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Mitochondrial Dysfunction in Obesity

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Abstract

Purpose of the Review—The review highlights recent findings regarding the functions of mitochondria in adipocytes, providing an understanding of their central roles in regulating substrate metabolism, energy expenditure, disposal of reactive oxygen species (ROS), and in the pathophysiology of obesity and insulin resistance, as well as roles in the mechanisms that affect adipogenesis and mature adipocyte function.

Recent Findings—Nutrient excess leads to mitochondrial dysfunction, which in turn leads to obesity-related pathologies, in part due to the harmful effects of ROS. The recent recognition of "ectopic" brown adipose in humans suggests that this tissue may play an underappreciated role in the control of energy expenditure. Transcription factors, PGC-1α and PRDM16, which regulate brown adipogenesis, and members of the TGF–β superfamily that modulate this process may be important new targets for anti-obesity drugs.

Summary—Mitochondria play central roles in ATP production, energy expenditure, and disposal of ROS. Excessive energy substrates lead to mitochondrial dysfunction with consequential effects on lipid and glucose metabolism. Adipocytes help to maintain the appropriate balance between energy storage and expenditure and maintaining this balance requires normal mitochondrial function. Many adipokines, including members of the TGF-beta superfamily, and transcriptional co-activators, PGC-1α and PRDM16, are important regulators of this process.

Keywords

adipose; mitochondria; obesity; reactive oxygen species; insulin resistance

Introduction

Mitochondrial dysfunction contributes to the pathogenesis of metabolic disorders. Affected tissues include those that participate in nutrient metabolism, including adipose, liver and skeletal muscle. Abnormal mitochondrial function results in lipid accumulation and insulin resistance, as cells require a balance between mitochondrial ATP synthesis through oxidative

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phosphorylation (OXPHOS), and dissipation of the proton gradient to minimize damage from reactive oxygen species (ROS). Growth and transcription factors that regulate mitochondrial gene expression contribute to the pathophysiology of obesity, insulin resistance and type-2 diabetes (T2D). Herein, we focus on factors linking mitochondrial dysfunction to obesity, with an emphasis on adipocytes and energy expenditure.

Roles of Mitochondria in adipocyte lipid metabolism

Mitochondrial biogenesis and activity increase dramatically during adipocyte differentiation, suggesting an important supportive role for this organelle [1]. Moreover, mitochondrial dysfunction in mature adipocytes has been linked to defects in fatty acid oxidation [2•], secretion of adipokines [3], and dysregulation of glucose homeostasis [4]. Reduction in the oxidative capacity of brown adipocytes results in impaired thermogenesis, and has been linked to diet-induced obesity [5••].

Several mitochondrial enzymes are essential in lipid metabolism, as mitochondria are the major site of fatty acid oxidation (FAO). Classically, negative energy balance results in enhanced lipolysis in white adipose tissues (WAT), providing non-esterified fatty acids (NEFA) as a substrate for FAO in liver and skeletal muscle, with associated insulin sensitization. In contrast, extended periods of nutrient excess result in NEFA accumulation, mitochondrial dysfunction and insulin resistance [6•]. Consistent with a mitochondrial role, primary mitochondrial disorders can also affect body fat storage leading to multiple symmetrical lipomatosis [7]. Inhibitors of mitochondrial respiration increase TG accumulation, and reduce FAO and glucose uptake in 3T3L1 pre-adipocytes [8], while mild mitochondrial uncoupling decreases the expression of transcription factors involved in adipocyte differentiation with subsequent reduction in TG accumulation [9•], suggesting that different levels of mitochondrial activity can have different effects on adipocyte lipid metabolism.

Uncoupling proteins

Mitochondrial respiration can be uncoupled by the controlled transfer of protons across the inner mitochondrial membrane, thereby dissipating the proton gradient to minimize the deleterious effects of ROS. The family of inner mitochondrial membrane uncoupling proteins (UCPs) plays important roles in thermogenesis in BAT and in regulating the disposal of mitochondrial ROS in other tissues [10]. UCP1 uncouples mitochondrial respiration from ATP production by causing protons to leak across the inner mitochondrial membrane, enabling energy dissipation in the form of heat, a process that is enhanced by NEFA and inhibited by purine nucleotides [10]. ROS that are normally generated by OXPHOS further activate UCPs, thereby dissipating the proton gradient and facilitating ROS disposal [11]. In this fashion, the deleterious effects of ROS can be delayed or even reversed.

Caloric intake and ROS: contributors to mitochondrial dysfunction

Mitochondrial oxidative dysfunction correlates with insulin resistance in skeletal muscle of obese and diabetic individuals [12•,13•]. This dysfunction correlates with reductions in mitochondrial numbers and size [14], and enzymatic oxidative capacity [15]. Reduced expression of OXPHOS genes and reduced oxygen consumption have also been observed in

obese individuals [16,17]. Adipocytes respond to metabolic challenges by altering the number, morphology and/or distribution of mitochondria within the cell, and by changing the metabolite, enzyme, and/or mitochondrial DNA (mtDNA) content.

Excessive caloric intake, increasing the mitochondrial substrate load, or mitochondrial dysfunction that precludes effective dissipation of the proton gradient can increase ROS production, causing cell damage, increased mutation rates of mtDNA, and apoptosis. High fat diet (HFD) and hyperglycemia increase ROS production in mouse adipocytes [18,19], and oxidative stress is increased in obese individuals and in adipose from genetically obese mice, causing abnormal adipokine production [20]. Addition of glucose or NEFAs to mature 3T3L1 adipocytes reduces mitochondrial biogenesis and gene expression, and increases ROS, causing insulin resistance [2•]. Similarly, TNF-alpha-mediated ROS accumulation leads to insulin resistance in 3T3L1 pre-adipocytes [21]. ROS reduce oxygen consumption in adipocytes, and block fatty acid oxidation (FAO), resulting in lipid accumulation [22•]. Finally, insulin resistance is mitigated by mitochondrial antioxidants or overexpression of mitochondrial scavengers [23•]. Therefore, excessive energy substrates result in increased ROS production, which in turn has significant consequences on mitochondrial function and energy substrate metabolism.

Mitochondria: roles in white and brown adipose tissues

In mammals, there are two general types of adipose tissue-- Brown adipose tissue (BAT) dissipates energy through thermogenesis, whereas white adipose tissue (WAT) specializes in energy storage. Adipocytes are derived from a multipotent mesenchymal stem cell (MSC) residing in the stromal vascular fraction (SVF) of adipose tissues [24]. However, BAT and WAT adipocytes arise from different precursor cells. The differences in BAT and WAT functions in energy metabolism are due in part to differences in mitochondrial physiology.

White adipose tissues

In situations of energy demand, WAT releases NEFA into circulation as an energy substrate. During periods of nutrient excess, WAT lipogenic enzymes use energy substrates to produce TG for storage. Although not typically viewed as a thermogenic tissue, mitochondrial biogenesis and UCP1 expression in WAT increases after adrenergic stimulation due to cold exposure or by treatment with beta3-adrenoreceptor (ADBR3) agonists [25•]. These increases correlate with a reduction of diet-induced obesity [26]. Moreover, *Adbr3* knockout mice have diminished BAT in white fat depots, indicating the importance of sympathetic input in this process [27]. Similar to rodents, ADBR3 has been detected in adult human WAT [28], and adrenergic stimulation can increase UCP1 expression [29]. Thus, the number of brown adipocytes within WAT varies, influenced by environmental factors.

Brown adipose tissues

Adipocytes within BAT depots share a common Myf5-positive precursor with myocytes [30,31]. In contrast, brown adipocytes residing within WAT depots are derived from a different precursor (*Myf5*-negative) and increase in number after adrenergic stimulation. These resident brown adipocytes arise through either differentiation of brown pre-adipocytes or through transdifferentiation of white adipocytes or their precursors (for excellent review

see [32•]). Brown adipocytes are thermogenic cells that play an important role in energy balance in rodents and humans. BAT thermogenesis is dependent on adrenergic stimulation of lipolysis and subsequent UCP1-dependent degradation of NEFA [33].

BAT and muscle mitochondria have similar metabolic profiles [34••]. The high oxidative capacity of both is due to their high mitochondrial density, expression of FAO enzymes and respiratory chain components. However BAT displays exclusive expression of UCP1. Under thermoneutral conditions UCP1 ablation in mice results in obesity and abolishes diet-induced thermogenesis [5]**. Overexpression of UCP1 in WAT reduces weight gain in obesity-prone mice due in part to increased energy expenditure and decreased fatty acid synthesis [35]. Recently, ectopic BAT has been found in mouse skeletal muscle and UCP1 mRNA levels were higher in this BAT in obesity-resistant mice than in obesity-prone mice [36]. Thus, although the number of brown adipocytes varies among different white fat depots and skeletal muscle, enhanced capacity for BAT recruitment and UCP1 expression may influence the susceptibility to obesity and indicates substantial heterogeneity and plasticity of BAT development. Human BAT is present in several areas, and its activity is stimulated by cold exposure, and inhibited by drugs that block beta-adrenergic signaling [37]. The amount and activity of human BAT is inversely correlated with age, glucose levels, body-mass index (BMI) and percent body fat [38••,39•,40•,41•]. Thus, these cells may be important contributors to thermogenesis in healthy adults. Furthermore, BAT progenitors can also be found in human skeletal muscle and these progenitors can differentiate into mature brown adipocytes [42]. Thus, BAT may also play an important role in the susceptibility to obesity and in regulating energy expenditure in humans, processes that are indelibly linked to mitochondrial function.

Mitochondria and Adipocyte Transcription Factors

There is great interest in understanding the roles of mitochondria in the differentiation of adipocytes, as affecting the brown versus white adipocyte fate decision has enormous implications for the treatment of human obesity. Several transcription factors participate in adipogenesis, and are summarized in table 1. Of particular interest are the PPAR gamma coactivator family (PGC) and PRD1-BF-1-RIZ1 homologous domain containing protein 16 (PRDM16), as they play major roles in mitochondrial biogenesis and function and in defining the characteristics of brown adipocytes.

Peroxisome proliferator activated receptor-gamma co-activator (PGC) family

The transcriptional co-activators PGC-1a and PGC-1b play important roles in the expression of genes involved in mitochondria biogenesis, fatty acid metabolism and lipid accumulation. Ablation of PGC1-α and -β in BAT pre-adipocytes impairs mitochondrial gene expression, density and respiration [43]. PGC-1α is reduced in adipose tissues of obese individuals [44], and in genetically-induced and diet-induced obese mice [45]. Thus, reduced PGC1 expression correlates with the impaired mitochondrial function and increased lipid accumulation that is characteristic of human metabolic disorders.

PRD1-BF-1-RIZ1 homologous domain containing protein 16 (PRDM16)

PRDM16 is selectively expressed in brown adipocytes [46] and is a transcriptional co-activator of PGC-1α and PGC-1β, increasing the expression of genes important for mitochondrial biogenesis, uncoupling, and OXPHOS [46,47]. Transgenic overexpression of PRDM16 in adipose increases mitochondrial gene expression in clusters of BAT-like cells within white adipose [46]. Also, PRDM16 interacts with C-terminal binding proteins, Ct-BP1 and Ct-BP2, to repress white adipocyte genes [47], and reducing PRDM16 in brown adipocytes blocks mitochondrial gene expression and increases myogenic markers [48]. PRDM16 binding to C/EBP beta activates the BAT developmental program [49••]. Thus, PRDM16 is an important early regulator of brown adipogenesis, increasing mitochondrial biogenesis, oxygen consumption and uncoupling.

Adipokines and growth factors

White adipose also has a prominent endocrine role, producing adipokines and hormones that regulate energy homeostasis, some affecting mitochondrial function (for excellent review see [75]).

Adiponectin

Adiponectin affects glucose and lipid metabolism, food intake and insulin sensitivity and stimulates FAO and glucose uptake in skeletal muscle cells [76]. Adiponectin increases PGC-1a expression, mitochondrial biogenesis, and FAO in myocytes [77••], and TZD treatment increases adiponectin expression and enhances mitochondrial function in human skeletal muscle [78•]. Thus, adiponectin plays an important role in processes that regulate mitochondrial energy expenditure.

TGF-β superfamily

The BMP subgroup of the TGF-β superfamily plays important roles in adipocyte differentiation. Although BMP2, BMP4 and BMP7 all participate [79–81], only BMP7 triggers the commitment to the brown adipocyte lineage [82]. BMP7 increases mitochondrial density and the expression of mitochondrial biogenesis genes through activation of p38 MAPK and PGC-1α [82]. Moreover, *Bmp7*-null mice have a reduction in BAT, and overexpression of BMP7 increases BAT and energy expenditure resulting in reduced adiposity [82]. Thus, BMP2 and BMP4 are involved in commitment to the adipocyte lineage, whereas BMP7 is an important regulator of the brown versus white adipocyte fate decision, and proteins that regulate BMP signaling may also have important effects on adipocyte differentiation, and energy expenditure.

The growth differentiation factors (GDFs) comprise another division of the TGF-β superfamily. *Gdf8* (myostatin)-null mice have increased muscle mass, are resistant to diet-induced obesity, and have improved insulin sensitivity [83,84]. Systemic administration of soluble myostatin type II receptor, (ActRIIb), inhibits myostatin, reduces body fat, and improves insulin sensitivity in mice with diet-induced obesity [85•]. Transgenic mice that overexpress myostatin in adipose tissue or skeletal muscle also have reduced fat mass and improved insulin sensitivity [86,87], and systemic administration of myostatin induces a

cachexia-like syndrome, with reductions in muscle and fat mass [88]. Since decreased fat accumulation has been observed with myostatin deficiency and overexpression, more than one mechanism is likely to contribute to its effects on adiposity, possibly, in part, by modulating BMP signaling, as myostatin selectively inhibits BMP7 *in vitro* [80].

GDF3 expression in adipocytes is affected by age and diet [89•], and correlates with changes in body mass and adiposity [90]. Systemic GDF3 overexpression in mice augments normal fat accumulation under high fat diet (HFD) conditions, defining GDF3 as a pro-adipogenic cytokine [91]. In contrast, mice lacking *Gdf3* accumulate less adipose under HFD conditions, due to increased basal metabolic rates [89,92]*. GDF3 binds BMP4 and inhibits BMP signaling [93,94•]. In adipose, GDF3 uses the activin type I receptor, Alk7, and the co-receptor Cripto (Andersson et al PNAS 2008), and mice lacking Alk7 also have decreased diet-induced fat accumulation [92]. Therefore, GDF3 may affect adiposity by modulating BMP signaling or by activating the Alk7 receptor.

Activins comprise another branch of TGF-β superfamily. Activin B is expressed in human adipose and its expression correlates directly with obesity and with cholesterol and insulin levels [95]. Activin B blocks lipolysis and increases TG accumulation in 3T3L1 cells by downregulating mitochondrial lipase expression [96•]. Mice with an activin B insertion allele at the activin A locus, have reduced adiposity [97•], are resistant to diet-induced obesity, have improved insulin sensitivity, and markedly increased energy expenditure [97•] with corresponding increases in mitochondrial gene expression and increased mitochondrial oxygen consumption [97•]. Taken together, these results support an important role for activin signaling in adipose metabolism, mitochondrial function and energy homeostasis.

Conclusions

Mitochondria control ATP production, energy expenditure, and disposal of ROS. Excessive energy substrates lead to mitochondrial dysfunction and abnormal lipid and glucose metabolism. Adipocyte differentiation involves changes in the abundance, morphology and organization of mitochondria, and abnormalities of these processes disrupt the balance between energy storage and expenditure. Brown adipose is an important regulator of thermogenesis and energy balance in humans. Adiponectin and members of the TGF-beta superfamily play roles in regulating brown and white adipogenesis, as well as transcriptional co-activators, PGC-1α and PRDM16. All are potential pharmacotherapeutic targets to treat metabolic disorders such as obesity, diabetes and insulin resistance.

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TABLE 1

ADIPOCYTE TRANSCRIPTION FACTORS: EFFECTS ON MITOCHONDRIA, ADIPOSITY AND INSULIN RESPONSE

GENE	ADIPOCYTE EFFECTS	MITOCHONDRIAL RELATIONSHIPS	ADIPOSE & INSULIN RESPONSE	REFERENCE
CREB	-stimulates adipogenesis (3T3-L1 cells)	-activated by mitochondrial dysfunction -triggers TG accumulation (3T3-L1 cells) -increases mitochondrial biogenesis and gene expression	-activated in obesity -induces IR*	[50–53•]
C/EBPα	-induces adipogenesis (3T3-L1) -involved in BAT-WAT differentiation *in vivo*	expression increases mitochondrial biogenesis and gene expression in BAT in a PPARγ-dependent manner	-C/EBPα deficiency induces IR	[54–58]
C/EBPβ	-increases adipogenesis (3T3-L1) -involved in BAT-WAT differentiation (*in vivo*) -interacts with PRDM16 in BAT	-expression increases mitochondrial biogenesis and gene expression in WAT	-lack of C/EBPβ protects against diet-induced obesity	[49,59–62]
C/EBPδ	-involved in BAT-WAT differentiation *in vivo*	-expression increases mitochondrial biogenesis and gene expression	-SNPs associated with altered lipid metabolism	[59,63]
PPARα	-dispensable for adipogenesis (*in vitro* and *in vivo*)	-expression increases mitochondrial gene expression in a PGC-1α-dependent manner	-PPARα deficiency is associated with late onset and diet-induced obesity	[64,65]
PPARγ	-increases adipogenesis (3T3-L1) -involved in BAT-WAT differentiation *in vivo* -interacts with PRDM16 in BAT	-expression increases mitochondrial biogenesis and gene expression -promotes NEFA uptake and TG accumulation in WAT	sequence variants are associated with obesity and IR	[1,46,66–68]
PPARδ	-co-repressor of PPARα and PPARγ -involved in BAT-WAT differentiation *in vivo*	-expression increases mitochondrial biogenesis and gene expression	-lack of PPARδ increases susceptibility to obesity -overexpression in adipose tissue reduces diet-induced obesity by stimulating thermogenesis	[69–71]
PGC1α	-involved in BAT-WAT differentiation -Interacts with PRDM16 in BAT	-expression increases mitochondrial biogenesis and gene expression	- PGC1α def. increases body fat -Obesity reduces PGC1α expression -polymorphisms associated with obesity	[4,44,45,72]
PGC1β	-involved in BAT-WAT differentiation -interacts with PRDM16 in BAT	- expression increases mitochondrial biogenesis and gene expression	-hypomorphic mutation causes mitochondrial dysfunction -sequence variants are associated	[43,73,74]

GENE	ADIPOCYTE EFFECTS	MITOCHONDRIAL RELATIONSHIPS	ADIPOSE & INSULIN RESPONSE	REFERENCE
			with obesity	
PRDM16	-involved in BAT-WAT differentiation	-expression increases mitochondrial biogenesis	NA	[46–49]