

Mitochondrial Function and Dysfunction in White Adipocytes and Therapeutic Implications

Fenfen Wang,¹ Phu M. Huynh,¹ and Yu A. An^{*1,2,3}

ABSTRACT

For a long time, white adipocytes were thought to function as lipid storages due to the sizeable unilocular lipid droplet that occupies most of their space. However, recent discoveries have highlighted the critical role of white adipocytes in maintaining energy homeostasis and contributing to obesity and related metabolic diseases. These physiological and pathological functions depend heavily on the mitochondria that reside in white adipocytes. This article aims to provide an up-to-date overview of the recent research on the function and dysfunction of white adipocyte mitochondria. After briefly summarizing the fundamental aspects of mitochondrial biology, the article describes the protective role of functional mitochondria in white adipocyte and white adipose tissue health and various roles of dysfunctional mitochondria in unhealthy white adipocytes and obesity. Finally, the article emphasizes the importance of enhancing mitochondrial quantity and quality as a therapeutic avenue to correct mitochondrial dysfunction, promote white adipocyte browning, and ultimately improve obesity and its associated metabolic diseases. © 2024 American Physiological Society. *Compr Physiol* 14:5581-5640, 2024.

Didactic Synopsis

Major teaching points

- White adipocytes have autocrine, paracrine, and endocrine functions in addition to their classical energy storage function.
- Although white adipocytes contain a small proportion of mitochondria, their mitochondria are essential in regulating white adipocyte function. Dysfunctional mitochondria are associated with impaired white adipocyte health.
- Normal mitochondria maintain white adipocyte viability, differentiation and adipogenesis, lipid and glucose metabolic homeostasis, adipokine secretion, browning, adipocyte heterogeneity determination, and stress condition protection.
- Dysfunctional mitochondria are linked to impaired white adipocyte function, including dysregulated adipocyte differentiation, increased apoptosis, imbalanced lipid and glucose metabolism, enhanced inflammatory factors secretion, and abnormal adipokine release.
- Enhancing mitochondrial function in white adipocytes contributes to the maintenance of white adipocyte function, which in turn benefits the overall metabolism of the body through interventions such as dietary components, secretory factors, pharmacological methods, and microRNAs.

Introduction

The rate of obesity continues to rise at an uncontrollable pace globally. While obesity *per se* is considered not life-threatening, people with obesity have a significantly higher incidence of deaths with other conditions, such as diabetes, cardiovascular diseases, and cancers. The most recent and notable example is the COVID-19 pandemic. Accumulating clinical evidence points out that obesity is the leading risk factor for COVID-19 patient hospitalization, severity, and death (4). White adipose tissue (WAT) lies at the heart of the obesity pandemic, and its overexpansion is the crucial signature of obesity development. While the WAT comprises distinct cell types, white adipocytes are undoubtedly the

*Correspondence to Yu.An@uth.tmc.edu

¹Department of Anesthesiology, Critical Care, and Pain Medicine, Center for Perioperative Medicine, McGovern Medical School, UT Health Science Center at Houston, Houston, Texas, USA

²Center for Metabolic and Degenerative Diseases, The Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases, McGovern Medical School, UT Health Science Center at Houston, Houston, Texas, USA

³Department of Biochemistry and Molecular Biology, McGovern Medical School, UT Health Science Center at Houston, Houston, Texas, USA

Published online, October 2024 (comprehensivephysiology.com)

DOI:10.1002/cphy.c230009

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major and fundamental residents. Therefore, a better and more thorough understanding of white adipocytes is crucial for fully covering the knowledge gaps in adipose biology. This further facilitates discovering the molecular underpinnings of how white adipocytes function physiologically and how they become dysfunctional during obesity.

Nowadays, white adipocytes are no longer considered merely lipid-laden cells, their secretion and energy expenditure roles are well appreciated. Although we are far from drawing the whole blueprint of white adipocytes, progress in recent decades has led to plenty of groundbreaking discoveries that open the horizons of adipocyte research. Among these, mitochondrial function and dysfunction in white adipocytes have received unexpected enthusiasm in the obesity and metabolism field. Initially, the importance of mitochondria in white adipocytes has been underestimated because of their limited number within cells. Despite the scarcity in quantity, mitochondria play an indispensable role in maintaining white adipocyte normal function, and numerous evidence concludes that mitochondrial dysfunction in white adipocytes is a hallmark of obesity.

Herein, we provide updated knowledge of how mitochondria contribute to white adipocyte health, and how their dysregulation is associated with obesity and other metabolic diseases. Beyond white adipocyte functions, the notion of mitochondria as a signaling hub communicating with other cells, tissues, and organs will be discussed. In addition to progress in basic research, we further summarize translational studies and therapeutic avenues against obesity and metabolic diseases from the white adipocyte mitochondrial aspect.

Beyond the Powerhouse: Overview of Mitochondrial Biology

It is widely accepted that mitochondria are descended from mitochondrial ancestors engulfed by eukaryotic cells. Mitochondrial ancestors refer to the protomitochondria, gram-negative bacteria harboring the tricarboxylic acid (TCA) cycle and being capable of electron transfer. This endosymbiont hypothesis was summarized in the book *Origin of Eukaryotic Cells*, published by Lynn Margulis in 1970 (332). When the protomitochondria are swallowed, instead of being digested, they form a symbiotic relationship with host cells: the endosymbiont gains more nutrients from the host, while the host can use the endosymbiont-generated energy to increase the competitiveness of hosts and to adapt to diverse living environments (168). In a symbiosis that benefits both the host and endosymbiont over the long term, the protomitochondria evolved into mitochondria. In protomitochondria, glycolysis in host cells is successfully coupled with the TCA cycle and oxidative phosphorylation (OXPHOS). According to the endosymbiotic hypothesis, we can explain many observations in mitochondria that make this kind of organelle unique:

1. Mitochondria possess their own DNA, which bears a striking resemblance to the circular DNA of bacteria (166, 167), and are devoid of histones (64).
2. Along with their own DNA and RNA polymerases, mitochondria can carry out independent replication and transcription (235).
3. Mitochondria contain an independent and complete protein synthesis system, and most of the characteristics of protein synthesis are more similar to the bacterial protein synthesis system than those of eukaryotic cells (33).
4. Mitochondria could divide and propagate by construction and scission, comparable with bacteria (262).
5. The mitochondrial outer membrane (OMM) resembles the inner membrane of eukaryotic cells, and the mitochondrial inner membrane (IMM) is similar to the plasma membrane of bacteria. The IMM contains essential proteins that function in OXPHOS and electron transport processes (104). From a structural view, mitochondria comprise four functional regions from outside to inside: OMM, mitochondrial intermembrane space (IMS), IMM, and mitochondrial matrix. OMM is smooth and functions as the boundary membrane of mitochondria. IMM folds inward to form the mitochondrial cristae responsible for the biochemical reactions. OMM and IMM divide the mitochondria into two compartments, the space between the two membranes is IMS, and the mitochondria matrix is packaged by IMM (143).

Maintenance of Mitochondrial Biogenesis

Maintenance of mitochondrial homeostasis requires a delicate coordination of two opposing processes, including generating new mitochondria through mitochondrial biogenesis and eliminating damaged mitochondria through mitophagy (415). Here, we first introduce mitochondrial biogenesis, and mitophagy will be discussed later.

The peroxisome proliferator-activated receptor gamma coactivator-1 (PPARGC1/PGC-1) family of transcriptional coactivators exerts a powerful regulation of metabolism (59, 178). The PGC-1 family consists of three individual proteins: PGC-1 α , PGC-1 β , and the PGC-related coactivator (PRC) (12, 263, 301). Particularly, PGC-1 α is frequently mentioned as a master regulator of mitochondrial biogenesis (18). Nuclear respiratory factors (NRF) 1 and 2 are coactivated by PGC-1 α , and they, in turn, control the transcription of mitochondrial transcription factor A (TFAM) (501). TFAM translocates to the mitochondrial matrix, promoting mitochondrial gene expression and DNA replication (501). Specifically, studies have reported the involvement of multiple signaling pathways in maintaining transcriptional activation during mitochondrial biogenesis (Figure 1), including the

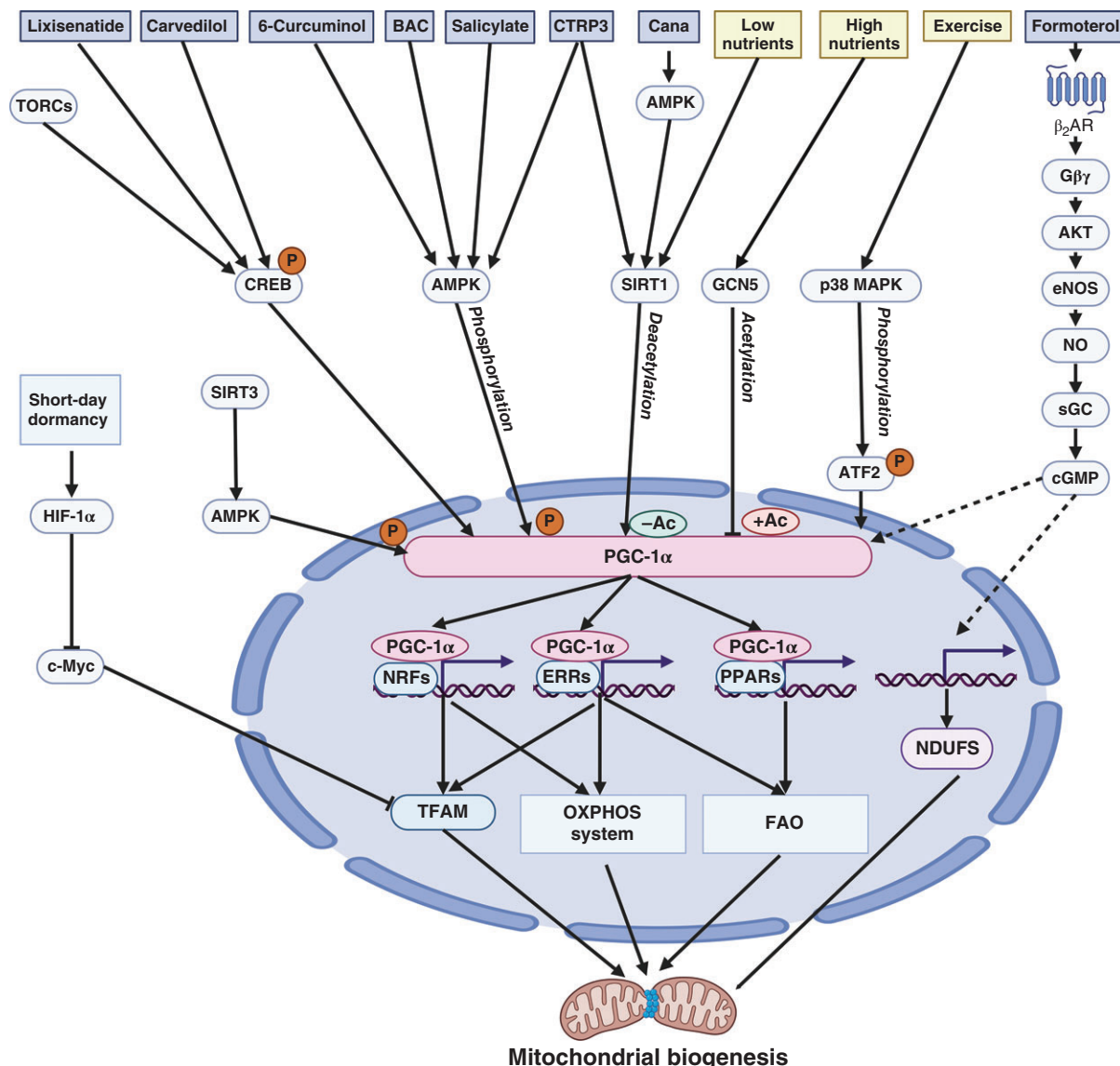


Figure 1 Mitochondrial biogenesis pathways. This figure illustrates multiple signaling pathways in maintaining transcriptional activation during mitochondrial biogenesis. PGC-1 α is the major regulator of mitochondrial biogenesis. AMPK, CREB, SIRT1, p38MAPK, and NO activate PGC-1 α gene transcription, which further enhances NRFs, PPARs, and ERRs to promote the genes of *Tfam*, OXPHOS system, and FAO. These genes, in turn, contribute to mitochondrial biogenesis. Specifically, lixisenatide (FDA-approved for the treatment of type 2 diabetes mellitus) and carvedilol (a licensed drug for the treatment of heart failure) promote mitochondrial synthesis through the CREB/PGC-1 α /NRF-1/TFAM signaling pathway. TORC1, a coactivator of CREB, and two other members of the TORCs family, TORC2 and TORC3, all strongly activate PGC-1 α transcription via CREB. CTRP3, 6-curcuminol (the main active ingredient in ginger extracts), BAC, and salicylate promote mitochondrial biogenesis by activating the AMPK-PGC-1 α signaling pathway. Cana (antidiabetic drug canagliflozin, sodium-glucose cotransporter 2 inhibitor) promotes mitochondrial biogenesis and function via the AMPK-SIRT1-PGC-1 α signaling pathway. CTRP3 also induces mitochondrial biogenesis through SIRT1-mediated PGC-1 α deacetylation. Notably, there are also results that contradict previous reports that SIRT1 negatively regulates mitochondrial biogenesis by inhibiting the activity of the PGC-1 α coactivator, leading to a reduction in mitochondrial number. Under low nutrient conditions, the SIRT1 activity is enhanced, leading to deacetylation of PGC-1 α and increased activity, whereas under high nutrient conditions, PGC-1 α is overacetylated by GCN5, and its activity is reduced. SIRT3 promotes mitochondrial biogenesis in an AMPK-dependent manner. The p38 MAPK is activated during exercise or muscle contraction and then enhances ATF2 phosphorylation. Following the phosphorylation, ATF2 binds to and promotes the CREB binding site on the PGC-1 α promoter, enhancing PGC-1 α expression. Formoterol acts on β_2 AR, then activates the G $\beta\gamma$ -Akt-eNOS-sGC-cGMP signaling pathway, and finally increases PGC-1 α and NDUFS1 mRNA expression to promote mitochondrial biogenesis. In addition, the HIF-1 α -c-Myc-TFAM signaling pathway is also involved in the regulation of mitochondrial biogenesis. Abbreviations: PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator-1 alpha; AMPK, AMP-activated protein kinase; CREB, cAMP response element-binding protein; SIRT1, sirtuin; p38 MAPK, p38 mitogen-activated protein kinase; NO, nitric oxide; NRFs, nuclear respiratory factors; PPARs, peroxisome proliferator-activated receptors; ERRs, estrogen-related receptors; TFAM, mitochondrial transcription factor A; OXPHOS, oxidative phosphorylation; FAO, fatty acid oxidation; TORCs, transducers of regulated CREB activity; CTRP3, adipokine C1q/tumor necrosis factor-related protein-3; BAC, benzoylaconine; Cana, canagliflozin; GCN5, general control nonrepressed protein 5; ATF2, activating transcription factor 2; β_2 -AR, beta-2 adrenergic receptor; G $\beta\gamma$, G-protein $\beta\gamma$ subunits; AKT, protein kinase B; eNOS, endothelial nitric oxide synthase; sGC, soluble guanylate cyclase; NDUFS1, NADH-ubiquinone oxidoreductase core subunit S1; cGMP, cyclic guanosine monophosphate; HIF-1 α , Hypoxia-inducible factor 1-alpha; c-Myc, cellular-myelocytomatosis viral oncogene. BioRender.com.

AMP-activated protein kinase α (AMPK)/PGC-1 α signaling pathway (112, 113, 579, 602), cAMP response element-binding protein (CREB)/PGC-1 α signaling pathway (569, 585), sirtuins (SIRT) pathway (118, 159, 372, 390, 436, 573, 583), p38 mitogen-activated protein kinase (MAPK)/PGC-1 α signaling pathway (3, 61), and nitric oxide (NO)/cyclic guanosine monophosphate (cGMP)-dependent pathway (58, 380). Meanwhile, hypoxia-inducible factor 1 alpha (HIF-1 α) inhibits mitochondrial biogenesis through decreasing the cellular-myelocytomatosis viral oncogene (c-Myc)-TFAM signaling pathway (303).

As the master regulator of mitochondrial biogenesis, PGC-1 α activation initiates mitochondrial DNA (mtDNA) transcription, which then stimulates a series of nuclear transcription factors, including NRF-1, NRF-2, and estrogen-related receptor- α (ERR- α), and increases the expression of TFAM. Next, with the help of specific translation factors such as initiation factors 2 and 3 (mtIF2 and mtIF3), elongation factors Tu, Ts, and G1 (mtEFTu, mtEFTs, and mtEFG1), translation release factor 1-like (mtRF1L), and recycling factors (mtRRF1 and mtRRF2), the mtDNA-encoded genes are translated into proteins. In addition, the translation activator of cytochrome c oxidase 1 (TACO1) binds to mtRNA and thus controls the level of mitochondrial proteins (415). Furthermore, peroxisome proliferator-activated

receptor gamma (PPAR γ) and retinoid x receptors (RXRs) are also transcription factors intricately involved in regulating mitochondrial biogenesis. For example, PPAR γ activation promotes PGC-1 α (101); PPAR γ and RXR form heterodimers and bind to PPAR response elements (PPREs) within the promoter regions of target genes involved in mitochondrial function and fatty acid oxidation (212, 597).

Mitochondrial Protein Import

Over 1000 distinct mitochondrial proteins are required to maintain mitochondrial function, but more than 99% of them are encoded by nuclear genes and produced by cytosolic ribosomes. Five different transport routes import precursors from the cytosol into mitochondria (Figure 2). These five major protein import pathways are classified according to the type of mitochondrial precursors (457, 503): N-terminal presequence precursors (1, 72, 242, 440, 503, 531), cysteine-rich precursors (73, 370, 506), β -barrel protein precursors (554), IMM carrier precursors (252, 479, 480), and α -helical OMM precursors (27, 205, 416). Translocase of the outer and inner mitochondrial membrane (TOM/TIM) complex is the key component for protein import from the cytosol into mitochondrial compartments.

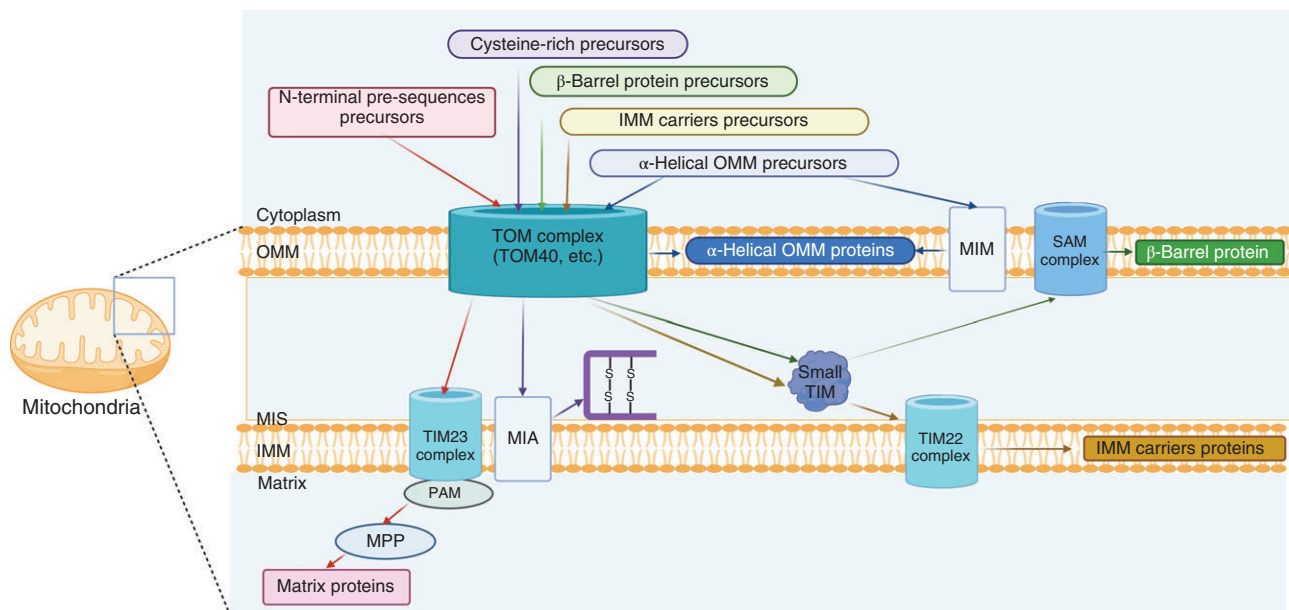


Figure 2 Mitochondrial protein import pathways. This figure illustrates an overview of mitochondrial protein import pathways. There are five main protein import pathways based on the types of mitochondrial precursor proteins. 1. N-terminal presequence precursors are transported from the cytoplasm to the mitochondria through the import channel formed by the mitochondrial TOM and the mitochondrial TIM23, and then they are imported into the stroma with the help of PAMs, and finally, the MPP removes the presequence to generate mature mitochondrial proteins. 2. TOM is firstly responsible for bringing proteins with cysteine motifs into MIS, and then the MIA system inserts disulfide bonds into the incoming proteins. 3. In the transport of β -barrel precursors, the TOM transports them to small TIM chaperones in the MIS, which are then inserted into the OMM by the SAM. 4. IMM carrier precursors are imported via TOM, the small TIM, and the carrier transporter enzyme TIM22. 5. α -Helical OMM precursors are inserted into the OMM via the TOM complex or the MIM. Abbreviations: TOM, outer membrane transporter enzyme; TIM, inner membrane transporter enzyme; PAMs, presequence transporter-associated motors; MPP, mitochondrial processing peptidase; MIS, membrane intermembrane space; MIA, mitochondrial intermembrane space assembly; OMM, mitochondrial outer membrane; IMM, mitochondrial inner membrane; SAM, sorting and assembly machine; MIM, mitochondrial import mechanism. BioRender.com.

In addition to the import of proteins, mitochondria also import other factors such as calcium and pyruvate that critically regulate the metabolic processes. A previous study shows that brown adipocytes dissipate energy by blocking mitochondrial pyruvate import. It is revealed that, even in the absence of adrenergic stimulation, pharmacological and genetic blockage of the mitochondrial pyruvate carrier (MPC) in brown adipocytes promotes lipid cycling and energy expenditure (524). According to Xue et al., the “thermoporter” protein complex is created when the mitochondrial calcium uniporter (MCU) contacts uncoupling protein 1 (UCP1) via the MCU regulator. The “thermoporter” allows calcium influx into the mitochondrial matrix to increase nicotinamide adenine dinucleotide (NADH) synthesis, which enhances thermogenesis in brown adipocytes, validated through gain- and loss-of-function studies (423).

In adipocytes, several factors have been identified to cause abnormal metabolic changes by affecting mitochondrial protein import. A high-fat diet (HFD) causes overexpressed amyloid precursor protein (APP) in WAT, and then APP is mislocalized to mitochondria. APP accumulation in mitochondria blocks the import of proteins through “clogging” the protein import channel, presumably through a physical interaction with the TOM/TIM complex (11, 483). In addition, a mitochondrial cysteine-catabolizing enzyme called 3-mercaptopyruvate sulfurtransferase (MPST), which produces pyruvate and sulfide species, regulates the mitochondrial protein import. *Mpst* ablation activates HIF-1 α , downregulates subunits of TOM/TIM complex, and impairs the import of mitochondrial proteins in white adipocytes. Mice with *Mpst* deletion further display increased body weight, elevated inguinal WAT mass, decreased metabolic rate, and impaired glucose/insulin tolerance upon HFD feeding (236).

A Dynamic Organelle: Mitochondrial Fusion and Fission

As mitochondria are indispensable organelles within most types of cells, maintaining stability and homeostasis of mitochondria are of the utmost importance. Therefore, the processes of fusion and fission that sustain mitochondrial number and morphology play a significant role in keeping the characteristics of this highly dynamic organelle. The precise counterbalance between fusion and fission promotes the fitness of mitochondria and their normal function, further contributing to the organism wellness. When cells suffer from metabolic and environmental stresses, mitochondrial fusion helps mitigating the stress through integrating the damaged mitochondria to form a complementation (551, 591). At the same time, fission is required to form a new mitochondrion by segregating or dividing one mitochondrion to two separate mitochondria (551, 591). Mitochondrial fission also contributes to quality control by allowing damaged mitochondria to be removed and promoting apoptosis (591).

The core machinery that mediates the two processes is large guanosine triphosphatases (GTPases) belonging to the dynamin family (194). Mitochondria fusion occurs through the fusion of OMM followed by the fusion of IMM. The OMM fusion mediators include mitofusin 1 (MFN1) and MFN2, both large GTPases homologs. Two opposing OMMs are contacted and fastened by the interaction between heptad-repeat region 2 (HR2) and the GTP domains of MFNs in trans, and then GTP hydrolysis drives the docking of OMM by guiding MFN conformational changes to augment contact sites and shorten distance between two membranes (53, 207, 286). Following the OMM fusion, the large GTPase optic atrophy 1 (OPA1) together with cardiolipin (CL) drives the fusion of IMM (22, 405). The contact and fastening of two IMM are mediated by the interactions between OPA1 and CL on either side of the membranes, induced by GTPase-mediated hydrolysis (509).

During mitochondrial fission, the endoplasmic reticulum (ER) plays a key function in the initial steps by promoting mitochondrial contraction when the ER tubes are attached to the mitochondria (146). Replication of mtDNA provides positional information for ER recruitment to the mitochondrial periphery (289). At the same time, as a multistep process, the recruitment of dynamin-related protein 1 (DRP1), a cytosolic protein in the GTPase family, plays a crucial role. DRP1 is kinetically recruited to the membranes of mitochondria and peroxisomes, where it oligomerizes and drives membrane contraction in a GTP-dependent manner (262). Then, DRP1 undergoes oligomerization and clusters around ER sites, which marks the onset of prestriction (509). After DRP1 is recruited to the OMM where it forms a loop structure, GTP hydrolysis amplifies OMM constriction, marking the sites for mitochondrial severance (336). There are plentiful proteins involved in the initial constriction of mitochondrial fission. As adaptors of DRP1, mitochondrial fission factor (MFF) (155) and mitochondrial dynamics proteins 49 and 51 (MiD49 and MiD51) (397) are recruited to the connected sites between mitochondria and ER. Notably, many cytoskeleton proteins are indispensable participants (258, 259, 295, 331). After the constriction process is completed, the final step is severance. As a GTPase, dynamin 2 (DNM2) is recruited to the position of DRP1-regulated constriction neck-like structure where it finishes its assembly and mitochondrial severance (135).

Mitochondrial fission and fusion are also essential processes that contribute to adipocyte fitness. Mitochondrial fission is essential for cell growth and division, providing sufficient numbers of mitochondria, sustaining cell polarity, and aiding in eliminating damaged mitochondria. Blockade of DRP1 inhibits mitochondrial fragmentation, which significantly ameliorates WAT abnormalities in obesity and diabetic conditions (137). Moreover, BCL2/adenovirus E1B 19-kDa interacting protein 3 (BNIP3), which regulates mitochondrial dynamics by interacting with the core fusion-fission machinery (275, 285), is involved in PPAR γ -mediated fragmentation of the adipose mitochondrial network, thereby improving

insulin sensitivity and limiting oxidative stress (510). Moreover, mitochondrial fission is associated with UCP1 activity in human browning white adipocytes (brite/beige). Specially, knockdown of *DRP1* impairs mitochondrial uncoupling respiration in beige adipocytes. In addition, human beige adipocytes with fragmented mitochondria show higher uncoupling activity (411). Furthermore, norepinephrine (NE) promotes the phosphorylation of *DRP1* and cleavage of *OPA1*, contributing to the fragmentation of mitochondria (555). However, obese mice exhibit reduced mitochondrial production, reduced *MFN2* and *OPA-1*, but increased *DRP1* protein and enhanced mitochondrial fragmentation (137), implicating a compensation of mitochondrial fission in response to obesity.

Mitochondrial Quality Control Programs

Mitochondria that influence the function of many essential cells and organisms further evolve mechanisms or pathways to monitor their own functions and respond rapidly to stress to restore organelle activity. Mitophagy and mitochondrial unfolded protein response (UPR_{mt}) are two effective ways mitochondria take advantage of to execute quality control programs.

Mitophagy

Mitophagy is a selective modality of autophagy that specifically eliminates damaged mitochondria (287). Simply put, damaged mitochondria are either randomly or explicitly selected for phagocytosis by autophagosomes. Subsequently, autolysosomes are created when autophagosomes combine with lysosomes and late endosomes to mediate the breakdown of mitochondria (560).

Currently, classical pathways mediating mitophagy include:

1. *Ubiquitin-mediated pathways*. Two crucial factors, the PTEN-induced putative kinase protein 1 (*PINK1*) and the E3 ubiquitin protein ligase (*Parkin*), cooperate to sense cellular stress and mediate mitophagy to clear damaged mitochondria (321). Under stressed conditions, *PINK1* is stabilized on the OMM in a TOM complex and facilitates *Parkin* recruitment (276, 388). Meanwhile, *PINK1* phosphorylates ubiquitin (232, 261), and the phosphorylation of ubiquitin recruits and activates *Parkin* (232, 261), resulting in an increase in its E3 ligase activity (256). Then, the activated *Parkin* ubiquitinates several protein components in OMM. Polyubiquitin chains are subsequently phosphorylated by *PINK1* and contribute to further recruitment and activation of *Parkin*, forming a feedforward loop that amplifies phosphoubiquitin (408). Many adapter proteins, including ubiquitin-binding protein p62, next to *BRCA1* gene 1 (*NBR1*), nuclear domain 10 protein 52 (*NDP52*), optineurin (*OPTN*), and Tax 1 binding protein 1 (*TAX1BP1*), recognize the phosphorylated polyubiquitin

chains on mitochondrial proteins and initiate autophagosome formation by binding to microtubule-associated protein 1A/1B-light chain 3 (*LC3*) (408). The kinase TNAK binding kinase 1 (*TBK1*) phosphorylates *OPTN*, thereby enhancing the *OPTN*-binding affinity to the ubiquitin chains (190, 429).

2. *Receptor-mediated pathway*. *LC3*-interacting region (*LIR*) is a shared feature of mitophagy receptors that can bind directly to the autophagy mediator *LC3* and recruit autophagosomes to mitochondria (321). *BNIP3* (420), *BCL2*-interacting protein-3-like (*BNIP3L*, better known as *NIX*) (453), *FUN14* domain containing 1 (*FUNDC1*) (311), *BCL2*-like-13 (*BCL2L13*) (393), *FKBP* prolyl isomerase 8 (*FKBP8*) (41), *NLR* family member X1 (*NLRX1*) (490, 611), autophagy and beclin 1 regulator 1 (*AMBRA1*) (490), and the *IMM* protein prohibitin 2 (*PHB2*) (548) receptors are reported to interact directly with *LC3* through a conserved *LIR* motif to mediate mitochondrial clearance when mitochondria face a damaging condition. In addition, lipids including *CL* and ceramides mediate mitophagy through interacting with *LC3* (92, 463). Enhancing the interaction between the above factors with *LC3* promotes receptor-mediated mitophagy. For example, mitophagy receptor involvement is enhanced by phosphorylation of the *LIR* structural domain of *NIX* (439). Similarly, the phosphorylation of *BNIP3* affects the binding process (620). Additionally, *FUNDC1* is phosphorylated by casein kinase 2 (*CK2*) and *Src* kinase in nonstressed situations to prevent *FUNDC1* interacting with *LC3* and triggering mitophagy. When the mitochondrial membrane potential (*MMP*) is lost, or when hypoxia occurs, dephosphorylation of *FUNDC1* by the mitochondria-localized phosphatase phosphoglycerate mutase 5 (*PGAM5*) increases the interaction between *FUNDC1* and *LC3*, eventually triggering mitophagy (78).

A growing body of research has explored that mitophagy contributes to the regulation of mitochondrial number and fitness in response to changes in intra- and extracellular environment. One aspect is that mitophagy is crucial for cell and tissue maturation during development and differentiation (453, 460, 477), and the other aspect is that mitophagy contributes to the quality control of mitochondria and prevention from deleterious conditions including neurodegeneration, inflammation, injury, aging, and cancer (391). To date, a large number of studies have found that imbalances in mitophagy are strongly associated with the development of many diseases, including neurological (293, 606), cardiovascular (297), skeletal (493, 598), muscular (277), hepatic (323), and metabolic disorders (468). Therefore, pharmacological or dietary interventions that can restore the balance of mitochondrial phagocytosis and facilitate the removal of irreversibly damaged mitochondria could serve as a potential treatment for a wide range of chronic diseases (115). However, the precise regulation of mitophagy against different targets remains to be addressed.

Mitochondrial Unfolded Protein Response (UPR_{mt})

UPR_{mt} is triggered by stress, leading to an increase in various genes encoding local mitochondrial molecular chaperones and proteases to facilitate the restoration of organelle protein homeostasis (589, 616).

In a groundbreaking research, investigators created a specific mitochondrial stress model in mammalian cells caused by repression of mitochondrial genome duplication and transcription, which results in the accumulation of mitochondrial chaperones (333). Then, they induced unfolded proteins by creating a mutant in a mitochondrial matrix protein ornithine transcarbamylase (OTC). These unfolded proteins led to an increase in transcriptions of nuclear genes encoding mitochondrial stress proteins, including mitochondrial chaperones chaperonin 60 (HSP60/Cpn60), chaperonin 10 (HSP10/Cpn10), mitochondrial isoform of DnaJ (mtDnaJ), and protease caseinolytic peptidase (ClpP). Genes encoding stress proteins of the ER were not transcriptionally upregulated, indicating a mitochondria-specific UPR. C/EBP homologous protein (CHOP) is a mitochondrial stress response element. In combination with CCAAT enhancer-binding protein β (C/EBP β), CHOP modulates the expression of mitochondrial stress genes in response to the cumulative accumulation of unfolded proteins (616). Analysis of the CHOP promoter deletion showed that transcriptional activation of the *Chop* gene by UPR_{mt} occurs through the activator protein-1 (AP-1) element (195), and c-Jun N-terminal kinase (JNK2) is vital in transmitting messages from mitochondria to the nucleus in the process of UPR_{mt} (195). At least two additional highly conserved sequences are discovered when the promoters of UPR_{mt}-responsive genes are more thoroughly analyzed, which are mitochondrial unfolded protein response element 1 (MURE1) and MURE2. With the exception of the Cpn60/10 bidirectional promoter, both of these extra elements are preserved in promoters of the other nine UPR_{mt} sensitive genes reported so far (5). Recently, increasing factors that govern UPR_{mt} have been identified in mammalian cells. These factors include the activating transcription factor 5 (ATF5) (homolog for *Caenorhabditis elegans* activating transcription factor associated with stress-1, ATFS-1) (138), activating transcription factor 4 (ATF4) (421), heat shock transcription factor 1 (HSF1) (499), SIRT, and the estrogen receptor (160). Given the intricacy of UPR_{mt} regulatory mechanisms and the versatility of UPR_{mt} pathway components, a better understanding of the role of UPR_{mt} on white adipocytes is warranted, and this section will be covered in detail in later texts.

Signaling Hub: Cross Talk Derived from Mitochondria

Recent studies have revealed another role for mitochondria beyond their traditional function as cellular powerhouses,

namely, the signaling role of mitochondria, through which mitochondria talk to other organelles, cells, tissues, and organs. The emerging concept of cross talk derived from mitochondria positions themselves as signaling hubs. Factors mediating cross talk derived from stressed mitochondria are referred to mitokines.

Specifically, mitokines are molecules released from cells or tissues that are diffusible in reaction to mitochondrial stress, transporting the salutary effects to other tissues (23). In a groundbreaking study in 2011, the group of Andrew Dillin raised the concept of the presence of mitokines in *C. elegans*, the product of perceived mitochondrial stress leading to an increase in longevity (124). A similar phenomenon was subsequently observed in *Drosophila*, where researchers found that mild mitochondrial stress contributes to mitochondrial dysfunction, slows aging-associated muscle degeneration, and extends lifespan. It was further proved that the transcriptional induction of *Drosophila* insulin-like growth factor binding protein 7 (IGFBP-7) is involved, which systematically antagonizes insulin signaling and promotes mitophagy (394). Subsequently, different mitokines have been defined and investigated in detail. Depending on their origins, mitokines can be distinguished as mitochondria-derived peptides (MDPs), metabolic cytokines, and small metabolites (23).

Mitochondria-derived peptides

MDPs are small and bioactive peptides encoded by short reading frames (sORFs) in mtDNA, which do not have the traditional characteristics of protein-coding genes (343). These MDPs can remain in the mitochondria, move into the cytosol, translocate into the nucleus, or be exported extracellularly to targeted organs (345). Currently, eight MDPs have been identified, including humanin (HN) (182), small humanin-like peptides (SHLP) 1-6 (95), and mitochondrial ORF of the 12S rRNA-c (MOTS-c) (279).

As the first MDP to be described, HN consists of 24 amino acid residues encoded from the 16S rRNA region of mtDNA in mammals (182, 345). Small humanin-like peptides, SHLPs 1-6, are biologically similar to humanin and are encoded from the 16S rRNA region (95). The expression of SHLPs is organ specific. In particular, SHLP1 was found in the heart, kidney, and spleen; SHLP2 in the liver, kidney, and muscle; SHLP3 in the brain, spleen, and prostate; and SHLP6 in the liver and kidney (95). Another MDP is MOTs-c, a 16 amino acid peptide encoded by a mitochondrial sORF found in 12S rRNA (279). The functions and disease relevance of the above MDPs are introduced in Table 1.

Metabolic cytokines

Some cytokines can also be referred to as mitokines since they are expressed in response to various mitochondrial injuries and increase stress resistance, resulting in organism health-promoting effects (23). Among these cytokines, fibroblast

Table 1 Tissue-specific roles and disease relevance of mitokines. This table illustrates mitokines secreted under various mitochondrial stress conditions and elucidates their specific action targets, their physiological functions, and their associations with pathological conditions.

Factors	Targeted tissues/cells	Physiological effects	Disease relevance
<i>Mitokine-mitochondria-derived peptides (MDPs)</i>			
HN(HNG)	Neuronal cells (180)	Suppress neuronal cell death (180)	FAD (180)
	Neuronal cells (181)	Interact with a tripartite receptor complex including GP130/IL6ST, WSX1, and CNTFR (181)	Neuroprotection (181)
	HEK293 and SH-SY5Y cells and mice hippocampus (246)	Activate the AKT/ERK1/2 and STAT3 pathways through the GP130/IL6ST receptor complex (246)	AD (246)
	Human glioblastoma-A172 cells (206)	Inhibit IGFBP-3-induced apoptosis (206)	Neurological disease (206)
	Human plasma (99)	Lower level in AD (99)	AD (99)
	Skeletal muscle/ <i>C. elegans</i> (245)	Induces autophagy, potentially contributing to improved skeletal function/induces lifespan extension in <i>C. elegans</i> by autophagy (245)	Age-related diseases (245)
	SH-SY5Y cells/mitochondria/aged mice (588)	Protect cells and mitochondria from A β toxicity/decrease age-related cognitive decline (588)	Cognitive aging (588)
	Human lens epithelial cells (580)	Decrease the intracellular ROS generation and enhance the mitochondrial function (580)	ARCs (580)
	Human plasma (98)	Increased in old age, with the highest levels found in centenarians (98)	Aging (98)
	Mice with mutations in the GH/IGF-I axis/plasma from untreated GH-deficient children (278)	Positively correlated with lifespan and regulated by the GH/IGF-I axis (278)	Aging (278)
	Hypothalamus, skeletal muscle, and cortex in aged rodents and circulating levels in aged mice and humans (365)	Decreased in aged samples (365)	Aging (365)
	<i>C. elegans</i> /HN transgenic mice, middle-aged mice with HNG/human CSF with AD, and circulation levels of children of centenarians (587)	Increase lifespan in <i>C. elegans</i> /improve metabolic health in mice/related to human mitochondrial health and longevity (587)	Aging (587)
	Wild-type human IAPP and cysteine mutants IAPP (386)	Specifically target misfolded amyloid seeds to inhibit IAPP misfolding (386)	T2DM (386)
	HEK293 and SH-SY5Y cells and mice hippocampus (246)	Activate the AKT/(ERK1/2) and STAT3 pathways through the GP130/IL6ST receptor complex (246)	T2DM (246)
	Zucker diabetic rat (365)	Decreases blood glucose (365)	T2DM (365)
	NIT-1 mouse pancreatic β cells/NOD mice (193)	Reduce apoptosis induced by cytokines/improve glucose tolerance and delay onset of diabetes (193)	NOD (193)
	Mice and Zucker diabetic fatty rats (365)	Improve overall insulin sensitivity (365)	T2DM (365)
	Human serum (425)	Decreased in T2DM patients (425)	T2DM (425)
	ApoE-KO mice fed on a high-cholesterol diet (384)	Protect endothelial function and the progression of atherosclerosis by modulating oxidative stress and apoptosis in the developing plaques (384)	Atherosclerosis (384)
	Heart of myocardial ischemia and reperfusion injury in mice (366)	Regulate apoptotic factors and activate the AMPK-NOS signaling pathway (366)	Acute myocardial infarction (366)
	Human aortic endothelial cells (20)	Against Ox-LDL-induced apoptosis (20)	Early atherosclerosis (20)
	Human umbilical vein endothelial cells (546)	Stop high glucose-induced monocyte adherence to endothelial cells (546)	Atherosclerosis in diabetes (546)
	Human aortic plasma (553)	Reduced in coronary endothelial dysfunction (553)	Coronary endothelial dysfunction (553)

(continued overleaf)

Table 1 (Continued)

Factors	Targeted tissues/cells	Physiological effects	Disease relevance
<i>Mitokine-mitochondria-derived peptides (MDPs)</i>			
	Human serum (617)	Decreased in patients with coronary heart disease (617)	Coronary heart disease (617)
	Human skeletal muscle and blood (532)	Elevated in circulating levels by acute endurance exercise (532)	Acute endurance exercise (532)
	Human vastus lateralis muscle biopsies and plasma (563)	Elevated in acute high-intensity exercise (563)	Acute high-intensity exercise (563)
	CSM14.1, HCT116, Cos7, SF268, and PC-3 cells (171)	Suppress apoptosis by suppressing Bax (171)	Apoptosis (171)
	Human skeletal muscle (306)	Reduced in advanced CKD (306)	CKD (306)
SHLP-2	3T3-L1 preadipocyte/NIT-1 mouse pancreatic β cells and 22Rv1 human prostate cells/neuronal cells/aged mice plasma (95)	Enhance adipocyte differentiation and insulin sensitivity/increase cell viability, reduce apoptosis, and enhance mitochondrial metabolism by increasing OCR and cellular ATP levels/prevent neuronal cell death/decreased in aged mice (95)	Aging-related neurodegenerative diseases (95)
	Age-related macular degeneration cells (371)	Enhance mitochondrial function, attenuate A β -induced cellular and mitochondrial toxicity and antiapoptosis (371)	Primary retinal disease/age-related macular degeneration (371)
	Wild-type human IAPP and cysteine mutants IAPP (386)	Specifically target misfolded amyloid seeds to inhibit IAPP misfolding (386)	T2DM (386)
	Anthropometry, whole-body dual-energy X-ray absorptiometry scans and fasted blood; mice fed a diet that induces hepatic lipid accumulation and damage (464)	Correlate positively with android fat and liver fat in individuals without diabetes (464)	Metabolic syndrome without T2DM (464)
	Human serum (570)	Lower level is linked with increased prostate cancer risk in white men (570)	Prostate cancer (570)
SHLP-3	3T3-L1 preadipocyte/NIT-1 mouse pancreatic β cells and 22Rv1 human prostate cells (95)	Enhance adipocyte differentiation and insulin sensitivity, increase cell viability, reduce apoptosis, and enhance mitochondrial metabolism by increasing OCR and cellular ATP levels (95)	Aging-related neurodegenerative diseases (95)
SHLP-6	NIT-1 mouse pancreatic β cells and 22Rv1 human prostate cells (95)	Boost apoptosis (95)	Aging (95)
	Human plasma (563)	Elevated in acute high-intensity exercise (563)	Acute high-intensity exercise (563)
MOTS-c	Mice in different ages (young (2 months), middle-aged (12 months), and old (22 months))/human skeletal muscle and circulation (428)	Enhance physical capacity and health span in mice/increased after exercise (428)	Aging (428)
	Aged hPD-MSCs (593)	Enhance mitochondrial homeostasis and decrease lipid synthesis (593)	Aging (593)
	Skeletal muscle (279)	Prevents from conducted insulin resistance and obesity and age-related insulin resistance by suppressing the folate cycle and its encumbered biosynthesis of purine and activating AMPK (279)	Age-dependent and diet-induced insulin resistance and diet-induced obesity (279)
	Adipose tissue (319)	Increases BAT activation, reduces ovariectomy-induced fat accumulation and inflammatory invasion in WAT, and improves energy dissipation and insulin sensitivity (319)	Ovariectomy-induced obesity and insulin resistance (319)

(continued overleaf)

Table 1 (Continued)

Factors	Targeted tissues/cells	Physiological effects	Disease relevance
<i>Mitokine-mitochondria-derived peptides (MDPs)</i>			
	BAT and WAT (318)	Enhance thermogenic gene expressions in BAT and induce browning of WAT possibly mediated by the phosphorylation of ERK signaling pathway (318)	Obesity (318)
	Anthropometry, whole-body dual-energy X-ray absorptiometry scans and fasted blood; mice fed a diet that induces hepatic lipid accumulation and damage (464)	Correlate positively with android fat and liver fat in individuals without diabetes (464)	Metabolic syndrome without T2DM (464)
	Human serum (122)	Reduced in obese male children and adolescents and inversely associated with insulin resistance and marker of obesity (122)	Insulin resistance and obesity (122)
	Human plasma (70)	Associated with insulin resistance in lean individuals (70)	Insulin resistance in lean individuals (70)
	Human serum (425)	Decreased in T2DM (425)	T2DM (425)
	Human plasma/differentiated C2C12 myotubes/diet-induced obese mice (266)	Prevent palmitic acid-induced atrophy of differentiated C2C12 myotubes/reduce plasma levels of myogenin in diet-induced obese mice through the PTEN-mTORC2-AKT-FOXO1 pathway/inversely proportional to myostatin levels (266)	Insulin resistance-induced skeletal muscle atrophy and muscle wasting phenotypes including sarcopenia (266)
	Human aortic plasma/aortic rings collected from rats and RAS mice (419)	Lower circulating levels in human subjects with impaired coronary endothelial function/improve endothelial function (419)	ED (419)
	MRSA-challenged mice/macrophages (600)	Improve the survival rate and decrease bacteria loads, reduce the serum inflammatory cytokines/enhance the phagocytic and bactericidal abilities of macrophages (600)	MRSA/sepsis (600)
	H9c2 cells (472)	Alleviate H ₂ O ₂ -induced inflammation and oxidative stress by inhibiting NF-κB and activating the Nrf2/ARE (472)	H ₂ O ₂ -induced inflammation and oxidative stress (472)
	Human skeletal muscle and serum (306)	Reduced in advanced CKD (306)	Advanced CKD (306)
<i>Mitokine-metabolic cytokines</i>			
FGF21	Human plasma (99)	Lower level in AD, reaches the highest levels in centenarian's offspring and becomes a candidate marker of healthy aging (99)	AD (99)
	Human plasma (98)	Increased in old age, with the highest levels found in centenarians (98)	Aging (98)
	Mice with skeletal muscle-specific <i>Atg7</i> KO (243)	KO mice exhibit significantly reduced adiposity and enhanced protection from diet-induced obesity and insulin resistance, accompanied by increased fatty acid oxidation and marked WAT browning by increasing FGF21 expression (243)	Diet-induced obesity and insulin resistance (243)
	Adipocyte-specific <i>Crif1</i> KO (AdKO) mice and AdKO mice with global <i>Fgf21</i> deletion mice (86)	Protect from obesity and insulin resistance (86)	Obesity and insulin resistance (86)
	Cardiac-specific <i>p32</i> KO mice (448)	Enhanced expression levels in the heart of KO mice (448)	Cardiomyopathy (448)
	Mice with <i>Dars2</i> depletion in the heart (117)	Function as a signal for cell-autonomous and systemic metabolic changes (117)	Mitochondrial diseases (117)

(continued overleaf)

Table 1 (Continued)

Factors	Targeted tissues/cells	Physiological effects	Disease relevance
GDF15	Human plasma (98)	Increased in old age, with the highest levels found in centenarians (98)	Aging (98)
	Mice with skeletal muscle-specific <i>Crif1</i> KO/ <i>ob/ob</i> mice with GDF15 (94)	Protection against obesity and insulin sensitivity in KO mice are associated with increased GDF15 secretion/reduced body weight and improved insulin sensitivity (94)	Obesity and insulin resistance (94)
	Adipocyte-specific <i>Crif1</i> KO (AdKO) and AdKO mice with global <i>Gdf15</i> deletion mice (86)	Elevate energy expenditure and protect from obesity and insulin resistance (86)	Obesity and insulin resistance (86)
	<i>Gfral</i> KO mice (126, 197)	KO mice are insensitive to the effects of recombinant human GDF15 on body weight, food intake, and glucose parameters (126). GFRAL is the receptor for GDF1 and mediates the metabolic effects of GDF15 (126, 197, 361, 582)	Metabolic homeostasis (126, 197, 361, 582)
	Human <i>Gdf15</i> transgenic mice (91)	Transgenic mice exhibit increased expression of key thermogenic and lipolytic genes in BAT and WAT to modulate metabolic activity (91)	Obesity and insulin resistance (91)
	Human plasma (99)	Increased in T2DM (99)	T2DM (99)
	<i>Gdf15</i> KO mice (352)	The aged KO mice exhibit enhanced migration of effector T cells and pro-inflammatory macrophages into the liver and adipose tissue and exacerbate liver damage and insulin resistance (352)	Liver damage and insulin resistance (352)
	Cardiac-specific <i>p32</i> KO mice (448)	Enhanced expression levels in the heart of KO mice (448)	Cardiomyopathy (448)
	<i>Gdf15</i> -KO and transgenic mice (244)	KO mice exhibit an exacerbation of NASH phenotypes, whereas transgenic mice alleviate NASH phenotypes and metabolic deterioration, metabolic issues (244)	NASH and NASH-related metabolic issues (244)
	<i>Gdf15</i> KO mice/CCL4-induced mice with GDF15 (93)	KO mice exhibit increased liver tissue inflammation and fibrosis/reduce the expression of pro-inflammatory cytokines and fibrotic mediators in CCL4-induced liver fibrosis and prevent T-cell activation (93)	Alcohol-induced and fibrotic liver diseases (93)
	Human serum (280)	Biomarker for predicting liver fibrosis and disease severity in chronic liver disease (280)	Chronic liver disease (280)
	Human serum and liver (314)	Biomarker for HCC and cirrhosis (314)	HCC and cirrhosis (314)
	<i>Suncus murinus</i> mice and lean or obese rats (50)	Induce appetite suppression by eliciting nausea and/or by engaging the emetic neural circuitry (50)	Anorexia (50)
	Human serum thyroid cancer cells (233)	Induced in thyroid cancer cells upon mitochondrial stress (233)	Thyroid cancer (233)
<i>Mitokine-small metabolites</i>			
Acetyl-CoA	T cells (402)	Enhance histone acetylation and <i>Ifng</i> transcription (402)	Autoinflammatory diseases (402)
	Lymphatic endothelial cells (559)	Rescue injury-induced lymphangiogenesis (559)	Injury-induced lymphangiogenesis (559)
	Pancreatic ductal adenocarcinoma cells (65)	Promote cellular plasticity and proliferation (65)	Pancreatic cancer (65)
	Pluripotent cells (357)	Lead to pluripotent cell differentiation, whereas inhibitor downstream delay differentiation by inhibiting upstream of acetyl-CoA (357)	Stem cells pluripotency (357)

(continued overleaf)

Table 1 (Continued)

Factors	Targeted tissues/cells	Physiological effects	Disease relevance
2-Oxoglutarate	Hypoxic cancer cells (504)	Maintain PHD activity under hypoxic conditions and lead to PHD-dependent hypoxic cell death (504)	Cell death (504)
α KG/succinate	Mouse ES cells (63)	Cell-permeable α KG supplementation directly supports ES cell self-renewal, while cell-permeable succinate promotes differentiation, contribute to the maintenance of cellular identity (63)	Cellular identity (63)
	Macrophages (313)	High α KG/succinate ratio modulates alternative activation, whereas a low ratio enhances the classically activated (M1) macrophage pro-inflammatory phenotype (313)	Macrophage polarization (313)
Succinate	Macrophages (502)	Enhance IL-1 β production during inflammation (502)	Inflammation (502)
	Macrophages (346)	Increased upon LPS stimulation when macrophages shift from generating ATP through oxidative phosphorylation to glycolysis; promote IL-1 β by macrophages while limiting IL-1RA and IL-10 (346)	Inflammation (346)
	Macrophages (305)	Cause the release of IL-1 β from macrophages in a SUCNR1-dependent manner (305)	RA (305)
	ATMs/myeloid-specific <i>Sucnr1</i> KO mice (238)	Anti-inflammatory response of ATMs/succinate-SUCNR1 signaling regulates the polarization of ATMs and attributes the function of succinate to anti-inflammation (238)	Obesity (238)
	Adipocyte-specific <i>Sucnr1</i> KO mice (528)	The succinate/SUCNR1 axis is identified as a metabolite-sensing pathway that mediates nutrition-related leptin dynamics to control systemic homeostasis (528)	Obesity (528)
	Adipose tissue/BAT/HFD-induced mice (347)	Selectively accumulate substantial amounts in adipose tissue upon exposure to cold/initiate thermogenesis in BAT/drive UCP1-dependent thermogenesis in BAT, thereby stimulating robust protection against diet-induced obesity and improving glucose tolerance (347)	Obesity (347)
	Ischemic heart, liver, brain, and kidney murine models of heart attack and stroke (90)	Accumulate in ischemic tissues/alleviate ischemia-reperfusion injury in heart attack and stroke by inhibition of ischemic succinate accumulation (90)	Heart attack and stroke (90)
Fumarate and succinate	<i>Sucnr1</i> KO mice (186)	Increase blood pressure but abolish in KO mice (186)	Hypertension (186)
	HEK293T cells and HeLa cells and mouse liver (571)	Alter genome-wide histone and DNA methylation and contribute to tumorigenesis (571)	Tumorigenesis (571)
Fumarate	Mammalian mitochondria (487)	As TEA maintains mitochondrial function under oxygen-limited conditions (487)	Cancer (487)
	FH-proficient cells (461)	Contribute to the aggressive features of FH-deficient tumors (461)	Hereditary leiomyomatosis and renal cell cancer (461)
	HLRCC cells (239)	Produce chronic proliferative signaling by disrupting cellular iron signaling (239)	HLRCC (239)
	Kidney (2)	Impair antioxidant response pathway (2)	FH-associated cysts and tumors (2)
	Human monocytes (16)	Key metabolite in the induction of training immunity (innate immune memory) (16)	Trained immunity (16)
2-HG	T _H 17 (575)	Facilitate T _H 17 cell differentiation (575)	Autoimmune diseases (575)
S-2-HG	CD8 ⁺ T-cell (516)	Enhance proliferation, persistence, and antitumor capacity (516)	Immune fate and function (516)

(continued overleaf)

Table 1 (Continued)

Factors	Targeted tissues/cells	Physiological effects	Disease relevance
Itaconate	Macrophages (492)	Increased in LPS-induced activation (492)	Inflammation (492)
	Macrophages and <i>Acod1/Irg1</i> KO mice (100)	Act as endogenous SDH inhibitor to cause succinate accumulation (100)	Inflammation (100)
	Macrophages/heart with ischemia-reperfusion (274)	Anti-inflammatory effects during macrophage activation and ischemia-reperfusion injury <i>in vitro</i> and <i>in vivo</i> (274)	Inflammation (274)
	Mice and human macrophages (348)	Anti-inflammatory metabolite that acts through Nrf2 to limit inflammation and regulate type I interferon (348)	Inflammation (348)
	Skin (21)	Ameliorate IL-17- $\text{I}\kappa\text{B}\zeta$ -driven skin pathology in a mouse model of psoriasis (21)	IL-17- $\text{I}\kappa\text{B}\zeta$ -mediated autoimmune diseases (21)
	3T3-L1 adipocytes/ <i>Acod1/Irg1</i> KO mice (147)	Attenuate inflammatory signaling/ <i>Acod1</i> plays a crucial role in regulating glucose homeostasis and obesity under normal and HFD conditions (147)	Obesity and metabolic dysfunction (147)
	MTB-infected lung tissue (476)	Increased in MTB-infected lung tissue (476)	Tuberculosis (476)
	Brown adipocytes, HEK293T cell, human B-lymphocytes (473)	Poison vitamin B ₁₂ (473)	Mitochondrial B ₁₂ metabolism (473)

Abbreviations: FAD, familial Alzheimer's disease; GP130/IL6ST, glycoprotein 130/interleukin 6 signal transducer; WSX1, the IL-27 receptor subunit; CNTFR, ciliary neurotrophic factor receptor alpha; AKT, protein kinase B; ERK1/2, extracellular signal-regulated kinase 1/2; STAT3, signal transducer and activator of transcription 3; AD, Alzheimer's disease; IGFBP-3, insulin-like growth factor-binding protein; A β , Beta-Amyloid; ROS, reactive oxygen species; ARCs, age-related cataracts; GH/IGF-1, growth hormone and insulin-like growth factor-1; CSF, cerebral spinal fluid; IAPP, islet amyloid polypeptide; T2DM, type 2 diabetes mellitus; NOD, nonobese diabetic mice; ApoE, apolipoprotein E; KO, knockout; Ox-LDL, oxidized low-density lipoprotein; CKD, chronic kidney disease; hPD-MSCs, human placenta-derived mesenchymal stem cells; BAT, brown adipose tissue; WAT, white adipose tissue; PTEN, CK2-phosphatase and tensin homolog; mTORC2, mammalian target of rapamycin complex 2; FOXO1, forkhead box protein O1; RAS, renal artery stenosis; ED, endothelial dysfunction; MRSA, Methicillin-resistant *S. aureus*; NF- κ B, nuclear factor kappa-light-chain enhancer of activated B cells; NRF2, nuclear factor erythroid 2-related Factor 2; ARE, antioxidative response element; ATG7, autophagy-related 7; CRIF1, growth arrest and DNA-damage-inducible proteins-interacting protein 1; p32, protein 32/complement component 1 Q subcomponent-binding protein; Dars2, mitochondrial aspartyl-tRNA synthetase; GFRAL, GDNF-family receptor alpha-like; NASH, nonalcoholic steatohepatitis; CCL4, carbon tetrachloride; HCC, hepatocellular carcinoma; IFN- γ , interferon γ ; PHD, prolyl hydroxylase; ES, embryonic stem; IL-1 β , interleukin-1 β ; LPS, lipopolysaccharide; ATP, adenosine triphosphate; IL-1RA, interleukin-1 receptor antagonist; IL-10, interleukin-10; RA, rheumatoid arthritis; ATMs, adipose tissue macrophages; SUCNR1, succinate receptor 1; HFD, high-fat diet; UCP1, uncoupling protein 1; TEA, terminal electron acceptor; FH, fumarate hydratase; HLRCC, hereditary leiomyomatosis and renal cell cancer; *Acod1/Irg1*, cis-aconitate decarboxylase; SDH, succinate dehydrogenase; IL-17, interleukin-17; $\text{I}\kappa\text{B}\zeta$, I kappa B zeta; MTB, mycobacterium tuberculosis.

growth factor 21 (FGF21) and growth differentiation factor 15 (GDF15), whose expressions are elevated in several mitochondrial disorders, have received the most thorough examinations. Table 1 provides a detailed description of their effects. Furthermore, the neuropeptide FMRF-like peptide (FLP-2) is a peptide secreted under mitochondrial stress that further impacts other cell types (111). Although it has not been formally proposed as a mitokine, FLP-2 works similar to a mitokine. Researchers identified the neuropeptide FLP-2 while studying cellular nonautonomous UPRmt in the nervous system. They found that deletion of FLP-2 significantly impairs cellular nonautonomous UPRmt signaling, while restricted expression of FLP-2 in neurons is sufficient to induce UPRmt in peripheral tissues (111, 469). Another potential mitokine with a similar pattern is serotonin. In probing the role of nutrient-responsive biogenic amines in

the involuntary induction of UPRmt, researchers performed a screening and discovered that the addition of serotonin, but not other biogenic amines, partially rescues the induction of cellular involuntary UPRmt due to *unc-31(e928)* mutation, suggesting that serotonin acts downstream of *unc-31* to mediate the induction of cellular nonautonomous UPRmt. The addition of serotonin in the polyglutamine model precisely activates UPRmt without impacting ER stress response or cell membrane stress response (34).

Mitochondria-derived small metabolites

Furthermore, recent studies have identified the intermediates of the TCA cycle, such as acetyl-CoA, itaconate, succinate, fumarate, and L-2-hydroxyglutarate (L-2-HG), as signaling carriers to communicate mitochondria with other cellular

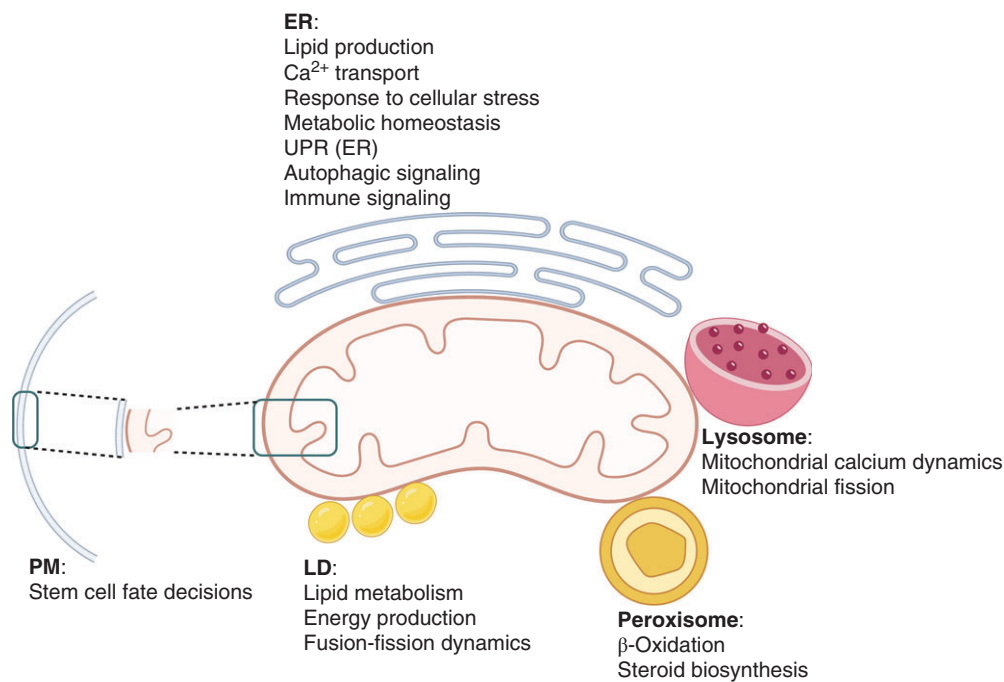


Figure 3 Mitochondrial cross talk with organelles. This figure illustrates that mitochondria interact closely and distinctly with different organelles, including the ER, PM, lysosomes, LD, and peroxisomes through proximity. Many physiological processes are modulated by mitochondria-other organelles interactions. These interactions regulate function and homeostasis not only at the organelle level but also at the cellular level. Abbreviations: ER, endoplasmic reticulum; PM, plasma membrane; LD, lipid droplets. BioRender.com.

components. The roles of these metabolites, characterized as mitokines, are described in detail in Table 1.

Mitochondrial Cross Talk with Organelles

Two structurally and functionally distinct membranes surround the mitochondria; IMM is mainly involved in the energy conversion, and OMM is the central platform of mitochondrial signaling (162). In the context of mitochondrial fission, it is notable that ER is involved in this progress by establishing a broad network interaction at membrane contact points with OMM (146). Numerous studies have found that mitochondria have profound interactions with other organelles including plasma membrane (PM), lysosomes, lipid droplets (LD), and peroxisomes. These interactions contribute to the functioning and homeostasis of mitochondria (162). Direct physical and functional contacts between mitochondria and other organelles are summarized in Figure 3.

Mitochondria and endoplasmic reticulum contact

Among many organelle contacts, the interaction of mitochondria with the ER has been the most delineated. The ER-mitochondrial contact site, so called the mitochondria-associated membrane (MAM), exerts a vital role in maintaining cellular homeostasis and determining cell fate and

emerges as an essential signaling hub that integrates nutrient and hormonal stimuli and adapts to cellular metabolism. Proteins expressed on tightly linked mitochondrial and ER membranes interact directly or indirectly to form multi-protein-linked complexes. These complexes have widely physiological roles, mainly including mitochondrial dynamics, Ca²⁺ signaling, apoptosis, and phospholipid exchange (514). By far, the best-known functions of MAM are involved in key cellular processes, including lipid production (519), Ca²⁺ transport, and response to cellular stress (176, 431–433).

Moving Ca²⁺ between the ER and mitochondria is a critical process in cell survival (37, 55, 71, 462). Importantly, with the expansion of research on MAM, recent studies have shown that MAM plays a vital role in metabolic homeostasis. In the TCA cycle, the three mitochondrial dehydrogenases that include pyruvate dehydrogenase, NAD-isocitrate dehydrogenase, and oxoglutarate dehydrogenase are regulated by changes in mitochondrial matrix calcium ions concentration (114), thus affecting the synthesis of adenosine triphosphate (ATP). Consistent with this, mitochondrial metabolism increases in the early phase of ER stress, mainly because increased coupling of MAMs promotes Ca²⁺ translocation (54). The inositol triphosphate receptor (InsP3R) is localized to the ER and regulates the activity of Ca²⁺ release channels. It has been shown that maintenance of OXPHOS at the resting cellular base requires sufficient NADH production by mitochondria, which requires mitochondrial uptake of Ca²⁺

released by InsP3R. In turn, the absence of Ca^{2+} transfer inhibits pyruvate dehydrogenase and activates AMPK, activating autophagy through a mechanism unrelated to mTOR (62). Several studies have shown that MAMs and insulin signaling pathways are related. Researchers have found that inhibition of cyclosporine D (CypD), a mitochondrial MAM protein, affects insulin signaling in hepatocytes after damaging the integrity of MAMs. Furthermore, significant alterations in MAM are seen in both *ob/ob* and diet-induced obese mice, which are ameliorated by rosiglitazone (515). Impairment of IP3R-mediated Ca^{2+} signaling in the liver of *CypD*-KO mice disrupts the interaction and function of MAMs, increases lipid accumulation, and activates protein kinase C ϵ (PKC ϵ), ultimately leading to hepatic insulin resistance (430). By studying the insulin signaling pathway in cardiac myocytes, researchers found that insulin-induced oxidative stimulation is transduced through Ca^{2+} transfer in MAMs. In turn, pharmacological inhibition of mitochondrial calcium uptake inhibits the activation of the classical insulin signaling pathway, AKT phosphorylation (173). In addition, MAMs function as nutrient sensors, adjusting according to different nutritional conditions (38, 175, 484, 508). However, whether MAMs-mediated Ca^{2+} signaling is affecting white adipocyte function and insulin sensitivity remains uncharacterized.

UPR occurs not only in mitochondria but also in the ER, so it is not surprising that MAMs and UPR are also connected. Several UPR factors are present in the MAM fraction. These include the UPR proteins inositol-requiring enzyme type 1 (IRE1), binding immunoglobulin protein (BIP), and protein kinase R-like endoplasmic reticulum kinase (PERK). When cells are under ER stress, a MAM-residing ER chaperone sigma-1 receptor (Sig-1R) enriches IRE1 in the MAM, facilitating IRE1 to function as a persistent and activated endonuclease (355). In Ca^{2+} -mediated ER stress, Sig-1Rs, which make a complex with BIP, dissociate from BIP, resulting in an expanded entry of Ca^{2+} signals into mitochondria through the IP3Rs (184). PERK, a key ER stress sensor for UPR, is uniquely enriched on MAMs. During reactive oxygen species (ROS)-mediated ER stress, PERK fully displays its role as a component of MAMs, facilitating the propagation of ROS signals between ER and mitochondria through its tethering function while maintaining the level of proapoptotic CHOP, showing its dual contribution to apoptosis (525). On the other hand, the integrity of MAMs also controls the activation of the UPR and the subsequent ER stress. This is mainly regulated by proteins within the MAM. For example, the multifunctional sorting protein phosphofurin acidic cluster sorting protein 2 (PACS-2) integrates ER-mitochondria communication, ER homeostasis, and apoptosis (525). The previously mentioned increase in Sig-1Rs in cells counteracts the ER stress response, whereas a decrease in Sig-1Rs promotes apoptosis (184). In addition, MAMs have an essential role in autophagic signaling and immune signaling (514). ER stress factors play crucial roles in maintaining white adipocyte insulin sensitivity; however, whether these effects are associated with their MAM locations is unknown.

Mitochondria and lysosome contact

In addition to mitophagy, mitochondria and lysosomes can interact directly through nondegradative processes, that is, the dynamic formation of membrane contacts between organelles in healthy mammalian cells (561).

Using high spatial and temporal resolution live cell microscopy, researchers determined that mitochondrial-lysosomal contacts can regulate mitochondrial calcium dynamics which are mediated through the lysosomal calcium efflux channel, transient receptor potential mucin 1 (TRPML1) (403). Mitochondrial-lysosome contact is thus a key contributor to intercellular calcium kinetics (403, 514). In addition, contact point dysfunction may mediate the pathogenesis of multiple human diseases that are genetically and functionally linked to defects in mitochondria and lysosomes, such as Charcot-Marie-Tooth disease type 2, Parkinson's disease, and lysosomal storage disorders (56, 412, 413, 444). It is worth noting that MFN2 is also involved in the mitochondrial-lysosomal junction, and a reduction in contact points is a unique feature in fibroblasts of patients carrying pathogenic variants of this OMM genes (409).

Mitochondria and plasma membrane contact

In mammalian cells, specific interactions regarding certain PM and mitochondria have been implied by observations via electron microscopy (396, 576). Moreover, recent findings document direct physical and functional interactions between the two. For example, researchers found that glutamate *N*-methyl-D-aspartate (NMDA) receptor facilitates PM-mitochondria interactions through structures called PM-mitochondria bridges, which are associated with endocytic vesicle in cultured rat astrocytes (107, 108). The connection between the mitochondrial protein Mdm36 and the PM localization protein nucleophosmin 1 (NUM1) allows for the anchoring or tethering of mitochondria to the PM in yeast (410). Similarly, in mammalian stem cells, the binding of mitochondrial MFN1 to the PM-associated protein kinase C ζ (PKC ζ) promotes tethering of mitochondria to the PM, resulting in asymmetric segregation of mitochondria to stem cell-like progeny, suggesting that mitochondrial-PM interactions may be involved in regulating stem cell fate decisions (566). Researchers also found that in yeast, the N-terminal coiled-coil structural domain of Num1 (Num1CC) interacts directly with phospholipid membranes and shows a strong preference for the mitochondria-specific phospholipid CL (410). However, in white adipocytes, the phenomenon and mechanism of PM-mitochondria contacts have not been revealed.

Mitochondria and lipid droplet contact

The colocalization of mitochondria and lipid droplets (LDs) has been observed in living oocytes using a fluorescence resonance energy transfer (FRET) receptor bleaching approach (491). Mechanistically, ablation of the soluble

N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) protein synaptosome-associated protein 23 (SNAP23) leads to reduced complex formation between mitochondria and LD, in parallel with reduced mitochondrial β -oxidation. Subcellular fractionation results suggest that the complex formed between mitochondria and LD could provide transport of fatty acid substrates to mitochondrial β -oxidation. These results implicate that the effect of SNAP23 on β -oxidation may be mediated by a reduction in the mitochondria-LD contacts (211).

A small number of proteins have been identified that localize to the mitochondria-LD junction. Using two super-resolution imaging methods, researchers found that perilipin 2 (PLIN2) and PLIN5 localize to LDs at different sites in human skeletal muscle, and that PLIN5 is abundant at the LD-mitochondria junction site (158). However, employing a fluorescent probe with the PLIN5 mitochondrial recruitment sequence did not successfully target the probe to mitochondria, indicating that the sequence is required but insufficient for targeting to mitochondria (31). Another mitochondria-LD junction protein is diacylglycerol acyltransferase 2 (DGAT2), an enzyme that catalyzes the last step of TAG synthesis in eukaryotes. DGAT has been shown to localize to different organelles in response to various stimuli. Under basal conditions, DGAT2 resides in the ER. When cells are loaded with oleate, DGAT2 colocalizes with the LD marker adipose differentiation-related protein (ADRP) while contains a mitochondrial targeting sequence in its N-terminal region (489). Indeed, DGAT2 is associated with mitochondria-LD in fibroblasts and adipocytes (264). The mitochondrial OMM mitoguardin 2 (MIGA2) connects mitochondria to LDs and to the ER. Specifically, a region at the C-terminus of MIGA2 is necessary and sufficient for its LDs targeting, while MIGA2 can also bind to the VAMP-associated protein (VAP) in the ER. Functional studies have shown that MIGA2 promotes efficient lipid storage in LD by linking mitochondria, LD, and the ER to promote *de novo* lipogenic processes (144).

LDs are closely linked to mitochondria in tissues that oxidize fat. Peridroplet mitochondria (PDM) have been thoroughly described in brown adipose tissue (BAT) in recent years. Studies demonstrated that PDM consists of a distinct protein composition and ridge-like structure and maintains adherence to LD in tissue homogenates. Further study revealed that PDM represents a separate mitochondrial population with a distinct structure and function that facilitates triglyceride synthesis (32). In addition, isolated LDs from mouse interscapular BAT bind tightly to mitochondria, assessed by morphological and biochemical assays. Proteomics analysis showed that proteins of LDs within BAT are mainly involved in lipid metabolism and energy production, and these proteins are significantly increased upon cold exposure (592). Compared to detailed composition analysis in BAT, less is understood regarding white adipocyte mitochondria-LD contacts. Further research is warranted in how the interaction between mitochondria and LD regulates white adipocyte lipids metabolism and white

adipose browning, which is an important target for increasing energy expenditure in treating obesity.

Mitochondria and peroxisome contact

Peroxisomes are significant metabolic regulators of cellular lipids and ROS and important nodes in the redox, lipid, inflammatory, and innate immunological signaling networks in mammals. To conduct these tasks, peroxisomes must physically and functionally interact with other organelles, such as mitochondria (140).

As early as 1977, researchers found a close spatial association between myocardial peroxisomes and mitochondria, LDs, and ER in the heart (130, 192). Later, different studies proved that mitochondria and peroxisomes are physically connected (209). Interestingly, a research team has also identified peroxisome fractions in the mitochondria of rat liver. It was further confirmed by immunoblotting and enzymatic activity assays that the peroxisomal fraction within mitochondria contains a large amount of β -oxidase (208). Recently, in mouse tumor Leydig cells, researchers found that dibutyryl-cAMP treatment rapidly induces peroxisomal proximity to mitochondria and the formation of peroxisomal-mitochondrial contacts/fusions. More importantly, endogenous acyl-CoA-binding domain (ACBD)2/ECI2 is the mediator to facilitate the exchange of metabolites and/or macromolecules between these two organelles to support steroid biosynthesis (130).

Functional Mitochondria: Protectors of Healthy White Adipocytes

WAT consists mainly of white adipocytes, which have a rounded morphology and are characterized by an exceptionally large LD that accounts for more than 90% of the cell body volume. Thus, all the other cellular components are pushed to the side of the LD (385). Owing to the dominant size of the LD, white adipocytes contain a small volume of cytoplasm and a low density of mitochondria. In addition to their unique morphology, as the most abundant adipocytes, white adipocytes play a critical role in energy homeostasis (356, 455). They work as an energy storage reservoir through retaining lipids. These stored lipids can be catabolized to produce energy by other organs through lipolysis.

Beyond their roles as energy storages, white adipocytes also exert paracrine and endocrine functions (240, 455, 541). As cells with secretion capacities, white adipocytes release substantial amounts of proteins and signaling molecules termed adipokines. The landmark discoveries that drew attention to the secretion function of white adipocytes are the identifications of leptin and adiponectin, hormones both dominantly derived and secreted from white adipocytes. Leptin, first identified in 1994 (610), signals through the long isoform of leptin receptor (LEPRb) and exerts most of its action in the brain (96, 106, 172, 610). As a pleiotropic

hormone, leptin covers multiple functions, including controlling appetite and energy balance (401), proliferation (273), and immunity (271). Adiponectin was firstly described in 1995 under the name adipose complement-related protein of 30 kDa (Acrp30) (456) and subsequently named others (198, 327, 369) and then uniformed to adiponectin (15). Unlike leptin, which acts majorly on the brain, adiponectin acts on a variety of tissues and organs, including the liver (35, 577), muscle (577), blood vessels (387), brain (417), bone (392), immune cells (498), kidney (445), and pancreatic β cells (586), to exert multiple effects, through adiponectin receptors AdipoR1, AdipoR2, and/or T-cadherin (229). Other factors, such as interleukin-6 (IL-6), tumor necrosis factor α (TNF α), monocyte chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor (PAI)-1, and resistin (240), can also be secreted by white adipocytes and exert profound impacts on local adipose tissue health and systemic energy homeostasis.

White adipocytes are highly dynamic cell types. The first signature for dynamic adipocytes is hypertrophy. During lipid storage or release, white adipocytes undergo rapid enlargement or shrinkage in size, respectively. However, enlargement exceeding certain size limits results in pathologically large adipocytes, termed hypertrophy. Besides cell size changes, white adipocyte number varies in response to different conditions, such as development and overnutrition. Adipocyte precursor cells give rise to newly generated white adipocytes, which is termed hyperplasia. The expansion of WAT employing hyperplasia confers metabolic benefits, while adipocyte hypertrophy is closely associated with insulin resistance and WAT dysfunction (378). There is another level of white adipocyte dynamics, which is referred to as the process of browning (or beiging). In response to cold challenge or beta-3 adrenergic receptor (β 3-AR) activation, white adipocytes transform to a histological and functional similarity to brown adipocytes (325). The browning or beiging changes include but are not limited to increased multilocular LD, enhanced mitochondria quantity, and promoted mitochondrial function. Recent findings highlight another remarkable plasticity of white adipocytes, dedifferentiation, that mature white adipocytes can be transformed into fibroblast-like precursors. During lactation, mature white adipocytes are transformed into precursors that resemble preadipocytes. The cells can return to their original state after lactation is completed (542). In line with this, mouse dermal white adipocytes are highly plastic and undergo reversible dedifferentiation (612).

Depending on its location in the body, WATs are categorized into subcutaneous and visceral WAT (sWAT and vWAT, respectively), and vWATs are often seen in six sublocations: perirenal, gonadal, epicardial, retroperitoneal, omental, and mesenteric. In addition to locations, sWAT and vWAT are quite distinct in terms of origins, microenvironments, gene and protein patterns, adipogenic capacities, and mitochondrial functions. It has been found that the main source of visceral WAT is the mesoderm of the lateral plate, and that visceral fat depots have a large number of cells expressing

Wilms' tumor 1 (Wt1) in late pregnancy, in contrast to sWAT or BAT that are not from Wt1-expressing cells (76). Furthermore, mast cells within vWAT express TNF- α and induce a pro-inflammatory microenvironment under obese conditions. Macrophages form a crown-like structure around hypertrophic adipocytes, which is much more obvious in vWAT (7). Additionally, gene transcriptions and protein expressions are distinct between sWAT and vWAT. Human studies have found lower leptin levels in vWAT than in sWAT in both lean and obese subjects. In lean subjects, the expression of toll-like receptor 4 (TLR4) and glucocorticoid receptor (GR) is significantly lower in vWAT, whereas TNF- α expression is the same in both WAT fat pads. In obese subjects, TNF- α and TLR4 expression is significantly higher in vWAT, but there is no difference in GR expression at these sites (599). Recent advances in single-cell/single-nuclei sequencing also provide higher resolution evidence of molecular distinction between different fat pads. For example, in adipocyte progenitor cells (APCs), the signature transcripts in sWAT are *Pparg*, intercellular adhesion molecule 1 (*Icam1*), preadipocyte factor 1 (*Pref1*), collagen type IV Alpha 2 chain (*Col4a2*), and in vWAT are *Pparg*, cluster of differentiation 36 (*Cd36*), fatty acid-binding protein 4 (*Fabp4*), and cluster of differentiation 34 (*Cd34*) (330). With respect to the strategy of isolation, Lin⁻/ICAM1⁺/CD142⁻ (342) or Lin⁻/PDGFR β ⁺/DPP4⁻ are considered cell-surface markers utilized in sWAT (470), whereas Lin⁻/PDGFR β ⁺/LY6C⁻/CD9⁻ can be utilized in vWAT (191, 342). In addition, the signature transcripts, isolation strategies of fibroadipogenic progenitors, and their physiological impacts are distinguished in these two WATs (191, 330, 342, 459, 470). The distinguished features at a single-cell level might further explain different adipogenic capacities and tissue functions among different fat pads. In an untargeted proteomics study examining the effect of excess androgens on protein expression in different adipose compositions, researchers found that sWAT and vWAT show different patterns of protein expressions (350). Difference in adipogenesis is observed in the subcutaneous stromal vascular fraction (SVF) with enhanced adipocyte differentiation compared to vWAT. Thermos-sensitizing factors secreted in visceral SVF are shown to inhibit preadipocyte differentiation, and secreting factors decorin (DCN) and Sparc-like 1 (*Sparc11*) might account for the suppressed adipogenesis in visceral preadipocytes (338). In addition, in humans, sWAT is found to have a higher intrinsic adipogenic capacity than vWAT (129). Notably, a lineage-tracing study in mice found that vWAT develops after birth, whereas sWAT develops between embryonic days 14 and 18. Furthermore, during HFD feeding, vWAT starts its expansion through adipogenesis as early as 4 weeks, while sWAT undergoes hypertrophy over a period of up to 12 weeks. This further highlights that differences in adipogenic potential of different WAT reservoirs depend on temporal regulations and nutrient conditions (543). Last but not least, visceral white adipocytes possess limited bioenergetic functions combined with higher amount of mitochondria-derived ROS compared

to subcutaneous adipocytes, suggesting that mitochondrial respiration also accounts for fat pad differences (458). The differences between sWAT and vWAT shown above support their distinct physiological impacts: increased sWAT is generally considered beneficial, whereas increased vWAT is associated with metabolic dysfunction (76, 599).

Although white adipocytes contain a small number of mitochondria, functional mitochondria are indispensable protectors of healthy white adipocytes. They are critical players in almost every aspect of adipocyte biology, including cell survival, cell protection, adipocyte differentiation and adipogenesis, lipid homeostasis, branched-chain amino acids (BCAA) metabolism, glucose homeostasis, adipokine secretion, browning of white adipocytes, and the determination of adipose heterogeneity.

Maintenance of White Adipocyte Viability and Cell Protection by UPRmt

Mitochondria have long been considered the energy center where the primary energy metabolism pathways of the cell occur, including pyruvate oxidation, fatty acid β -oxidation, the TCA cycle, and OXPHOS, which transform chemical energy from carbohydrates, lipids, and proteins into ATP and make it available to cells in the form of usable energy (395, 556). Consistent with this, the enzymes that control these processes are also found only in mitochondria (128). Similar to other cells containing mitochondria, white adipocytes rely on mitochondria-produced ATP to support their viable existence and then conduct various metabolic pathways, including TAG synthesis, gluconeogenesis, and fatty acid re-esterification (282).

As a strategy for the organelle to cope with stress and to benefit its health, a few studies have shown that UPRmt also plays a vital role in adipose metabolism and protects against obesity. A cohort study found that UPRmt-related genes, including CHOP, HSP60, ClpP, and HtrA serine peptidase 2 (HTRA2), display a significant reduction in WAT of cotwins with a higher body mass (225). Upon studying the effects of saturated and unsaturated fatty acids on UPRmt in white adipocytes, researchers found that an unsaturated fat diet can induce UPRmt-associated proteins ClpP and HSP60, while a saturated fat diet attenuates the expression of ClpP, highlighting a possibility that UPRmt plays a crucial role in response to different types of fat diets (40).

Several family members of SIRT1s that engage in UPRmt regulate adipose tissue metabolism. For instance, SIRT1 activator SRT1720 (unrelated to resveratrol) enhances glucose metabolism and insulin sensitivity in adipose tissue in Zucker *fa/fa* rats (349). Another activator of SIRT1, resveratrol (RSV), attenuates the accumulation of WAT mass contaminant with smaller white adipocytes. RSV therapy safeguards mice from diet-induced obesity and insulin resistance (272). RSV-activated SIRT1 reduces fat accretion in differentiated adipocytes by inhibition of PPAR γ activity

through interacting with its cofactors silencing mediator of retinoid and thyroid hormone receptors (SMRT) and nuclear receptor corepressor (NCoR) (407). A systemic SIRT1 overexpression results in decreased body weight and fat mass and reduced plasma cholesterol, insulin, and fasted glucose levels (48). SIRT2 overexpression suppresses differentiation, while its reduction facilitates adipogenesis, presumably through the acetylation/phosphorylation of FOXO1 (219). SIRT3 is induced by calorie restriction (CR) in both WAT and BAT, partially mediating the beneficial effects of CR (475). Although the SIRT family executes essential functions in white adipocytes, the dependency on UPRmt has not been teased out.

Furthermore, different opinions have been expressed that UPRmt is not always advantageous to the organism, or that the regulator ClpP may be dispensable for initiating UPRmt. One study reported that *ClpP* knockout mice show beneficial phenotypes, including selective upregulation of mitochondrial biogenesis genes in WAT, the reduction in adiposity, the enhancement in energy expenditure, and the improvement in insulin sensitivity; in addition, *ClpP* knockout mice are sheltered from diet-induced obesity, glucose intolerance, insulin resistance, and hepatic steatosis (39).

White Adipocyte Differentiation and Adipogenesis

There is plenty of research confirming that mitochondria play an essential role in differentiation from adipocyte precursor cells to white adipocytes, termed adipogenesis (Figure 4). Enhancement in mitochondrial metabolism, biogenesis, and ROS production, which are dependent on mTORC1 signaling in the early stage, is required to initiate and promote the differentiation of adipocytes. Specifically, ROS generated from complex III is indispensable for initiating adipocyte differentiation and is thought to play a crucial role in this messaging process (511). In differentiating preadipocytes, mitochondria are required to produce and maintain sufficient ATP levels to support the high energy-consuming lipogenesis process while maintaining normal cellular activity (320). Oxygen consumption is also required to be coupled to the synthesis of ATP in the early stage of 3T3-L1 differentiation and becomes uncoupled during adipocyte maturation (123). Consistent with the previous results, mitochondria biogenesis is markedly increased during the differentiation of preadipocytes, evidenced by a marked upregulation of mitochondrial protein levels (320, 557, 558) and relative abundance of mtDNA copy number (228). As a mitochondrial mitophagy receptor, BCL-2-like protein 13 (BCL2L13) facilitates adipogenesis by increasing OXPHOS (151). Interferon-stimulated gene 12b1 (ISG12b1), which is exclusively detected in mitochondria, is expressed at a 400-fold higher level in adipocytes compared with stromal-vascular cells and is significantly induced during the terminal phase of adipogenesis. Functionally, ISG12b1 inhibits the biogenesis

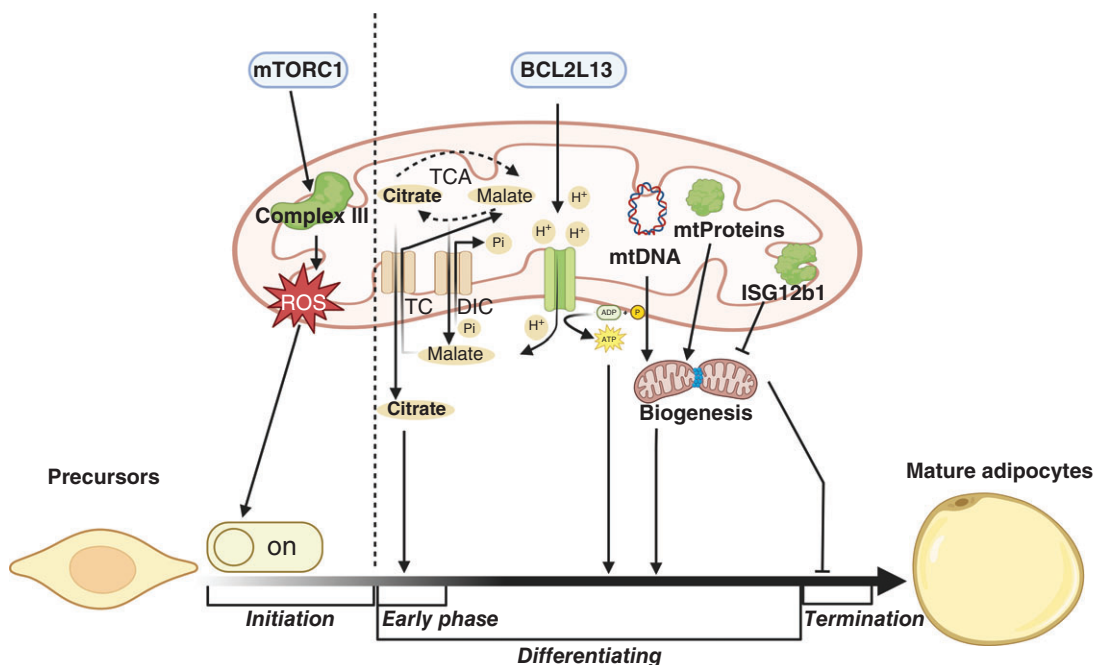


Figure 4 Adipocyte differentiation and adipogenesis. This figure illustrates that mitochondria play an essential role in the various stages of differentiation from adipocyte precursor cells to mature white adipocytes. At the initiation stage of adipocyte differentiation, ROS production by mTORC1-promoting complex III is indispensable for initiating adipocyte differentiation. At the preadipocyte differentiation stage, the mitochondrial output of citrate plays a crucial role in the accumulation of lipid droplets. As a mitochondrial mitogenic receptor, BCL2L13 promotes adipogenesis by increasing OXPHOS, while at the same time, mtProtein levels and the relative abundance of mtDNA copy numbers are significantly upregulated, suggesting that mitochondrial biogenesis is significantly increasing. At the end of adipogenesis, ISG12b1 inhibits mitochondrial biogenesis and adipocyte differentiation. Abbreviations: ROS, reactive oxygen species; mTORC1, mammalian target of rapamycin complex 1; BCL2L13, Bcl-2-like protein 13; OXPHOS, oxidative phosphorylation; mtProteins, mitochondrial proteins; mtDNA, mitochondrial DNA; ISG12b1, interferon-stimulated gene 12b1; DIC, dicarboxylate carrier; TC, tricarboxylate carrier; TCA, tricarboxylic acid cycle. BioRender.com.

of mitochondria and the differentiation of adipocytes (290), serving as a negative regulator and terminator of adipocyte differentiation. In addition, a study using selective inhibitors of mitochondrial dicarboxylate carrier (mDIC) or tricarboxylate carrier (TC) highlights the crucial role of citrate export from mitochondria for accumulation of LD in differentiating 3T3-L1 preadipocytes (230). At the molecular level, adipogenesis and mitochondrial biogenesis share common transcription factors, including PPAR γ , C/EBP α , CREB, ERR α , and the gene expression coactivator PGC-1 α (109). Specifically, PPAR γ is a robust inducer and the master regulator of adipogenesis. The agonist of PPAR γ , rosiglitazone, evokes changes in morphology and density of mitochondria (558), providing strong evidence for an intrinsic coordination between adipocyte differentiation and mitochondrial function. Researchers have determined that the mitochondrial network in new adipocytes undergoes fragmentation and redistribution around LD compared to preadipocytes on day 0. Both DRP1, which controls fission, and MFN2, which controls fusion, show an increase in their gene and protein levels during the first 9 days of differentiation. Meanwhile, *Tfam* and *Nrf1* gene expressions remain constant, mitochondria transit to uncoupled respiration, and its membrane potential drops. Genes related to

lipid oxidation (*Ucp2*, *Cd36*, and *Cpt1*), as well as *Pgc1 α* and *Nrf2* expressions, all show an elevation. On day 6, an increase in antioxidant enzymes and a suppression in the production of ROS are seen. According to the aforementioned findings, mitochondria adjust to the increasing number of LD by redistributing their network and engaging in uncoupled respiration (123).

In addition, autophagy/mitophagy modulates the process of adipocyte differentiation by controlling the biogenesis of mitochondria. Inactivation of autophagy-related 7 (ATG7) in 3T3-L1 cells reduces the expression of crucial proteins, including C/EBP α and PPAR γ for adipocyte differentiation, and limits TAG accumulation. Adipocyte-specific *Atg7* knockout mice show reduced white adipose mass with enhanced mitochondria number in white adipocytes (478). Notably, the time point of inhibition of autophagy is critical for adipose differentiation (123). During differentiation of 3T3-L1 cells, mitochondria show dynamic changes, with the onset of differentiation associated with a 50% reduction in mitochondrial copy number on day 2, followed by rapid mitochondrial biogenesis. Considering that autophagy is crucial for successful adipose differentiation, inhibited autophagy at various stages of differentiation of 3T3-L1 cells prevents adipose differentiation only during the first

two days of differentiation. Autophagy inhibition between days 0 and 2 may inhibit mitotic clonal expansion and mitochondrial network remodeling, further impacting adipocyte differentiation (482).

Maintenance of Lipid Homeostasis

Lipid metabolism consists of the dynamic regulation of lipid uptake, utilization, synthesis, and release, which are all essential functions of white adipocytes. Fatty acid uptake and activation are crucial components in cellular lipid uptake and are mainly mediated by fatty acid transporter proteins (FATPs) and fatty acid translocase CD36 (163). Few studies have addressed the relationship between mitochondria and fatty acid uptake. Limited insights have provided that endogenous FATP3 is partially colocalized with mitochondria in a vesicular compartment and localized to the ER when overexpressed (400). In mature brown adipocytes, bone morphogenetic protein 7 (BMP7) increases mitochondrial activity through increased fatty acid uptake and oxidation, mediated by the fatty acid transporters CPT1 and CD36 (512). An early study provides direct evidence of CD36 contributing to white adipocyte mitochondrial biogenesis and lipid oxidation functions, and it concludes that hexarelin, a growth hormone-releasing peptide that interacts with CD36, promotes fat mobilization and mitochondrial biogenesis in white adipocytes (437).

Remarkably, both lipogenesis (*de novo* lipid synthesis) and lipolysis (hydrolysis of TAG) require assistance from mitochondria (Figure 5). On one hand, mitochondria produce the metabolic intermediate responsible for the proper functioning of these two processes. For instance, citrate is used as the key precursor for lipogenesis, and malonyl-CoA inhibits β -oxidation through CPT1 transporters (188). The glyceroneogenesis pathway (383) and mitochondrial cataplerosis (358) derived adequate glycerol 3-phosphate that is required to maintain TAG synthesis in white adipocytes. On the other hand, mitochondria provide space for fatty acid breakdown. As a product of lipolysis, fatty acids (mainly long-chain fatty acids (LCFA)) are transferred to the mitochondrial matrix (281), whereas medium-chain fatty acids (MCFA) are free to enter the mitochondrial matrix, its only site of activation (109), where they finally undergo β -oxidation.

The synthesis of phospholipids also occurs in the mitochondria. For example, phosphatidylethanolamine (PE) is synthesized in IMM besides in the ER because the phosphatidylserine (PS) decarboxylase (PSD) that decarboxylates PS to PE is restricted to the IMM (49). Phospholipid production requires phospholipid precursors from phosphatidic acid. The mitochondrial membrane contains enzymes that regulate phosphatidic acid formation, such as ER-related acyltransferases that convert 1-acylglycerol-3-phosphate into phosphatidic acid, present in the OMM (520). CL catalyzed by cardiolipin synthase (CLS) primarily occurs within the IMM (520).

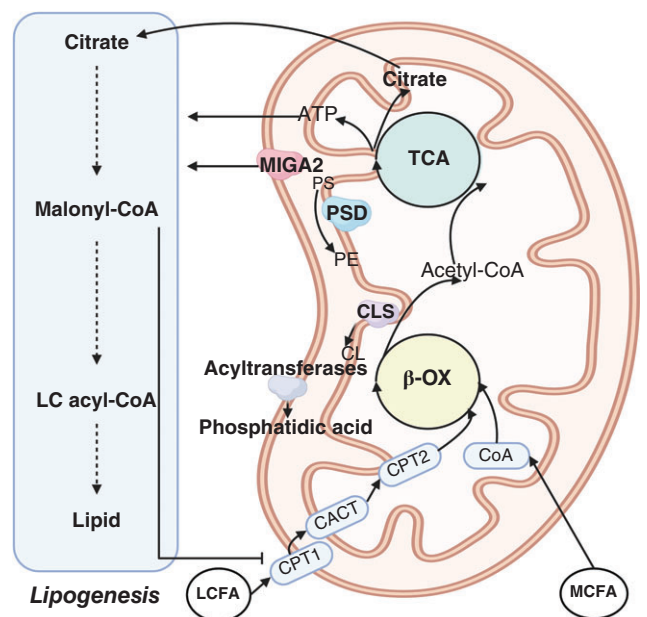


Figure 5 Maintenance of lipid homeostasis. This figure illustrates that mitochondria engage in lipogenesis, lipid β -oxidation, and the synthesis of phospholipid and cardiolipin by providing metabolic intermediates and metabolic space. Citrate is a critical precursor for lipogenesis, while malonyl-CoA inhibits β -OX via the CPT1 transporter. LCFA specifically transfers through CPT1 in the OMM, CACT in the IMM, into the mitochondrial matrix, and subsequently into the β -OX with the help of CPT2 in the mitochondrial matrix. In contrast, MCFA are free to enter the mitochondrial matrix to be activated by binding to CoA and finally undergo β -OX in the mitochondrial matrix. Mitochondria are indispensable for the production of phospholipids, and PSD located in the IMM decarboxylates PS to PE. CLS at the IMM catalyzes the synthesis of CL, and acyltransferase located in the OMM converts 1-acylglycerol-3-phosphate to phosphatidic acid. In addition, the OMM protein MIGA2 links mitochondria to the LD and facilitates the synthesis of TAG from nonlipid precursors. Abbreviations: β -OX, beta-oxidation; CPT-1/2, carnitine palmitoyl transferase 1/2; LCFA, long-chain fatty acids; OMM, mitochondrial outer membrane; CACT, carnitine-acylcarnitine translocase; IMM, mitochondrial inner membrane; MCFA, medium-chain fatty acids; CoA, coenzyme A; PSD, phosphatidylserine decarboxylase; PS, phosphatidylserine; PE, phosphatidylethanolamine; CLS, cardiolipin synthase; CL, cardiolipin; MIGA2, mitoguardin 2; LD, lipid droplets; TAG, triacylglycerol; ATP, adenosine triphosphate; TCA, tricarboxylic acid cycle; LC acyl-CoA, long-chain acyl-coenzyme A. BioRender.com.

Furthermore, ATP production also dictates the processes of lipogenesis and lipolysis. As mitochondrial ATP production decreases, so does the lipogenesis rate in mice (257). Thus, administration of an uncoupling agent, 2,4-dinitrophenol, suppresses lipogenesis (438). In adipocytes, the OMM protein MIGA2 links the mitochondria to the LD and promotes the synthesis of TAG from nonlipid precursors. MIGA2 further links the lipogenic reaction in mitochondria to TAG production in the ER, thereby promoting efficient lipid storage in the LD (144). In addition, the amount of mtDNA displays a significant positive relationship with lipogenesis rate in humans (228). ATP synthesis of mitochondria and lipolysis are also tightly connected, evidenced by the fact that catecholamine-stimulated lipolysis is eliminated by inhibitors or uncouplers of the electron transport chain (131).

Similarly, in an APP-induced white adipocyte mitochondrial dysfunction model, white adipocyte lipolysis is drastically suppressed when ATP production is impaired. At the same time, insulin-stimulated inhibition of lipolysis also requires ATP because it is essential for binding insulin to the insulin receptor and the downstream signals (488).

As mentioned earlier, PDM refers to the mitochondria proximal to LD (31). Compared with cytoplasmic mitochondria, PDM shows enhancement in malonyl-CoA formation, which contributes to increased lipid synthesis, decreased lipolysis, and decreased lipid β -oxidation (32). Furthermore, PDM displays a higher level of complex I + III hyperassembly than cytoplasmic mitochondria (32). While the role of PDM in white adipocytes needs more direct investigations, the relationship between mitochondrial mass and LD expansion rate suggests that PDM may be required in lipogenesis and the formation of LD during the early period of white adipocyte differentiation (31).

In addition, during the process of glyceroneogenesis, mitochondrial pyruvate dehydrogenase is an essential player in the metabolic switch between glucose and fatty acid utilization, and its inhibition by pyruvate dehydrogenase kinase 4 (PDK4) when glucose is low allows pyruvate to be used for glyceroneogenesis (57).

The Location for Branched-chain Amino Acids Metabolism

Catabolism of BCAA, that is, leucine, isoleucine, and valine, occurs only in mitochondria. Interestingly, adipocytes are crucial cells for the catabolism of BCAA. The catabolism of leucine and the expression of BCAA catabolism enzymes are sharply increased when the mass of mitochondria is increased during the process of adipogenesis (142, 248). Moreover, without changed food intake, mice with depletion of mitochondrial branched-chain aminotransferase enzyme overall display an elevation in BCAA level of plasma and a decrease in adiposity and body weight, concomitant with an increase in energy expenditure, a significant improvement in glucose and insulin tolerance, and protection from diet-induced obesity (471).

Maintenance of Glucose Homeostasis

Recent studies highlight the role of mitochondria in regulating glucose homeostasis in white adipocytes, mainly through the modulation of insulin actions in adipocytes. Administration of mitochondrial respiratory inhibitors or uncoupling reagents significantly reduces insulin-stimulated glucose uptake in adipocytes (535). Mitochondrial biogenesis and the copy number of mtDNA are downregulated in WAT in HFD-fed rats, and these rats show elevated glucose levels and reduced glucose uptake by white adipocytes (495). Overexpression of PGC-1 α induced mitochondrial biogenesis, and enhanced

mitochondrial function significantly restores insulin-induced glucose uptake in white adipocytes (156). Beyond the glucose homeostasis in white adipocytes, mitochondria in white adipocytes further contribute to systemic glucose metabolism and insulin sensitivity. More details regarding the systemic impact will be discussed in the “Dysfunctional Mitochondria: Unhealthy White Adipocytes and Obesity” section.

Secretion of Adipokines

It is now well recognized that white adipocytes have a powerful paracrine/endocrine function in addition to lipid storage and release. They can secrete plenty of adipokines, including adiponectin, leptin, TNF- α , IL-6, interleukin-1 (IL-1), plasminogen activator inhibitor-1 (PAI-1), fasting-induced adipose factor, adenosine, and many others (189). Mitochondria are closely related to adipokine synthesis and secretion. Mitochondrial biogenesis stimulation through treatment of endothelial nitric oxide synthase (eNOS) or the mitochondrial transcription factor NRF1 overexpression can empower the synthesis of adiponectin (253, 254). Compromised mitochondrial function induced by chemicals or cytokines such as indinavir, chloramphenicol, carbonyl cyanide chlorophenylhydrazone (CCCP), oligomycin, and TNF- α augments ER stress, leading to a reduction in adiponectin transcription through activation of JNK and consequent induction of activating transcription factor 3 (ATF3) (254). As a reciprocal regulatory mechanism, adiponectin overexpression in turn increases mitochondrial density in white adipocytes (17). However, the direct causative relationship between adipokine secretion and mitochondria remains elusive in white adipocytes.

Mitochondrial Regulation of Browning

In terms of mitochondrial content, white adipocytes contain fewer mitochondria than brown adipocytes. Mobilization of fuels in brown adipocyte mitochondria speeds up heat generation by enhancing the activity of mitochondrial IMM protein UCP1 (375). UCP1, when activated, uncouples the respiratory chain from electron transport, thus preventing the production of ATP and promoting energy dissipation in the form of heat (596). Therefore, UCP1 is the critical molecule executing the thermogenic function in thermogenic (brown and beige) adipocytes. As previously mentioned, white adipocytes are highly plastic and dynamic cells. They can be induced into brown-like (beige) adipocytes under conditions such as cold exposure and activation of β 3-AR, a process called the browning/beiging of white adipocytes; obtaining a higher number of mitochondria and enhancing mitochondrial biogenesis are key for the browning/beiging process. Similar to brown adipocytes, beige adipocytes are enriched with mitochondria expressing UCP1, which exerts thermogenic functions and results in energy consumption (466).

To investigate the difference in mitochondria in white and brown adipocytes, Forner and colleagues directly and accurately compared the *in vivo* mouse mitochondrial proteome of white and brown adipocytes through high-resolution quantitative mass spectrometry (139). The analysis shows that brown adipocyte mitochondria resemble their muscle counterparts and exhibit prominent OXPHOS, fatty acid metabolism, and TCA cycle functions. By contrast, white adipocyte mitochondria are characterized by anabolic functions, such as glucose and fatty acid biosynthesis. Moreover, WAT also predominantly expresses several isoforms of the aldehyde dehydrogenase superfamily, implying that white adipose has prominent detoxification functions, similar to hepatocytes, and is capable of transforming foreign and endogenous molecules (139). It is worth noting that white adipocytes exclusively express the following proteins in mitochondria: MOSC domain-containing protein 1 (MOSC1), which reduces amino oximes to amines (183); acyl-coenzyme A synthetase (ACSM5); and acetyl-CoA synthetase 2-like (ACSS1), which preferentially utilizes acetate and oxidizes it under ketogenic conditions (150, 449). By contrast, PDK4 is only detected in brown adipocytes (14). PDK4 inhibits the pyruvate dehydrogenase complex, reduces the conversion of pyruvate to acetyl-CoA, and assists in reducing metabolism and preserving glucose by reducing its conversion to acetyl-CoA. These data provide a theoretical basis for a better understanding of mitochondria in white and brown adipocytes and guide on artificially promoting the transformation of white adipocytes into brown adipocytes through regulating mitochondrial proteome.

Physiologically, different forms of physical activity, such as high-intensity interval training (HIIT), moderate-intensity continuous training (MICT), exercises, cardiovascular workouts, and strength training, have the potential to induce the browning of WAT (360). Regarding the mechanism, studies found that Irisin, a PGC-1 α -dependent muscle-secreting factor induced by exercise, enhances energy consumption and ameliorates insulin resistance by activating white adipocyte browning (51). Moreover, adipocyte-specific deletion of serine/threonine-protein kinase 3 (*Stk3*)/*Stk4* increases WAT browning and protects mice from HFD-induced obesity by reducing BNIP3-dependent mitophagy (82). Notably, in aged mice, tumor suppressor p53 in induced dedifferentiated adipocytes reduces mitophagy in aged white adipocytes, leading to the browning of white adipocytes and the improvement in insulin sensitivity of aged white adipocytes (149).

Determination of White Adipocyte Heterogeneity

There is emerging evidence showing that adipocyte heterogeneity exists not only in different locations of fat pads but also within an individual fat pad. Adipocyte heterogeneity can be observed in adipocyte metabolic measurements,

including glucose uptake, lipogenesis, lipolytic reactions, lipid accumulation, glycolysis, OXPHOS, and fatty acid uptake. The abovementioned cellular metabolisms are significantly heterogeneous even within size-matched adipocytes of a single fat depot (164, 237, 283, 451, 521). In addition, single-cell RNA-seq technology has also provided abundant evidence for WAT heterogeneity, however, primarily focusing on nonadipocytes (127, 494, 527, 552). Only a few studies investigate white adipocyte heterogeneity by single nuclei (sn)-RNA-Seq (424, 454).

Even with only a few hints, it is suggested that the activity of mitochondria may determine the heterogeneity of white adipocytes. The Tontonoz group identifies a subpopulation of white adipocytes that display higher expression of genes associated with mitochondrial activity. Thermogenic stimuli, including β 3-AR activation and cold treatment, promote the genes expressions of mitochondrial programs (*Ucp1*, *Pgc1 α* , cell death-inducing DFFA-like effector A (*Cidea*), and iodothyronine deiodinase 2 (*Dio2*)) and lipolysis programs (*Adrb3* also known as β 3-AR, lipase E (*Lipe*), vascular endothelial growth factor A (*Vegfa*), and patatin-like phospholipase domain containing 2 (*Pnpla2*)) in this white adipocyte subpopulation (424). Similarly, the Sparks group performed sn-RNA-Seq using white adipocytes and concluded that mature white adipocytes can be divided into two clusters. One cluster of white adipocytes displays higher gene expression related to mitochondrial capacity (NADH: ubiquinone oxidoreductase core subunit VI (NDUFV1)/ATP synthase membrane subunit C locus 3 (ATP5MC3)), whereas the other cluster oppositely exhibits lower-level genes expression related to mitochondrial functions (552).

Dysfunctional Mitochondria: Unhealthy White Adipocytes and Obesity

Herein, we adapt the definition of mitochondrial dysfunction as reduced mitochondrial activity, damaged mitochondrial structure, and decreased intracellular energy production, which may impair cellular function or induce cell death and, in the long run, may lead to tissue or organ collapse (260). While whether mitochondrial dysfunction is a cause or consequence of impaired adipocyte function and obesity is still in debate, it is clear that dysfunctional mitochondria are strongly associated with unhealthy white adipocytes and systemic metabolic defects, a significant manifestation of obesity.

Evidence of Mitochondrial Dysfunction in White Adipocytes under Obesity

A growing body of experimental evidence has identified mitochondrial dysfunction in adipocytes under obesity. Indeed, *ob/ob* mice show a decrease in mitochondrial mass

(89, 517, 557), mitochondrial genes (557), and mitochondrial size (89, 517). Functionally, impaired mitochondrial respiration is indicated by reduced adipocyte oxygen consumption rate (OCR) (89, 517) and fatty acid oxidation (89) in *ob/ob* mice. Another research reported that both HFD-fed mice and *db/db* mice display lower levels of mitochondrial genes that are involved in ATP production, energy uncoupling, mitochondrial ribosomal proteins, TOMs, TIMs, HSPs, and transcription factors, including PGC-1 α , PGC-1 β , ERR α , and PPAR α . When treating diet-induced obese or *db/db* mice with rosiglitazone, the decreased mitochondrial genes are restored and reduced mitochondrial activity is improved (441). In humans, population-based studies have shown consistent results. Lower body mass is associated with a higher mitochondrial respiration rate and higher mitochondria number in WAT (304). A comparison made between congenic twins revealed significantly lower mtDNA levels and reduced mitochondrial mass in WAT of obese twins despite possessing the same mtDNA sequence (364). In another study conducted in Japanese and Italian populations, lipid metabolism and obesity-related factors (including but not limited to body weight, body mass index, and waist and hip circumference intra-abdominal fat) are suggested to be linked to the mitochondrial DNA 15497 guanine/adenine (Mt15497G \rightarrow A) (300, 389). The Chakrabarti group compared the state of mitochondrial OXPHOS of sWAT from nonobese, nonobese type 2 diabetes mellitus (T2DM), obese nondiabetic, and obese T2DM subjects. Obese nondiabetic and obese T2DM individuals display a significant reduction in mitochondrial transmembrane electrical potential, inorganic phosphate utilization, and electron transport chain activity compared with nonobese and nonobese T2DM individuals. It is worth noting that lean T2DM individuals show a considerable mitochondrial index compared to lean individuals without diabetic conditions. Moreover, obese T2DM individuals display much lower respiratory chain activities (complexes I, I–III, and II–III) and phosphorylation capacity in white adipocyte mitochondria in comparison to the obese individual (75). The above observations argue that obesity *per se* is sufficient to suppress mitochondrial function in white adipocytes.

In addition, the mitochondrial function of white adipocytes declines along with aging development. For instance, cytochrome C oxidase subunit 5B (COX5B), a major component of the mitochondrial complex IV, shows a significant suppression when adipocytes undergo aging-induced hypertrophy, presumably due to a hypoxic condition. The age-dependent suppression of COX5B gene expression has also been observed in human white adipocytes (485).

However, inconsistent reports argued that when normalized to adipocyte cell size and/or number, diet-induced obesity does not show impairment in adipocyte mitochondrial function. Nevertheless, although mitochondrial respiration remains identical after normalization, enhanced mitochondrial ROS production has been repeatedly reported within WAT under an HFD challenge (414).

Abnormal Adipocyte Differentiation

It is shown in the previous section that mitochondria play an essential role in the differentiation of precursor cells into adipocytes. A reasonable presumption is that if mitochondria become dysfunctional, it will inevitably affect the differentiation of precursor cells in which ROS plays a significant role. Preadipocyte signaling is inhibited by the mitochondria-generated ROS, as evidenced by the complex I inhibitor rotenone and the inhibitor of ATP synthase, oligomycin, which augment H₂O₂ and inhibit the growth of preadipocytes without inducing necrosis or apoptosis. Additionally, modest uncoupling significantly boosts preadipocyte proliferation by reducing ROS production (67).

Mechanistically, mitochondrial ROS may modulate the expression of CHOP-10/C/EBP homologous protein, also known as growth arrest and DNA damage 153 (GADD153), as anti-adipogenic signaling molecules in adipocyte differentiation (66). Treatment with different concentrations of rotenone (mitochondrial respiratory chain inhibitors) demonstrates that mitochondrial dysfunction inhibits the differentiation of primary rat preadipocytes in a dose-dependent manner (320). The developmental fate and functional properties of adipose platelet-derived growth factor receptor β (PDGFR β^+) cells, a group of precursors in WAT recently received much attention, are tightly regulated by mitochondrial metabolism. These cells are incapable of undergoing adipogenesis due to mitochondrial metabolic changes when manipulating mitochondrial protein containing Asn-Glu-Glu-Thr (mitoNEET) levels (222).

White Adipocyte Apoptosis

Multicellular organisms employ a sort of programmed cell death known as apoptosis (169). By eliminating harmful and unwanted cells, apoptosis is essential for preserving cellular homeostasis. Inducing adipocyte apoptosis is a reasonable way to remove dysfunctional adipocytes in obese individuals (609). In vertebrates, the mitochondrial route is the primary pathway for apoptosis (170); it is thus unsurprising that mitochondria play a fundamental role in mediating white adipocyte cell death and turnover (Figure 6).

It is reported that Homeobox A5 (HOXA5) can increase apoptosis in murine white adipocytes through the mitochondrial apoptosis pathway including increasing mitochondrial proapoptotic markers BAX, BH3 interacting domain death agonist (BID), BCL2 associated agonist of cell death (BAD), caspase-9, caspase-3, and decreasing the mitochondrial anti-apoptotic marker B-cell lymphoma 2 (BCL2). Moreover, the same study also identified HOXA5 as a vital transcription factor that can bind to the promoter region of BAX and enhance the transcription expression of *Bax* (133). Another study revealed that an apoptosis-promoting effect of thiazolidinediones (TZDs) is mediated by PPAR γ -dependent pathway in mature 3T3-L1 cells, which is achieved by inhibiting

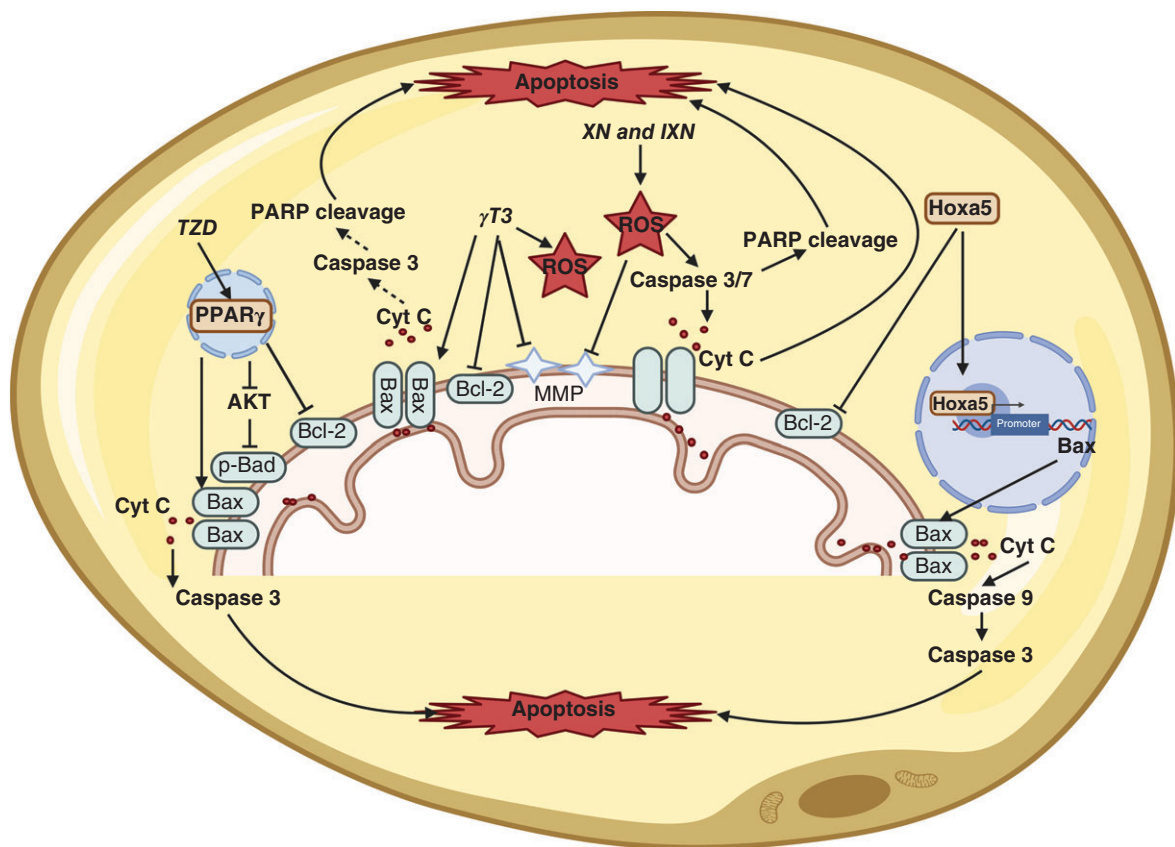


Figure 6 White adipocyte apoptosis. This figure illustrates that the mitochondria-mediated apoptotic pathway results in white adipocyte programmatic cell death and adipocyte turnover. HOXA5 increases the mitochondrial proapoptotic markers BAX, BID, BAD, caspase-9, and caspase-3 and decreases the mitochondrial antiapoptotic marker BCL-2 to promote apoptosis in white adipocytes. In addition, HOXA5 binds to the promoter region of BAX and enhances the transcriptional expression of BAX. TZDs inhibit AKT protein levels and inhibit its phosphorylation through the PPAR γ -dependent pathway, which reduces BAD phosphorylation, BCL-2 protein levels and activates the mitochondrial apoptosis pathway-mediated apoptosis in adipocytes. γ T3 decreases MMP, increases ROS formation, decreases BCL-2 expression, leads to the release of Cyt C from mitochondria to the cell membrane as well as enhances the expression of CD95 and BAX, enhances caspase-3 activation, and cleaves PARP to promote apoptosis in adipocytes. XN and IXN increase ROS levels, thereby decreasing MMP, activating caspase-3/7, and leading to apoptotic biochemical changes such as PARP cleavage and cytochrome c release, which induce apoptosis. Abbreviations: HOXA5, homeobox A5; BAX, Bcl-2-associated X-protein; BID, BH3 interacting domain death agonist; BAD, BCL2-associated agonist of cell death; BCL-2, B-cell lymphoma 2; TZDs, thiazolidinediones; AKT, protein kinase B; PPAR γ , peroxisome proliferator-activated receptor gamma; γ T3, gamma-tocotrienols; MMP, mitochondrial membrane potential; ROS, mitochondrial reactive oxygen species; Cyt C, cytochrome C; CD95, cluster of differentiation 95; PARP, poly(ADP-ribose) polymerase; XN, xanthohumol; IXN, isoxanthohumol. BioRender.com.

AKT-1 protein level and inhibition of its phosphorylation, reducing BAD phosphorylation and BCL2 protein levels, and thereby activating the mitochondrial apoptosis pathway (572). In addition, gamma-tocotrienols (γ T3) also show a proapoptotic effect in 3T3-L1 adipocytes, probably through mitochondrial apoptosis mediated by reducing the MMP, increasing the formation of ROS, decreasing the expression of BCL2, leading to the release of cytochrome *c* (Cyt C) from mitochondria to cytosol, enhancing the expression of cluster of differentiation 95 (CD95) and BAX, and activating caspase-3 and the cleavage of poly(ADP-ribose) polymerase (PARP) (568).

Mitochondria play a significant role in the induction of apoptosis of adipocytes by some natural compounds. For example, xanthohumol (XN) and isoxanthohumol (IXN), as

flavonoids, can exert anti-obesity effects by activating the mitochondrial pathway and caspase-3/7 to induce apoptosis in 3T3-L1 adipocytes. Particularly, they increase intracellular ROS levels, which lower MMP and activate caspase-3/7, and lead to apoptotic biochemical changes such as PARP cleavage and Cyt C release. XN exerts higher effectiveness than IXN in this process (581).

Abnormal Lipid Metabolism

Several studies have examined the effects of specific mitochondrial dysfunction models on white adipocyte lipid homeostasis (Figure 7). The Kahn group generated an adipocyte-specific *Tfam* knockout mice model to induce

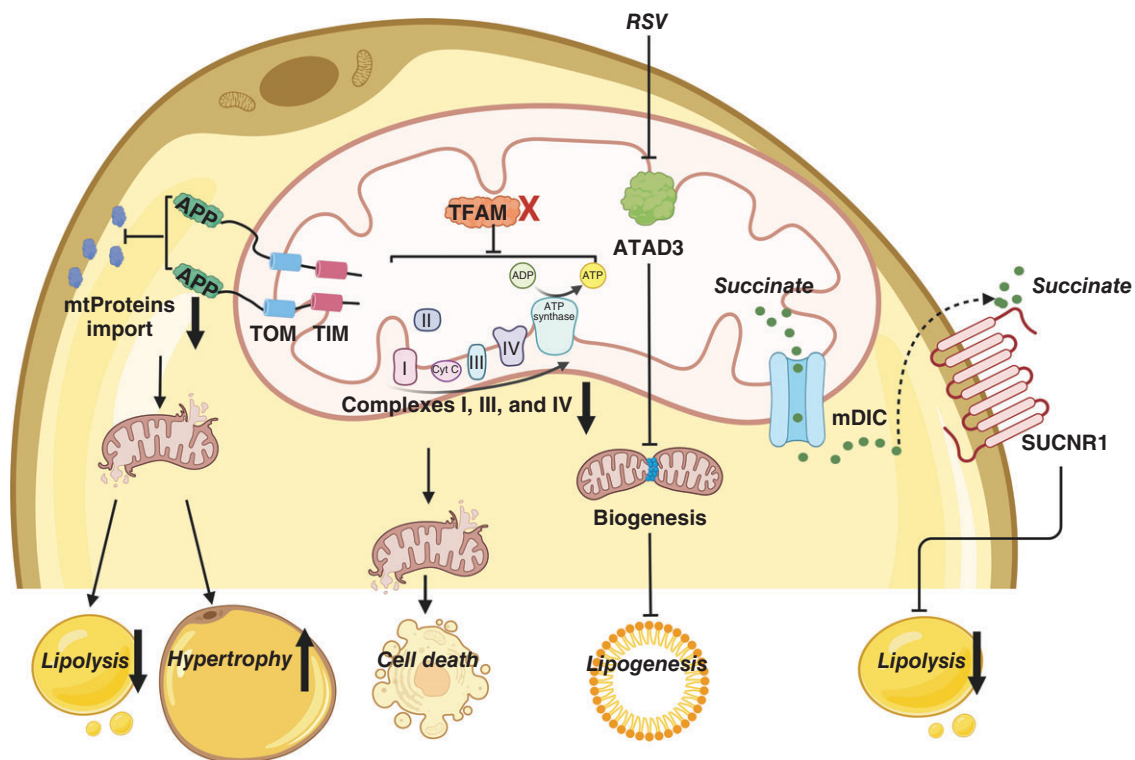


Figure 7 Abnormal lipid metabolism. This figure illustrates that mitochondrial dysfunction leads to abnormal lipid metabolism, including dysregulated lipogenesis and lipolysis in white adipocytes. Dysregulated lipid metabolism eventually disturbs the storage function of white adipocytes. In white adipocytes, deletion of TFAM decreases complexes I, III, and IV in the oxidative respiratory chain, which in turn induces mitochondrial dysfunction and increases adipocyte death. Overexpression of APP in adipocytes promotes mitochondrial dysfunction, leading to reduced lipolysis of white adipose with concomitant significant hypertrophy. mDIC transfers succinate from the mitochondrial matrix to the cell membrane, where it interacts with SUCNR1 to block lipolysis. RSV inhibits adipogenesis during adipocyte differentiation by suppressing mitochondrial ATAD3 expression and inhibiting mitochondrial mass biogenesis. Abbreviations: TFAM, mitochondrial transcription factor A; APP, amyloid precursor protein; mDIC, mitochondrial dicarboxylate carrier; SUCNR1, succinate receptor 1; RSV, resveratrol; ATAD3, ATPase family AAA Domain-containing protein 3; TOM, translocase of the outer membrane; TIM, translocase of the inner membrane; mtProteins, mitochondrial proteins. BioRender.com.

mitochondrial dysfunction. These mice display reduced lipid storage and promoted adipocyte cell death; however, they are protected from diet-induced obesity (526). APP is heavily investigated in the realm of neuroscience as it makes a vital contribution to the pathogenesis of Alzheimer's disease (AD) through the production of toxic amyloid beta ($A\beta$) aggregates that may lead to neurodegeneration (363). Adipocyte-specific and mitochondrial-targeted *App* overexpression in mice results in mitochondrial dysfunction in white adipocytes and further suppresses catecholamine-stimulated lipolysis accompanied by significant hypertrophy of white adipocytes (11). mDIC is mainly expressed in WAT and is encoded by the gene *Slc25a10*. It moves succinate from the mitochondrial matrix to the cell membrane, where succinate can interact with the succinate receptor (SUCNR1) and prevent lipolysis by blocking the cAMP phosphorylation hormone-sensitive lipase (pHSL) pathway. Adipocyte-specific *mDIC* overexpression inhibits adipocyte lipolysis *in vivo* and *in vitro* (10). However, during obesity, white adipocyte mDIC-mediated succinate transport becomes dysfunctional, resulting in unleashed fatty acid release and

systemic lipotoxicity. In a study addressing the effects of resveratrol on mitochondria in adipocytes, it is found that resveratrol inhibits lipogenesis during adipocyte differentiation in mice and humans, associated with inhibition of mitochondrial mass gain and mitochondrial remodeling. At the molecular level, resveratrol inhibits insulin signaling by reducing phosphorylated AKT and suppressing mitochondrial ATPase family AAA domain-containing protein 3 (ATAD3) expression, a pivotal regulator of mitochondrial biogenesis and lipogenesis (294).

Abnormal Glucose Metabolism and Insulin Signaling

Research has confirmed that mitochondrial dysfunction has a strong link with systemic insulin resistance and T2DM (Figure 8). Population-based studies have found that insulin resistance is frequently encountered in aged individuals with reduced adipocyte OXPHOS activity (317). As mentioned, glucose tolerance is compromised in the adipocyte

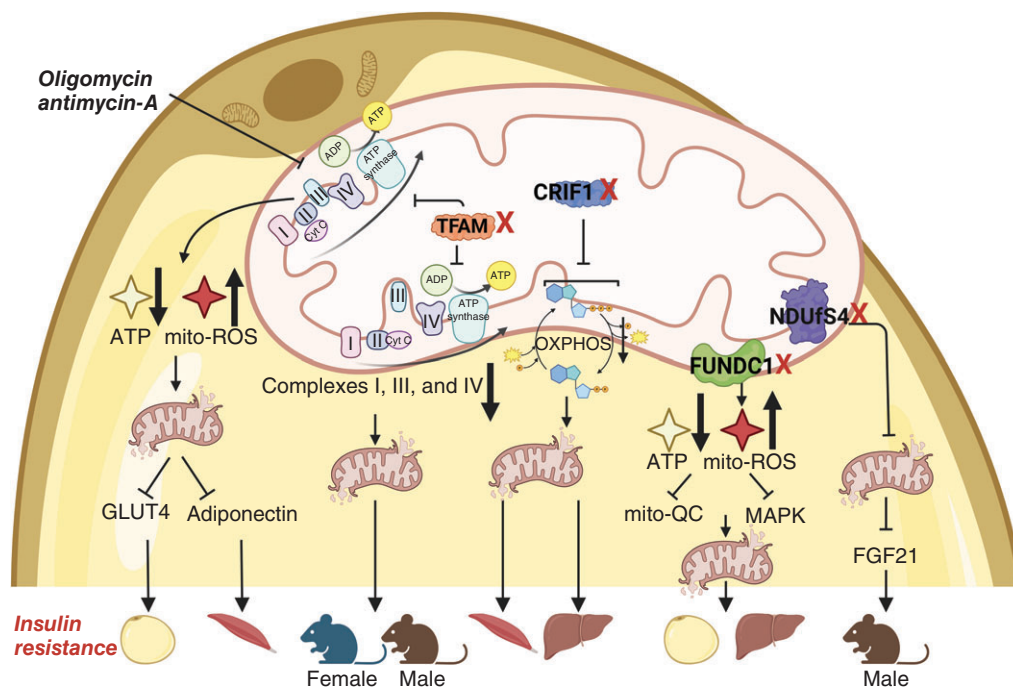


Figure 8 Abnormal glucose metabolism and insulin signaling. This figure illustrates that distinct mitochondrial dysfunction models upon white adipocytes share similar consequences of abnormal glucose metabolism and impaired insulin signaling in local adipose tissues and in systemic organs. In white adipocytes, on the one hand, deletion of TFAM inhibits complexes I, III, and IV, causing mitochondrial damage, which in turn triggers insulin resistance; on the other hand, deletion of TFAM and treatment with respiratory inhibitors suppress the respiratory chain, increase mito-ROS, decrease ATP, and trigger mitochondrial damage, which furthermore inhibits GLUT4 transport and insufficient secretion of adiponectin. Ultimately, the above events trigger insulin resistance in AT and muscle. CRIF1 deficiency affects mitochondrial OXPHOS, leading to insulin resistance in AT and muscle. Deletion of the mitochondrial OMM protein FUNDC1 leads to mitochondrial MAPK breaks and uncontrolled mito-QC, triggering insulin resistance in AT and the liver (563). Deletion of NDUFS4 causes mitochondrial damage and inhibits FGF21 secretion, which in turn leads to insulin resistance in male mice. Abbreviations: TFAM, mitochondrial transcription factor A; mito-ROS, mitochondrial reactive oxygen species; ATP, adenosine triphosphate; GLUT4, glucose transporter type 4; AT, adipose tissue; CRIF1, CR6-interacting factor 1; OXPHOS, oxidative phosphorylation; OMM, mitochondrial outer membrane; FUNDC1, FUN14 domain containing 1; MAPK, mitogen-activated protein kinases; mito-QC, mitochondrial quality control; NDUFS4, NADH:ubiquinone oxidoreductase subunit S4; FGF21, fibroblast growth factor 21. BioRender.com.

mitochondrial dysfunction model (adipocytes-specific *Tfam* knockout) under chow diet or HFD. These mice not only display insulin resistance in adipocytes but also show higher fasting glucose and insulin levels, indicating systemic insulin resistance (526). Both respiratory inhibitor treatment and *Tfam* knockdown induce mitochondrial dysfunction, which leads to increased intracellular ROS and promoted insulin resistance in adipocytes. The molecular mechanism is attributed to inactivation of insulin signaling suppression of translocation of glucose transporter type 4 (GLUT4) and insufficient adipocyte secretion of adiponectin, an insulin sensitizer (535). Adipocyte-specific *Crif1*-deficiency mice become insulin resistant, although they show average growth and development (446). Mitochondrial OMM protein FUNDC1 is a newly identified mitophagy receptor (311). Mice with impaired mitophagy and immobilized mitochondrial quality control caused by deletion of *Fundc1* suffer from more severe obesity and insulin resistance when fed with HFD (565). When the complex I subunit NADH:ubiquinone oxidoreductase core subunit s4 (*Ndufs4*) gene is specifically

deleted in adipose tissue, the promoted diet-induced weight gain and glucose intolerance are observed in male mice (85). A protein in the mitochondrial matrix called mitochondrial ferritin (FtMT) chelates iron. White adipocyte-specific overexpression of *FtMT* perturbs mitochondria, and overexpressing mice exhibit glucose intolerance under HFD treatment. It is noteworthy that *FtMT*-overexpressing mice show substantial β -cell proliferation despite glucose intolerance, suggesting that mitochondria-damaged adipocytes may send distress signals to the pancreas, and elevated FGF21 and GDF15 are likely to play roles as the signaling mitokines (267). Aberrant mitochondrial dynamics also impinge on the glucose metabolism of white adipocytes. MFN2 is a crucial factor that promotes mitochondrial fusion and mitochondrial-ER interactions. Adipocyte-specific knockdown of *Mfn2* leads to increased food intake and adiposity in mice by decreased glucose uptake by adipocytes on chow diet and HFD (329). More efforts are required to explore the novel modulatory aspect of mitochondrial dynamics in adipocyte and systemic glucose homeostasis.

White Adipose Tissue Inflammation

Earlier seminal findings by Drs. Gokhan Hotamisligil and Bruce Spiegelman made the discovery that obesity induces the expression of TNF- α , a classic inflammatory protein, in the adipose tissue of rodents and humans; furthermore, they found that a significant increase in circulating TNF- α can be attributed to adipose tissue and hypothesized

that TNF- α mediates obesity-associated insulin resistance (196). Following work by others (549, 574) identified the presence of macrophage-specific gene expression in transcripts from mouse adipose tissue. Adipose inflammation is now recognized as a hallmark of obesity and associated metabolic dysfunctions (136). A growing body of research has found that mitochondrial dysfunction in white adipocytes is strongly linked with WAT inflammation (Figure 9) through a

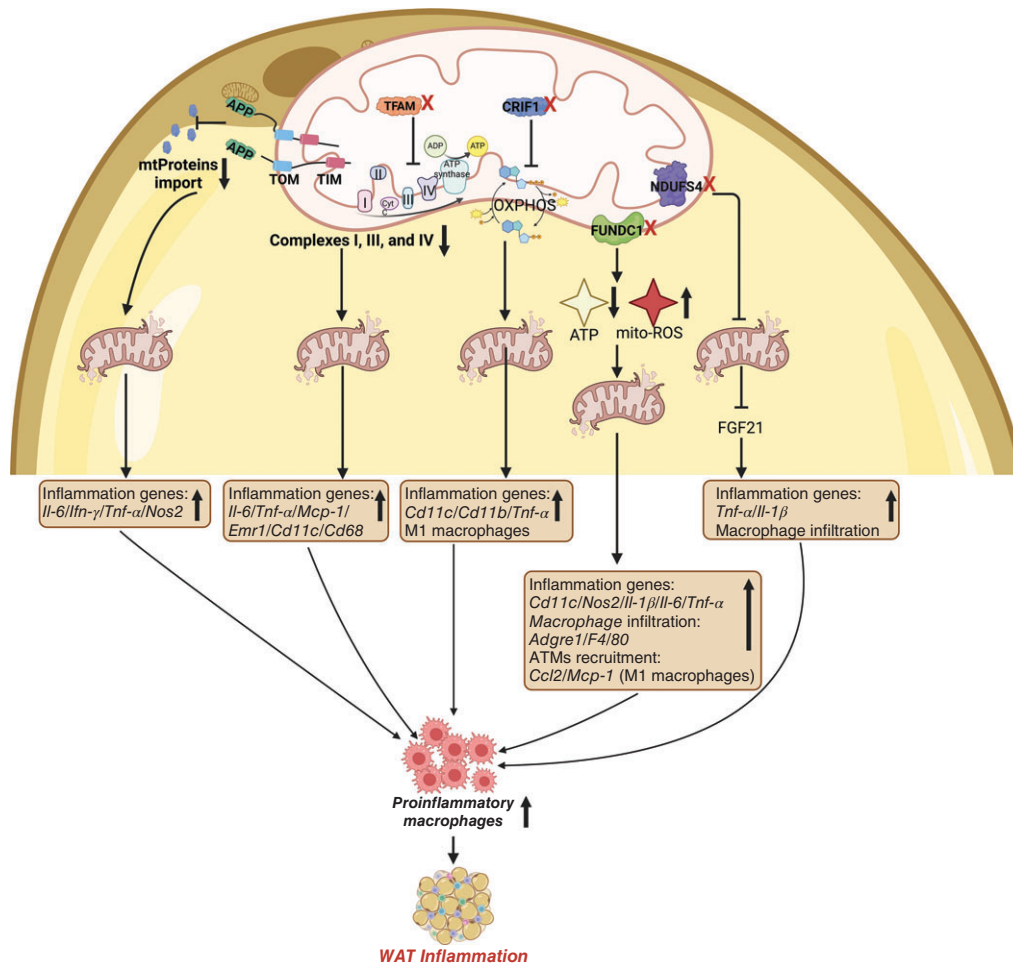


Figure 9 White adipose tissue inflammation. This figure illustrates that mitochondrial dysfunction in white adipocytes leads to changes in inflammatory factor secretion from adipocytes, adipose immune cell infiltration, and overall inflammation in white adipose tissue. In white adipocytes, mitochondrial dysfunction induced by TFAM knockout leads to elevated levels of inflammatory gene transcripts, resulting in adipose tissue inflammation. Suppressed OXPHOS triggered by CRIF1 deficiency promotes a marked increase in immune cell infiltration, with an increase in the secretion of MCP1 and TNF- α and an enhancement in the relative expression of pro-inflammatory M1 macrophage gene expressions. Abrogation of FUNDC1 results in more adipose tissue-associated macrophage infiltration and increased inflammatory gene expression. APP overexpression and its mitochondrial mistargeting promote an enhanced inflammatory program. Deletion of the NDUFS4 promotes elevated levels of inflammatory genes associated with mitochondrial damage by inhibiting FGF21 secretion. Abbreviations: TFAM, mitochondrial transcription factor A; OXPHOS, oxidative phosphorylation; CRIF1, CR6-interacting factor 1; MCP1, monocyte chemoattractant protein 1; TNF- α , tumor necrosis factor α ; M1, classically activated macrophages; FUNDC1, FUN14 domain containing 1; APP, amyloid precursor protein; NDUFS4, NADH:ubiquinone oxidoreductase subunit S4; FGF21, fibroblast growth factor 21; mtProteins, mitochondrial proteins; TOM, translocase of the outer membrane; TIM, translocase of the inner membrane; IL-6, interleukin-6; I γ , interferon-gamma; Ccl2/Mcp1, chemokine [C-C motif] ligand 2/monocyte chemoattractant protein 1; Emr1, EGF-like module-containing mucin-like hormone receptor-like 1, also known as F4/80, encoded by the Adgre1; Cd11c, cluster of differentiation 11c; Cd68, cluster of differentiation 68; Cd11b, cluster of differentiation 11b; Nos2, nitric oxide synthase 2; Il-1 β , interleukin 1 β ; ATMs, adipose tissue macrophages. BioRender.com.

pro-inflammatory cross talk between adipocytes and immune cells. Several mouse models of adipocyte mitochondrial dysfunction display increased inflammatory cell infiltration and enhanced inflammatory gene programs. For instance, in addition to dysregulation of lipid and glucose metabolism, *Tfam* knockout in adipocytes also results in higher transcriptional levels of inflammation genes including *Il-6*, *Tnfa*, and monocyte chemoattractant protein 1 (*Mcp1*) and macrophage markers (F4/80 (encoded by the *Adgre1*), integrin subunit alpha X (*Cd11c*), and cluster of differentiation 68 (*Cd68*) in WAT) (526). Examination of adipose tissue from *Cri1* insufficient mice shows significant immune cell recruitment in WAT with increased secretion of MCP1 and TNF- α . Further analysis found that WAT shows higher expression of F4/80, enhanced relative expression of pro-inflammatory classically activated macrophages (M1), macrophage markers (*Cd11c*, *Cd11b*, and *Tnfa*), and predominated F4/80⁺/CD11c⁺/cluster of differentiation 206 (CD206)⁻ macrophage infiltration, triggering a pro-inflammatory response in WAT (446). Ablation of *Fundc1* in mice induces a substantial increase in the remodeling of WAT, evidenced by a heightened infiltration of adipose tissue-associated macrophages, as indicated by the upregulation of the macrophage marker F4/80. Additionally, there is a pronounced shift toward M1-like macrophage polarization, with an increased expression of key genes such as *Cd11c*, *Nos2*, interleukin 1 β (*Il1b*), *Il-6*, and *Tnfa*, corroborated by an increase in the population of pro-inflammatory adipose tissue macrophages (ATMs) detected through flow cytometry. The chemokine [C-C motif] ligand 2 (*Ccl2/Mcp-1*) may serve as a pivotal signaling factor for the recruitment of ATMs (565). Gene expression profiling verifies that the inflammatory program of both sWAT and vWAT is augmented following adipocyte-specific *App* overexpression and mitochondrially mistargeting mice (11). Specific deletion of the gene for complex I subunit *Ndufs4* in adipose tissue results in elevated levels of adipose inflammatory genes upon HFD feeding in male mice. FGF21 in adipocyte-specific *Ndufs4* knockout sWAT is decreased and might be responsible for increased local inflammation (85). However, the underlying mechanisms of how mitochondrial defects enhance pro-inflammatory factor secretion from white adipocytes remain unclear. Moreover, besides well-known pro-inflammatory cytokines or chemokines, whether novel adipokines or mitokines can mediate the cross talk between adipocytes and immune cells needs further investigations.

Notably, some studies have elucidated that mitophagy is strongly associated with WAT inflammation. Both overactivated mitophagy and defected mitophagy promote inflammation. For example, WATs from adipocyte-specific thioredoxin 2 (*Trx2*) knockout mice exhibit excessive mitophagy, inflammation, and lipolysis and systemically exhibit hyperglycemia, hepatic insulin resistance, and hepatic steatosis. Mechanistically, increased ROS production and nuclear factor kappa-light-chain enhancer of activated B cells (NF- κ B)-dependent autophagy receptor sequestosome 1 (p62/SQSTM1) promote mitophagy, and inhibition of

ROS or NF- κ B significantly ameliorates glucose and lipid metabolism dysregulation in *Trx2* knockout mice (185). Another study found that mitophagy defects are closely related to metabolic disorders (565). *Fundc1* knockout mice develop severe HFD-induced obesity and insulin resistance, and mitophagy defects, in turn, impair mitochondrial quality control in the WAT and exacerbate inflammation in the WAT, manifested as macrophage infiltration and polarization of M1-like macrophages (565). In addition, microRNA-103 (miR103) exacerbates WAT inflammation by inhibiting mitophagy (614). It seems that a balanced mitophagy is required for WAT inflammation resolution.

In humans, results from population analyses showed that obese individuals show downregulated global expression of mitochondrial oxidative pathways, concomitantly downregulated mtDNA quantity, mtDNA-dependent translation systems, and protein levels of the OXPHOS machinery compared to their leaner siblings. Pathway analysis showed that fatty acid oxidation, ketone body production and catabolism, and downshift of the TCA cycle are inversely associated with adiposity, insulin resistance, and inflammatory cytokine levels (187).

Although detailed mechanisms regarding how mitochondrial dysfunction in adipocytes relates to adipose tissue inflammation remain under exploration, several opinions have been raised (562). One possibility is compromised mitochondrial function results in adipocyte apoptosis, which drives the recruitment of inflammatory cells to perform their clearance task. In addition, white adipocytes can secrete several pro-inflammatory cytokines, such as IL-6 and TNF- α , and these pro-inflammatory factors are exacerbated when white adipocytes face mitochondrial stress. Moreover, under a certain degree of mitochondrial dysfunction, white adipocytes turn hypertrophic and subsequently result in a hypoxic environment, facilitating the recruitment and activation of inflammatory cells within adipose tissues. Indeed, loss of function or inhibition of HIF-1 α improves adipose tissue inflammation and benefits systemic energy homeostasis. Lastly, it is hypothesized that an active cross talk between white adipocytes and adipose tissue immune cells, particularly macrophages, exists to coordinate adipocyte status and immune responses. Mitochondrial dysfunction might alter the cross talk and result in an uncontrolled and unresolved adipose tissue inflammation. In a healthy state, the interaction between immune cells and white adipocytes is a finely regulated balance that helps maintain overall metabolic and immune homeostasis (74, 77, 201). However, in the context of obesity and related metabolic diseases, the balance between white adipocytes and immune cells is disrupted, leading to chronic low-grade inflammation, also known as metabolic inflammation (74, 77, 125, 201). Interactions between immune cells and white adipocytes in healthy and diseased states are critical to unraveling the mechanisms of metabolic dysfunction associated with obesity and its related complications. Therapeutic strategies aimed at restoring the balance between immune response and adipose

tissue function are expected to improve the management of obesity-induced inflammation and its complications.

Dysregulation of Adipokine Secretion

White adipocytes are not merely a reservoir for energy but an endocrine cell type that can secrete numerous factors named adipokines (455). As one of the fundamental adipokines, adiponectin exerts several beneficial impacts on metabolism, which covers an improvement in insulin sensitivity and a diminution in the atherosclerotic process (334). Most importantly, plasma adiponectin levels are inverse to body mass index and waist circumference (152). Plasma adiponectin levels show reduction in obese individuals, which is different from other adipokines (455). It is shown that damaged mitochondrial function triggers a series of mechanisms involving ER stress, JNK, and ATF3 to reduce adiponectin synthesis, which explains the low adiponectin levels in the plasma of the obese population (254).

The results of mice with adipocyte *Tfam* deletion further confirm the reduction in circulating adiponectin and leptin levels under the condition of mitochondrial dysfunction (526). Similarly, adiponectin expression is downregulated in a dose-dependent manner in adipocytes with mitochondrial dysfunction induced by oligomycin administration or

Tfam knockdown (535). Specific overexpression of *FtMT* in adipose tissue causes a significant decrease in intracellular and circulating adiponectin levels (267). In a mouse model of thymidine kinase 2 (*Tk2*)-deficiency-induced mtDNA depletion, moderate mtDNA depletion and hypotrophy are observed in WAT as well as a severe decrease in *Leptin* mRNA and thermogenesis-related genes in WAT. Further analysis of serum shows a dramatic decrease in the circulating levels of leptin and resistin (529). The above results emphasize that abnormal mitochondria profoundly affect adipokine secretion of white adipocytes (Figure 10).

Mitochondrial Iron-level Dysregulation

Iron plays a crucial role in adipose tissue homeostasis and mitochondrial function. In adipose tissue, iron deficiency is associated with obesity, mainly due to its effects on inflammation (322). Iron further exerts effects on the thermogenesis of adipocytes. Iron deficiency affects the production of beige adipocytes and the direction of brown adipocyte differentiation (292, 322). However, excess iron in adipose tissue can lead to decreased insulin sensitivity due to mitochondrial dysfunction and changes in adipokines (322). Manipulations in iron-controlling components in white adipocyte mitochondria further impact on mitochondrial and adipocyte health

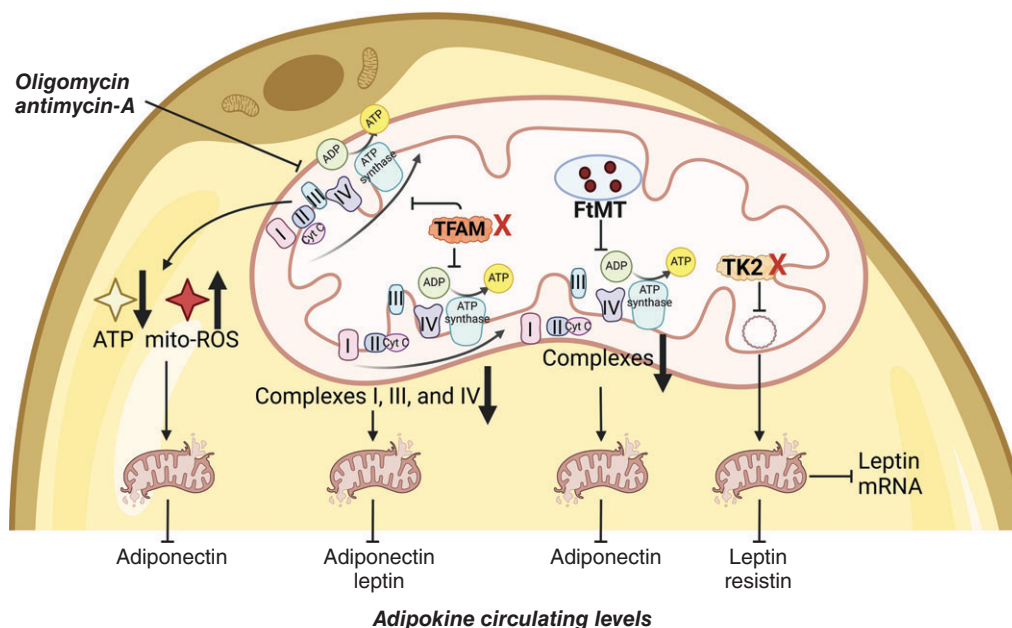


Figure 10 Dysregulation of adipokines. This figure illustrates that mitochondrial dysfunction leads to the dysregulation of adipokines, such as adiponectin, leptin, and resistin in white adipocytes, further affecting their circulating levels. In white adipocytes, TFAM deficiency reduces circulating levels of adiponectin and leptin. Moreover, adiponectin expression in adipocytes is dose-dependently downregulated in mitochondrial dysfunctions induced by oligomycin and antimycin-A administration and TFAM deletion. Overexpression of FtMT results in a significant decrease in circulating and intracellular adiponectin levels. In a mouse mtDNA depletion model induced by TK2 deficiency, leptin mRNA is severely reduced in adipose tissues, and circulating levels of leptin and resistin are drastically decreased. Abbreviations: TFAM, mitochondrial transcription factor A; FtMT, mitochondrial ferritin; mtDNA, mitochondrial DNA; TK2, thymidine kinase 2; ATP, adenosine triphosphate; mito-ROS, mitochondrial reactive oxygen species. BioRender.com.

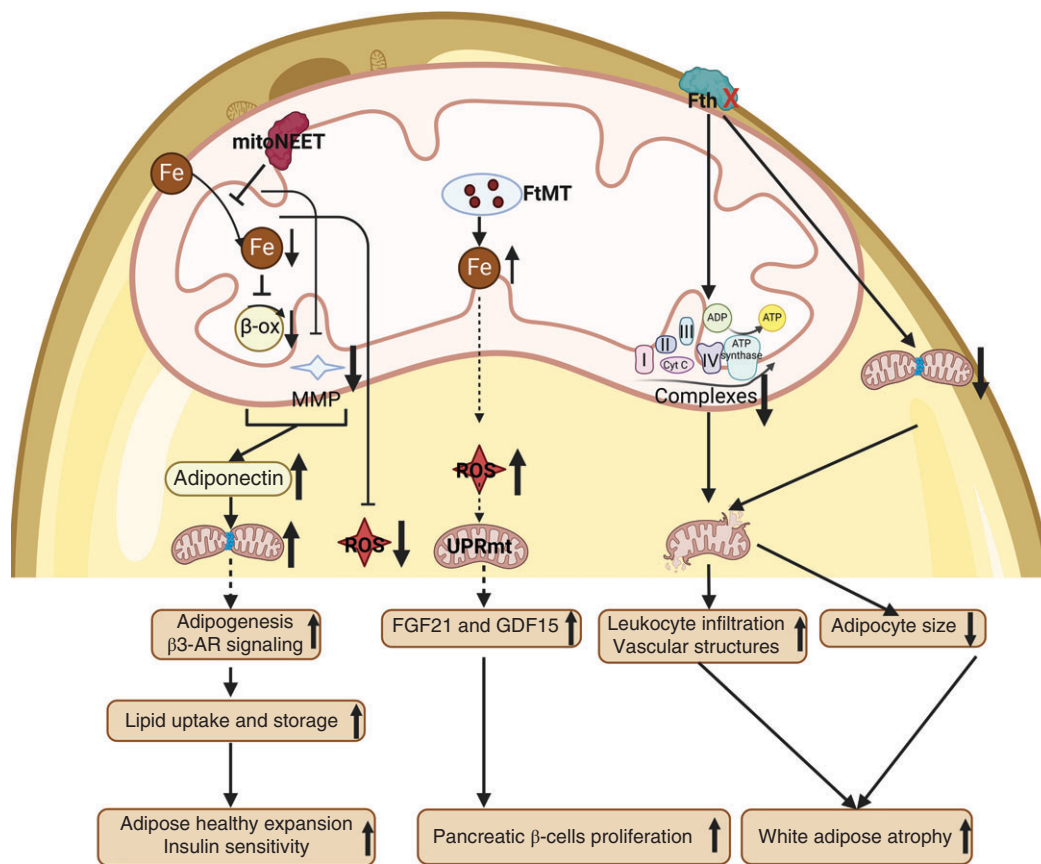


Figure 11 Mitochondrial iron-level dysregulation. This figure illustrates that manipulation of several proteins mediating mitochondrial iron homeostasis results in altered mitochondrial function in white adipocytes, further leading to changes in adipocyte health and systemic energy homeostasis. In white adipocytes, mitoNEET inhibits mitochondrial iron transport into the matrix, which decreases the rate of β -OX, the MMP, and the level of ROS-induced damage, whereas it increases adiponectin production, triggering a compensatory upregulation of mitochondrial biogenesis, adipogenesis, and β 3-AR signaling. Excess lipid uptake and storage leads to adipose tissue expansion, resulting in improvement in systemic insulin sensitivity. Overexpression of FtMT promotes iron aggregation, which in turn may promote UPRmt induced by ROS. FtMT-induced iron overload enhances FGF21 and GDF15 release from white adipocytes, and these two factors act on the pancreas to produce protective effects. Fth deficiency results in decreased mitochondrial biogenesis, reduced mitochondrial number, and reduced expression of mitochondrial electron transport chain proteins, leading to mitochondrial dysfunction, leukocyte infiltration, vascularity and adipocyte size reduction, and profound adipocyte atrophy. Abbreviations: MitoNEET, CDGSH iron-sulfur domain; β -OX, β -oxidation; MMP, mitochondrial membrane potential; ROS, reactive oxygen species; β 3-AR, β -3 adrenergic receptor; FtMT, mitochondrial ferritin; UPRmt, mitochondrial unfolded protein response; FGF21, fibroblast growth factor 21; GDF15, growth differentiation factor 15; Fth, ferritin heavy chain. BioRender.com.

(Figure 11). The knockdown of transferrin or chelation of iron with deferoxamine significantly inhibits adipogenesis and mitochondrial biosynthesis, which suggests that the regulation of iron supply is crucial to achieve optimal adipocyte differentiation, presumably reached by regulating mitochondrial biogenesis (354). Regulation of cellular iron content by the ferritin heavy/heart chain (FTH) supports mitochondrial function. *Fth* deficiency causes mitochondrial dysfunction in WAT, including reduced expression of mitochondrial polymerase γ (*Polg*), citrate synthase (*Cs*), cytochrome *c* oxidase 1 (*Cox1*), cytochrome *b* (*Cytb*), and superoxide dismutase 2 (*Sod2*) mRNA, reduced mitochondrial biogenesis driver PGC-1 α , and decreased mitochondrial number, along with decreased expression of mitochondrial electron

transport chain proteins. In addition, it also leads to profound atrophy of WAT, associated with the presence of leukocyte infiltration, abnormal vascular structures, and the reduction in adipocyte area (45). When given a dietary challenge, mice with overexpressed adipocyte-specific *FtMT* become leaner, but they also display a glucose intolerance, a decrease in adiponectin, an increase in ROS damage, and an elevation in GDF15 and FGF21, which are indicators of abnormal adipose metabolism. Because the primary biological function of FtMT is to sequester excess iron (288), FtMT causes iron overload in adipose mitochondria. Furthermore, *FtMT*-overexpressing mice display significant pancreatic β -cell proliferation, indicating a mitochondrial iron overload-induced interorgan signaling axis from adipocytes to pancreatic β cells (267).

This may be the result of excess iron-induced UPRmt and mitokine secretion (267).

As another mitochondrial protein controlling iron levels, mitoNEET is an OMM protein and an iron-sulfur cluster transfer protein. *mitoNEET* overexpression results in a significant imbalance in mitochondrial iron metabolism in adipocytes, manifested by a significant decrease in iron content, leading to a decrease in β -oxidation and a lower MMP. Thus, impaired mitochondrial function triggers compensatory upregulation of mitochondrial biogenesis, adipogenesis, and β 3-AR signaling. Furthermore, reduced mitochondrial activity enhances lipid uptake and storage, resulting in an overly expanded adipose tissue mass, but meanwhile, insulin sensitivity is surprisingly enhanced with increased adiponectin levels (268). In addition, the effects of mitoNEET on adiposity at different HFD feeding times show enhanced browning signatures and limited WAT expansion under earlier HFD exposure (approximately 12 weeks) and, by contrast, disappeared browning and rapid WAT expansion and weight gain under a prolonged HFD feeding (269).

Mitochondrial Gene Defects and Obesity

Many diseases are caused or contributed by gene mutations in mitochondrial genes. Specific to adipocyte dysfunction and obesity, mtDNA mutations are frequently observed in rodents and humans. One study reported that in the absence of Cockayne syndrome (CS) A or B, mtDNA mutations accumulate, especially in adipocytes of sWAT, which appears to mediate the loss of adipocytes through apoptosis (36). Similarly, WAT in *Tk2* H126N knockin mice, a model of mtDNA depletion, shows decreased gene expressions of thermogenesis and mitochondrial programs (529). However, by contrast, in another mtDNA mutation model induced by *Polg* mutation, the results show a smaller size of white adipocytes, reduced macrophage infiltration, and declined inflammation of the tissues, indicating a healthy adipocyte phenotype (533). In addition, several mutations in mitochondrial tRNA genes are associated with diabetes and metabolic diseases, which include the tRNA^{Thr} mutation m.10003T>C (308), the tRNA^{Glu} mutations m.14709T>C (344), and m.14692A>G (540). Notably, a unique m.5802A>G mutation in the tRNA^{Cys} gene, which is found on the H (heavy) strand of mtDNA, has been discovered in recent investigations as a possible risk factor for obesity in the pedigree (539). Apparently, there is no linear but complex relationship between mitochondrial gene defects, adipocyte dysfunction, and obesity. Particularly, more novel obesity-causing gene mutations still need to be discovered in human patients and validated in rodent models. With limited evidence published, human studies have revealed that the fat mass and obesity-associated (FTO) locus shows the strongest known GWAS association with a body-mass index (BMI) in people (486). Recent mechanistic research demonstrates that the FAO locus-encoded *Irx5* mediates the upregulation of APP in white adipocytes,

causing impaired mitochondrial respiration and elevated fat accumulation, and thus promoting obesity (44).

Interventions that Modulate Mitochondrial Function in White Adipocytes to Treat Metabolic Diseases

Since mitochondrial dysregulations in white adipocytes are well recognized in obesity conditions, research also takes a step further toward translational investigations to explore potential interventions that modulate adipocyte mitochondrial function to ameliorate adipocyte dysfunction, obesity, and its associated metabolic defects.

Dietary Composition Management

Dietary composition restriction

The intervention of CR is a promising way to promote white adipocyte health by decreasing the adipose inflammation and inducing the browning of WAT (Figure 12). A report by the group of Sadeesh K. Ramakrishnan highlighted that mitochondrial biogenesis plays a dominant role in the formation of beige adipocytes induced by CR (351). Single amino acid restriction also contributes to enhanced mitochondrial function in white adipocytes (Figure 12). Methionine restriction (MR) in the diet promotes an increased number of multilocular and UCP1-expressing cells along with a marked improvement in the mitochondrial content, size, and cristae density in inguinal WAT. In addition, MR is found to increase the expression of multiple enzymes in the TCA cycle, as it also increases the components of respiratory complexes I, II, and III. A marked increment in respiratory capacity measured using multiple substrates is demonstrated in a further evaluation in isolated mitochondria by high-resolution respiration assay. These results together point out that morphological, transcriptional, and biochemical remodeling of inguinal white adipocyte mitochondria is modulated by MR and further augments the synthetic and oxidative capacity of adipose tissue (399). Similarly, leucine deprivation also promotes the browning of WAT (537, 594).

Natural bioactive compounds

Many of the synthetic medications that are utilized today are built on the foundation of naturally produced chemicals. In the past three decades, around 50% of approved medications come either directly or indirectly from natural products (522). New research reveals that several dietary substances, particularly phytochemicals, may be potential options for managing obesity. Some of these substances may prevent obesity by increasing adipose browning and enhancing white adipocyte mitochondrial respiration (88, 339) (Figures 13 and 14).

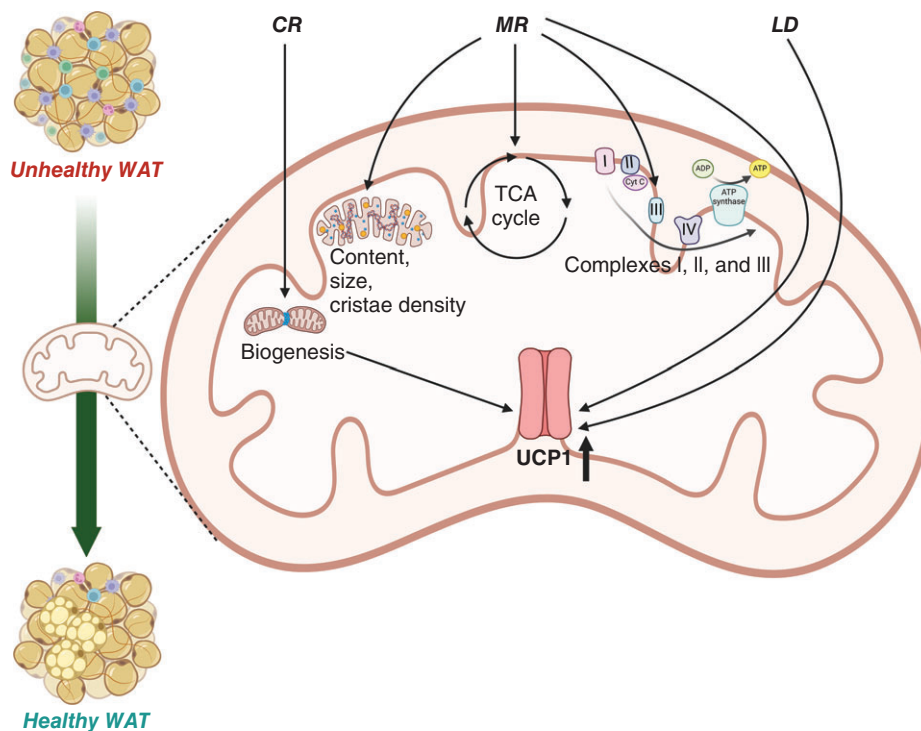


Figure 12 Dietary composition restriction modulates white adipose tissue health.

This figure illustrates that dietary composition restriction promotes white adipose tissue shift from an unhealthy to a healthy state by modulating mitochondrial function. In white adipocytes, CR promotes UCP1 expression by facilitating mitochondrial biogenesis; MR promotes UCP1 expression by increasing mitochondrial content, size, and cristae density, expression of enzymes in the TCA cycle, and the components of respiratory complexes I, II, and III. LD also results in increased UCP1 expression. Abbreviations: CR, caloric restriction; UCP1, uncoupling protein 1; MR, methionine restriction; TCA, tricarboxylic acid cycle; LD, leucine deprivation. BioRender.com.

Artemisinin C

Artemisinin C (3,5-diallyl-4-hydroxycinnamic acid) (ArtC) is the major component of Brazilian green propolis. In murine C3H10T1/2 cells and primary inguinal WAT-derived adipocytes, ArtC strongly assists in generating brown-like adipocytes. This considerable induction is caused by enhanced PRD1-BF-1-RIZ1 homologous domain-containing protein-16 (PRDM16) stability and PPAR activation. Additionally, the oral administration of ArtC significantly increases the number of brown-like adipocytes and the expression of the proteins UCP1 and PRDM16 in the inguinal WAT of mice, independent of the β 3-AR signaling pathway of the sympathetic nervous system (SNS) (379).

Berberine

Some species of flowering plants contain the naturally occurring alkaloid berberine (BBR). The formation of beige adipocytes is significantly induced by BBR in inguinal but not epididymal adipose depots. Through a mechanism involving AMPK and PGC-1 α , BBR also increases the expression of UCP1 and other thermogenic genes in primary white adipocytes. Additionally, the thermogenic program

can be activated by BBR without the need for AMPK in the ventromedial nucleus of the hypothalamus (VMH) (613).

Capsaicin

Capsaicin (CAP) is a component of chili peppers and is widely used in food as a spice. When CAP was administered to rats on an HFD, *Ucp1* mRNA expression in WAT is increased (223). Inducing a beige phenotype in differentiating 3T3-L1 preadipocytes is also seen at low dosages of CAP (19). Additionally, CAP stimulates WAT browning, which prevents obesity in mice via activating the transient receptor potential cation channel subfamily V member 1 (TRPV1) channels. Specifically, CAP stimulates a rise in intracellular Ca^{2+} in TRPV1 channels, activating calcium/calmodulin-dependent protein kinase type II (CaMKII)/AMPK, which phosphorylates and activates SIRT1. This leads to deacetylation of PPAR γ and PRDM16 and facilitates their interaction to promote WAT browning (25).

Celastrol

Tripterygium wilfordii, often known as “Thunder of God Vine,” is a Chinese herbal remedy, and celastrol is one of

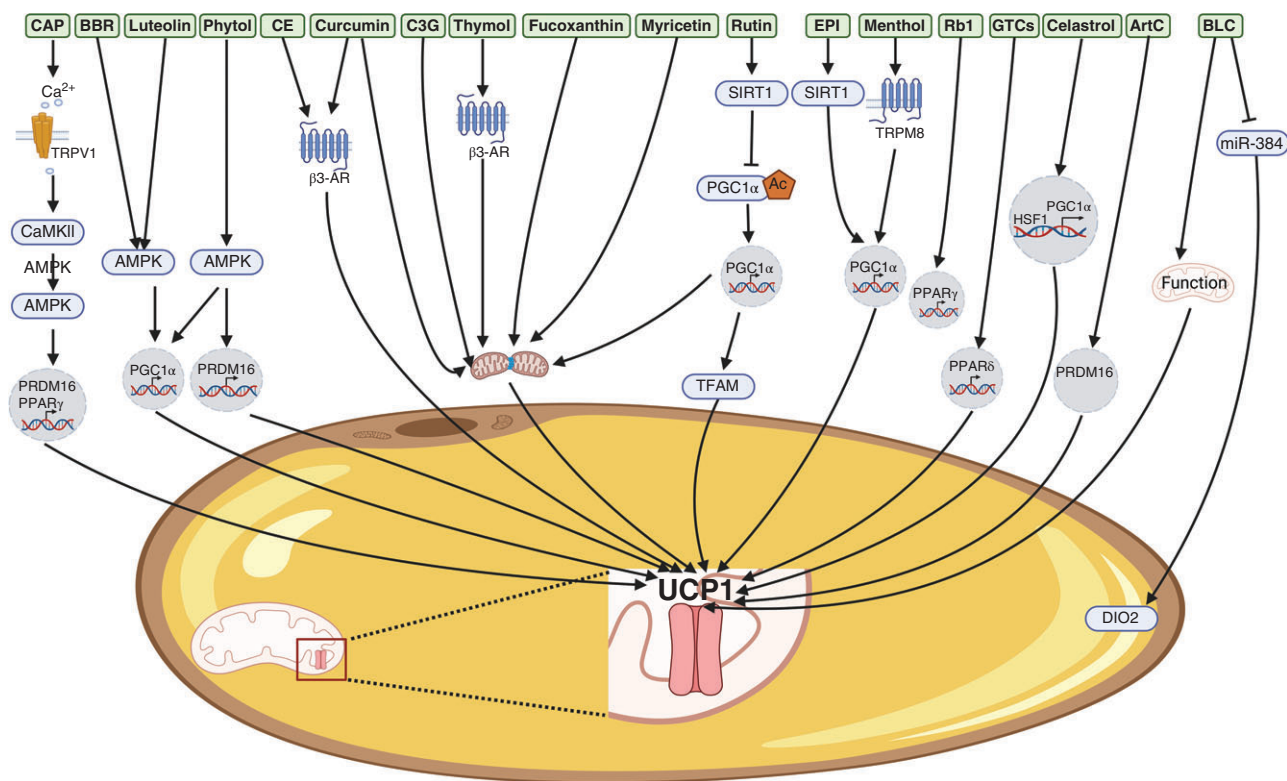


Figure 13 Natural bioactive compounds modulate white adipocyte mitochondrial function. This figure illustrates that through a variety of mechanisms, natural bioactive compounds promote white adipocytes' transition to a healthy state by increasing UCP1 or DIO2 expression in mitochondria through a number of different signaling pathways detailed in this figure. Notably, most natural bioactive compounds were evaluated in rodent models or *in vitro* cell lines. Abbreviations: UCP1, uncoupling protein 1; DIO2, Iodothyronine deiodinase 2; CAP, capsaicin; BBR, berberine; CE, cinnamon extract; C3G, cinnamon extract; EPI, (-)-epicatechin; Rb1, ginsenoside Rb1; GTCs, green tea catechins; ArtC, artemisinin C; BLC, β -Lapachone; TRPV1, transient receptor potential cation channel subfamily V member 1; CaMKII, calcium-calmodulin/dependent protein kinase II; AMPK, AMP-activated protein kinase; PRDM16, PR/SET domain 16; PPAR γ , peroxisome proliferator-activated receptor gamma; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator-1 alpha; β 3-AR, β -3 adrenergic receptor; SIRT1, sirtuin 1; Ac, acetylation; TFAM, mitochondrial transcription factor A; TRPM8, transient receptor potential cation channel subfamily M (melastatin) member 8; PPAR δ , peroxisome proliferator-activated receptor delta; HSF1, heat shock transcription factor 1; MiR-384, microRNA 384. BioRender.com.

its main active ingredients (452). In mice fed under HFD, celastrol administration decreases weight gain, fat mass, hepatic steatosis, and insulin resistance without changes in food intake, activity level, or respiratory exchange ratio. In this investigation, celastrol administration elevates beige (transmembrane protein 26 (*Tmem26*), TNF receptor superfamily member 9 (*Cd137*), speckled protein 100 kDa (*Sp100*), T-box transcription factor 1 (*Tbx1*), solute carrier family 27 member 1 (*Scl27a1*), *Hsp70*, and browning genes (*Prdm16*, *Ucp1*, *Cidea*, and fatty acid elongase 3 (*Elovl3*)) in the inguinal WAT. Furthermore, heat shock factor 1 (HSF1) and PGC-1 α are required for the celastrol stimulation of these thermogenic genes since the browning effect is attenuated in white adipocytes generated from the inguinal WAT of *Hsf1*- or *Pgc1 α* -null mice (324).

Cinnamon

Cinnamon is a spice that is made from the bark of plants in the genus *Cinnamomum* and is a member of the Lauraceae

family (270). In 3T3-L1 adipocytes, cinnamon extract (CE) induces the classic brown adipocyte multilocular phenotype. *In ex vivo* research, CE enhances the markers for brown adipocytes in subcutaneous white adipocytes extracted from *db/db* and HFD mice. However, in the adipocytes separated from perinephric and epididymal adipose tissue, CE exerts no appreciable impact on UCP1 expression. The CE-enhanced UCP1 expression is decreased by a β 3-AR antagonist, showing that the β 3-AR activity is involved in the action of CE. The body weight of HFD-fed mice is decreased after an oral CE administration by dramatically increasing UCP1 expression in the sWAT *in vivo* (270).

Curcumin

The bioactive polyphenol curcumin is obtained from the rhizomes of turmeric. In mice, curcumin increases resistance to cold. The development of beige adipocytes, elevated thermogenic gene expression, and increased mitochondrial biogenesis in inguinal WAT may contribute to enhanced

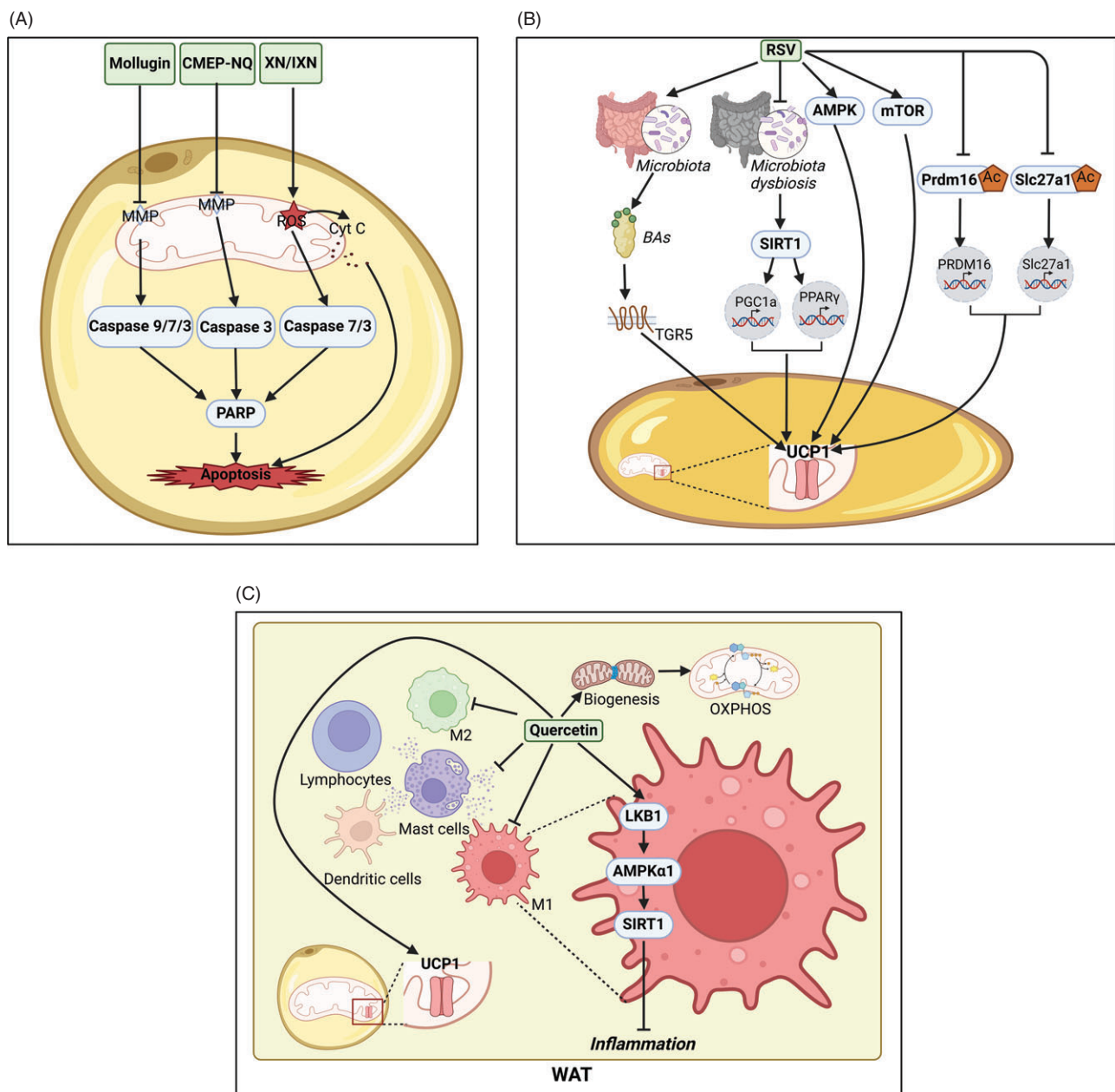


Figure 14 Natural bioactive compounds promote white adipocyte mitochondrial health. (A) Mollugin, CMEP-NQ, and XN/IXN promote mitochondrial-dependent apoptosis in white adipocytes. (B) RSV promotes white adipocytes' transition to a healthy state by increasing mitochondrial UCP1 via various signaling pathways and transcriptional regulations. (C) Quercetin exerts multiple effects on white adipocyte health, such as increasing mitochondrial UCP1, promoting mitochondrial biogenesis, and reducing adipose inflammation by impacting differential immune cells within the adipose tissue. Abbreviations: CMEP-NQ, 2-carbomethoxy-2,3-epoxy-3-prenyl-1,4-naphthoquinone; XN, xanthohumol; IXN, isoxanthohumol; RSV, resveratrol; UCP1, uncoupling protein 1; MMP, mitochondrial membrane potential; ROS, reactive oxygen species; Cyt c, cytochrome c; PARP, poly (ADP-ribose) polymerase; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; PRDM16, PR/SET Domain 16; Ac, acetylation; Slc27a1, solute carrier family 27 member 1; BAs, bile acids; TGR5, Takeda G-protein-coupled receptor 5; SIRT1, sirtuin 1; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator 1 alpha; PPAR γ , peroxisome proliferator-activated receptor gamma; M2, alternatively activated macrophage; M1, classically activated macrophage; OXPHOS, oxidative phosphorylation; LKB1, liver kinase B1; AMPK α 1, protein kinase AMP-activated catalytic subunit alpha 1. BioRender.com.

cold tolerance. Additionally, curcumin increases plasma NE levels, a hormone that can augment WAT browning, and encourages the expression of the *Adrb3* gene in inguinal WAT (545). In white adipocytes, curcumin

induces browning, increases mitochondrial biogenesis, and increases protein levels of HSL and phosphorylated acyl-CoA carboxylase (ACC) by activating AMPK (316).

Cyanidin-3-glucoside

A naturally occurring anthocyanin substance called cyanidin-3-glucoside (C3G) can be found in various fruits and vegetables. With increased mitochondrial biogenesis, C3G induces the transcription of UCP1 and produces beige adipocytes in sWAT of *db/db* mice (590).

(-)-Epicatechin

(-)-Epicatechin (EPI) is the most abundant flavonoid in cacao. The protein expression levels of SIRT1, PGC-1 α , UCP1, and DIO2 are increased in the abdominal adipose tissue, followed by an EPI administration by gavage in mice (174).

Fucoxanthin

Fucoxanthin, the primary carotenoid in brown algae with an uncommonly heterogeneous structure, reduces the mass of WAT and increases the metabolic rate associated with enhancement in mitochondrial biogenesis and fusion genes in both inguinal WAT and epididymal WAT (567). UCP1 is visibly expressed in the WAT, and WAT weight is dramatically decreased in mice administered with fucoxanthin (326). However, human adipocytes treated with fucoxanthin or fucoxanthinol did not exhibit any elevations in OCR or mRNA expression levels for *UCP1*, *CPT1*, and *GLUT4* in contrast to animal research. The mRNA levels of lipid metabolism-related genes and the lipolytic enzymes showed no notable alterations (427).

Green tea catechins and extract

The polyphenolic substances known as green tea catechins (GTCs) are found in the dry, unfermented leaves of the *Camellia sinensis* plant. The most prevalent catechin in green tea, accounting for 50% to 80% of the total catechin content, is epigallocatechin-3-gallate, which is also thought to be the most biologically active compound in green tea (241). Administration of GTCs consistently increases the expression of UCP1 in sWAT and vWAT through PPAR δ (578). Another study discovered that mice fed with HFD and given green tea extract (GTE) show upregulated biomarkers of beige adipocytes in WAT. Transducin-like enhancer protein-3 (TLE-3) is decreased in WAT by GTE, which also increases genes linked in several browning pathways (79).

Gypenosides

Gypenosides are triterpenoid saponins isolated from the *Gynostemma pentaphyllum* plant. Gypenosides supplementation significantly improves BAT activity and WAT browning in mice receiving an HFD. In both brown and white adipocytes, the expression of genes related to mitochondrial function and fatty acid oxidation is elevated (309).

Ginsenoside Rb1

Ginsenoside Rb1 is identified in the plant *Panax ginseng* (Ginseng), a chemical compound of the ginsenoside family. Ginsenoside Rb1 boosts browning and basal glucose absorption, as seen by the significantly higher levels of *Ucp1*, *Pgc1 α* , and *Prdm16* mRNA expressions in 3T3-L1 mature adipocytes. PPAR γ activity is also increased by ginsenoside Rb1. GW9692, a PPAR antagonist, eliminates the browning effect induced by Rb1, implicating that ginsenoside Rb1 induces PPAR γ to increase the browning of 3T3-L1 adipocytes (359).

β -Lapachone

β -Lapachone (BLC) is a naphthoquinone that was first discovered in the South American jungle in the Bignoniaceae tree *Tabebuia avellanada* Lorentz ex Griseb. In mice given HFD, BLC increases the browning of WAT (increased the expression of UCP1), reduces body weight gain, and improves metabolic parameters. Likewise, BLC-treated animals consume considerably more calories than untreated mice. In SVF-differentiated adipocytes, BLC boosts the expression of genes exclusive to brown adipocytes *in vitro*. The regulation of *Dio2* by miR-382 partially allows for the control of browning in WAT by BLC, which eventually prevents diet-induced obesity (87).

Luteolin

Luteolin (3',4',5,7-tetrahydroxyflavone) is a flavone found in a variety of fruits, vegetables, and medicinal plants such as peppermint, thyme, and parsley. Dietary luteolin triggers browning and thermogenesis via the AMPK/PGC-1 α pathway (607).

Menthol

As the main component of peppermint or peppermint oil, menthol is often added as a cooling and flavoring agent to foods, mouthwashes, toothpaste, and medications. It has been found to exert cooling effects by acting on transient receptor potential melatonin 8 (TRPM8), which is one of a temperature-sensitive channel and also known as the cold and menthol receptor-1, and is therefore commonly used as its agonist (6). The cold-sensing receptor TRPM8 is also expressed in human white adipocytes; menthol and icilin activation of this receptor causes an increase in UCP1 expression and a rise in mitochondrial membrane potential, glucose absorption, and heat production. Following TRPM8 activation, the production of a "brown-like" phenotype in human white adipocytes is supported by changes in the intracellular location and ultrastructural shape of mitochondria but not by changes in the genes directing mitochondrial biogenesis (443). White adipocytes *in vitro* express higher levels of thermogenic genes as a result of menthol activating

TRPM8. Additionally, a membrane-permeable calcium chelator BAPTA-AM and the protein kinase A (PKA) inhibitor KT5720 prevent menthol-induced elevations of thermogenic genes, implying that increased *Ucp1* and *Pgc1 α* mRNA expression caused by menthol-induced Ca^{2+} may be mediated by PKA phosphorylation in white adipocytes. Additionally, in HFD-induced obese mice, dietary menthol increases WAT “browning” and accelerates glucose metabolism (215).

Mollugin and 2-carbomethoxy-2,3-epoxy-3-prenyl-1,4-naphthoquinone (CMEP-NQ)

Mollugin and 2-carbomethoxy-2,3-epoxy-3-prenyl-1,4-naphthoquinone (CMEP-NQ), which are anthraquinones and naphthoquinones, respectively, are two potential anti-obesity components isolated from *Rubia cordifolia* L. (210). Mollugin treatment of 3T3-L1 preadipocytes demonstrates the appearance of apoptosis, loss of MMP, and subsequent activation of caspases including caspase-9, caspase-3, and -7, which leads to PARP cleavage (226). Additionally, CMEP-NQ stimulated apoptotic processes in 3T3-L1 cells, such as loss of mitochondrial membrane potential, activation of caspase-3, degradation of PARP, and labeling of positive apoptotic DNA fragments (227) (Figure 14A).

Myricetin

A natural flavonoid called myricetin (3,5,7,3',4',5'-hexahydroxyflavone cannabiscetin) can be found in a variety of food or drinks, including wine, onions, bayberries, grapes, and tea. Myricetin boosts the expression of thermogenic proteins, causes beige adipocyte development, and triggers mitochondrial biogenesis in inguinal WAT. Myricetin consistently increases the expression of the thermogenic genes in $\text{C}_3\text{H}_{10}\text{T}_{1/2}$ cells during the development of brown adipocytes. Additionally, after myricetin administration, $\text{C}_3\text{H}_{10}\text{T}_{1/2}$ cells, adipose tissues, and plasma all show considerably higher adiponectin levels (179).

Phytol

A plastidial isoprenoid called phytol (3,7,11,15-tetramethylhexadec-2-en-1-ol) is present in plant foods such as grains, fruits, and vegetables. It is a plentiful component of the chlorophyll molecule in nature (497). By increasing the expression of the brown adipocyte marker genes *Ucp1*, *Prdm16*, *Pgc1 α* , pyruvate dehydrogenase (*Pdh*), and cytochrome complex, phytol treatment accelerates the browning of inguinal WAT and reduces body weight gain in mice. The AMPK signaling pathway seems to be predominantly responsible for this impact on WAT (603).

Quercetin

One of the primary flavonoids found in human diets is quercetin (3,3',4',5,7-pentahydroxyflavone), which can be

found in berries, apples, broccoli, and onions (377). Quercetin promotes expression of browning genes in differentiated 3T3-L1 adipocytes and in the WAT of mice fed with HFD (265, 284). In addition, in obese mice caused by the Western diet, quercetin reduces immune cell activation and accumulation (including macrophages, lymphocytes, dendritic cells, and mast cells), boosts the expression of antioxidant enzymes while decreasing the expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, increases mtDNA content and OXPHOS (251), and attenuates mast cell and macrophage infiltration in epididymal WAT (120). Mechanistically, quercetin may exert its effects via the liver kinase B1 (LKB1)/AMPK α 1/SIRT1 pathway (120) (Figure 14C).

Resveratrol

Resveratrol (3,5,4'-trihydroxystilbene) (RSV) is a polyphenolic compound enriched in *Polygonum cuspidatum*. Red wine, peanuts, grapes, berries, red cabbage, spinach, and grapes all contain traces of RSV. Recent research suggests that RSV supplementation may improve metabolic health by reducing weight gain and increasing energy expenditure by triggering WAT browning and thermogenesis (202, 299, 544). RSV induces adipose browning in an AMPK α 1-dependent manner (544). There are additional mechanisms that may be involved in RSV-mediated beige adipocyte formation. For example, RSV may be mediated in part by the gut microbiota-bile acids (BAs)-G-protein-coupled bile acid receptor 1 (TGR5)/UCP1 pathway for WAT browning (203). In addition, RSV treatment effectively reduced gut microbial dysbiosis in HFD-fed mice. Later studies revealed that SIRT1 signaling appears to be a crucial step in the RSV-induced gut microbiota remodeling that favorably impacts WAT browning (299). Additionally, the administration of RSV or nicotinamide (NR, a B3 vitamin and NAD⁺ precursor) alters the methylation marks in *Prdm16* and solute carrier family 27 member 1 (*Slc27a1*), two genes linked to WAT browning. *In vitro* experiments showed that in 3T3-L1 adipocytes, RSV and NR directly affect DNA methylation mechanisms and promote browning characteristics (465). Activation of mTOR may also be involved in the RSV-enhanced browning of white adipocytes. Treatment with MHY1485, an activator of mTOR, reproduces the effect of RSV on browning markers in 3T3-L1 adipocytes (315). Intriguingly, obese human volunteers treated with trans-RSV for 4 weeks display improved glycemic and lipid profiles along with increased mRNA levels of *UCP1*, *PRDM16*, *PGC1A*, *SIRT1*, and fibronectin type III domain-containing 5 (*FNDC5*) in the sWAT (13) (Figure 14B).

Rutin

Rutin (3,3,4,5,7-pentahydroxyflavone-3-rhamnoglucoside), a polyphenolic bioflavonoid derived from a variety of plants and fruits, has been used clinically as a capillary stabilizer for many years without causing any significant side effects. Both

genetically obese (*db/db*) and diet-induced obese mice show dramatically reduced adiposity, increased energy expenditure, and improved glucose homeostasis after receiving rutin treatment. In both obese mouse models, rutin causes the appearance of beige adipocytes in sWAT. Rutin directly binds to and stabilizes SIRT1, causing hypoacetylation of the PGC-1 α protein. This in turn triggers TFAM transactivation, which increases the number of mitochondria and UCP1 activity in WAT (595).

Sudachitin

Sudachitin (5,7,4'-trihydroxy-6,8,3-trimethoxyflavone) is a polymethoxyflavone that can be discovered in the peel of *Citrus sudachi*. *Ucp1* and *Ucp3* mRNA transcriptional levels are considerably higher in sudachitin-treated mice, suggesting that WAT acquires a brown-like phenotype and may have boosted thermogenesis (513).

Thymol

Thymol (5-methyl-2-isopropylphenol) is a naturally occurring monoterpene phenolic component of essential oils that is derived from a variety of fragrant plants, including varieties of thyme (83). Thymol elevates the expression of a group of brown fat-specific markers, including PPAR γ , PPAR δ , pAMPK, pACC, HSL, Perilipin (PLIN), CPT1, 1-aminocyclopropane-1-carboxylic acid oxidase (ACO), PGC-1 α , and UCP1, and accelerates mitochondrial biogenesis in 3T3-L1 cells. Furthermore, the activation of β 3-AR, AMPK, PKA, and p38 MAPK is well coordinated with the increased expression of UCP1 and other brown fat-specific markers by thymol (83).

Xanthohumol and isoxanthohumol

As already mentioned, some flavonoids can exert anti-obesity effects by activating the mitochondrial pathway and caspase-3/7 to induce apoptosis in 3T3-L1 adipocytes, including XN and IXN. The specific mechanism of action is described in detail in the previous section (581).

In addition, certain lipids, specifically *n*-3 polyunsaturated fatty acids (PUFA), have the capacity to cause browning. One of the bioactive *n*-3 PUFAs, eicosapentaenoic acid (EPA), can induce browning of sWAT (615). Accordingly, feeding mice with fish oil, which is high in *n*-3 PUFA, causes significant browning of sWAT (24).

Taken together, although promising results of promoting mitochondrial health and inducing browning through treatment of these natural bioactive compounds have been shown, it should be acknowledged that most of these compounds are only evaluated in *in vitro* cell lines or in rodent models. Without unambiguous evidence in humans, it remains preliminary to propose these compounds as potential therapeutics to correct adipocyte dysfunction and obesity.

Metabolites

Many small metabolites have been recognized as browning inducers and mitochondrial function enhancers in white adipocytes. An essential metabolic intermediate called lactate increases functional UCP1 levels to cause the browning of mouse white adipocytes. Additionally, in human cells, lactate also induces browning changes. PPAR γ signaling is required for lactate to impact *Ucp1* expression independently of the PPAR α and HIF-1 pathways (68).

Retinoic acid (RA), a bioactive metabolite of vitamin A, stimulates browning of WAT by boosting beige adipogenesis in PDGFR α^+ adipose progenitors and enhances adipose vascularity by activating the VEGFA/VEGF receptor 2 (VEGFR2) signaling. RA binds to the VEGFA promoter by activating the RAR/retinoid X receptor (RXR) heterodimer. The binding of VEGFA and RA triggers p38 MAPK, which phosphorylates RAR and directs it to the *Prdm16* promoter, resulting in the browning of WAT. At the same time, RA also promotes angiogenesis through the VEGFA/VEGFR2 signaling (534). In addition, RA acts on *Ucp1* gene expression. However, all-trans RA (ATRA) has distinct effects on UCP1 expression in mouse and human adipocytes. In contrast to ATRA increasing *Ucp1* expression in mouse adipocytes by activating RARs, ATRA has no effect on UCP1 levels in human adipocytes (362). ATRA further encourages WAT to develop browning characteristics in mice (340).

Furthermore, rats administered with inorganic nitrate in their drinking water exhibit enhanced expression of genes and proteins of brown adipocytes and β -oxidation genes in WAT and increased oxygen consumption. The process of browning seems to involve the conversion of nitrate to NO, which raises cGMP and activates protein kinase G (PKG), augmenting the expression of *Pgc1 α* and other essential browning genes (434).

β -Aminoisobutyric acid (BAIBA) is discovered by a metabolite screening in a culture medium from myocyte over-expressing *Pgc1 α* (435) and is produced by the catabolism of thymidine. It activates thermogenic genes in white adipocytes through PPAR α (435). In addition, BAIBA also upregulates FFA oxidation in mitochondria in adipocytes, thereby reducing fat accumulation in mice (28, 328). As a small molecule myokine, BAIBA induces a brown adipose-like phenotype in human pluripotent stem cells, which enhances glucose homeostasis in mice. Exercise in humans raises plasma BAIBA concentrations, which are inversely correlated with metabolic risks (435).

As an amino acid not used in protein synthesis, a diet enriched with citrulline (CIT) upregulates UCP1, PGC-1 α , and TFAM in WAT of lean and diet-induced obese mice (221). Conjugated linoleic acid (CLA), a cluster of dietetic fatty acids, increases CPT1b and PGC-1 α expression. Most importantly, CLA enhances UCP1 in the WAT of obese mice without affecting the levels of β 3-AR (550) and by a mechanism unrelated to PPAR α (406). Rats given the synthetic fatty acid 2-hydroxyoleic acid (2-OHOA), one of the C18 fatty

acids, show enhanced UCP1 expression by the cAMP/PKA pathway-dependent transcription factor CREB in WAT, which leads to a reduction in body and fat mass (530).

Additionally, as the primary precursor and catabolic product of ATP, adenosine increases the expression of thermogenic markers in human brown and white adipocytes. Adenosine signals can be delivered by adenosine A1 and A3 receptors via G inhibitory alpha subunit (Gi) or by A_{2A} and A_{2B} receptors via G stimulatory alpha subunit (Gs) (141). Mice fed with HFD and treated with an A_{2A} agonist (PSB-0777) prevent diet-induced obesity and induce browning with a markedly enhanced level of UCP1 and PGC-1 α in WAT (165).

Similarly, inosine, a metabolite produced during apoptosis, is shown to control thermogenic adipocyte formation and prevent obesity. Inosine treatment results in the browning of WAT evidenced by *in vitro* and *in vivo* experiments. Specifically, *in vitro*, inosine administration increases the mRNA level of *Ucp1* and *Pgc1 α* ; *in vivo*, mice treated with inosine showed higher mRNA level of *Ucp1*, *Pgc1 α* , and *Prdm16* in inguinal WAT. Adipocyte-specific deletion of equilibrium nucleoside transporter 1 (ENT1, SLC29A1), which can transport inosine, demonstrates significantly increased mRNA levels of *Ucp1* and *Pgc1 α* , indicating enhanced browning of white adipocytes (376).

Succinate impacts mitochondrial function in adipocytes, particularly in brown adipose tissue. It promotes brown adipose tissue thermogenesis, energy dissipation, and mitochondrial proteome remodeling (157, 298, 347). Furthermore, in a study examining the metabolic function of stearoyl coenzyme A desaturase 1 (*Scd1*), researchers found that deletion of *Scd1* in mature adipocytes expressing *Fabp4* or *Ucp1* did not affect thermogenesis in mice. This effect is dependent on the accumulation of succinate in adipocyte progenitors, which promotes mitochondrial complex II activity (310). In addition, mitochondria-derived succinate exerts anti-lipolytic effects in white adipocytes, preventing ectopic lipotoxicity (10). Nevertheless, whether succinate is considered a therapeutic method to ameliorate metabolic disorders remains an open question.

The strategy of dietary restriction mentioned earlier mentions that amino acid restriction enhances mitochondrial function. In addition to this, increasing certain amino acid contents also enhances mitochondrial function. For example, adding BCAA leucine to the drinking water in HFD-fed mice for 2 months increases mitochondrial biogenesis and fatty acid oxidation in BAT, enhancing insulin sensitivity and glucose metabolism (291, 584). In another study, researchers fed a normal calorie diet to obese mice to induce weight loss while adding leucine to their drinking water and found a significant increase in mRNA levels of *Ucp1*, *Ucp3*, *Cox3*, and *Cox4* in the WAT (43). Consistently, dietary leucine supplementation promotes browning of WAT (618). Furthermore, with increasing dietary histidine content, *Ucp1* mRNA increases in BAT (234). Additionally, dietary arginine supplementation promotes the loss of WAT and increases mitochondrial production and function in BAT (335).

Secretion Factors

A growing body of research suggests that secretory factors, including neurosecretory factors, thyroid hormones, adipokines, cardiac natriuretic peptides, exercise-inducible factors, and mitokines, regulate mitochondrial biogenesis and function through common or unique pathways, thereby facilitating the health of white adipocytes (Figure 15).

Neurosecretory factors

The β -AR signaling system is the central signaling mechanism that controls nonshivering thermogenesis in brown and beige adipocytes. The central nervous system (CNS)/SNS is stimulated by cold to secrete NE that binds to the β -AR and activates the adenylate cyclase to produce cAMP. In turn, cAMP activates PKA, which has several downstream targets, including transcription factors, to enhance the expression of thermogenic and mitochondrial genes (8, 231, 341). Thus, NE is a central molecule in the process of browning of WAT. Additionally, in response to environmental cues (cold and enriched environment), the hypothalamus produces brain-derived neurotrophic factor (BDNF), which selectively modulates WAT to cause enhanced browning and increased energy expenditure (60). However, when differentiated adipocytes are treated with BDNF, the differentiation and the browning of adipocytes are unexpectedly inhibited through unknown reasons (220).

As a sleep-regulating hormone produced by the brain, melatonin administration has been evaluated in both lean littermates and Zucker diabetic fatty (ZDF) rats, a model of obesity-related T2DM. It induces browning of inguinal WAT along with increased UCP1 and PGC-1 α (217). Mechanistically, melatonin is found to increase brown adipocytes in ZDF rats through adipocyte trans-differentiation and *de novo* adipogenesis. In addition, it also promotes beige mesenchymal stem cell adipogenesis in humans (450). Furthermore, long-term oral melatonin supplementation enhances mitochondrial respiration in white and beige adipocytes while lowering their oxidative state and susceptibility to apoptosis. Therefore, melatonin effects on ZDF mice with obesity-associated metabolic diseases, such as diabetes and dyslipidemia, by preventing mitochondrial dysfunction (218).

Thyroid hormones

An early study on rats found that triiodothyroacetic acid (TRIAC), a triiodothyronine (T3) metabolite, causes ectopic expression of UCP1 in abdominal WAT at low dosages (337). Furthermore, in sWAT of *ob/ob* mice, the thyroid hormone receptor (TR) agonist GC-1 induces a brown-like pathway of adaptive thermogenesis. The activation of UCP1 in primary white adipocytes further reveals a direct action of GC-1 on WAT browning (302). Consistent with this, T3 treatment is sufficient to increase the expression of *Ucp1* mRNA in mouse 3T3-L1 preadipocytes. T3 increases TR β expression, which

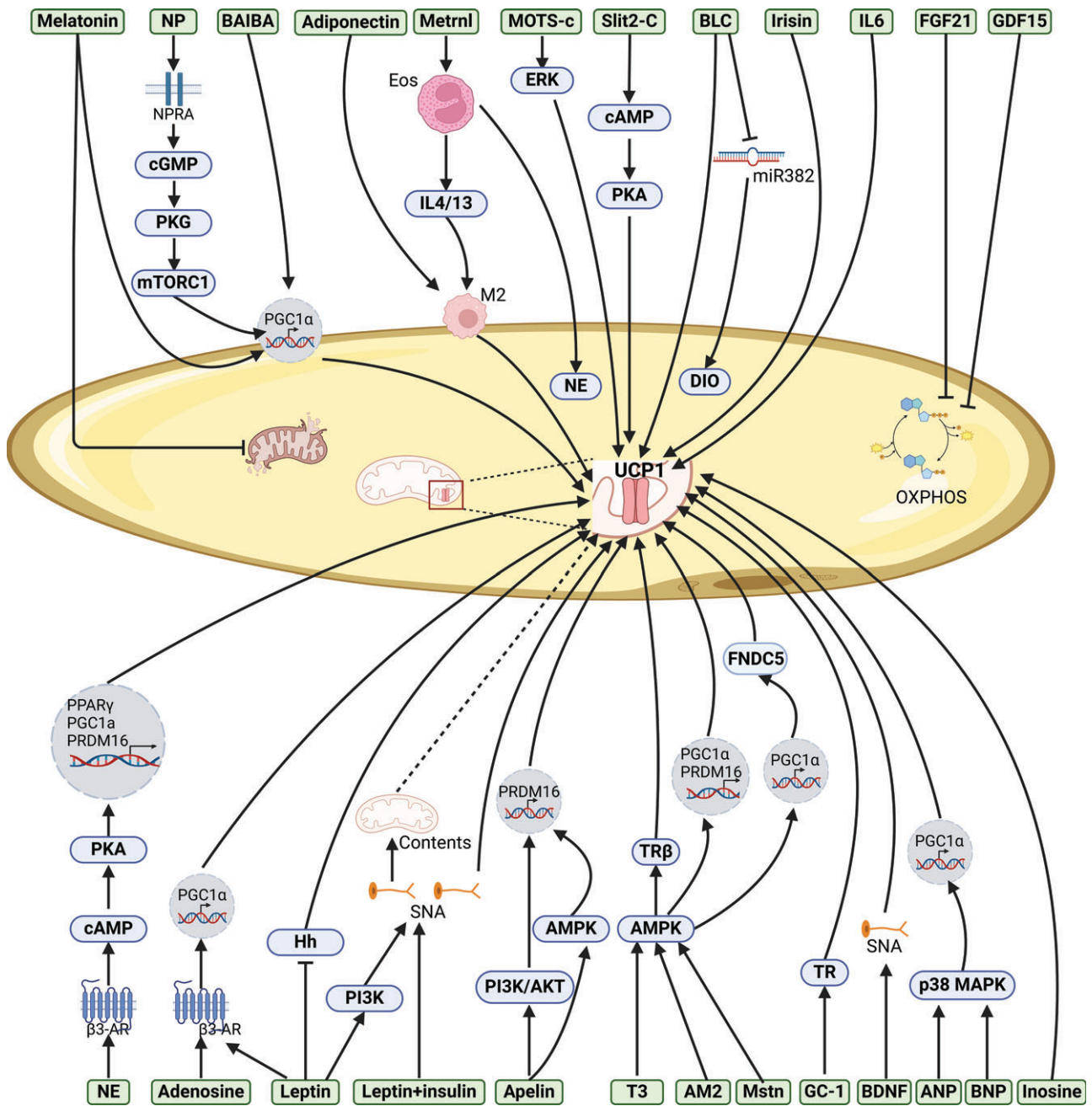


Figure 15 Secretion factors modulate white adipocyte mitochondrial function. This figure illustrates that secretion factors, including neurosecretory factors, thyroid hormones, adipokines, cardiac natriuretic peptides, exercise-induced factors, and mitokines, regulate mitochondrial biogenesis and function through shared or unique pathways, thereby promoting white adipocyte health. Abbreviations: NP, natriuretic peptide; BAIBA, β-aminoisobutyric acid; Metnrl, Meteorin-like; MOTs-c, mitochondrial ORF of the 12S rRNA type-c; Slit2-C, slit guidance ligand 2; BLC, β-Lapachone; IL6, interleukin 6; FGF21, fibroblast growth factor 21; GDF15, growth differentiation factor 15; NE, norepinephrine; T3, triiodothyronine; AM2, adrenomedullin 2; Mstn, myostatin; GC-1, thyroid hormone receptor-β agonist; BDNF, brain-derived neurotrophic factor; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; cGMP, cyclic guanosine monophosphate; PKG, protein kinase G; mTORC1, mammalian target of rapamycin complex 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; Eos, eosinophils; IL4/13, interleukin 4/13; M2, alternatively activated macrophage; ERK, extracellular signal-regulated kinase; cAMP, cathelicidin antimicrobial peptide; PKA, protein kinase A; MiR-382, microRNA 382; DIO2, iodothyronine deiodinase 2; OXPHOS, oxidative phosphorylation; β3-AR, beta-3 adrenergic receptor; PPARγ, peroxisome proliferator-activated receptor gamma; PRDM16, PR/SET domain 16; Hh, hedgehog; PI3K, phosphoinositide 3-kinases; SNA, sympathetic nerve activity; AKT, protein kinase B; TRβ, thyroid hormone receptor β; TR, thyroid hormone receptor; FNDC5, fibronectin type III domain-containing 5; p38MAPK, p38 mitogen-activated protein kinases. BioRender.com.

in turn induces thermogenesis by activating AMPK (536). In a case study of a patient with a history of thyroid cancer who is supplemented with thyroid hormone, gene expression analysis of abdominal WAT demonstrates an enhanced browning program, with a fivefold increase in *UCP1* expression (481). When T3 is administered to human multipotent adipose-derived stem cells (hMADs) during differentiation, *UCP1* expression and mitochondrial biogenesis increase. Additionally, T3 enhances OCR of hMADs, however, only being observed with a rather high dosage (481).

Adipokines

Among enormous adipocyte-derived adipokines, leptin and adiponectin are the two major adipokines of interest. Leptin is largely produced by adipocytes in WAT, which serves crucial physiological roles both directly (in an autocrine action) and indirectly (most notably via the nervous system). Peripheral leptin therapy in *ob/ob* mice elevates *UCP1* expression in WAT, mediated by β 3-AR (97). In-depth studies have shown that phosphoinositide 3-kinase (PI3K) activation and selective phosphatase and tensin homolog (PTEN) ablation in leptin-sensitive neurons control sympathetic nerve activity (SNA) in WAT, resulting in increased mitochondrial content and *UCP1* expression. A follow-up study found that leptin and insulin work synergistically to induce weight loss and WAT browning by impacting hypothalamic neurons by increasing SNA (116). Mechanistically, the forkhead box C2 protein (FOXC2) is involved in leptin-mediated browning of WAT. Through constructive control of the leptin signal and the STAT3-PRDM16 complex, FOXC2 promotes the browning of WAT (154). The Hedgehog (Hh) signaling pathway has also been reported to be engaged in leptin-mediated browning. Leptin enhances browning by inhibiting the Hh signaling pathway (538). Irisin, a soluble protein released from the myokine fibronectin type III domain-containing five (FNDC5) after cleavage in muscle, works on white adipocytes to enhance *UCP1* expression and browning in WAT (51). However, leptin seems contradictory to irisin's beneficial effects. Through processes independent of NO, leptin administration reduces *Fndc5* and *Pgc1 α* expression in sWAT of wild-type and *ob/ob* mice. Additionally, leptin boosts *Tmem26* expression while decreases irisin-induced expression of *Ucp1* and cell death, inducing DFFA-like effector C (*Cidec*) in sWAT (51).

Adiponectin is well known for its multifunctional roles due to its antidiabetic, anti-inflammatory, anti-obesity, and anti-atherosclerosis properties. In 3T3-L1 adipocytes, adiponectin administration significantly accelerates adipocyte differentiation and browning (220). In animal experiments, researchers found that sleeve gastrectomy significantly increases serum and WAT adiponectin levels and further increases SIRT1 expression, thus promoting the browning of WAT (312). In cold exposure, *adiponectin*-null mice exhibit reduced body temperature, significantly reduced expression of thermogenic regulatory genes in BAT and sWAT, reduced mitochondrial

content, and reduced expression of mitochondrial fusion genes, due to inhibited adrenergic activation and down-regulated β 3-AR, insulin signaling, and the AMPK-SIRT1 pathway (547). Another independent investigation demonstrates that chronic cold exposure results in significantly elevated adipocyte production of adiponectin in sWAT, which activates alternatively activated macrophages (M2) in the SVF. Thus, adiponectin is shown to promote the activation and thermogenic program of beige adipocytes (204). Human data suggest that obese individuals have lower circulatory adiponectin levels (220). All the above studies show the positive effect of adiponectin on AT thermogenesis. Notwithstanding, it should be noted that opposite results exist. *Adiponectin*-null mice have been shown to have higher body temperature, higher expression of thermogenic genes, and significant browning of sWAT compared to control mice. Mechanistically, the anti-thermogenic effect of adiponectin is independent of either AdipoR1 or AdipoR2 but through an inhibition of β 3-AR expression in brown adipocytes (418). *AdipoR1* overexpressing mice show reduced glucose uptake under cold-induced conditions, increased size of brown and beige adipocytes, decreased body temperature in mice, and decreased body temperature on the surface of BAT. The thermogenic genes and mitochondria-related genes are reduced in BAT and beige WAT, while the whitening genes are significantly increased (81). Given these controversial results, part of the reasons may be mouse line differences, housing conditions, and distinct compensations from other adipokines. Furthermore, it is worth noting that adiponectin is available in different molecular weights, high, medium, and low. Studies have shown that different molecular weights of adiponectin have opposite effects (373, 447). Therefore, distinguished browning effects from different molecular weight adiponectin require to be further delineated.

In addition, adiponectin/leptin ratio is a marker of adipose tissue dysfunction. A significant negative correlation is found between the adiponectin/leptin ratio and serum amyloid A concentration, a marker of adipose tissue dysfunction (148).

Apelin is a recent addition to the adipokine family (52). Apelin has been known for its anti-obesity and antidiabetic activities and controls different elements of energy metabolism through apelin receptor (APJ) (69). Apelin stimulates a browning phenotype by boosting the expression of the *Ucp1* gene and transcription factors that regulate the PI3K/AKT and AMPK pathways in white adipocytes (507). However, higher levels of brain apelin cause a localized inflammatory state in the hypothalamus, which is linked to decreased energy expenditure and possibly reduced BAT activity and thermogenesis (121).

Cardiac natriuretic peptides

The cardiac natriuretic peptide (NP) family has three peptides including atrial natriuretic peptide (ANP), brain or B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). In human adipocytes, both ANP and BNP elevate

the expression of PGC-1 α and UCP1, enhance mitochondrial biogenesis, and boost uncoupled and total respiration, all in a p38 MAPK-dependent manner. BNP infusion in mice significantly elevates *Ucp1* and *Pgc1 α* expression in WAT and BAT, showing promoted mitochondrial respiration and energy expenditure (47). In addition, in both mouse and human adipocytes, NP-cGMP signaling is found to activate mTORC1 by PKG. By directly phosphorylating raptor at Serine 791 with PKG, NP-natriuretic peptide receptor A (NPRA)-PKG signaling activates mTORC1. After BNP is administered to mice, the mTORC1 inhibitor rapamycin completely prevents the induction of *Ucp1* and *Pgc1 α* expression in inguinal WAT (307).

Exercise-induced factors

It is well known that exercise is beneficial to systemic metabolic health. Growing studies show that during exercise, muscles act as secretory organs, which can release factors (myokines) affecting other organs, such as the adipose tissue, to exert their profound effects.

Meteorin-like (*Metnl*), a circulating factor, is induced in skeletal muscles after exercise and adipose tissue after cold exposure. *Metnl* promotes an upregulation of genes associated with adipocytes browning, mitochondrial functions, and anti-inflammatory programs. Excessive *Metnl* administration results in eosinophil trafficking into WAT and raising local interleukin 4/13 (IL-4/13), encouraging alternate macrophage activation and elevated NE in WAT, explaining how *Metnl* induces WAT browning (426).

As a PGC-1 α -dependent myokine induced by exercise and encoded by *Fndc5*, irisin significantly induces the browning of white adipocytes along with elevated expression of mitochondrial genes (51). Many studies conducted on irisin over a long time have yielded controversial results, especially regarding the circulating levels of irisin after exercise. However, with the advancement in technology, circulating levels of irisin in humans can be detected in a non-antibody-dependent manner, that is, by mass spectrometry, and the results show that both acute and chronic exercise promote an increase in irisin levels in humans (105, 213).

As a controversial secreted protein, IL-6 is usually considered a pro-inflammatory factor, but during exercise, IL-6 is considered a myokine. In addition to its local effects on muscle, exercise-induced IL-6 is also involved in the process of WAT browning, manifesting itself in elevating UCP1 expression in inguinal WAT (250). Studies in human populations have also shown that exercise-induced IL-6 promotes lipolysis and FFA oxidation in adipocytes (518).

As the only myokine that decreases after exercise, myostatin (MSTN) also regulates the function of adipocytes. *Mstn*-null mice display WAT browning (467, 601). Furthermore, HFD-challenged mice treated with anti-myostatin antibody demonstrate browning of WAT in accordance with stimulation of fatty acid oxidation and increased energy expenditure. Mechanistically, suppression of myostatin

increases PGC-1 α expression and irisin production mediated by the AMPK-PGC1 α -FNDC5 pathway in muscle, which subsequently drive irisin-stimulated WAT browning (119).

Mitokines

Mitokines emerge as crucial factors that prevent metabolic deficiency implicated by recent research. Researchers found that mitokines, including GDF15 and FGF21, have favorable influences on obesity and insulin resistance in the context of reduced OXPHOS in adipocytes in mice (86). Notably, GDF15 is reported to provoke anorexia by invoking nausea and/or engaging the emetic nerve circuit (50). Thus, local use, such as adipose tissue administration, may effectively avoid its adverse effects. MTOS-c, a novel discovered peptide which is secreted by mitochondria, promotes the browning of WAT regulated by the pathway of phosphorylation of ERK (318).

Adipose-derived extracellular vesicles

Extracellular vesicles are a collection of exosomes, microvesicles, and apoptotic bodies. They are novel signaling messengers that mediate intercellular communication and tissue cross talk. Those derived from adipose tissue are known as adipose-derived extracellular vesicles (ADEVs), which are mainly derived from adipocytes, immune cells, mesenchymal stem cells, and endothelial cells. ADEVs engage in a variety of adipose tissue functions, including adipogenesis, growth, release of adipokines, and tissue remodeling, as well as participation in the immune microenvironment. In addition to participating in the metabolism of adipose tissue itself, ADEVs can carry adipose tissue messages to the liver, brain, heart, and skeletal muscle to regulate the metabolism of these organs (200). Particularly, under conditions of mitochondrial stress, ADEVs carry mitochondrial fragments from adipocytes into the circulatory system and are taken up by cardiomyocytes, with the result that compensatory antioxidant signaling is generated in the heart to protect cardiomyocytes from acute oxidative stress (103). This groundbreaking study not only provides evidence that mitochondria can be delivered and transferred between different cells but also provides promising hints for the development of extracellular vesicle agents for treating metabolic diseases. Another study independently found that stress-stimulated brown adipocytes release ADEVs containing damaged mitochondrial components, which are cleared by adipose tissue-resident macrophages to maintain tissue homeostasis (442). This study further emphasizes the importance of ADEVs for the maintenance of metabolic homeostasis and inspires that ADEVs are novel carriers of therapeutics. It is worthwhile to mention that ADEVs have been thoroughly discussed in a recent excellent article, particularly focusing on how EVs are regulated under various stress conditions, including damaged-induced “energetic stress” (102).

Others

In addition, two other secreted peptides have been shown to improve lipid function by ameliorating mitochondrial function. These are adrenomedullin 2 (AM2), secreted peptides of the calcitonin gene-related peptide (CGRP) superfamily, and Slit2-C, a 180-kDa member of the Slit extracellular protein family. Through increased AMPK phosphorylation and reduced PGC-1 α acetylation, which result in interactions between PGC-1 α and PRDM16, AM2 has been shown to produce browning of rat primary adipocytes *in vitro* as well as a range of metabolism-improving effects (605). Through the PKA signaling pathway, Slit2-C activates a thermogenesis program in adipocytes as a PRDM16-regulated secreted protein (496).

Pharmacological Interventions

Thiazolidinediones

Several pharmacological approaches that have been assessed or clinically approved in the treatment of obesity and/or insulin resistance show benefits in adipocyte mitochondrial health through increased mitochondrial biogenesis. Rosiglitazone, belonging to the family of TZDs that can promote insulin sensitivity, enhances the gene expressions that encode mitochondrial proteins, increases mitochondrial mass, and positively alters the structure of mitochondria. Consequently, white adipocyte function is significantly improved, as evidenced by elevated oxygen consumption and augmented oxidation of palmitate (558). Equivalent results are obtained from human studies. Pioglitazone, another type of thiazolidinediones, can elevate the expression of PGC-1 α and the copy number of mtDNA and promote the oxidative capacity in white adipocytes (46). However, adverse cardiovascular effects from utilizations of TZDs have prevented their wide applications, and searching for a safer insulin sensitizer that promotes adipocyte mitochondrial health still requires more research attentions (381).

Mitochondrial-specific antioxidants

As mentioned previously, oxidative stress resulting from mitochondrial dysfunction is one of the causes that trigger metabolic defects. Therefore, mitochondria-targeted antioxidants may contribute to the improvement in adipocyte health and the treatment of obesity and metabolic diseases. R- α -lipoic acid, a mitochondria-targeted antioxidant, increases OCR and fatty acid oxidation and promotes the expression of mitochondrial biogenesis-related genes in 3T3-L1 adipocytes when coadministered with acetyl-L-carnitine that acts as a dual ligand for PPAR γ /PPAR α (474). Indeed, clinical use of several mitochondrial antioxidants, including vitamin E, N-acetylcysteine, glutathione, and coenzyme Q10, may alleviate excessive production of ROS and improve hyperglycemia in diabetic patients (145). Other mitochondrial

antioxidants such as ubiquinone (MitoQ) (132) and mito-TEMPO (214) alleviate metabolic complications. Although numerous studies have demonstrated the beneficial effects of antioxidants in the treatment of diseases, they have also demonstrated that the efficacy of antioxidants is low during long-term supplementation (282). Therefore, further studies are necessary to optimize the concentrations and durations of mitochondria-targeted antioxidant supplementations to achieve optimal therapeutic effects.

β 3-Adrenergic receptor agonist

Adrenergic stimulation is highly effective in promoting lipid oxidation and thermogenesis in mitochondria, which in turn promotes the browning of WAT. Therefore, many strategies to achieve improvement of white adipocytes by increasing mitochondrial function have focused on stimulating β 3-AR (216).

Early mouse studies revealed that long-term administration of the β 3-AR agonist CL-316,243 causes the development of browning adipocytes within WAT, such as the mesenteric, inguinal, epididymal, and retroperitoneal fat depots (161). It is encouraging that mirabegron is an agonist detailed as a pharmacological compound that shows both promising and minimal cardiovascular side effects (30). In 2012, mirabegron (Myrbetriq[®]) was approved by the Food and Drug Administration (FDA) for the treatment of overactive bladder disorder by a mechanism that acts on the β 3-AR in the bladder to relax smooth muscle and thus increase urine storage (382). Recent studies have also demonstrated that the effects of mirabegron are comparable to intermittent cold exposure and provide more direct evidence of weight loss than exercise. Based on these recent discoveries, mirabegron is regarded as the most effective and the safest β 3-AR agonist for treating metabolic diseases (30); however, its clinical usage remains questionable.

Other small molecules

Selective activation of PPAR α by fenofibrate enables WAT browning in a model of diet-induced obesity (422). Browning is promoted in WAT when a bile acid sensor (farnesoid X receptor, FXR) is stimulated by its agonist, fexaramine (505). Liraglutide, a clinically used glucagon-like peptide-1 receptor (GLP-1R) agonist, increases BAT thermogenesis and WAT browning in mice via central injection, independent of food intake changes. In a longitudinal trial, liraglutide and another GLP-1R agonist, exenatide, promote energy expenditure in obese T2DM patients treated with the medications for one year (29). CPAG-1 is an activator of progesterone receptor membrane component 2 (PGRMC2). PGRMC2 is an intracellular hemoglobin chaperone and a single-channel transmembrane protein localized to the ER and nuclear envelope (224, 398), belonging to the membrane-associated progesterone receptor (MAPR) family with a

noncovalent plasma-binding domain (247). CPAG-1 promotes the browning of inguinal WAT and reduces fibrosis and inflammation in epididymal WAT in HFD-fed mice (153). BML-260, a well-known potent inhibitor of the bispecific phosphatase JSP-1, enhances UCP1 expression in white adipocytes. Furthermore, it activates OXPHOS genes and increases mitochondrial activity of adipocytes *in vitro* and *in vivo*. Mechanistic investigations reveal that the effect of BML-260 on adipocytes is partly through the activation of CREB, STAT3, and PPAR signaling pathways and unexpectedly independent of JSP-1 (134). YC-1, a general HIF- α inhibitor, and PT2385, a specific HIF-2 α inhibitor, both show an induction of the browning of inguinal WAT under cold tolerance. Specifically, HIF-2 α downregulates PKA catalytic subunit alpha (PKA C α) via induction of miR-3085-3p expression to inhibit PKA activity. Specific knockdown of *Hif-2 α* in adipocytes spurs beige adipocyte preservation, with a concomitant increase in PKA C α upon rewarming after the cold stimulation (177). The diabetes drug canagliflozin (Cana), an SGLT2 inhibitor, reduces hyperglycemia by increasing urinary glucose excretion. Cana treatment also reduces body weight. *In vitro* experiments show that energy expenditure of mature adipocytes is significantly enhanced by Cana treatment, mainly due to increased mitochondrial biogenesis in adipocytes, but not associated with SGLT2 inhibition. A significant increase in mitochondrial OXPHOS and fatty acid oxidation is also observed. Mechanistically, Cana promotes mitochondrial biogenesis and function via the AMPK-SIRT1-PGC-1 α signaling pathway. *In vivo* treatment of mice also shows that Cana increases AMPK phosphorylation and expressions of SIRT1 and PGC-1 α in sWAT, along with enhanced mitochondrial function. This suggests that Cana induces mitochondrial biogenesis and function through the AMPK-SIRT1-PGC-1 α signaling pathway, directly increasing adipocyte energy expenditure (583).

ER stress is implicated in adipose dysfunction in obesity and metabolic diseases. The latest study found that abrogation of the serine/threonine-protein kinase/endoribonuclease inositol-requiring enzyme 1 α (IRE1 α) (a key sensor of ER stress) RNase activity with 4 μ 8C alleviates the suppressed browning of inguinal WAT in HFD-challenged mice. Mechanistically, IRE1 α is shown to degrade *Pgc1 α* mRNA through its RNase activity, thereby downregulating the mitochondrial and thermogenic gene program in white adipocytes (80).

MicroRNAs

MicroRNAs are functional small RNAs and hold great potential as therapeutic agents. Various microRNA subtypes and their functions have also been investigated concerning adipose tissue physiology and WAT browning. In response to cold exposure, it has been demonstrated that microRNAs control both BAT activation and sWAT browning. When exposed to cold, adipocyte-specific miR-455 transgenic mice

exhibit pronounced browning of sWAT (604). Overexpression of BAT-specific miR-32 boosts BAT thermogenesis, enhances circulating FGF21 levels, and promotes WAT browning. Through the direct repression of its targeted gene transducer of ERBB2.1 (*Tob1*), miR-32 promotes the production and secretion of FGF21 from BAT by activating p38 MAPK signaling (374). When 3T3-L1 and C₃H₁₀T_{1/2} adipocytes undergo adipogenic differentiation, miR-669a-5p expression is elevated. The supplementation of miR-669a-5p promotes adipogenesis and induces browning of 3T3-L1 and C₃H₁₀T_{1/2} cells. In addition, mice exposed to cold display increased miR-669a-5p expression in inguinal WAT, potentially controlling beige adipocyte differentiation and fatty acid oxidation (500).

Promising Therapeutic Targets

Additional mouse studies have proposed viable targets that effectively modulate mitochondrial function in adipocytes and further benefit metabolic health.

A recent study found that mice with a deletion of surfeit locus protein 1 (*Surf1*), a complex IV assembly protein that reduces the activity of cytochrome *c* oxidase, display increased mitochondrial biogenesis in adipocytes with decreased lipid storage, elevated fatty acid oxidation, smaller adipocytes, lower body weight, and enhanced insulin sensitivity (110). This suggests that inhibition of SURF1 might be a potential therapeutic to ameliorate mitochondrial function and promote adipocyte health.

Similarly, WAT in mice lacking *ClpP*, a mitochondrial protease, shows higher expression of mitochondrial biogenesis, chaperones, respiration, and corrected mitochondrial fission/fusion in accordance with reduced adiposity (39).

BNIP3, a mitochondrial protein that plays a regulatory role in mitochondrial quality, improves mitochondrial bioenergetics upon rosiglitazone treatment, indicating that BINP3 is a novel, promising therapeutic target for the restoration of mitochondrial homeostasis in insulin-resistant conditions (84).

In addition, a balanced mitochondrial function needs to be maintained in adipocytes to ensure its normality. Modifying mitochondrial function by altering mitochondrial mitoNEET expression affects the dynamics of cellular and systemic lipid homeostasis. *mitoNEET* overexpression enhances lipid uptake and storage, leading to a healthy expansion of white adipocytes. Despite the resulting massive obesity, the benign aspect of adipose tissue expansion prevails, along with preserved insulin sensitivity. In contrast, the reduction in mitoNEET expression improves mitochondrial respiratory capacity by enhancing iron content in the stroma, which ultimately corresponds to a reduction in weight gain on an HFD. However, this exceeding enhancement in mitochondrial respiratory capacity leads to increased oxidative stress in adipocytes and subsequent glucose intolerance. Apparently, regulating mitoNEET to maintain mitochondrial

homeostasis holds the potential of treating obesity and insulin resistance (268).

New perspectives reveal that proteins that regulate changes in mitochondrial dynamics play an essential role in the browning of WAT. For instance, DRP1, which drives mitochondrial fission, promotes mitochondrial uncoupling and thus contributes to the browning of human white adipocytes (411). Its absence in mouse adipose tissue reduces lipolysis and impairs the overall body energy expenditure (296). Mitochondrial fusion protein OPA1 also plays a crucial role in heat production and WAT browning (26, 404). It is shown that adipocyte-specific *Opal* deficiency inhibits the urea cycle and differentiation of preadipocytes into beige adipocytes, which is restored by fumaric acid supplementation (26). Moreover, mice lacking *Opal* in adipocytes have impaired adaptive thermogenesis, reduced cold-induced sWAT browning, and decreased resistance to diet-induced obesity (404). Furthermore, by balancing mitophagy and PGC-1 α -mediated mitochondrial biogenesis in white adipocytes, Parkin can modulate mitochondrial homeostasis, suggesting that it is a potential therapeutic target in adipocytes to combat obesity and obesity-related diseases (353). However, mitophagy has been shown to facilitate the clearance of mitochondria during the transition from beige to white adipocytes, hence restricting the thermogenic competence of these cells. Therefore, suppression of mitophagy to preserve beige adipocytes may have therapeutic potential (564). In the transitional phase, the autophagic pathway is essential for mitochondrial clearance from beige to white adipocytes. Autophagy inhibition by thermogenic adipocyte-specific deletion of autophagy-related 5 (*Atg5*) or autophagy-related 12 (*Atg12*) prevents loss of beige adipocytes after withdrawal of external stimuli, maintains high thermogenic capacity, and prevents diet-induced obesity and insulin resistance (9). Earlier studies with adipocyte-specific knockout of *Atg7* have identified the effect of autophagy on adipose tissue metabolism, demonstrated by leaner mice with reduced white adipose mass and enhanced insulin sensitivity. An increase in browning signatures characterizes WAT in *Atg7* knockout mice. BAT function is also enhanced by *Atg7* deletion. A profound increase in fatty acid β -oxidation rates and a decrease in body mass are observed. *In vitro* experiments have confirmed the above *in vivo* observations by inhibiting autophagy or lysosomal function with inhibitors or knocking down *Atg7*. Considering the crucial role of mitophagy/autophagy in mediating the reversal of the browning process, inhibiting the autophagy pathway rather than activating it might be more promising for improving adipose function and obesity (608).

In large-scale population and mouse analyses, estrogen receptor 1 (ESR1) expression in adipose tissue is shown to be negatively correlated with adiposity and positively correlated with genes involved in mitochondrial metabolism and metabolic health parameters. In adipocyte-specific *Esr1* knockout mice, the study proves that ESR1 regulates adipocyte mitochondrial function. The deletion of ESR1

markedly decreases the expression of Polg, a unique mammalian mtDNA polymerase currently known to be engaged in the duplication of the mitochondrial genome, and results in a significant reduction in the mtDNA copy number in white adipocytes (619).

8-Oxoguanine DNA glycosylase (OGG1), located both in the nucleus and mitochondria, is an enzyme that identifies and cleaves the most common oxidatively induced DNA lesion, 8-oxo-7,8-dihydroguanine (8-OXOG) (367). Studies found that mice overexpression of mitochondrially targeted OGG1 display reduced inflammation in adipose tissue, lower body weight, and higher insulin sensitivity, mediated by the improved mitochondrial respiration in WAT (255).

In addition, Notch, which governs cell fate in development, is also involved in the browning of WAT. The research found that *Notch* deletion in adipose tissues contributes to the browning of WAT with increased expression of UCP1 and enhanced levels of mitochondrial density (42). Modulation of Notch activity might hold the potential to impact white adipocyte mitochondrial function positively.

While adipocyte-specific overexpression of *App* suppresses mitochondrial respiration by clogging the protein import channel, the ablation of *App* in adipocytes restores the damaged mitochondrial function. It exerts a marked beneficial effect on reducing body weight gain and systemic metabolic insufficiency. In addition, adipose tissue APP elevation has been observed in human obesity, diabetes, and other metabolic diseases, which implies that inhibition of APP in adipocytes has a great potential to develop into a metabolic disorder treatment (11).

A downstream effector of β 3-AR signaling in WAT, cyclooxygenase-2 (COX-2) is a rate-limiting enzyme in prostaglandin synthesis and necessary for browning of WAT. The overexpression of COX-2 in WAT and the differentiation of mesenchymal progenitors toward a brown adipocyte phenotype by prostaglandins lead to brown adipogenesis in WAT, enhance energy expenditure, and protect mice from HFD-induced obesity (523).

Constitutively active Gq protein expression in mice lowers UCP1 expression in BAT, energy expenditure, and the quantity of brown-like/beige cells in WAT. Additionally, Gq expression in human WAT shows an inverse relationship with UCP1 expression (249).

PTEN is a bispecific phosphatase with protein phosphatase activity and lipid phosphatase activity (368). Through manipulating PTEN expression in a single adipose depot using a unique delivery system (a two-cassette, adipose-specific rAAV-Rec2 vector that delivers Cre recombinase to inguinal WAT in *Pten*^{fllox/fllox} mice), researchers reported that specific unilateral *Pten* knockout of inguinal WAT enhances beige adipocyte markers, including UCP-1 and PGC-1 α (199).

Conclusions and Future Perspectives

Obesity has become an epidemic, and white adipocytes are at the forefront of obesity pathophysiology. Despite having

a limited number of mitochondria, the contribution of these organelles to adipose health is receiving increasing attention. Mitochondria function as the “powerhouse” of adipocytes and play crucial roles in white adipocyte differentiation, glucose and lipid homeostasis, adipokine and mitokine secretion, and protection from stress. Dysfunctional mitochondria can deleteriously affect white adipocyte health and lead to obesity-related issues. Recent translational discoveries have shown that improving mitochondrial health through various therapeutic avenues can promote white adipocyte browning and maintain functional adipocytes. These therapeutic avenues hold enormous potential to be developed into treatments for obesity and associated metabolic diseases in humans.

Progress on elucidating the critical role of mitochondria in white adipocyte homeostasis brings plenty of excitement to the field, but many knowledge gaps remain when looking forward.

1. Firstly, recent advances in single-cell sequencing allow researchers to depict the mature white adipocyte heterogeneity, and the results point out that mitochondrial function might be a critical determinant of adipocyte heterogeneity. However, the mechanisms mitochondria essentially drive white adipocyte heterogeneity remain unknown; the relationships among distinct subpopulations determined by distinct mitochondrial function remain unexplored; and finally, how these distinct subpopulations of white adipocyte behave during obesity development remains unresolved.
2. Secondly, the complexity of mitochondrial regulation of lipid homeostasis in white adipocytes is not fully understood. While mitochondria provide necessary substrates for *de novo* lipogenesis, on the other hand, the breakdown of triglycerides—lipolysis—is also dictated by mitochondria-generated energy levels. Fat storage is considered the fundamental role of white adipocytes, but excessive fat accumulation is further appreciated as a hallmark of obesity. Thus, the coordination between lipogenesis and lipolysis by mitochondrial regulation needs further investigation to fully understand how to maintain cellular and systemic lipid homeostasis.
3. Thirdly, mitochondrial quality control programs have been investigated in other cell types relatively intensively. However, they are not well described in white adipocytes. Future efforts are warranted to identify the essential contributions of mitochondrial quality control programs, including mitophagy and UPR_{mt}, to adipocyte health. Furthermore, how white adipocytes cope with mitochondrial stress needs to be elucidated.
4. Fourthly, previous research of decades has uncovered the importance of white adipocyte-derived adipokines in communicating with other cells, tissues, and organs and maintaining systemic energy homeostasis. An emerging area of mitochondria-derived signals, particularly mitokines,

is welcomed by the field. Using white adipocyte-specific mitochondrial dysfunction models, novel mitokines that are secreted in response to mitochondrial stress conditions and their functions in metabolism are expected to be discovered. More interestingly, an intriguing release of mitochondria organelles via extracellular vesicles has been described in mitochondrially stressed white adipocytes, and these ejected mitochondria are shown to exert a mitohormesis signaling role in remote organs (103). These new and exciting findings further expand the horizons of white adipocyte mitochondria-derived signal studies.

5. Lastly, how to translate the basic research of white adipocyte mitochondria into therapeutic applications remains challenging. The treatment window for a therapeutic intervention to correct mitochondrial dysfunction needs to be determined. By far, therapeutic methods evaluated *in vitro* or *in vivo* mainly focus on enhancing mitochondria biogenesis and quantity to transform white adipocytes into brown/beige adipocytes. Other mechanisms of mitochondrial protection need to be utilized to develop novel therapeutic avenues against mitochondrial defects. Last but not least, moving these findings from cell culture and rodent models to human applications requires extensive time and resource investments.

In conclusion, the role of mitochondria in white adipocyte homeostasis is a complex and rapidly evolving field, and future research will continue to expand our understanding of the mechanisms underlying the pathophysiology of obesity and the potential therapeutic avenues to treat it.

Related Articles

- Accumulation and Release of Chemicals by Adipose Tissue Adiposity
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Acknowledgements

This work is supported by National Institutes of Health (NIH) grants K01-DK125447, R03-DK135783, and P30-DK056338 (Pilot Award) to Y.A.A. and American Diabetes Association (ADA) Postdoctoral Fellowship Award 11-23-PDF-23 to F.W. We apologize for the omission of any relevant references due to page limitations.

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