascular risk and worse overall prognosis. As both T2DM and cardiovascular diseases are age related, we propose cellular senescence and the SASP as the underlying mechanism linking both diseases. Here, we summarize some evidence supporting this view.

Atherosclerotic cardiovascular disease is the major cause of mortality in patients with diabetes (138, 145). In patients, high glucose levels and lipid concentrations remain independent risk factors for the development of atherosclerosis (14, 138). However, studies in rodents have suggested that hyperglycemia could be more important than lipid abnormalities in the pathophysiology of atherosclerosis (Table 2) (155). On the other hand, large clinical trials have clearly demonstrated that glucose control in T1DM decreases the incidence of cardiovascular events, whereas the link between intensive glucose control and a decrease in cardiovascular risk in patients with T2DM is less pronounced (6). In general, the relative contributions of hyperglycemia and lipid abnormalities in atherosclerotic plaque formation are difficult to distinguish because of the lack of precise animal models (6).

Patients with T2DM have a threefold increased risk of myocardial infarction compared with healthy subjects (39). HF is also a leading mortality cause in patients with diabetes (39). High glucose levels in T2DM promote the formation of advanced glycation end products, which are particularly prone to cross-link with extracellular proteins, such as collagen and elastin, altering their structural properties and leading to impaired cardiac relaxation and ventricular stiffness (85, 142). In addition, two important signaling pathways, NF-κB and MAPK, are associated with cardiac dysfunction in diabetes, in part because of their role in chronic inflammation and ROS production (115).

CONCLUSIONS

Aging is considered to be the most important independent risk factor for cardiovascular diseases such as atherosclerosis and HF (164). In addition, the existence of concomitant age-associated diseases such as diabetes increases the risk of developing atherosclerosis and HF. Unraveling the incompletely understood cellular and molecular mechanisms behind aging is necessary to better prevent or cure these diseases.

In this review, we have linked aging and diabetes as important risk factors of cardiovascular disease to senescence and the SASP. Cellular senescence is a fundamental mechanism of aging and appears to play a crucial role in the onset and prognosis of cardiovascular disease. Senescence is both a cause and a consequence of diabetes and plays an important role in its cardiovascular complications. As such, senescence and the SASP could provide the missing link between aging, diabetes, and cardiovascular disease.

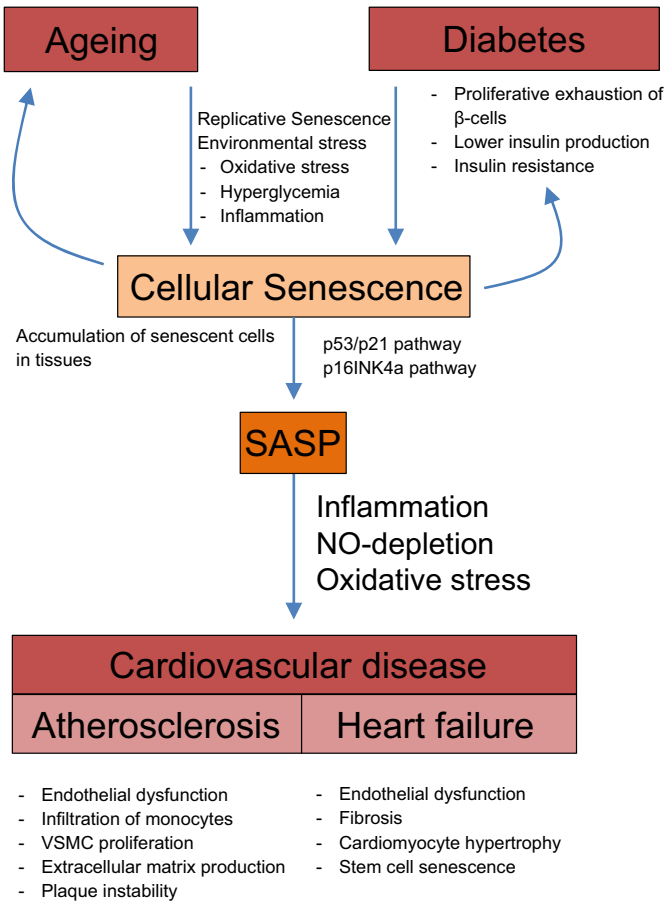

Fig. 5. Senescence-associated secretory phenotype (SASP) is a central factor in age- and diabetic-related cardiovascular disease (CVD). This paradigm may reveal new therapeutic possibilities. First, targeting the most important consequences of SASP [inflammation, oxidative stress, and reduced nitric oxide (NO) bioavailability] could prevent or treat associated CVD. Second, blockade of SASP production by senescent cells will attenuate the inflammatory environment causing cellular senescence in neighboring cells. VSMC, vascular smooth muscle cell.

Indeed, the SASP is a trigger of chronic inflammation, oxidative stress, and decreased NO bioavailability, which are hallmarks of all three pathologies. Senescent cells secrete a myriad of inflammatory mediators with NF-κB as their central regulator. Oxidative stress, with an important role for mitochondria, is both a cause and consequence of cellular senescence with an important role. Endothelial senescence reduces NO production through eNOS uncoupling, influencing neighboring cells such as cardiomyocytes and VSMCs. Eventually, a complex interplay among these different mechanisms results in age- and diabetes-associated cardiovascular damage.

The paradigm that the SASP is at the center of different age-associated pathologies (102) may lead to the discovery of new therapeutic avenues (Fig. 5). In a first approach, molecular determinants of the most important consequences of the SASP (inflammation, oxidative stress, and reduced NO bioavailability) can be targeted. This strategy is already being tested in both experimental and clinical studies, such as targeting inflammatory cytokines in atherosclerosis or increasing NO bioavailability in HF (16, 38). A second target is inhibition of SASP production by senescent cells. This novel approach would prevent the paracrine effect of senescent cells on neighboring cells, breaking the vicious circle of senescence induction and further SASP secretion and eventually reducing the inflammatory environment in the affected tissue. This strategy could be applied to prevent or treat cardiovascular disease, particularly in the context of aging and diabetes.

GRANTS

This work was supported by an Industrieel onderzoeksfonds - Strategisch basisonderzoek IOF-SBO grant from the University of Antwerp and by Fund for Scientific Research Flanders Grant1.5.011.18N.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

H.S. and V.S. prepared figures; H.S., K.L., and V.S. drafted manuscript; H.S., K.L., A.B.G., G.R.Y.D.M., and V.S. edited and revised manuscript; H.S., K.L., A.B.G., G.R.Y.D.M., and V.S. approved final version of manuscript.

REFERENCES

1. **Ackermann M, Chao L, Bergstrom CT, Doebeli M.** On the evolutionary origin of aging. *Aging Cell* 6: 235–244, 2007. doi:10.1111/j.1474-9726.2007.00281.x.
2. **Acosta JC, Banito A, Wuestefeld T, Georgilis A, Janich P, Morton JP, Athineos D, Kang T-W, Lasitschka F, Andrulis M, Pascual G, Morris KJ, Khan S, Jin H, Dharmalingam G, Snijders AP, Carroll T, Capper D, Pritchard C, Inman GJ, Longerich T, Sansom OJ, Benitah SA, Zender L, Gil J.** A complex secretory program orchestrated by the inflammasome controls paracrine senescence. *Nat Cell Biol* 15: 978–990, 2013. doi:10.1038/ncb2784.
3. **Acosta JC, O'Loghlen A, Banito A, Guijarro MV, Augert A, Raguz S, Fumagalli M, Da Costa M, Brown C, Popov N, Takatsu Y, Melamed J, d'Adda di Fagagna F, Bernard D, Hernando E, Gil J.** Chemokine signaling via the CXCR2 receptor reinforces senescence. *Cell* 133: 1006–1018, 2008. doi:10.1016/j.cell.2008.03.038.
4. **Anker SD, von Haehling S.** Inflammatory mediators in chronic heart failure: an overview. *Heart* 90: 464–470, 2004. doi:10.1136/hrt.2002.007005.
5. **Anversa P, Hiler B, Ricci R, Guideri G, Olivetti G.** Myocyte cell loss and myocyte hypertrophy in the aging rat heart. *J Am Coll Cardiol* 8: 1441–1448, 1986. doi:10.1016/S0735-1097(86)80321-7.
6. **Averill MM, Bornfeldt KE.** Lipids versus glucose in inflammation and the pathogenesis of macrovascular disease in diabetes. *Curr Diab Rep* 9: 18–25, 2009. doi:10.1007/s11892-009-0005-x.
7. **Avolio E, Gianfranceschi G, Cesselli D, Caragnano A, Athanasakis E, Katare R, Meloni M, Palma A, Barchiesi A, Vascotto C, Toffoletto B, Mazzega E, Finato N, Aresu G, Livi U, Emanueli C, Scoles G, Beltrami CA, Madeddu P, Beltrami AP.** Ex vivo molecular rejuvenation improves the therapeutic activity of senescent human cardiac stem cells in a mouse model of myocardial infarction. *Stem Cells* 32: 2373–2385, 2014. doi:10.1002/stem.1728.
8. **Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, Saltness RA, Jeganathan KB, Verzosa GC, Pezeshki A, Khazaie K, Miller JD, van Deursen JM.** Naturally occurring p16Ink4a-positive cells shorten healthy lifespan. *Nature* 530: 184–189, 2016. doi:10.1038/nature16932.
9. **Baker DJ, Weaver RL, van Deursen JM.** p21 both attenuates and drives senescence and aging in BubR1 progeroid mice. *Cell Rep* 3: 1164–1174, 2013. doi:10.1016/j.celrep.2013.03.028.
10. **Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, van de Sluis B, Kirkland JL, van Deursen JM.** Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature* 479: 232–236, 2011. doi:10.1038/nature10600.
11. **Bautista-Niño PK, Portilla-Fernandez E, Vaughan DE, Danser AHJ, Roks AJM.** DNA damage: a main determinant of vascular aging. *Int J Mol Sci* 17: 748, 2016. doi:10.3390/ijms17050748.
12. **Beckman JA, Creager MA, Libby P.** Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 287: 2570–2581, 2002. doi:10.1001/jama.287.19.2570.
13. **Bennett MR, Sinha S, Owens GK.** Vascular smooth muscle cells in atherosclerosis. *Circ Res* 118: 692–702, 2016. doi:10.1161/CIRCRESAHA.115.306361.
14. **Bertoluci MC, Rocha VZ.** Cardiovascular risk assessment in patients with diabetes. *Diabetol Metab Syndr* 9: 25, 2017. doi:10.1186/s13098-017-0225-1.
15. **Birket MJ, Casini S, Kosmidis G, Elliott DA, Gerencser AA, Baartscheer A, Schumacher C, Mastroberardino PG, Elefanty AG, Stanley EG, Mummery CL.** PGC-1α and reactive oxygen species regulate human embryonic stem cell-derived cardiomyocyte function. *Stem Cell Reports* 1: 560–574, 2013. doi:10.1016/j.stemcr.2013.11.008.
16. **Brånén L, Hovgaard L, Nitulescu M, Bengtsson E, Nilsson J, Jovinge S.** Inhibition of tumor necrosis factor-alpha reduces atherosclerosis in apolipoprotein E knockout mice. *Arterioscler Thromb Vasc Biol* 24: 2137–2142, 2004. doi:10.1161/01.ATV.0000143933.20616.1b.
17. **Bruder-Nascimento T, da Silva MA, Tostes RC.** The involvement of aldosterone on vascular insulin resistance: implications in obesity and type 2 diabetes. *Diabetol Metab Syndr* 6: 90, 2014. doi:10.1186/1758-5996-6-90.
18. **Brutsaert DL.** The indispensable role of cardiac endothelium in the structure and function of the heart. *Verh K Acad Geneeskd Belg* 65: 75–116, 2003.
19. **Burd CE, Sorrentino JA, Clark KS, Darr DB, Krishnamurthy J, Deal AM, Bardeesy N, Castrillon DH, Beach DH, Sharpless NE.** Monitoring tumorigenesis and senescence in vivo with a p16(INK4a)-luciferase model. *Cell* 152: 340–351, 2013. doi:10.1016/j.cell.2012.12.010.
20. **Burton DGA, Giles PJ, Sheerin ANP, Smith SK, Lawton JJ, Ostler EL, Rhys-Williams W, Kipling D, Faragher RGA.** Microarray analysis of senescent vascular smooth muscle cells: A link to atherosclerosis and vascular calcification. *Exp Gerontol* 44: 659–665, 2009. doi:10.1016/j.exger.2009.07.004.
21. **Campisi J, d'Adda di Fagagna F.** Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol* 8: 729–740, 2007. doi:10.1038/nrm2233.
22. **Ceriello A, Morocutti A, Mercuri F, Quagliaro L, Moro M, Damante G, Viberti GC.** Defective intracellular antioxidant enzyme production in type 1 diabetic patients with nephropathy. *Diabetes* 49: 2170–2177, 2000. doi:10.2337/diabetes.49.12.2170.
23. **Cesselli D, Beltrami AP, D'Aurizio F, Marcon P, Bergamin N, Toffoletto B, Pandolfi M, Puppato E, Marino L, Signore S, Livi U, Verardo R, Piazza S, Marchionni L, Fiorini C, Schneider C, Hosoda T, Rota M, Kajstura J, Anversa P, Beltrami CA, Leri A.** Effects of age and heart failure on human cardiac stem cell function. *Am J Pathol* 179: 349–366, 2011. doi:10.1016/j.ajpath.2011.03.036.
24. **Chen J, Huang X, Halicka D, Brodsky S, Avram A, Eskander J, Bloomgarden NA, Darzynkiewicz Z, Goligorsky MS.** Contribution of p16INK4a and p21CIP1 pathways to induction of premature senescence of human endothelial cells: permissive role of p53. *Am J Physiol Heart*

Circ Physiol 290: H1575–H1586, 2006. doi:10.1152/ajpheart.00364.2005.

25. **Chien Y, Scuoppo C, Wang X, Fang X, Balgley B, Bolden JE, Premsrirut P, Luo W, Chicas A, Lee CS, Kogan SC, Lowe SW.** Control of the senescence-associated secretory phenotype by NF-κB promotes senescence and enhances chemosensitivity. *Genes Dev* 25: 2125–2136, 2011. doi:10.1101/gad.17276711.
26. **Childs BG, Baker DJ, Kirkland JL, Campisi J, van Deursen JM.** Senescence and apoptosis: dueling or complementary cell fates? *EMBO Rep* 15: 1139–1153, 2014. doi:10.15252/embr.201439245.
27. **Childs BG, Baker DJ, Wijshake T, Conover CA, Campisi J, van Deursen JM.** Senescent intimal foam cells are deleterious at all stages of atherosclerosis. *Science* 354: 472–477, 2016. doi:10.1126/science.aaf6659.
28. **Childs BG, Durik M, Baker DJ, van Deursen JM.** Cellular senescence in aging and age-related disease: from mechanisms to therapy. *Nat Med* 21: 1424–1435, 2015. doi:10.1038/nm.4000.
29. **Coppé J-P, Desprez P-Y, Krtolica A, Campisi J.** The senescence-associated secretory phenotype: the dark side of tumor suppression. *Annu Rev Pathol* 5: 99–118, 2010. doi:10.1146/annurev-pathol-121808-102144.
30. **Coppé J-P, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, Nelson PS, Desprez P-Y, Campisi J.** Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol* 6: 2853–2868, 2008. doi:10.1371/journal.pbio.0060301.
31. **Costa E, Fernandes J, Ribeiro S, Sereno J, Garrido P, Rocha-Pereira P, Coimbra S, Catarino C, Belo L, Bronze-da-Rocha E, Vala H, Alves R, Reis F, Santos-Silva A.** Aging is associated with impaired renal function, INF-gamma induced inflammation and with alterations in iron regulatory proteins gene expression. *Aging Dis* 5: 356–365, 2013.
32. **Coughlan MT, Thorburn DR, Penfold SA, Laskowski A, Harcourt BE, Sourris KC, Tan ALY, Fukami K, Thallas-Bonke V, Nawroth PP, Brownlee M, Bierhaus A, Cooper ME, Forbes JM.** RAGE-induced cytosolic ROS promote mitochondrial superoxide generation in diabetes. *J Am Soc Nephrol* 20: 742–752, 2009. doi:10.1681/ASN.2008050514.
33. **Csiszar A, Wang M, Lakatta EG, Ungvari Z.** Inflammation and endothelial dysfunction during aging: role of NF-κB. *J Appl Physiol* 105: 1333–1341, 2008.
34. **d'Adda di Fagagna F.** Living on a break: cellular senescence as a DNA-damage response. *Nat Rev Cancer* 8: 512–522, 2008. doi:10.1038/nrc2440.
35. **Dalmau I, Vela JM, González B, Castellano B.** Expression of LFA-1α and ICAM-1 in the developing rat brain: a potential mechanism for the recruitment of microglial cell precursors. *Brain Res Dev Brain Res* 103: 163–170, 1997. doi:10.1016/S0165-3806(97)81792-0.
36. **Davalos AR, Coppe J-P, Campisi J, Desprez P-Y.** Senescent cells as a source of inflammatory factors for tumor progression. *Cancer Metastasis Rev* 29: 273–283, 2010. doi:10.1007/s10555-010-9220-9.
37. **Davignon J, Ganz P.** Role of endothelial dysfunction in atherosclerosis. *Circulation* 109, *Suppl* 1: III27–III32, 2004. doi:10.1161/01.CIR.0000131515.03336.f8.
38. **De Keulenaer GW, Segers VFM, Zannad F, Brutsaert DL.** The future of pleiotropic therapy in heart failure. Lessons from the benefits of exercise training on endothelial function. *Eur J Heart Fail* 19: 603–614, 2017. doi:10.1002/ejhf.735.
39. **De Rosa S, Arcidiacono B, Chiefari E, Brunetti A, Indolfi C, Foti DP.** Type 2 diabetes mellitus and cardiovascular disease: genetic and epigenetic links. *Front Endocrinol (Lausanne)* 9: 2, 2018. doi:10.3389/fendo.2018.00002.
40. **Demaria M, Ohtani N, Youssef SA, Rodier F, Toussaint W, Mitchell JR, Laberge R-M, Vijg J, Van Steeg H, Dollé MET, Hoeijmakers JHJ, de Bruin A, Hara E, Campisi J.** An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. *Dev Cell* 31: 722–733, 2014. doi:10.1016/j.devcel.2014.11.012.
41. **DeRubertis FR, Craven PA, Melhem MF.** Acceleration of diabetic renal injury in the superoxide dismutase knockout mouse: effects of tempol. *Metabolism* 56: 1256–1264, 2007. doi:10.1016/j.metabol.2007.04.024.
42. **Donato AJ, Morgan RG, Walker AE, Lesniewski LA.** Cellular and molecular biology of aging endothelial cells. *J Mol Cell Cardiol* 89: 122–135, 2015. doi:10.1016/j.yjmcc.2015.01.021.
43. **Dong K, Ni H, Wu M, Tang Z, Halim M, Shi D.** ROS-mediated glucose metabolic reprogram induces insulin resistance in type 2 diabetes. *Biochem Biophys Res Commun* 476: 204–211, 2016. doi:10.1016/j.bbrc.2016.05.087.
44. **Du W, Wong C, Song Y, Shen H, Mori D, Rotllan N, Price N, Dobrian AD, Meng H, Kleinstein SH, Fernandez-Hernando C, Goldstein DR.** Age-associated vascular inflammation promotes monocytosis during atherogenesis. *Aging Cell* 15: 766–777, 2016. doi:10.1111/acel.12488.
45. **Duncan JG, Fong JL, Medeiros DM, Finck BN, Kelly DP.** Insulin-resistant heart exhibits a mitochondrial biogenic response driven by the peroxisome proliferator-activated receptor-alpha/PGC-1alpha gene regulatory pathway. *Circulation* 115: 909–917, 2007. doi:10.1161/CIRCULATIONAHA.106.662296.
46. **Ekstrand M, Gustafsson Trajkovska M, Perman-Sundelin J, Fogelstrand P, Adiels M, Johansson M, Mattsson-Hultén L, Borén J, Levin M.** Imaging of intracellular and extracellular ROS levels in atherosclerotic mouse aortas ex vivo: effects of lipid lowering by diet or Atorvastatin. *PLoS One* 10: e0130898, 2015. doi:10.1371/journal.pone.0130898.
47. **Erusalimsky JD.** Vascular endothelial senescence: from mechanisms to pathophysiology. *J Appl Physiol* 106: 326–332, 2009.
48. **Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N.** Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res Clin Pract* 105: 141–150, 2014. doi:10.1016/j.diabres.2014.04.006.
49. **Fee D, Grzybicki D, Dobbs M, Ihyer S, Clotfelter J, Macvilay S, Hart MN, Sandor M, Fabry Z.** Interleukin 6 promotes vasculogenesis of murine brain microvessel endothelial cells. *Cytokine* 12: 655–665, 2000. doi:10.1006/cyto.1999.0599.
50. **Ferrand M, Kirsh O, Griveau A, Vindrieux D, Martin N, Defossez P-A, Bernard D.** Screening of a kinase library reveals novel pro-senescence kinases and their common NF-κB-dependent transcriptional program. *Aging (Albany NY)* 7: 986–1003, 2015. doi:10.18632/aging.100845.
51. **Fiordaliso F, Leri A, Cesselli D, Limana F, Safai B, Nadal-Ginard B, Anversa P, Kajstura J.** Hyperglycemia activates p53 and p53-regulated genes leading to myocyte cell death. *Diabetes* 50: 2363–2375, 2001. doi:10.2337/diabetes.50.10.2363.
52. **Forbes JM, Cooper ME.** Mechanisms of diabetic complications. *Physiol Rev* 93: 137–188, 2013. doi:10.1152/physrev.00045.2011.
53. **Franceschi C, Campisi J.** Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci* 69, *Suppl* 1: S4–S9, 2014. doi:10.1093/gerona/glu057.
54. **Fransen P, Van Assche T, Guns P-J, Van Hove CE, De Keulenaer GW, Herman AG, Bult H.** Endothelial function in aorta segments of apolipoprotein E-deficient mice before development of atherosclerotic lesions. *Pflugers Arch* 455: 811–818, 2008. doi:10.1007/s00424-007-0337-9.
55. **Franzoni F, Ghiadoni L, Galetta F, Plantinga Y, Lubrano V, Huang Y, Salvetti G, Regoli F, Taddei S, Santoro G, Salvetti A.** Physical activity, plasma antioxidant capacity, and endothelium-dependent vasodilation in young and older men. *Am J Hypertens* 18: 510–516, 2005. doi:10.1016/j.amjhyper.2004.11.006.
56. **Fridman AL, Tainsky MA.** Critical pathways in cellular senescence and immortalization revealed by gene expression profiling. *Oncogene* 27: 5975–5987, 2008. doi:10.1038/onc.2008.213.
57. **Frustaci A, Kajstura J, Chimenti C, Jakoniuk I, Leri A, Maseri A, Nadal-Ginard B, Anversa P.** Myocardial cell death in human diabetes. *Circ Res* 87: 1123–1132, 2000. doi:10.1161/01.RES.87.12.1123.
58. **Fyhrquist F, Tiitu A, Saijonmaa O, Forsblom C, Groop P-H; FinnDiane Study Group.** Telomere length and progression of diabetic nephropathy in patients with type 1 diabetes. *J Intern Med* 267: 278–286, 2010. doi:10.1111/j.1365-2796.2009.02139.x.
59. **Gao X, Belmadani S, Picchi A, Xu X, Potter BJ, Tewari-Singh N, Capobianco S, Chilian WM, Zhang C.** Tumor necrosis factor-alpha induces endothelial dysfunction in Lepr(db) mice. *Circulation* 115: 245–254, 2007. doi:10.1161/CIRCULATIONAHA.106.650671.
60. **Getz GS, Reardon CA.** Animal models of atherosclerosis. *Arterioscler Thromb Vasc Biol* 32: 1104–1115, 2012. doi:10.1161/ATVBAHA.111.237693.
61. **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* 10: e003806, 2017. doi:10.1161/CIRCHEARTFAILURE.116.003806.

62. **Glass GE, Chan JK, Freidin A, Feldmann M, Horwood NJ, Nanchahal J.** TNF-α promotes fracture repair by augmenting the recruitment and differentiation of muscle-derived stromal cells. *Proc Natl Acad Sci USA* 108: 1585–1590, 2011. doi:10.1073/pnas.1018501108.
63. **Gorenne I, Kavurma M, Scott S, Bennett M.** Vascular smooth muscle cell senescence in atherosclerosis. *Cardiovasc Res* 72: 9–17, 2006.
64. **Goytisolo FA, Blasco MA.** Many ways to telomere dysfunction: in vivo studies using mouse models. *Oncogene* 21: 584–591, 2002. doi:10.1038/sj.onc.1205085.
65. **Grahame TJ, Schlesinger RB.** Oxidative stress-induced telomeric erosion as a mechanism underlying airborne particulate matter-related cardiovascular disease. *Part Fibre Toxicol* 9: 21, 2012. doi:10.1186/1743-8977-9-21.
66. **Grootaert MO, da Costa Martins PA, Bitsch N, Pintelon I, De Meyer GR, Martinet W, Schrijvers DM.** Defective autophagy in vascular smooth muscle cells accelerates senescence and promotes neointima formation and atherogenesis. *Autophagy* 11: 2014–2032, 2015. doi:10.1080/15548627.2015.1096485.
67. **Grootaert MOJ, Moulis M, Roth L, Martinet W, Vindis C, Bennett MR, De Meyer GRY.** Vascular smooth muscle cell death, autophagy and senescence in atherosclerosis. *Cardiovasc Res* 114: 622–634, 2018. doi:10.1093/cvr/cvy007.
68. **Groppo R, Richter JD.** CPEB control of NF-kappaB nuclear localization and interleukin-6 production mediates cellular senescence. *Mol Cell Biol* 31: 2707–2714, 2011. doi:10.1128/MCB.05133-11.
69. **Gu HF, Ma J, Gu KT, Brismar K.** Association of intercellular adhesion molecule 1 (ICAM1) with diabetes and diabetic nephropathy. *Front Endocrinol (Lausanne)* 3: 179, 2013.
70. **Gu J, Wang S, Guo H, Tan Y, Liang Y, Feng A, Liu Q, Damodaran C, Zhang Z, Keller BB, Zhang C, Cai L.** Inhibition of p53 prevents diabetic cardiomyopathy by preventing early-stage apoptosis and cell senescence, reduced glycolysis, and impaired angiogenesis. *Cell Death Dis* 9: 82, 2018. doi:10.1038/s41419-017-0093-5.
71. **Handa M, Vanegas S, Maddux BA, Mendoza N, Zhu S, Goldfine ID, Mirza AM.** XOMA 052, an anti-IL-1β monoclonal antibody, prevents IL-1β-mediated insulin resistance in 3T3-L1 adipocytes. *Obesity (Silver Spring)* 21: 306–309, 2013. doi:10.1002/oby.20004.
72. **Hara E, Tsurui H, Shinozaki A, Nakada S, Oda K.** Cooperative effect of antisense-Rb and antisense-p53 oligomers on the extension of life span in human diploid fibroblasts, TIG-1. *Biochem Biophys Res Commun* 179: 528–534, 1991. doi:10.1016/0006-291X(91)91403-Y.
73. **Harley CB, Futcher AB, Greider CW.** Telomeres shorten during ageing of human fibroblasts. *Nature* 345: 458–460, 1990. doi:10.1038/345458a0.
74. **Harrison DG, Widder J, Grumbach I, Chen W, Weber M, Searles C.** Endothelial mechanotransduction, nitric oxide and vascular inflammation. *J Intern Med* 259: 351–363, 2006. doi:10.1111/j.1365-2796.2006.01621.x.
75. **Hayflick L.** The limited in vitro lifetime of human diploid cell strains. *Exp Cell Res* 37: 614–636, 1965. doi:10.1016/0014-4827(65)90211-9.
76. **Hayflick L, Moorhead PS.** The serial cultivation of human diploid cell strains. *Exp Cell Res* 25: 585–621, 1961. doi:10.1016/0014-4827(61)90192-6.
77. **Head T, Daunert S, Goldschmidt-Clermont PJ.** The aging risk and atherosclerosis: a fresh look at arterial homeostasis. *Front Genet* 8: 216, 2017. doi:10.3389/fgene.2017.00216.
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 AMJ, Magnuson MA, Dor Y, Ben-Porath I.** p16(Ink4a)-induced senescence of pancreatic beta cells enhances insulin secretion. *Nat Med* 22: 412–420, 2016. doi:10.1038/nm.4054.
79. **Hoffmann J, Haendeler J, Aicher A, Rössig L, Vasa M, Zeiher AM, Dimmeler S.** Aging enhances the sensitivity of endothelial cells toward apoptotic stimuli: important role of nitric oxide. *Circ Res* 89: 709–715, 2001. doi:10.1161/hh2001.097796.
80. **Hubackova S, Krejcikova K, Bartek J, Hodny Z.** IL1- and TGFβ-Nox4 signaling, oxidative stress and DNA damage response are shared features of replicative, oncogene-induced, and drug-induced paracrine 'bystander senescence'. *Aging (Albany NY)* 4: 932–951, 2012. doi:10.18632/aging.100520.
81. **Hubackova S, Kucerova A, Michlits G, Kyjacova L, Reinis M, Korolov O, Bartek J, Hodny Z.** IFNγ induces oxidative stress, DNA damage and tumor cell senescence via TGFβ/SMAD signaling-dependent induction of Nox4 and suppression of ANT2. *Oncogene* 35: 1236–1249, 2016. doi:10.1038/onc.2015.162.
82. **Huh MI, Kim YH, Park JH, Bae SW, Kim MH, Chang Y, Kim SJ, Lee SR, Lee YS, Jin EJ, Sonn JK, Kang SS, Jung JC.** Distribution of TGF-β isoforms and signaling intermediates in corneal fibrotic wound repair. *J Cell Biochem* 108: 476–488, 2009. doi:10.1002/jcb.22277.
83. **Hutter E, Renner K, Pfister G, Stöckl P, Jansen-Dürr P, Gnaiger E.** Senescence-associated changes in respiration and oxidative phosphorylation in primary human fibroblasts. *Biochem J* 380: 919–928, 2004. doi:10.1042/bj20040095.
84. **Jay SM, Murthy AC, Hawkins JF, Wortzel JR, Steinhauser ML, Alvarez LM, Gannon J, Macrae CA, Griffith LG, Lee RT.** An engineered bivalent neuregulin protects against doxorubicin-induced cardiotoxicity with reduced proneoplastic potential. *Circulation* 128: 152–161, 2013. doi:10.1161/CIRCULATIONAHA.113.002203.
85. **Jia G, DeMarco VG, Sowers JR.** Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. *Nat Rev Endocrinol* 12: 144–153, 2016. doi:10.1038/nrendo.2015.216.
86. **Jin W, Patti M-E.** Genetic determinants and molecular pathways in the pathogenesis of Type 2 diabetes. *Clin Sci* 116: 99–111, 2009.
87. **Jing H, Kase J, Dörr JR, Milanovic M, Lenze D, Grau M, Beuster G, Ji S, Reimann M, Lenz P, Hummel M, Dörken B, Lenz G, Scheidereit C, Schmitt CA, Lee S.** Opposing roles of NF-κB in anti-cancer treatment outcome unveiled by cross-species investigations. *Genes Dev* 25: 2137–2146, 2011. doi:10.1101/gad.17620611.
88. **Johnson JL.** Emerging regulators of vascular smooth muscle cell function in the development and progression of atherosclerosis. *Cardiovasc Res* 103: 452–460, 2014. doi:10.1093/cvr/cvu171.
89. **Jun J-I, Lau LF.** The matricellular protein CCN1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing. *Nat Cell Biol* 12: 676–685, 2010. doi:10.1038/ncb2070.
90. **Jurk D, Wilson C, Passos JF, Oakley F, Correia-Melo C, Greaves L, Saretzki G, Fox C, Lawless C, Anderson R, Hewitt G, Pender SL, Fullard N, Nelson G, Mann J, van de Sluis B, Mann DA, von Zglinicki T.** Chronic inflammation induces telomere dysfunction and accelerates ageing in mice. *Nat Commun* 2: 4172, 2014. doi:10.1038/ncomms5172.
91. **Katsuumi G, Shimizu I, Yoshida Y, Minamino T.** Vascular senescence in cardiovascular and metabolic diseases. *Front Cardiovasc Med* 5: 18, 2018. doi:10.3389/fcvm.2018.00018.
92. **Kayama Y, Raaz U, Jagger A, Adam M, Schellinger IN, Sakamoto M, Suzuki H, Toyama K, Spin JM, Tsao PS.** Diabetic cardiovascular disease induced by oxidative stress. *Int J Mol Sci* 16: 25234–25263, 2015. doi:10.3390/ijms161025234.
93. **Kim J-A, Wei Y, Sowers JR.** Role of mitochondrial dysfunction in insulin resistance. *Circ Res* 102: 401–414, 2008. doi:10.1161/CIRCRESAHA.107.165472.
94. **Kirchner H, Shaheen F, Kalscheuer H, Schmid SM, Oster H, Lehnert H.** The telomeric complex and metabolic disease. *Genes (Basel)* 8: 176, 2017. doi:10.3390/genes8070176.
95. **Kleemann R, Zadelaar S, Kooistra T.** Cytokines and atherosclerosis: a comprehensive review of studies in mice. *Cardiovasc Res* 79: 360–376, 2008. doi:10.1093/cvr/cvn120.
96. **Krizhanovsky V, Lowe SW.** Stem cells: the promises and perils of p53. *Nature* 460: 1085–1086, 2009. doi:10.1038/4601085a.
97. **Krizhanovsky V, Xue W, Zender L, Yon M, Hernando E, Lowe SW.** Implications of cellular senescence in tissue damage response, tumor suppression, and stem cell biology. *Cold Spring Harb Symp Quant Biol* 73: 513–522, 2008. doi:10.1101/sqb.2008.73.048.
98. **Kröller-Schön S, Jansen T, Schüler A, Oelze M, Wenzel P, Hausding M, Kerahrodi JG, Beisele M, Lackner KJ, Daiber A, Münzel T, Schulz E.** Peroxisome proliferator-activated receptor γ, coactivator 1α deletion induces angiotensin II-associated vascular dysfunction by increasing mitochondrial oxidative stress and vascular inflammation. *Arterioscler Thromb Vasc Biol* 33: 1928–1935, 2013. doi:10.1161/ATVBAHA.113.301717.
99. **Kuilman T, Michaloglou C, Mooi WJ, Peeper DS.** The essence of senescence. *Genes Dev* 24: 2463–2479, 2010. doi:10.1101/gad.1971610.
100. **Kuilman T, Michaloglou C, Vredeveld LCW, Douma S, van Doorn R, Desmet CJ, Aarden LA, Mooi WJ, Peeper DS.** Oncogene-induced

senescence relayed by an interleukin-dependent inflammatory network. *Cell* 133: 1019–1031, 2008. doi:10.1016/j.cell.2008.03.039.
101. **Kültz D.** Molecular and evolutionary basis of the cellular stress response. *Annu Rev Physiol* 67: 225–257, 2005. doi:10.1146/annurev.physiol.67.040403.103635.
102. **Lakatta EG.** So! What's aging? Is cardiovascular aging a disease? *J Mol Cell Cardiol* 83: 1–13, 2015. doi:10.1016/j.yjmcc.2015.04.005.
103. **Le ONL, Rodier F, Fontaine F, Coppe J-P, Campisi J, DeGregori J, Laverdière C, Kokta V, Haddad E, Beauséjour CM.** Ionizing radiation-induced long-term expression of senescence markers in mice is independent of p53 and immune status. *Aging Cell* 9: 398–409, 2010. doi:10.1111/j.1474-9726.2010.00567.x.
104. **Lees H, Walters H, Cox LS.** Animal and human models to understand ageing. *Maturitas* 93: 18–27, 2016. doi:10.1016/j.maturitas.2016.06.008.
105. **Lemmens K, Segers VF, Demolder M, Michiels M, Van Cauwelaert P, De Keulenaer GW.** Endogenous inhibitors of hypertrophy in concentric versus eccentric hypertrophy. *Eur J Heart Fail* 9: 352–356, 2007. doi:10.1016/j.ejheart.2006.10.002.
106. **Leri A, Franco S, Zacheo A, Barlucchi L, Chimenti S, Limana F, Nadal-Ginard B, Kajstura J, Anversa P, Blasco MA.** Ablation of telomerase and telomere loss leads to cardiac dilatation and heart failure associated with p53 upregulation. *EMBO J* 22: 131–139, 2003. doi:10.1093/emboj/cdg013.
107. **Liechty KW, Crombleholme TM, Cass DL, Martin B, Adzick NS.** Diminished interleukin-8 (IL-8) production in the fetal wound healing response. *J Surg Res* 77: 80–84, 1998. doi:10.1006/jsre.1998.5345.
108. **Lim SL, Lam CS, Segers VF, Brutsaert DL, De Keulenaer GW.** Cardiac endothelium-myocyte interaction: clinical opportunities for new heart failure therapies regardless of ejection fraction. *Eur Heart J* 36: 2050–2060, 2015. doi:10.1093/eurheartj/ehv132.
109. **Lin H, Yan J, Wang Z, Hua F, Yu J, Sun W, Li K, Liu H, Yang H, Lv Q, Xue J, Hu ZW.** Loss of immunity-supported senescence enhances susceptibility to hepatocellular carcinogenesis and progression in Toll-like receptor 2-deficient mice. *Hepatology* 57: 171–182, 2013. doi:10.1002/hep.25991.
110. **Liu P, Li C, Zhao Z, Lu G, Cui H, Zhang W.** Induced effects of advanced oxidation processes. *Sci Rep* 4: 4018, 2014. doi:10.1038/srep04018.
111. **Liu Y, Drozdov I, Shroff R, Beltran LE, Shanahan CM.** Prelamin A accelerates vascular calcification via activation of the DNA damage response and senescence-associated secretory phenotype in vascular smooth muscle cells. *Circ Res* 112: e99–e109, 2013. doi:10.1161/CIRCRESAHA.111.300543.
112. **Lynch K, Pei M.** Age associated communication between cells and matrix: a potential impact on stem cell-based tissue regeneration strategies. *Organogenesis* 10: 289–298, 2014. doi:10.4161/15476278.2014.970089.
113. **Ma D, Zhu W, Hu S, Yu X, Yang Y.** Association between oxidative stress and telomere length in Type 1 and Type 2 diabetic patients. *J Endocrinol Invest* 36: 1032–1037, 2013. doi:10.3275/9036.
114. **Madonna R, De Caterina R.** Cellular and molecular mechanisms of vascular injury in diabetes—part II: cellular mechanisms and therapeutic targets. *Vascul Pharmacol* 54: 75–79, 2011. doi:10.1016/j.vph.2011.03.007.
115. **Mariappan N, Elks CM, Sriramula S, Guggilam A, Liu Z, Borkhsenious O, Francis J.** NF-kappaB-induced oxidative stress contributes to mitochondrial and cardiac dysfunction in type II diabetes. *Cardiovasc Res* 85: 473–483, 2010. doi:10.1093/cvr/cvp305.
116. **Mariotti M, Castiglioni S, Bernardini D, Maier JAM.** Interleukin 1 alpha is a marker of endothelial cellular senescent. *Immun Ageing* 3: 4, 2006.
117. **Markowski DN, Thies HW, Gottlieb A, Wenk H, Wischnewsky M, Bullerdiek J.** HMGA2 expression in white adipose tissue linking cellular senescence with diabetes. *Genes Nutr* 8: 449–456, 2013. doi:10.1007/s12263-013-0354-6.
118. **Mason DX, Jackson TJ, Lin AW.** Molecular signature of oncogenic ras-induced senescence. *Oncogene* 23: 9238–9246, 2004. doi:10.1038/sj.onc.1208172.
119. **Masutomi K, Yu EY, Khurts S, Ben-Porath I, Currier JL, Metz GB, Brooks MW, Kaneko S, Murakami S, DeCaprio JA, Weinberg RA, Stewart SA, Hahn WC.** Telomerase maintains telomere structure in normal human cells. *Cell* 114: 241–253, 2003. doi:10.1016/S0092-8674(03)00550-6.
120. **Matsushita H, Chang E, Glassford AJ, Cooke JP, Chiu C-P, Tsao PS.** eNOS activity is reduced in senescent human endothelial cells: Preservation by hTERT immortalization. *Circ Res* 89: 793–798, 2001. doi:10.1161/hh2101.098443.
121. **Matthews C, Gorenne I, Scott S, Figg N, Kirkpatrick P, Ritchie A, Goddard M, Bennett M.** Vascular smooth muscle cells undergo telomere-based senescence in human atherosclerosis: effects of telomerase and oxidative stress. *Circ Res* 99: 156–164, 2006. doi:10.1161/01.RES.0000233315.38086.bc.
122. **McCarroll SA, Murphy CT, Zou S, Pletcher SD, Chin C-S, Jan YN, Kenyon C, Bargmann CI, Li H.** Comparing genomic expression patterns across species identifies shared transcriptional profile in aging. *Nat Genet* 36: 197–204, 2004. doi:10.1038/ng1291.
123. **Melov S.** Geroscience approaches to increase healthspan and slow aging. *F1000Res* 5: F1000 Faculty Rev-785, 2016. doi:10.12688/f1000research.7583.1.
124. **Mikhed Y, Daiber A, Steven S.** Mitochondrial oxidative stress, mitochondrial DNA damage and their role in age-related vascular dysfunction. *Int J Mol Sci* 16: 15918–15953, 2015. doi:10.3390/ijms160715918.
125. **Minamino T, Komuro I.** Vascular cell senescence: contribution to atherosclerosis. *Circ Res* 100: 15–26, 2007. doi:10.1161/01.RES.0000256837.40544.4a.
126. **Minamino T, Miyauchi H, Yoshida T, Ishida Y, Yoshida H, Komuro I.** Endothelial cell senescence in human atherosclerosis: role of telomere in endothelial dysfunction. *Circulation* 105: 1541–1544, 2002. doi:10.1161/01.CIR.0000013836.85741.17.
127. **Mohamed HG, Idris SB, Ahmed MF, Åstrøm AN, Mustafa K, Ibrahim SO, Mustafa M.** Influence of type 2 diabetes on local production of inflammatory molecules in adults with and without chronic periodontitis: a cross-sectional study. *BMC Oral Health* 15: 86, 2015. doi:10.1186/s12903-015-0073-z.
128. **Mora AL, Bueno M, Rojas M.** Mitochondria in the spotlight of aging and idiopathic pulmonary fibrosis. *J Clin Invest* 127: 405–414, 2017. doi:10.1172/JCI87440.
129. **Morgan RG, Ives SJ, Lesniewski LA, Cawthon RM, Andtbacka RHI, Noyes RD, Richardson RS, Donato AJ.** Age-related telomere uncapping is associated with cellular senescence and inflammation independent of telomere shortening in human arteries. *Am J Physiol Heart Circ Physiol* 305: H251–H258, 2013. doi:10.1152/ajpheart.00197.2013.
130. **Morley JE.** Diabetes and aging: epidemiologic overview. *Clin Geriatr Med* 24: 395–405, 2008. doi:10.1016/j.cger.2008.03.005.
131. **Muñoz-Espín D, Cañamero M, Maraver A, Gómez-López G, Contreras J, Murillo-Cuesta S, Rodríguez-Baeza A, Varela-Nieto I, Ruberte J, Collado M, Serrano M.** Programmed cell senescence during mammalian embryonic development. *Cell* 155: 1104–1118, 2013. doi:10.1016/j.cell.2013.10.019.
132. **Muñoz-Espín D, Serrano M.** Cellular senescence: from physiology to pathology. *Nat Rev Mol Cell Biol* 15: 482–496, 2014. doi:10.1038/nrm3823.
133. **Musarò A, Giacinti C, Pelosi L, Dobrowolny G, Barberi L, Nardis C, Coletti D, Scicchitano BM, Adamo S, Molinaro M.** Stem cell-mediated muscle regeneration and repair in aging and neuromuscular diseases. *Eur J Histochem* 51, *Suppl* 1: 35–43, 2007.
134. **Nakano-Kurimoto R, Ikeda K, Uraoka M, Nakagawa Y, Yutaka K, Koide M, Takahashi T, Matoba S, Yamada H, Okigaki M, Matsubara H.** Replicative senescence of vascular smooth muscle cells enhances the calcification through initiating the osteoblastic transition. *Am J Physiol Heart Circ Physiol* 297: H1673–H1684, 2009. doi:10.1152/ajpheart.00455.2009.
135. **Naylor RM, Baker DJ, van Deursen JM.** Senescent cells: a novel therapeutic target for aging and age-related diseases. *Clin Pharmacol Ther* 93: 105–116, 2013. doi:10.1038/clpt.2012.193.
136. **Nelson G, Wordsworth J, Wang C, Jurk D, Lawless C, Martin-Ruiz C, von Zglinicki T.** A senescent cell bystander effect: senescence-induced senescence. *Aging Cell* 11: 345–349, 2012. doi:10.1111/j.1474-9726.2012.00795.x.
137. **Nishio Y, Kanazawa A, Nagai Y, Inagaki H, Kashiwagi A.** Regulation and role of the mitochondrial transcription factor in the diabetic rat heart. *Ann N Y Acad Sci* 1011: 78–85, 2004. doi:10.1196/annals.1293.009.
138. **Norhammar A, Mellbin L, Cosentino F.** Diabetes: Prevalence, prognosis and management of a potent cardiovascular risk factor. *Eur J Prev Cardiol* 24: 52–60, 2017. doi:10.1177/2047487317709554.
139. **Ohta H, Wada H, Niwa T, Kirii H, Iwamoto N, Fujii H, Saito K, Sekikawa K, Seishima M.** Disruption of tumor necrosis factor-alpha

gene diminishes the development of atherosclerosis in ApoE-deficient mice. *Atherosclerosis* 180: 11–17, 2005. doi:10.1016/j.atherosclerosis.2004.11.016.

140. **Okamoto H, Hribal ML, Lin HV, Bennett WR, Ward A, Accili D.** Role of the forkhead protein FoxO1 in beta cell compensation to insulin resistance. *J Clin Invest* 116: 775–782, 2006. doi:10.1172/JCI24967.
141. **Orjalo AV, Bhaumik D, Gengler BK, Scott GK, Campisi J.** Cell surface-bound IL-1alpha is an upstream regulator of the senescence-associated IL-6/IL-8 cytokine network. *Proc Natl Acad Sci USA* 106: 17031–17036, 2009. doi:10.1073/pnas.0905299106.
142. **Ozasa N, Furukawa Y, Morimoto T, Tadamura E, Kita T, Kimura T.** Relation among left ventricular mass, insulin resistance, and hemodynamic parameters in type 2 diabetes. *Hypertens Res* 31: 425–432, 2008.
143. **Palmer AK, Tchkonia T, LeBrasseur NK, Chini EN, Xu M, Kirkland JL.** Cellular senescence in type 2 diabetes: a therapeutic opportunity. *Diabetes* 64: 2289–2298, 2015. doi:10.2337/db14-1820.
144. **Parrinello S, Coppe J-P, Krtolica A, Campisi J.** Stromal-epithelial interactions in aging and cancer: senescent fibroblasts alter epithelial cell differentiation. *J Cell Sci* 118: 485–496, 2005. doi:10.1242/jcs.01635.
145. **Pasquel FJ, Gregg EW, Ali MK.** The evolving epidemiology of atherosclerotic cardiovascular disease in people with diabetes. *Endocrinol Metab Clin North Am* 47: 1–32, 2018. doi:10.1016/j.ecl.2017.11.001.
146. **Passos JF, Saretzki G, Ahmed S, Nelson G, Richter T, Peters H, Wappler I, Birket MJ, Harold G, Schaeuble K, Birch-Machin MA, Kirkwood TBL, von Zglinicki T.** Mitochondrial dysfunction accounts for the stochastic heterogeneity in telomere-dependent senescence. *PLoS Biol* 5: e110, 2007. doi:10.1371/journal.pbio.0050110.
147. **Paulus WJ, Tschöpe C.** A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 62: 263–271, 2013. doi:10.1016/j.jacc.2013.02.092.
148. **Perrott KM, Wiley CD, Desprez P-Y, Campisi J.** Apigenin suppresses the senescence-associated secretory phenotype and paracrine effects on breast cancer cells. *Geroscience* 39: 161–173, 2017. doi:10.1007/s11357-017-9970-1.
149. **Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM.** C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 286: 327–334, 2001. doi:10.1001/jama.286.3.327.
150. **Prattichizzo F, Giuliani A, Recchioni R, Bonafè M, Marcheselli F, De Carolis S, Campanati A, Giuliodori K, Rippo MR, Brugè F, Tiano L, Micucci C, Ceriello A, Offidani A, Procopio AD, Olivieri F.** Anti-TNF-α treatment modulates SASP and SASP-related microRNAs in endothelial cells and in circulating angiogenic cells. *Oncotarget* 7: 11945–11958, 2016. doi:10.18632/oncotarget.7858.
151. **Rabinovitch A.** An update on cytokines in the pathogenesis of insulin-dependent diabetes mellitus. *Diabetes Metab Rev* 14: 129–151, 1998. doi:10.1002/(SICI)1099-0895(199806)14:2<129::AID-DMR208>3.0.CO;2-V.
152. **Rangel-Zúñiga OA, Corina A, Lucena-Porras B, Cruz-Teno C, Gómez-Delgado F, Jiménez-Lucena R, Alcalá-Díaz JF, Haro-Mariscal C, Yubero-Serrano EM, Delgado-Lista J, López-Moreno J, Rodríguez-Cantalejo F, Camargo A, Tinahones FJ, Ordovás JM, López-Miranda J, Pérez-Martínez P.** TNFA gene variants related to the inflammatory status and its association with cellular aging: From the CORDIOPREV study. *Exp Gerontol* 83: 56–62, 2016. doi:10.1016/j.exger.2016.07.015.
153. **Raymond RJ, Dehmer GJ, Theoharides TC, Deliargyris EN.** Elevated interleukin-6 levels in patients with asymptomatic left ventricular systolic dysfunction. *Am Heart J* 141: 435–438, 2001. doi:10.1067/mhj.2001.113078.
154. **Reed AL, Tanaka A, Sorescu D, Liu H, Jeong E-M, Sturdy M, Walp ER, Dudley SC Jr, Sutliff RL.** Diastolic dysfunction is associated with cardiac fibrosis in the senescence-accelerated mouse. *Am J Physiol Heart Circ Physiol* 301: H824–H831, 2011. doi:10.1152/ajpheart.00407.2010.
155. **Renard CB, Kramer F, Johansson F, Lamharzi N, Tannock LR, von Herrath MG, Chait A, Bornfeldt KE.** Diabetes and diabetes-associated lipid abnormalities have distinct effects on initiation and progression of atherosclerotic lesions. *J Clin Invest* 114: 659–668, 2004. doi:10.1172/JCI200417867.
156. **Ritschka B, Storer M, Mas A, Heinzmann F, Ortells MC, Morton JP, Sansom OJ, Zender L, Keyes WM.** The senescence-associated secretory phenotype induces cellular plasticity and tissue regeneration. *Genes Dev* 31: 172–183, 2017. doi:10.1101/gad.290635.116.
157. **Robles SJ, Adami GR.** Agents that cause DNA double strand breaks lead to p16INK4a enrichment and the premature senescence of normal fibroblasts. *Oncogene* 16: 1113–1123, 1998. doi:10.1038/sj.onc.1201862.
158. **Rodier F, Campisi J.** Four faces of cellular senescence. *J Cell Biol* 192: 547–556, 2011. doi:10.1083/jcb.201009094.
159. **Rota M, LeCapitaine N, Hosoda T, Boni A, De Angelis A, Padin-Iruegas ME, Esposito G, Vitale S, Urbanek K, Casarsa C, Giorgio M, Lüscher TF, Pelicci PG, Anversa P, Leri A, Kajstura J.** Diabetes promotes cardiac stem cell aging and heart failure, which are prevented by deletion of the p66shc gene. *Circ Res* 99: 42–52, 2006. doi:10.1161/01.RES.0000231289.63468.08.
160. **Salminen A, Kauppinen A, Kaarniranta K.** Emerging role of NF-κB signaling in the induction of senescence-associated secretory phenotype (SASP). *Cell Signal* 24: 835–845, 2012. doi:10.1016/j.cellsig.2011.12.006.
161. **Sarvas JL, Khaper N, Lees SJ.** The IL-6 paradox: context dependent interplay of SOCS3 and AMPK. *J Diabetes Metab Suppl* 13: 2013. doi:10.4172/2155-6156.S13-003.
162. **Satoh M, Fujimoto S, Haruna Y, Arakawa S, Horike H, Komai N, Sasaki T, Tsujioka K, Makino H, Kashihara N.** NAD(P)H oxidase and uncoupled nitric oxide synthase are major sources of glomerular superoxide in rats with experimental diabetic nephropathy. *Am J Physiol Renal Physiol* 288: F1144–F1152, 2005. doi:10.1152/ajprenal.00221.2004.
163. **Schloot NC, Hanifi-Moghaddam P, Goebel C, Shatavi SV, Flohé S, Kolb H, Rothe H.** Serum IFN-gamma and IL-10 levels are associated with disease progression in non-obese diabetic mice. *Diabetes Metab Res Rev* 18: 64–70, 2002. doi:10.1002/dmrr.256.
164. **Seals DR, Brunt VE, Rossman MJ.** Strategies for optimal cardiovascular aging. *Am J Physiol Heart Circ Physiol*. In press. doi:10.1152/ajpheart.00734.2017.
165. **Segers VF, De Keulenaer GW.** Pathophysiology of diastolic dysfunction in chronic heart failure. *Future Cardiol* 9: 711–720, 2013. doi:10.2217/fca.13.53.
166. **Segers VF, Lee RT.** Stem-cell therapy for cardiac disease. *Nature* 451: 937–942, 2008. doi:10.1038/nature06800.
167. **Segers VF, Tokunou T, Higgins LJ, MacGillivray C, Gannon J, Lee RT.** Local delivery of protease-resistant stromal cell derived factor-1 for stem cell recruitment after myocardial infarction. *Circulation* 116: 1683–1692, 2007. doi:10.1161/CIRCULATIONAHA.107.718718.
168. **Segers VFM, Brutsaert DL, De Keulenaer GW.** Cardiac remodeling: endothelial cells have more to say than just NO. *Front Physiol* 9: 382, 2018. doi:10.3389/fphys.2018.00382.
169. **Sentilhes L, Michel C, Lecourtois M, Catteau J, Bourgeois P, Laudenbach V, Marret S, Laquerrière A.** Vascular endothelial growth factor and its high-affinity receptor (VEGFR-2) are highly expressed in the human forebrain and cerebellum during development. *J Neuropathol Exp Neurol* 69: 111–128, 2010. doi:10.1097/NEN.0b013e3181ccc9a9.
170. **Shakeri H, Gevaert AB, Schrijvers DM, De Meyer GRY, De Keulenaer GW, Guns PDF, Lemmens K, Segers VF.** Neuregulin-1 attenuates stress-induced vascular senescence. *Cardiovasc Res* 114: 1041–1051, 2018. doi:10.1093/cvr/cvy059.
171. **Shenouda SM, Widlansky ME, Chen K, Xu G, Holbrook M, Tabit CE, Hamburg NM, Frame AA, Caiano TL, Kluge MA, Duess M-A, Levit A, Kim B, Hartman M-L, Joseph L, Shirihai OS, Vita JA.** Altered mitochondrial dynamics contributes to endothelial dysfunction in diabetes mellitus. *Circulation* 124: 444–453, 2011. doi:10.1161/CIRCULATIONAHA.110.014506.
172. **Shim JH, Park J-Y, Lee M-G, Kang HH, Lee TR, Shin DW.** Human dermal stem/progenitor cell-derived conditioned medium ameliorates ultraviolet a-induced damage of normal human dermal fibroblasts. *PLoS One* 8: e67604, 2013. doi:10.1371/journal.pone.0067604.
173. **Shin WS, Szuba A, Rockson SG.** The role of chemokines in human cardiovascular pathology: enhanced biological insights. *Atherosclerosis* 160: 91–102, 2002. doi:10.1016/S0021-9150(01)00571-8.
174. **Song Y, Shen H, Schenten D, Shan P, Lee PJ, Goldstein DR.** Aging enhances the basal production of IL-6 and CCL2 in vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* 32: 103–109, 2012. doi:10.1161/ATVBAHA.111.236349.
175. **Sprague AH, Khalil RA.** Inflammatory cytokines in vascular dysfunction and vascular disease. *Biochem Pharmacol* 78: 539–552, 2009. doi:10.1016/j.bcp.2009.04.029.
176. **Spranger J, Kroke A, Möhlig M, Hoffmann K, Bergmann MM, Ristow M, Boeing H, Pfeiffer AFH.** Inflammatory cytokines and the

risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Diabetes* 52: 812–817, 2003. doi:10.2337/diabetes.52.3.812.

177. **Steil GM, Trivedi N, Jonas JC, Hasenkamp WM, Sharma A, Bonner-Weir S, Weir GC.** Adaptation of β-cell mass to substrate oversupply: enhanced function with normal gene expression. *Am J Physiol Endocrinol Metab* 280: E788–E796, 2001. doi:10.1152/ajpendo.2001.280.5.E788.
178. **Szade A, Grochot-Przeczek A, Florczyk U, Jozkowicz A, Dulak J.** Cellular and molecular mechanisms of inflammation-induced angiogenesis. *IUBMB Life* 67: 145–159, 2015. doi:10.1002/iub.1358.
179. **Tamura Y, Izumiyama-Shimomura N, Kimbara Y, Nakamura K, Ishikawa N, Aida J, Chiba Y, Matsuda Y, Mori S, Arai T, Fujiwara M, Poon SS, Ishizaki T, Araki A, Takubo K, Ito H.** Telomere attrition in beta and alpha cells with age. *Age (Dordr)* 38: 61, 2016. doi:10.1007/s11357-016-9923-0.
180. **Tavana O, Zhu C.** Too many breaks (brakes): pancreatic β-cell senescence leads to diabetes. *Cell Cycle* 10: 2471–2484, 2011. doi:10.4161/cc.10.15.16741.
181. **Taye A, Abouzied MM, Mohafez OMM.** Tempol ameliorates cardiac fibrosis in streptozotocin-induced diabetic rats: role of oxidative stress in diabetic cardiomyopathy. *Naunyn Schmiedebergs Arch Pharmacol* 386: 1071–1080, 2013. doi:10.1007/s00210-013-0904-x.
182. **Uemura S, Matsushita H, Li W, Glassford AJ, Asagami T, Lee K-H, Harrison DG, Tsao PS.** Diabetes mellitus enhances vascular matrix metalloproteinase activity: role of oxidative stress. *Circ Res* 88: 1291–1298, 2001. doi:10.1161/hh1201.092042.
183. **Van Herck JL, De Meyer GRY, Martinet W, Van Hove CE, Foubert K, Theunis MH, Apers S, Bult H, Vrints CJ, Herman AG.** Impaired fibrillin-1 function promotes features of plaque instability in apolipoprotein E-deficient mice. *Circulation* 120: 2478–2487, 2009. doi:10.1161/CIRCULATIONAHA.109.872663.
184. **Vasilaki A, Jackson MJ.** Role of reactive oxygen species in the defective regeneration seen in aging muscle. *Free Radic Biol Med* 65: 317–323, 2013. doi:10.1016/j.freeradbiomed.2013.07.008.
185. **Vermeulen Z, Hervent AS, Dugaucquier L, Vandekerckhove L, Rombouts M, Beyens M, Schrijvers DM, De Meyer GRY, Maudsley S, De Keulenaer GW, Segers VFM.** Inhibitory actions of the NRG-1/ErbB4 pathway in macrophages during tissue fibrosis in the heart, skin, and lung. *Am J Physiol Heart Circ Physiol* 313: H934–H945, 2017. doi:10.1152/ajpheart.00206.2017.
186. **Vermeulen Z, Segers VF, De Keulenaer GW.** ErbB2 signaling at the crossing between heart failure and cancer. *Basic Res Cardiol* 111: 60, 2016. doi:10.1007/s00395-016-0576-z.
187. **Verzola D, Gandolfo MT, Gaetani G, Ferraris A, Mangerini R, Ferrario F, Villaggio B, Gianiorio F, Tosetti F, Weiss U, Traverso P, Mji M, Deferrari G, Garibotto G.** Accelerated senescence in the kidneys of patients with type 2 diabetic nephropathy. *Am J Physiol Renal Physiol* 295: F1563–F1573, 2008. doi:10.1152/ajprenal.90302.2008.
188. **von Scholten BJ, Reinhard H, Hansen TW, Schalkwijk CG, Stehouwer C, Parving H-H, Jacobsen PK, Rossing P.** Markers of inflammation and endothelial dysfunction are associated with incident cardiovascular disease, all-cause mortality, and progression of coronary calcification in type 2 diabetic patients with microalbuminuria. *J Diabetes Complications* 30: 248–255, 2016. doi:10.1016/j.jdiacomp.2015.11.005.
189. **Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE.** Circulating interleukin-6 in relation to adiposity, insulin action, and insulin secretion. *Obes Res* 9: 414–417, 2001. doi:10.1038/oby.2001.54.
190. **Wang M, Jiang L, Monticone RE, Lakatta EG.** Proinflammation: the key to arterial aging. *Trends Endocrinol Metab* 25: 72–79, 2014. doi:10.1016/j.tem.2013.10.002.
191. **Wang P, Han L, Shen H, Wang P, Lv C, Zhao G, Niu J, Xue L, Wang QJ, Tong T, Chen J.** Protein kinase D1 is essential for Ras-induced senescence and tumor suppression by regulating senescence-associated inflammation. *Proc Natl Acad Sci USA* 111: 7683–7688, 2014. doi:10.1073/pnas.1310972111.
192. **Westermeier F, Riquelme JA, Pavez M, Garrido V, Díaz A, Verdejo HE, Castro PF, García L, Lavandero S.** New molecular insights of insulin in diabetic cardiomyopathy. *Front Physiol* 7: 125, 2016. doi:10.3389/fphys.2016.00125.
193. **Westhoff JH, Hilgers KF, Steinbach MP, Hartner A, Klanke B, Amann K, Melk A.** Hypertension induces somatic cellular senescence in rats and humans by induction of cell cycle inhibitor p16INK4a. *Hypertension* 52: 123–129, 2008. doi:10.1161/HYPERTENSIONAHA.107.099432.
194. **Whaley-Connell A, Govindarajan G, Habibi J, Hayden MR, Cooper SA, Wei Y, Ma L, Qazi M, Link D, Karuparthi PR, Stump C, Ferrario C, Sowers JR.** Angiotensin II-mediated oxidative stress promotes myocardial tissue remodeling in the transgenic (mRen2) 27 Ren2 rat. *Am J Physiol Endocrinol Metab* 293: E355–E363, 2007. doi:10.1152/ajpendo.00632.2006.
195. **Xu S, Cai Y, Wei Y.** mTOR Signaling from Cellular Senescence to Organismal Aging. *Aging Dis* 5: 263–273, 2013.
196. **Xue W, Zender L, Miething C, Dickins RA, Hernando E, Krizhanovsky V, Cordon-Cardo C, Lowe SW.** Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. *Nature* 445: 656–660, 2007. doi:10.1038/nature05529.
197. **Yin H, Pickering JG.** cellular senescence and vascular disease: novel routes to better understanding and therapy. *Can J Cardiol* 32: 612–623, 2016. doi:10.1016/j.cjca.2016.02.051.
198. **Yoshida Y, Shimizu I, Katsuumi G, Jiao S, Suda M, Hayashi Y, Minamino T.** p53-Induced inflammation exacerbates cardiac dysfunction during pressure overload. *J Mol Cell Cardiol* 85: 183–198, 2015. doi:10.1016/j.yjmcc.2015.06.001.
199. **Zaccardi F, Webb DR, Yates T, Davies MJ.** Pathophysiology of type 1 and type 2 diabetes mellitus: a 90-year perspective. *Postgrad Med J* 92: 63–69, 2016. doi:10.1136/postgradmedj-2015-133281.
200. **Zhang J, Patel JM, Block ER.** Enhanced apoptosis in prolonged cultures of senescent porcine pulmonary artery endothelial cells. *Mech Ageing Dev* 123: 613–625, 2002. doi:10.1016/S0047-6374(01)00412-2.
201. **Zhang J, Patel JM, Li YD, Block ER.** Proinflammatory cytokines downregulate gene expression and activity of constitutive nitric oxide synthase in porcine pulmonary artery endothelial cells. *Res Commun Mol Pathol Pharmacol* 96: 71–87, 1997.
202. **Zhang N, Yang Z, Xiang S-Z, Jin Y-G, Wei W-Y, Bian Z-Y, Deng W, Tang Q-Z.** Nobiletin attenuates cardiac dysfunction, oxidative stress, and inflammatory in streptozotocin: induced diabetic cardiomyopathy. *Mol Cell Biochem* 417: 87–96, 2016. doi:10.1007/s11010-016-2716-z.