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Review

# Mitochondrial regulation and white adipose tissue homeostasis

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**The important role of mitochondria in the regulation of white adipose tissue (WAT) remodeling and energy balance is increasingly appreciated. The remarkable heterogeneity of the adipose tissue stroma provides a cellular basis to enable adipose tissue plasticity in response to various metabolic stimuli. Regulating mitochondrial function at the cellular level in adipocytes, in adipose progenitor cells (APCs), and in adipose tissue macrophages (ATMs) has a profound impact on adipose homeostasis. Moreover, mitochondria facilitate the cell-to-cell communication within WAT, as well as the crosstalk with other organs, such as the liver, the heart, and the pancreas. A better understanding of mitochondrial regulation in the diverse adipose tissue cell types allows us to develop more specific and efficient approaches to improve adipose function and achieve improvements in overall metabolic health.**

## Highlights

Regulation of mitochondrial activity in white adipocytes is an essential component of adipose tissue and systemic metabolic homeostasis.

Additional cells in adipose tissue (progenitors, endothelial cells, immune cells) are also critically regulated by mitochondrial activity in the respective cells.

Intercellular and interorgan exchange of mitochondria is an important new mechanism of information exchange between cells and tissues.

A key feature of the regulation of mitochondrial activity in adipose tissue is the choice of the preferred carbon source in the respective cells within adipose tissue, that is, use of carbohydrate through glycolysis versus use of lipids for oxidative phosphorylation.

The choice of substrate for energy production exerts a profound impact on the characteristic metabolic features of the various cell types that make up adipose tissue and their impact on tissue and systemic energy homeostasis.

## Overview of adipose tissue remodeling

Adipose tissue remodeling is a complex process involving multiple cell types, including adipocytes, adipocyte progenitors, endothelial cells, and immune cells. Although dominating in terms of volume contribution, adipocytes account for less than 50% of cellular content in a WAT depot. Among the nonadipocyte fractions, approximately 55% are APCs ($CD31^{-}CD45^{-}CD34^{+}$), 37% are immune cells, and 8% are endothelial cells in human WAT [1,2]. This cellular homeostasis is delicately regulated upon various metabolic challenges. However, the cell types and mechanisms that account for initiating adipose remodeling remain to be defined. Adipocytes, however, display a rapid reaction in response to excess caloric intake. Hypertrophy (an enlargement in cell size) and hyperplasia (an increase in cell number by *de novo* adipogenesis) are the main mechanisms of adipocyte plasticity. As short as 3 days of high-fat diet (HFD) feeding can lead to an increase in tissue mass and adipocyte size in visceral WAT (VWAT) in mice, concomitant with macrophage infiltration, inflammation, and insulin resistance [3]. Hyperplasia in VWAT appears within 4–7 days of HFD exposure and is independent of adipocyte hypertrophy, as it occurs in young and old mice [4,5]. Of note, adipose tissue remodeling occurs in a depot-specific manner [6], as hyperplasia is mainly observed in VWAT and to a much lesser extent in subcutaneous WAT (SWAT). This is despite the fact that both VWAT and SWAT increase in mass and display insulin resistance. Likewise, distinct patterns of adipose inflammation and extracellular matrix remodeling are also observed in different fat pads [7,8]. These depot-specific features are likely due to the local microenvironment, as well as the cellular and functional heterogeneity of the adipose progenitor pool [9,10].

Mitochondria play an essential role in cellular bioenergetics and signaling transduction. Different types of adipocytes, including white, beige, and brown adipocytes, exhibit distinct mitochondrial abundance, function, and plasticity [11]. Brown adipocytes contain a high density of mitochondria with remarkable thermogenic potential. Conversely, white adipocytes, as the primary lipid-storing cells, have fewer mitochondria. Beige adipocytes are heterogeneously distributed within WAT,

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are recruited from distinct beige progenitor pools, or may even undergo transdifferentiation from white adipocytes. In the process, these beige cells display notable increases in mitochondrial activity and thermogenesis [11,12]. Moreover, adipocytes can lose their cellular identity and exhibit myofibroblast-like features with mitochondrial deficits upon long-term HFD feeding [13,14]. Although mitochondrial function in WAT is far less studied compared with brown adipocytes, the critical role of mitochondria in controlling adipose tissue function and systemic metabolic homeostasis is increasingly appreciated, far beyond the basic energetic roles seen for cellular homeostasis in many other cell types. Mitochondrial function in adipocytes and other cell types in adipose tissue, including APCs and ATMs within WAT, exerts a profound effect on tissue dynamics, cellular function, and intercellular communication (Figure 1). Thus, adipose tissue mitochondria have the ability to integrate systemic metabolic cues and facilitate adaptive adipose tissue remodeling to maintain overall metabolic health in the entire system. Here, we review our current knowledge about the role of mitochondria in adipose tissue remodeling. We focus on the mitochondrial role in APCs, adipocytes, and ATMs. In addition, we will briefly discuss the mitochondrial role in cell–cell communication within adipose tissues and distal organs.

## Regulation of mitochondrial activity in white APCs

APCs are residing in the reticular interstitium within adipose tissue [15,16]. These cells have an essential role for proper WAT remodeling in terms of adipogenesis, inflammation, and lipid handling under physiological and pathophysiological conditions. Adipogenesis is simultaneously accompanied by increased mitochondrial biogenesis, activity, and reactive oxygen species (ROS) production [17,18]. Accordingly, the differentiation process reprograms the energy status from glycolytic to oxidative metabolism, and thus acquires and maintains a mature adipocyte phenotype [19]. In this regard, a large number of studies suggest that a dysfunction of mitochondrial metabolism or a dysregulation of ROS production, either by genetic manipulation of mitochondrial components or by pharmacological inhibitors, is sufficient to alter adipogenesis, particularly in cultured preadipocyte cell lines or in the stromal vascular fraction (SVF) of adipose tissues [20–22]. However, with the recent discoveries of distinct classes of APCs, more precise and specific studies on their lineage potential and function have been possible, particularly in the context of depot-specific settings.

The adipose tissue mesenchymal stem cell pool represents a dynamic and heterogeneous set of cells [23,24]. With the advances of single-cell transcriptomics, different types of APCs and adipose regulatory progenitor cells (ARCs) have been described in different WAT depots in rodents and humans. The heterogeneity of adipose progenitors seems to be dependent on age, metabolic status, and the depot-specific microenvironment. In murine SWAT, different adipogenic cell populations are described, including PDGFRβ$^{+}$DPP4$^{-}$ APCs, CD142$^{high}$ APCs, as well as committed preadipocytes [15,23–25]. By contrast, in murine VWAT, APCs can be defined as PDGFRβ$^{+}$LY6C$^{-}$ CD9$^{-}$ cells [23]. In parallel, ARCs can also be specified, including PDGFRβ$^{+}$LY6C$^{+}$ cells that correspond to fibroinflammatory progenitors (FIPs) in VWAT [23] and interstitial DPP4$^{+}$ cells [15] and aging-dependent adipogenic Fmod$^{+}$ fibroblasts (AFFs) [25] in SWAT. These regulatory cells are more reluctant to undergo adipogenesis and are involved in adipose tissue inflammation and extracellular matrix remodeling. For instance, FIPs provoke an inflammatory response and reduce the adipogenic capability of APCs in a paracrine manner [23]. Moreover, FIPs activate inflammatory cascades through a Toll-like receptor (TLR) 4-dependent manner shortly after a HFD challenge is initiated in mice and further promote adipose tissue inflammation and insulin resistance [26], highlighting their significant impact on cell–cell interactions during adipose remodeling. As compared with APCs, FIPs have a much greater mitochondrial activity and exhibit higher metabolic rates in response to fatty acid treatment in cultures or upon an acute stimulus with HFD *in vivo* [27]. As such, the distinct metabolic properties in the progenitors have an important effect on their role in adipose tissue remodeling.

## Glossary

**Acetaminophen-induced liver injury:** a common drug-induced acute liver damage model caused by acetaminophen overdose, resulting in excessive mitochondrial oxidative stress, inflammation, and hepatocyte dysfunction.
**HOMA-IR:** It is a widely used indicator of insulin resistance.
**Mitohormetic:** the beneficial role of mitochondrial stress (e.g., reactive oxygen species) at a reduced level that protects cells against harmful insults.
**Rosiglitazone:** an agonist of the nuclear receptor, peroxisome proliferator-activated receptor-γ (PPARγ), the key transcription factor for adipocyte differentiation. Treatment of rosiglitazone improves hyperglycemia and insulin resistance in obesity.

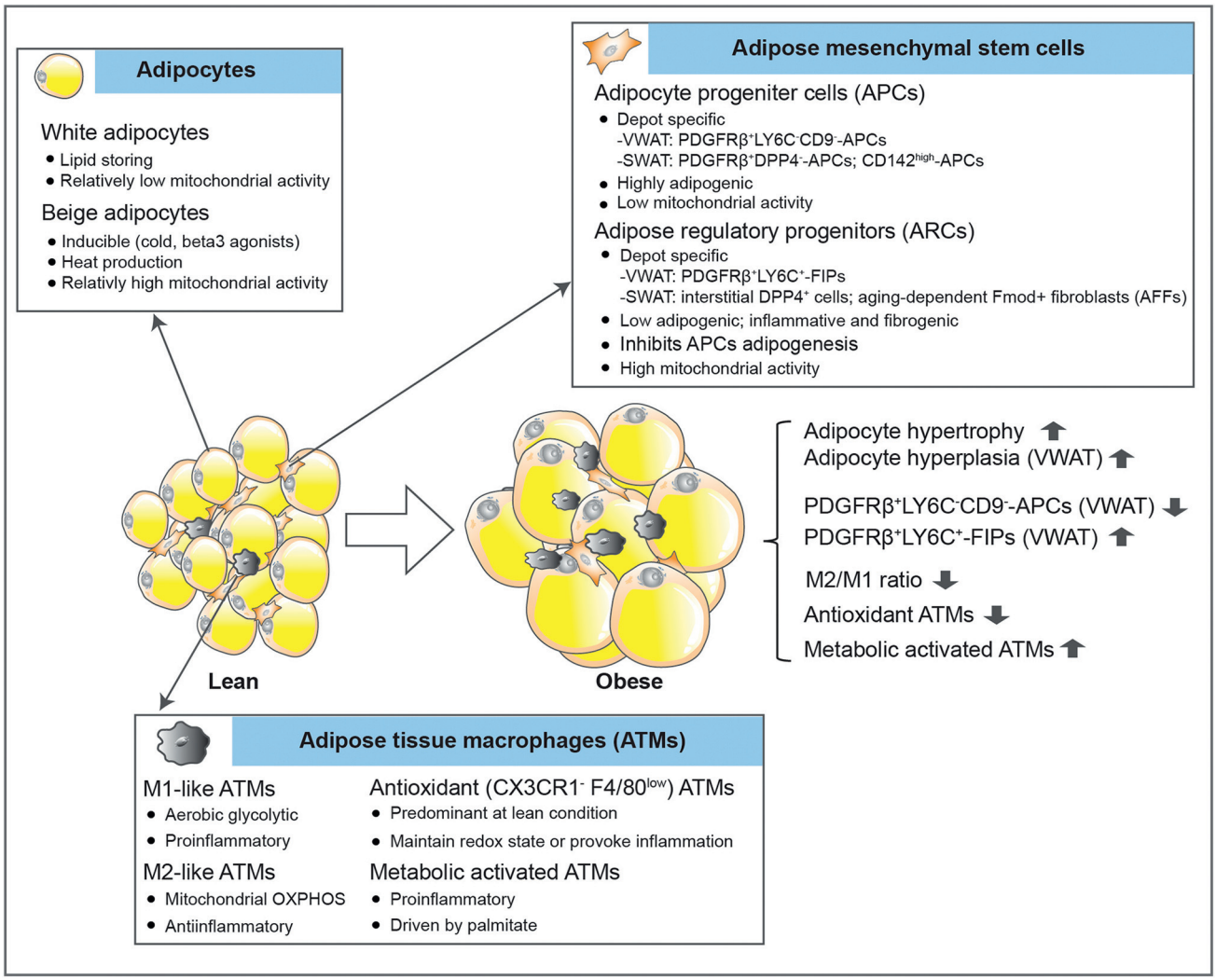


Figure 1. Intracellular homeostasis in white adipose tissue. Abbreviations: APC, adipocyte progenitor cell; FIP, fibroinflammatory progenitor; OXPHOS, oxidative phosphorylation; sWAT, subcutaneous white adipose tissue; VWAT, visceral white adipose tissue.

In fact, recent findings highlight mitochondrial metabolism as a critical factor in determining the cell lineage fate and function of APCs. Impaired mitochondrial activity (with a physiologically relevant reduction obtained through ectopic expression of the protein mitoNEET, an outer mitochondrial membrane protein that regulates oxidative capacity [28]) has a profound effect on the behavior of adipose progenitors in mice [27]. Specifically, mitoNEET in PDGFRβ$^+$ cells enhances an inflammatory response in FIPs and suppresses the adipogenic capacity in APCs in VWAT. Moreover, mitoNEET rapidly shifts the ratio of FIPs to APCs at the onset of diet-induced obesity, with an increase in FIPs and a concomitant decrease in APCs in VWAT [27]. This mitochondrial regulation is a common feedback mechanism, as it also occurs in PDGFRβ$^+$DPP4$^+$ and PDGFRβ$^+$DPP4$^-$ progenitors in SWAT, regardless of the depot-specific gene signatures of the APCs. As a result, suboptimal mitochondrial function in progenitor cells leads to adipose tissue inflammation, partial lipodystrophy, and resulting hepatosteatosis in mice, and this process is reversible upon reconstituting full mitochondrial function [27].

Multiple types of APCs have been described in both VWAT (omental) and SWAT (abdominal) from obese subjects, with a common molecular signature and similar adipogenic potential [2]. However, these studies have been largely limited to obese patients who received cosmetic surgery or bariatric bypass surgery rather than healthy lean individuals. In the single-cell transcriptomic analyses, there is only limited overlap among APCs between VWAT and SWAT by cell clustering [2], similar to the situation in murine fat depots [24], further highlighting the heterogeneity of the adipose progenitor pool. In addition, different APC subtypes exhibit distinct metabolic and endocrine features [29]. Of note, subpopulations of APCs significantly change with an altered metabolic disease status, for example, as a function of fasting glycemia and homeostatic model assessment of insulin resistance (**HOMA-IR**) (see Glossary). Among these cell populations, a subset of $CD34^{-}$ APCs derived from SWAT displays a high level of enrichment of thermogenic and mitochondrial markers and is committed to beige adipogenesis upon differentiation [29]. Moreover, beige adipocytes can be derived from pluripotent stem cells [30,31]. As such, it is possible that mitochondrial function also contributes to lineage commitment and function of some subtypes of human adipose progenitors.

## Mitochondrial role in determining adipocyte function

Despite the relatively low abundance of mitochondria in white adipocytes, in recent years, numerous studies have highlighted the important role of mitochondria in maintaining white adipocyte function and health. Mitochondrial dysfunction in white adipocytes is considered a hallmark of obesity [32]. It is not surprising that mitochondrial activity is heterogeneous among distinct fat depots. In rodents, adipocytes have a higher respiratory capacity, with a higher mitochondrial respiratory chain content in SWAT compared with VWAT. By contrast, VWAT displays increased ROS production compared with SWAT [33]. In humans, lean body mass is associated with a higher mitochondrial respiratory capacity, paralleled by an increase in mitochondrial number in SWAT [34]. In addition, mitochondrial activity in white adipocytes declines with aging. For instance, the mitochondrial complex IV component COX5B was significantly repressed along with aging-induced adipocyte enlargement, in a hypoxia-inducible factor 1-alpha (HIF1α)-dependent manner [35]. Moreover, an age-dependent reduction in COX5B gene expression was also observed in human WAT, implicating a conserved mechanism of mitochondrial decline in rodents and humans [35]. However, other reports have come to different conclusions. A recent study argued that HFD feeding did not impair adipocyte mitochondrial respiratory capacity when normalized to adipocyte cell size and/or number. Nevertheless, increased mitochondrial ROS was shown to be an enduring characteristic within WAT exposed to both short-term and long-term HFD challenges [36].

In the past few years, studies using rodent models carrying genetic manipulations of mitochondrial components greatly expanded our insights about mitochondrial regulation of adipocyte function. Peroxiredoxin 3 (Prx3), a thioredoxin-dependent mitochondrial peroxidase, is abundantly expressed in white adipocytes and reduced in the obese state. Deletion of *Prx3* impaired mitochondrial biogenesis and enhanced oxidative stress in adipocytes, and further caused systemic glucose intolerance and insulin resistance [37]. Paraoxonase 2 (PON2) is a lactonase that primarily locates to the endoplasmic reticulum and to mitochondria. Deletion of *PON2* lowered mitochondrial respiration and resulted in adipocyte hypertrophy in WAT, and thus promoted diet-induced obesity [38]. Mitochondrial ferritin (FtMT) is a mitochondrial matrix protein and plays a key role in iron balance. A critical role of FtMT in adipocyte mitochondrial function and energy metabolism is apparent during obesity. Adipocyte-specific overexpression of FtMT enhanced local ROS damage and caused lipodystrophy and insulin resistance [39]. In addition, deletion of *Hsp60*, a key mitochondrial matrix chaperone, reduced mitochondrial respiration and caused insulin resistance locally in VWAT. However, these mice exhibited a systemic benefit in weight gain and glucose metabolism likely due to enhanced adipocyte hyperplasia [40].

Furthermore, mitochondrial transporters located on the outer and inner membranes are major components that are essential for mitochondrial function. Specific roles of such transporters in white adipocyte function are increasingly appreciated. The mitochondrial dicarboxylate carrier (mDIC; or SLC25A10) is highly expressed in white adipocytes [41]. In adipocytes, mDIC controls lipolysis through export of the tricarboxylic acid (TCA) cycle intermediate succinate from mitochondria to the cytosol. As a result, a specific deletion of *mDIC* in adipocytes leads to unconstrained fatty acid release and subsequent hepatic lipotoxicity [42].

In addition to the aforementioned mitochondria-resident factors, proteins mistargeted to mitochondria could also lead to alterations in adipocyte mitochondrial function. In 2019, an unexpected role of amyloid precursor protein (APP) in mitochondrial impairment was identified due to its unconventional mislocalization in adipocyte mitochondria. This mislocalization of APP significantly comprised mitochondrial protein import and reduced mitochondrial respiration, eventually promoting obesity [43]. A recent study further echoed the importance of APP in regulating adipocyte mitochondrial function. Deletion of Irx5, a homeobox transcription factor, protected mice from diet-induced obesity by enhancing adipose metabolic machinery due to APP reduction in white adipocytes. In addition, a knockdown of *App* significantly increased mitochondrial respiration in adipocytes [44]. Thus, targeting APP might provide a powerful therapeutic approach to improve adipocyte function and diet-induced obesity. Another example for unconventional mitochondrial localization in adipocytes is forkhead box protein O1 (FoxO1). FoxO1 is not exclusively located in the cytosol or nucleus in adipocytes; it is also located in mitochondria where it binds to mitochondrial DNA (mtDNA). Under starvation conditions, FoxO1 is dephosphorylated and then shuttled from mitochondria to the nucleus. Therefore, FoxO1 could be considered a nutrient-stress sensor and a mitonuclear communicator in white adipocytes [45].

Mitochondria are not only regulated by components located in mitochondria, but there are also additional intracellular and extracellular factors that are indispensable for maintaining mitochondrial health in adipocytes. These factors mainly fall into the categories of epigenetic factors [46–48], miRNAs [49,50] and long noncoding RNAs (lncRNAs) [51,52], inflammatory molecules [53,54], hormones [55–60], and other factors [61–64] (summarized in Table 1).

## Mechanisms defending mitochondrial function in adipocytes

Mitochondrial dysfunction in white adipocytes is not always associated with obesity and metabolic deficiency. In a model of adipose-specific deletion of fumarate hydratase (FH), despite severe abnormalities in mitochondria and depletion of ATP, these mice were protected from obesity and insulin resistance. However, this improvement was diminished under thermoneutral conditions [64]. In another study, Han *et al*. demonstrated that adipocyte-specific deletion of manganese superoxide dismutase (MnSOD) activated mitochondrial biogenesis and enhanced mitochondrial respiration, thereby protecting from diet-induced obesity and insulin resistance, possibly through a robust adaptive response [65]. Different pathways mediate such adaptive responses to mitochondrial stress and are involved in mitochondrial quality control through mechanisms related to mitophagy and secretion of stress signals.

### Mitophagy

Mitophagy, a process that selectively clears damaged mitochondria, is an essential quality control mechanism for mitochondrial homeostasis. FUNDC1 is a newly defined mitophagy receptor, and *Fundc1* deficiency causes defective mitophagy in adipocytes, enhances adipose tissue inflammation, and exacerbates diet-induced obesity [66]. Although mitophagy is essential for adipocyte mitochondrial quality control, the classical mediator of mitophagy, parkin, is dispensable for mitochondrial regulation in adipocytes, suggesting a parkin-independent mitochondrial quality control

Table 1. Factors that maintain mitochondrial health in adipocytes

| Factor | Function in regulating white adipocyte mitochondria | Function on adipocyte function and/or WAT homeostasis | Refs |
|---|---|---|---|
| Epigenetic factors | | | |
| DNA methyltransferase 1 (DNMT1) | DNMT1 is a major DNA methylation mediator. Deletion of *Dnmt1* in adipocytes inhibits mitochondrial fission. | Deletion of *Dnmt1* in adipocytes promotes adipocyte hypertrophy and WAT dysfunction. | [46] |
| N-acetyltransferase 2 (NAT2) | Human NAT2 regulates insulin resistance. Deletion of the mouse ortholog *Nat1*, both *in vitro* in 3T3-L1 adipocytes and *in vivo* in adipocytes, promotes mitochondrial dysfunction by increasing intracellular ROS levels, enhancing mitochondrial fragmentation, and decreasing mitochondrial respiration. | *Nat1*-deficient mice show a decreased ability to utilize fat for energy and a decrease in basal metabolic rate without affecting thermogenesis. | [47] |
| Sirtuin-3 (SIRT3) | The deacetylase SIRT3 is a key player in mitochondrial biology. However, adipocyte SIRT3 is dispensable for maintaining mitochondrial function in adipose tissues and whole-body energy homeostasis, since lack of *Sirt3* in adipocytes does not alter mitochondrial respiration. | Lack of *Sirt3* has no impact on systemic glucose and lipid metabolism. | [48] |
| miRNAs | | | |
| miR-494-3p | miR-494-3p regulates mitochondrial biogenesis and thermogenesis in WAT. | miR-494-3p mediates the browning of WAT. | [49] |
| miR-30a | miR-30a modulates human adipocyte mitochondrial function by regulating the expression of ubiquitin carrier protein 9 (*Ubc9*). | Enforced expression of a miR-30a mimic promotes browning of human white adipocytes. | [50] |
| Long noncoding RNAs (lncRNAs) | | | |
| Blnc1 | Overexpression of Blnc1 in VWAT via adenovirus increases mtDNA content and enhanced expression of mitochondria-related genes via stimulating the transcription of *Pgc1b*. | The lncRNA blnc1 protects against diet-induced obesity in mice. | [51] |
| AK079912 | Overexpression of lncRNA *AK079912* in white preadipocytes increases thermogenesis-related genes, whereas inhibition of AK079912 reduces mtDNA copy number and mitochondrial electron transport chain (ETC) complex protein levels in white adipocytes. | Knockdown of *AK079912* inhibits browning of white adipocytes, as judged by a reduction in brown fat-specific genes. | [52] |
| Inflammation molecules | | | |
| CD47 | CD47 is a transmembrane receptor functioning in self-recognition and immune cell infiltration. In white adipocytes, CD47 regulates lipolysis and mitochondrial fuel availability. | CD47 enhances energy expenditure in mice. | [53] |
| Bone morphogenetic protein receptor type 2 (BMPR2) | In white adipocytes, deletion of the inflammation factor, *BMPR2*, impaired fatty acid oxidation and oxidative phosphorylation. | Deletion of *BMPR2* reduces white adipocyte lipolysis and enhanced apoptotic cell death. | [54] |
| Hormones | | | |
| Prostaglandin E | Deletion of prostaglandin E receptor subtype 4 (*EP4*) in white adipocytes increases mitochondrial biogenesis and oxidative phosphorylation. | Deletion of *EP4* positively regulates healthy WAT remodeling and promotes fat mass loss in mice. | [55] |
| Brain-derived neurotrophic factor (BDNF) | BDNF, a neuronal factor, enhances white adipocyte mitochondrial biogenesis and thermogenesis through sympathetic activation in mice. In differentiated 3T3-L1 adipocytes, BDNF administration enhances mitochondrial fission, increases browning markers, and alters mitochondrial dynamic genes. | BDNF exerts an important role in promoting white adipocyte browning *in vitro*. | [56] |
| Estrogen [estradiol (E2)] | E2 promotes mitochondrial function through activating of both G protein-coupled estrogen receptor (GPER) and estrogen receptor α (ERα). In addition, ERα regulates the mtDNA polymerase γ subunit Polg1 to maintain mitochondrial function in white adipocytes. Deletion of ERα (*Esr1*) in adipocytes reduces mtDNA content and decreases mitochondrial activity in an E3 ubiquitin ligase parkin-dependent pathway. | E2 prevents inflammation in white adipose tissue. | [57,58] |
| Testosterone | Testosterone exerts opposite effects compared with E2, resulting in decreased mitochondrial biogenesis in white adipocytes. | Testosterone further decreases adiponectin production in white adipocytes. | [59] |
| Betatrophin | Betatrophin is a negative regulator of white adipocyte mitochondrial biogenesis. Knockdown of *Betatrophin* increases mitochondrial content and mitochondrial biogenesis markers through the activation of the AMPK signaling pathway. | Downregulation of betatrophin induces a browning process in white adipocytes. | [60] |

Table 1. (continued)

| Factor | Function in regulating white adipocyte mitochondria | Function on adipocyte function and/or WAT homeostasis | Refs |
|---|---|---|---|
| Others | | | |
| Biliverdin reductase A (BVRA) | Adipocyte-specific deletion of *BVRA*, a protein highly expressed in the spleen and liver, decreases the number of mitochondria in white adipocytes. | Adipocyte-specific deletion of *BVRA* promotes adipocyte hypertrophy and obesity. | [61] |
| ESRRG and PERM1 | ESRRG and PERM1 are two key regulators of the PGC1α transcriptional network, which positively regulates mitochondrial function during cold exposure. | ESRRG and PERM1 are essential for browning of white adipocytes. | [62] |
| Caloric restriction (CR) | In white adipocytes, CR enhances mitochondrial biogenesis via a leptin signaling-dependent Srebp-1c/FGF21/Pgc1α axis. | CR improves whole-body metabolism and promotes healthy WAT remodeling. | [63,64] |

mechanism in these cells [67]. Mitofusin 2 (Mfn2), a key component involved in mitochondrial fusion and mitochondrion–endoplasmic reticulum interactions, is a crucial player in adiposity and body weight regulation. A knockdown of *Mfn2* specifically in mature adipocytes led to enhanced food intake, increased adiposity, and impaired glucose tolerance [68]. BCL2/adenovirus E1B 19-kDa protein-interacting protein 3 (BNIP3) has been suggested to be a mitochondrial quality regulator. In adipocytes, BNIP3 improves mitochondrial bioenergetics, particularly with **rosiglitazone** treatment [69]. In an independent study, the peroxisome proliferator-activated receptor-γ (PPARγ)–BNIP3 axis was further demonstrated to be a key factor mediating adipose mitochondrial reticulum fragmentation, thereby ameliorating oxidative stress, and improving insulin sensitivity [70]. The E3 ubiquitin ligase membrane-associated RING-CH-type finger 5 (MARCH5) is known to modulate mitochondrial dynamics and is also involved in regulating mitochondrial dynamics and cellular metabolism in adipocytes as well, likely in a PPARγ-dependent manner [71]. Heme oxygenase 1 (HO-1) is another important factor regulating mitochondrial bioenergetics through changing cellular heme-derived carbon monoxide and bilirubin. Deletion of *HO-1* in adipocytes significantly decreased the mitochondrial fusion–fission ratio, therefore promoting mitochondrial dysfunction and adipose tissue damage [72]. Autophagy pathways are also involved in mitochondrial function in adipocytes. For instance, ablation of autophagy in adipocytes through deleting *Atg3* or *Atg16L1* impaired mitochondrial function and enhanced lipid peroxidation, and initiated an adipose–liver crosstalk via lipid peroxide-induced Nrf2 signaling in mice. As a result, these mice developed impaired glucose tolerance and insulin resistance [73].

### Stress signal secretion

In an established model of adipocyte mitochondrial dysfunction, deletion of the essential mitoribosomal protein CR6-interacting factor 1 (*Crif1*) led to significantly impaired oxidative phosphorylation (OXPHOS) [74,75]. In *Crif1*-depleted adipocytes, angiopoietin-like 6 (Angptl6) and fibroblast growth factor 21 (FGF21) were identified as two associated secretory factors in response to mitochondrial stress, highlighting a potential protective role of the Angptl6–FGF21 axis during mitochondrial dysfunction in adipocytes [76]. In addition, another signal molecule GDF15 was also induced upon mitochondrial stress, as observed in adipocyte-specific FtMT-transgenic mice [39]. In response to mitochondrial stress in adipocytes, these mice displayed remarkable pancreatic β-cell hyperplasia, suggesting a potential adipocyte-to-pancreas interorgan signaling axis governed by mitochondrial function [39].

## Mitochondrial regulation in ATMs

Components of the adipose tissue immune system establish a unique microenvironment that is crucial for maintaining adipose homeostasis and metabolic health. Multiple types of adaptive and innate immune cells exist in WAT, including B cells, T cells, natural killer (NK) cells, innate

lymphoid cells (ILCs), dendritic cells (DCs), eosinophils, and macrophages. A recent study using single-cell transcriptomics provided a landscape of homeostatic and inflammatory networks in human healthy SWAT and also unveiled many distinct adipose tissue immune cell types, including subsets of ILCs, DCs, and macrophage populations that accumulate only in obese SWAT [77]. The distinct immunoregulatory mechanisms governing adipose physiology have been extensively reviewed previously [78–81]. Here, we focus mostly on the mitochondrial regulation, especially in ATMs.

ATMs are the numerically dominant immune cell type in WAT and display a high level of dynamic behavior, with a dramatic increase in the obese state (>50% of leukocytes) compared with the lean state (where they represent only 5–10% of leukocytes) [78,82,83]. Adipose tissue inflammation in obesity is considered to be associated with a switch from an anti-inflammatory M2 subtype toward a proinflammatory M1 phenotype. In addition, M1 macrophages are suggested to utilize aerobic glycolysis, whereas M2 macrophages rely more heavily on mitochondrial OXPHOS for energy demand [84]. In this regard, mitochondrial function has a critical role in this phenotypic conversion. Inhibition of OXPHOS prevents M1-to-M2 polarization as suggested in bone marrow-derived macrophages and peripheral blood monocyte-derived macrophages, whereas inhibiting nitric oxide production by inducible nitric oxide synthase (iNOS) inhibitors, which enhances mitochondrial function in M1 macrophages, improves M2 reprogramming [85]. Consistent with this, a deficiency of mitochondrial OXPHOS biases ATMs in VWAT toward a M1 polarization, adipose inflammation, and insulin resistance in obese mice carrying a myeloid-specific deletion of *Crif1*, an essential mitoribosomal factor for the biogenesis of OXPHOS subunits [86]. Conversely, increasing OXPHOS by GDF15 promotes a M2 phenotype and reverses insulin resistance [86].

However, major ATMs exhibit distinct mitochondrial energetics from the classic M1/M2 macrophages. For instance, ATMs isolated from lean VWAT exhibit a low metabolic rate with reduced OXPHOS and glycolysis, whereas ATMs from obese VWAT are highly energetically active with enhanced OXPHOS and glycolysis [87]. In line with these observations, both in obese (but not lean!) mice and humans, ATMs in VWAT and SWAT gain a phenotype that is molecularly and metabolically distinct from classic M1/M2 macrophages, driven by palmitate-mediated pathways, but independent of proinflammatory and anti-inflammatory pathways [88]. These metabolically activated ATMs can exert a proinflammatory effect and likely mediate an important role in buffering excess lipids during obesity [88]. By contrast, major ATMs in VWAT under lean conditions are defined as antioxidant macrophages ($CX3CR1^{-/}F4/80^{low}$), as opposed to M1/M2 macrophages [87]. Obesity leads to an increase in full-length and reduced truncated oxidized phospholipids (OxPLs) in WAT. Accordingly, the antioxidant ATMs adjust their bioenergetic status and antioxidant response, by sensing these OxPLs, to either maintain redox homeostasis or provoke inflammation [87]. As such, mitochondrial metabolism has an important role in regulating the phenotypic switch and function of different ATMs.

ATMs mediate adipocyte bioenergetics via paracrine mechanisms. Conditioned media (CM) from interleukin (IL)-10/transforming growth factor (TGF) β-activated macrophages ($CD163^{high}$/$CD40^{low}$) reduce ATP-coupled mitochondrial respiration by decreasing complex III activity, whereas CM from lipopolysaccharide (LPS)/interferon (IFN) γ-activated macrophages ($CD163^{low}$/$CD40^{high}$) enhance mitochondrial activity in human white adipocytes [89]. Thus, ATMs are critical mediators within the distinct microenvironment, exerting an important effect on adipose tissue energy homeostasis.

Thus, it is worth seeing whether targeting mitochondrial function in ATMs can modify their phenotype or function to improve adipose remodeling during obesity. To this end, a recent study

characterized a near-infrared heptamethine cyanine fluorophore (IR-61) that selectively targets ATMs in VWAT rather than other immune cells in fat or other tissues, such as the liver or spleen [90]. Indeed, IR-61 preferentially accumulates in ATM mitochondria and enhances mitochondrial OXPHOS by increasing mitochondrial complex content and activity via the ROS–Akt–Acly pathway [90]. As a consequence, IR-61 suppresses M1 macrophage activation and prevents adipose inflammation, weight gain, and insulin resistance in obese mice [90]. This pharmacological study however awaits confirmation through more classical genetic means.

## Mitochondrial regulation of cell-to-cell communication

As a central player in energetic metabolism across cell types, mitochondrial activity drives cell-to-cell communication locally in WAT (Figure 2), and mitochondrial activity can also carry effects to distal organs (Figure 3). Intercellular mitochondria transfer provides a common mechanism for

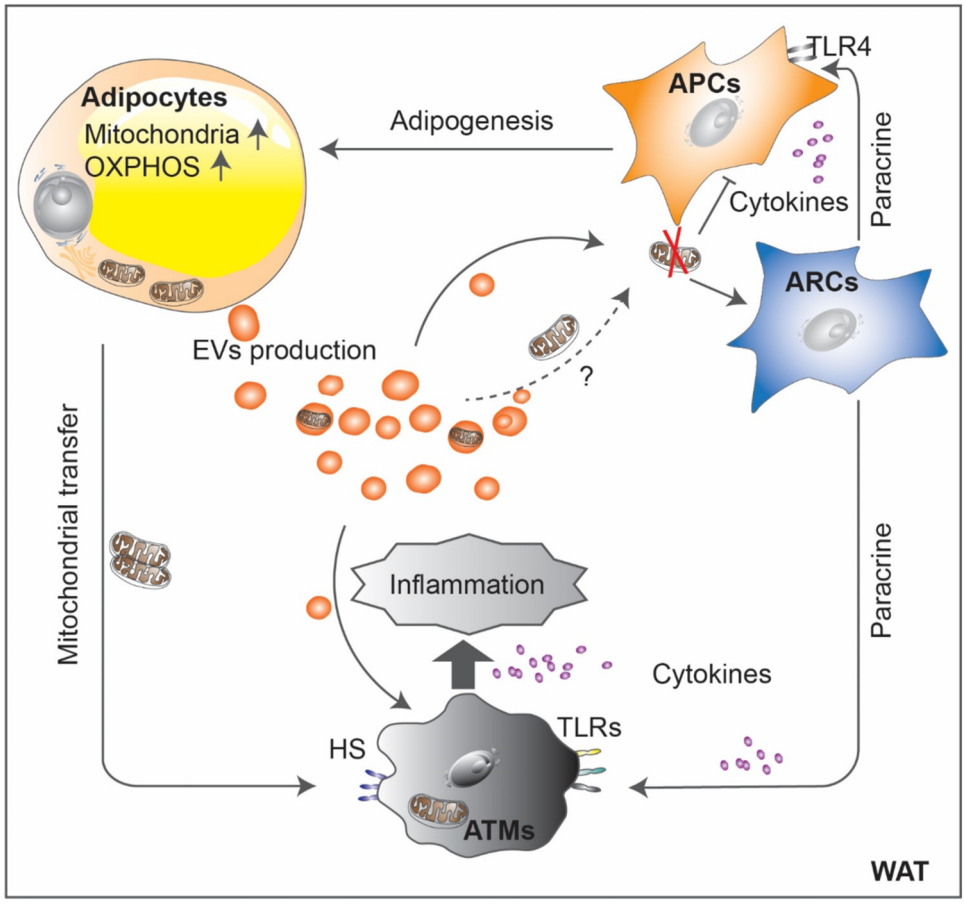


Figure 2. Mitochondrial regulation of intercellular communication in white adipose tissue. Adipocyte progenitor cells (APCs) differentiate into adipocytes and gain increased mitochondrial content and OXPHOS activity. Mitochondrial dysfunction reduces adipogenic potential of APCs, whereas it promotes the inflammatory effects of adipose regulatory progenitor cells (ARCs), which in turn inhibits adipogenesis and enhances inflammation in a cytokine-mediated paracrine manner. White adipocytes secrete extracellular vesicles (EVs) that link different adipose cell types such as progenitor cells and adipose tissue macrophages (ATMs) for adapting metabolic alterations. In addition, adipocytes directly transfer mitochondria to ATMs via a heparan sulfate (HS)-dependent mechanism. In obesogenic conditions, ATMs are activated toward proinflammatory polarization and further promote inflammation in WAT. Abbreviations: OXPHOS, oxidative phosphorylation; TLR, Toll-like receptor; WAT, white adipose tissue.

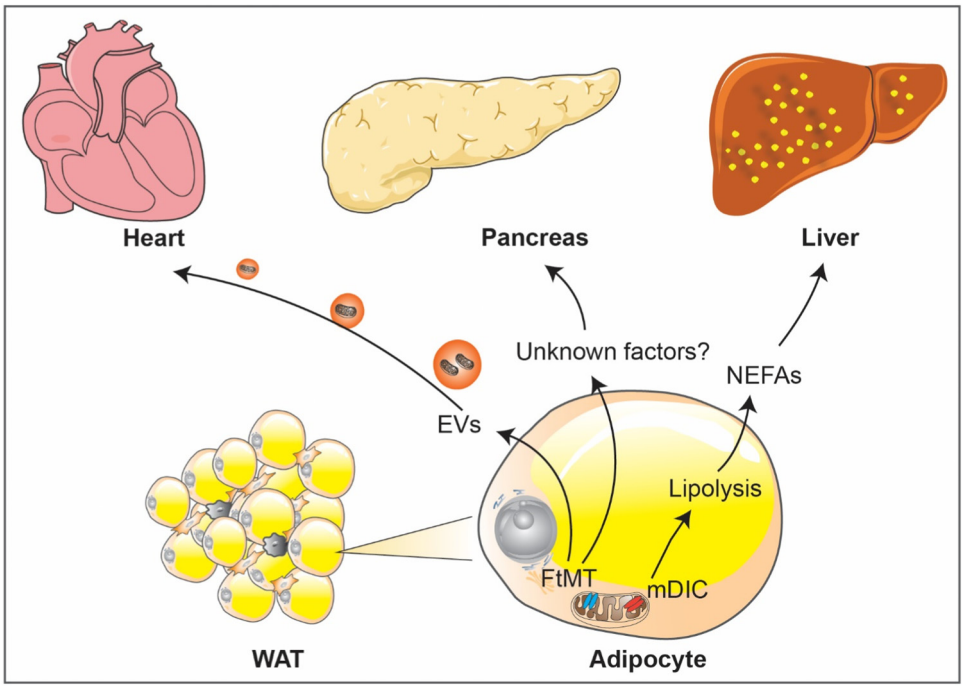


Figure 3. Mitochondrial regulation of white adipose tissue-derived interorgan communication. The mitochondrial dicarboxylate carrier (mDIC) controls lipolysis in adipocytes. Deletion of *mDIC* in adipocytes leads to unconstrained fatty acid release and subsequent hepatic lipotoxicity. Moreover, mitochondrial dysfunction in adipocytes, as seen in the adipocyte-specific mitochondrial ferritin (FtMT)-transgenic mice, promotes remarkable pancreatic β-cell hyperplasia by an unclear mechanism. In addition, adipocytes produce EVs carrying mitochondrial-derived components. In the FtMT-transgenic mice, compromised mitochondrial vesicles packaged into EVs that derived from adipocytes exert potent mitohormetic effects on cardiomyocytes by inducing mild ROS-mediated damage that preconditions the heart to more severe oxidative stress, such as in an ischemia/reperfusion model. Abbreviations: NEFAs, non-esterified fatty acids; WAT, white adipose tissue; EV, extracellular vesicle.

energetic synchronization that typically occurs in stem cells that often serve as 'the donor', toward other cell types, such as neurons, cardiomyocytes, epithelial cells, and macrophages [91]. This mitochondrial trafficking is important for multifunctional cellular activity during tissue homeostasis under various physiological and pathological conditions. For example, a recent study demonstrated that mitochondria transfer also occurs from adipocytes to ATMs via a heparan sulfate (HS)-dependent mechanism [92]. Moreover, this transfer is reduced in the obese state probably due to a phenotypic switch of macrophages [92]. In addition, myeloid-specific deletion of the HS biosynthetic gene *Ext1* decreases mitochondrial uptake in ATMs, increases adiposity, and reduces energy expenditure and glucose tolerance in mice [92]. Thus, this adipocyte-to-macrophage mitochondrial transfer exerts a vital role in maintaining metabolic homeostasis locally and systemically. However, it remains poorly understood how this transfer affects adipocyte and ATM functions and how it further translates into metabolic controls. Also, whether other cell types within the adipose stroma, such as APCs and epithelial cells, are also involved in this mitochondrial transfer event remains unexplored.

Adipocytes are an active source of extracellular vesicles (EVs), which modulate metabolism in adipose tissue and beyond, by facilitating intercellular or interorgan crosstalk [93,94]. For instance, extensive interchange of cellular material occurs between adipocytes and endothelial cells via EVs in response to metabolic signaling, such as fasting/refeeding and obesity [95]. Secreted EVs have a vital role in regulating mitochondrial dynamics. A number of studies

suggested that EVs from some cell types contain active and functional mitochondria or mitochondrial components, including mesenchymal stem cells [96,97], endothelial cells [98], monocytes [99], and adipocytes [100,101]. Accordingly, EVs carrying mitochondrial-derived components modify the energetic status of recipient cells and can compromise cellular functions. In the case of cardiomyocytes, mitochondrial vesicles packaged into EVs derived from compromised adipocytes exert potent **mitohormetic** effects on the heart by inducing mild ROS-mediated damage that precondition the heart to more severe oxidative stress, such as in the context of an ischemia/reperfusion assay [101]. Yet, mechanisms underlying the secretion and the targeting of mitochondria or mitochondrial components remain largely unknown and constitute a very fertile research area for the future.

Additional effects can be seen for 'mitotherapies' through administration of exogenous mitochondria intravenously, exhibiting significant benefits for hepatic function and oxidative metabolism in obese mice [102] or mice with **acetaminophen-induced liver injury** [103]. In addition, mitotherapy increases mitochondrial activity in the brain and ameliorates cognitive function in Alzheimer's disease mice [104]. Hence, these studies provide new strategies of enhancing intercellular mitochondrial transfer or mitotherapy, for the treatment of mitochondrial dysfunction-related metabolic diseases including obesity.

## Concluding remarks

Research in the past several years focused on mitochondrial regulation in WAT homeostasis has significantly advanced our understanding of how mitochondria critically contribute to adipose tissue health. Far beyond their basic roles as the 'powerhouse' of the cell, mitochondria exert multifaceted effects on adipocytes, APCs, and other adipose tissue-resident cells. It is increasingly appreciated that mitochondrial metabolism is a critical factor in determining the cell lineage fate and function of APCs. Mitochondrial regulation is indispensable for determining mature adipocyte function, and it also exerts a profound impact on the microenvironment within WAT. One of the most important breakthroughs during the past few years is the realization that mitochondria are important mediators of cell-to-cell crosstalk, either within the WAT or in the crosstalk from adipose tissue to other organs.

Moving forward to the next phase, many outstanding questions remain (see Outstanding questions). Further studies into the relationship between mitochondrial function and the cellular heterogeneity among adipocytes in different fat pads will be essential for a better understanding for fat depot differences. To address this important question, the development of specific genetic tools for the expression in distinct adipocyte subpopulations and the subsequent genetic manipulation of mitochondrial components in these adipocyte subtypes are urgently needed. Although single-cell transcriptomics has been extensively applied in many other tissues and cell types, it remains a technology that is very challenging for white adipocytes. Regarding a better understanding of adipose SVF heterogeneity driven by mitochondrial metabolism, the use of high-throughput analysis, such as single-cell RNA sequencing of the SVF, is less challenging compared with white adipocytes. Thus, upon identification of distinct cell populations in the SVF, specific manipulation of the key mitochondrial components in each of these cell types is the next obvious step.

Therapeutic potential and translational feasibility remain at the forefront of WAT mitochondrial research. A detailed time course analysis for each WAT mitochondrial dysfunction model described in previous studies will need to be carried out to determine the treatment window for a therapeutic intervention to reverse the mitochondrial defects. Furthermore, recently identified key mitochondrial pathway regulators need to be tested for their potential to improve adipose tissue function under obese conditions. Factors that are considered to be protective against

### Outstanding questions

Does mitochondrial function drive the heterogeneity of adipocytes in different fat pads?

Similarly, does mitochondrial function determine the heterogeneity of the adipose tissue SVF?

Does the manipulation of mitochondrial respiration in adipocyte progenitor cells improve adipogenesis?

Furthermore, what are the potential therapeutic avenues toward modifying adipose tissue mitochondrial function to improve obesity and metabolic disease?

How do we therapeutically modify mitochondrial function in a targeted way to improve adipose tissue health in obesity and metabolic diseases?

mitochondrial dysfunction, miRNAs that positively regulate WAT mitochondrial function and promote WAT browning activity, EVs that are derived from the WAT containing mitochondrial components or even functional mitochondria, as well as healthy mitochondrial transplants are particularly interesting for future efforts. Last but not least, moving from current cellular and rodent model-centered research to more human-relevant clinical research is warranted. So far, only correlations between reduced mitochondrial activity and the development of obesity in the clinical setting have been established. Specific ways to improve adipose health and obesity through targeting mitochondrial pathways in patients have not yet been explored. Inducing selective beiging for WAT as well as induction of protective mechanisms against mitochondrial dysfunction through small-molecule chemistry bear significant promise for the future antiobesity approaches.

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## Declaration of interests

The authors declare no conflicts of interest.

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