

Review Article

Metabolic syndrome and related conditions

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Macrophage and Adipocyte Mitochondrial Dysfunction in Obesity-Induced Metabolic Diseases

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Obesity is one of major health burdens of modern society as it contributes to the growing prevalence of its related comorbidities, such as diabetes, cardiovascular diseases, and some cancers. A series of innate immune cells, especially macrophages, and adipocytes have been implicated in the pathogenesis of obesity. Mitochondrial dysfunction, which is induced by obesity, are critical mediators in initiating inflammation in macrophages and adipocytes, and subsequent systemic insulin resistance. In this review, we discuss new findings on how obesity impairs mitochondrial function in macrophages and adipocytes and how this dysfunction contributes to obesity and its comorbidities. We also summarize drugs that treat metabolic diseases by targeting mitochondrial dysfunction.

Keywords: Adipocytes; Inflammation; Insulin resistance; Macrophages; Mitochondria; Obesity

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INTRODUCTION

Obesity has become a global epidemic and has nearly tripled since 1975. In 2016, more than 1.9 billion adults, accounting for 39% of the world of adult population, were overweight. Of these, over 650 million were obese [1]. Obesity increases risks for many diseases, particularly insulin resistance (IR), type 2 diabetes mellitus and recent COVID-19 [2,3]. It is well-known that the continuous excessive nutrient intake leads to obesity, resulting in a low-grade chronic inflammation. Hypertrophic adipocytes could produce proinflammatory

cytokines, which provide a chemotactic gradient to recruit innate and adaptive immune cells into adipose tissue [4]. Among the adipose tissue immune cells, macrophages are the most abundant and can account for up to 40% of all stromal vascular cells in obesity [5]. These macrophages are suggested to be the major source of inflammatory cytokines that cause local and systematic IR [5]. In obese adipose tissues, macrophages are biased toward M1 phenotype and produce pro-inflammatory cytokines. In contrast, M2 macrophages dominate in adipose tissue of lean subjects [6].

Mitochondria are considered as “powerhouse of the

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cell” because they are the main sites of adenosine triphosphate (ATP) production. Mitochondria are exquisitely sensitive to their environs and can be damaged easily. For instance, excessive lipid accumulation could lead to abnormal mitochondrial function as manifested by defective β -oxidation, and elevated oxidative stress [7]. Mitochondrial dysfunction leads to ineffective dissipation of proton gradient, which increases reactive oxygen species (ROS) production and mitochondrial DNA mutation [8]. In addition, electron transport chain (ETC) uncoupling, reduced oxidative phosphorylation (OXPHOS), decreased biogenesis, and altered mitochondrial dynamics are important features of mitochondrial dysfunction [8,9]. Damaged or dysfunctional mitochondria lead to an array of complex diseases including obesity and diabetes [10]. For example, mitochondrial ROS alters insulin/insulin receptor substrate signaling pathways [11]. Alternatively, overexpression of mitochondrial antioxidant enzyme eliciting H_2O_2 (included in ROS) decreases the loss of insulin sensitivity induced by high-fat diet (HFD) [12].

In this review we discuss the role of mitochondrial dysfunction in macrophages and adipocytes and their roles in deteriorating obesity-induced inflammation and IR. We also review the cross-talk between these two cells influenced by their mitochondrial alterations. Lastly, we summarize drugs that targeting mitochondria for treating metabolic disorders. Our summary will help to build an integral framework of macrophages and adipocytes in regulating metabolic diseases based on mitochondrial function.

REGULATION OF MITOCHONDRIAL FUNCTION IN MACROPHAGES

Macrophages, an essential component of innate immunity, serve as the first line of defense against infection and regulate chronic inflammation and related pathologies [13]. Metabolically activated macrophages in adipose tissues are uncovered that they both have pro-inflammatory and anti-inflammatory functions during obesity progression and do not respond to the classical duality between M1 and M2 macrophages [14-16]. Otherwise, fat-resident macrophages are widely defined as pro-inflammatory M1 and anti-inflammatory M2 macrophages [17]. Generally speaking, M1 macrophages rely on glycolysis for their metabolic demands, while M2 macrophages depend on OXPHOS pathway

[18,19]. In a state of obesity, activated hypoxia-inducible factor-1 shifts cellular fuel consumption from OXPHOS towards glycolysis and promotes M1 macrophages polarization [6,20]. In addition, activation of CD36 by extracellular lipid ligands stimulates nuclear factor- κ B to downregulate ETC component and promotes mitochondrial ROS production, which promotes expression of M1-related genes [20]. Defective mitochondrial oxidative function in macrophages due to myeloid-specific deletion of the CR6-interacting factor 1 (Crif1) gene, an essential mitochondrial factor required for biogenesis of OXPHOS subunits, results in M1 polarization and systematic IR associated with adipose inflammation [21]. Furthermore, impaired OXPHOS in macrophage disturbs STAT6 activation, then diminishes growth/differentiation factor 15 (GDF15) secretion in adipose tissues. Whereas, the administration of rGDF15 upregulates oxidation metabolism of macrophages and leads to M2-like polarization, eventually reverses IR in ob/ob mice and HFD-fed mice with myeloid-specific deletion of Crif1 gene [21,22].

Activation of the NOTCH1 pathway provides another mechanism to reprogram mitochondrial metabolism for M1 macrophage polarization. Lipopolysaccharides (LPS), which belongs to pathogen-associated molecular patterns (PAMP), is released by HFD-induced dysbiosis, leading to the activation of NOTCH in macrophages. NOTCH1 activation increases mitochondrial glucose oxidation in M1 macrophages. Meanwhile, NOTCH1 activation liberates its intracellular domain (NICD), which translocates to nuclear and promotes mtDNA transcription in M1 macrophages. Thus, increased mtDNA expression leads to enhanced mtROS levels, which in turn augments expression of M1 genes. Inhibition of myeloid NOTCH1 signaling attenuates hepatic M1 macrophages activation and hepatic inflammation in obesity-alcohol synergistic ASH mouse model [23].

Fatty acid, acting as a kind of damage-associated molecular pattern (DAMP), could induce inflammation in macrophages then leading to obesity-associated IR. Palmitic acid (PA), which is abundantly accumulated after HFD feeding, decreases mitochondrial membrane potential and releases mtDNA from mitochondria to cytoplasm in Kupffer cells. Released mtDNA is oxidized by ROS, and then directly binds to the nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome. Subsequently, activated NLRP3 inflammasome induces caspase-1 activation and interleukin (IL)-

β maturation to accelerate nonalcoholic steatohepatitis development [24]. Of note, palmitate also decreases AMP-activated protein kinase (AMPK) activity and impairs autophagy, leading to accumulation of mtROS and consequent activation of the NLRP3 inflammasome [25]. In addition, palmitate causes mitochondria fragmentation in human macrophages through inducing dynamic-related protein 1 (DRP1) oligomerization, a key executor of mitochondrial fission. Inhibition of DRP1 and overexpression of a dominant-negative mutant both attenuate palmitate-induced mitochondrial fission [26]. Some studies have demonstrated that mitochondrial fission is related with elevated intracellular ROS production, inflammation and IR [27,28]. However, mitochondrial fission in macrophages is suggested as a protective mechanism attenuating inflammatory responses elicited by fatty acid in response to fat overload [26]. Accordingly, mitochondrial fission is required for glucose-stimulated insulin secretion in β cells and protects hepatocytes from IR during HFD feeding [29,30].

Microglia cells are yolk-sac-derived macrophages invading brain at the early embryonic stages. Similar to macrophages, microglia cells can also change shape constantly in response to surrounding micro-environment to maintain homeostasis [31]. Diet-induced obesity (DIO) triggers microglia activation and hypothalamic inflammation as early as day 3 after HFD challenge [32]. Furthermore, HFD induces high expression of uncoupling protein 2 (UCP2) mRNA in hypothalamic microglia, and a rapid but transient change in microglial mitochondrial morphology that is associated with activated DRP1, like a significant decrease in mitochondrial size and an increase in mitochondrial numbers. Selective depletion of microglia UCP2 not only decreases mitochondrial respiration and ATP production, but also inhibits DRP1 and microglia activation and prevents DIO [32]. These results suggest a close relationship between mitochondrial dysfunction and microglia activation in the initiation of obesity.

Taken together, excessive nutrient shifts the energy supply from OXPHOS to glycolysis and reprograms macrophage polarization into M1 macrophages. In addition, mtDNA release, mtROS production and mitochondrial dynamics in macrophages could all be affected by over-nutrition and contribute to obesity-induced inflammation.

REGULATION OF MITOCHONDRIAL FUNCTION IN ADIPOCYTES

Based on a cross-sectional study, the size of visceral adipocytes is negatively related with insulin sensitivity and regarded as an IR determinant [33]. The hypertrophic adipocytes are inclined to activate endoplasmic reticulum (ER) and mitochondrial stress responses [34], which trigger cell death in adipocytes and initiate adipose tissue inflammation [35]. In human study, mtDNA content, mtDNA-encoded transcripts, mitochondrial mass, and OXPHOS protein levels in adipose tissue are all downregulated in the obese individuals compared with the lean co-twins [36]. *ESR1* (encoding estrogen receptor alpha [ER α]) is a gene associated with mitochondrial biogenesis, whose expression is inversely related with adiposity but positively related with insulin sensitivity [37]. Recent study found that the anti-obesity ER α in adipocytes regulates mitochondrial function and energy homeostasis in adipose tissue by controlling mtDNA copy number and mitochondrial remodeling. Reduced ER α function could impair mitochondrial function, promote adiposity and disrupt metabolic homeostasis [37].

Cyclic GMP-AMP (cGAMP) synthase (cGAS) is a cytosolic DNA sensor that is activated in response to pathogen infection [38]. The product of cGAS, cGAMP, binds to the ER-associated adaptor protein STING, leading to the activation of downstream targets, such as TBK1 and IRF3 and consequent activation of the type-I interferon response. Recent studies have emphasized that activation of cGAS-STING pathway could also be triggered by HFD-induced mtDNA release, eventually leading to increased chronic sterile inflammation [39,40]. Fat-specific overexpression of disulfide bond A oxidoreductase-like protein (DsbA-L), a chaperone-like protein originally identified in the mitochondrial matrix, prevents HFD-induced obesity and activation of the cGAS-STING pathway. Conversely, fat-specific knockout of DsbA-L impairs mitochondrial function and promotes mtDNA release, leading to the activation of the cGAS-STING pathway and IR [39]. Further studies have demonstrated that activation of cGAS-STING pathway inhibits adipocyte cAMP-PKA signaling and thermogenesis thus contributing to over-nutrition-induced obesity [41].

Adiponectin, the most abundant adipokine produced by adipocytes, could improve insulin sensitivity and re-

duce systematic inflammation [42-44]. Plasma concentration of adiponectin is decreased in obese individuals [45]. It is suggested that impaired mitochondrial function reduces adiponectin synthesis in adipocytes *via* activation of c-Jun NH2-terminal kinase (JNK) and consequent induction of activating transcription factor3 (ATF3) [46]. Other researchers have further investigated that the inhibition of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1), whose overexpression in adipocyte produces typical features of metabolic syndrome, increases mitochondrial biogenesis in adipocyte and plasma adiponectin level [47].

Mitochondrial dysfunction plays a detrimental role in metabolic stress, while mitophagy clears damaged mitochondria to exert the role of mitochondrial quality control and maintain metabolic homeostasis. PTEN-induced putative kinase 1 (Pink1) and Parkin, which mediate mitophagy and protect mitochondria from metabolic stress, are activated in adipocyte treated with PA [48]. Others uncover Pink1 and Parkin deficiency promoted mtDNA release and activated cGAS-STING pathway to induce inflammatory phenotype [49], whereas the detailed mechanism remains to be explored. Global or brown adipocyte-specific knockout of PINK1 manifests brown adipose tissue (BAT) dysfunction, such as decreased expression of UCP1 and proliferator-activated receptor γ coactivator 1 α (PGC-1 α) [50]. Mechanically, *pink1* deficiency leads to NLRP3 inflammasome activation and subsequent BAT dysfunction. Knockout of Pink1 reverses BAT dysfunction found in the *nlrp3*^{-/-} mice [50]. Autophagy-mediated mitochondrial clearance, mediated by autophagy-related genes (*atg*), is also found to mediate beige-to-white adipocytes transition [51,52]. Adipocyte-specific depletion of *atg5* or *atg12* promotes beiging of white adipocytes, and protects from DIO and IR [51]. Accordingly, adipocyte-specific ablation of *atg7* protects mice from HFD-induced obesity. Although *atg7* deficiency induces defective autophagy, along with mitophagy, higher mitochondrial content and increased β -oxidation occur in adipose tissue. Inactivation of autophagy by *atg7* ablation alters adipogenesis, leading to the production of adipose tissue with lots of anti-obesity and anti-diabetes features (Fig. 1) [53]. These contrasting results could be due to the distinct role of mitophagy in different adipocytes (brown *versus* white adipocytes). Distinguishing downstream signaling pathways of those mitophagy component may also contribute to these inconsistent results.

Further investigations are needed to understand the role of mitophagy in obesity thoroughly.

It is well known that pattern recognition receptors (PRR) play an important role in mediating inflammation and modulating obesity. PRR activation in brown adipocytes induces inflammation and significantly downregulates UCP1 expression and mitochondrial respiration [54]. Knockout of Toll-like receptor 4 (TLR4), a prominent family of PRR, increases body weight and decreases body temperature, while improves glucose metabolism in HFD feeding mice. TLR4 deficiency inhibits HFD-induced mitochondrial translocation of nuclear factor of activated T-cells 2 (NFATC2) in adipocytes, which reduces IL-1 β expression and mitochondrial oxidative stress leading to decreased adipose inflammation and ultimately ameliorated IR [55].

Taken together, HFD-induced obesity leads to mitochondrial dysfunction in adipocytes, triggering innate immune response and regulating energy consumption, ultimately causing systematic inflammation and IR.

CROSS-REGULATION OF MITOCHONDRIAL FUNCTION BETWEEN MACROPHAGES AND ADIPOCYTES

As mitochondrial dysfunctions in both macrophages

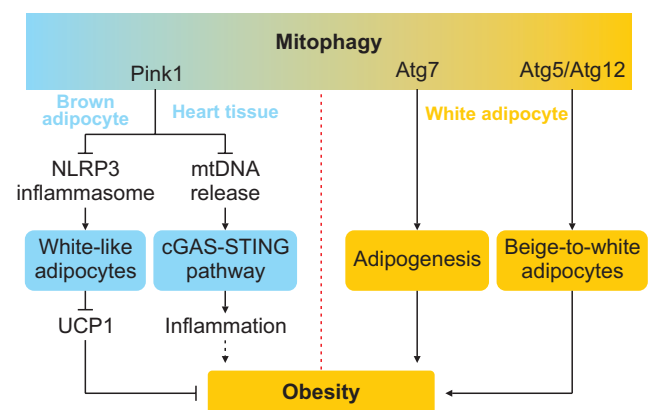


Fig. 1. The Yin-yang roles of mitophagy in obesity. PTEN-induced putative kinase 1 (Pink1) deficiency activates nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, leading to decreased uncoupling protein 1 (UCP1) expression and diminishes energy expenditure. Pink1 deficiency also promotes mtDNA release and subsequent activation of the cyclic GMP-AMP synthase (cGAS)-STING pathway in heart tissue, leading to exacerbated systematic inflammation, which may ultimately contribute to obesity. Conversely, ablation of *Atg5/Atg12* inhibits mitophagy and restrains beige-to-white fat transition, revealing a negative role of mitophagy in energy consumption. *Atg7* deficiency alleviates obesity by inhibiting adipogenesis.

and adipocytes are involved in obesity, their connection deserves some special attention. Adiponectin, which is well-known to activate AMPK, shifts macrophage polarization from M1 to M2 and then suppresses adipose tissue inflammation [47]. Adipose-specific ablation of FUNDC1, a newly characterized mitophagy receptor in maintaining a healthy mitochondria pool, displays impaired mitophagy and decreases ATP levels accompanied by elevated total ROS and mtROS in white adipose tissue (WAT). FUNDC1 deficiency also facilitates M1 polarization of ATMs *via* activating MAPK signaling and pro-inflammatory responses as obesity develops [56].

Activation of TLR4 and NLRP3 inflammasome induces IL-1 β production in macrophages, which has been shown to attenuate thermogenesis by stimulating oxidative stress and decreasing mitochondrial membrane potential in adipocytes [57]. By activating p53 signaling, nitric oxide produced by M1 macrophages suppresses peroxisome proliferator-activated receptor γ (PPAR γ) coactivator 1 α (PGC-1 α) to decrease mitochondrial biogenesis in preadipocytes, which interrupts preadipocytes differentiate to mature adipocytes [58]. The expression of IL-25, also named IL-17E, is reduced in serum, liver and WAT in DIO animal model. The administration of exogenous IL-25 could stimulate M2 macrophages polarization and thereby improve the mitochondrial respiratory capacity in adipocytes as indicated by the increased expression of CPT1 α , NAD⁺/NADH ratio, ATP production and oxygen consumption rate. IL-25-educated macrophages also promotes lipolysis and inhibits lipogenesis in adipocytes to prevent from obesity [59].

Thus, obesity may induce mitochondrial dysfunction to decrease adiponectin production in adipocytes, causing decreased M2 macrophages and increased adipose tissue inflammation. In turn, activated macrophages interrupt mitochondrial function in adipocytes to influence obesity process.

DIABETES DRUGS TARGETING MITOCHONDRIAL FUNCTION

Metformin, a well-known diabetes drug, lowers glycemia level by reducing hepatic glucose production and improving glucose intake and utilization in the peripheral tissues [60]. Emerging evidences support that metformin exhibits immune-modulatory features, such as macrophage polarization [61]. For instance, metformin

could inhibit LPS-induced pro-IL-1 β production in bone marrow-derived macrophage *via* suppressing mitochondrial complex I and ROS production [62,63]. Rosiglitazone, a PPAR γ agonist to improve insulin sensitivity and glycemia [64], could promote mitochondrial biogenesis, expression of mitochondrial protein in adipocytes to increase plasma adiponectin level [46]. Resveratrol (RSV), a polyphenolic phytoalexin, has many effects on metabolic diseases, such as obesity and diabetes. RSV could improve IR in HFD feeding rats, which may be linked with increased mitochondrial activity of brown adipocytes, but not white adipocytes [65]. In addition, RSV and metformin inhibits DRP1 activation *via* activating AMPK, and then prevent mitochondrial fission in adipocytes [66]. TM5411, a novel orally active plasminogen activator inhibitor-1 inhibitor, prevents HFD-induced body weight gain and IR. Of note, TM5411 restores HFD-induced downregulation of genes involved in mitochondrial biogenesis and function in adipocytes, indicating that it could maintain mitochondrial fitness to prevent obesity and obesity-related metabolic disorders [67]. These results show that improving mitochondrial functions is able to improve obesity and its related complications. Further investigations are needed to elucidate the detailed mechanisms by which mitochondrial dysfunction in innate immunity promotes obesity-related comorbidities, which may provide more efficient and precise treatment to choose.

CONCLUSIONS

In this review, we have discussed how mitochondrial dysfunction contributes to obesity-related inflammation and IR, focusing mainly on macrophages and adipocytes. HFD-induced DAMP and PAMP such as PA and LPS lead to excessive mtROS production in macrophages and subsequent pro-inflammatory immune responses and M1 macrophage polarization in adipose tissue. Mitochondrial fission, induced by HFD, also enhances ROS levels. Downregulated ETC components and altered energy support (upregulated glycolysis and downregulated OXPHOS) promote M1 polarization, which disrupts mitochondrial biogenesis through inhibiting PGC-1 α . Moreover, adiponectin and downstream AMPK activation, which could suppress M1 polarization but promote mitophagy, are both suppressed by obesity. Summarily, these HFD-induced macrophage and adipocyte mitochondrial alternations all contribute

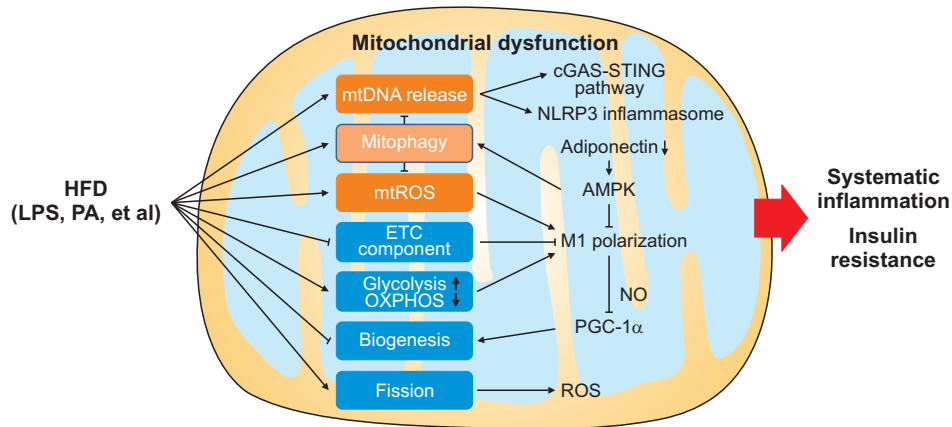


Fig. 2. Schematic diagram showing diet-induced mitochondrial dysfunction in obesity-related inflammation and insulin resistance. High-fat diet (HFD) could induce mitochondrial dysfunction *via* diet-derived lipopolysaccharides (LPS) and palmitic acid (PA). Subsequently, released mtDNA in the cytosol activates the cyclic GMP-AMP synthase (cGAS)-STING pathway and NLRP3 inflammasome, then triggering inflammatory response. In addition, downregulated electron transport chain (ETC) component and the altered ratio of glycolysis to oxidative phosphorylation (OXPHOS) cause M1 polarization, then produce nitric oxide (NO) to prevent mitochondrial biogenesis by diminishing proliferator-activated receptor γ coactivator 1 α (PGC-1 α). Mitophagy is activated in obese individual. Of note, mitochondrial dysfunction inhibits adiponectin production, resulting in reduced AMP-activated protein kinase (AMPK) activation and consequently attenuated mitophagy and increased M1 polarization. HFD-induced fission enhances reactive oxygen species (ROS) level. All these mitochondrial dysfunctions contribute to obesity-related inflammation and insulin resistance.

to systematic inflammation and IR (Fig. 2). However, the effect of HFD on mitophagy remains to be further determined given that HFD feeding have been found to either promotes mitophagy *via* upregulating PINK1 expression [48] or suppressing mitophagy by downregulation of adiponectin expression [25,47] (Fig. 2). It is demonstrated that Parkin and PINK1 increase by about two-fold after 12 weeks of HFD [68]. By contrast, adiponectin levels in mice are not significantly decreased until HFD feeding for 20 weeks [69]. Herein, it is possible that at the early stage of HFD feeding, increased mitophagy plays a major role in reducing mtDNA release and mtROS production to maintain homeostasis, while mitophagy is suppressed by decreased adiponectin at a late period of HFD feeding leading to metabolic imbalance.

Although much progress has been made on the understanding of the regulation and roles of mitochondrial function in macrophages and adipocytes in obesity, many questions remain to be explored. For example, it remains to be determined on whether the mitochondrial-facilitated cross-talk between macrophages and adipocytes also exists in other metabolic tissues such as the intestine, liver, and heart. It is also unclear whether and how altering mitochondrial function in either macrophages and adipocytes modulate their interaction with other tissue resident cells especially immune

cells. More studies would also be needed to verify the alternation of mitochondrial dysfunction in metabolic diseases in humans.

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Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Writing – original draft: LW. Writing – review & editing: all authors.

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