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REVIEW

Intervening in Adipocyte Senescence: Lipid Prodrugs as an Emerging Strategy for Metabolic Disease Treatment

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Abstract
The accelerating aging of the global population has made aging and its related diseases major public health challenges in the 21st century. Adipose tissue is not only an energy reservoir but also a crucial endocrine organ and metabolic regulator. Its dysfunction is closely linked to aging and the development of multiple diseases. This review outlines the key characteristics of adipocyte senescence and discusses its pathological contributions to obesity, type 2 diabetes, metabolic dysfunction-associated steatotic liver disease, and cardiovascular diseases. It also summarizes current intervention strategies for adipocyte senescence, including senolytics, senomorphics, caloric restriction, physical exercise, and gene editing. We propose lipid prodrugs as promising adipose tissue delivery platforms that can be coupled with diverse therapeutic agents to increase the local concentration of drugs and minimize systemic toxicity. By utilizing the unique lipid metabolism of adipocytes, this strategy offers a new avenue for therapeutic intervention in adipocyte senescence and its associated metabolic disorders.

Keywords Adipocyte senescence · Aging · Lipid prodrug delivery · Metabolic diseases · Obesity · Type 2 diabetes

1 Introduction

With the accelerated aging of the global population, aging has emerged as a major health challenge of this century. This process is accompanied by a decline in physiological functions and metabolic dysregulation, significantly increasing the risk of chronic diseases [1]. These age-related diseases severely impair the quality of life of elderly people and impose a substantial economic burden on healthcare systems.

During the aging process, metabolic system dysfunction becomes prominent and is characterized by impaired insulin sensitivity, dyslipidemia and systemic chronic inflammation [2]. In recent years, increasing evidence has revealed that adipose tissue is a major driver of organismal aging and age-related diseases [3]. Beyond its role as an energy reservoir, adipose tissue is a central endocrine organ that synthesizes and secretes a wide array of hormones, cytokines, and growth factors, exerting pleiotropic effects on systemic physiology and metabolic homeostasis [4].

Adipose tissue is classified into white adipose tissue (WAT), brown adipose tissue (BAT), and beige adipose tissue on the basis of its morphological, functional, and distributional characteristics [5]. WAT is the predominant fat depot in the human body and is primarily responsible for energy storage. In obesity, the expansion of WAT is accompanied by immune cell infiltration and dysregulated adipokine secretion, making it a significant contributor to metabolic diseases [6]. BAT primarily generates heat through nonshivering thermogenesis to maintain body temperature [7]. Beige adipocytes are inducible thermogenic adipocytes that typically reside within WAT. Upon exposure to stimuli such as cold, exercise, or β-adrenergic receptor activation, they undergo a "browning" process, upregulating the expression of thermogenic genes such as *UCP1* and *PGC-1α* and increasing energy expenditure [8]. The activation of beige adipocytes may offer therapeutic benefits for obesity and metabolic disorders.

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At a young age, adipose tissue exhibits high plasticity and metabolic flexibility, and responds to energy fluctuations through adipocyte hyperplasia and hypertrophy. Adipose progenitor cells (APCs) possess strong differentiation potential and effectively maintain metabolic homeostasis. However, adipose tissue undergoes significant degenerative changes with aging, including adipose redistribution (increased visceral fat and reduced subcutaneous fat), diminished thermogenic function in BAT and beige adipose tissue, impaired proliferative and differentiation capacity of APCs, senescent cell accumulation, and a chronic low-grade inflammatory microenvironment [9]. Collectively, these changes drive adipose dysfunction, converting it from being a metabolic regulator to being a driver of metabolic disorders.

Therefore, adipose tissue aging is not only an early indicator of organismal aging but also a critical link between aging and metabolic disorders. Unraveling the mechanisms and systemic metabolic impacts of adipocyte senescence is critical for developing therapeutic strategies to alleviate age-related diseases. This review outlines the key features of adipocyte senescence, examines their effects on systemic metabolic homeostasis, and summarizes current intervention strategies for adipocyte senescence, aiming to provide theoretical foundations and novel perspectives for future research.

2 Characteristics of Mature Adipocyte Senescence

The senescence-associated secretory phenotype (SASP) is a hallmark of senescent adipocytes and serves as the primary mediator of local and systemic inflammation as well as metabolic dysfunction. Senescent adipocytes secrete a broad spectrum of SASP factors, including proinflammatory cytokines, chemokines and proteases [10]. Activation of the SASP is primarily coordinated by the nuclear factor kappa B (NF-κB) and DNA damage response (DDR) signaling pathways [11]. In adipose tissue, SASP-related factors recruit and activate immune cells (e.g., macrophages and neutrophils) through paracrine signaling, resulting in the development of a chronic low-grade inflammatory microenvironment. This inflammatory milieu not only accelerates the senescence of neighboring adipocytes but also directly impairs insulin signaling, thereby promoting insulin resistance [12].

At the molecular level, senescent adipocytes exhibit increased levels of senescence-associated proteins such as $p16^{INK4a}$, $p21^{CIP1}$, and p53, while elevated senescence-associated β-galactosidase (SA-β-gal) activity is a classic hallmark of senescence [13–15]. Notably, cell cycle regulation during adipocyte senescence is dynamic and complex. Research has revealed that mature human adipocytes under conditions of obesity and hyperinsulinemia can re-enter the cell cycle, accompanied by increased cell volume, nuclear size, and nuclear DNA content [16]. However, this aberrant cell cycle reactivation is followed by more severe cell cycle arrest and an exacerbated senescent phenotype, reflecting an aberrant stress response that ultimately compromises cellular function.

Mitochondria are the metabolic core of adipocytes, and their functional integrity is essential for maintaining metabolic homeostasis. Senescent adipocytes exhibit significant mitochondrial degeneration, characterized by structural and functional impairments: mitochondrial cristae become blurred, fragmented, or even lost, accompanied by reduced membrane potential ($\Delta\Psi m$), decreased ATP production and increased reactive oxygen species (ROS) generation [17]. Concurrently, impaired mitophagy further exacerbates the accumulation of dysfunctional mitochondria. Excess ROS can damage proteins, lipids, and DNA [18]. DNA damage in turn activates the DDR pathway, reinforcing the p53–p21 axis and thereby sustaining senescence. Moreover, elevated ROS also act as potent signaling molecules that activate proinflammatory pathways, such as NF-κB signaling [19].

Despite metabolic impairment, senescent adipocytes develop resistance to apoptosis, enabling their long-term persistence and sustained influence on the microenvironment. This resistance primarily results from the reprogramming of BCL-2 family protein expression: the antiapoptotic protein BCL-2 is markedly upregulated during adipogenesis, whereas proapoptotic proteins such as BAX remain relatively stable, leading to a reduced BAX/BCL-2 ratio [20]. This resistance enables senescent adipocytes to evade clearance and accumulate in adipose tissue, sustaining chronic inflammation and metabolic dysfunction through persistent SASP secretion [21].

3 Adipocyte Senescence Exacerbates Metabolic Disorders and Associated Complications

3.1 Obesity

Obesity and adipocyte senescence are reciprocally reinforcing: obesity triggers adipocyte senescence, which in turn exacerbates obesity and its metabolic complications [22]. Obesity drives adipocyte senescence through multiple mechanisms. Hypoxia is a critical factor in cellular senescence. In obese individuals, it activates hypoxia-inducible factor (HIF)-mediated signaling, which stimulates the transcription of senescence-associated genes and promotes inflammatory responses, driving adipose tissue dysfunction [23]. Hypoxia also induces mitochondrial dysfunction and

ROS production. The accumulated ROS directly damage DNA, thereby activating senescence signaling pathways [24, 25]. Moreover, in obesity, increased immune cell infiltration and the secretion of proinflammatory factors (e.g., TNF-α and IL-1β) further reinforce a pro-senescent inflammatory microenvironment.

Conversely, adipocyte senescence exacerbates obesity primarily because of impaired adipogenic capacity. PPARγ, a master regulator of adipogenesis and amino acid catabolism, is markedly downregulated in senescent adipocytes, and its downstream lipogenic enzymes are suppressed by SASP factors such as TNF-α and IL-1β [26]. SASP also inhibits the proliferation and differentiation of APCs, thereby compromising their adipogenic capacity. In conditions of energy excess, the failure to store lipids via healthy adipocyte hyperplasia drives pathological hypertrophy of existing adipocytes [27]. Hypertrophic adipocytes are more prone to rupture, and this cell death further recruits immune cells and amplifies local inflammation, thereby establishing a vicious cycle.

3.2 Type 2 Diabetes Mellitus (T2DM)

Adipocyte senescence plays a critical role in T2DM, as evidenced by the elevated expression of senescence markers in adipose tissue from diabetic patients and mouse models [28].

Senescent adipocytes exacerbate insulin resistance and diabetes progression through multiple pathways. First, SASP factors such as TNF-α and IL-6 disrupt insulin signaling [29]. Specifically, TNF-α binding to its receptor activates sphingomyelinase, which reduces IRS-1 tyrosine phosphorylation and enhances its serine phosphorylation, thereby suppressing insulin receptor kinase activity and impairing signal transduction [29, 30]. IL-6 induces SOCS-3 expression, which inhibits insulin receptor autophosphorylation, IRS-1/PI3K coupling, and Akt activation, ultimately blocking glucose transporter 4 (GLUT4) membrane translocation and impairing glucose uptake [31]. Second, senescent adipocytes exhibit enhanced lipolysis, resulting in the release of large amounts of free fatty acids (FFAs). These FFAs cause lipotoxic damage to pancreatic β-cells, leading to cell death and impaired insulin secretion [32]. Additionally, elevated FFAs disrupt mitochondrial function in β-cells and muscle cells, inducing oxidative stress that further exacerbates insulin resistance and impairs glucose uptake [33]. These alterations result in hyperglycemia, which synergizes with elevated FFAs to promote glucolipotoxicity, thereby aggravating oxidative stress and inflammation in β-cells [34]. Furthermore, adipocyte senescence involves a marked reduction in adiponectin secretion. As a key adipokine, adiponectin plays vital roles in insulin sensitization, anti-inflammation, and fatty acid oxidation [35]. Its decline signifies the loss of this crucial protective factor, which consequently exacerbates insulin resistance and impairs systemic metabolic homeostasis. Notably, hyperglycemia can induce adipocyte senescence. In the diabetic microenvironment, hyperglycemia drives advanced glycation end-products (AGEs) accumulation, oxidative stress, and chronic inflammation, which in turn cause DNA damage, telomere shortening, and excessive SASP factor secretion, thereby accelerating adipocyte senescence [36]. In summary, adipocyte senescence and T2DM form a bidirectional vicious cycle, in which adipocyte senescence promotes insulin resistance and T2DM progression, while hyperglycemia further exacerbates adipocyte senescence.

3.3 Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

MASLD is a chronic metabolic disorder characterized by aberrant hepatic lipid deposition, and its pathogenesis is closely linked to adipocyte function. Adipocyte senescence exacerbates hepatic lipid accumulation and injury through multiple mechanisms. Senescent adipocytes exhibit enhanced lipolysis, resulting in the release of FFAs into circulation, which subsequently enter the liver via the portal venous system [37]. Inside hepatocytes, FFAs bind to FABP1 and activate PPARα, thereby upregulating genes involved in fatty acid oxidation. However, under aging conditions, reduced FABP1 expression compromises PPARα-mediated signaling, leading to impaired mitochondrial β-oxidation, ultimately exacerbating lipotoxicity and accelerating MASLD progression [38]. Furthermore, hepatic FFA accumulation also elevates the levels of triglycerides, free cholesterol, and other lipid metabolites, creating a lipotoxic environment. This environment impairs mitochondrial function and drives ROS production, which exacerbates oxidative stress and ultimately induces cellular injury [39]. Moreover, SASP factors released from senescent adipocytes reach the liver via circulation, where they activate hepatic Kupffer cells and trigger cytokine release and immune cell recruitment, establishing a chronic low-grade inflammatory microenvironment [40]. Sustained inflammation and oxidative stress can trigger hepatocyte death and activate hepatic stellate cells (HSCs), which drive liver fibrosis and subsequent cirrhosis [41]. Adipocyte senescence promotes insulin resistance, indirectly exacerbating MASLD progression. Under these conditions, the liver exhibits “selective insulin resistance”, in which FOXO1-mediated gluconeogenesis suppression is attenuated, whereas the AKT/mTORC1-SREBP-1c lipogenic axis remains active or even becomes hyperactivated under hyperinsulinemia [42]. This imbalance sustains elevated

SREBP-1c levels, which upregulate the expression of lipogenic genes such as fatty acid synthase (*FASN*), thereby promoting hepatic lipogenesis and exacerbating intrahepatic lipid accumulation and MASLD progression.

3.4 Cardiovascular Disease

Adipocyte senescence is a critical driver of age-related cardiovascular diseases. Its detrimental effects on the cardiovascular system are mediated by multiple pathophysiological processes, including metabolic disturbances, chronic low-grade inflammation, endocrine dysfunction, and intrinsic vascular abnormalities [43].

At the metabolic level, senescent adipose tissue exhibits impaired lipid storage capacity and enhanced lipolysis. Consequently, elevated circulating triglycerides and FFAs promote hepatic steatosis [44]. This hepatic lipid overload promotes increased secretion of very low-density lipoprotein (VLDL), which is subsequently converted to low-density lipoprotein (LDL) in circulation. Elevated circulating LDL infiltrates the arterial intima and undergoes oxidative modification. Tissue-resident macrophages engulf these modified lipids and transform into foam cells [45]. The formation and accumulation of foam cells represent early hallmarks of atherosclerosis [46]. These foam cells secrete proinflammatory factors, amplifying local inflammation, recruiting additional immune cells, and promoting smooth muscle cell migration and proliferation, ultimately leading to the formation of mature atherosclerotic plaques [47]. Persistent inflammation within the plaque undermines its stability and increases the risk of rupture. Plaque rupture can trigger thrombosis, which can acutely occlude the vessel lumen, leading to clinical events such as myocardial infarction and stroke [48, 49].

At the endocrine level, senescent adipocytes exhibit an imbalanced adipokine profile. The production of protective factors, such as adiponectin and fibroblast growth factor 21 (FGF21), is reduced, whereas the secretion of detrimental factors, including leptin, resistin, and osteopontin (OPN), is increased. These adipokines differentially regulate cardiovascular function [50]. Elevated leptin is associated with hypertension [51]. Resistin induces vascular inflammation, lipid accumulation, and plaque vulnerability [52]. Reduced adiponectin compromises vascular endothelial protection and anti-atherosclerotic function [53]. OPN drives the transformation of cardiac fibroblasts into myofibroblasts, promoting myocardial interstitial fibrosis and left ventricular diastolic dysfunction [54]. Conversely, FGF21 coordinates inter-organ crosstalk among the liver, adipose tissue, kidneys, and vasculature by activating the ACE2/angiotensin-(1–7) (Ang-(1–7)) axis, thereby counteracting angiotensin II-induced hypertension and vascular injury [55].

The functional transformation of perivascular adipose tissue (PVAT) represents another core mechanism. Healthy PVAT maintains vascular homeostasis through the release of bioactive molecules, including nitric oxide (NO), hydrogen sulfide (H_2S), Ang-(1–7), adiponectin, prostacyclin, and methyl palmitate [56]. Under conditions of aging or obesity, PVAT shifts to a proinflammatory phenotype and secretes increased levels of inflammatory adipokines and cytokines, thereby disrupting vascular homeostasis and promoting hypertension.

Furthermore, adipose tissue-derived noncoding RNAs and exosomes have diverse effects on the cardiovascular system [57]. For instance, exosomes released by hypertrophic adipocytes are enriched in miR-802-5p, which, upon uptake by cardiomyocytes, exacerbates myocardial insulin resistance by suppressing HSP60 expression [58]. Small extracellular vesicles (sEVs) derived from BAT deliver cardioprotective miRNAs (miR-125b-5p, miR-128-3p, and miR-30d-5p) to the heart, inhibiting the activation of the pro-apoptotic MAPK pathway and attenuating myocardial ischemia/reperfusion (MI/R) injury [59]. The pathological contributions of senescent adipocytes to obesity, T2DM, MASLD, and cardiovascular disease are summarized in Fig. 1.

4 Current Strategies for Attenuating Adipocyte Senescence

4.1 Senolytics

Senolytics selectively induce apoptosis in senescent cells. Eliminating these cells mitigates their detrimental effects on surrounding tissues and ameliorates aging-related pathologies, including metabolic disorders and cardiovascular diseases [60, 61]. Several compounds have shown efficacy in eliminating senescent adipocytes. For example, the combination of dasatinib and quercetin (D + Q) is a senolytic regimen [62]. It targets distinct senescence-associated anti-apoptotic pathways (SCAPs); specifically, dasatinib primarily inhibits tyrosine kinase activity to block pro-survival signals, whereas quercetin predominantly suppresses the PI3K/AKT and BCL-2 pathways. This synergistic interaction reduces the senescent cell burden in adipose tissue. In obese animal models, D + Q administration reduces SASP secretion from adipose tissue, improves insulin sensitivity, alleviates systemic inflammation, and restores adipocyte function, thereby ameliorating glucose and lipid metabolic disorders [22].

Several BCL-2 inhibitors have been identified as senolytic agents. For example, Navitoclax (ABT-263) has demonstrated potential in clearing senescent cells. In obese mouse models, treatment with navitoclax was shown to

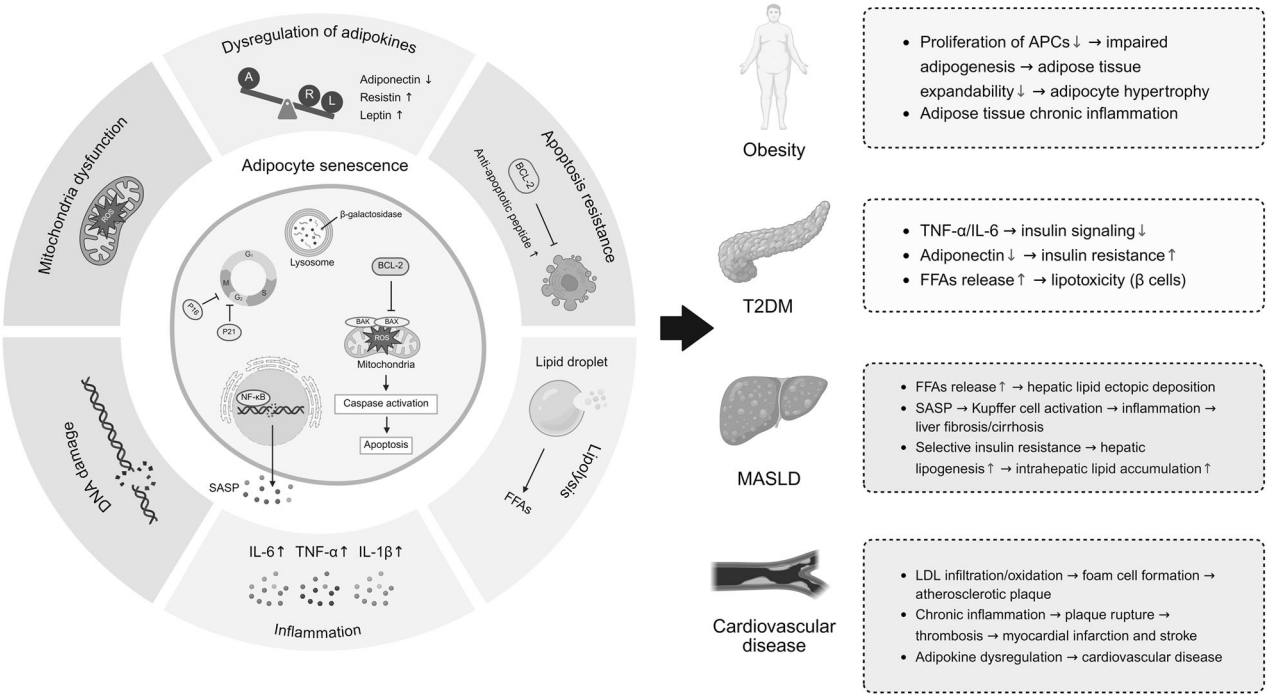

Fig. 1 Adipocyte senescence drives disease progression through multiple pathological mechanisms, including persistent SASP secretion, increased lipolysis with free fatty acid spillover, lipotoxicity, chronic inflammation, and adipokine dysregulation. These alterations collectively promote obesity, insulin resistance, hepatic lipid deposition, and atherosclerosis, establishing a vicious cycle between adipocyte senescence and systemic metabolic dysfunction (illustrated using https://BioRender.com)

reduce SA-β-gal-positive areas in WAT, along with improving insulin sensitivity and glucose tolerance [63]. Furthermore, fisetin, a natural compound, also has senolytic activity and clears various types of senescent cells, including adipocytes. In aged mice, fisetin improved metabolic parameters and extended healthspan [64]. Currently, the therapeutic potential of fisetin against age-related metabolic diseases such as obesity and T2DM has been evaluated in multiple clinical trials [65].

4.2 Senomorphics

Senomorphics alleviate the detrimental effects of senescent cells without eliminating them, either by suppressing SASP secretion or modulating senescence-related signaling pathways [66]. They are particularly suitable when senescent cells retain physiological functions, such as tissue repair and wound healing. Metformin, a classic antidiabetic drug, exhibits notable senomorphic activity. It acts through multiple mechanisms: activating AMPK and inhibiting mTOR signaling, which in turn modulates cellular metabolism, suppresses aberrant protein synthesis, and promotes autophagy, thereby alleviating aging-associated metabolic disturbances and stress responses. Additionally, metformin reduces SASP secretion via NF-κB inhibition [67]. These actions collectively delay adipocyte senescence and improve insulin sensitivity and lipid homeostasis. Preclinical studies have indicated that metformin suppresses chronic inflammation, extends lifespan, and enhances metabolic function [68]. It is currently being investigated in the Targeting Aging with Metformin (TAME) clinical trial to evaluate its potential for delaying human aging [69]. Rapamycin, another potent senomorphic agent, inhibits mTOR signaling, thereby reducing SASP secretion, enhancing autophagy, and improving mitochondrial function [70]. Rapamycin also enhances immune function, extends lifespan, and mitigates various age-related pathologies in mice [71]. Natural compounds such as resveratrol can upregulate SIRT1 expression and suppress the SASP, thereby exerting anti-senescence effects [72]. Resveratrol also has cardiovascular protective effects, including improving endothelial function, inhibiting plaque formation, and mitigating oxidative stress and inflammation [73]. Other natural compounds with anti-inflammatory and antioxidant activities, such as apigenin and kaempferol, have also shown potential for inhibiting the SASP in adipocytes [74, 75]. The key features of these anti-senescence drugs are summarized in Table 1.

4.3 Caloric Restriction (CR)

CR is a strategy that ameliorates obesity and metabolic health, thereby indirectly alleviating adipocyte senescence [76]. It delays aging in various mammalian models and reduces oxidative damage while enhancing metabolic

Table 1 Anti-senescence drugs and their mode of action

Drugs	Mechanism of action	Side effects and challenges	References
Dasatinib + Quercetin (D + Q)	Dasatinib inhibits tyrosine kinases. Quercetin modulates PI3K/AKT signaling and suppresses SASP secretion. The combination synergistically drives senescent cells into apoptosis.	Dasatinib may cause myelosuppression, fluid retention, pleural effusion. Quercetin is generally well tolerated, high doses may cause gastrointestinal adverse reactions.	[124, 125]
Fisetin	Activates AMPK/SIRT1 and inhibits SASP secretion.	Low oral bioavailability and insufficient long-term safety data.	[126]
Navitoclax (ABT-263)	Inhibits BCL-2 family proteins (BCL-2, BCL-xL, BCL-w), reactivating the intrinsic apoptotic pathway in senescent cells.	Thrombocytopenia (due to BCL-xL inhibition) severely restricts clinical use.	[127]
Metformin	Activates AMPK, inhibits mTOR and NF-κB signaling, lowering SASP secretion.	Common GI effects (diarrhea, nausea); rare but serious risk of lactic acidosis; long-term administration requires vitamin B12 monitoring.	[128–130]
Rapamycin	Inhibits mTOR signaling, enhances autophagy, reduces SASP release, and alleviates cellular senescence.	Hyperglycemia, insulin resistance, dyslipidemia, oral ulceration, immunosuppression (increased infection risk).	[131, 132]
Resveratrol	Activates SIRT1, decreases oxidative stress, and reduces SASP secretion.	Low oral bioavailability limiting clinical application; high doses may raise nephrotoxicity risk.	[133, 134]
Pterostilbene	Activates SIRT1, reduces ROS generation, and suppresses SASP expression.	Higher bioavailability than resveratrol; long-term effects of high doses remain unknown.	[135, 136]
Apigenin	Inhibits JAK/STAT and NF-κB signaling, reducing SASP secretion.	Poor aqueous solubility and low oral bioavailability; safe at dietary levels, while high doses may affect thyroid function.	[137, 138]
Kaempferol	Reduces oxidative stress, inhibits NF-κB and MAPK signaling, and suppresses SASP secretion.	Safe as a dietary constituent; poor bioavailability restricts therapeutic potential.	[139, 140]

function. A two-year randomized controlled trial in healthy nonobese individuals revealed that CR reduced metabolic rates and oxidative stress markers, which supports the "Rate of Living Theory" and the "Oxidative Damage Theory of Aging" [77].

CR modulates adipose tissue aging through multiple molecular mechanisms. Its primary effects include optimizing glucose metabolism and enhancing insulin sensitivity [78]. By lowering blood glucose levels, CR decreases nonenzymatic glycation reactions and AGE formation, which in turn attenuate RAGE signaling and reduce NOX2-mediated ROS production [79]. In adipocytes, suppression of the AGE-RAGE axis inhibits NF-κB activation and SASP expression, thereby reducing the paracrine effects of senescent adipocytes and delaying functional decline in adjacent tissues [80]. At the molecular pathway level, CR activates AMPK by increasing the AMP/ATP ratio, which in turn suppresses mTORC1 signaling, promotes ULK1-mediated autophagy initiation, and drives TFEB-dependent lysosome biogenesis. This process facilitates the clearance of damaged mitochondria and misfolded proteins, maintaining intracellular homeostasis in adipocytes [81]. AMPK activation also inhibits lipid synthesis and enhances fatty acid oxidation through acetyl-CoA carboxylase (ACC) phosphorylation, ultimately improving energy utilization efficiency and reducing lipid accumulation in adipose tissue [82]. At the epigenetic level, CR activates SIRT1 by increasing the levels of NAD^+, which deacetylates transcription factors such as PGC-1α and FOXO1, enhancing mitochondrial biogenesis and antioxidant gene expression [83]. Adipose tissue-specific SIRT1 overexpression improves mitochondrial respiratory function, reduces lipid accumulation, and delays cellular senescence.

4.4 Physical Exercise

Physical exercise has multiple beneficial effects on the metabolic homeostasis of adipose tissue. In terms of energy metabolism, exercise enhances energy expenditure by activating BAT and inducing beige adipocyte formation within WAT, thereby reducing lipid accumulation [84]. These effects are associated with improved mitochondrial function, upregulated UCP1 expression, and enhanced fatty acid oxidation [85]. Exercise also promotes mitochondrial biogenesis and function by increasing the activity of key regulatory proteins such as PGC-1α, SIRT1, and AMPK. Furthermore, prolonged endurance exercise promotes mitophagy to remove damaged mitochondria and reduce oxidative stress, thereby delaying adipose tissue aging and supporting healthy remodeling [86].

Exercise also alleviates insulin resistance in senescent adipocytes. A high-fat diet induces senescent cell accumulation in adipose tissue, impairing insulin signaling and causing insulin resistance, whereas regular exercise

effectively inhibits this process [87]. In terms of anti-inflammatory effects, exercise reduces the levels of proinflammatory cytokines (e.g., TNF-α, IL-6, and IL-1β) while increasing the levels of anti-inflammatory mediators such as IL-10 and adiponectin in adipose tissue [88–90]. This modulation of inflammation helps restore adipose tissue function and protects other metabolic organs from chronic inflammation. Furthermore, exercise promotes the release of irisin from muscle. Irisin expression in muscle is reduced in aged mice, and its supplementation counteracts aging-related sarcopenia, promotes the browning of WAT, and ameliorates adipose tissue fibrosis, hepatic lipid deposition, and insulin resistance [91].

4.5 Gene Editing

Gene editing technologies offer a strategy for targeting adipocyte senescence. The CRISPR/Cas9 system enables direct intervention in key genes and signaling pathways associated with adipocyte senescence through gene knockout, activation, or suppression [92]. For instance, the use of CRISPR interference (CRISPRi) to suppress FABP4 expression reduces inflammatory cytokines, improves lipid metabolism, and delays senescence in adipocytes [93]. Conversely, CRISPR activation (CRISPRa) can upregulate gene expression by targeting specific promoters or enhancers. CRISPRa targeting the UCP1 promoter in human white preadipocytes successfully induced the formation of human brown-like (HUMBLE) cells, which upon transplantation into obese mice led to reduced body weight and improved insulin sensitivity [94]. Similarly, activation of the *Sim1* or *Mc4r* gene rescued metabolic abnormalities caused by haploinsufficiency, reducing body weight and fat accumulation [95]. In addition to direct gene editing, CRISPR/Cas9 also facilitates the establishment of disease models for studying aging mechanisms. For example, CRISPR/Cas9-mediated leptin receptor knockout in rats generates obesity models with adipocyte hypertrophy and multiple metabolic disturbances [96].

Despite these promising results, the translation of CRISPR-based interventions to adipose tissue faces substantial hurdles. First, efficient in vivo delivery of CRISPR components to adipocytes remains challenging. Second, mature adipocytes are terminally differentiated postmitotic cells that rely primarily on nonhomologous end joining (NHEJ) rather than high-fidelity homology-directed repair (HDR), limiting precise template-directed gene correction and resulting in unpredictable insertions or deletions at the target site. Third, the delivery of bacterial-derived Cas9 and viral vectors may elicit host immune responses, raising safety concerns for clinical translation.

In addition to genetic strategies, pharmacological interventions such as senolytics and senomorphics also face limitations, including insufficient tissue specificity and systemic side effects. For instance, the platelet toxicity of navitoclax and the immunosuppressive effects of rapamycin limit their long-term clinical use [97]. These limitations highlight the need for delivery systems that concentrate therapeutic agents within adipose tissue while minimizing systemic toxicity. In this context, lipid prodrug strategies offer a promising approach for intervention in adipocyte senescence.

5 Potential of Lipid Prodrugs as a Delivery Platform for Adipocyte Senescence Intervention

5.1 Fundamental Concepts and Structural Design

Lipid prodrugs represent an emerging strategy in which bioactive molecules are covalently linked to lipid carriers via cleavable bonds, releasing the parent drug upon enzymatic or metabolic activation in vivo. This design exploits the unique lipid uptake and metabolism of adipocytes, including the high expression of lipoprotein lipase (LPL), fatty acid transport proteins (FATPs), and scavenger receptor CD36, which provide a molecular basis for delivery [98]. Structurally, these prodrugs are typically constructed by conjugating active drug molecules to lipid moieties (e.g., fatty acids, triglycerides, or phospholipids) via linkers such as ester or amide bonds, which are cleaved by esterases, phospholipases, or acidic conditions [99]. Among these, long-chain fatty acids are widely used as lipid moieties because of their high affinity for adipocytes, significantly enhancing drug enrichment in adipose tissue. Moreover, rational prodrug design must consider the physicochemical properties of parent drugs, linker stability, release kinetics, and off-target toxicity to minimize adverse systemic effects [100]. Therefore, lipid prodrugs represent a strategy based on adipose tissue pathophysiology, offering a valuable approach to adipocyte senescence intervention.

5.2 Delivery Mechanisms and Pharmacokinetic Characteristics

The delivery of lipid prodrugs is achieved primarily through three synergistic mechanisms: passive distribution, active uptake, and microenvironment-responsive drug release. Passive distribution relies on the high lipophilicity of prodrug molecules, which facilitates membrane permeation and accumulation in lipid-rich adipose tissue. This distribution provides the basis for initial drug enrichment. In addition, active uptake exploits the unique molecular recognition mechanisms of adipocytes. For example, long-chain fatty acid components trigger CD36 receptor-mediated

endocytosis, which enables specific intracellular delivery of drug molecules and enhances delivery efficiency [101]. Furthermore, the enzymatic profile and acidic microenvironment of senescent adipocytes favor localized prodrug release, enabling linker cleavage by specific enzymes or acidic environments, thereby releasing active drugs to act upon adipocytes [102]. In terms of pharmacokinetics, lipid prodrugs differ from the parent drug primarily in their lymphatic absorption, as demonstrated in Fig. 2. Lipophilic drugs are preferentially incorporated into chylomicrons for lymphatic delivery. Specifically, compounds with a LogP ≥ 5 are assembled into chylomicrons in intestinal epithelial cells and subsequently absorbed by the lymphatic system, thereby bypassing hepatic first-pass metabolism [103]. The metabolic process primarily involves enzymatic hydrolysis, releasing the parent drug for pharmacological action, while the unmetabolized prodrug is cleared via hepatobiliary or renal pathways. It is crucial to emphasize that the release rate and metabolic stability of the prodrug are key determinants of its efficacy and safety, and careful optimization is needed in the design phase.

A critical consideration regarding the targeting specificity of lipid prodrugs is the expression profiles of key uptake mediators in senescent versus healthy adipocytes. Although adipocytes express high levels of CD36 and FATPs to support their physiological lipid storage function, direct evidence demonstrating the differential expression of these transporters between senescent and nonsenescent adipocytes remains lacking. Consequently, lipid prodrugs are likely to accumulate in both healthy and senescent adipocytes, achieving adipose tissue delivery rather than senescent adipocyte-selective targeting. The therapeutic rationale therefore depends on a critical premise: whether the pharmacological action is senolytic, senomorphic, or metabolic modulatory, the drug must not harm healthy adipocytes. This limitation demands explicit acknowledgment and rigorous preclinical validation in lipid prodrug design.

5.3 Unique Advantages of Lipid Prodrugs as an Adipose Tissue Delivery Platform

Compared with traditional drug delivery systems, lipid prodrugs offer distinct advantages for the intervention of adipocyte senescence. Their enhanced lipophilicity promotes preferential distribution and accumulation within adipose tissue, which improves local drug availability while reducing systemic exposure and dose-limiting toxicity. The rational design of the linker enables sustained release, which can prolong drug action, reduce dosing frequency, and improve patient compliance. Collectively, these advantages suggest the use of lipid prodrugs as a promising strategy for adipose tissue delivery and metabolic disease intervention, as shown in Fig. 3. For example, Mattarei and colleagues developed triglyceride-mimetic prodrugs in which the active ingredient pterostilbene is linked to the glycerol backbone via a carbamate bond [104]. This prodrug mimics the absorption pathway of dietary lipids, enabling lymphatic delivery and accumulation in WAT after oral administration. In obese mouse

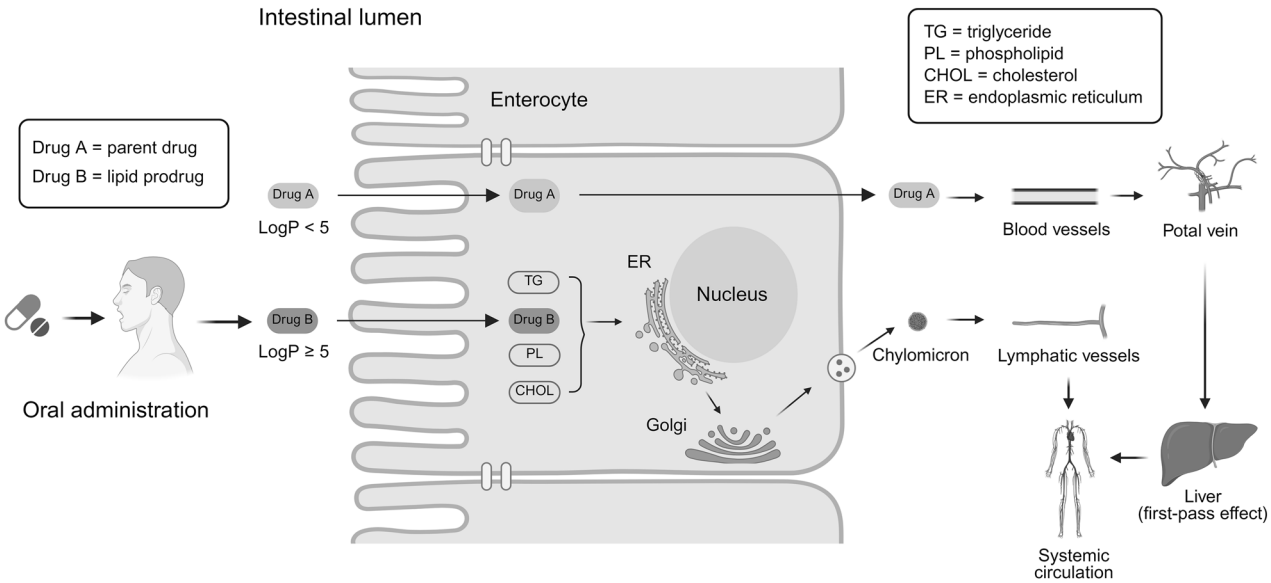

Fig. 2 Lipid prodrugs mimic the absorption pathway of dietary lipids. After oral administration, they are incorporated into chylomicrons in intestinal epithelial cells, transported via intestinal lymphatic vessels, and enter systemic circulation, thereby bypassing hepatic first-pass metabolism. For highly lipophilic compounds, this route can significantly increase oral bioavailability (illustrated using https://BioRender.com)

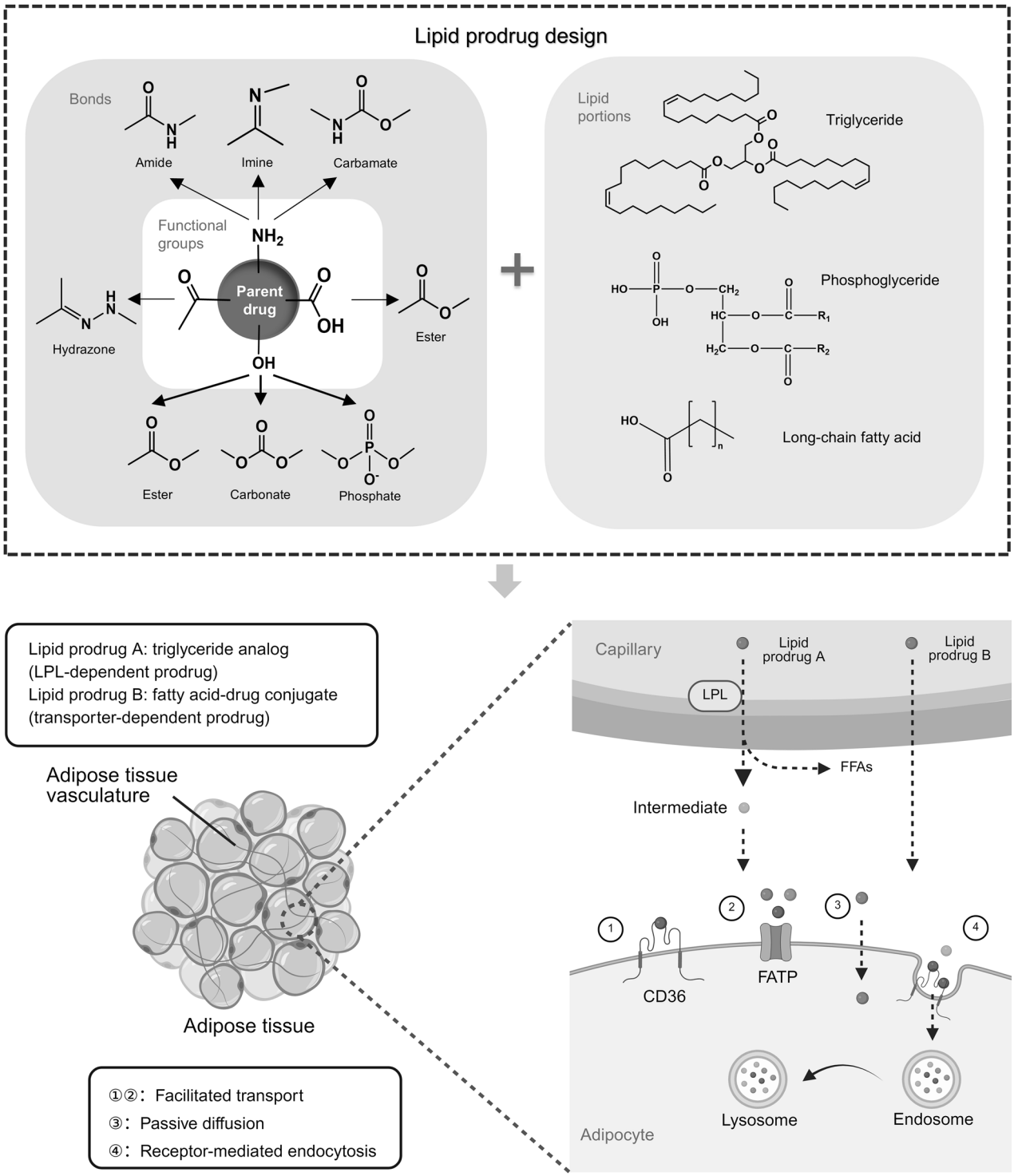

Fig. 3 Lipid prodrug strategies achieve adipose tissue delivery to alleviate adipocyte senescence. Lipid prodrugs enter adipocytes via passive diffusion or active transport mediated by CD36/FATP, followed by intracellular hydrolysis to release active molecules. This strategy enhances local drug delivery to adipose tissue, thereby modulating senescent cells while minimizing systemic toxicity (illustrated using https://BioRender.com)

models, this strategy successfully achieved in situ drug release within adipose tissue, providing experimental evidence for the delivery of drugs to adipose tissue with reduced systemic exposure.

It is important to emphasize that lipid prodrugs do not constitute a standalone anti-senescence mechanism but rather an adipose tissue delivery platform that can be coupled with diverse therapeutic agents, including senolytics,

senomorphics, mitochondrial protectants, and metabolic modulators. By exploiting the endogenous lipid metabolic system of adipocytes, this strategy concentrates bioactive compounds in adipose tissue, thereby enhancing local efficacy while reducing systemic exposure. The following sections discuss the potential applications of this platform for intervening in adipocyte senescence.

6 Potential Applications of Lipid Prodrugs in Intervention with Adipocyte Senescence

6.1 Delivery of Senolytic Agents

Senolytic drugs, which selectively induce apoptosis in senescent cells, represent a key strategy for eliminating these cells from adipose tissue and fundamentally reversing the aging microenvironment. However, their systemic application is often limited by poor adipose tissue selectivity and off-target toxicity. The lipid prodrug strategy addresses this challenge by enhancing drug lipophilicity, enabling these compounds to mimic the absorption of dietary lipids [105]. This provides a solution for achieving adipose tissue delivery and reducing systemic toxicity.

Navitoclax, a BCL-2 inhibitor, has been demonstrated to reduce the senescent cell burden in WAT and improve glucose metabolism in obese mouse models [63]. However, its clinical application has been limited by thrombocytopenia. To increase specificity and reduce toxicity, researchers have employed a prodrug strategy involving the conjugation of a galactose moiety to Navitoclax, resulting in the formation of Nav-Gal [106]. This prodrug is specifically activated in senescent cells by elevated lysosomal β-galactosidase activity. The subsequent cleavage of the galactose moiety releases the active drug locally, enabling the selective elimination of senescent cells while reducing toxicity to platelets [107]. This activatable prodrug strategy demonstrates the feasibility of prodrug activation in target cells. For adipose tissue applications, conjugating senolytics to long-chain fatty acids (e.g., palmitic acid) via enzyme-cleavable linkers (e.g., ester bonds) could generate lipid prodrugs that facilitate cellular uptake by adipocytes through fatty acid transporters such as CD36. These prodrugs can subsequently utilize the lipase-rich microenvironment of adipose tissue to achieve localized hydrolysis, releasing the active drug and clearing senescent adipocytes with reduced systemic toxicity.

Natural senolytic compounds, such as fisetin and quercetin, have emerged as promising candidates because of their availability and safety. However, flavonoids commonly face challenges, including poor oral bioavailability and rapid metabolism [108]. Covalent conjugation to triglycerides or long-chain fatty acids can fundamentally alter their pharmacokinetics [109]. Coadministration with lipid-based formulations containing long-chain fatty acids has been shown to enhance the lymphatic transport of quercetin and improve its systemic exposure by bypassing hepatic first-pass metabolism [110, 111]. Building upon this principle, covalent lipid conjugation strategies are expected to further improve the oral bioavailability of senolytic flavonoids, enabling more effective intervention in adipocyte senescence.

6.2 Delivery of Senomorphics

Rapamycin, a potent mTOR inhibitor, suppresses the secretion of SASP and delays senescence in various cell types [112]. Despite its inherent lipophilicity, systemic administration of rapamycin still induces side effects such as immunosuppression. The application of the lipid prodrug strategy to rapamycin is expected to increase its adipose selectivity. Although no rapamycin-based lipid prodrugs have been reported, the presence of a modifiable hydroxyl group in its molecular structure makes it a suitable candidate for triglyceride-mimetic prodrug design. This approach would enable the prodrug to mimic dietary triglyceride pharmacokinetics, achieving effective mTOR inhibition and SASP modulation in adipose tissue. By reducing systemic exposure, this strategy could alleviate immunosuppressive and metabolic side effects, thereby offering a new strategy for the intervention of adipocyte senescence.

Resveratrol represents another class of promising senomorphic agents. It modulates senescence-associated signaling by activating SIRT1, which promotes PGC-1α deacetylation and enhances mitochondrial biogenesis [113]. Concurrently, inhibition of the NF-κB pathway reduces the expression of SASP factors such as IL-6 and TNF-α [114]. However, its clinical application is limited by low oral bioavailability and rapid metabolism [115]. Coupling resveratrol with a triglyceride backbone can increase its lipophilicity, which is expected to promote its concentration within adipose tissue. This would suppress local NF-κB activation and SASP expression, ultimately ameliorating adipocyte senescence.

6.3 Delivery of Mitochondria-Targeted Drugs

Mitochondrial dysfunction and oxidative stress are central drivers of adipocyte senescence [116]. Therefore, the delivery of mitochondrial protectants or antioxidants to adipose tissue is a fundamental therapeutic strategy for adipocyte senescence. Among these strategies, increasing intracellular NAD^+ levels is promising. As a critical precursor to NAD^+, nicotinamide riboside (NR) has been shown to support energy metabolism, maintain mitochondrial function, facilitate DNA repair, and delay the aging process [117]. Although NR-based lipid prodrugs for

adipose tissue delivery have not been reported, the hydroxyl group on its ribose moiety offers a site for esterification with long-chain fatty acids, suggesting its potential to be developed into lipid prodrugs. Within adipocytes, the prodrug is hydrolyzed to release NR locally. This subsequently elevates intracellular NAD^+ levels, activating the SIRT1/PGC-1α axis to increase mitochondrial biogenesis and fatty acid oxidation, thereby restoring energy metabolism homeostasis in senescent adipocytes [118]. Elamipretide (MTP-131) is a tetrapeptide that acts on the inner mitochondrial membrane to reduce ROS production and increase mitochondrial energy generation [119]. Given the presence of modifiable functional groups in its structure, MTP-131 could be converted into a lipid prodrug for delivery to adipose tissue. In addition to mitochondrial protection, lipid prodrug technology can also be applied to deliver thermogenic agents, such as mitochondrial uncouplers or β3-adrenergic receptor agonists, to promote the conversion of white adipocytes to beige or brown adipocytes, effectively reducing lipid accumulation through increased energy expenditure. By modulating metabolism and energy balance within adipocytes, such strategies could mitigate senescence and indirectly ameliorate metabolic disorders, including obesity and T2DM.

6.4 Delivery of Metabolic Modulators

In addition to directly clearing senescent cells, modulating key metabolic nodes is another key strategy for alleviating adipocyte senescence. Several metabolic modulators have demonstrated potential for ameliorating systemic glucose and lipid metabolic disorders. PPARγ agonists are classic agents for improving insulin sensitivity. Rosiglitazone is a representative agent that enhances insulin sensitivity and promotes adipocyte differentiation. However, systemic administration may lead to adverse effects such as edema and cardiovascular risks [120, 121]. The lipid-based modification of rosiglitazone enables local PPARγ activation in adipose tissue, which promotes healthy adipocyte differentiation and enhances glucose and lipid metabolism, thereby delaying cellular senescence and restoring adipose tissue function. AMPK agonists represent another class of metabolic modulators. MK-8722, a potent systemic AMPK agonist, has substantial glucose-lowering effects and enhances fatty acid oxidation in preclinical studies, but its systemic administration may induce cardiac hypertrophy [122]. Lipidization of MK-8722 could enable local AMPK activation in adipocytes, which stimulates glucose uptake, suppresses lipid synthesis, and enhances mitochondrial function, ultimately ameliorating energetic deficits and oxidative stress in senescent adipocytes. The ACC inhibitor NDI-010976 improves systemic metabolic homeostasis by suppressing fatty acid synthesis and promoting fatty acid oxidation, and its central role in hepatic lipid metabolism is well established [123]. Notably, this molecule also has regulatory potential in adipose tissue metabolism. Lipid derivatization of its carboxyl or hydroxyl groups could generate prodrugs that preferentially accumulate and are activated in adipose tissue, enabling local ACC inhibition and thereby mitigating age-related lipid accumulation and associated inflammation.

7 Conclusions

Adipocyte senescence represents a critical event in the organismal aging process and acts as a key factor in multiple age-related metabolic diseases. This review details the hallmarks of senescent adipocytes at both the molecular and cellular levels: persistent SASP secretion, elevated senescence biomarkers, mitochondrial dysfunction, and apoptosis resistance. Collectively, these alterations drive adipose tissue dysfunction, which promotes the development of obesity, T2DM, MASLD, and cardiovascular diseases through mechanisms such as chronic inflammation, lipotoxicity, and adipokine imbalance.

With respect to interventional strategies, traditional approaches such as senolytics and senomorphics have demonstrated potential. However, their clinical application is often limited by insufficient adipose tissue selectivity, systemic side effects, and poor bioavailability. Gene editing allows precise intervention but faces safety and delivery challenges. The lipid prodrug strategy offers a new direction by utilizing the properties of adipocytes. This approach enables adipose tissue delivery by covalently linking active drug molecules to lipid carriers. Its lymphatic absorption pathway bypasses hepatic first-pass metabolism and enhances oral bioavailability, whereas lipid-mimetic design enables drug enrichment in adipose tissue and localized drug release, thereby facilitating therapeutic effects against adipocyte senescence.

While lipid prodrugs show significant promise, further research is needed to optimize linker design, refine release kinetics, and establish long-term safety. Additionally, rigorous clinical validation is crucial for translating basic research findings into clinical applications. Overall, adipose tissue-enriched delivery strategies offer a promising avenue to combat adipocyte senescence and alleviate the societal burdens associated with aging.

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