Mitochondria and endocrine function of adipose tissue

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Abstract

Excess of adipose tissue is accompanied by an increase in the risk of developing insulin resistance, type 2 diabetes (T2D) and other complications. Nevertheless, total or partial absence of fat or its accumulation in other tissues (lipotoxicity) is also associated to these complications. White adipose tissue (WAT) was traditionally considered a metabolically active storage tissue for lipids while brown adipose tissue (BAT) was considered as a thermogenic adipose tissue with higher oxidative capacity. Nowadays, WAT is also considered an endocrine organ that contributes to energy homeostasis. Experimental evidence tends to link the malfunction of adipose mitochondria with the development of obesity and T2D. This review discusses the importance of mitochondrial function in adipocyte biology and the increased evidences of mitochondria dysfunction in these epidemics. New strategies targeting adipocyte mitochondria from WAT and BAT are also discussed as therapies against obesity and its complications in next future.

Key words: mitochondria, white adipose tissue, brown adipose tissue, obesity, type 2 diabetes, lipids, lipotoxicity, reactive oxygen species, beta-oxidation

Introduction

With the growing pandemic of human obesity and its associated complications, interest in improving our understanding of the development, function and manipulation of white adipose tissue (WAT) has increased considerably (1). Particularly, the study of the adipocyte offers a great opportunity to explore the metabolic problems associated with the development of obesity (2). Excess adipose tissue is accompanied by an increase in the risk of developing insulin resistance and type 2 diabetes, dyslipidemia, hypertension, metabolic syndrome, coronary heart disease and stroke (3). The relationship between obesity and such complications is well-established at epidemiological level; however the mechanisms that explain this relationship are not fully defined.

Paradoxically, not only the excess of adipose tissue, but also the total or partial absence of fat or its accumulation in other tissues is associated with an increase in the risk of cardiometabolic complications (4). Furthermore, there is a paradox that many obese patients are metabolically healthy despite having fat accumulation, while other patients, who are only moderately obese, develop metabolic syndrome. In these circumstances, when the oxidative capacity and the storage capacity of adipocytes are compromised, the ectopic lipid accumulation triggers lipotoxicity (5). This lipotoxic process is associated with an non-adipose based accumulation of triglycerides and other specific lipid metabolites such as ceramides and diacylglycerides with an effect on the metabolism of these tissues to inhibit the action of insulin and other deleterious effects (6).

WAT was traditionally considered a metabolically active storage tissue for lipids. Nowadays, many studies have demonstrated that WAT is also an endocrine organ that contributes to energy homeostasis, not only through the storage or release of lipids, but also

by secreting adipokines with effects in other tissues. Adipocytes help to maintain the appropriate balance between energy storage and expenditure and they maintain this balance through matching oxidative phosphorilation (OXPHOS), and dissipation of the proton gradient to minimize damage from reactive oxygen species (ROS). Mitochondria in adipose tissue play central roles in ATP production, energy expenditure and disposal of ROS. Excessive energy substrates, typically occurring in situations of obesity and metabolic syndrome, may lead to mitochondrial dysfunction with consequential effects on lipid and glucose metabolism (7). Abnormal mitochondrial function results in lipid accumulation and insulin resistance.

For example patients with lipodystrophic syndromes showing peripheral lipoatrophy, increased visceral WAT and insulin resistance suffer from mitochondrial injury. Impaired mitochondrial is also presented in HIV-treated patients with highly active antiretroviral therapy (HAART), which leads to lipodystrophy and ectopic fat storage (8). On the other hand, patients with non-alcoholic steatohepatitis have shown mitochondrial failure characterized by increased lipid peroxidation, alteration in mitochondria structure, depletion in mtDNA and low OXPHOS activity (9).

Aging is associated with obesity, alterations in body fat distribution, and insulin resistance. Insulin resistance is often observed in elderly people with reduced OXPHOS activity similarly to obese patients with high risk for type 2 diabetes. Studies in mice with a defective catalytic subunit of mtDNA polymerase develop a phenotype associated with reduced lifespan and premature onset of aging-related phenotype with reduced subcutaneous fat and increased lipid accumulation in non-fatty tissues (10).

In all these situations, treatments with targeted action on adipose tissue, more specifically in the mitochondria, increasing their oxidative capacity could have beneficial effects. 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 in the form of triglyceride (TG)-containing intracellular droplets as well as to secrete hormones that regulate energy balance. The high oxidative capacity of BAT is due to its high mitochondrial density, expression of fatty acid oxidation enzymes and respiratory chain components, similarly to the muscle (11). Since the identification of discrete areas containing metabolically active BAT in adult humans, promoting proliferation and differentiation of brown fat cell precursors or by inducing white-to-brown fat trans-differentiation, could not only be useful to address the problem of obesity, but also prevent the side effects associated with obesity (12).

Mitochondrial activity in white and brown adipocyte biology.

The functions of the adipocyte can be classified in three aspects. Firstly, its contribution to lipid metabolism: adipocytes take up free fatty acids and convert them into triglycerides for long-term storage. Secondly, adipocytes break down triglycerides into fatty acids and glycerol via lipolysis for release into blood during periods of energetic need. And finally, since diverse molecules secreted by WAT such as leptin, TNF-α, adiponectin, resistin and others are linked to obesity and insulin resistance, the view of WAT has shift from a merely storage tissue to endocrine organ with a great influence in other tissues.. Furthermore, adipocytes are actively involved in other metabolic processes such as angiogenesis, dissolution and reform of extracellular matrix metabolism of steroids,

immune response and hemostasis. We can therefore say that adipose tissue must maintain its functionality, which is otherwise affected by obesity (13).

WAT is one of the largest depots in humans, with large lipid droplets and its function is essential for health maintenance, while BAT contains multilocular adipocytes or cells with a large number of lipid droplets (11). The BAT has a large number of mitochondria and its specialty is the production of heat, therefore, it a tissue that controls a significant proportion of energy expenditure. Another difference between both depots is that BAT originates from the myogenic (Myf5+) lineage differently to the WAT, which is mesenchymal in origin (Figure 1) (14). Despite different functionality and origin, both tissues share many features in common.

In the past few years, BAT was believed to be only present in the newborn infants in non-pathological situations to regulate post-partum thermogenic processes. However, several research studies using positron emission computed tomography/computed tomography (PET/ CT) analysis have shown that BAT was located in the neck and upper-chest regions of adult humans (15-17). Interestingly, these fat depots were reported to increase with exposure to low temperature, to be higher in women than in men and to decrease with age and body fat mass (18). Recently it has been shown that BAT acts as a nonshivering thermogenesis effector in humans, with an increase in BAT density upon cold exposure and reduced BAT triglyceride content (19). Because of these findings, BAT has now considered to be a promising therapeutic target to combat obesity in humans.

The role of mitochondria in WAT has been less studied, in part due to its lower content compared to that found in BAT. However, the observations that the mitochondria number in adipose tissue from obese people is reduced, suggest that impaired

mitochondrial activity could predispose to obesity and mitochondria biogenesis is also altered in obesity (7).

Although the main function of these organelles in the adipocytes is cellular respiration and oxidation of reducing equivalents, they participate in a considerable group of anabolic and catabolic cellular processes.

a) Mitochondrial biogenesis in adipogenesis.

Adipocytes are most likely derived from mesenchymal stems cells (MSCs), although the precise cellular linage of white adipocytes remains unknown at the present moment. The adipocyte differentiation develops as a two-step process. First, pluripotent MSCs undergo a process known as determination. This process results in fibroblast-like cells that appear morphogically identical to pluripotent MSCs but are, at that moment, only capable to differentiate into adipocytes. As a result, MSCs in this state of postdetermination are thereafter referred to as either preadipocytes or adipoblasts. The second stage of differentiation is the process of the formation of the structurally mature adipocytes from the fibroblast-like preadipocytes and is commonly referred to as adipogenesis. The conversion of preadipocytes to adipocytes has studied using diverse cellular models in vitro and modified genetically mice (20). The acquisition of the adipocyte phenotype is characterize by chronological and sequential changes in the activity of several transcription factors such as cAMP responsive element-binding protein (CREB), CCAAT/enhancer-binding protein (C/EBP) family members and the peroxisomal proliferator-activated receptor gamma (PPARγ), which control the expression of different genes encoding proteins and effectors in TG accumulation and other characteristics of differentiated adipocytes (21) (Figure 2).

PPARγ is a member of the family of nuclear hormone receptors most implied in the regulation of the adipogenic program. Besides controlling adipogenesis, the PPARγ also has a fundamental role in the control of insulin sensitivity, demonstrated by being an important therapeutic target for the treatment of the diabetes. At least four transcripts of mRNAs exist that codifies two different proteins, PPARγ1 and PPAR γ2. Whereas PPARγ1 express in an ubiquos form, PPARγ2 is the exclusive form in the white and brown adipose tissue in physiological conditions. The lack of both isoforms of PPARγ produces embryonic lethality, due to a lack of placental development (22). The tetraploid rescue of the mutant mice without PPARγ and obtained chimerical mice from blastocystos PPAR γ-/- and PPAR γ+/+ shows that the cells without PPARγ do not contribute to the development of adipocytes. Different murine models with partial lack have been generated from the PPARγ function. PPARγ2 knockout mice do not have an obvious metabolic phenotype in basal conditions (23, 24). However, when it is crossed with leptin-deficient obese mouse (ob/ob), the double knock-out "POKO" mouse displays diabetes and insulin resistance from an early age despite being leaner than an ob/ob mouse (25, 26) .

PPARγ is assisted in the transcriptional activation of its target genes by the participation of the PPARγ coactivator 1 (PGC-1) family of proteins. The first member was originally discovered as binding activator of PPARγ in BAT (27). PGC-1α is induced in parallel to other genes in the control of both adipogenesis and adaptive thermogenesis. But PGC-1α also increases mitochondrial biogenesis, mitochondrial gene expression and oxygen consumption, suggesting a strong coordination between the biogenesis of the mitochondria and energy balance (28). Additional, homologous proteins to PGC-1α have been identified. While PGC-1 related coactivator PRC is ubiquitously expressed, PGC-

1β/PGC-1 related estrogen receptor coactivator (PERC) is expressed in tissues with high energy consumption, including BAT (29, 30). Overexpression of PGC-1β in 3T3-L1 adipocytes in vivo (31), similarly to PGC-1α (32), increases mitochondrial biogenesis and activity. However, in vivo studies demonstrated significant differences between them in their regulation at physiological level. Genetic ablation of PGC-1α resulted in greatly reduced capacity for cold-induced adaptive thermogenesis (33). Several knockout mice of PGC-1β have been reported (34-36) and different lessons have been learnt. Both PGCs could play complementary roles in energy homeostasis. However, according to Lelliot *et al*., PGC-1β would set the tone for both basal and stress-stimulated mitochondrial activity. Conversely, upregulation of PGC-1α would allow the cell to cope with increasing energy demands during physiological stress (37).

Recent molecular studies have demonstrated the dramatic changes in the components of mitochondria present in adipocytes during the process of adipogenesis. Mitochondrial proteins are detectable in differentiating 3T3-L1 adipocytes within four days after differentiation program, increasing numbers of mitochondria up to ten days post-differentiation. This up-regulation of mitochondria biogenesis appears to be coordinated with the initiation of adipogenesis, as activation of PPARγ, as well as the other transcriptions factors closely associated to adipogenesis (Figure 2). Coordination of both the processes of adipogenesis and mitochondria biogenesis suggests that mitochondria play an important role in the differentiation and maturation of adipocytes. Only mitochondria can provide the key substrates and factors necessary to support the lipogenesis during adipogenesis (38, 39). This mitochondrial biogenesis is accompanied by the remodelling of

mitochondria with changes in enzymes involved in fatty acid metabolism, such as acyl-CoA synthetase and forms of acyl-CoA dehydrogenase.

Energetically, the adipocyte differentiation program requires a large amount of ATP content once the cells become fully metabolically active, since the sustained synthesis of fatty acids, is one of the most energy-consuming process in the cell. Finally, glycerol 3-phosphate, the substrate for fatty acid esterification, is produced exclusively by the mitochondria and is needed for the packaging of the lipids in the form of triglycerides in the lipid droplets. WAT mitochondria contain high levels of fatty β-oxidation, which provides an important source of ATP to the mature adipocytes.

It has also been shown that adipocyte development and differentiation is associated with increases in the relative abundance of mtDNA, and up-regulation of the component of the mtDNA replication and expression of the mtDNA encoded components of OXPHOS system, concomitant with increased mitochondrial number. In BAT PGC-1α and PGC-1β enhance expression of nuclear factors that stimulate mtDNA replication and transcription, with the result of up-regulation of specific thermogenic genes (40). In WAT, PPARγ ligands that promote adipogenesis also increase mtDNA levels.

In contrast, the number of mitochondria in mature white adipocytes is significantly lower than that observed during the process of differentiation. Moreover, depending on the anatomical position, mature adipocytes present different mitochondrial content and have different metabolic activity. Thus epidydimal (visceral) adipocytes have more mitochondrial content than inguinal (subcutaneous) adipocytes (41). Before the induction of differentiation; the cells contain diffuse distributed mitochondria. As adipogenesis develops, the cytoplasmatic volume containing mitochondria decreases, with a predominate

substitution with a single, large lipid droplet that occupies nearly the whole cytoplasmatic space Removal of the bulk of this cytoplasmatic content, particularly the removal of excess of mitochondria has not been well investigated. Morphological studies with electron microscopy have clearly shown that massive autophagy activation as well as the recruitment of WAT mitochondria by autophagosomes occurs during 3T3-L1 adipogenesis (42).

b) Autophagic degradation of mitochondria during WAT differentiation.

WAT differentiation process involves a substantially remodelling of progenitors cells to result in a tissue highly optimized to exert its function. Recent studies have shown that autophagy plays an important role in the process of cell remodelling during the adipogeneisis.

Autophagy is a process by which cells degrade macromolecular intracellular material via sequestration in a double membrane structure, known as autophagosome, which then delivers the enclosed material to a lysosome for degradation. When autophagy activity is inactivated or reduced in adipocyte progenitor cells, they lose their ability to differentiate into normal white adipocytes. It has been shown that MEFs obtained from mice with a heterozygous deletion of essential autophagy key genes, *atg5* or *atg7*, failed when stimulated to differentiate into adipocytes.. These findings were also replicated in preadipocytic 3T3-L1 cells either via pharmacological agents or via stable transfection with shRNA direct against either *atg7* or *atg5* (43).

A mouse model in which the *atg7* gene was conditionally knocked-out in adipose tissue had reduced WAT mass when compared to wild-type littermates. These mice also

displayed increase insulin sensitivity and were resistant to high fat diet-induced obesity (42). Notably, white adipocytes from this mouse model had a significantly increased number of mitochondria were observed in normal WAT cells. This was also accompanied by a presence of small lipid droplets rather than a single big droplet. The observed massive accumulation of mitochondria in autophagy-deficient cells provided evidences of the critical role of autophagy in mitochondria degradation during adipogenesis. It is not clear whether the selective and specific degradation of mitochondria via autophagy, known as mitophagy, or a general process of autophagy is responsible of clearance of excess mitochondria during the adipocyte differentiation.

c) Mitochondria in lipid metabolism in adipocytes.

The mitochondria in adipose tissue play a critical role in lipogenesis by providing key intermediates for the synthesis of triglycerides (TG). The generation of glycerol 3-phosphate to sustain TG synthesis is generated by glyceroneogenic pathway and mitochondrial anaplerosis. The generation of acetyl-CoA fatty activation and synthesis before their sterification into TG also requires mitochondria. Medium-chain fatty acid activation occurs in the mitochondrial matrix and phospholipid synthesis is placed in the outer mitochondrial membrane. Moreover, mtDNA levels, as marker for mitochondrial number, were found to be strongly related to lipogenesis in white adipocytes (44), suggesting that lipogenic capacity is determined by mitochondrial content..

Mitochondria in adipocytes also are involved in the regulation of lipolysis. Fatty acids resulting from lipolysis can be oxidized by the fatty acid β-oxidation pathway into the mitochondria matrix compartment. This process of removal of fatty acids within white

adipocytes by fatty acid-induced mitochondrial β-oxidation would protect the organism against fatty acid leakage out of adipocytes, thereby preventing lipotoxicity-induced insulin resistance in other organs such as liver, muscle or beta cells. A decrease in intracellular ATP in white adipocytes induced by uncouplers or inhibitors of the mitochondrial respiratory chain can inhibit the lipolysis stimulated by catecholamines.

d) Mitochondria in thermogenesis in adipose tissue.

In contrast to the lipid storage function of WAT, BAT is primarily a tissue that provided heat via the dissipation of energy, a process known as thermogenesis. The largest part of cellular thermogenesis comes from mitochondria. Mitochondria participate in energy expenditure through fatty acid oxidation and the oxidation of reduced nicotinamine adenine dinucleotide and reduced flavin adenine dinucleotide. During mitochondrial respiration, the electron transport chain oxidises the reduced coenzymes by transferring electrons along several protein complexes to oxygen, the final electron acceptor. During this process, protons are transferred across the inner mitochondrial membrane to generate a proton gradient which is used by the ATP synthese complex to convert ADP to ATP However a large part of this mitochondrial respiration energy is spontaneously dissipated as heat in BAT (45). When animals are subject to cold environment or ingest surplus energy, their sympathetic nervous is stimulated and catecholamines are released. Catecholamines activate adenyl cyclase, which is able to accelerate the conversion of ATP to cAMP. cAMP then activates type 2 deiodinase (DIO2), which converts thyroid hormone T4 to T3, resulting in enhanced local thyroid hormone signalling. In addition, cAMP also activates lipase to release free fatty acids (FFA) from triacyglycerol. These FAA act as fuel

of the thermogenesis and are activators, together with the thyroid hormones, of the inner mitochondrial membrane uncoupling protein-1 (UCP1) (Figure 2). The family of UCPs plays important roles in the thermogenesis process. UCP-1 uncouples mitochondrial respiration from ATP production by causing protons to leak across the inner membrane, enabling energy dissipation as heat.

Using UCP-1 knockout mice (46), an alternative uncoupling protein-independent mitochondrial thermogenesis has been proposed during cold exposure in which leptin was required (47). This thermogenic effect of leptin is mediated by triiodothyronine (T3) and implicates sarco/endoplasmic reticulum Ca (2+)-adenosin triphospatase (SERCA). The authors observed cells within fat depots with morphological features of brown adipocytes but without UCP-1 expression. These adipocytes displayed elevated fat oxidation, induction of thermogenic genes such as DIO2, mitochondrial α-glycerolphospate dehydrogenase or PGC-1α, acquiring properties that enable them to be thermogenic during cold adaptation independently from the protein UCP-1.

Another mitochondrial thermogenesis mechanism is the reduced nicotinamide adenine dinucleotide glycerol-3- phosphate shuttle. In this mechanism there is a transfer of electrons to the complex III of the respiratory chain, with the loss of energy as heat. Mice deficient in this mechanism exhibited a significant reduction in energy expenditure (48).

e) Mitochondria ROS and hypoxia sensing in adipocytes.

Mitochondria are important source of reactive oxygen species (ROS). Excessive caloric intake can increase ROS production, causing cell damage, increased mutations in mtDNA and apoptosis. In addition to this, hyperglycaemia increases ROS causing insulin

resistance in adipocytes (49). ROS reduce oxygen consumption in adipocytes and block fatty acid oxidation, resulting in lipid accumulation (50). While high levels of ROS have toxic effects in proliferation and differentiation of adipocytes (51), low levels are required for cell signalling inside and outside of mitochondria and also for hypoxia sensing. A modest increase in ROS production through mitochondrial leakage when oxygen initially falls below optimal levels has been suggested to induce the hypoxic inducible factor (HIF)-1 stability in order to protect further rises in ROS production (52). Hypoxic conditions have been seen in adipose tissue from obese patients, which could be related to dysregulation of adipokines and inflammation responses during obesity (53).

Mytochondrial dysfunction in adipocytes.

Experimental evidence tends to incriminate the malfunction of adipose mitochondria in obesity and T2D. Mitochondria activity impairment in adipocytes is usually associated with reduced fatty acid β-oxidation, leading to an increase in cytosolic free fatty acids that alter glucose uptake.

Mitochondrial dysfunction increases endoplasmic reticulum stress and reduces adiponectin transcription by a pathway depending on the activation of c-Jun-NH2-terminal kinases and of activating transcription factor-3, which may explain the lower plasma adipocnectin concentration found on obese patients. The abundance of the mitochondrial population is lower in white adipocytes from epidydimal fat pads in ob/ob mice when compared with related fat cells from aged-matched lean mice. Insulin sensitizer and PPARγ rosiglitazone triggers mitochondrial biogenesis in white adipocytes from ob/ob mice, a process accompanied by a remodelling of both mitochondria shape and size. The

abundance of gene transcripts encoding mitochondria proteins is decreased with the onset of obesity, and half of them were found to be up-regulated after treatment with rosiglitazone.

In 3T3-L1 preadipocytes, mitochondrial OXPHOS inhibitors as well as mitochondrial protein synthesis inhibitors impair respiration, leading to TG accumulation (54). However, the cells maintain a fibroblast phenotype and do not acquire adipogenic markers. This TG accumulation has also been shown in the differentiation of 3T3-L1, suggesting that lipid accumulation is not essential for driving adipogenesis. For both processes, however, the inhibition is dependent on CREB, a ubiquitous transcription factor involved in general cellular functions that are activated in response to impaired mitochondria activity (55).

As was mentioned before, high ROS concentrations from mitochondria impairment exert deleterious effects in adipocytes. ROS have been demonstrated to inhibit preadipocyte 3T3-L1 proliferation (56) and differentiation (51). In these conditions, the expression of PPARγ and adiponectin was down-regulated and the expression of proinflammatory adipokines was up-regulated. Furthermore increased ROS production has been found in mouse models of obesity, with overexpression of NADPH oxidase and repression of antioxidant enzymes such as superoxide dismutase 2, gluthathione peroxidase and catalase (57). Similarly, tumor necrosis factor α, (TNFα) decreases endothelial nitric oxide synthase expression and mitochondrial biogenesis in adipose tissue from obese mice (58).

Most reports focus on excessive mitochondrial ROS and mitochondrial-dependent apoptosis as the common end point of the cell dysfunction under lipotoxic conditions.

However, recent literature also describes protein phosphorylation in the mitochondria caused by alteration in kinases activities as crucial for the contribution of mitochondria to cellular dysfunction in lipotoxicity leading to cell death (59). Protein phosphorylation events have also been associated to altered mitophagy in the development of lipotoxicity (60).

In another context, mtDNA levels and expression may influence overall adipocyte physiology. A recent study with mild reduction in mtDNA levels and respiratory chain activity in 3T3-L1 adipocytes caused impaired insulin signalling and glucose transport (61). Interestingly, in obese models such as ob/ob or db/db mice, the levels of mtDNA are very low, which can be increased with treatment of PPARγ agonists (62). But not only in obesity, it has been also reported that mtDNA levels are low in adipose tissue from type 2 diabetic patients (63). Recent studies have supported a new relationship between mtDNA polymorphisms with obesity (64) and with diabetes (65), however the effects of these polymorphisms in the adipose tissue function or expansion and whether they are cause or consequence of disease pathogenesis is unknown (66).

In recent years, some of the proteins that participate in mitochondrial fusion and fission have been associated to muscle mitochondrial dysfunction in obesity and T2D. PPARγ coactivators (PGCs) are positive regulators of mitofusin 2 (Mfn2), a mitochondrial membrane protein that participates in mitochondrial fusion in skeletal muscle (67, 68). Moreover, Mfn2 is induced in BAT by conditions associated with enhanced energy expenditure such as cold or β(3)-adrenergic agonist treatment (67). Alterations in the mitochondrial regulatory pathways constituted by these nuclear co-factors and Mfn2 in adipose tissue may also be related to pathophysiology of obesity and T2D.

Different treatments of disease with mitochondria of adipose tissue as target.

The gradual acceleration of the obesity epidemic suggests that efforts to control it through public health and drug initiatives are not necessarily working. Therapies to counter obesity are currently based on stimulating anorexigenic signals in the central nervous system to suppress appetite or inhibit the absorption of nutrients in the intestine. Despite the increased efforts to understand the relationship between fat, diabetes and cardiovascular risk factors, there are only a low number of drugs on the market that act directly on adipose tissue. These drugs cannot be considered a treatment to reverse or prevent the development of obesity, but to prevent metabolic complications of obesity.

Effects of PPARγ agonists on adipose tissue mitochondria.

The thiazolidinediones (TZDs) belong to the class of antidiabetic drugs and they are powerful stimulators of the differentiation of adipose tissue. In addition, these PPARγ agonists and related factors play a role in many metabolic processes such as the mobilization of lipids from the fat, the neogenesis of glycerol, the production of glucose in the liver as well as the utilization of glucose in muscle and the pancreatic beta cell function (69). All these factors contribute to the insulin sensitization effect of TZDs. The mitochondrial oxidation of fatty acids by adipocytes likely plays an important role in while-body lipid homeostasis control. Treatments with TZDs are associated with increase of mitochondria number in adipocytes, which could explain the beneficial effects of these drugs (39, 63). Studies have linked the effect of rosiglitazone to mitochondrial modifications in white adipose tissue of obese mice. Rosiglitazone triggers mitochondrial

biogenesis in white adipocytes from ob/ob mice, accompanied with remodelling of mitochondria shape and size (39). This increase is much more evident in visceral than in subcutaneous fat as it was shown in rats (70) and could explain the apparent redistribution of fat from omental to subcutaneous depots. .

Another TZD, pioglitazone, has also been shown to stimulate mitochondrial biogenesis through PGC1-α and to increase fatty acid β-oxidation in subcutaneous fat from diabetic patients (63). Activation of fatty acid oxidation, which translates to increased energy expenditure is a potential strategy to prevent or limit fat accumulation in obese humans, and requires identification of new pharmacological compounds.

Mitochondrial uncoupling and UCPs targets in the trans-differentiation of WAT to BAT.

Several studies have demonstrated that any treatment for obesity other than reducing energy intake has to increase energy expenditure to elevate resting metabolic rate. The uncoupling of mitochondrial OXPHOS could be a therapeutic approach. Strategies used to dissipate energy as heat and to decrease ATP production through increase proton leak have been proposed.

2-4-Dinitrophenol was used as artificial uncoupler with a significant reduction in body weight in the absence of dietary restriction via an increased metabolic rate, although it was discontinued due to side effects such as uncontrolled hyperthermia, tachycardia, diaphoresis and tachypnoea (71). The protonophore FCCP produced also a mild mitochondrial uncoupling, with a reduced intracellular TG content and lipid synthesis and enhanced lipolysis though decrease in the transcriptional activity of PPARγ and C/EBPs (72).

Molecular pathways able to modulate adaptive thermogenesis in WAT should provide a safe way to increase energy expenditure. Uncoupling proteins are implicated in adaptive thermogenesis, fatty acid oxidation, aging, prevention of ROS formation and body weight regulation. *In vitro* studies have demonstrated that overexpression of UCP-1 in both BAT and WAT in transgenic aP2-ucp-1 mice and preadipocytes during adipocyte differentiation reduce accumulation of lipids.

Mitochondrial biogenesis and UCP-1 expression in WAT increases after adrenergic stimulation due to cold exposure or by treatment with β3-adrenoceptor (ADBR3) agonists. ADBR3 KO mice have diminished BAT in white fat depots. ADBR3 has been detected in adult human WAT, and adrenergic stimulation can increase UCP-1 expression.

The presence of adipocytes in WAT with brown-like adipocytes (brite adipocytes) has opened new approaches in order to increase energy expenditure. The increase correlates with a reduction of diet-induced obesity. Different studies have shown up-regulation of UCP-1 or increase mitochondria biogenesis in white adipose tissue. Ectopic expression of PGC-1α in WAT leads to mitochondria biogenesis and UCP-1 up-regulation and studies in rodents with treatment with thyroid hormone analogues or deletions of receptor-interacting protein 140 (RIP140) and retinoblastoma protein (pRb) showed increased UCP-1 gen expression in white adipocytes. In addition, all trans-retinoic acid treatment increased UCP-1 expression in WAT. From all these studies, how to transform white adipocytes into highly oxidative brown adipocytes remains an interesting but still difficult challenge (73). And just recently, a PGC1-α-dependent myokine called Irisin was also shown to drive brown-fat-like development of subcutaneous white fat and thermogenesis, stimulating

UCP1 expression. Irisin caused a significant increased in total body energy expenditure and resistance to obesity-linked insulin resistance (74).

PRD1-BF-1-RIZ1 homologous domain containing protein 16 (PRDM16) is an important early regulator of brown adipogenesis. The study of this regulator led to the discovery that skeletal muscle and some depots of BAT share a common myogenic factor 5 (Myf5) expressing progenitors (14). PRDM16 is selectively expressed in brown adipocytes and is a transcriptional coactivator of PGC1α and PGC1β, increasing expression of genes important for mitochondrial biogenesis, uncoupling and OXPHOS. Transgenic overexpression of PRDM16 in adipose increases mitochondrial gene expression in clusters of BAT cells within white adipose tissue. Bone morphogenetic protein 7 (BMP7), which can promote PRDM16, is another potential therapeutic agent to induce brown fat differentiation (75), although it use will need to be monitored due to its effect on angiogenesis and bone formation.

The question of thermogenic brown adipose tissue in humans remains open, as it has been proposed that these adipocytes could be pharmaceutically activated to combat obesity and age-related diseases. Recently it has been shown how exposure to cold temperature rapidly promoted alternative activation of adipose tissue macrophages, which secrete catecholamines to induce thermogenic gene expression in brown adipose tissue and lipolysis in white adipose tissue (76, 77). Moreover the idea of BAT transplantation in humans becomes interestingly appealing due to the increasing knowledge of stem cell technology (78).

*Inhibition of mitophagy in adipose tissue as therapeutic treatment***.**

Another potential therapeutic intervention targeting mitochondria in adipose tissue would be possible through the use of lipophilic pharmacological inhibitors of autophagy that could have implications for intervention in obesity and insulin resistance. This intervention derives from the whole-body metabolism changes that were observed in *atg7* conditional knockout mice. How the inactivation of autophagy in adipose tissue improves whole-organism metabolism is not yet fully understood. But of interest was the enhanced free fatty acid metabolism through increased levels of mitochondria. The autophagy-deficient white adipocytes showed increased fatty acid b-oxidation rates, which could be responsible for the decreased fed plasma levels of free fatty acids. Clinical studies are being performing with a drug approved for the FDA, the hydroxychloroquine. The mechanism of this drug is preventing the development of type 2 diabetes by autophagy inhibition.

In the same direction of BAT transplantation, another potential therapeutic approach is inactivation of autophagy *ex vivo* with the manipulation of adipose stem cells. These cells isolated from adipose tissue from adults obese and diabetic patients, could be propagated, genetically manipulated *in vitro*, and then be transplanted back with to the same individual to create autophagy-compromised adipose tissue in those patients.

Increase in mitochondrial oxidation in WAT by bioactive food components.

Recent studies have shown that different dietary components known as bioactive food components could increase oxidative capacity in WAT.

A diet rich in marine 3-omega long chain polyunsaturated fatty acids (PUFA) such as eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) increased mitochondrial

biogenesis, reduced WAT mass and increased fatty acid oxidation in rodents (79) and humans (80). This protected against the metabolic dysregulation found in insulin resistance and obesity in rodents and improved insulin sensitivity in humans. Also a lowering of TAG and inflammation effect in adipose tissue was also seen as beneficial effects of PUFAs (81).

Polyphenols also may have beneficial effects in obesity and its complications increasing mitochondrial biogenesis and oxidative capacity in WAT. Polyphenol resveratrol is able to stimulate SIRT, a deacetylase that targets PGC-1α and other mitochondrial transcription factors such as ERR-α, NRF-1 and TFAM. Studies in mice fed with a diet containing resveratrol showed beneficial effects by reducing fat mass, improving metabolic parameters (insulin, glucose, insulin grow factor-1) and increasing lifespan (82, 83). These effects were also associated with up-regulation of the same genes in diabetes. Other polyphenols such as quercetin (84), proanticyanidines (85) and synthetic mimetics direct at SIRT activation with beneficial effects may be attractive candidates against obesity and diabetes.

Vitamin B3 is another nutritional component with direct effects in energy metabolism during the development of obesity. The protective effects were associated to mitochondrial biogenesis, possibly mediated by SIRT1, and increased stress resistance of mitochondria in addition to other beneficial effects on HDL cholesterol or adipokine secretion (86).

Further evidence shows that retinoids could also have the potential to enhance mitochondrial activity in adipose tissue. All trans retinoic acid (ATRA) treatment reduced obesity by increased mitochondrial UCP-1 expression in WAT and other features of WAT

trans-differentiation to BAT (32, 87), although its application will require safety assessment due to its implication in development.

Summary

The study of the adipocyte offers new challenges to be able to explore the metabolic problems associated with the development of obesity and age-derived complications. Excess of adipose tissue is accompanied by an increase in the risk of developing insulin resistance and type 2 diabetes. However, the total or partial absence of adipose tissue or fat accumulation in other tissues, together with the toxic process called lipotoxicity, is also associated with an increase in the risk of metabolic complications associated to obesity. Adipocytes help to maintain the appropriate balance between energy storage and expenditure. The observations that impaired mitochondrial activity could predispose to obesity and mitochondria biogenesis is also decreased in obesity demonstrate an important role of mitochondria in complications associated to obesity. Intervention targeting mitochondria in adipose tissue could offer new strategies of treatment. Interestingly, the high oxidative capacity of BAT due to its high mitochondrial density, expression of fatty acid oxidation enzymes and respiratory chain components and the discovery of its presence in humans, make this tissue and its mitochondria one of the targets in treatment of obesity complications. Efforts are underway to bring more challenges in terms of trans-differentiation of WAT to BAT, BAT transplantation into humans and activation of WAT mitochondria through bioactive dietary components.

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Figure legends

Figure 1. Model of origin of adipocytes in different fat depots. Progenitor cells derived from mesenchimal stem cells may yield progenitor cells expressing or not Myf5 (Myf5+ or Myf5-). The Myf5+ progenitor cells may differentiate into brown adipocytes or into myotubes. Myf5- progenitor cells may differentiate into preadipocytes, which may differentiate into white preadipocytes and then in mature white adipocytes. There are inducible brown adipocytes in subcutaneous WAT that are not derived from Myf5+ progenitor cells, which origin is under discussion: from brown preadipocytes or from trans-differentiation of matures white adipocytes. Mitochondria is present in preadipocytes and mature adipocytes in both WAT and BAT.

Figure 2. Mitochondrial functions in adipocytes from WAT and BAT. In adipocytes, pyruvate derived form glucose by glycolysis is converted into acetyl-CoA in the matrix. Alternatively, fatty acids from lipolysis can be taken into the mitochondrial matrix and be oxidized to acetyl-CoA through the fatty acid β-oxidation. The acetyl groups are oxidized via the TCA cycle. The electrons derived form oxido-reduction reactions are finally accepted by O_2. The energy retrieved from electrochemical proton gradient in the respiratory chain is used for ATP synthesis. However, in brown adipocytes, UCP-1 uncouples the respiratory chain of ATP production, converting the metabolic energy in heat. The activity of transcription factors is turn on during both processes of adipogenesis and mitochondrial biogenesis in WAT and BAT.