

Review

Mitochondrial dysfunction in adipocyte differentiation: implications for obesity and metabolic syndrome intervention

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Abstract

Mitochondrial dysfunction critically disrupts adipocyte remodeling by impairing the thermogenic browning process essential for combating obesity through the upregulation of uncoupling protein 1 (UCP1) and mitochondrial biogenesis. Deficiencies in mitochondrial metabolism, dynamics (including fusion/fission), and autophagy suppress adipocyte plasticity, directly inhibiting UCP1 expression and destabilizing the PPAR- γ /PGC-1 α and adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) signaling pathways. These disruptions reduce energy expenditure, exacerbate insulin resistance, and promote metabolic syndrome. Moreover, mitochondrial inactivation intersects with neurodegenerative disorders via oxidative stress induced by β -amyloid and α -synuclein aggregation, amplifying systemic metabolic dysregulation. Structural mitochondrial anomalies further impede lipid utilization and adipose tissue adaptation, but unresolved crosstalk between mtDNA and nuclear DNA complicates therapeutic targeting. Future research must prioritize spatio-temporal mapping of mitochondrial dynamics in adipocyte differentiation via single-cell omics to identify key regulatory nodes. Addressing these mechanisms could unlock precision therapies, such as gene editing, to restore mitochondrial function, enhance adipocyte browning, and mitigate obesity, related pathologies alongside neurodegenerative and age-associated diseases.

Key words mitochondria, mitochondrial dysfunction, adipocyte browning, obesity, metabolic syndrome

Introduction

The global prevalence of obesity has reached alarming levels, escalating into a major public health crisis that now affects over two billion people worldwide [1]. Most epidemiological data on obesity rely on body mass index (BMI). The World Health Organization defines overweight as a BMI between 25.0 and 29.9 kg/m², whereas obesity is classified as a BMI $\geq$ 30.0 kg/m². Severe obesity, associated with heightened health risks, is characterized by a BMI $\geq$ 40 kg/m² [2]. Notably, a BMI > 30 kg/m² serves as the standard threshold for adult obesity, and when the BMI exceeds 40 kg/m², the risk of obesity-related mortality increases by 100% compared with individuals with a normal weight [3].

Regional analyses highlight significant global trends in obesity prevalence. In China, the standardized mean BMI increased from 22.7 kg/m² in 2004 to 24.4 kg/m² in 2018, whereas the prevalence of obesity increased sharply from 3.1% to 8.1% [4]. This trend is not

isolated: globally, both men and women exhibit parallel increases in obesity rates. Gender disparities persist across all regions, with the prevalence of obesity being higher among women (18%) than among men (14%). The global age-standardized obesity rate climbed from 8.8% in 1990 to 18.5% in 2022, with the incidence in males increasing from 4.8% to 14.0% over the same period. Between 1990 and 2022, obesity rates rose by more than 20% among women in 49 regions and among men in 24 regions [5]. These escalating trends underscore the profound public health impact of obesity and the urgent need for targeted interventions.

Literature Search and Screening Methodology

This narrative review synthesizes interdisciplinary evidence on the mechanisms and therapeutic implications of mitochondrial dysfunction in adipocyte differentiation, obesity, and metabolic syndrome. To ensure representativeness and broad applicability, systematic

literature searches were conducted across PubMed, Web of Science, and Scopus using core keyword combinations encompassing mitochondrial function, adipocyte differentiation, obesity, and their complications. The literature screening employed stringent criteria: inclusion criteria were restricted to (1) original studies (cell culture, animal models, or human subjects) directly investigating pathological mitochondria-adipocyte/metabolic disease relationships and (2) high-quality English-language reviews. The exclusion criteria included unrelated topics, nonmitochondrial mechanisms, conference abstracts without full texts, and non-English publications. During evidence synthesis, priority was given to mechanistically rigorous original research. Impact journals, particularly large-scale animal studies and clinically relevant human investigations, actively incorporate balanced perspectives on contentious issues.

Classification of Adipocytes and Their Roles in the Progression of Obesity

Adipose tissue is a special form of connective tissue that is composed mainly of adipocytes loaded with lipids, and it is the main energy reserve of the body [6]. Placental mammals possess three functionally distinct adipocyte subtypes: (1) white adipocytes, which are dedicated to energy storage; (2) brown adipocytes, which are specialized for energy dissipation; and (3) beige adipocytes, which are capable of inducible thermogenesis [7]. White adipocytes accumulate excess energy as triglycerides (TGs) within large unilocular lipid droplets, whereas brown adipocytes utilize mitochondrial uncoupling protein 1 (UCP1)-mediated uncoupled respiration to dissipate energy as heat, offering potential antiobesity effects. Beige adipocytes emerge either through the transdifferentiation of white adipocyte precursors or *de novo* differentiation of stromal cells in white adipose depots, resulting in UCP1-dependent thermogenic capacity comparable to that of brown adipocytes. This thermogenic program is coordinately regulated by key transcriptional regulators, including PPAR- γ coactivator 1 α (PGC-1 α) and PR domain-containing 16 (PRDM16) [8].

White adipocytes: energy storage and metabolic plasticity

Originating from Myf5⁺ mesodermal precursors, white adipocytes constitute the primary functional unit of adipose tissue. Their defining morphology, a large unilocular lipid droplet occupying > 90% of the cytoplasm and a sparse mitochondrial network, is exquisitely adapted for efficient energy storage as TGs [9]. These cells maintain systemic energy homeostasis through regulated TG cycling: storing lipids during nutrient excess and mobilizing free fatty acids (FFAs) via lipolysis upon metabolic demand (fasting, cold, exercise).

Beyond passive storage, white adipocytes exhibit significant metabolic plasticity, are centrally regulated by nuclear receptors such as PPAR- γ , and function as dynamic endocrine/paracrine organs [10]. They secrete key regulators, including leptin (energy balance), adiponectin (insulin sensitivity), and TNF- α (inflammation), and engage in intercellular communication (e.g., via exosomal miRNAs with macrophages). Thus, white adipocytes are active signaling hubs whose dysfunction underpins metabolic disease pathogenesis [11].

Brown adipocytes: regulation of mitochondrial thermogenesis and energy expenditure

Brown adipocytes, which counterbalance thermogenesis to white

adipocytes, function as dedicated energy-dissipating units, serving as essential physiological counterbalances to the lipid-accumulating role of white adipocytes. Brown adipocytes exhibit a specialized morphology antithetical to white fat: their multilocular lipid droplets and ultradense mitochondrial network directly. This architecture enables their defining mechanism, UCP1-mediated uncoupling of oxidative phosphorylation (OXPHOS), which diverts energy from ATP synthesis toward heat production, creating a unidirectional energy sink [12].

The master regulator PRDM16 orchestrates this thermogenic identity by coactivating brown-specific genes (e.g., direct UCP1 enhancer binding) while repressing white adipogenic programs (notably PPAR- γ -driven lipid anabolism) and recruiting Sirtuin (SIRT) 1 to optimize mitochondrial oxidation [13]. Therefore, this regulatory mechanism provides a new approach for treating pathological changes in white adipose tissue caused by obesity.

Beige adipocytes: inducible thermogenesis and metabolic flexibility

Beige adipocytes constitute an inducible thermogenic cell population that arises within white adipose tissue depots following chronic cold exposure or β 3-adrenergic stimulation. Beige adipocytes possess the ability for bidirectional differentiation (Figure 1), which enables beige fat cells to adapt dynamically to metabolic challenges [14]. Like brown adipocytes, beige adipocytes increase systemic energy expenditure through UCP1-dependent thermogenesis, which is mediated by mitochondrial biogenesis and increased oxidative capacity [15].

Adipocyte phenotypic plasticity: whitening and browning

Adipocytes exhibit substantial phenotypic plasticity and are capable of bidirectional interconversion between white and beige states in response to metabolic demands. During positive energy balance, beige adipocytes undergo “whitening”. Conversely, energy-demanding conditions induce adipose tissue “browning” through reciprocal phenotypic transitions (Figure 1).

The browning of adipocytes is kinetically regulated through dynamic shifts in thermogenic metabolism. When OXPHOS activity decreases, the mitochondrial electron transport chain (ETC) exhibits reduced uncoupling, which simultaneously compromises ATP synthesis efficiency and diminishes thermogenic output [16].

Adipocyte browning is coordinately regulated through integrated metabolic and transcriptional networks. The central regulator PPAR- γ orchestrates this process by (1) activating UCP1 expression via PRDM16/PGC-1 α -mediated mitochondrial biogenesis and (2) suppressing the lipid storage genes fatty acid synthase (FAS)/acetyl-CoA carboxylase (ACC) [17,18]. FAS catalyzes *de novo* lipogenesis, whereas ACC produces malonyl-CoA, a potent inhibitor of carnitine palmitoyltransferase-1 (CPT-1). CPT-1 acts as a crucial regulator of mitochondrial fatty acid uptake. Its increased activity drives efficient β -oxidation, concurrently generating metabolic intermediates (e.g., acetyl-CoA, NADH) that serve as ligands and activators for the PPAR- γ /PGC-1 α transcriptional complex. This creates a feed-forward amplification loop, perpetuating mitochondrial fatty acid catabolism and associated gene expression [19,20]. Inhibition of FAS/ACC reduces malonyl-CoA levels, relieves CPT-1 suppression and promotes β -oxidation-derived acetyl-CoA production. This metabolic shift both fuels UCP1-mediated thermogenesis and

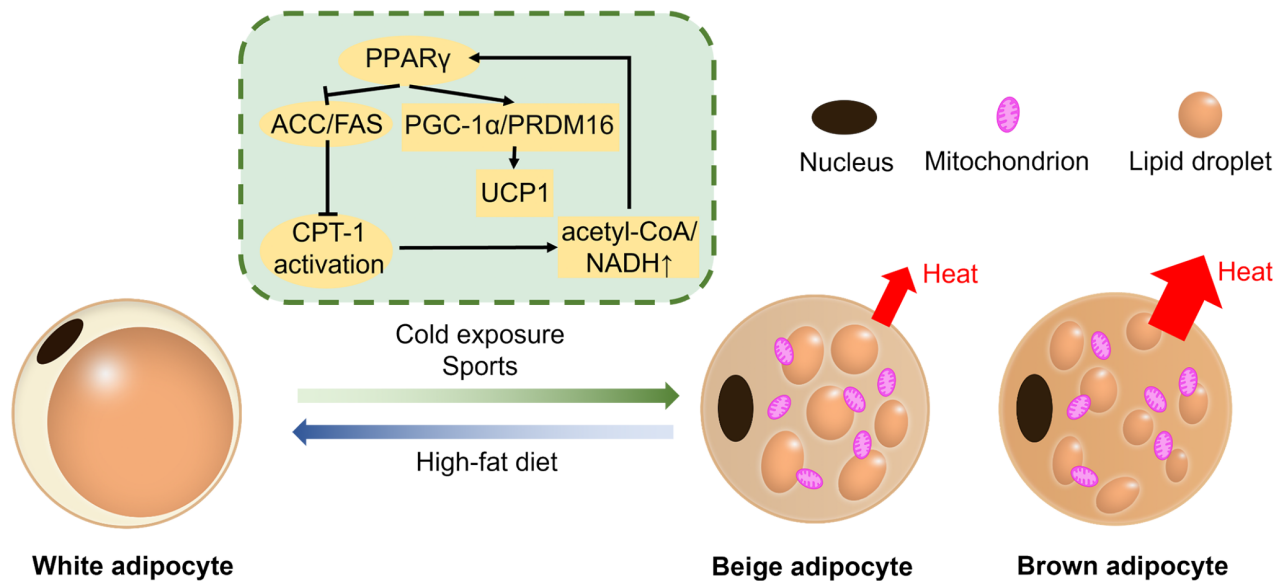


Figure 1. Mitochondrial determinants of phenotypic plasticity and energy expenditure in adipocytes External stimuli affect the phenotypic transformation of adipocytes by regulating mitochondrial functions, such as mitochondrial biogenesis, OXPHOS efficiency and dynamic balance. A high-fat diet inhibits mitochondrial activity, leading to the “whitening” of white adipocytes and exacerbating energy storage. Cold or exercise activates AMPK, PPAR- γ and other signaling pathways, promoting mitochondrial proliferation and browning and enhancing thermogenesis.

activates the PPAR- γ /PGC-1 α pathway to increase mitochondrial function [21].

In total, the plasticity of adipocytes is regulated through processes such as OXPHOS and fatty acid β -oxidation, and this regulatory process can be controlled by a regulatory network centered on PPAR- γ . This multilayered control mechanism presents promising therapeutic targets for metabolic disorders.

What Are the Mitochondrial Dysfunctions? Metabolic dysfunction

Mitochondrial metabolic dysfunction can be classified into imbalances in energy production, redox reactions, and calcium homeostasis. Energy metabolism disorders are caused by defects in the tricarboxylic acid (TCA) cycle or the ETC. Reactive oxygen species (ROS) imbalance results from intensified ETC electron leakage and insufficient compensatory antioxidant systems. Calcium homeostasis imbalance manifests as calcium overload, which triggers the opening of the mitochondrial permeability transition pore (mPTP). Among these factors, energy metabolism disorders are the foundation, whereas ETC dysfunction exacerbates ROS production and calcium buffering failure. Calcium overload further inhibits energy synthesis and amplifies oxidative stress, forming a positive feedback loop of “energy-ROS-calcium”, which jointly drives apoptosis and tissue damage.

Disorders of energy metabolism

Mitochondria serve as the energy hubs of eukaryotic cells, primarily generating ATP through OXPHOS, an integrated process requiring tight coordination between the TCA cycle and the ETC [22]. Cellular metabolism begins with glycolysis, which converts glucose to pyruvate with minimal ATP. Pyruvate then enters mitochondria and is oxidatively decarboxylated to acetyl-CoA by pyruvate dehydrogenase, producing NADH [23]. In the TCA cycle, acetyl-CoA undergoes a series of consecutive oxidative decarboxylation reactions. Each cycle generates three NADH molecules, one flavin adenine dinucleotide

(FADH₂) and one guanosine triphosphate (GTP), and simultaneously releases carbon dioxide as metabolic waste [24]. These reduced electron carriers (NADH/FADH₂) subsequently donate electrons to the ETC. Electrons flow from either complex I or II through ubiquinone, complex III, cytochrome C, and finally complex IV, where they reduce molecular oxygen to water [25].

The energy conversion mechanism of the abovementioned OXPHOS process is systematically explained by the chemiosmotic hypothesis [26]. This theory was proposed by Peter Mitchell in 1961, who emphasized that the ETC releases free energy through the stepwise oxidation of NADH and FADH₂, driving protons from the mitochondrial matrix across the inner membrane to the intermembrane space (IMS), thereby forming an electrochemical proton gradient composed of a proton concentration gradient and transmembrane potential [27]. When protons flow back into the matrix along the concentration gradient through ATP synthase, the conformational changes facilitate the catalysis of ADP condensation with inorganic phosphate to form ATP [28]. This model discards the traditional high-energy intermediate product hypothesis and establishes the spatial dependence of membrane structural integrity, directed proton transport, and energy coupling, providing support for understanding biological energy conversion.

Mitochondrial dysfunction in energy metabolism primarily manifests through two interconnected pathological mechanisms: (1) impaired ETC activity and (2) reduced OXPHOS efficiency. The first insult occurs at the TCA cycle level, where damaged enzymes reduce the production of NADH/FADH₂ generation and consequently limit electron donors for the ETC. For example, mutations in isocitrate dehydrogenase (IDH) lead to a decrease in α -ketoglutarate, causing dysfunction of the TCA cycle and a reduction in NADH production. A decrease in α -ketoglutarate dehydrogenase activity or inactivation induced by ROS reduces the conversion of α -ketoglutarate to succinyl coenzyme A, thereby reducing NADH production; harmful variations or a lack of

mitochondrial malic dehydrogenase results in the obstruction of the oxidation of malic acid to oxaloacetic acid, thereby reducing NADH production [29]. Concurrently, ETC complex dysfunction impedes electron flow, abolishing proton pumping capacity [30]. The second insult arises from the collapse of the proton-motive force. Without a maintained proton gradient, ATP synthase loses its thermodynamic driving force, precipitating a dramatic decline in ATP synthesis [31]. Taken together, these two metabolic disorders of mitochondria form a vicious cycle, resulting in a failure of the biological energy supply.

Imbalance of ROS

Mitochondrial ROS are in physiological equilibrium through coordinated generation. The primary source of mitochondrial ROS stems from electron leakage during OXPHOS, particularly at the quinone-binding sites of complexes I and III in the ETC, where incomplete oxygen reduction generates superoxide anions ($O_2^{\cdot-}$) [32]. Additional minor ROS production occurs through side reactions of TCA cycle enzymes during normal metabolic activity [33]. To counterbalance ROS production, mitochondria employ a sophisticated antioxidant defense system involving both enzymatic and nonenzymatic components. Superoxide dismutase 2 (SOD2) catalyzes the conversion of $O_2^{\cdot-}$ to H_2O_2 , which is subsequently detoxified to water by glutathione peroxidase and catalase [34]. The mitochondrial matrix further contains reducing agents such as glutathione, thioredoxin, and ascorbic acid that directly scavenge reactive intermediates [35]. In addition to direct neutralization, mitochondria regulate ROS levels through redox-sensitive signaling pathways that modulate both production and clearance mechanisms [36].

Oxidative stress arises from a disruption in the equilibrium between ROS production and elimination. Excess ROS generation overwhelms antioxidant defenses, inducing pathological oxidative stress that impairs mitochondrial function via ETC impairment, which exacerbates electron leakage and superoxide/hydrogen peroxide accumulation [37]. The accumulated ROS inflict distinct molecular damage: $O_2^{\cdot-}$ directly oxidizes iron-sulfur cluster proteins, further disrupting ETC function [38], whereas H_2O_2 undergoes Fenton chemistry with free iron ions to generate highly reactive hydroxyl radicals that oxidatively modify lipids, proteins, and nucleic acids [39,40]. Concurrently, antioxidant defenses become overwhelmed, and SOD2 activity becomes saturated by excessive $O_2^{\cdot-}$ substrate, while the glutathione system is depleted due to NADPH insufficiency, leading to glutathione oxidation and loss of H_2O_2 detoxification capacity [41].

Calcium ion homeostasis imbalance

Mitochondria function as central regulators of cellular Ca^{2+} homeostasis through dynamic ion transport mechanisms. The mitochondrial calcium uniporter (MCU), the core channel for mitochondrial Ca^{2+} uptake, is a conserved heterooctamer of 4 MCU and 4 essential MCU regulator (EMRE) subunits. EMRE stabilizes MCU and bridges the regulatory proteins MICU1/2. The MICU1/2 heterodimer senses the IMS Ca^{2+} concentration via EF-hand domains to regulate Ca^{2+} influx, whereas efflux is mediated by the Na^+/Ca^{2+} exchanger and mPTP, collectively forming a calcium regulatory network [42]. Physiological Ca^{2+} oscillations activate key dehydrogenases, such as pyruvate dehydrogenase phosphatase, α -ketoglutarate dehydrogenase, and IDH, to increase NADH production, thereby coupling ETC activity with ATP synthesis to meet cellular energy demands [43]. Mitochondrial Ca^{2+} uptake

further amplifies redox signaling through calcium-dependent activation of ROS generation, modulating critical processes, including autophagy and proliferation [44].

Pathological calcium overload disrupts mitochondrial function via multiple mechanisms. Sustained cytoplasmic Ca^{2+} elevation drives excessive MCU-mediated mitochondrial uptake, inducing matrix Ca^{2+} overload. This metabolic crisis impairs ATP synthesis through two distinct pathways: (1) persistent mPTP opening collapses the membrane potential, abolishing proton gradient-driven ATP production and triggering crista structural disintegration [45], and (2) Ca^{2+} -phosphate precipitation depletes free matrix Ca^{2+} at the expense of OXPHOS capacity [46]. TCA cycle inhibition and ROS overproduction synergistically exacerbate mitochondrial dysfunction. Overall, mitochondrial function affects MCU, thereby causing a calcium ion imbalance and ultimately inhibiting ATP synthesis.

Structural abnormalities

In addition to metabolic perturbations, structural integrity is equally crucial for mitochondrial function, and its dysregulation constitutes a second key facet of dysfunction. There are two main types of mitochondrial structural abnormalities: kinetic imbalance and autophagy clearance defects. Kinetic imbalance refers to the abnormal regulation of fission and fusion.

Mechanisms of dynamic imbalance in mitochondrial structural abnormalities

Mitochondrial dynamics describe the regulated changes in mitochondrial morphology and distribution. This process encompasses fusion, where mitochondria merge via membrane fusion to form larger organelles, and fission, which increases the number of mitochondria and decreases their size [47]. Normally, mitochondrial fusion or fission is maintained by a network of microtubule regulatory proteins through which mitochondria shuttle throughout the cytoplasm to complete mitochondrial fusion or fission [48].

Mitochondrial fission is primarily mediated by dynamin-related protein 1 (DRP1). Recruited to the mitochondrial outer membrane by receptor proteins (e.g., MFF, FIS1, and MID49/51), DRP1 constricts the membrane through GTP hydrolysis to execute mitochondrial division [49]. When DRP1 is hyperactivated, excessive mitochondrial fission and fragmentation are induced [50]. In contrast, mitochondrial fusion relies on the coordinated action of the outer membrane proteins mitofusin 1/2 (MFN1/2) and the inner membrane protein optic atrophy 1 (OPA1). MFN1/2 mediate outer membrane fusion, whereas OPA1 maintains ETC integrity by regulating inner membrane morphology and crista structure assembly. Under conditions of abnormal mitochondrial membrane potential, OPA1 is proteolytically cleaved into short fragments by the metalloprotease OMA1, leading to crista disorganization, fragmentation of the crista network, and the subsequent triggering of apoptotic signaling [51]. The functional impairment of MFN1/2 impedes mitochondrial outer membrane fusion, disrupting the architecture of the mitochondrial network. Similarly, OPA1 dysfunction not only inhibits inner membrane fusion but also disrupts crista morphology, impairs the assembly of ETC complexes, and exacerbates functional decline [49].

Mitochondrial quality and quantity control

Mitophagy selectively removes dysfunctional mitochondria, maintaining mitochondrial quality. Depolarization of the mitochondrial membrane potential triggers this autophagic degradation [52].

Mitophagy is regulated primarily by the PINK1/PARKIN pathway [53]. Under conditions of mitochondrial depolarization or oxidative stress, PINK1 is stabilized and accumulates on damaged mitochondria [53]. PINK1 recruits and phosphorylates cytoplasmic PARKIN, triggering its mitochondrial translocation. Activated PARKIN ubiquitinates outer membrane proteins, recruiting autophagy receptors. These receptors bind LC3 on autophagosomes via their LC3-interacting region, initiating mitochondrial phagocytosis. Subsequent autophagosome-lysosome fusion enables the degradation of mitochondrial components [53]. Conversely, PINK1/PARKIN pathway dysfunction disrupts ubiquitination signaling, impairing the recognition and clearance of defective mitochondria. Additionally, BNIP3-NIX can directly interact with LC3 to activate alternative mitophagy pathways [54]. Overall, mitophagy failure results in the pathological accumulation of dysfunctional mitochondria, exacerbating oxidative stress and energy deficits.

Genetic deficits

Genetic lesions affecting either the mitochondrial or nuclear genome represent fundamental causes of mitochondrial failure. Mitochondrial gene defects include mutations in mitochondrial DNA (mtDNA) and nuclear DNA.

mtDNA mutations

mtDNA mutations impair mitochondrial function via three primary mechanisms: (1) The m.3243A > G mutation disrupted the structure of leucine tRNA and reduced the translation efficiency of the ND1 and ND6 mRNAs. These factors compromise complex I assembly, exacerbate electron leakage, and trigger ROS overproduction [55]. (2) Large deletions: the 4977 bp “common deletion” eliminates subunits of complexes I, IV, and V, forcing glycolytic dependency and amplifying ROS generation [56]. (3) Copy number reduction: diminished mtDNA levels are correlated with decreased OXPHOS activity and impaired ETC function [57].

Nuclear DNA mutations

Pathogenic variants in NDUFB1, encoding a critical ETC complex I subunit, impair electron transfer from NADH to coenzyme Q. This defect reduces proton gradient generation efficiency and ATP synthesis while promoting $O_2 \cdot^-$ overproduction via electron leakage [58]. Concurrent defects in mitochondrial protein transport systems exacerbate metabolic dysregulation. Dysfunction of the translocase of the inner mitochondrial membrane (TIMM) complex disrupts nuclear-encoded soluble protein import, leading to OXPHOS substrate deprivation and aberrant metabolite accumulation [59]. Similarly, translocase of outer mitochondrial membrane (TOMM) complex activity blocks precursor protein translocation into the matrix, inducing ATP depletion and activating compensatory mitophagy [59,60]. In summary, mutations in nuclear-encoded mitochondrial DNA can lead to defects in some mitochondrial functional proteins, ultimately affecting OXPHOS and causing dysfunction of the mitochondria.

Mitochondrial Dysfunction Affects Adipocyte Differentiation

Mitochondrial ROS signaling: a double-edged sword in adipocyte differentiation

Studies have demonstrated that moderate ROS elevation serves as a critical signaling cue, particularly during the transdifferentiation of

white adipocytes into beige adipocytes [61]. For example, in adipocyte-specific *Sod2*-knockout mice, mitochondrial superoxide accumulation unexpectedly promoted beige adipogenesis in inguinal white adipose tissue, as indicated by increased cell populations, mitochondrial biogenesis, and UCP1-mediated respiratory capacity. Similarly, excessive ROS accumulation in brown adipose tissue amplifies mitochondrial uncoupling and fatty acid oxidation, thereby increasing basal proton leak respiration and thermogenic output [62].

Physiological ROS generated during exercise stimulate beige adipogenesis, indicating that modulating the adipose tissue redox balance represents a novel therapeutic strategy for metabolic syndrome [61]. Preclinical studies have demonstrated that natural compounds mitigate metabolic disorders by balancing mitochondrial ROS and antioxidant defenses. For example, magnoflorine ameliorates cardiac mitochondrial dysfunction in diabetic mice by attenuating complex I respiration driven by fatty acid oxidation [63]. Similarly, the diterpenoid rotenone activates peroxiredoxin 3 (Prdx3), significantly reducing hepatic lipid accumulation in high-fat diet-induced nonalcoholic fatty liver disease (NAFLD) models [64]. Overall, targeting ROS pathways is a promising approach for treating obesity-related metabolic complications. Future translational studies must validate efficacy and safety across diverse human populations to bridge mechanistic insights and clinical applications.

Mitochondrial dysfunction regulates adipogenic signaling pathways

Mitochondria, as central hubs of cellular energy metabolism, critically regulate adipocyte differentiation through key signaling pathways. Accumulating evidence indicates that mitochondrial dysfunction disrupts adipogenesis via dysregulation of AMPK-, PPAR- γ -, and mTOR-dependent cascades (Figure 2).

AMPK pathway

AMPK serves as a sensor of the cellular energy status and restores ATP homeostasis under energy-deficient conditions [65]. Mitochondrial dysfunction, which impairs ATP production, strongly activates AMPK.

AMPK plays a central role in brown adipocyte differentiation, primarily by upregulating UCP1 expression [66]. Mechanistically, AMPK promotes demethylation of the PRDM16 promoter by upregulating α -KG, thereby increasing its transcriptional activity and expression [67]. As previously noted, PRDM16 is a key transcriptional regulator that drives white-to-beige/brown adipose tissue conversion and thermogenesis through UCP1 activation and mitochondrial biogenesis. Furthermore, AMPK enhances its own activity by suppressing cell death-inducing DFFA-like effector a (CIDEA)-mediated ubiquitin-proteasome degradation, creating a positive feedback loop that amplifies AMPK signaling and accelerates brown adipocyte differentiation [68]. Pharmacological AMPK activation similarly promotes white adipocyte browning, as demonstrated by AMPK activators that increase mitochondrial content and fatty acid oxidation, thereby enhancing thermogenesis in white adipose tissue [69].

Targeted activation of the AMPK signaling pathway represents a core therapeutic strategy against obesity and metabolic diseases with significant translational potential. Natural compounds effectively regulate lipid metabolism, promote white adipose tissue browning, and improve metabolic health through AMPK-dependent

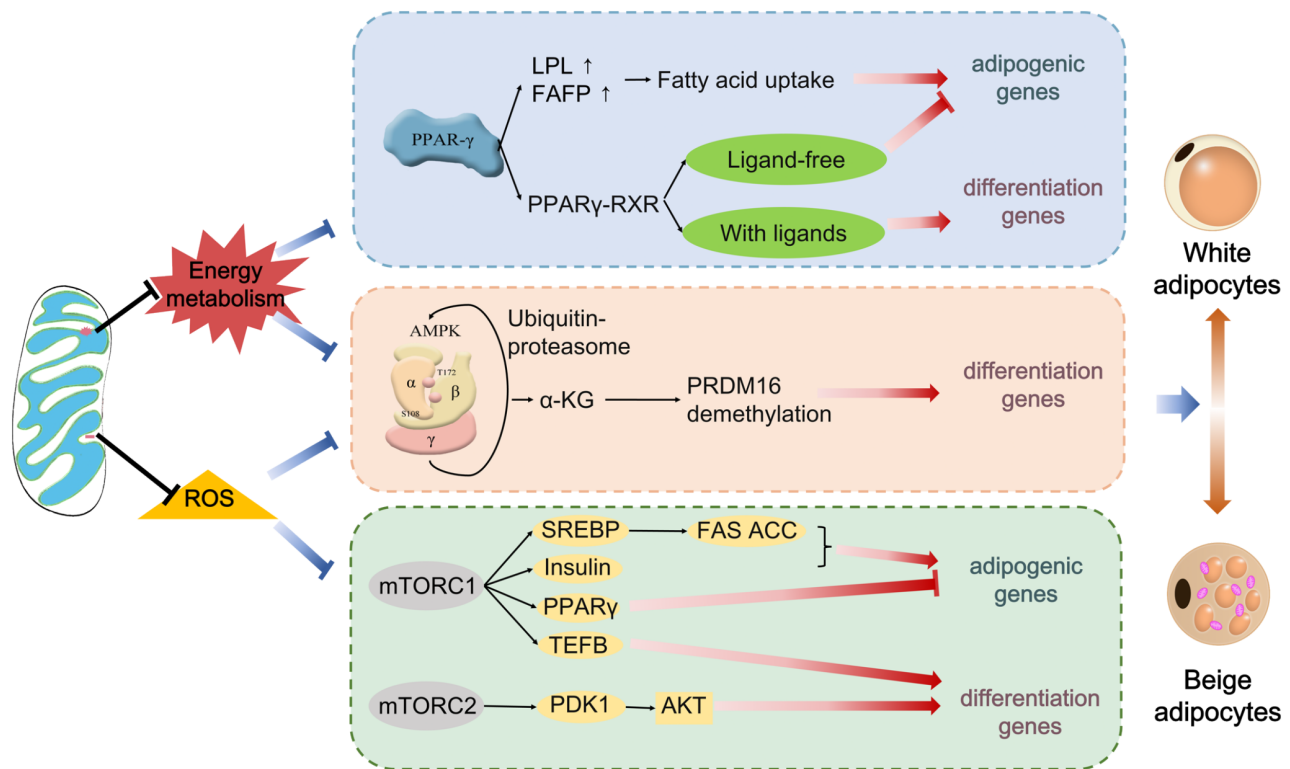


Figure 2. Mitochondrial dysfunction regulates adipocyte differentiation through AMPK/PPAR- γ /mTOR crosstalk Mitochondrial dysfunction disrupts adipocyte differentiation through tripartite signaling hub dysregulation. The AMPK axis promotes adipose browning via epigenetic remodeling mechanisms, including DNA demethylation. PPAR- γ serves as the master transcriptional regulator of lipogenic programming, coordinating lipid metabolism gene expression and thermogenic adaptation. The mTOR pathway has dual functions: mTORC1 stimulates lipogenesis through the activation of SREBP, whereas mTORC2 regulates fat metabolism through signaling mediated by AKT phosphorylation.

mechanisms. Berberine (BBR) activates AMPK α phosphorylation in a concentration- and time-dependent manner, suppresses lipogenic gene expression, reduces lipid deposition, increases insulin sensitivity, and activates Nrf2-mediated antioxidant defense to ameliorate metabolic dysfunction [70]. Ginger-derived phenolic compounds directly enhance adipocyte mitochondrial function via AMPK activation, increasing mitochondrial abundance and OXPHOS-related gene expression while reducing lipid accumulation [71]. Adult stem cell (ASC) complex supplementation increases AMPK phosphorylation and UCP1 expression, driving energy expenditure, thermogenesis, and lipid oxidation in preclinical models [72]. The marine bioactive compound Ecklonia bicyclis water extract concomitantly improves lipid metabolism, glucose homeostasis, and antioxidant capacity through AMPK activation, downregulating the expression of adipogenic transcription factors (PPAR- γ , C/EBP α , and SREBP-1c) while upregulating the NRF2/HO-1/NQO1 pathways [73]. Additionally, the thiophene derivative TCA cycle upregulates lipid storage droplet protein 5 (PLIN5) to activate AMPK, enhancing lipid droplet-mitochondrial coupling and promoting mitochondrial biogenesis [74]. Overall, regulating this pathway is a potential strategy for treating metabolic disorders.

PPAR- γ pathway

AMPK activation increases SIRT1 activity to deacetylate and modulate downstream SIRT1 targets, and BBR acts as a selective PPAR- γ activator within the AMPK/SIRT1 pathway, suppressing transcriptional activity and lipid storage [75].

PPAR- γ serves as a pivotal transcriptional regulator that governs adipocyte differentiation and lipid homeostasis. Mechanistically, PPAR- γ acetylation enhances histone acetylation levels, induces chromatin relaxation, and affects the plasticity of fat cells [76]. This nuclear receptor directly activates lipid-processing genes, including lipoprotein lipase (LPL) and fatty acid transport protein (FATP), thereby promoting fatty acid uptake, esterification, and subsequent triglyceride storage [77]. The regulatory network extends through dynamic interactions with transcriptional coregulators. In its unliganded state, PPAR- γ forms heterodimers with the retinoid X receptor (RXR) to recruit corepressor complexes containing histone deacetylases (HDACs), effectively suppressing adipogenic gene expression while initiating white adipose tissue browning [78]. Ligand binding induces conformational changes that displace corepressors and recruit coactivators with histone acetyltransferase (HAT) activity, driving the expression of differentiation markers and thermogenic genes, including UCP1 [78]. This dual regulatory mechanism coordinates lipid storage with energy expenditure through the temporal control of transcriptional programs.

The PPAR- γ pathway is a central mechanism that regulates adipocyte browning, making it an attractive drug target for combating obesity and metabolic disorders. Pharmacological strategies have been developed to effectively induce adipocyte browning by directly or indirectly modulating this pathway. Rosiglitazone, a PPAR- γ agonist, has been shown to be effective in inducing white adipose tissue (WAT) browning. In animal

experiments, long-term treatment significantly upregulated UCP1 and β 3-adrenergic receptor expression in inguinal and epididymal WAT and enhanced their functional activities, including mitochondrial respiratory capacity, glucose uptake, and the calcium signaling response, which confer beige adipocyte-like features [67]. Similarly, the agonist GQ-16 increases UCP1 expression and thermogenic gene transcription in BAT and WAT depots while reducing adiposity [79]. PPAR- γ activity is further modulated by posttranslational mechanisms. Cold-induced upregulation of protein arginine methyltransferase 4 (PRMT4) methylates PPAR- γ , strengthening its interaction with PRDM16 to activate thermogenic programs. PRMT4 overexpression accelerates browning and reduces obesity, highlighting the PRMT4-PPAR- γ axis as a novel therapeutic strategy [80]. Metabolic pathway modulation indirectly regulates PPAR- γ complex function. Inhibition of the branched-chain amino acid transaminase 2 (Bcat2) reduces the level of branched-chain ketoacid (BCKA)-derived acetyl-CoA, impairing PRDM16 acetylation. This stabilizes the PPAR- γ /PRDM16 complex, enhancing WAT browning and energy expenditure [81], suggesting that metabolic reprogramming is a viable strategy against obesity.

mTOR signaling pathways

Mitochondrial dysfunction-induced ROS accumulation exerts concentration-dependent effects on mTOR complexes. Mammalian target of rapamycin exists as two structurally distinct complexes (mTORC1/2) with differential sensitivity to oxidative stress [82]. Experimental evidence indicates that supraphysiological ROS concentrations suppress mTORC1 activity via AMPK activation of the LKB1/AMPK/TSC2 axis [83]. Moreover, mTORC2 has bimodal regulatory characteristics: moderate oxidative stress reinforces its autophagy-inhibitory function, whereas severe oxidative stress provokes mTORC2-dependent cellular senescence through autophagic pathway activation [84]. This redox-sensitive regulatory network ultimately disrupts adipogenic differentiation through coordinated modulation of mTORC1/2 activities.

mTORC1 exerts multilevel control over adipogenesis through PPAR- γ suppression and metabolic reprogramming. Mechanistically, mTORC1-mediated inhibition of PPAR- γ attenuates downstream lipogenic gene expression, effectively suppressing adipocyte differentiation [85]. Concurrently, mTORC1-activated SRPK2 phosphorylates the splicing factor SRSF1 and enhances its binding to FAM120A. FAM120A directly interacts with the adipogenic transcription factor SREBP1 at the active promoter to promote the expression of sterol regulatory element-binding protein (SREBP)-dependent lipogenic enzymes and inhibit adipose tissue browning [86]. Moreover, mTORC1 can respond to insulin [87]. Nutrient sufficiency reinforces mTORC1 activity to block transcription factor EB (TFEB) nuclear translocation and suppress UCP1 expression. Conversely, cold exposure or energy deprivation inactivates mTORC1, enabling TFEB-mediated activation of lipophagy, PGC-1 α -driven mitochondrial biogenesis, and subsequent thermogenic programming [88]. Taken together, these findings indicate that mTORC1 regulates adipocyte differentiation, adipose tissue function, and key metabolic pathways.

mTORC2 regulates lipid metabolism mainly through AKT phosphorylation. mTORC2 phosphorylates AKT at T308 via PDK1 to increase its kinase activity, which in turn phosphorylates SIN1, further increasing the kinase activity of mTORC2. Activated mTORC2, in turn, phosphorylates AKT at S473, which catalyzes full activation [89]. Full activation of AKT is one of the central

drivers of adipocyte differentiation and lipid metabolism. Fat-specific AKT knockout mice exhibit severe lipodystrophy with complete loss of subcutaneous and interscapular brown adipose tissue [90]. As a consequence, mTORC2 indirectly affects adipocyte differentiation by regulating full AKT activation.

The centrality of the mTOR pathway in lipid metabolism establishes it as a promising pharmacological target. The key regulatory nodes identified through basic research include SIK3, whose inhibition enhances mTORC1-dependent browning gene expression and mitochondrial function [91], and bone morphogenetic protein 11 (BMP11/GDF11), which induces white adipocyte browning through mTORC1-COX2 signaling. BMP11 depletion impairs thermogenic and lipolytic protein expression in adipocytes [92]. These findings suggest that SIK3 and BMP11 are therapeutic targets for mTOR-mediated browning. Clinically, sildenafil treatment induced browning in human subcutaneous white adipose tissue (sWAT) via cGMP-PKG-mTOR signaling, as manifested by the following findings: multilocular UCP1⁺ adipocytes, reduced adipocyte size, elevated UCP1 expression (protein/mRNA), increased mitochondrial density, and increased oxygen consumption [93].

Mitochondrial structural abnormalities affect adipocyte differentiation

Mitochondrial dynamics

Mitochondrial fusion is orchestrated by the dynamin-related GTPases MFN1, MFN2, and OPA1. Experimental evidence has demonstrated that OPA1-mediated crista remodeling enhances white adipose tissue browning through mitochondrial network stabilization [94]. DRP1-mediated hyperdivision inhibits differentiation by disrupting ridge structure, ultimately suppressing adipocyte maturation [95]. These opposing processes establish that fusion promotes differentiation, whereas excessive fission exacerbates metabolic dysregulation.

Mitochondrial dynamics critically influence metabolic disease management in humans. Diabetes-induced mitochondrial dysfunction directly contributes to metabolic dysregulation and chronic diabetic complications [96]. Clinically, metformin reverses mitochondrial dysfunction in type 2 diabetes (T2D) patients' leukocytes while downregulating fission mediators and upregulating fusion proteins (MFN2, OPA1) [97], indicating that mitochondrial functional restoration through dynamic regulation constitutes a key therapeutic mechanism. These findings establish the modulation of mitochondrial dynamics as a viable strategy for developing targeted diabetes therapies.

Mitophagy

The conversion of beige adipocytes to white adipocytes is critically regulated by mitophagy. For example, concurrent depletion of the autophagic protein ATG7 in white and brown adipocytes reduces the interscapular brown adipose tissue mass and diminishes lipid droplet deposition due to elevated β -oxidation [98]. ATG7-knockout mice presented decreased UCP1 expression and mitochondrial marker levels in brown adipose tissue, impairing thermogenic capacity and leading to lipid droplet accumulation [98]. Similarly, PINK1/PARKIN-mediated mitophagy provides metabolic support for the phenotypic transformation of adipocytes by clearing dysfunctional mitochondria, and PARKIN knockout suppressed mitophagy activity, unexpectedly increasing the activation of browning factors such as PGC-1 α [99].

Mitophagy has significant clinical importance in metabolic

disorders. Substantial evidence has demonstrated the key role of mitophagy in regulating T2D and its complications, with deficiencies directly contributing to insulin resistance pathogenesis [100]. Restoration of mitophagy function therefore represents a promising therapeutic strategy for obesity and metabolic syndrome. Experimental models confirmed this potential: enkeletin activates mitophagy to attenuate cardiac microvascular ischemia-reperfusion (I/R) injury [101], whereas various phytochemical compounds preserve β -cell function through mitophagy induction [100].

Mitochondrial Dysregulation in Obesity and Its Associated Pathogenesis of Metabolic Syndrome

Mitochondrial-adipose axis dysfunction drives obesity pathogenesis through three pathological axes: the metabolic axis, where impaired brown fat oxidation reduces energy expenditure, inducing insulin resistance and fatty liver disease; the circulatory axis, where sustained oxidant stress damages the endothelium, increases myocardial ischemic susceptibility, and accelerates cardiovascular remodeling; and the systemic axis, where chronic low-grade inflammation accelerates aging pathologies and establishes neurodegenerative comorbidities. These axes maintain relative independence yet interconnect through shared positive feedback between mitochondrial dysfunction and inflammation-metabolism.

Mitochondrial dysfunction inhibits fat browning: the initial pathology of obesity

Adipose tissue browning represents a critical thermogenic adaptation for energy dissipation and obesity resistance. Notably, obesity-associated mitochondrial dysfunction disrupts this process through coordinated molecular mechanisms, exacerbating energy imbalance and metabolic syndrome progression.

Mechanistically, ETC dysfunction induces excessive ROS production and lipid peroxidation, suppressing PPAR- γ -driven adipogenesis. Mitochondrial calcium overload exacerbates metabolic failure by disrupting the membrane potential and depleting thermogenic substrates, creating a vicious cycle [102].

Concurrently, impaired mitochondrial dynamics (excessive DRP1-mediated fission compromising ETC assembly and MFN2/OPA1 deficiency disrupting crista integrity) and defective PINK1/PARKIN-mediated mitophagy directly impair metabolic flexibility, diminish thermogenesis, and suppress PGC-1 α -dependent mitochondrial biogenesis, thereby attenuating browning capacity [103]. Furthermore, reduced AMPK activity impedes PRDM16 demethylation and CPT-1-mediated fatty acid oxidation, whereas elevated ROS inhibits mTORC1/SREBP-driven lipogenesis and mTORC2/AKT signaling. PPAR- γ phosphorylation additionally disrupts its heterodimerization with RXR.

The mitochondrial basis of insulin resistance: the core hub of metabolic syndrome

Insulin resistance, the central pathophysiological hallmark of metabolic syndrome, is mechanistically linked to mitochondrial dysfunction through insulin signaling pathway disruption [104]. Mitochondria-associated endoplasmic reticulum membranes (MAMs) serve as critical modulators of this process by coordinating calcium flux, maintaining lipid homeostasis, and regulating redox reactions to preserve insulin sensitivity. Adipose-specific MAMs impairment disrupts PPAR- γ -driven adipose browning programs, resulting in compromised thermogenic capacity and progressive

insulin resistance exacerbation [105,106].

In the liver, MAMs act as nutrient-sensing hubs. Structural disruption of MAMs impairs insulin signaling, whereas moderate stabilization restores glucose homeostasis. Conversely, excessive ER-mitochondrial tethering exacerbates metabolic dysfunction via lipotoxic metabolite accumulation, reflecting a U-shaped regulatory relationship [107]. In skeletal muscle, transient MAMs enhancement alleviates early insulin resistance, but chronic hyperconnectivity induces abnormal insulin receptor substrate-1 (IRS-1) phosphorylation and ectopic lipid deposition.

An imbalance in mitochondrial dynamics further exacerbates metabolic dysregulation. Excessive DRP1-mediated fission suppresses insulin signaling through reduced ATP synthesis and increased ROS production. Pharmacological inhibition of DRP1 or promotion of mitochondrial fusion restores mitochondrial network integrity and improves insulin sensitivity [108,109]. Rooted in adipose mitochondrial failure, systemic insulin resistance emerges as the pivotal amplifier of metabolic dysregulation, orchestrating lipid toxicity in peripheral tissues. In summary, MAMs dysfunction impairs the imbalance of mitochondrial dynamics, which can affect insulin signaling, thereby leading to insulin resistance.

Mitochondrial dysfunction in NAFLD

The liver is a core target organ of insulin resistance, and NAFLD is caused by a combination of mitochondrial β -oxidation disorders and lipotoxicity. NAFLD, characterized by metabolic syndrome-driven hepatic lipid accumulation, represents the predominant chronic liver pathology globally. Mechanistically, excessive fructose consumption activates SREBP1c-mediated *de novo* lipogenesis, whereas peripheral insulin resistance exacerbates triglyceride synthesis through increased FFA hepatic influx [110]. NAFLD-associated mitochondrial impairment manifests through dual pathological axes: diminished β -oxidation capacity coupled with ETC suppression, culminating in ATP synthesis deficiency and ROS overproduction that drive hepatocyte apoptosis and fibrotic transformation [111]. Ultrastructural mitochondrial lesions, including crista fragmentation and network disassembly, establish a self-reinforcing pathogenic loop by impairing bioenergetic flux [112]. When encapsulated, OXPHOS and ultrastructural mitochondrial disorders promote the development of NAFLD by damaging the production of biological energy and the accumulation of lipid energy.

Mitochondrial dysfunction in ischemia-reperfusion injury and cardiovascular remodeling

Obesity-related mitochondrial ROS overload increases myocardial sensitivity to ischemia-reperfusion injury (IRI). Mitochondria function as the cellular bioenergetic hub, with their core role being ATP production and redox homeostasis maintenance via OXPHOS. However, this function is severely compromised during I/R injury: ischemia inhibits ETC complex I, causing NADH/succinate accumulation and ATP depletion; reperfusion exacerbates complex I electron leakage, triggering excessive ROS generation and activating oxidative damage and proinflammatory cascades [113]. Heart failure involves mitochondrial ROS overproduction and impaired PPAR α /PGC-1 α signaling in cardiomyocytes, leading to bioenergetic failure similar to that observed in ischemia-reperfusion injury. While current therapies partially improve symptoms, targeting mitochondrial dysfunction, particularly by restoring OXPHOS

efficiency and redox balance, has emerged as a central strategy to mitigate metabolic impairment in the failing myocardium [114].

Emerging therapeutic strategies targeting mitochondrial restoration focus on two approaches: AMPK activation to rebalance ETC redox states and DRP1 inhibition to prevent pathological fission, thereby preserving mitochondrial network integrity [115]. PPAR- α/γ coactivation has synergistic benefits by enhancing fatty acid β -oxidation and adipose thermogenesis, suggesting novel pathways for mitigating IRI and obesity-related cardiometabolic deterioration. In particular, mitochondrial dysfunction can exacerbate cardiac injury, and cardiac injury in turn further aggravates mitochondrial dysfunction, thus forming a mutually reinforcing vicious cycle. Combining AMPK activation and DRP1 inhibition restores mitochondria, while PPAR- α/γ coactivation increases fat burning, suggesting new metabolic disease treatments.

Systemic consequences: mitochondrial aging and metabolic-neurocomorbidity

Mitochondrial energy failure in neurodegenerative diseases

Mitochondrial energy metabolism dysfunction in neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, involves bidirectional interactions with adipocyte browning through a metabolism-neural network. Adipocyte browning activates the PGC-1 α /UCP1 pathway, enhancing mitochondrial thermogenesis and systemic metabolism while releasing adiponectin [116]. Similarly, in neurodegenerative diseases, ATP depletion caused by ETC impairment suppresses brown adipose tissue activity via the hypothalamic-sympathetic axis, exacerbating a vicious metabolic-neurological cycle.

Mitochondrial senescence and metabolic decline during aging

The decline in body function associated with aging is closely related to mitochondrial dysfunction, which is characterized by the accumulation of mtDNA mutations, abnormal epigenetic regulation, impaired mitophagy, and reduced biogenesis, leading to bioenergy failure and oxidation [117]. Studies have demonstrated that aging-associated mitochondrial dysfunction, characterized by the loss of membrane potential and excessive ROS accumulation, exacerbates the aging process by promoting proinflammatory phenotypes and metabolic disturbances. Furthermore, dysregulated communication between mitochondria and the nuclear genome, including mtDNA leakage, may further amplify aging-related signaling pathways [118]. In brief, aging increases ROS and inflammation via fragmented networks and defective autophagy, accelerating tissue decline.

Summary and Expectations

Mitochondria, which are central to cellular energy metabolism, play pivotal roles in the pathogenesis of obesity and related metabolic disorders through multiple mechanisms. This review synthesizes evidence highlighting mitochondrial dysfunction, manifested as metabolic impairment, structural anomalies, and genetic defects, as critical regulators of adipocyte differentiation and metabolic homeostasis. This dysfunction disrupts adipocyte plasticity by suppressing differentiation, perturbing signaling pathways, and destabilizing metabolic balance. In obesity, mitochondrial defects exacerbate metabolic syndrome via the inhibition of adipocyte browning, aggravation of insulin resistance, and promotion of

NAFLD and reperfusion injury. Furthermore, mitochondrial dysfunction intersects with neurodegenerative diseases and aging, amplifying metabolic dysregulation. Collectively, these processes establish a vicious cycle driven by energy deficits, oxidative stress, and signaling pathway dysregulation, which underpins obesity-related pathologies.

Despite progress in understanding the role of mitochondrial dysfunction in metabolic diseases, key questions remain unresolved. First, the cooperative mechanisms between mtDNA and nuclear DNA in regulating mitochondrial function require elucidation, particularly how mtDNA mutations disrupt OXPHOS to exacerbate metabolic disorders. Importantly, specific nuclear-encoded factors sense and respond to mtDNA stress signals (e.g., mtDNA release, cf-mtDNA as DAMPs) to initiate adaptive or pathological transcriptional responses in adipose tissue. Second, systematic investigations into mitochondrial morphological abnormalities and their impact on adipocyte browning are lacking. Future studies should address how specific structural alterations suppress UCP1 expression via metabolic substrate utilization or ROS signaling. Single-cell multiomics can be leveraged to map the trajectory of mitochondrial dynamics within distinct adipocyte progenitors and mature subpopulations and establish causal links to phenotypic switching. Third, while mitochondrial Ca²⁺ homeostasis has been well studied, the roles of other ions in adipocyte differentiation remain unexplored. Fourth, adipocyte plasticity research must transition from static classifications to dynamic regulatory network analyses. Single-cell sequencing and metabolomics could identify key nodes in phenotype switching, enabling spatiotemporally precise interventions such as gene editing for obesity management. To construct single-cell omics data, computational modeling of the AMPK/PPAR- γ /mTOR signaling network dynamics during browning/whitening transitions is needed to identify key regulatory nodes. This will enable the development of spatiotemporally precise interventions, such as adipose tissue-specific gene editing targeting key mitochondrial dynamics genes (e.g., DRP1 and OPA1), in obesity models to evaluate their precise control over browning and metabolic homeostasis. Finally, the bidirectional crosstalk among mitochondrial dysfunction, neurodegeneration, and aging, particularly via metabolic-neural networks, warrants deeper exploration. Addressing these gaps will advance therapeutic strategies for metabolic and neurodegenerative diseases.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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