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Review

Heart Failure: Lipid Metabolism Disorders Driving Cellular Senescence Through a Vicious Cycle, and Possible Intervention Strategies

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Abstract

Heart failure (HF) is major and growing global health challenge, with lipid metabolism dysregulation recognized as a significant contributing factor. This review focuses on the emerging concept of the "metabolism-senescence axis", which plays a central role in disease development progression. Excess lipid metabolites, especially ceramides and diacylglycerols, contribute to cardiomyocyte injury through multiple mechanisms, including mitochondria dysfunction, promoting oxidative stress, and interfering with normal metabolic signals. The senescence-associated secretory phenotype (SASP) promotes a pro-senescent tissue microenvironment, thereby disrupting the normal metabolic balance and creating a vicious cycle that seriously affects heart structure and function. This review examines the molecular events underlying this process, including cellular injury, impaired fatty acid oxidation, oxidative stress, activation of the p53/p21 and p16INK4a/Rb, signaling pathways, and SASP-mediated metabolic dysfunction. We further discuss the rationale for combinatorial strategies targeting both metabolic dysfunction and cellular senescence, proposing that simultaneous intervention in these interconnected pathways may represent a promising therapeutic approach to delay the progression of HF and improve patient outcomes.

Keywords: heart failure; lipid metabolism; cellular senescence; lipotoxicity; senescence-associated secretory phenotype; metabolism-senescence axis

1. Introduction

Heart failure (HF) is a clinical syndrome associated with structural or functional cardiac abnormality and characterized by decreased ventricular filling and/or lower ejection fraction [1]. Globally, the lifelong burden of HF is increasing due to longer life expectancy and the aging population. In the United States, more than 8 million adults are likely to be affected by HF in 2030, with annual direct medical costs exceeding $70 billion [2]. HF is not a sign of complete arrest of heart function, but rather of the heart not functioning sufficiently well to cope with the body's needs [3]. In most settings, HF falls into three categories according to the current ESC guidelines: HF with reduced ejection fraction (HFrEF, LVEF ≤40%), HF with mildly reduced ejection fraction (HFmrEF, LVEF 41–49%), and HF with preserved ejection fraction (HFpEF, LVEF ≥50%). HFpEF is more prevalent in older adults, women, and individuals with metabolic syndrome. It currently lacks effective evidence-based treatments [4]. A recent study found that HFpEF accounts for >50% of newly diagnosed HF cases, with the incidence being particularly high amongst people aged ≥65 years [5]. Several interacting factors are at play in HF, including dyslipidemia, causing cellular senescence and disease progression. Dysregulated lipid metabolism is closely associated with cellular senescence, and contributes to inflammation, oxidative stress, and mitochondrial damage [6,7]. Intracellular lipid accumulation (cholesterol, triglycerides) arising from diseased lipid metabolism induces lipotoxicity in cardiomyocytes, leading to apoptosis and fibrosis [8]. Lipid metabolism is also associated with insulin resistance, inflammatory cytokine release, and oxidative stress, causing cellular senescence [9,10]. Lipid metabolic disorders have revealed an important and complex interplay with cellular senescence. These disorders facilitate cellular senescence through the activation of oxidative stress and inflammation, while senescent cells further disrupt lipid metabolism by releasing senescence-associated secretory phenotype (SASP) factors [11].

This review provides a brief overview of the central role of lipid metabolism in HF. It also presents the molecular mechanisms by which aberrant lipid metabolism causes cellular senescence. We present important pathways from lipotoxic stress and mitochondrial dysfunction to dysregulated metabolic signaling leading to cellular senescence programs. We also discuss how senescent cells contribute to metabolic dysfunction and tissue aging through the secretion of SASP factors, thus creating a self-reinforcing "metabolism–senescent" vicious cycle. Guided by these mechanistic insights, we discuss potential interventions, including upstream strategies for regaining metabolic home-

ostasis, and downstream combination therapies to remove senescent cells and neutralize their effects. These perspectives are aimed at developing a new model and guidelines for the prevention and treatment of HF.

2. Dysregulated Lipid Metabolism as the Key Pathogenic Mechanism in Heart Failure

2.1 Physiology of Cardiac Lipid Metabolism

The heart is very energetic and uses fatty acid oxidation (FAO) in order to meet its energy needs. In normal conditions, circulating fatty acid (FA) bound to albumin is transported to cardiomyocytes by FA transport proteins (e.g., FATP, CD36) on the sarcolemma [12]. Once inside the cell, activated FAs follow two major metabolic paths: (1) mitochondrial β-oxidation to produce ATP, or (2) esterification to triglycerides (TGs) in the endoplasmic reticulum for storage in lipid droplets (LDs) [13,14]. The main regulatory machinery is peroxisome proliferator-activated receptor α (PPARα) and its coactivator PGC-1α. PPARα/PGC-1α upregulates genes involved in FA uptake (e.g., CD36), activation, and key β-oxidation enzymes (e.g., CPT1, MCAD) required for efficient FA usage [15,16,17]. Dysregulated lipid metabolism, characterized by excessive fatty acid accumulation and impaired β-oxidation, leads to cardiomyocyte dysfunction and disrupts cardiac metabolic homeostasis, thereby contributing to the pathogenesis of heart failure [16,17]. FA uptake and oxidation are also important steps in cardiac lipid metabolism. FA enters the heart via membrane transporters such as CD36, responds to acyl-CoA in the cytoplasm, and is then β-oxidized in mitochondria [15,17]. This requires catalysis by carnitine palmitoyltransferase-1B (CPT-1B), the rate-limiting enzyme for FA metabolism in the mitochondria [17]. Peroxisomes also catalyze FAO by shortening very long-chain FAs, but the products must be transferred to mitochondria for complete oxidation [18]. FAO directly affects cardiac energy supply and function [19]. Studies indicate that increased FAO in the diabetic heart is not accompanied by increased activity of the TCA cycle and oxidative phosphorylation, leading to insufficient energy supply and ATP levels [20].

2.2 Myocardial Ectopic Fat Deposition

Cardiac ectopic fat accumulation refers to the abnormal deposition of lipids in non-adipose tissues such as the myocardium. This phenomenon is closely associated with insulin resistance and the progression of HF [21,22]. In mammals, multiple cell types are capable of forming LDs under specific conditions. Although circulating lipids are the heart's primary energy substrate, TGs stored in cardiomyocyte LDs are indispensable for maintaining cardiac lipid homeostasis. As readily mobilizable TG reservoirs, LDs allow the heart to adapt to fluctuating energy demands and variable circulating FA supply [23]. LDs consist of a neutral lipid core surrounded by a phospholipid monolayer membrane enriched with specific proteins. Morphologically, smaller LDs have a higher surface-area-to-volume ratio [24], a characteristic that can substantially influence their metabolic activity. The absence of PLIN5 increases myocardial infarct size, worsens cardiac dysfunction, and aggravates mitochondrial damage following ischemia/reperfusion injury, effects that are potentially linked to elevated oxidative stress [25]. Conversely, cardiomyocyte-specific overexpression of Plin5 leads to severe TG accumulation comparable to that observed in adipose triglyceride lipase (ATGL)-deficient mice. Unlike the mouse model, however, this does not result in cardiac dysfunction or reduced lifespan [26].

Beyond physiological lipid storage, genetic alterations can drive pathological cardiac lipid deposition. The most severe phenotype results from defective adipose triglyceride lipase (ATGL) function, leading to marked myocardial lipid accumulation and even premature death [27]. The extent of LD accumulation in cardiomyocytes depends on three core processes: neutral lipid synthesis, surface phospholipid assembly, and TG hydrolysis [15]. Given the limited capacity for *de novo* FA synthesis from carbohydrates in the normal heart, TGs within LDs primarily originate from circulating lipoproteins and non-esterified FAs. The final step in TG biosynthesis is catalyzed by diacylglycerol acyltransferase (DGAT), which esterifies a third FA onto the diacylglycerol (DAG) backbone. Mammalian cells express two DGAT isoenzymes that together mediate LD formation. Studies have shown that simultaneous knockout of both DGAT enzymes in adipocytes is required to completely block LD generation [28]. DGAT1 deficiency in the heart reduces LD formation and causes its substrate, DAG, to accumulate in cardiomyocytes [29]. Notably, decreased DGAT1 expression has been observed in cardiac tissues from patients with end-stage HF [30]. Conversely, cardiac-specific DGAT1 overexpression increases TG levels and reduces DAG content without inducing cardiac dysfunction [31]. Further studies indicate that DGAT1 transgenic hearts exhibit enhanced tolerance to ischemia/reperfusion injury, potentially due to more efficient utilization of stored TGs [32]. In various lipotoxicity models, transgenic DGAT1 expression improves cardiac function by concurrently reducing DAG and ceramide levels [33]. Collectively, this evidence positions DAG as a central intermediate in TG metabolism and highlights its critical role in the lipotoxicity triggered when FA is diverted into LD storage rather than oxidized.

2.3 Lipotoxicity-Induced Myocardial Injury

The energy metabolism of cardiomyocytes undergoes profound alterations in HF, characterized by a shift from predominant FA utilization toward increased glucose consumption [34]. Although FAO remains the primary energy source [35], a marked imbalance arises in lipid uptake, metabolism, and utilization. This disturbance leads to abnormal accumulation of various lipid metabolites, includ-

ing ceramide and DAG, within cardiomyocytes in HF [36]. Ceramide plays a pivotal role in lipotoxic signal transduction, linking lipid-mediated inflammatory responses with inhibition of insulin signaling [37]. Specifically, the activation of Toll-like receptor 4 (TLR4) signaling via the IKKβ–NF-κB axis can promote *de novo* ceramide biosynthesis [38]. However, activation of this pathway itself requires ceramide generated through acid sphingomyelinase–mediated catalysis [39]. Ceramide not only acts as a key effector in TLR4-induced insulin resistance [38], but it also disrupts Akt activation through two independent mechanisms: (1) activation of protein phosphatase 2A (PP2A), leading to Akt dephosphorylation, and (2) stimulation of PKCζ, which impairs Akt translocation to the plasma membrane [40,41]. Studies in AC16 human cardiomyocytes have demonstrated that C6-ceramide inhibits the phosphorylation of Akt and its downstream target glycogen synthase kinase 3β in a concentration-dependent manner, consistent with findings in skeletal muscle cells and adipocytes [42]. Beyond regulating Akt phosphorylation, ceramide can also directly suppress IRS1 phosphorylation [43]. In addition, ceramide activates mixed-lineage kinase 3 (MLK3), which may indirectly modulate IRS1 function through stress-activated protein kinase pathways, including p38 MAPK and JNK [44,45,46,47,48]. While MLK family kinases are known to regulate cardiomyocyte stress responses, further investigation is required to clarify whether ceramide affects cardiac insulin signaling via this kinase family [49]. Beyond insulin signaling, ceramide promotes cardiomyocyte apoptosis via MAPK pathways (ERK, p38 MAPK, JNK) [50].

DAG persistently activates PKCδ, promoting serine phosphorylation of p66Shc and its mitochondrial translocation, thereby exacerbating oxidative stress-induced apoptosis [51]. These pathways synergize with endoplasmic reticulum stress–induced CHOP signaling to downregulate the anti-apoptotic protein Bcl-2 and upregulate the pro-apoptotic protein Bim, ultimately initiating programmed cell death [52]. With respect to inflammation, ceramide promotes 26S proteasomal degradation of IκBα via activation of the IKK complex, thereby relieving inhibition of NF-κB p65 and driving the expression of pro-inflammatory factors such as TNF-α and IL-6 [53]. Lipotoxicity also induces oxidative mitochondrial DNA (mtDNA) damage. The released oxidized mtDNA acts as a damage-associated molecular pattern (DAMP) to activate the NLRP3 inflammasome, promoting caspase-1-mediated maturation and release of IL-1β and IL-18 [52]. DAG upregulates TLR4 expression via the PKCθ–p38 MAPK axis, thereby enhancing the sensitivity of the NF-κB pathway. Long-chain acyl-CoA inhibits histone deacetylase (HDAC) activity, promoting the transcription of inflammation-related genes [54,55]. The ceramide metabolite sphingosine-1-phosphate (S1P) activates the RhoA/ROCK pathway via S1PR2, promoting (MCP-1) expression and accelerating inflammatory cell infiltration [56]. These intertwined pathways constitute the core mechanism of lipotoxic myocardial injury, wherein different lipid intermediates exert multilevel, multitarget regulatory effects by acting on specific nodes within signal transduction networks [39]. Cross-talk is known to occur among ceramide, DAG, and long-chain acyl-CoA. For example, ceramide enhances DAG-mediated activation of PKCδ via PP2A, whereas long-chain acyl-CoA modulates membrane receptor signaling by regulating protein palmitoylation. Such interactions amplify lipotoxic injury [42,57]. Pharmacological inhibition of the rate-limiting ceramide biosynthetic enzyme serine palmitoyltransferase (SPT) with myriocin, or genetically via heterozygous deletion of SPT subunits, ameliorates contractile dysfunction in LpLGPI mice, providing *in vivo* evidence for the role of ceramide in lipotoxic cardiomyopathy [58]. This functional improvement is accompanied by reduced mortality, decreased expression of atrial and brain natriuretic peptides, and a metabolic shift from FA to glucose oxidation in cardiac energy metabolism [58].

3. From Dysregulation of Lipid Metabolism to Cellular Senescence: Mechanisms and Signaling Pathways

Profound remodeling of cardiac lipid metabolism occurs under pathological conditions such as obesity, diabetes, and metabolic syndrome, characterized by increased FA uptake, impaired β-oxidation, and abnormal accumulation of toxic lipid intermediates. Collectively, these abnormalities promote cellular senescence through interconnected molecular mechanisms. In the cardiovascular system, cellular senescence has been implicated in myocardial remodeling (age-related, chemotherapy-induced [59], and post-injury [60,61]), HF, atherosclerosis, and aortic aneurysms, as reviewed previously [62,63,64,65].

3.1 The Direct Pro-Senescence Effect of Lipotoxicity

As summarized in Table 1 (Ref. [50,51,52,54,55,56,66,67]), lipotoxicity induced by ceramide and DAG is the main target of cardiomyocyte senescence in HF. In lipid-mediated senescence signaling, the cyclin-dependent kinase inhibitors p21 and p16 engage in crosstalk with the PKC and MAPK pathways, leading to reciprocal activation, with oxidative stress being critical for HFpEF and HFrEF [68]. The central mechanism of ceramide-induced senescence is sustained activation of stress-activated protein kinases [69]. Ceramide acts as a second messenger that directly activates p38 MAPK and JNK-dependent phosphorylation chains [50]. Activated p38 MAPK activates and stabilizes p53, as well as transactivating its downstream target, the cyclin-dependent kinase inhibitor p21 [70]. Upregulation of p21 significantly inhibits cyclin E/CDK2 activity, keeping retinoblastoma (Rb) protein in its dephosphorylated active state, and interrupting the cell cycle at G1 [71]. The JNK pathway, also activated by ceramide, contributes to cell cycle arrest

Table 1. Mechanisms of lipid metabolism disorders driving myocardial senescence.

Lipid or damage-associated mediator	Target pathways/mechanisms	Senescence markers	Evidence level/model	Associated HF phenotypes	Reference numbers
Ceramide	Activation of p38 MAPK/JNK → p53 stabilization Activation of PKC/PP2A → inhibition of Akt signaling Activation of MLK3 → p38 MAPK/JNK activation Activation of NLRP3 inflammasome via mtDNA	p21 ↑ p16INK4a ↑ SA-β-gal activity ↑	*in vivo*: Inhibition of SPT with myriocin attenuates cardiac senescence and dysfunction in LpLGPI mice. *in vitro*: AC16 cardiomyocytes	Lipotoxic cardiomyopathy Insulin resistance Cardiomyocyte apoptosis HFpEF	[50]
DAG	Activation of PKCδ → p66Shc phosphorylation Activation of PKCθ → p38 MAPK axis → TLR4 upregulation Activation of PKC → IRS1 phosphorylation at Ser1101	p16INK4a ↑ (via ATF3/C/EBPβ)	*in vivo*/*in vitro*: DGAT1 overexpression reduces DAG and improves cardiac function	Lipotoxic cardiomyopathy Oxidative stress Insulin resistance	[51,52,66]
Long-chain Acyl-CoA	Inhibition of HDAC → pro-inflammatory gene transcription Allosteric inhibition of ETC complexes I/III → increased ROS	Activation of DNA damage response	*in vitro*: Models of metabolic cardiomyopathy	Mitochondrial dysfunction Inflammation	[55,67]
Oxidized mtDNA	Acts as a DAMP to activate NLRP3 inflammasome → IL-1β/IL-18 release	SASP-associated inflammatory markers ↑	*in vivo*/*in vitro*: High-fat diet models	Sterile inflammation Myocardial fibrosis	[54]
S1P	Activation of S1PR2/RhoA/ROCK pathway → MCP-1 upregulation	Paracrine senescence via inducing inflammation	*in vivo*: Myocardial ischemia/reperfusion models	Pro-inflammatory microenvironment Ventricular remodeling	[56]

DAG, diacylglycerol; PKC, Protein Kinase C; MLK3, mixed-lineage kinase 3; NLRP3, NOD-like receptor protein 3; HDAC, histone deacetylase; DAMP, damage-associated molecular pattern; MCP-1, monocyte chemoattractant protein-1; DGAT1, diacylglycerol acyltransferase 1; S1P, sphingosine-1-phosphate. "↑" indicates an increase/upregulation.

by controlling transcription factors (c-Jun and ATF2) [42,72]. This suggests that ceramide is central to senescence biomarkers, such as increased senescence-associated β-galactosidase activity and upregulated p16INK4a and p21 expression [73,74].

An *in vivo* study demonstrated that inhibition of *de novo* ceramide synthesis (e.g., with myriocin) or downregulation of gene expression reduces cardiac senescence and improves cardiac function [42,72]. DAG accumulates in cardiomyocytes filled with LDs, triggering pro-senescence signaling through specific protein kinase isoforms (PKC, PKCδ) [75]. Activation of PKC is associated with insulin/PI3K/Akt survival signaling via phosphorylation of IRS1 at Ser1101 and p38 MAPK, and increased threonine/tyrosine phosphorylation of p38 MAPK [76]. Enhanced p38 MAPK activation stabilizes and promotes p16INK4a by the transcription factors ATF3 and C/EBPβ [66].

PKCδ translocates to mitochondria, where it phosphorylates components of the mitochondrial permeability transition pore, inducing mitochondrial membrane potential collapse and cytochrome c release, thereby exacerbating senescence-associated mitochondrial dysfunction [77,78]. Lipotoxicity activates the NLRP3 inflammasome through multiple mechanisms: DAG promotes NLRP3 phosphorylation and oligomerization via PKCδ; oxidized lipids directly bind NLRP3 as damage-associated molecular patterns (DAMPs); and mitochondrial dysfunction leads to the release of mtDNA and cardiolipin, which provide additional activation signals [79]. Activated caspase-1 cleaves pro-IL-1β and pro-IL-18 into their mature cytokine forms and also cleaves gasdermin D (GSDMD) to induce membrane pore formation, thereby promoting unconventional secretion of SASP factors [52]. These mediators activate NF-κB and JAK–STAT pathways via autocrine and paracrine mechanisms, thereby establishing a pro-aging inflammatory microenvironment [80,81].

3.2 The Central Mediating Role of Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction serves as a central bridge in the progression of HF, linking lipid metabolism disor-

ders to cellular senescence and driving cardiomyocytes into an irreversible senescent state through precise molecular cascades. The initiating event—impaired FAO—triggers a series of interconnected molecular processes. Impairment of FAO causes an imbalance in substrate supply to the electron transport chain, leading to abnormal accumulation of long-chain acyl-CoAs in the mitochondrial matrix. These intermediates allosterically inhibit the activities of Complex I and III, thereby increasing electron leakage, inducing depolarization of mitochondrial membrane potential, and triggering bursts of superoxide anion production [67]. Oxidative modification of cardiolipin further compromises the stability of respiratory chain supercomplex assembly, creating a vicious cycle of reactive oxygen species (ROS) generation [82]. Notably, translocation of cardiolipin from the inner to the outer mitochondrial membrane enables specific binding to LC3, which is crucial for the autophagic clearance of damaged mitochondria [83]. Under persistent lipotoxic stress, downregulation of cardiolipin synthase reduces cardiolipin content, markedly weakening LC3-mediated mitophagy and resulting in the accumulation of dysfunctional mitochondria [84].

Continuous ROS production leads to extensive molecular damage. Mitochondrial DNA (mtDNA), which lacks histone protection and has limited repair capacity, is a primary oxidative target. Accumulation of oxidative base lesions (e.g., 8-oxoguanine) induces genomic instability and impairs transcription of mitochondrially encoded respiratory chain subunits [85]. Nuclear DNA is also severely affected, particularly via oxidative telomeric damage that accelerates telomere shortening and activates the p53 pathway through a telomere dysfunction–induced DNA damage response [86]. At the level of the DNA damage response, ataxia-telangiectasia mutated (ATM) kinase is recruited to double-strand breaks, activating checkpoint kinases 1 and 2 (Chk1/Chk2) via phosphorylation cascades. These kinases phosphorylate multiple p53 sites (Ser15, Ser20), disrupting its interaction with MDM2. This stabilizes p53 and increases its transcriptional activity [71]. Activated p53 transactivates p21, which induces G1/S phase arrest by inhibiting the activities of cyclin E/CDK2 and cyclin D/CDK4/6 complexes [87]. Oxidative stress also directly upregulates p16INK4a expression through epigenetic mechanisms. Reduced SIRT1 activity due to NAD+ depletion leads to hyperacetylation of histone H3K9 and H3K27 in the p16INK4a promoter region, generating an open chromatin conformation that facilitates the binding of transcription factors [88]. p16INK4a competitively inhibits CDK4/6, preventing Rb phosphorylation and maintaining its binding to E2F, thereby reinforcing cell cycle arrest [89].

LDs play a complex regulatory role. Under sustained impairment of FAO, LDs expand as neutral lipid reservoirs, and overexpression of PLIN2 suppresses PINK1/Parkin-mediated mitophagy by hindering OPTN binding to ubiquitinated mitochondria [90]. This dysregulated LD–mitochondria interaction creates a metabolic vicious cycle: dysfunctional mitochondria fail to oxidize FAs efficiently, leading to further LD expansion. In turn, excessive LDs sequester essential cofactors required for FAO, further exacerbating its impairment [91]. Compromised FAO enhances USP30 activity through mechanisms that are not yet fully elucidated. This blocks mitophagy by removing ubiquitin from proteins on the outer mitochondrial membrane [92]. Pharmacological inhibition of USP30 restores mitophagy efficiency in high-fat diet–induced metabolic cardiomyopathy and improves cardiac function [93].

3.3 Alterations in Cellular Signaling Pathways in the Context of Lipid Metabolic Dysregulation

Major changes in key metabolic sensing and regulatory processes are key to cellular senescence in failing hearts, with an important signaling node being aberrant activation of the PI3K/Akt/mTOR/SREBP axis [94]. In addition to its glucose regulatory function, Akt is responsible for SREBPs and directly activates sterol regulatory element–binding proteins (SREBP-1c) by phosphorylation [95]. Activated SREBPs enter the nucleus and upregulate major lipogenic genes (e.g., FAS, ACC), leading to *de novo* lipogenesis and abnormal lipid accumulation in cardiomyocytes [96]. This mechanism is amplified in diabetic cardiogenesis and HF, leading to a vicious cycle of disordered lipid metabolism. SREBP activation promotes low-grade inflammation by upregulating NLRP3 inflammasome components, such as caspase-1 activation and IL-1β maturation and release [97]. Inflammation and metabolic dysregulation contribute to cellular senescence by forming a complementary mechanism: (1) a reduced autophagic flux impairs the clearance of damaged cellular components, and (2) an increase in ribosome biogenesis and protein translation (i.e., IL-1α) enhances cellular senescence [98]. This contrasts with the downregulation of the longevity-related factor SIRT1, which normally inhibits SREBP transcription activity via deacetylation and promotes FAO [9]. In failing hearts, decreased NAD+ levels reduce SIRT1 activity by releasing the repression of SREBPs and by impairing mitochondrial function, resulting in lipid accumulation and oxidative stress [99]. Thus, hyperactivation of the PI3K/Akt/mTOR/SREBP pathway, together with SIRT1 downregulation, is a pro-aging metabolic signaling network that provides molecular information on the development of HF [100]. The molecular mechanisms described above, encompassing the roles of ceramide, DAG, and other lipid mediators in driving cellular senescence, are summarized in Table 1.

4. The Association Between Cellular Senescence and Heart Failure

Cellular senescence is an irreversible state of cell cycle arrest characterized by telomere shortening, accumulation of DNA damage, and formation of the senescence-

associated secretory phenotype (SASP) [101]. Experimental models that induce or attenuate senescence in the cardiovascular system have linked senescence to myocardial remodeling (age-related, chemotherapy-induced [59], and post-injury [60,61]), HF, atherosclerosis, and aortic aneurysms, as reviewed elsewhere [62,63,64,65,102,103,104].

4.1 The SASP: A Hallmark of Senescent Cells

The SASP comprises bioactive molecules secreted by senescent cells. These alter their own behavior and broadly influence the surrounding tissue microenvironment [105]. The SASP is complex and dynamic, encompassing pro-inflammatory factors (cytokines, chemokines), matrix-remodeling proteases, growth factors, and lipids, all of which may play important roles in the pathobiology of chronic diseases [106]. During aging, SASP-expressing cells trigger a self-perpetuating inflammatory signaling loop involving NF-κB, TGF-β, IL-1α, and IL-6 pathways [107]. The senescence response exerts paracrine effects on neighboring cells, inducing inflammation, promoting atherosclerosis, causing cardiac circulatory dysfunction, and increasing risk factors for chronic heart failure (CHF) [108]. This suggests that inhibiting pro-inflammatory signaling or modulating the inflammatory microenvironment may alleviate aging and aging-associated diseases such as CHF [109]. Importantly, SASP-associated phenotypes constitute an independent risk factor for CHF in the elderly [110]. This concept was first explicitly articulated in 2008 by Campisi and colleagues, and subsequently characterized further by others [111].

Physiologically, the SASP plays a crucial transient role in local tissue remodeling and repair by mediating reconstruction of the extracellular matrix (ECM), recruiting immune cells to clear senescent cells, and attracting progenitor cells [112]. Different cardiac cell types communicate via paracrine SASP signaling. Senescent cardiac cells exert detrimental effects on healthy neighboring cells through SASP factors. Fibroblasts and endothelial cells produce typical SASP molecules (e.g., IL-6, CXCL1, CXCL2, TNF, VEGF, MMP1/2/3, PAI-1) [113]. In contrast, senescent cardiomyocytes secrete atypical SASP components, including TGFβ2, GDF15, and EDN3 [114]. The paracrine effects of the SASP on healthy neighboring cells include fibroblast activation and differentiation, reduced angiogenic potential, diminished eNOS activity, a prothrombotic phenotype in endothelial cells, and cardiomyocyte death and hypertrophy. Unlike other cardiac cell types, cardiomyocytes do not produce a typical SASP profile. Instead, their SASP is enriched in atypical components (EDN3, GDF15, TGFβ2) that promote fibroblast activation, cardiomyocyte hypertrophy, and cardiac endothelial dysfunction, indicating potent paracrine actions [115]. *In vivo* and *in vitro* studies have demonstrated an association between the IGF1 signaling pathway and the SASP in senescent cardiomyocytes. Compared with age-matched wild-type mice, aged mice with cardiomyocyte-specific Igf1r knockout exhibit reduced senescence markers and SASP components in cardiac tissue, accompanied by improved cardiac function [116]. Another study showed that Ctsk knockout attenuated cardiac hypertrophy and decreased cardiac IGF1, p21, and p16 levels in mice, suggesting a link between IGF1 signaling, cardiac hypertrophy, and cellular senescence [117].

4.2 The Vicious Cycle of SASP in Exacerbating Metabolic Dysregulation

Fig. 1 provides a comprehensive schematic overview of this deleterious "metabolism-senescence" vicious cycle. SASP factors released by senescent cardiomyocytes are associated with decreased cardiovascular function. IL-6, TNFα, and chemokines are key SASP factors that block FAO and enhance lipid accumulation by interfering with important metabolic signals [118]. IL-8 directly suppresses PPARα transcription by JAK–STAT3 activation, downregulates its downstream targets CPT1A and MCAD, and impairs FAO in cardiomyocytes. TNFα activates NF-κB, which triggers serine phosphorylation of IRS-1 (e.g., Ser307) and disrupts insulin signal transduction, thereby impairing glucose uptake and utilization [38]. Impaired insulin signaling impacts glucose uptake and utilization, forcing cardiomyocytes to rely on incomplete FAO, thereby promoting energy deprivation and increased lipid uptake. SASP-mediated MCP-1/CCL2 induces pro-inflammatory M1 macrophages to infiltrate cardiac tissue via CCR2. These proliferating immune cells release additional TNFα and IL-1β, thus forming a pro-inflammatory positive-feedback loop that persists during PPARα regulation [119]. SASP-mediated matrix metalloproteinases (MMPs), such as MMP-9, promote cardiac fibrosis by degrading the ECM and activating latent TGF-β, thus promoting cardiac fibroblast-to-myofibroblast differentiation. This fibrotic tissue alters cardiac mechanical properties and diffusion gradients, which may constrain nutrient and oxygen delivery and severely limit cardiomyocyte metabolic efficiency [120]. SASP factors are also implicated in mitochondrial dysfunction in adjacent cardiomyocytes through paracrine signaling. This mechanism may involve caspase-8 activation and Bid cleavage mediated by soluble FAS ligand (sFasL), which in turn contributes to mitochondrial membrane collapse and ROS production. Such a "bystander effect" amplifies the impact of cellular senescence. Critically, the chronic inflammatory state established by the SASP and metabolic dysregulation are tightly related and form a "metabolism–inflammation–senescence" axis. The resultant fibrotic tissue alters the cardiac mechanical characteristics and diffusion gradient, which can potentially reduce nutrient and oxygen absorption and indirectly impair the metabolic efficiency of cardiomyocytes [120]. Notably, the SASP factors induce mitochondrial dysfunction in neighboring cardiomyocytes through paracrine signal-

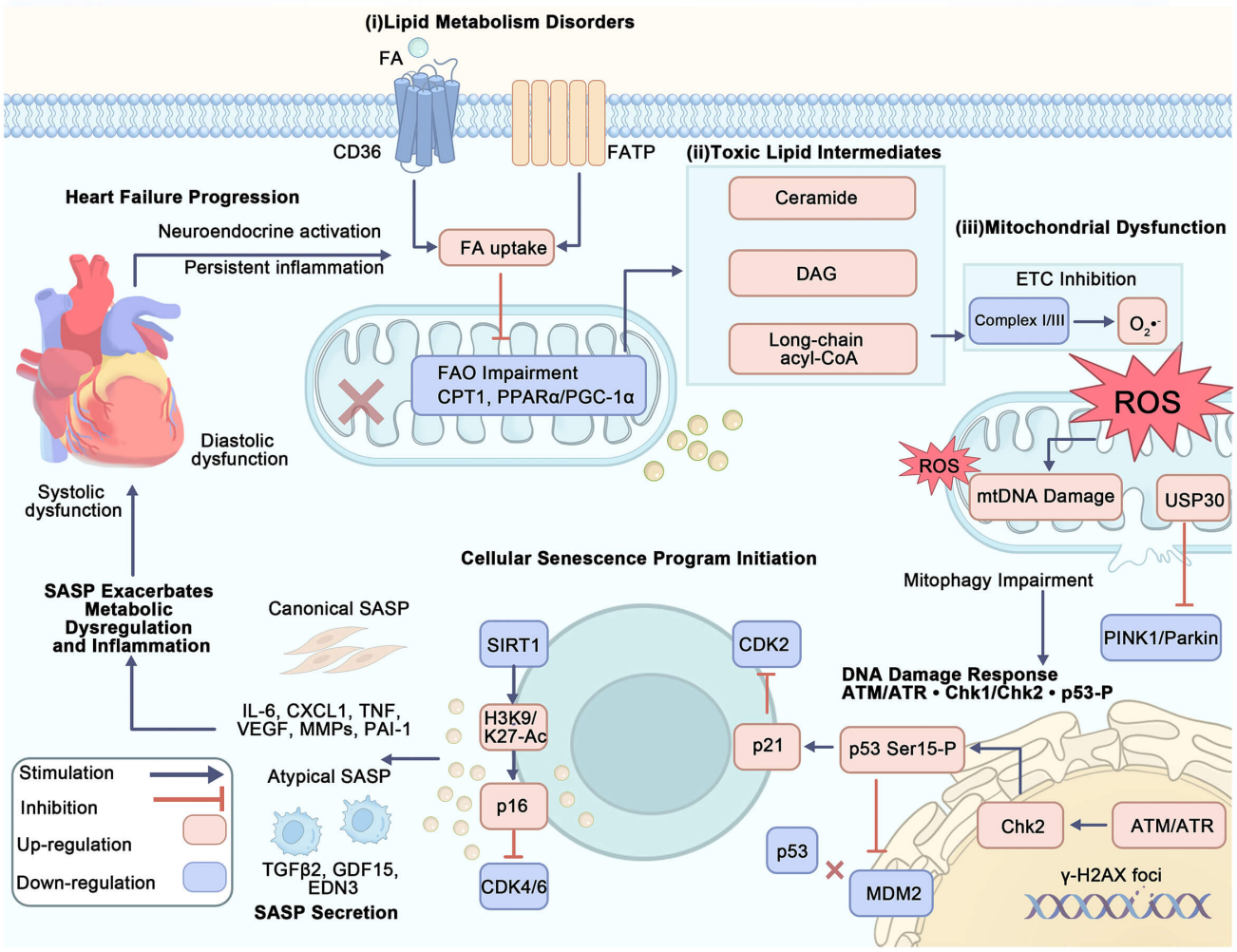

Fig. 1. Schematic overview of the "metabolism-senescence" vicious cycle in heart failure. (i) Lipid metabolism disorders initiate the process through increased fatty acid (FA) uptake (CD36/FATP) and impaired FAO (CPT1/PPARα/PGC-1α downregulation). (ii) Toxic lipid intermediates—ceramide (via TLR4/NF-κB), DAG (from DGAT1 deficiency), and long-chain acyl-CoA—accumulate in cardiomyocytes. (iii) Mitochondrial dysfunction and oxidative stress ensue, characterized by ROS burst, mtDNA damage, and impaired mitophagy (USP30 upregulation). (iv) DNA damage response is activated (ATM/ATR → Chk1/Chk2 → p53 Ser15 phosphorylation). (v) Cellular senescence program initiates via p53/p21 and p16/Rb pathways, marked by γ-H2AX foci. (vi) SASP is released: canonical (IL-6, TNF, MMPs) from fibroblasts/endothelial cells and atypical (TGFβ2, GDF15, EDN3) from senescent cardiomyocytes. (vii) SASP exacerbates metabolic dysregulation, creating a feedback loop that further impairs FAO and promotes FA uptake. (viii) Heart failure progression results from cumulative injury, with neuroendocrine activation and persistent inflammation feeding back to worsen initial lipid disorders. The figure was created by the authors with PowerPoint.

ing. Mechanistically, soluble Fas ligand (sFasL) has been shown to engage its receptor, initiating caspase-8 activation and subsequent cleavage of Bid. This proteolytic cascade leads to the dissipation of mitochondrial membrane potential and enhanced ROS generation [121]. This 'bystander effect' propagates the senescent phenotype, thereby exacerbating metabolic dysfunction and tissue remodeling in the failing heart.

Critically, the chronic inflammatory state established by the SASP and metabolic dysregulation are tightly intertwined, forming a "metabolism–inflammation–senescence" triangular cycle: lipotoxicity drives cellular senescence, senescent cells secrete SASP factors, and the SASP exacerbates metabolic dysregulation and inflammation, thereby inducing further senescence and ultimately worsening cardiac function [122]. The SASP factors include pro-inflammatory cytokines (IL-6, IL-8, MCP-1) and MMPs, which act in an autocrine and paracrine manner on cardiomyocytes and fibroblasts, thereby forming a positive-feedback loop that aggravates myocardial fibrosis and contractile dysfunction [123]. In addition, bioactive lipids secreted by senescent cardiomyocytes, such as ceramide and DAG, directly promote intracellular lipid accumulation and exacerbate mitochondrial dysfunction and oxida-

tive stress by activating PKC and the NLRP3 inflammasome, thereby perpetuating a metabolism-inflammation vicious cycle. Taken together, these findings indicate that targeting SASP factors may represent a novel therapeutic strategy to delay HF progression. This self-perpetuating pathological axis, culminating in heart failure progression, is depicted in Fig. 1.

5. Therapeutic Options for the "Metabolism-Senescence Axis"

The imbalance between dysregulated lipid metabolism and cellular senescence in HF has motivated intervention options that can be broadly categorized as upstream (improving metabolism) or downstream (clearing senescent cells). These interventions are targeted at the harmful "metabolism-senescence" axis, thus creating a new treatment approach for HF.

5.1 Upstream Alternatives to Improving Lipid Metabolism

5.1.1 Metabolic Flexibility

Based on the EMPEROR-preserved and DELIVER trials, the 2023 HF guideline update presented a class I, level of evidence A recommendation for the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors for patients with HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF). SGLT2 inhibitors such as empagliflozin were shown to substantially improve clinical outcomes in patients with HF [124]. Their cardioprotective effect can be explained in part by the remodeling of cardiac energy metabolism. SGLT2 inhibitors promote the production and utilization of ketone bodies. These are more efficient than FAs, thereby reducing the mitochondrial oxidative load and ROS generation [125]. The osmotic diuretic and antihypertensive effects of SGLT2 inhibitors reduce cardiac preload and afterload, indirectly improving the myocardial metabolic microenvironment [124]. Exercise training increases exercise capacity and decreases structural and functional cardiac remodeling [1]. Exercise also decreases myocardial capillary rarefaction and lipid metabolic dysregulation in rats with aortic stenosis–induced HF [126].

5.1.2 Improving Fatty Acid Oxidation and Reducing Lipotoxicity

Peroxisome proliferator-activated receptor (PPAR) modulators such as the selective PPARα/δ modulator pemafibrate can enhance FAO and mitochondrial function [127]. PGC-1α and its downstream targets (e.g., CPT1B, MCAD) promote FA uptake and oxidation and improve mitochondrial biogenesis [128]. Mitochondria-targeted antioxidants (e.g., MitoQ) accumulate in the mitochondrial matrix, efficiently scavenging excess ROS and mitigating oxidative stress [128]. MitoQ attenuates pressure overload-induced cardiac dysfunction [128]. In animal models, MitoQ attenuates pressure overload–induced myocardial hypertrophy and fibrosis and improves mitochondrial function [129]. L-carnitine, an essential cofactor in the carnitine palmitoyltransferase (CPT) system critical for mitochondrial FA import, enhances FAO flux and reduces the accumulation of toxic lipid intermediates (e.g., long-chain acyl-CoAs) when used as a supplement [42,129]. Targeting ceramide synthesis with inhibitors such as myriocin effectively reduces cardiac ceramide levels, improves insulin sensitivity, and attenuates cardiac dysfunction in animal models of obese and diabetic cardiomyopathy [130].

5.2 Downstream Clearing of Senescent Cells and Controlling Their Harm

In the last decade, basic and translational research has helped to elucidate the relevance of cellular senescence and its functional effects on the metabolic reprogramming of pathways involved in cardiac aging. These pathways include autophagy, oxidative stress, epigenetic changes, chronic inflammation, and control of the myocyte contractile phenotype [131].

5.2.1 Dasatinib + Quercetin (D+Q)

Dasatinib (D) is one of the most studied senolytic drugs with a known underlying mechanism of action. It is a multi-target tyrosine kinase inhibitor that suppresses hyperactivated pro-survival pathways (especially SCF/c-Kit) in senescent cells, primarily by targeting SRC family kinases and ephrin receptors [60]. Quercetin (Q) is a flavonoid that disrupts senescent survival homeostasis via suppression of the anti-apoptotic proteins BCL-2 and BCLXL [132].

Preclinical evidence strongly supports the potential of D+Q in cardiac disease models. In aged mice, D+Q treatment improved cardiac function and carotid vascular reactivity [133]. Using a human heart-on-a-chip model of cardiac fibrosis, Mourad et al. [134] demonstrated that D+Q treatment improved contractile function, reduced passive tension, and downregulated senescence-related gene expression. These tissue-engineered human models provide compelling evidence for the potential efficacy of senolytics in cardiac disease.

5.2.2 Vericiguat: Modulating the sGC-cGMP Axis to Attenuate Cardiac Remodeling and Senescence

The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling cascade is indispensable for preserving cardiovascular homeostasis. In heart failure, diminished NO bioavailability coupled with reduced sGC activity compromises cGMP production, thereby exacerbating myocardial and vascular dysfunction [135]. Vericiguat, a direct stimulator of sGC, binds to its β subunit and elevates intracellular cGMP concentrations via an NO-independent mechanism, promoting vasodilation and conferring cardioprotective effects [136]. Beyond its hemodynamic actions, preclinical evidence suggests that vericiguat may modulate pathways potentially

relevant to cellular senescence. In a murine model of pressure overload induced by transverse aortic constriction, vericiguat administration attenuated myocardial hypertrophy and fibrosis while restoring mitochondrial integrity and energy-regulating proteins, suggesting enhanced bioenergetic capacity [137]. However, direct evidence—such as modulation of senescence markers (e.g., p16, p21, SA-β-gal) or SASP factors—is currently lacking and warrants dedicated investigation.

5.2.3 Safety Evaluation and Risk Management of Senolytic Agents and Vericiguat

Current preclinical and early clinical evidence suggests that major senotherapeutic agents have a safety window at certain doses, but their long-term safety profile and agent risks need to be addressed in detail. Safety characteristics differ significantly between drug classes:

Senolytics: D+Q inhibitors can influence hematopoietic stem cell function via inhibition of c-Kit, and cause dose-dependent myelosuppression such as thrombocytopenia and neutropenia [138]. Fisetin modulates 5-HT3R, which often induces nausea and vomiting, and thus cannot be dosed over an extended time [139].

Vericiguat: Vericiguat is generally well-tolerated. The most common adverse event is symptomatic hypotension [140]. A meta-analysis showed no significant increase in serious adverse events versus placebo [141]. Prior hypotension history is the strongest predictor of hypotension/syncope. Additional signals including gastrointestinal bleeding warrant monitoring.

5.3 Combination and Multi-Target Strategies: Synergistic Effects of Concurrent Upstream and Downstream Intervention

Because of the complexity and self-perpetuation of the "metabolism–senescence axis" in HF, single-target therapy is unlikely to be successful. Recently, a combination strategy that targets upstream metabolic dysregulation and downstream cellular senescence has achieved considerable success. The main aim is to break this pathological axis via multi-target therapies.

Mechanistically, upstream metabolic modulators direct downstream senotherapeutics to a better microenvironment. By improving heart energy metabolism and reducing oxidative stress, SGLT2 inhibitors may promote senolytics to kill senescent cells [142]. By increasing mitochondrial function, PPAR agonists may suppress senescence by modulating p16INK4a expression, thus serving as a complementary strategy for senolytic therapy [143].

From a mechanistic perspective, sequential intervention strategies may offer theoretical advantages. Upstream metabolic modulators like SGLT2 inhibitors can modulate the metabolic microenvironment, encompassing aspects such as nutrient availability and inflammatory status [144]. This rationale is further strengthened by evidence that SGLT2 inhibitors may themselves exert indirect senolytic effects. For instance, canagliflozin has been shown to increase 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR), which enhances immune-mediated clearance of senescent cells [145]. Thus, the dual action of optimizing the microenvironment while directly priming senescent cell elimination suggests that metabolic modulators and senolytics could act synergistically. Nevertheless, clinical studies validating such sequential approaches are currently lacking.

However, combination therapy is also challenging. Drug–drug interactions can have adverse effects. The optimal timing, duration, and long-term safety of the two regimens are important. It will be important in future work to develop patient stratification with multi-omics, to develop novel personalized drug delivery systems, and to use artificial intelligence models to predict optimal drug combinations. Well-designed clinical trials are needed to determine the optimal timing, duration, and long-term safety of such regimens. Such trials should facilitate the translation of strategies targeting the "metabolism–senescence axis" from concept to clinical practice, thereby providing more effective therapeutic options for HF.

6. Conclusion

HF progression is driven by a cycle between dysregulated lipid metabolism and senescence. The most significant mechanisms are: (1) direct pro-senescent signaling by toxic lipids such as ceramide; (2) mitochondrial damage through oxidative stress promoting p53/p21 and p16INK4a/Rb; and (3) a pro-senescent microenvironment due to altered metabolic signaling, including SIRT1 downregulation and mTOR activation. This cycle is followed by the SASP, causing metabolic dysregulation and thus a self-amplifying pathological axis. Treatments that target this axis include a combination of upstream measures that promote metabolic homeostasis (e.g., SGLT2 inhibitors, PPAR modulators) and downstream measures that remove senescent cells (i.e., senolytics). Combined therapies that use a sequence of metabolic modulators and senolytic treatment have demonstrated synergy. Further work includes the development of accurate senescence markers, the design of customized combination strategies, and long-term safety analysis allowing the implementation of a strategy based on the "metabolism–senescence axis", thereby opening new avenues for HF therapy.

Author Contributions

WH and RX conceived the review and supervised the project. WH, RX, QW, and YQZ contributed to the conceptualization and design of the review framework. PL and JJK performed the literature search, screening, and data extraction, and wrote the initial draft. QW and YQZ conducted the critical analysis and synthesis of the retrieved literature, and participated in the interpretation of key find-

ings. All authors contributed to manuscript revision and approved the final version. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work, ensuring its accuracy and integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the author used ChatGPT to check spelling and grammar throughout the text. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

References

[1] Hu SS, Wang ZW. Summary of the "Report on Cardiovascular Health and Diseases in China 2022". Chinese Journal of Cardiac Critical Care. 2023; 21: 577–600. (In Chinese)

[2] Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. Circulation. 2023; 147: e93–e621. https://doi.org/10.1161/CIR.0000000000001123

[3] Baman JR, Ahmad FS. Heart Failure. JAMA. 2020; 324: 1015. https://doi.org/10.1001/jama.2020.13310

[4] Capone F, Sotomayor-Flores C, Bode D, Wang R, Rodolico D, Strocchi S, et al. Cardiac metabolism in HFpEF: from fuel to signalling. Cardiovascular Research. 2023; 118: 3556–3575. https://doi.org/10.1093/cvr/cvac166

[5] Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nature Reviews. Cardiology. 2017; 14: 591–602. https://doi.org/10.1038/nrcardio.2017.65

[6] Li Y, Wu X, Pan J, Gong L, Min D. Hepatocyte steatosis activates macrophage inflammatory response accelerating atherosclerosis development. Zhejiang Da Xue Xue Bao. Yi Xue Ban = Journal of Zhejiang University. Medical Sciences. 2023; 52: 751–765. https://doi.org/10.3724/zdxbyxb-2023-0315

[7] Omasa T, Okuyama S, Sawamoto A, Nakajima M, Furukawa Y. Effects of *Citrus kawachiensis* Peel in Frailty-like Model Mice Induced by Low Protein Nutrition Disorders. Antioxidants (Basel, Switzerland). 2023; 12: 779. https://doi.org/10.3390/antiox12030779

[8] De Cauwer A, Loustau T, Erne W, Pichot A, Molitor A, Stemmelen T, et al. *Dicer1* deficient mice exhibit premature aging and metabolic perturbations in adipocytes. iscience. 2022; 25: 105149. https://doi.org/10.1016/j.isci.2022.105149

[9] Yamamoto T, Sano M. Deranged Myocardial Fatty Acid Metabolism in Heart Failure. International Journal of Molecular Sciences. 2022; 23: 996. https://doi.org/10.3390/ijms23020996

[10] Zhou J, Chong SY, Lim A, Singh BK, Sinha RA, Salmon AB, et al. Changes in macroautophagy, chaperone-mediated autophagy, and mitochondrial metabolism in murine skeletal and cardiac muscle during aging. Aging. 2017; 9: 583–599. https://doi.org/10.18632/aging.101181

[11] Cieslik KA, Sekhar RV, Granillo A, Reddy A, Medrano G, Heredia CP, et al. Improved Cardiovascular Function in Old Mice After N-Acetyl Cysteine and Glycine Supplemented Diet: Inflammation and Mitochondrial Factors. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2018; 73: 1167–1177. https://doi.org/10.1093/gerona/gly034

[12] Bonen A, Han XX, Habets DDJ, Febbraio M, Glatz JFC, Luiken JJFP. A null mutation in skeletal muscle FAT/CD36 reveals its essential role in insulin- and AICAR-stimulated fatty acid metabolism. American Journal of Physiology. Endocrinology and Metabolism. 2007; 292: E1740–E1749. https://doi.org/10.1152/ajpendo.00579.2006

[13] Chen J, Aronowitz P. Congestive Heart Failure. The Medical Clinics of North America. 2022; 106: 447–458. https://doi.org/10.1016/j.mcna.2021.12.002

[14] Barger PM, Kelly DP. PPAR signaling in the control of cardiac energy metabolism. Trends in Cardiovascular Medicine. 2000; 10: 238–245. https://doi.org/10.1016/s1050-1738(00)00077-3

[15] Da Dalt L, Cabodevilla AG, Goldberg IJ, Norata GD. Cardiac lipid metabolism, mitochondrial function, and heart failure. Cardiovascular Research. 2023; 119: 1905–1914. https://doi.org/10.1093/cvr/cvad100

[16] Li W, Yao M, Wang R, Shi Y, Hou L, Hou Z, et al. Profile of cardiac lipid metabolism in STZ-induced diabetic mice. Lipids in Health and Disease. 2018; 17: 231. https://doi.org/10.1186/s12944-018-0872-8

[17] Puri K, Lal N, Shang R, Ghosh S, Flibotte S, Dyer R, et al. Diabetes Mellitus Severity and a Switch From Using Lipoprotein Lipase to Adipose-Derived Fatty Acid Results in a Cardiac Metabolic Signature That Embraces Cell Death. Journal of the American Heart Association. 2019; 8: e014022. https://doi.org/10.1161/JAHA.119.014022

[18] Zhang Y, Bharathi SS, Beck ME, Goetzman ES. The fatty acid oxidation enzyme long-chain acyl-CoA dehydrogenase can be a source of mitochondrial hydrogen peroxide. Redox Biology. 2019; 26: 101253. https://doi.org/10.1016/j.redox.2019.101253

[19] Acosta-Montaño P, Rodríguez-Velázquez E, Ibarra-López E, Frayde-Gómez H, Mas-Oliva J, Delgado-Coello B, et al. Fatty Acid and Lipopolysaccharide Effect on Beta Cells Proteostasis and its Impact on Insulin Secretion. Cells. 2019; 8: 884. https://doi.org/10.3390/cells8080884

[20] Dong S, Zhang R, Liang Y, Shi J, Li J, Shang F, et al. Changes of myocardial lipidomics profiling in a rat model of diabetic cardiomyopathy using UPLC/Q-TOF/MS analysis. Diabetology & Metabolic Syndrome. 2017; 9: 56. https://doi.org/10.1186/s13098-017-0249-6

[21] Wu T, Huang T, Ren H, Shen C, Qian J, Fu X, et al. Metabolic Coordination Structures Contribute to Diabetic Myocardial Dysfunction. Circulation Research. 2025; 136: 946–967. https://doi.org/10.1161/CIRCRESAHA.124.326044

[22] Li H, Fan J, Zhao Y, Zhang X, Dai B, Zhan J, et al. Nuclear miR-320 Mediates Diabetes-Induced Cardiac Dysfunction

by Activating Transcription of Fatty Acid Metabolic Genes to Cause Lipotoxicity in the Heart. Circulation Research. 2019; 125: 1106–1120. https://doi.org/10.1161/CIRCRESAHA.119.314898

[23] Kienesberger PC, Pulinilkunnil T, Nagendran J, Dyck JRB. Myocardial triacylglycerol metabolism. Journal of Molecular and Cellular Cardiology. 2013; 55: 101–110. https://doi.org/10.1016/j.yjmcc.2012.06.018

[24] Suzuki J, Shen WJ, Nelson BD, Patel S, Veerkamp JH, Selwood SP, et al. Absence of cardiac lipid accumulation in transgenic mice with heart-specific HSL overexpression. American Journal of Physiology. Endocrinology and Metabolism. 2001; 281: E857–E866. https://doi.org/10.1152/ajpendo.2001.281.4.E857

[25] Zheng P, Xie Z, Yuan Y, Sui W, Wang C, Gao X, et al. Plin5 alleviates myocardial ischaemia/reperfusion injury by reducing oxidative stress through inhibiting the lipolysis of lipid droplets. Scientific Reports. 2017; 7: 42574. https://doi.org/10.1038/srep42574

[26] Pollak NM, Schweiger M, Jaeger D, Kolb D, Kumari M, Schreiber R, et al. Cardiac-specific overexpression of perilipin 5 provokes severe cardiac steatosis via the formation of a lipolytic barrier. Journal of Lipid Research. 2013; 54: 1092–1102. https://doi.org/10.1194/jlr.M034710

[27] Haemmerle G, Lass A, Zimmermann R, Gorkiewicz G, Meyer C, Rozman J, et al. Defective lipolysis and altered energy metabolism in mice lacking adipose triglyceride lipase. Science (New York, N.Y.). 2006; 312: 734–737. https://doi.org/10.1126/science.1123965

[28] Harris CA, Haas JT, Streeper RS, Stone SJ, Kumari M, Yang K, et al. DGAT enzymes are required for triacylglycerol synthesis and lipid droplets in adipocytes. Journal of Lipid Research. 2011; 52: 657–667. https://doi.org/10.1194/jlr.M013003

[29] Liu L, Trent CM, Fang X, Son NH, Jiang H, Blaner WS, et al. Cardiomyocyte-specific loss of diacylglycerol acyltransferase 1 (DGAT1) reproduces the abnormalities in lipids found in severe heart failure. The Journal of Biological Chemistry. 2014; 289: 29881–29891. https://doi.org/10.1074/jbc.M114.601864

[30] Lin LC, Liu ZY, Yang JJ, Zhao JY, Tao H. Lipid metabolism reprogramming in cardiac fibrosis. Trends in Endocrinology and Metabolism: TEM. 2024; 35: 164–175. https://doi.org/10.1016/j.tem.2023.10.004

[31] Liu Q, Siloto RMP, Lehner R, Stone SJ, Weselake RJ. Acyl-CoA:diacylglycerol acyltransferase: molecular biology, biochemistry and biotechnology. Progress in Lipid Research. 2012; 51: 350–377. https://doi.org/10.1016/j.plipres.2012.06.001

[32] Zhao M, Bian R, Xu X, Zhang J, Zhang L, Zheng Y. Sphingolipid Metabolism and Signalling Pathways in Heart Failure: From Molecular Mechanism to Therapeutic Potential. Journal of Inflammation Research. 2025; 18: 5477–5498. https://doi.org/10.2147/JIR.S515757

[33] Liu L, Shi X, Bharadwaj KG, Ikeda S, Yamashita H, Yagyu H, et al. DGAT1 expression increases heart triglyceride content but ameliorates lipotoxicity. The Journal of Biological Chemistry. 2009; 284: 36312–36323. https://doi.org/10.1074/jbc.M109.049817

[34] Ballard FB, Danforth WH, Naegle S, Bing RJ. Myocardial metabolism of fatty acids. The Journal of Clinical Investigation. 1960; 39: 717–723. https://doi.org/10.1172/JCI104088

[35] Fucho R, Casals N, Serra D, Herrero L. Ceramides and mitochondrial fatty acid oxidation in obesity. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2017; 31: 1263–1272. https://doi.org/10.1096/fj.201601156R

[36] Schulze PC. Myocardial lipid accumulation and lipotoxicity in heart failure. Journal of Lipid Research. 2009; 50: 2137–2138. https://doi.org/10.1194/jlr.R001115

[37] Bikman BT, Summers SA. Ceramides as modulators of cellular and whole-body metabolism. The Journal of Clinical Investigation. 2011; 121: 4222–4230. https://doi.org/10.1172/JCI57144

[38] Holland WL, Bikman BT, Wang LP, Yuguang G, Sargent KM, Bulchand S, et al. Lipid-induced insulin resistance mediated by the proinflammatory receptor TLR4 requires saturated fatty acid-induced ceramide biosynthesis in mice. The Journal of Clinical Investigation. 2011; 121: 1858–1870. https://doi.org/10.1172/JCI43378

[39] D'Souza K, Nzirorera C, Kienesberger PC. Lipid metabolism and signaling in cardiac lipotoxicity. Biochimica et Biophysica Acta. 2016; 1861: 1513–1524. https://doi.org/10.1016/j.bbalip.2016.02.016

[40] Stratford S, Hoehn KL, Liu F, Summers SA. Regulation of insulin action by ceramide: dual mechanisms linking ceramide accumulation to the inhibition of Akt/protein kinase B. The Journal of Biological Chemistry. 2004; 279: 36608–36615. https://doi.org/10.1074/jbc.M406499200

[41] Powell DJ, Hajduch E, Kular G, Hundal HS. Ceramide disables 3-phosphoinositide binding to the pleckstrin homology domain of protein kinase B (PKB)/Akt by a PKCzeta-dependent mechanism. Molecular and Cellular Biology. 2003; 23: 7794–7808. https://doi.org/10.1128/MCB.23.21.7794-7808.2003

[42] Park TS, Hu Y, Noh HL, Drosatos K, Okajima K, Buchanan J, et al. Ceramide is a cardiotoxin in lipotoxic cardiomyopathy. Journal of Lipid Research. 2008; 49: 2101–2112. https://doi.org/10.1194/jlr.M800147-JLR200

[43] Miura A, Kajita K, Ishizawa M, Kanoh Y, Kawai Y, Natsume Y, et al. Inhibitory effect of ceramide on insulin-induced protein kinase Czeta translocation in rat adipocytes. Metabolism: Clinical and Experimental. 2003; 52: 19–24. https://doi.org/10.1053/meta.2003.50011

[44] Jaeschke A, Davis RJ. Metabolic stress signaling mediated by mixed-lineage kinases. Molecular Cell. 2007; 27: 498–508. https://doi.org/10.1016/j.molcel.2007.07.008

[45] Galadari S, Rahman A, Pallichankandy S, Galadari A, Thayyullathil F. Role of ceramide in diabetes mellitus: evidence and mechanisms. Lipids in Health and Disease. 2013; 12: 98. https://doi.org/10.1186/1476-511X-12-98

[46] Sathyanarayana P, Barthwal MK, Kundu CN, Lane ME, Bergmann A, Tzivion G, et al. Activation of the Drosophila MLK by ceramide reveals TNF-alpha and ceramide as agonists of mammalian MLK3. Molecular Cell. 2002; 10: 1527–1533. https://doi.org/10.1016/s1097-2765(02)00734-7

[47] Xu Z, Maroney AC, Dobrzanski P, Kukekov NV, Greene LA. The MLK family mediates c-Jun N-terminal kinase activation in neuronal apoptosis. Molecular and Cellular Biology. 2001; 21: 4713–4724. https://doi.org/10.1128/MCB.21.14.4713-4724.2001

[48] Kanety H, Hemi R, Papa MZ, Karasik A. Sphingomyelinase and ceramide suppress insulin-induced tyrosine phosphorylation of the insulin receptor substrate-1. The Journal of Biological Chemistry. 1996; 271: 9895–9897. https://doi.org/10.1074/jbc.271.17.9895

[49] Ola A, Kerkelä R, Tokola H, Pikkarainen S, Skoumal R, Vuolteenaho O, et al. The mixed-lineage kinase 1-3 signalling pathway regulates stress response in cardiac myocytes via GATA-4 and AP-1 transcription factors. British Journal of Pharmacology. 2010; 159: 717–725. https://doi.org/10.1111/j.1476-5381.2009.00567.x

[50] Chen CL, Lin CF, Chang WT, Huang WC, Teng CF, Lin YS. Ceramide induces p38 MAPK and JNK activation through a mechanism involving a thioredoxin-interacting protein-mediated pathway. Blood. 2008; 111: 4365–4374. https://doi.org/10.1182/blood-2007-08-106336

[51] Hannun YA, Obeid LM. Principles of bioactive lipid signalling:

lessons from sphingolipids. Nature Reviews. Molecular Cell Biology. 2008; 9: 139–150. https://doi.org/10.1038/nrm2329
[52] Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. Immunity. 2012; 36: 401–414. https://doi.org/10.1016/j.immuni.2012.01.009
[53] Kawai T, Akira S. TLR signaling. Seminars in Immunology. 2007; 19: 24–32. https://doi.org/10.1016/j.smim.2006.12.004
[54] Zhang LX, Zhao Y, Cheng G, Guo TL, Chin YE, Liu PY, et al. Targeted deletion of NF-kappaB p50 diminishes the cardioprotection of histone deacetylase inhibition. American journal of physiology. Heart and circulatory physiology. 2010; 298: H2154–H2163. https://doi.org/10.1152/ajpheart.01015.2009
[55] Zhao T, He L, Wong LP, Mei S, Xia J, Xu Y, et al. Derepressing nuclear pyruvate dehydrogenase induces therapeutic cancer cell reprogramming. Cell Metabolism. 2025; 37: 1667–1681.e13. https://doi.org/10.1016/j.cmet.2025.05.009
[56] Pettus BJ, Chalfant CE, Hannun YA. Ceramide in apoptosis: an overview and current perspectives. Biochimica et Biophysica Acta. 2002; 1585: 114–125. https://doi.org/10.1016/s1388-1981(02)00331-1
[57] Auge N, Garcia V, Maupas-Schwalm F, Levade T, Salvayre R, Negre-Salvayre A. Oxidized LDL-induced smooth muscle cell proliferation involves the EGF receptor/PI-3 kinase/Akt and the sphingolipid signaling pathways. Arteriosclerosis, Thrombosis, and Vascular Biology. 2002; 22: 1990–1995. https://doi.org/10.1161/01.atv.0000043453.21629.3b
[58] Abdalla S, Fu X, Elzahwy SS, Klaetschke K, Streichert T, Quitterer U. Up-regulation of the cardiac lipid metabolism at the onset of heart failure. Cardiovascular & Hematological Agents in Medicinal Chemistry. 2011; 9: 190–206. https://doi.org/10.2174/187152511797037583
[59] Dookun E, Walaszczyk A, Redgrave R, Palmowski P, Tual-Chalot S, Suwana A, et al. Clearance of senescent cells during cardiac ischemia-reperfusion injury improves recovery. Aging Cell. 2020; 19: e13249. https://doi.org/10.1111/acel.13249
[60] Walaszczyk A, Dookun E, Redgrave R, Tual-Chalot S, Victorelli S, Spyridopoulos I, et al. Pharmacological clearance of senescent cells improves survival and recovery in aged mice following acute myocardial infarction. Aging Cell. 2019; 18: e12945. https://doi.org/10.1111/acel.12945
[61] Salerno N, Marino F, Scalise M, Salerno L, Molinaro C, Filardo A, et al. Pharmacological clearance of senescent cells improves cardiac remodeling and function after myocardial infarction in female aged mice. Mechanisms of Ageing and Development. 2022; 208: 111740. https://doi.org/10.1016/j.mad.2022.111740
[62] Witham MD, Granic A, Miwa S, Passos JF, Richardson GD, Sayer AA. New Horizons in cellular senescence for clinicians. Age and Ageing. 2023; 52: afad127. https://doi.org/10.1093/ageing/afad127
[63] Booth LK, Redgrave RE, Tual-Chalot S, Spyridopoulos I, Phillips HM, Richardson GD. Heart Disease and Ageing: The Roles of Senescence, Mitochondria, and Telomerase in Cardiovascular Disease. Sub-cellular Biochemistry. 2023; 103: 45–78. https://doi.org/10.1007/978-3-031-26576-1_4
[64] Booth LK, Redgrave RE, Folaranmi O, Gill JH, Richardson GD. Anthracycline-induced cardiotoxicity and senescence. Frontiers in Aging. 2022; 3: 1058435. https://doi.org/10.3389/fragi.2022.1058435
[65] Dookun E, Passos JF, Arthur HM, Richardson GD. Therapeutic Potential of Senolytics in Cardiovascular Disease. Cardiovascular Drugs and Therapy. 2022; 36: 187–196. https://doi.org/10.1007/s10557-020-07075-w
[66] Kim KH, Park B, Rhee DK, Pyo S. Acrylamide Induces Senescence in Macrophages through a Process Involving ATF3, ROS, p38/JNK, and a Telomerase-Independent Pathway. Chemical Research in Toxicology. 2015; 28: 71–86. https://doi.org/10.1021/tx500341z
[67] Anderson EJ, Kypson AP, Rodriguez E, Anderson CA, Lehr EJ, Neufer PD. Substrate-specific derangements in mitochondrial metabolism and redox balance in the atrium of the type 2 diabetic human heart. Journal of the American College of Cardiology. 2009; 54: 1891–1898. https://doi.org/10.1016/j.jacc.2009.07.031
[68] Kienesberger PC, Pulinilkunnil T, Nagendran J, Young ME, Bogner-Strauss JG, Hackl H, et al. Early structural and metabolic cardiac remodelling in response to inducible adipose triglyceride lipase ablation. Cardiovascular Research. 2013; 99: 442–451. https://doi.org/10.1093/cvr/cvt124
[69] Chang WT, Wu CY, Lin YC, Wu MT, Su KL, Yuan SS, et al. C_2-Ceramide-Induced Rb-Dominant Senescence-Like Phenotype Leads to Human Breast Cancer MCF-7 Escape from *p*53-Dependent Cell Death. International Journal of Molecular Sciences. 2019; 20: 4292. https://doi.org/10.3390/ijms20174292
[70] Bulavin DV, Saito S, Hollander MC, Sakaguchi K, Anderson CW, Appella E, et al. Phosphorylation of human p53 by p38 kinase coordinates N-terminal phosphorylation and apoptosis in response to UV radiation. The EMBO Journal. 1999; 18: 6845–6854. https://doi.org/10.1093/emboj/18.23.6845
[71] Gartel AL, Tyner AL. The role of the cyclin-dependent kinase inhibitor p21 in apoptosis. Molecular Cancer Therapeutics. 2002; 1: 639–649.
[72] Holland WL, Brozinick JT, Wang LP, Hawkins ED, Sargent KM, Liu Y, et al. Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance. Cell Metabolism. 2007; 5: 167–179. https://doi.org/10.1016/j.cmet.2007.01.002
[73] de Mello VDF, Lankinen M, Schwab U, Kolehmainen M, Lehto S, Seppänen-Laakso T, et al. Link between plasma ceramides, inflammation and insulin resistance: association with serum IL-6 concentration in patients with coronary heart disease. Diabetologia. 2009; 52: 2612–2615. https://doi.org/10.1007/s00125-009-1482-9
[74] Chokshi A, Drosatos K, Cheema FH, Ji R, Khawaja T, Yu S, et al. Ventricular assist device implantation corrects myocardial lipotoxicity, reverses insulin resistance, and normalizes cardiac metabolism in patients with advanced heart failure. Circulation. 2012; 125: 2844–2853. https://doi.org/10.1161/CIRCULATIONAHA.111.060889
[75] Steinberg SF. Structural basis of protein kinase C isoform function. Physiological Reviews. 2008; 88: 1341–1378. https://doi.org/10.1152/physrev.00034.2007
[76] Li Y, Soos TJ, Li X, Wu J, Degennaro M, Sun X, et al. Protein kinase C Theta inhibits insulin signaling by phosphorylating IRS1 at Ser(1101). The Journal of Biological Chemistry. 2004; 279: 45304–45307. https://doi.org/10.1074/jbc.C400186200
[77] Murriel CL, Mochly-Rosen D. Opposing roles of delta and epsilonPKC in cardiac ischemia and reperfusion: targeting the apoptotic machinery. Archives of Biochemistry and Biophysics. 2003; 420: 246–254. https://doi.org/10.1016/j.abb.2003.08.038
[78] Samstad EO, Niyonzima N, Nymo S, Aune MH, Ryan L, Bakke SS, et al. Cholesterol crystals induce complement-dependent inflammasome activation and cytokine release. Journal of Immunology (Baltimore, Md.: 1950). 2014; 192: 2837–2845. https://doi.org/10.4049/jimmunol.1302484
[79] Duewell P, Kono H, Rayner KJ, Sirois CM, Vladimer G, Bauernfeind FG, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature. 2010; 464: 1357–1361. https://doi.org/10.1038/nature08938
[80] He WT, Wan H, Hu L, Chen P, Wang X, Huang Z, et al. Gasdermin D is an executor of pyroptosis and required for interleukin-1β secretion. Cell Research. 2015; 25: 1285–1298. https://doi.

org/10.1038/cr.2015.139
[81] Acosta JC, Banito A, Wuestefeld T, Georgilis A, Janich P, Morton JP, et al. A complex secretory program orchestrated by the inflammasome controls paracrine senescence. Nature Cell Biology. 2013; 15: 978–990. https://doi.org/10.1038/ncb2784
[82] Paradies G, Paradies V, Ruggiero FM, Petrosillo G. Role of Cardiolipin in Mitochondrial Function and Dynamics in Health and Disease: Molecular and Pharmacological Aspects. Cells. 2019; 8: 728. https://doi.org/10.3390/cells8070728
[83] Chu CT, Ji J, Dagda RK, Jiang JF, Tyurina YY, Kapralov AA, et al. Cardiolipin externalization to the outer mitochondrial membrane acts as an elimination signal for mitophagy in neuronal cells. Nature Cell Biology. 2013; 15: 1197–1205. https://doi.org/10.1038/ncb2837
[84] Shen Z, Ye C, McCain K, Greenberg ML. The Role of Cardiolipin in Cardiovascular Health. BioMed Research International. 2015; 2015: 891707. https://doi.org/10.1155/2015/891707
[85] Yakes FM, Van Houten B. Mitochondrial DNA damage is more extensive and persists longer than nuclear DNA damage in human cells following oxidative stress. Proceedings of the National Academy of Sciences of the United States of America. 1997; 94: 514–519. https://doi.org/10.1073/pnas.94.2.514
[86] Barnes RP, Fouquerel E, Opresko PL. The impact of oxidative DNA damage and stress on telomere homeostasis. Mechanisms of Ageing and Development. 2019; 177: 37–45. https://doi.org/10.1016/j.mad.2018.03.013
[87] Ota H, Akishita M, Eto M, Iijima K, Kaneki M, Ouchi Y. Sirt1 modulates premature senescence-like phenotype in human endothelial cells. Journal of Molecular and Cellular Cardiology. 2007; 43: 571–579. https://doi.org/10.1016/j.yjmcc.2007.08.008
[88] Kim WY, Sharpless NE. The regulation of INK4/ARF in cancer and aging. Cell. 2006; 127: 265–275. https://doi.org/10.1016/j.cell.2006.10.003
[89] Daigh LH, Saha D, Rosenthal DL, Ferrick KR, Meyer T. Uncoupling of mTORC1 from E2F activity maintains DNA damage and senescence. Nature Communications. 2024; 15: 9181. https://doi.org/10.1038/s41467-024-52820-6
[90] Galloway CA, Yoon Y. Mitochondrial morphology in metabolic diseases. Antioxidants & Redox Signaling. 2013; 19: 415–430. https://doi.org/10.1089/ars.2012.4779
[91] Bingol B, Tea JS, Phu L, Reichelt M, Bakalarski CE, Song Q, et al. The mitochondrial deubiquitinase USP30 opposes parkin-mediated mitophagy. Nature. 2014; 510: 370–375. https://doi.org/10.1038/nature13418
[92] Mengus C, Neutzner M, Bento ACPF, Bippes CC, Kohler C, Decembrini S, et al. VCP/p97 cofactor UBXN1/SAKS1 regulates mitophagy by modulating MFN2 removal from mitochondria. Autophagy. 2022; 18: 171–190. https://doi.org/10.1080/15548627.2021.1922982
[93] Sun N, Barta H, Chaudhuri S, Chen K, Jin J, Luo H, et al. Mitophagy mitigates mitochondrial fatty acid β-oxidation deficient cardiomyopathy. Nature Communications. 2025; 16: 5465. https://doi.org/10.1038/s41467-025-60670-z
[94] Fonseka O, Raja R, Ross C, Gare SR, Zhang J, Hille SS, et al. XBP1s-EDEM2 Prevents the Onset and Development of HFpEF by Ameliorating Cardiac Lipotoxicity. Circulation. 2025; 151: 1583–1605. https://doi.org/10.1161/CIRCULATIONAHA.124.072194
[95] Laplante M, Sabatini DM. mTOR signaling in growth control and disease. Cell. 2012; 149: 274–293. https://doi.org/10.1016/j.cell.2012.03.017
[96] Porstmann T, Santos CR, Griffiths B, Cully M, Wu M, Leevers S, et al. SREBP activity is regulated by mTORC1 and contributes to Akt-dependent cell growth. Cell Metabolism. 2008; 8: 224–236. https://doi.org/10.1016/j.cmet.2008.07.007
[97] Shimano H, Sato R. SREBP-regulated lipid metabolism: convergent physiology - divergent pathophysiology. Nature Reviews. Endocrinology. 2017; 13: 710–730. https://doi.org/10.1038/nrendo.2017.91
[98] Düvel K, Yecies JL, Menon S, Raman P, Lipovsky AI, Souza AL, et al. Activation of a metabolic gene regulatory network downstream of mTOR complex 1. Molecular Cell. 2010; 39: 171–183. https://doi.org/10.1016/j.molcel.2010.06.022
[99] Horton JD, Goldstein JL, Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. The Journal of Clinical Investigation. 2002; 109: 1125–1131. https://doi.org/10.1172/JCI15593
[100] Moon YA, Liang G, Xie X, Frank-Kamenetsky M, Fitzgerald K, Koteliansky V, et al. The Scap/SREBP pathway is essential for developing diabetic fatty liver and carbohydrate-induced hypertriglyceridemia in animals. Cell Metabolism. 2012; 15: 240–246. https://doi.org/10.1016/j.cmet.2011.12.017
[101] Wong LSM, de Boer RA, Samani NJ, van Veldhuisen DJ, van der Harst P. Telomere biology in heart failure. European Journal of Heart Failure. 2008; 10: 1049–1056. https://doi.org/10.1016/j.ejheart.2008.08.007
[102] Owens WA, Walaszczyk A, Spyridopoulos I, Dookun E, Richardson GD. Senescence and senolytics in cardiovascular disease: Promise and potential pitfalls. Mechanisms of Ageing and Development. 2021; 198: 111540. https://doi.org/10.1016/j.mad.2021.111540
[103] Hoffmann J, Richardson G, Haendeler J, Altschmied J, Andrés V, Spyridopoulos I. Telomerase as a Therapeutic Target in Cardiovascular Disease. Arteriosclerosis, Thrombosis, and Vascular Biology. 2021; 41: 1047–1061. https://doi.org/10.1161/ATVBAHA.120.315695
[104] Wang Z, Liu W, Zhang M, Yan J, Fei J, Zhang K, et al. Canthaxanthin Mitigates Cardiovascular Senescence in Vitro and in Vivo. Frontiers in Bioscience (Landmark edition). 2024; 29: 70. https://doi.org/10.31083/j.fbl2902070
[105] Li R, Teng Y, Guo Y, Ren J, Li R, Luo H, et al. Aging-related decrease of histone methyltransferase SUV39H1 in adipose-derived stem cells enhanced SASP. Mechanisms of Ageing and Development. 2023; 215: 111868. https://doi.org/10.1016/j.mad.2023.111868
[106] Wang B, Han J, Elisseeff JH, Demaria M. The senescence-associated secretory phenotype and its physiological and pathological implications. Molecular Cell Biology. 2024; 25: 958–978. https://doi.org/10.1038/s41580-024-00727-x
[107] Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. Frontiers in Immunology. 2018; 9: 586. https://doi.org/10.3389/fimmu.2018.00586
[108] Ryczkowska K, Adach W, Janikowski K, Banach M, Bielecka-Dabrowa A. Menopause and women's cardiovascular health: is it really an obvious relationship? Archives of Medical Science: AMS. 2022; 19: 458–466. https://doi.org/10.5114/aoms/157308
[109] Seeger T, Haffez F, Fischer A, Koehl U, Leistner DM, Seeger FH, et al. Immunosenescence-associated microRNAs in age and heart failure. European Journal of Heart Failure. 2013; 15: 385–393. https://doi.org/10.1093/eurjhf/hfs184
[110] Shinmura K. Cardiac Senescence, Heart Failure, and Frailty: A Triangle in Elderly People. The Keio Journal of Medicine. 2016; 65: 25–32. https://doi.org/10.2302/kjm.2015-0015-IR
[111] Coppé JP, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biology. 2008; 6: 2853–2868. https://doi.org/10.1371/journal.pbio.0060301
[112] Wajapeyee N, Serra RW, Zhu X, Mahalingam M, Green MR. Oncogenic BRAF induces senescence and apoptosis through

pathways mediated by the secreted protein IGFBP7. Cell. 2008; 132: 363–374. https://doi.org/10.1016/j.cell.2007.12.032
[113] Kuilman T, Michaloglou C, Vredeveld LCW, Douma S, van Doorn R, Desmet CJ, et al. Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. Cell. 2008; 133: 1019–1031. https://doi.org/10.1016/j.cell.2008.03.039
[114] Xu M, Pirtskhalava T, Farr JN, Weigand BM, Palmer AK, Weivoda MM, et al. Senolytics improve physical function and increase lifespan in old age. Nature Medicine. 2018; 24: 1246–1256. https://doi.org/10.1038/s41591-018-0092-9
[115] Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nature Reviews. Endocrinology. 2018; 14: 576–590. https://doi.org/10.1038/s41574-018-0059-4
[116] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. Cell. 2023; 186: 243–278. https://doi.org/10.1016/j.cell.2022.11.001
[117] Hua Y, Robinson TJ, Cao Y, Shi GP, Ren J, Nair S, et al. Cathepsin K knockout alleviates aging-induced cardiac dysfunction. Aging Cell. 2015; 14: 345–351. https://doi.org/10.1111/acel.12276
[118] Fang CL, Liu B, Wan M. "Bone-SASP" in Skeletal Aging. Calcified Tissue International. 2023; 113: 68–82. https://doi.org/10.1007/s00223-023-01100-4
[119] Kanda H, Tateya S, Tamori Y, Kotani K, Hiasa KI, Kitazawa R, et al. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. The Journal of Clinical Investigation. 2006; 116: 1494–1505. https://doi.org/10.1172/JCI26498
[120] Spinale FG. Myocardial matrix remodeling and the matrix metalloproteinases: influence on cardiac form and function. Physiological Reviews. 2007; 87: 1285–1342. https://doi.org/10.1152/physrev.00012.2007
[121] Luo Y, Yu Y, Zeng F, Yi Y, Lu Z, Lin B, et al. Acetylation of FABP3 alleviates radioimmunotherapy-induced cardiomyocyte senescence by modulating long-chain polyunsaturated fatty acid metabolism. International Immunopharmacology. 2025; 160: 114912. https://doi.org/10.1016/j.intimp.2025.114912
[122] Childs BG, Durik M, Baker DJ, van Deursen JM. Cellular senescence in aging and age-related disease: from mechanisms to therapy. Nature Medicine. 2015; 21: 1424–1435. https://doi.org/10.1038/nm.4000
[123] Chen GY, Nuñez G. Sterile inflammation: sensing and reacting to damage. Nature Reviews. Immunology. 2010; 10: 826–837. https://doi.org/10.1038/nri2873
[124] Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. The New England Journal of Medicine. 2020; 383: 1413–1424. https://doi.org/10.1056/NEJMoa2022190
[125] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England Journal of Medicine. 2015; 373: 2117–2128. https://doi.org/10.1056/NEJMoa1504720
[126] de Souza SLB, Mota GAF, da Silva VL, Vileigas DF, Sant'Ana PG, Gregolin CS, et al. Effects of early exercise on cardiac function and lipid metabolism pathway in heart failure. Journal of Cellular and Molecular Medicine. 2023; 27: 2956–2969. https://doi.org/10.1111/jcmm.17908
[127] Pradhan AD, Paynter NP, Everett BM, Glynn RJ, Amarenco P, Elam M, et al. Rationale and design of the Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study. American Heart Journal. 2018; 206: 80–93. https://doi.org/10.1016/j.ahj.2018.09.011
[128] Goh KY, He L, Song J, Jinno M, Rogers AJ, Sethu P, et al. Mitoquinone ameliorates pressure overload-induced cardiac fibrosis and left ventricular dysfunction in mice. Redox Biology. 2019; 21: 101100. https://doi.org/10.1016/j.redox.2019.101100
[129] Mingorance C, Rodriguez-Rodriguez R, Justo ML, Herrera MD, de Sotomayor MA. Pharmacological effects and clinical applications of propionyl-L-carnitine. Nutrition Reviews. 2011; 69: 279–290. https://doi.org/10.1111/j.1753-4887.2011.00387.x
[130] Chaurasia B, Summers SA. Ceramides in Metabolism: Key Lipotoxic Players. Annual Review of Physiology. 2021; 83: 303–330. https://doi.org/10.1146/annurev-physiol-031620-093815
[131] Xu M, Tchkonia T, Ding H, Ogrodnik M, Lubbers ER, Pirtskhalava T, et al. JAK inhibition alleviates the cellular senescence-associated secretory phenotype and frailty in old age. Proceedings of the National Academy of Sciences of the United States of America. 2015; 112: E6301–E6310. https://doi.org/10.1073/pnas.1515386112
[132] Zhu Y, Tchkonia T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, et al. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. Aging Cell. 2015; 14: 644–658. https://doi.org/10.1111/acel.12344
[133] Roos CM, Zhang B, Palmer AK, Ogrodnik MB, Pirtskhalava T, Thalji NM, et al. Chronic senolytic treatment alleviates established vasomotor dysfunction in aged or atherosclerotic mice. Aging Cell. 2016; 15: 973–977. https://doi.org/10.1111/acel.12458
[134] Mourad O, Mastikhina O, Khan S, Sun X, Hatkar R, Williams K, et al. Antisenescence Therapy Improves Function in a Human Model of Cardiac Fibrosis-on-a-Chip. ACS Materials Au. 2023; 3: 360–370. https://doi.org/10.1021/acsmaterialsau.3c00009
[135] Butler J, Fioretti F, McMullan CJ, Anstrom KJ, Barash I, Bonaca MP, et al. Vericiguat and mortality in heart failure and reduced ejection fraction: the VICTOR trial. European Heart Journal. 2026; 47: 683–697. https://doi.org/10.1093/eurheartj/ehaf655
[136] Hao WR, Chen CC, Li FA, Chen HY, Liu JC, Cheng TH, et al. Therapeutic Impact of Vericiguat on Ventricular Remodeling in a Pressure-Overload Heart Failure Model. Life (Basel, Switzerland). 2025; 15: 1763. https://doi.org/10.3390/life15111763
[137] Butler J, McMullan CJ, Anstrom KJ, Barash I, Bonaca MP, Borentain M, et al. Vericiguat in patients with chronic heart failure and reduced ejection fraction (VICTOR): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet (London, England). 2025; 406: 1341–1350. https://doi.org/10.1016/S0140-6736(25)01665-4
[138] Chang J, Wang Y, Shao L, Laberge RM, Demaria M, Campisi J, et al. Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. Nature Medicine. 2016; 22: 78–83. https://doi.org/10.1038/nm.4010
[139] Zhu Y, Doornebal EJ, Pirtskhalava T, Giorgadze N, Wentworth M, Fuhrmann-Stroissnigg H, et al. New agents that target senescent cells: the flavone, fisetin, and the BCL-X_L inhibitors, A1331852 and A1155463. Aging. 2017; 9: 955–963. https://doi.org/10.18632/aging.101202
[140] Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. The New England Journal of Medicine. 2020; 382: 1883–1893. https://doi.org/10.1056/NEJMoa1915928
[141] Ma J, Guo S, Jiang H, Li B. Efficacy and safety of vericiguat in heart failure: a meta-analysis. The Journal of International Medical Research. 2023; 51: 3000605231159333. https://doi.org/10.1177/03000605231159333
[142] Packer M. Critical Reanalysis of the Mechanisms Underlying the Cardiorenal Benefits of SGLT2 Inhibitors and Reaffirmation

of the Nutrient Deprivation Signaling/Autophagy Hypothesis. Circulation. 2022; 146: 1383–1405. https://doi.org/10.1161/CIRCULATIONAHA.122.061732

[143] Triposkiadis F, Xanthopoulos A, Butler J. Cardiovascular Aging and Heart Failure: JACC Review Topic of the Week. Journal of the American College of Cardiology. 2019; 74: 804–813. https://doi.org/10.1016/j.jacc.2019.06.053

[144] La Grotta R, Frigé C, Matacchione G, Olivieri F, de Candia P, Ceriello A, et al. Repurposing SGLT-2 Inhibitors to Target Aging: Available Evidence and Molecular Mechanisms. International Journal of Molecular Sciences. 2022; 23: 12325. https://doi.org/10.3390/ijms232012325

[145] Katsuumi G, Shimizu I, Suda M, Yoshida Y, Furihata T, Joki Y, et al. SGLT2 inhibition eliminates senescent cells and alleviates pathological aging. Nature Aging. 2024; 4: 926–938. https://doi.org/10.1038/s43587-024-00642-y