Integrated control of brown adipose tissue

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Abstract
Brown adipose tissue (BAT) has evolved as a unique thermogenic organ that allows placental mammals to withstand cold environmental temperatures through the dissipation of metabolic energy in the form of heat. Although traditionally believed to be lost shortly after birth, metabolically active BAT depots have recently been identified in a large percentage of human adults. Besides classical brown cells, a distinct type of thermogenic adipocytes named beige or brite (brown in white) cells are recruited in white adipose tissue depots under specific stimuli. Given the well-known energy-dissipating properties of thermogenic adipose tissue and its function of metabolic sink for glucose and lipids, this tissue has attracted considerable research interest as a possible target for treating obesity and metabolic disease. The complex network of interorgan connections that regulate BAT and brite tissue mass and function is a major hurdle for the development of therapeutic strategies against metabolic disorders. This review provides an overview of the current knowledge on the regulation of BAT and brite adipose tissue function. The possibility of targeting these tissues to treat obesity and other metabolic disorders is also discussed. Heart Metab. 2016;69:9-14

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Adipose tissue: much more than a fat reservoir

Adipose tissue is a complex organ that significantly affects the physiology and pathophysiology of an organism. Originally viewed as a lipid droplet–containing inert variant of connective tissue, adipose tissue is now recognized to be an integral component in nutrient homeostasis, energy metabolism, and modulation of inflammatory pathways. In addition, the distribution of adipose tissue depots has an important role in defining secondary sexual characteristics in several species, including humans.

Traditionally, two forms of adipose tissue are distinguished based on their particular morphological, physiological, and biochemical characteristics: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT is the largest store of energy in humans. Morphologically, white adipocytes are characterized by the presence of a single large lipid...
droplet that makes up the majority of the cell volume, with the cytoplasm and nucleus found at the cell periphery. These cells possess few mitochondria. Besides being an energy-storing tissue, WAT and its resident macrophages also act as an endocrine organ by releasing an array of signaling molecules, collectively termed adipokines. Adiponectin, leptin, interleukin (IL) 6, tumor necrosis factor α (TNF-α), resistin, and omentin 1 are among the best known adipokines. Alterations in WAT plasticity and expandability in the context of overnutrition are key factors in the pathogenesis of obesity-associated metabolic dysregulations. Indeed, the imbalance between proinflammatory and anti-inflammatory adipokines is involved in the development of insulin resistance and diabetes through a state of chronic low-grade inflammation.

BAT differs markedly from WAT. Brown adipocytes contain multiple small lipid droplets, conferring a multilocular appearance, and are enriched in mitochondria. BAT is densely innervated by the sympathetic nervous system (SNS) and is highly vascularized (up to five capillaries per cell). The main function of BAT is nonshivering thermogenesis (NST), which serves to maintain body temperature in small mammals and hibernating species and allows human newborns to cope with the thermal shock of delivery. Indeed, brown adipocytes actively oxidize fatty acids and glucose to sustain heat generation through uncoupling mitochondrial substrate oxidation from adenosine triphosphate (ATP) production (Figure 1). A role for BAT beyond thermogenesis has also been postulated. Studies in experimental rodents have shown that brown adipocytes may release a number of signaling molecules with autocrine and paracrine actions (eg, triiodothyronine, prostaglandins, angiotensinogen, IL-1α, IL-6, insulin-like growth factor 1, fibroblast growth factors [FGF] 2 and 21). However, the actual existence of BAT-derived endocrine factors and their relevance to human health are yet to be established.

A distinct type of brown adipocyte has recently been identified, termed the beige or brite (brown in white) adipocyte. Beige cells share characteristics both with white (ie, low basal expression of uncoupling protein 1 [UCP1]) and brown adipocytes (ie, presence of multilocular fat droplets and high mitochondrial density); however, their gene-expression pattern is distinct from either WAT or BAT. In response to stress stimuli (eg, chronic cold exposure, exercise, and severe adrenergic stress), pharmacological treatments (eg, long-term treatment with peroxisome proliferator-activated receptor γ [PPARγ] agonists), and pathological conditions (eg, cancer cachexia), brite adipocytes appear at WAT anatomical sites through differentiation of precursor cells that are distinct from BAT and closer to the white-cell lin-

**Abbreviations**

BAT: brown adipose tissue; BMP: bone morphogenetic protein; FGF: fibroblast growth factor; IL: interleukin; NST: nonshivering thermogenesis; SNS: sympathetic nervous system; THRβ: thyroid hormone receptor β; UCP1: uncoupling protein 1; WAT: white adipose tissue

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**Fig. 1** Simplified representation of the metabolic activity of a brown adipocyte. Energy produced via oxidation of glucose and fatty acids is used to generate heat through dissipation of the mitochondrial proton-motive force by uncoupling protein 1 (UCP1) located in the mitochondrial inner membrane. Artwork by Francesco Antognarelli.
eage. This phenomenon, known as “browning” of WAT, is followed by the triggering of a thermogenic program similar to that of BAT (Figure 2). Beige cells can also be induced by a vast array of endocrine factors and drugs via both central (SNS activation) and peripheral stimuli.

This review summarizes the current understanding of signaling pathways that orchestrate BAT- and brite adipose tissue–mediated thermogenesis. The possibility of targeting NST to treat metabolic disorders is also discussed.

**BAT and brite adipose tissue thermogenesis: burning from within**

About 140 million years ago, the emergence of BAT-mediated NST in placental mammals offered these animals a remarkable evolutionary advantage by enabling them to maintain body temperature in the cold. Briefly, cutaneous thermal receptors activated by exposure to cold environmental temperatures send signals to thermoregulatory areas of the hypothalamus. This evokes efferent SNS signaling and subsequent stimulation of β3-adrenoceptors in BAT, followed by intracellular lipolysis, activation of the mitochondrial electron transport chain, and uncoupling of respiration (Figure 2). UCP1, a mitochondrial carrier protein inserted into the inner mitochondrial membrane, is the main actor in BAT-mediated NST. Indeed, UCP1 promotes a state of metabolic inefficiency by inducing maximum mitochondrial respiration through dissipation of the proton-motive force in the form of heat (Figure 1). Cold adaptation is achieved through different mechanisms in wild-type and UCP-ablated mice. Indeed, UCP1-null mice may still develop cold tolerance after adaptation; however, contrary to their NST-competent littermates, they can rely only on shivering for heat production.

Although BAT depots have long been assumed to regress shortly after birth, recent studies using 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18FDG-PET/CT) have revealed that human adults possess BAT located in cervical-supraclavicular (the most common location), perirenal/adrenal and paravertebral regions, and around the major arteries. Indeed, BAT depots are highly prevalent in adult humans. The abundance of BAT is greater in women than in men, and it is inversely related to outdoor temperature, age, β-blocker use, body mass index, percent body fat, and plasma glucose levels.

Interestingly, recent studies employing three-dimensional magnetic resonance imaging in combination with histologi-
cal and biochemical analyses have shown that, while BAT in the cervical region consists of classic brown adipocytes, BAT depots found in other anatomical sites possess a molecular signature consistent with beige cells. In addition, gene-expression profiling of BAT samples obtained from the supravacular region revealed that molecular markers of both brown and beige adipocytes coexist in human adults. This finding suggests that human BAT might indeed consist of both brown and recruitable beige adipocytes.

As previously mentioned, BAT prevalence and activity are lower in overweight and obese persons than in lean individuals. On the other hand, weight loss via bariatric surgery increases BAT activity in morbid obese patients. Weight loss also leads to the appearance of functional BAT depots in obese persons previously void of such tissue. BAT activity is also inversely associated with diabetes and fasting glucose levels. Interestingly, prolonged (5-8 hours) cold-induced BAT activation has been shown to improve resting energy expenditure, whole-body glucose disposal, plasma glucose oxidation, and insulin sensitivity in middle-aged, overweight men with 18FDG-PET/CT-detectable BAT. Collectively, these observations raise the possibility that BAT dysfunction might contribute to the development of obesity and insulin resistance.

As a whole, evidence accumulated so far strongly suggests a pivotal role for BAT in energy balance and metabolic homeostasis. This tissue may therefore be a promising target for interventions against obesity and other metabolic disorders.

Integrating central and peripheral signals: BAT choreography

The regulation of BAT mass and function is achieved via a complex profusion of signals and feedback systems involving multiple organs and tissues. Almost all organs may produce, on exposure to either physiological or pathological stimuli, specific signals that positively or negatively modulate BAT activity.

According to the classical view, sympathetic neuro-adipose connections induce the BAT thermogenic program and browning of WAT in response to cold exposure. A cold environment may also activate a thermogenic circuit consisting of eosinophils, cytokines, and alternatively activated (type 2/M2) macrophages. Once activated by eosinophil-derived ILs 4 and 13, M2 macrophages are recruited to subcutaneous WAT and release catecholamines to activate the WAT-browning process and drive thermogenesis.

Several neuropeptides and hormones—including leptin, thyroid hormones, estradiol, brain-derived neurotrophic factor (BDNF), irisin, FGF21, bone morphogenetic protein (BMP) 7 and 8B, glucagon-like peptide 1, nesfatin-1, and cannabinoids—modulate BAT function by acting both centrally (on different hypothalamic nuclei) and peripherally to adapt thermogenesis and energy homeostasis to various stimuli (Figure 2).

Exercise has been shown to confer some of its beneficial effects through the induction of WAT browning. Exercise-derived myokines and metabolites (eg, irisin, IL-6, β-aminobutyric acid [BAIBA], lactate, meteorin-like peptide, and FGF21) stimulate beige adipocyte development and increase energy expenditure.

Conversely, under obesity conditions, WAT browning is impaired by multiple factors, including increased activation of signaling pathways that inhibit beige adipocyte development (eg, transforming growth factor β and TNF-α) and concomitant reduced SNS activity.

A number of other signaling molecules are involved in the formation and activation of brown adipocytes. Identifying their peripheral and central targets would be useful for fine-tuning whole-body energy expenditure and improving metabolic control.

Targeting BAT to fight metabolic disorders

Excess body weight and obesity result from a prolonged imbalance between energy intake and energy expenditure. It follows that, in obese persons, fat mass reduction can be achieved either by decreasing food consumption or by increasing energy expenditure to obtain a sustained negative energy balance. Unfortunately, this is not easily attained, because of the sedentary lifestyle and the unrestricted availability of calorie-dense, inexpensive food that characterize modern societies. Indeed, with the exception of bariatric surgery, most anti-obesity interventions tackling energy intake result in moderate, often temporary, improvements. Thus far, pharmacological agents that have been proposed to increase energy expenditure...
have been either ineffective or toxic. Finally, physical activity—the most physiological way of burning energy—is not easy to sustain in the long term.

Recent years have seen the emergence of the possibility to achieve weight loss through harnessing the thermogenic properties of BAT.\textsuperscript{19} Whereas chronic cold exposure is obviously not a strategy worth pursuing, an alternative might be the administration of certain sympathomimetic agents (Figure 2). For instance, the highly specific $\beta_3$-adrenoceptor agonist CL-316,243 promotes thermogenesis, induces BAT hypertrophy and the appearance of brown adipocytes in WAT, and reduces obesity in rats on a high-fat diet.\textsuperscript{20} CL-316,243 administration was shown to increase insulin action and fat oxidation in lean men, though the effects were markedly diminished after 8 weeks of treatment.\textsuperscript{21} The compound did not affect resting energy expenditure, body weight, or body composition at any time over the course of treatment. In contrast, acute administration of the $\beta_3$-adrenoceptor agonist L-796568 increases lipolysis and energy expenditure in overweight men.\textsuperscript{22} Similar to observations for CL-316,243, L-796568 effects are lost with long-term administration of the compound, likely as a result of $\beta_3$-adrenoceptor downregulation.\textsuperscript{23}

The stimulation of the thyroid hormone receptor $\beta$ (THR$\beta$) might be an alternative strategy to increase BAT-mediated thermogenesis (Figure 2). For instance, the selective THR$\beta$ agonist GC-24 improves metabolic control in rats fed a hypercaloric diet.\textsuperscript{24} Furthermore, treatment with GC-1, another selective THR$\beta$ agonist, increases energy expenditure and prevents fat mass accumulation in rats.\textsuperscript{25} Notably, administration of chenodeoxycholic acid has been shown to activate type 2 iodothyronine deiodinase (DIO2) in BAT of healthy women, resulting in increased whole-body energy expenditure and mitochondrial uncoupling in brown adipocytes.\textsuperscript{26}

A very appealing strategy may be the transformation of the more abundant WAT into beige fat. In this regard, a number of compounds may be explored, including BMP4 and BMP7, FGF19 and FGF21, natriuretic peptides, BAIBA, capsinoids, and inhibitors of phosphodiesterase 5 (eg, sildenafil) (Figure 2).\textsuperscript{27} Further studies are needed to establish the effectiveness and safety profiles of such compounds in order to avoid undesired side effects such as those encountered with other BAT activators (eg, cardiovascular toxicity).

**Conclusion**

The escalating prevalence of obesity carries a number of detrimental consequences, including an increased risk of type 2 diabetes, dyslipidemia, cardiovascular disease, and several cancers. With the exception of bariatric surgery, none of the available interventions achieve substantial weight loss over the long term. The recent discovery of active BAT and recruitable beige cells in most human adults, together with the role played by these tissues in energy balance and insulin sensitivity, has sparked considerable interest into the possibility of targeting BAT to treat obesity and its negative correlates. Whereas a number of factors and pathways that enhance BAT and beige fat recruitment and function in rodents are known, the mechanisms of activation of these tissues in humans are only partly characterized. This is reflected in the conflicting results from interventions targeting BAT in rodents and humans. An increased understanding of the function and regulation of BAT is therefore instrumental for devising pharmacological and nutritional interventions that harness the thermogenic properties of this tissue to treat obesity and other metabolic disorders.

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