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REVIEW

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Fatty acid metabolism and the basis of brown adipose tissue function

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ABSTRACT

Obesity has reached epidemic proportions, leading to severe associated pathologies such as insulin resistance, cardiovascular disease, cancer and type 2 diabetes. Adipose tissue has become crucial due to its involvement in the pathogenesis of obesity-induced insulin resistance, and traditionally white adipose tissue has captured the most attention. However in the last decade the presence and activity of heat-generating brown adipose tissue (BAT) in adult humans has been rediscovered. BAT decreases with age and in obese and diabetic patients. It has thus attracted strong scientific interest, and any strategy to increase its mass or activity might lead to new therapeutic approaches to obesity and associated metabolic diseases. In this review we highlight the mechanisms of fatty acid uptake, trafficking and oxidation in brown fat thermogenesis. We focus on BAT's morphological and functional characteristics and fatty acid synthesis, storage, oxidation and use as a source of energy.

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Introduction

Importance of adipose tissue in obesity

Current life styles and continuous nutrient excess are increasing the incidence of obesity at an alarming rate, especially at younger ages. Worldwide there are more than 600 million obese subjects and, importantly, most of the world's population live in countries where overweight and obesity kills more people than underweight.[1] Very worrisome are the concurrent and parallel increases in the prevalence of pathologic conditions associated with obesity such as insulin resistance, cardiovascular and Alzheimer disease, cancer, and type 2 diabetes.

Over the last 2 decades the obesity epidemic has put a spotlight on the adipose tissue as a key player in the mechanisms involved in obesity-related disorders. Human fat consists of energy-storing white adipose tissue (WAT) and brown adipose tissue (BAT), which controls thermogenesis by dissipating energy to produce heat. In addition to adipocytes, adipose tissue is well vascularized and contains connective tissue and numerous immune cells such as macrophages, T and B cells, mast cells and neutrophils.[2] It has been demonstrated that obesity-induced insulin resistance is due to several factors: ectopic fat deposition,[3] increased inflammation and endoplasmic reticulum (ER) stress,[4,5] adipose tissue hypoxia and mitochondrial dysfunction,[6,7] and impaired adipocyte expansion and angiogenesis.[8-10] Fat is also an active endocrine tissue that secretes hormones such as leptin, adiponectin or resistin and inflammatory cytokines such as tumor necrosis factor α (TNFα), interleukin (IL)-6, IL-1β, etc. in response to several stimuli. Adipose tissue is therefore a complex and active organ controlling very important metabolic pathways such as energy expenditure, appetite, insulin sensitivity, endocrine and reproductive functions, inflammation and immunity.

Rediscovery of human active BAT

The fusion of positron-emission tomography (PET) and computed tomography (CT) images has allowed radiologists to retrieve both functional and structural information from a single image. In the course of using PET-CT to detect and stage tumors in humans, active BAT that increased after cold exposure was rediscovered.[11,12] Until that moment BAT was considered exclusive to rodents and human neonates. However, the breakthrough came in 2009, when 5 independent research groups used PET-CT to identify the presence

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and relevance of BAT in adult humans.[13-17] All showed major depots of metabolically active fat in the cervical-supravicular region. Furthermore, these depots expressed type 2 iodothyronine deiodinase (DIO2), the β3-adrenergic receptor, and the brown adipocyte-specific protein, uncoupling protein 1 (UCP1), which physiologically uncouples ATP production from mitochondrial respiration, thereby dissipating energy as heat.[18] The expression of these proteins indicated the potential responsiveness of human BAT to both hormonal and pharmacological stimuli. Here, we review the possibility that BAT could be induced to enhance its lipid-burning function even further and thus be an effective target to fight against obesity and associated metabolic disorders.

Brown adipose tissue characteristics

BAT localization and morphology

Our knowledge of BAT has been significantly influenced by studies in rodent models. There, BAT is situated at the interscapular, cervical, mediastinal and retroperitoneal regions.[19] While in infants BAT is mainly found in the interscapular area, in adult humans BAT is localized in a region extending from the anterior neck to the thorax.[20]

In contrast to white adipocytes, which are unilocular, with polygonal morphology that optimizes their fat storing capacity, brown adipocytes are multiloculate and their color is due to their high mitochondrion content and vascular suply.[21] BAT thermogenesis takes place in its numerous, densely-packed mitochondria containing the BAT-specific inner membrane protein UCP1. Multilocular lipid stores provide a rapid source of fatty acids (FAs) for activated mitochondria. FAs released into the circulation by the WAT are also an important source of FAs for brown adipocytes. Thermogenesis is classified into: 1) Obligatory thermogenesis, which takes into account the standard metabolic rate (energy used for basic function of cells and organs) and the heat generated during food metabolism (digestion, absorption, processing and storing of energy); and 2) Adaptive thermogenesis or heat production in response to environmental temperature and diet. Adaptive thermogenesis can be further divided into: cold-induced shivering thermogenesis, which takes place in skeletal muscle; cold-induced non-shivering thermogenesis, which takes place mainly in brown fat; and diet-induced thermogenesis triggered by overfeeding, which also takes place in BAT.[22] Thus, BAT generates heat, with 2 main consequences: protection against cold exposure via non-shivering thermogenesis; and dissipation of the excess of energy from food. Therefore, BAT can be considered as an organ that burns off excess lipids, and further examination of this property may lead to the development of novel strategies against diet-induced obesity.

Molecular BAT signature: beige and brown adipocytes

Comprehensive research is being done to define the still under debate cellular heterogeneity of human fat.[23] At least 2 types of thermogenic adipocyte exist in rodents and humans: classical brown adipocytes and beige (also called brite) adipocytes. They have both anatomical and developmental differences. While brown adipocytes are mainly located in the above-mentioned BAT depots, beige adipocytes co-locate with white adipocytes in WAT near vascular and neural innervation and appear in response to certain stimuli, such as chronic cold exposure or β3-adrenergic signaling. In adult humans the ratio of brown to beige increases as one moves deeper within the neck and back.[20,24-27]

BAT releases endocrine factors such as insulin-like growth factor I (IGF-1), IL-6 or fibroblast growth factor 21 (FGF21).[28] Brown adipocytes differ from white adipocytes due to their high expression of DIO2, the lipolytic regulator cell death-inducing DNA fragmentation factor-α-like effector A (CIDEA), and the transcription co-regulators PR domain-containing 16 (PRDM16) and peroxisome proliferator activated receptor gamma coactivator 1 α (PGC1α).[29,30] Beige and brown adipocytes have overlapping but distinct gene expression patterns.[31] Both express the main thermogenic and mitochondrial genes, including *Ucp1*. However, some surface markers such as CD137, TBX1 and TMEM26 seem to be specific to murine beige adipocytes[24,27] while other genes, like *Zic1* and *Lhx8*, appear to specifically mark classic brown adipocytes.[20,32] Basal UCP1 expression and uncoupled respiration before hormonal stimulation are highest in brown fat cells and lower in beige cells, the lowest being found in white fat cells.[27] However, stimulation with a β3-adrenergic agonist elevates UCP1 expression in beige cells to levels seen in brown fat cells (fold-change compared to white cells).[27,33] This suggests that beige cells have a unique molecular signature with a dual role. They store energy in the absence of thermogenic stimuli but initiate heat production when appropriate signals are received.[27] White-to-beige conversion of adipocytes is a potential therapeutic approach to targeting obesity; however, the signals involved in this process still remain unclear.

Brown adipocytes arise from mesenchymal precursor cells common to the myogenic cell lineage and express myogenic factor 5 (*Myf5*).[34] Beige adipocytes derive from precursor cells that differ from those in classical BAT and are closer to the white adipocyte cell lineage.

Thus, while brown adipocytes come from a $Pax7^+$/$Myf5^+$ lineage shared with skeletal muscle, white and beige adipocytes derive from $Pax7^-$/$Myf5^-$ cells via distinct precursor cells. Beige adipocytes differentiate following activation by cold or other stimuli, and when the cold challenge is ceased, they become inactive, taking on the morphology of a white adipocyte.[35] However, the cell lineage and developmental origin of the adipose tissue is not so simple. Individual brown and white fats contain a mixture of adipocyte progenitor cells derived from $Myf5^+$ and $Myf5^-$ lineages, with numbers varying depending on the depot location. In fact, beige adipocytes in the retroperitoneal WAT are $Myf5^+$.[36] For further information about the developmental origin of white, beige and brown adipocytes see other excellent reviews.[34,37,38]

At least 2 mechanisms have been postulated to occur during the browning process: transdifferentiation of white into beige adipocytes *vs.* de novo brown adipogenesis. The transdifferentiation process is the conversion of a differentiated somatic cell type into another one.[39] The transdifferentiation of white into beige adipocytes has been reported in several studies.[40-43] On the other hand, Lee *et al.* have shown that β3-adrenergic stimulation induces the proliferation and further differentiation of precursors in WAT.[44] Furthermore, Myf5+ precursors have also been reported to differentiate into white adipocytes.[36,45] Thus, whether the browning process arises from transdifferentiation or *de novo* brown adipogenesis is far from being fully understood. One could hypothesize that the 2 processes might take place simultaneously and to a different extend depending on the adipose depot or browning stimuli.

BAT activity in pathological conditions

Human studies showed that BAT was reduced in aging and in obese and diabetic patients, indicating that BAT participates in both cold-induced and diet-induced thermogenesis.[13] This significant discovery highlights that any strategy able to increase the mass or activity of BAT could potentially be a promising therapy for obese and diabetic patients. In contrast, enhanced BAT activation has been described as a negative effect on cancer cachexia.[46] In this study, mice with cachexia-inducing colorectal tumor showed increased BAT activity despite thermoneutrality, indicating that BAT activation may contribute to impaired energy balance in cancer cachexia. Hibernoma is another BAT pathological condition. A hibernoma is a benign tumor of BAT that up to date has no clear explanation of its cause. It is very rare in humans and it is successfully treated by complete surgical excision.[47,48] It has shown to express UCP1 and thus potentially contribute to whole-body energy balance.

Activators of thermogenesis

Despite some controversy, a large body of evidence indicates that browning entails the enhancement of thermogenesis within WAT, i.e. increased expression and activity of UCP1 in what are normally considered WAT depots.[49] Several factors have been described to activate the browning of the adipose tissue such as irisin,[50] natriuretic peptides,[51] bone morphogenetic protein 7 (BMP7)[52] and BMP8b,[53] norepinephrine,[54] meteorin-like,[55] bile acids,[56] adenosine,[57] or FGF21.[58] Interestingly, recent studies have shown activation of human BAT by the β3-adrenergic receptor agonist mirabegron.[59] β3-adrenergic receptor is expressed in humans on the surfaces of brown and white adipocytes and urinary bladder. Cypess *et al.* administered 200 mg of oral mirabegron, currently approved to treat overactive bladder, to healthy and young humans. Mirabegron acutely stimulated human BAT thermogenesis and increased resting metabolic rate. Further studies would be needed to explore the specificity of mirabegron's mechanism of action, possible adverse effects such as tachycardia, and the dose used, which was 4-fold higher than that prescribed for overactive bladder.

Although a large number of browning agents have been described (extensively reviewed elsewhere)[60,61] some studies showed that browning was a secondary consequence of enhanced heat loss, *e.g.* because of fur disruption in rodents.[49] The search for potential therapeutic browning agents to increase metabolism at thermoneutrality, to function through mechanisms other than those affecting heat loss and to finally decrease obesity should thus continue.

Fatty acid storage

FA synthesis, storage and metabolism are essential during thermogenesis because they are required for UCP1 proton transport activity in BAT.[62,63] Fundamentally, brown adipocytes have 2 mechanisms to obtain lipids: FA uptake via lipoproteins carriers and *de novo* FA synthesis, also known as lipogenesis.

Fatty acid uptake

While brown adipocytes synthesize FAs, the enzyme lipoprotein lipase (LPL), bound at the endothelial cell surface, is the major source of FAs in BAT.[64] After a meal, dietary lipids are transported by chylomicrons and very low density proteins (VLDL) via lymphatic vessels into the bloodstream. Once triglyceride (TG) rich-

lipoproteins reach the bloodstream, LPL hydrolyzes them into free FAs (FFAs) and monoacylglycerol (MG) for BAT uptake. Indeed, BAT is an efficient modulator of triglyceridemia and it is contemplated as a major plasma lipid-clearing organ in rodents.[65-67] In fact, FA uptake under cold exposure is higher in BAT than in skeletal muscle.[65] Under cold exposure, the β3-adrenergic pathway enhances BAT FA flux and clearance via increased expression and activity of LPL.[65] However, the increase in LPL activity has also been shown to trigger adiposity and insulin resistance.[68] Adipocyte-specific LPL KO animals show an increase in FAs derived from lipogenesis and a decrease in polyunsaturated FAs, accompanied by an increase in the expression of lipogenic genes.[69] Glycosylphosphatidylinositol-anchored high density lipoprotein binding protein 1 (GPIHBP1) transports LPL across capillary endothelial cells, and GPIHBP1 KO mice show mislocated LPL in many tissues, including BAT,[70] decreased TG content and deficient lipolysis,[71] Administration of PPARγ agonists, such as rosiglitazone, in rodents increases BAT TG clearance and LPL activity, while lipogenesis is not increased. This suggests that under rosiglitazone treatment brown adipocytes metabolize FAs derived from TG hydrolyzed from lipoproteins or recycled from lipolysis.[72]

Fatty acid transport

Once FAs are released by LPL, they are taken up into cells by plasmatic membrane receptors and transported for further utilization or storage.[65,73-75] The most important FA transporters in BAT are the following (Fig. 1):

Cluster of differentiation 36 (CD36)

This integral membrane protein is expressed in BAT among other tissues.[73] CD36 belongs to the class B scavenger receptor family of cell surface proteins, whose main function is to translocate FAs, released by LPL activity, across the plasmatic membrane and thus provide a substrate for BAT thermogenesis.[65] Under cold exposure, CD36 expression and activity increase (Fig. 1).[65] However, CD36 is not a simple translocase; it is considered a lipid sensor and a regulator of FA uptake and transport in adipocytes.[76-78] CD36 KO mice die after 24 hours of cold exposure, which implicates CD36 in thermogenesis.[65] In addition, CD36 genetic variability has been associated with body weight differences in humans.[79]

FA transport proteins (FATPs)

There are 6 isoforms of FATPs. FATP1 and 4 can be found specifically in BAT (extensively reviewed elsewhere).[80] These proteins translocate FAs into cells.[81] They display very long-chain acyl-CoA synthetase activity,[64,82] and their overexpression increases FA uptake.[83]

G-protein-coupled receptors (GPCRs)

GPCRs comprise a family of proteins that respond to several ligands, and trigger a cascade of intracellular signaling (extensively reviewed elsewhere).[84] GPR41 (also known as FFA3) and GPR120 are activated by medium and long-chain FFA in BAT, and they are considered as sensors that maintain cell lipid homeostasis.[85] Interestingly, GRP120 mRNA expression increases under cold exposure (3).[86]

Fatty acid binding proteins (FABPs)

Once in the cytoplasm, FFAs are minimally soluble. To prevent disruption of membrane or lipotoxicity, cells have soluble proteins that bind FFAs and transport them.[87] Brown adipocytes harbour 3 different isoforms: FABP3, FABP4 and FABP5.[88] FABP4, commonly known as adipocyte protein 2 (aP2), has been extensively used as a marker of adipocyte differentiation.[89] Although FABP4 is the most abundantly expressed isoform in BAT, only FABP3 and FABP5 are increased by cold exposure in rats.[88,90] Interestingly, FABP3 is overexpressed in mice with diet-induced obesity and in UCP1 KO mice, and it is associated with increased thermogenesis.[91] Thus, FFAs bind to FABPs present in brown adipocytes and are either stored or utilized to maintain thermogenesis (Fig. 1).

Lipogenesis

De novo FA synthesis or lipogenesis is the metabolic pathway that synthesizes FAs and ultimately induces TG synthesis.[92,93] Excellent studies on WAT report that glucose uptake, a preliminary step in *de novo* FA synthesis, is also involved in the regulation of lipogenesis.[94,95] Whether BAT contributes to this process is still unclear. A recent study examined the dynamics of *de novo* lipogenesis and lipolysis in classic brown, subcutaneous beige and classic white adipose tissues during chronic β3-adrenergic receptor stimulation.[96] Sustained β3-adrenergic stimulation increased *de novo* lipogenesis, TG turnover, and the expression of genes involved in FA synthesis and oxidation similarly in all adipose depots indicating that FA synthesis and FAO are tightly coupled during chronic β3-adrenergic stimulation.

Lipogenesis takes place in the cytosol and it can be summarized in 3 steps: synthesis of FAs from acetyl-CoA,

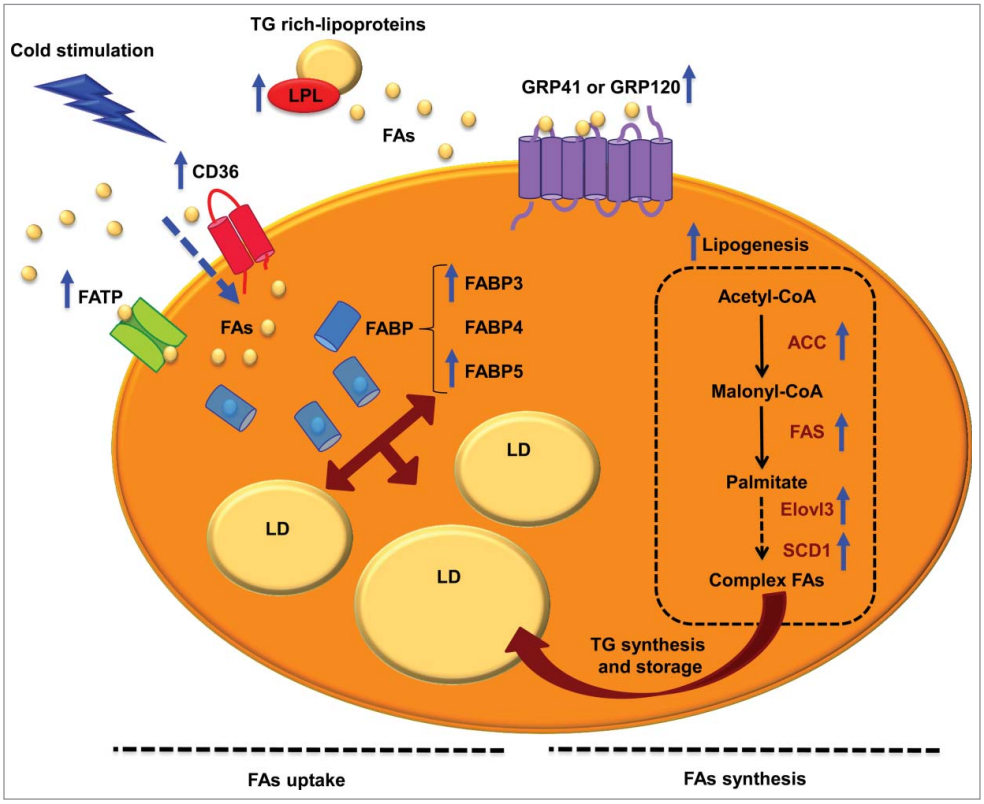

Figure 1. FA uptake and lipogenesis in brown adipocytes. Schematic representation of FA uptake, transport, synthesis and storage in brown adipocytes, which provide substrate to mitochondria for thermogenesis. While brown adipocytes synthesize FAs, the enzyme lipoprotein lipase (LPL) is the major source of FAs in BAT. Once triglyceride (TG) rich-lipoproteins reach the bloodstream, LPL hydrolyzes them into FFAs for BAT uptake. FAs are sensed and taken up by FFAs 3 (FFA3) proteins, cluster of differentiation 36 (CD36) and/or FA transport proteins (FATPs). Inside the cytoplasm, FAs are transported by FA binding proteins (FABP). On the other hand, FAs can be synthesized by lipogenesis. This process takes place in the cytosol, and the first phase begins with the formation of malonyl-CoA from acetyl-CoA by the action acetyl-CoA caboxylase (ACC). Then, FA synthetase (FAS) catalyzes various reactions to finally generate palmitate, a 16-carbon saturated FA. In BAT, the last phases of lipogenesis are carried out by very long chain FA 3 (ELOVL3) and stearoyl-CoA desaturase 1 (SCD1). Once FAs are synthesized they can be esterified, becoming available for FAO or stored as TG in lipid droplets (LD). Blue arrows indicate enhanced processes or expression of proteins after cold stimulation and β3-adrenergic receptor activation.

elongation and desaturation. Lipogenesis begins with the carboxylation of acetyl-CoA to malonyl-CoA, the committed step catalyzed by acetyl-CoA carboxylase (ACC), which requires biotin cofactor.[97,98] Finally, FA synthetase (FAS), a multifunctional cytosolic protein, catalyzes different reactions to form palmitate, a 16-carbon saturated FA.[93] It has been shown that adipose-specific FAS KO mice have increased energy expenditure, which comes from the browning of subcutaneous WAT.[99]

In the second phase of lipogenesis, FAs derived from the FAS enzymatic reaction, are elongated by membrane-bound enzymes mostly localized in the ER.[93] This process is induced by the elongation of very long chain FA (ELOVL) proteins, which have 7 members in mice and humans.[100] Among them, Elovl3 is expressed in BAT,[101] and its expression and activity are upregulated under cold conditions to re-establish the intracellular pool of TG and preserve lipid homeostasis.[102-104] ELOVL3 KO mice are resistant to diet-induced obesity, showing an increase in energy expenditure.[104]

The final phase of lipogenesis is the desaturation of FAs. This process is catalyzed by desaturases, such as stearoyl-CoA desaturases (SCDs), which introduce double bonds at a specific position in a FA chain.[93,97] SCD1 is the predominant isoform in adipose tissue and liver, and its downregulation in liver prevents diet-induced obesity.[105,106] SCD1 KO mice show an increase in glucose uptake and glycogen metabolism, higher energy expenditure and basal thermogenesis in BAT.[107]

Once FAs have been synthesized they can be esterified to be used for fatty acid oxidation (FAO) or stored as TG in lipid droplets. In BAT, the proper levels of TG are associated with thermogenic activity.[108] Since TG are composed of molecules of glycerol and 3 esterified FAs, TG synthesis depends on intracellular levels of glycerol-3-phosphate (G3P), the activated form of glycerol and

first intermediary in TG synthesis. Thus, G3P levels are preserved under rigorous control in brown adipocytes.[66] It has been shown that rosiglitazone, a PPARγ agonist, increases BAT glycerolkinase activity, which phosphorylates glycerol generating G3P.[67] Since G3P comes from glucose, glucose metabolism plays a key role in BAT, as an important glucose-clearing organ, specifically under sympathetic activation.[65] In fact, G3P is a major substrate for BAT respiration.[109]

In conclusion, coordinated FA uptake, transport and synthesis contribute to thermogenesis in BAT (Fig. 1). For this reason, the maintenance of the intracellular pool of TG to preserve lipid homeostasis in brown adipocytes is so important.[110,111] Indeed, any of these processes might be a potential target in the treatment of obesity-related disorders, such as insulin resistance and diabetes.

Fatty acid storage

Cells package the excess of intracellular lipids in a phylogenetically conserved organelle called lipid droplet, preventing the lipotoxicity of lipids and cholesterol in the cytoplasm.[112,113] Lipid droplets are composed of a neutral lipid core (cholesteryl ester and TGs) covered by a phospholipid monolayer, which contains proteins that regulate lipolysis. Among the lipid droplet membrane proteins found in brown adipocytes we will highlight fat storage-inducing transmembrane protein 2 (FITM2/FIT2), CIDEA and fat-specific protein 27 (FSP27 or CIDEC).

FITM2/FIT2 is strongly expressed in brown adipocytes and it determines the number of new lipid droplets formed in these cells.[114] FIT2 KO mice show few but larger lipid droplets in interscapular BAT without changes in cellular TG levels.[115] Thus, FIT2 is not essential for lipid droplet formation but it is required for normal storage of TG *in vivo*.

CIDEA is one of the 3 members of cell death-inducing DFF45-like effector (CIDE) family of proteins, which has emerged as an important regulator for various aspects of metabolism.[116] CIDEA is highly expressed in lipid droplet membranes and mitochondria of brown adipocytes. It is involved in the browning phenomenon and it is considered as a BAT differentiation marker.[117,118] CIDEA plays an inhibitory role during thermogenesis because it negatively modulates the activity of UCP1, being the first protein known to interact directly with an uncoupler protein.[119-121] Moreover, CIDEA mRNA and protein are down-regulated after cold exposure[121] and CIDEA-null mice are resistant to diet-induced obesity.[118]

FSP27 also belongs to the CIDE family, and it is overexpressed during adipogenesis in BAT. It has been proposed as a novel lipid droplet protein that promotes TG storage and inhibits lipolysis, playing a key role in body energy homeostasis.[122,123] FSP27 interacts directly with another lipid droplet protein, perilipin 1, which is involved in lipolysis by indirect activation of the adipose triglyceride lipase (ATGL) at the lipid droplet surface.[123] Furthermore, FSP27 KO mice have larger lipid droplets and higher TG serum levels.[124]

Thus, the above-mentioned proteins involved in FA storage contribute to the multilocular phenotype of brown adipocytes. Lipid droplets prevent lipotoxicity and provide FAs as substrates for mitochondrial thermogenesis. Therefore, the regulation and function of these proteins might be a target for enhancing BAT activity.

Fatty acids as a source of energy

Lipolysis

Intracellular lipolysis is the catabolic process that allows cells to obtain FAs and glycerol from the breakdown of TG stored in lipid droplets. Cells use these FAs and glycerol endogenously in times of metabolic need with the exception of WAT, which can also export them to circulation so they can reach other tissues in fasting or exercise periods.[125] In BAT, lipolysis is vital to its main physiological function, the cold response. To raise body temperature BAT dissipates energy as heat and mobilizes FAs from the breakdown of TGs stored in lipid droplets to mitochondria for thermogenesis.[108] Lipolysis can be classified in 2 types depending on the pH-optimum of action of the enzymes involved. Accordingly, there is neutral lipolysis, which relies on 3 key enzymes that work at a pH-optimum of 7, and acid lipolysis that depends on lysosomal degradation of TG by acidic lipases. Next we will focus on neutral lipolysis.

Neutral lipolysis

Neutral lipolysis takes place in the cytosol and it is the result of the action of 3 consecutive lipases that hydrolyze each ester bond of TG to obtain 3 FAs and glycerol. The 3 major lipases are ATGL, hormone sensitive lipase (HSL) and monoacylglycerol lipase (MGL).

ATGL/Desnutrin/calcium-independent phospholipase A2 ζ (iPLA2ζ) was discovered in 2004 by 3 independent laboratories.[126-128] It is strongly expressed in both WAT and BAT and performs the first step of TG lipolysis, the hydrolysis of TG into diacylglycerides (DG) and FAs (Fig. 2).[129] It exhibits high substrate specificity for TG and it is associated with lipid droplets.[126] ATGL regulation is complex and mRNA or protein levels of the enzyme do not always correlate with enzyme activity.

This happens because ATGL has strong post translational regulation that often requires accessory proteins.[130] CGI-58 (Comparative gene identification-58) is a coactivator of ATGL that is necessary for full hydrolase activity.[131] On the other hand, G0S2 (G0/G1 switch gene 2) inactivates ATGL.[132] ATGL deficient mice accumulate TGs in all organs and have enlarged fat depots, especially BAT, which also displays defective thermogenesis.[133] Moreover, aP2-ATGL overexpressing mice display increased lipolysis and FAO in WAT and increased thermogenesis, resulting in higher energy expenditure and resistance to obesity.[134] Microarrays from ATGL KO BAT indicate a decrease in mRNA expression of genes involved in FAO and down-regulation of PPARα target genes.[135,136] In addition, a study using ATGL knock down brown adipocytes demonstrated that ATGL is required for the maximal induction of genes involved in FAO and mitochondrial electron transport.[137] All together, these results point to the crucial role of lipolysis and its first step, TG hydrolysis by ATGL, in thermogenesis.

HSL performs the second step in TG lipolysis, hydrolyzing DG into MG and FAs (Fig. 2).[138] Similarly to ATGL, HSL mRNA and protein expression are highest in WAT and BAT.[139,140] Although DG are its preferred substrate, HSL can also hydrolyze TG, cholesterol esters, MGs and retinyl esters.[141] Before ATGL was known, HSL was believed to be the rate-limiting enzyme for TG hydrolysis. However, HSL-/- mice efficiently hydrolyze TG and accumulate large amounts of DG, indicating that, *in vivo*, HSL has a more important role as a DG than as a TG hydrolase.[142] Activation of HSL occurs in 2 steps: protein phosphorylation and binding to perilipins.[143] HSL has 5 putative phosphorylation sites and

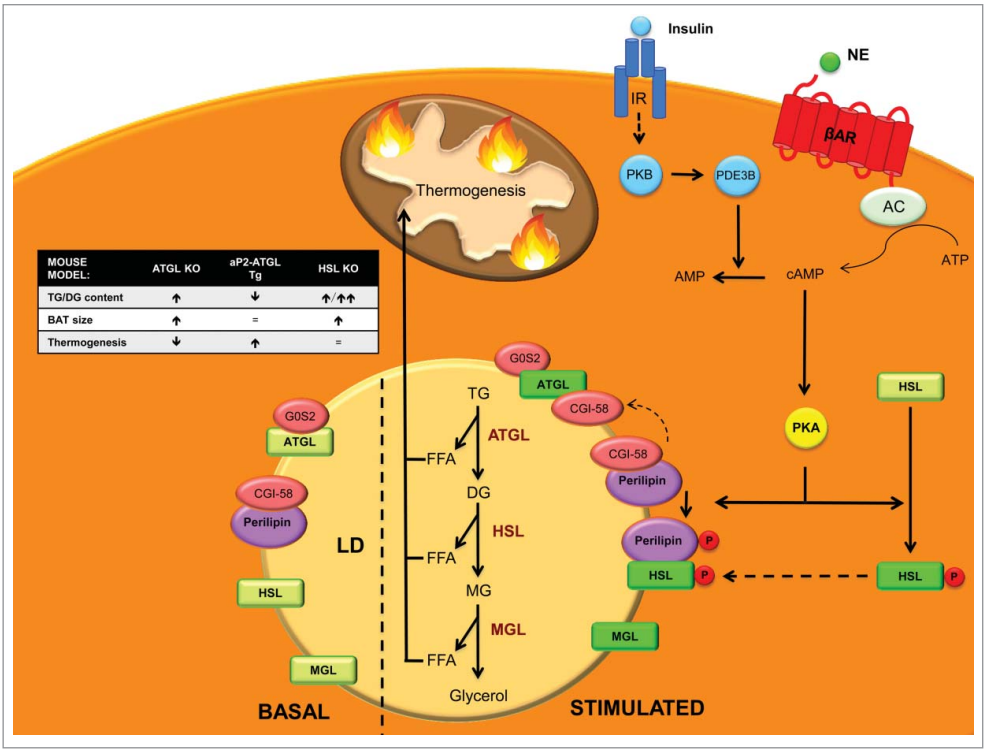

Figure 2. Neutral lipolysis players and regulation in BAT. Neutral lipolysis allows cells to obtain 3 free fatty acids (FFAs) and glycerol from the hydrolysis of triglycerides (TG). Three enzymes control this process: adipose triglyceride lipase (ATGL), which hydrolyzes TG into diacylglycerol (DG), hormone sensitive lipase (HSL), which has high affinity for DG and converts them into monoacylglycerols (MG) and monoacylglycerol lipase (MGL), which finalizes the hydrolysis of MG into glycerol and FFA that are used as a fuel for thermogenesis. In basal state ATGL is inhibited by G0/G1 switch gene 2 (G0S2) and ATGL co-activator comparative gene identification-58 (CGI-58) is kidnapped by perilipin. In addition, HSL is located in the cytosol and thus unable to reach its substrates. Upon β3-adrenergic stimulation, adenyl cyclase (AC) increases cAMP levels that activate protein kinase A (PKA), which phosphorylates HSL promoting its translocation to the membrane of lipid droplets (LD). PKA also phosphorylates perilipin, which releases CGI-58 that can then fully activate ATGL. Phosphorylated perilipin also enhances HSL activity. On the other hand, insulin stimulation, through protein kinase B (PKB) activates phosphodiesterase 3B (PDE3B) which converts cAMP into AMP decreasing PKA activation and its lipolytic action. Figure insert: mouse models of the enzymes involved in neutral lipolysis. ATGL KO mice accumulate TGs and have enlarged BAT, which displays defective thermogenesis.[133] aP2-ATGL overexpressing mice show a reduction in TGs and increased thermogenesis.[134] HSL KO mice accumulate TGs and specially large amounts of DG leading to an enlarged BAT.[142]

one of the most widely studied kinases that regulate its activity is cAMP-dependent Protein Kinase (PKA). Other kinases include AMPK, extracellular signal-regulated kinase (ERK), glycogen synthase kinase-4 and Ca^{2+}/calmoduline dependent kinase II.[130]

Glucagon, adrenaline or β3-adrenergic agonist stimulation, through adenyl cyclase (AC) activation increases cyclic AMP (cAMP) levels within the cell. This activates PKA that in turn phosphorylates HSL on serines 659 and 660, promoting its translocation from the cytoplasm to lipid droplets, where it acts on its substrates (Fig. 2).[144] Perilipins have an important role mediating this translocation, and PKA-mediated phosphorylation of perilipin is necessary for HSL translocation to lipid droplets and full induction of HSL activity. On the other hand, insulin activates cAMP phosphodiesterase, promoting cAMP hydrolysis, lowering PKA activity, HSL activation and lipolysis.[144] Mice lacking HSL display normal thermogenesis[145] and are not cold sensitive despite a lipolytic defect that results in brown adipocyte hypertrophy due to TG and DG accumulation. Apparently, during HSL deficiency sufficient amounts of FAs that are not HSL-dependent are mobilized for mitochondrial heat production. Later work on HSL null mice established that HSL KO mice are resistant to high-fat diet (HFD) effects due to an increase in energy expenditure.[146] This was linked to increased UCP1 and carnitine palmitoyltransferase (CPT) 1 expression levels in white adipocytes as well as an increase in white adipocyte mitochondrial size (see section 4.2.1 for more information). White adipocytes had increased basal O_2 consumption and increased uncoupling. In addition, HSL is required to sustain normal expression levels of retinoblastoma protein (pRb) and receptor interacting protein 140 (RIP140), which both promote differentiation into the white, rather than the brown, adipocyte lineage. Thus, HSL may be involved in the determination of white versus brown adipocytes during adipocyte differentiation.[146]

MGL specifically hydrolyzes MG derived from intracellular and extracellular TG hydrolysis and phospholipid hydrolysis into FAs and glycerol, culminating the lipolysis process (Fig. 2). It is ubiquitously expressed in tissues and localizes in cell membrane, cytoplasm and lipid droplets.[147] MGL has been implicated in the degradation of the bioactive MG 2-arachidonoyl glycerol, which is a potent endogenous agonist of cannabinoid receptors.[148]

Upon lipolysis stimulation the most important mechanisms regulating lipolysis are: 1) Activation of ATGL by CGI-58; and 2) PKA-mediated phosphorylation of HSL and perilipin 1 (Fig. 2). In basal state, CGI-58 is bound and kidnaped by perilipin 1, and thus unable to activate ATGL. In addition, HSL is located in the cytosol far from its substrates. Upon hormonal stimulation, PKA phosphorylates HSL, promoting its translocation to the lipid droplet surface, where it hydrolyzes its substrates.[149,150] In addition, PKA phosphorylates perilipin 1, liberating CGI-58, which is then available to bind and activate ATGL.[151]

The final result of lipolysis is the provision of energy to the cell in the form of FFAs and glycerol. Elevated levels of FFAs can be toxic for cells.[8] Brown adipocytes can prevent this lipotoxicity by matching this increment in FFAs with an increase in oxidative capacity. β3-adrenergic stimulation triggers lipase activation, resulting in a rise of lipolytic products that act as ligands of PPARα and PPARδ. PPAR activation promotes expression of oxidative genes such as UCP1 or PGC1α and as a result expands the oxidative capacity to match FA supply.[137] These findings highlight the importance of coupling lipolysis with increased oxidative capacity, which ultimately depends on the uptake of FAs to the mitochondria for FAO by carnitine acyltransferases.

Fatty acid oxidation

Consistent with its physiological role, BAT presents one of the highest FAO rates in the body.[152] Most of the oxidation of longchain fatty acids (LCFAs) to acetyl-CoA takes place in the mitochondrial matrix, although peroxisomal FAO has also been implicated in thermogenesis.

Mitochondrial fatty acid oxidation

Traditionally, research on the regulation of BAT thermogenesis has focused on the central role of UCP1 in maximizing rates of proton leak and heat production. In fact, FAs and HFD activate UCP1 and diet-induced thermogenesis.[153-155] However, studies by Yu *et al.*[156] support the hypothesis that additional systems and genes cooperate in the thermogenic system. These authors demonstrated that cold induces simultaneous FA synthesis and FAO in murine BAT. Similar conclusions were obtained by Mottillo et al.[96] In addition, it has recently been reported in primary brown adipocyte culture that intracellular FA levels are critical for thermogenesis[157] and that in rodents maximal BAT thermogenesis relies on the levels of LCFA pool, which activates entry to the mitochondria.[158] Acyl-CoA synthetase-1 (ACSL) mediates the conversion of FAs to acyl-CoA and specifically directs them toward mitochondrial FAO via the CPT1 system (Fig. 3). Experiments with ACSL KO mice showed that ACSL is required for cold thermogenesis.[159]

The CPT system permits the entry of LCFAs into the mitochondrial matrix, where they can undergo FAO.

The first component of the system, CPT1 is located on the mitochondrial outer membrane (Fig. 3). This enzyme catalyzes the *trans* esterification of a fatty acyl group from CoA to carnitine, which is considered the rate-limiting step in the regulation of mitochondrial FAO of FAs.[160,161] Acylcarnitines are shuttled to the mitochondrial matrix by the transporter carnitine/acylcarnitine translocase (CACT). Once inside the mitochondria, acylcarnitines are converted to acyl-CoA by CPT2, located in the inner mitochondrial membrane, and can thus enter the FAO cycle. There are 3 isoforms of CPT1, denoted CPT1A,[162,163] CPT1B[164] and CPT1C.[165] They differ in their sequence, tissue distribution, intracellular location, kinetics and malonyl-CoA sensitivity. CPT1B is strongly expressed in BAT, skeletal muscle, heart, testis and, in some species, in WAT (human, rat and hamster)[108,166] while CPT1A is predominant in other tissues such as liver, kidney, lung, ovary, spleen, brain, intestine, mouse WAT and pancreas. CPT1C appears to be expressed exclusively in the neurons and testis. While CPT1A and B are located on the mitochondrial outer membrane and both isoforms are involved in the regulation of the flux of FAs into the mitochondria, CPT1C has been found on the ER membrane[167] and its function seems to be related with ceramide metabolism rather than FAO.[168,169]

CPT1A and B isoforms have high sequence similarity but show important kinetic differences. In particular, they differ in their affinities for the substrate carnitine and their physiological inhibitor malonyl-CoA,[170] which is synthesized from acetyl-CoA by ACC and is degraded by malonyl-CoA decarboxylase.[171] CPT1B has higher affinity for the inhibitor malonyl-CoA and lower affinity for carnitine than CPT1A.[172,173] Doh et al.[152] examined the relation between the long-chain FAO rate and the CPT1A and CPT1B activity in different tissues. They found that all the tissues containing CPT1B showed a strong positive correlation between palmitate oxidation rate and the CPT1 activity and, among the tissues with CPT1B (heart, red and white gastrocnemius and BAT), BAT showed the highest palmitate oxidation and CPT1 activity. In addition, mice lacking CPT1B die during cold-exposure as a result of their inability to perform thermogenesis.[174] These observations indicate that CPT1B may play an important role in enhancing BAT

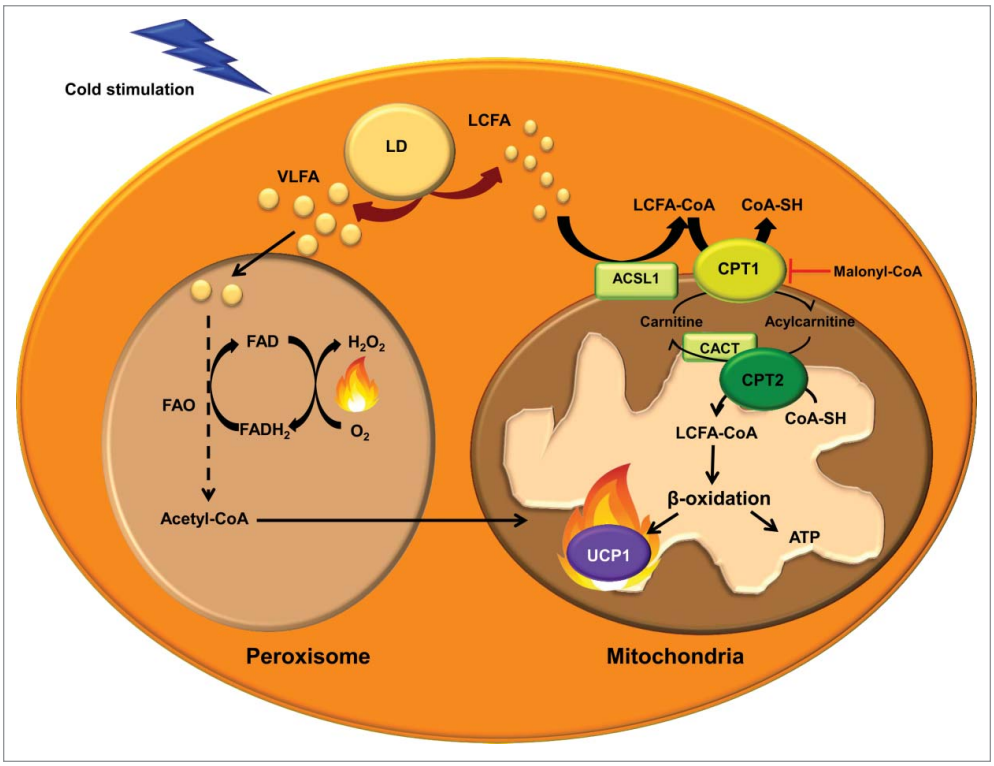

Figure 3. Mitochondrial and peroxisomal fatty acid oxidation. Transport of long-chain fatty acids (LCFAs) from the cytosol to the mitochondrial matrix for FAO involves the activation to acyl-CoA by acyl-CoA synthetase-1 (ACSL), conversion of LCFA-CoA to LCFA-carnitines by carnitine palmitoyltransferase (CPT) 1, translocation across the inner mitochondrial membrane by the carnitine/acylcarnitine translocase (CACT) and reconversion to LCFA-CoA by CPT2. These acyl-CoAs are β-oxidized and render acetyl-CoA. The entry of acetyl-CoA to the tricarboxylic acid cycle generates NADH and FADH. These cofactors transfer the electrons to the electron transport chain, where the protons are transported to the mitochondrial intermembrane space to generate energy as ATP. UCP1 dissipates the proton gradient, releasing energy as heat. Very long chain fatty acids (VLFA) enter the peroxisome to be shortened by peroxisomal FAO. Shortened acyl-CoAs and acetyl-CoA are transported to the mitochondria to be completely oxidized.

thermogenesis. Indeed, inhibitors of CPT1 also inhibit mitochondrial respiration driven by LCFA in murine BAT.[158] Interestingly, BAT of diabetic rats showed decreased CPT1 activity and FAO.[175] Further, a recent study in adipose CPT2 KO mice demonstrated that FAO is required for both acute cold adaptation and the induction of thermogenic genes in BAT.[176] Taking into account the effect that this and other mitochondrial FAO alterations[177] produce in thermogenesis and cold intolerance, it could be an appealing strategy to enhance FAO in BAT mitochondria to increase energy expenditure and fight against obesity-induced metabolic disorders. Studies enhancing FAO by CPT1 overexpression in the context of obesity have shown a decrease in TG content and an improvement in insulin sensitivity.[178-188] These results indicate that activation of FAO may provide the basis for the development of novel treatment options for obesity.[189]

Peroxisomal fatty acid oxidation

Oxidation of very long chain FAs preferentially occurs in peroxisomes rather than in mitochondria (Fig. 3).[190] However, FAO in peroxisomes is not carried to completion. Since peroxisomes, unlike mitochondria, lack a citric-acid cycle and respiratory chain, shorter FAs can be shuttled to the mitochondria to be oxidized. During cold exposure peroxisomal FAO is also activated in BAT.[191] Furthermore, catalase protein, a marker of the quantity of peroxisomes, is dramatically increased in rat BAT under cold exposure.[192] However, the contribution of peroxisomal FAO to thermogenesis is not well established. Acetyl-CoAs produced by peroxisomal FAO may enter the mitochondria to fuel UCP1-mediated thermogenesis. Alternatively, a recent review by Lodhi *et al.*[193] suggests that peroxisomal FAO may contribute to adaptive thermogenesis independently of UCP1 by the generation of heat instead of ATP. Peroxisomes do not have a respiratory chain and the electrons from $FADH_2$, obtained in the first step of peroxisomal FAO, are transferred by the flavoprotein acyl-CoA oxidase directly to O_2 producing H_2O_2, and energy is released as heat.

In summary, mitochondrial and peroxisomal FAO are necessary for thermogenesis in BAT, and enhancing these catabolic processes is an unexplored strategy in our fight against the current obesity epidemic.

Future directions: BAT fat-burning power as a potential therapy against obesity

Despite the considerable current effort made worldwide, the prevalence of obesity and associated metabolic diseases is rising exponentially, jointly with their healthcare costs. The first line therapy is based on behavioral modifications, including healthy eating and exercise. However, this meets limited success when it comes to long-term maintenance of weight loss. Bariatric surgery achieves a sustained weight loss over the years, but its cost and associated dangers reduce its clinical indication to morbidly obese patients.[194] Moreover, the endocrine effects of bariatric surgery seem to be more important than the mechanically induced food restriction, which has led many researchers to assess obesity treatments based on the endocrine modifications derived from it.[195] Interestingly, bariatric surgery also leads to alterations in the microbiome.[196]

Even though the list of potential anti-obesity drugs is increasing, the approval of new anti-obesity drugs has met relatively limited success. This is due to the history of withdrawals of anti-obesity drugs from the market due to serious adverse effects (i.e., dinitrophenol, fenfluramine, dexfenfluramine, phenylpropanolamine, sibutramine and rimonabant).[197,198] This has led US Food and Drug Administration (FDA) and European Medicines Agency (EMA) to make it harder for pharmaceutical corporations to market new anti-obesity drugs, especially in the case of the European regulator.[199] Today, the lipase inhibitor orlistat is approved by both FDA and EMA but it has shown limited long-term effectiveness.[200] In the US, the serotonergic lorcaserin is also approved,[201,202] but its European marketing authorization application has been withdrawn because of the lack of evidence regarding safety in tumorogenesis in long-term use.[203] Liraglutide, a previously approved antidiabetic drug, has recently been approved by both regulators for an anti-obesity indication.[204,205] Nonetheless, the fixed-dose combination of bupropion/naltrexone, which is described to act in the central nervous system (CNS) by increasing POMC neuron activity, has obtained marketing approval as an anti-obesity drug by the FDA,[206] but the EMA seems to be much more conservative regarding the approval of weight-management drug with effect on the CNS.[207]

The mechanisms of action of obesity-management drugs are classified into 3 groups:[208] 1) centrally acting medications impairing dietary intake (including bupropion/naltrexone and lorcaserin); 2) medications that act peripherally to impair dietary absorption (e.g., orlistat); and 3) medications that increase energy expenditure, whose effect is mediated by CNS. We propose that the increase in energy expenditure is a promising way to manage obesity, but only if this could be achieved via a direct effect on peripheral tissues without involving the CNS. Thus, some of the collateral effects, which caused other drugs to be withdrawn, would be overcome. Here we highlight an increase in FAO as a potential approach to enhance energy expenditure in peripheral tissues.

Several studies enhancing FAO by CPT1 overexpression in the context of obesity have shown an improved metabolic phenotype.[178-187] Thus, an increasing body of evidence highlights FAO activation as a potential target to develop novel anti-obesity strategies.

The pathogenesis of obesity is multifactorial and complex. However, the rediscovery of active BAT in adult humans and its relevance in metabolism has put a spotlight on this tissue as a potential target for therapies against obesity and metabolic diseases. A large number of activators of thermogenesis are increasingly being identified. This year, the β3-adrenergic receptor agonist mirabegron, the first compound able to stimulate human BAT thermogenesis and to increase resting metabolic rate, has been described.[59] Although further studies are needed to explore the specificity of its mechanism of action and potential adverse effects, mirabegron provides the first evidence of human BAT thermogenesis stimulation.

As a controller of thermogenesis BAT is a good modulator of triglyceridemia, an important consumer of glucose and the major plasma lipid-clearing organ in rodents. Furthermore, diabetes has been shown to decrease CPT1 activity and FAO in rat BAT.[175] Thus, strategies designed to enhance the fat-burning power of BAT and to increase lipid mobilization and oxidation could be very useful in the treatment of obesity and associated pathologies. Traditionally, most research has focused on the activation of BAT thermogenesis through UCP1. However, recent studies have shown that cold stimulates both FA synthesis and FAO in murine BAT.[96,156] Moreover, BAT peroxisomal FAO may generate heat independently of UCP1.[193] BAT transplantation is another strategy proving BAT's lipid-burning capacity in obesity. BAT transplantation to HFD-induced obese mice has shown a beneficial effect improving whole-body energy metabolism by increasing FAO-related genes such as PPARα, PGC1α, CPT1B and UCP1 in endogenous BAT.[209] Although the present review is focused on obesity, it is noteworthy to mention the role of BAT in atherosclerosis. Data showing both a positive and negative effect of BAT activation in the development of atherosclerosis have been reported.[210,211] On the one hand, Dong et al.[210] showed that sustained cold exposure accelerated the atherosclerotic plaque development by increasing plasma levels of small low-density lipoproteins (LDL) in apolipoprotein E (*ApoE*) and LDL receptor (*LDLr*) deficient atherosclerosis mouse models. On the other hand, Berbee et al.[211] reported that APOE*3-Leiden.CETP mice (a model for human-like lipoprotein metabolism) treated with Western diet, to induce hyperlipidaemia and atherosclerosis, plus CL316243 (a β3-adrenergic receptor agonist) had fewer atherosclerotic lesions. In this case BAT activation lead to enhanced uptake of FAs from TG-rich lipoproteins into BAT and increased hepatic clearance of cholesterol-enriched remnants and lower plasma cholesterol levels. The apparent opposite effects between the 2 studies could be explained by the different mouse model used. ApoE and LDL receptor are essential for hepatic clearance of TG-rich lipoprotein remnants. Thus, this pathway is blocked in *ApoE* (-/-) or *LDLr* (-/-) mice but not in APOE*3-Leiden.CETP mice. In fact, the antiatherogenic effect seen by Berbee *et al.* was blunted in *ApoE* (-/-) or *LDLr* (-/-) mice. Importantly, mice treated with the β3-receptor agonist lost weight and had increased FAO. This indicates that the beneficial effect of BAT activation on atherosclerosis could be the consequence of decreased obesity and enhanced FAO shedding light into FAO as a potential target to fight against obesity-induced metabolic disorders such as atherosclerosis.

At least 3 questions still need to be answered before increased BAT FAO can become an effective approach for obesity therapy. First, it is not known whether FAO enhancement might reach a limit in BAT, in which thermogenesis is tightly adjusted to the environmental temperature. Second, since increasing flux through FAO would only make sense together with a corresponding enhancement of energy demand,[212] the physiological relevance of this strategy might be questioned if the individual is at thermoneutrality. Third, secondary effects of BAT pharmacological activation may include excessive body temperature or increased food intake as a compensatory effect to re-establish energy balance. Increased BAT FAO may augment mitochondrial burning capacity through an increase in the number of mitochondria and/or the increased expression of UCPs, and thus dissipate the excess of energy as heat and ATP. These could well alleviate the mitochondrial pressure found in lipid overload states.

In summary, an increase in FAO and BAT mass and/or activity could indeed be one of the underlying protective mechanisms against obesity-induced metabolic abnormalities. Although more research is needed, we strongly believe that enhancing BAT thermogenic power through increased FAO may be available in the near future as a therapy to treat obesity and its associated severe diseases.

Abbreviations

AC	adenyl cyclase
ACC	acetyl-CoA carboxylase
AMPK	AMP-dependent protein kinase
ATG	autophagy-related protein
ATGL	adipose triglyceride lipase
BAT	brown adipose tissue

BMP8b	bone morphogenetic protein 8b
cAMP	cyclic AMP
CIDEA	cell death-inducing DNA fragmentation factor-α-like effector A
CGI-58	comparative gene identification-58
CNS	central nervous system
CPT	carnitine palmitoyltransferase
DG	diacylglycerol
DIO2	type 2 iodothyronine deiodinase
ELOVL	elongation of very long chain FA
ER	endoplasmic reticulum
FA	fatty acid
FAO	fatty acid oxidation
FFA	free fatty acids
FGF21	fibroblast growth factor 21
G0S2	G0/G1 switch gene 2
GPCRs	G-protein-coupled receptors
HFD	high-fat diet
HSL	hormone-sensitive lipase
IGF-1	insulin-like growth factor I
IL-1β	interleukin-1β
IL-6	interleukin-6
KO	knockout
LAL	lysosomal acid lipase
MEFs	primary mouse fibroblasts
MG	monoacylglycerol
MGL	monoacylglycerol lipase
Myf5+	myogenic factor 5-positive
iPLA2ζ	calcium-independent phospholipase A2 ζ
PGC1α	peroxisome proliferator activated receptor gamma coactivator 1 alpha
PKA	protein kinase A
PKB	protein kinase B
PRDM16	PR domain-containing 16
pRb	retinoblastoma protein
RIP140	receptor interacting protein 140
TG	triglyceride
TNFα	tumor necrosis factor α
UCP1	uncoupling protein-1
WAT	white adipose tissue

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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