Brown Adipose Tissue: Research Milestones of a Potential Player in Human Energy Balance and Obesity

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Abstract

Obesity and diabetes mellitus are worldwide epidemics driven by the disruption in energy balance. In recent years, it was discovered that functional brown adipose tissue (BAT), once thought to exist mainly in infants, is present in adults, and can be detected during cold stimulation, and is associated with decreased adiposity. Brown fat pads were shown to be highly vascularized and metabolically active and on stimulation, they caused enhanced energy expenditure and increased glucose and fatty acid uptake. These observations drew attention to the possibility that nonshivering thermogenesis mediated by activation of BAT might be important in human energy balance and a potential tool to counter obesity. Recent investigations have revealed significant advances in the understanding of the role of BAT-mediated thermogenesis, uncovering essential knowledge on the origin, differentiation, activation, and regulation of BAT in both murine models and humans. In addition to classic BAT depots, transformation of white adipocytes into brown-like adipocytes, and the development of "beige" cells from distinct precursors, were demonstrated in different animal models and resulted in increased thermogenic activity. Several transcription factors, activating proteins, and hormones are increasingly identified as regulating the development and function of both brown-like adipocytes and classic brown fat pads. This review will summarize the evolution of research on BAT in humans, in light of the renewed scientific interest and growing body of evidence showing that recruitment and activation of BAT and browning of white adipose tissue can affect energy expenditure and may be a future feasible target in the treatment of metabolic diseases.

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Introduction

Obesity is a major public health problem and a worldwide epidemic contributing to the development of dyslipidemia, type 2 diabetes, and cardiovascular diseases [1]. It often results from a derangement in energy balance, impairing the equilibrium between energy intake and expenditure. The treatment of patients with obesity requires significant efforts in lifestyle modifications, which are often difficult to implement and only transiently successful. Other approaches, such as drug treatments and bariatric surgery, are accompanied by risks and are suitable for limited groups of the obesogenic population. Hence, considerable efforts are aimed at developing novel therapeutic tools to aid in countering obesity. A possible approach that recently drew interest in the medical scientific community was to increase energy expenditure through the stimulation of brown adipose tissue (BAT). BAT is a unique adipose tissue; its main function is to generate heat by dissipating chemical energy. It has largely been investigated in the past for its role in small mammals, allowing nonshivering thermogenesis in response to low temperatures, and was thought to be present only in newborns and small children among humans [2]. Apart from the defense against cold, BAT thermogenesis was demonstrated in multiple studies in mammals to increase energy expenditure, affecting excess of lipids and accumulation of fat. The activation of BAT is mainly under the control of the sympathetic nervous system, in which the adrenergic response triggers energy uptake of fatty acids and carbohydrates into BAT and stimulates thermogenic activity. This activity is mediated, in particular, by the hypothalamus and is regulated by a wide range of transcriptional factors and regulators. In recent years, there has been growing evidence that BAT is active in not only small mammals and newborns but also

adult humans. Imaging modalities such as ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) enabled recognition and measurement of the mass and activity of BAT in humans, and recent investigations have enriched our understanding of the prevalence, clinical correlations, activators, and regulatory systems of BAT. These findings raised the possibility that BAT is metabolically active in adults and is a significant tissue that may be potentially recruited to aid in therapeutic efforts addressing excess fat accumulation, dyslipidemia, and metabolic diseases. Obstacles to achieve these goals include the low amount of BAT in humans compared with rodents, especially in obese and older individuals, and strategies to increase the mass and function of BAT, thereby sustaining its activity.

The aim of this article is to review broad themes of recent research on BAT and its influence on energy balance, obesity, and metabolic diseases. The evolution of research on BAT in humans will be reviewed, with a focus on the up-to-date evidence for the development, stimulation, regulation, and transcriptional control of BAT thermogenesis. Furthermore, recent investigations linking BAT and cardiometabolic activity will be highlighted, including the role of natriuretic peptides (NPs), epicardial fat, and lipoprotein metabolism.

The Obesity Epidemic and Energy Balance

Obesity has become a major global public health problem in recent decades, and it has reached epidemic proportions in not only high-income countries but also most middle-income societies. Data from the World Health Organization indicate that the number of people with obesity has increased more than 2-fold worldwide since 1980 and 65 % of the world's population today lives in countries where overweight and obesity are responsible for more deaths than underweight [1]. Obesity affects approximately one-third of the US adult population, with an additional similar proportion of the population known to be overweight [3]. It is also an impending problem for young individuals; more than 40 million children younger than 5 years of age were defined as overweight by the World Health Organization in 2010 and are at an increased risk for cardiovascular diseases in the future as adults because of childhood overweight [4]. Obesity is now a leading cause of morbidity, disability, and premature mortality, contributing to various medical comorbidities and complications. Adiposopathy ("sick fat") results in endocrine and immune derangements and contributes to cardiovascular diseases both directly and indirectly through worsening of major risk factors for cardiovascular disease [5]. It is correlated with hypertension, insulin resistance and diabetes mellitus, dyslipidemia, and physical inactivity and is associated with a significant increase in the number of cardiovascular events and the risk of mortality.

Energy balance, simplistically, is composed of energy intake, energy expenditure, and energy storage. Obesity often results from an imbalance between energy intake (food eaten) and expenditure, which is composed of the basal metabolic rate (from rest and obligatory energy) and physical work including physical activity and nonexercise adaptive thermogenesis [6, 7]. The major environmental factors that contribute to imbalance in this equation are reduced physical activity in the sedentary population and increased energy intake from high-calorie foods and drinks.

Previous reports support the hypothesis that increased food intake is the main cause of obesity in modern populations, owing to an increased supply of cheap, palatable, high-caloric energy foods, which have become more accessible in recent decades and thereby encouraging food consumption [8]. The decline in daily life physical activities over the past century has been substantial, deriving from industrialization, urbanization, development of motorized transportation, etc., and resulting in marked changes in daily lifestyle. Physical activity can be divided into occupational (work-related) and leisure-time activities. Although leisure-time activities partially maintain their importance in developed societies, in the past decades, there has been a progressive decline in the percentage of individuals employed in occupations that require intense physical activity. Even though physical activity reduces the likelihood of developing obesity, there is debate concerning the extent of the impact of exercise on the obesity epidemic [9, 10].

The human body possesses several processes for dynamic physiological adaptations to alteration in body weight. For example, gain of weight results in increased energy expenditure due to a higher rest metabolic rate and eventually, a further increase in energy intake to sustain the increased weight [11]. All the components of energy balance interact with each another, and a deviation in energy balance results in compensatory changes of its various components. Food restriction results in a compensatory reduction in the resting metabolic rate and a decrease in energy expenditure, parallel to increased hunger, thus reducing the success of long-term maintenance of weight loss [12, 13].

The concept of "high-energy flux" suggests that human physiology is biased toward achieving efficient energy balance at a high level of energy intake and expenditure, which is achieved in a sedentary environment by weight gain instead of a high level of physical activity. Thus, optimal energy balance may be easier to achieve at high-energy throughput by increasing physical activity in the population and entering the "regulated zone" of energy balance [14].

Other environmental and circumstantial factors might have influenced the obesity epidemic in recent decades. Factors that have been suggested to promote obesity are changes in smoking habits, sleep disorders with reduced sleeping periods, and environmental contaminants. Furthermore, genetic predispositions, gene-environment interactions, and epigenetic modifications may contribute to mechanisms regulating obesity.

An important environmental factor that may have a role in energy balance and obesity is reduced exposure to ambient temperature variability in daily life, mainly reduced exposure to seasonal cold [15]. This reduced exposure occurs as a result of the wide-scale accessibility to cheap and efficient energy sources, exposure to air conditioning and central heating, reduction in outdoor activities, and an increase in temperature-controlled environments and consequently, increased time spent indoors. This "thermal comfort" zone has been observed in recent decades in developed countries, manifesting as a reduction in seasonal exposure to mild cold and increase in domestic winter temperatures. This thermal comfort zone is suggested to negatively affect energy expenditure and contribute to the rise in obesity prevalence in the population by reducing thermogenic capacity and the need for physiological thermogenesis [15].

Overall, long-term dysregulation of energy balance is a key component of the obesity epidemic. However, influencing energy balance by intensive lifestyle modifications in obese individuals is not easy to implement in our obesogenic environment. Caloric

restriction is accompanied by an unpleasant hunger sensation and compensations leading to a reduced basal metabolic rate and reduced physical activity. Moreover, it should be noted that drugs suppressing appetite were partially withdrawn from the market because of severe adverse effects and are often not tolerated because of safety issues and potential side effects. A combination of caloric restriction and structured exercise may lead to more effective weight loss [16]. However, intense physical activity is often difficult for obese individuals, and it is suggested that small changes in an individual's lifestyle may have only a minor effect on weight loss and the prevention of obesity [17]. Because of the limited efficacy of medications and behavioral interventions, bariatric surgery techniques have increased substantially in recent years and provide a viable therapeutic option for severely obese patients with serious comorbidities. Bariatric surgery has been shown to improve metabolic dysfunction and decrease inflammatory cytokine levels. In addition, it was recently demonstrated to be associated with a reduced number of long-term cardiovascular events in obese adults [18] and contribute to better glycemic control in obese diabetic patients [19,20]. However, these procedures are invasive, have potential perioperative and long-term complications, and are currently a viable therapeutic option for a relatively small number of patients with morbid obesity and severe comorbidities. Therefore, methods to increase energy expenditure are still needed in order to provide other viable therapeutic options for patients with obesity and metabolic complications. Such therapies will further facilitate the positive effects of lifestyle changes, translating into weight reduction and improved cardiometabolic health. The unique features of BAT, enabling removal of a large amount of lipids from the circulation to activate thermogenesis, produce heat and affect energy expenditure, mark it as a potential therapeutic target in obese subjects.

Characteristics and Evolutionary Considerations of Brown and White Adipocytes

Adipose tissue is composed of white and brown adipocytes, which are able to accumulate lipids in droplets intracellularly. White adipose tissue (WAT) is an energy-storing tissue that has evolutionarily enabled humans to survive for longer periods between meals, storing energy mainly as triglycerides and releasing fatty acids during fasting periods. WAT comprises the majority of adipose tissue in the human body, and in recent decades, when food has been cheap and widely available, it has contributed to obesity worldwide. Morphologically, white adipocytes have few mitochondria; they are composed of a peripherally located nucleus and a large single, spherical, lipid vacuole that functions as a storage droplet. It can increase in size and expand its volume by several times. WAT has endocrine activity, secreting hormones such as leptin and adiponectin, and is involved in the regulation of insulin sensitivity.

BAT consists of brown adipocytes, characterized by multiple, small, multilocular lipid droplets with a central nucleus and a high number of mitochondria, thus differing morphologically from WAT. BAT is highly vascularized tissue innervated by sympathetic nerve fibers. The mitochondria of BAT are unique in expressing uncoupling protein 1 (UCP1) in the inner mitochondrial membrane. This protein, when activated, separates (uncouples) electron transport in the respiratory chain (substrate oxidation) from generation of adenosine triphosphate and thus releases the energy stored as heat. Expression of UCP1 converts chemical energy, which originates mainly from fatty acids, into thermal energy, generating heat and resulting in thermogenesis. UCP1 is characteristically present in BAT and is not expressed in regular WAT.

BAT is highly present and active in newborns. Its evolutionary function is to generate heat for the newborn's body when no other ways of producing heat, such as skeletal muscle shivering thermogenesis, have yet developed. This nonshivering thermogenic role of BAT, which maintains the core temperature during exposure to cold, is also seen in small mammals. Children have a high amount of active BAT, but the amount and activity of BAT declines rapidly after puberty. In adults, BAT is concentrated in the trunk, and the largest regions of BAT mass are found in humans in the supraclavicular and neck regions, which evolutionarily might have been important in providing warm blood to the brain. A smaller amount of BAT is found in humans around the spinal cord and the paravertebral and peri-aortic regions.

BAT in Adult Humans

Previous literature has indicated that BAT may have a potential role in regulation of not only body temperature during cold exposure but also body weight and lipid metabolism. The physiology and activity of BAT have been scientifically investigated, mainly in rodents, in numerous studies in recent decades. These studies have confirmed the presence of BAT and shown the benefits of activating BAT for regulation of body weight. Various examples from animal studies are as follows: "cafeteria-fed" animals had increased mass and function of BAT; surgical excision of BAT in mice resulted in increased body weight; overexpression of transgenic mice with UCP1 protected against obesity; and adrenergic stimulation of the beta3-adrenoreceptor resulted in appearance of BAT in WAT regions, accompanied by increased expression of UCP1 and reduction in body weight [21].

BAT was initially noticed in humans several decades ago. The function of BAT in infants was described in the 1960s, and the question of the clinical significance of BAT in adults was then raised in the 1970s [22,23]. Interestingly, a highly quoted work from Finland in 1981 demonstrated that outdoor workers had BAT surrounding their neck arteries much more often than indoor workers, suggesting that working in the cold can retain BAT [24]. Pheochromocytoma, a catecholamine-secreting tumor of the adrenal medulla, was shown to be associated with activation of BAT in the 1980s; this finding suggested that human BAT has the potential for thermogenic activity and may contribute to weight loss through the high level of catecholamines activating BAT [25]. Catecholamines can induce weight loss through different pathways. However, it has been shown that FDG-PET uptake in BAT was no longer apparent after resection of a pheochromocytoma tumor [26]. Indeed, a recent study correlated elevated plasma levels of metanephrine and BAT activity, providing evidence that catecholamines stimulate BAT thermogenesis in the presence of an adrenal tumor and are negatively associated with adiposity [27]. However, BAT has been generally considered to be nonfunctional with no significant physiological relevance in healthy adult humans until recent years.

The renewed interest in BAT in humans

The renewed interest in BAT occurred as a result of an incidental finding. In the 1990s, FDG-PET scans were performed by radiolo-

gists to detect increased glucose uptake in tumors and identify metastatic progression. During these scans in patients with cancer, radiologists noticed a repeated pattern of bilateral symmetrical glucose uptake in the upper chest and neck regions, initially ascribed to artifacts or muscle uptake because of their symmetrical distribution [28]. After combining FDG tomography with CT, it became possible to determine the composition of this symmetrical uptake and this mass was identified as adipose tissue. In 2002, using hybrid PET/CT imaging, Hany and colleagues elegantly suggested that the symmetrical FDG uptake was related to adipose tissue and probably represented activated BAT during the increased sympathetic activity induced by the cold stress in the imaging room [29]. Several other reports discussing FDG-PET uptake in BAT in adult humans were published soon after, mainly in nuclear medicine journals [30,31]. Surprisingly, it took another several years until Nedergaard and colleagues raised awareness of the "unexpected evidence for active BAT in adult humans" and its potential to be of metabolic significance in human physiology and in the efforts to combat obesity [32]. Still, because of the retrospective nature of the FDG-PET studies, the presence of active BAT in humans was believed to be apparent in only a small percentage of adults.

This notion changed after the results of parallel prospective studies from several independent working groups were presented in 2009. Cypess and colleagues retrospectively analyzed FDG-PET/CT scans performed in 1972 patients for various diagnostic reasons [33]. Concentrations of depots of BAT were identified in regions of the anterior neck and thorax. Positive scans were seen in 7.5% of women and 3% of men (this low percentage was because the studies were performed in a nonstimulated state and PET/CT identifies uptake mainly in tissues with increased metabolic activity). The probability of detection of BAT was inversely correlated with age, outdoor temperature, use of a beta-blocker, and body mass index (BMI) in the older patients. Additionally, UCP1 activity was identified in 33 biopsy specimens from the same cervical and supraclavicular regions in which BAT was observed on PET/CT.

At the same time, prospective studies were conducted to intentionally examine BAT activity in cold stressed subjects. Lichtenbelt et al. found BAT activity using FDG-PET/CT in 23 of 24 healthy men during mild exposure to cold (15 °C for 2 h while ensuring that there was no cold-induced shivering thermogenesis by muscles) but not under thermoneutral conditions. This activity had negative correlation with BMI, suggesting that the reduced BAT activity in obese individuals may make it a target for the treatment of obesity [34]. Saito and colleagues also demonstrated that cold-induced uptake was observed on FDG-PET/CT in 27 of 32 young healthy volunteers but in only 2 of 24 elderly subjects, with no detectable uptake in warm conditions. The BAT activity was inversely correlated with BMI and was higher during the winter months [35]. Another study performed at the same time examined histologic samples of adipose tissue from the neck of patients undergoing thyroid surgery [36]. UCP1 activity was found in one-third of the 35 patients, with evidence of BAT precursors. BAT had high sympathetic innervation and capillary density. Virtanen et al. additionally showed that exposure to cold increased FDG-PET/CT glucose uptake 15-fold in the supraclavicular area of 5 healthy volunteers [37]. Three of their subjects underwent tissue biopsies from areas corresponding to the glucose uptake, showing that these tissues express messenger RNA for markers of BAT and substantial levels of UCP1 protein and cytochrome *c* (a mitochondrial marker that is abundant in BAT).

Collectively, these studies in humans demonstrated the presence of BAT mass and activity in adults based on cold-induced glucose uptake tests and biopsies, showing variability (30–100%) in study results based on age, BMI values, gender, and ambient temperature. However, these values were much greater than those of the earlier retrospective PET/CT studies, which reported a low prevalence of BAT in adult humans, varying from 2.5% to 8.5% of tested individuals because of thermoneutral noncold-induced conditions.

The next step was to confirm that BAT is indeed metabolically active in humans and contributes to cold-induced nonshivering thermogenesis. Researchers recently measured blood perfusion in BAT using a technique of intravenous injection of $[^{15}O]H_2O$ and a dynamic PET/CT emission scan. They found that cold activation of BAT leads to a greater than 2-fold increase in the perfusion rate of the tissue in parallel to elevated glucose uptake, reflecting the dense vascularity of this tissue and the increased oxygen requirement. Moreover, increased blood flow was associated with whole-body energy expenditure during cold exposure, indicating active thermogenesis [38]. Others have also shown that increased energy expenditure after exposure to cold in healthy volunteers is correlated to BAT activity quantified from FDG uptake [39].

Recently, Quellet and colleagues found that cold activation of BAT is associated with not only increased blood flow but also higher oxidative metabolism in the tissue [40]. This finding was confirmed by exposing healthy subjects to controlled cold and injecting a bolus of labeled radioactive acetate into their blood. The acetate is distributed to tissues according to their proportional blood flow. In this technique, loss of radioactivity from a tissue is an indication of active oxidative metabolism, and the radioactivity disappeared from BAT with a half-life of minutes in cold but not in warm subjects. Furthermore, nonesterified fatty acid uptake was quantified, showing increased uptake in cold-activated supraclavicular BAT in comparison to subcutaneous adipose tissue and resting skeletal muscles; these results suggest increased utilization of triglycerides as a source of energy for BAT thermogenesis.

A recent study using oxygen-15 PET imaging that evaluated the relationship between BAT oxidative metabolism and FDG uptake reported that despite elevated glucose uptake in BAT of adult humans, activated BAT did not contribute much to total energy expenditure [41]. The low activity of BAT depots in human subjects may reflect the low density of the brown adipocytes, and thus, the abundance of these cells would need to be increased in order to impact energy expenditure.

FDG-PET/CT is currently the imaging modality of choice for investigating BAT activity noninvasively. Recent developments in magnetic resonance imaging (MRI) may aid in the evaluation of BAT activity without exposure to ionizing radiation and with possibly better reproducibility and reduced cost. Recent studies have demonstrated the feasibility of measuring the volume and function of BAT in vivo using routine MRI sequences [42]. Other novel imaging techniques, including infrared thermography and new imaging tracers such as 4-^{18}F-fluorobenzyltriphenylphosphonium (^{18}F-FBnTP), are promising noninvasive tools for detection and monitoring of BAT in humans [43,44].

BAT and its association with obesity in humans

The central question is whether the presence, amount, or activity of BAT influences the tendency of an individual to become obese. It has previously been shown that BAT negatively correlates with the development of obesity in rodents. Mice that lack beta-adrenergic receptors or UCP1 protein have been shown to become obese [45,46]. Human studies in recent years verified these results, showing negative correlations between BAT activity and various measures of obesity, including BMI, percent body fat, and body fat content [33–35,37,47,48]. The decline of BAT activity with age was shown to be associated with accumulation of body fat [48], suggesting that BAT may contribute to adiposity in humans. Interestingly, in this study, adiposity increased with age in the BAT-negative group but not in the BAT-positive group, suggesting that BAT may protect against age-related accumulation of body fat. These results are supported by findings showing increased energy expenditure in subjects with higher BAT activity. A recent investigation of morbidly obese patients before and after weight loss induced by bariatric surgery reported an increase in the number of subjects with active BAT 1 year after surgery, as measured by FDG-PET/CT. After weight loss, the BAT-positive subjects had significantly higher nonshivering thermogenesis compared with BAT-negative subjects, suggesting the recruitment of BAT in humans [49]. Obesity may confer insulation to the body, and thus, lower BAT activity may be an adaptive trait of obesity, whereas a decrease in insulation may be apparent because of the loss of subcutaneous adipose tissue after weight loss. However, it is arguable whether the lack of BAT is the cause or the consequence of the change in body composition.

Other clinical correlations

BAT is now confirmed to be present in adulthood. However, there is a clear decline in age-related function and mass of BAT in the majority of studies, and BAT is inversely associated with aging [35,48,50–52]. Several analyses have shown that BAT is more prevalent in women than in men [33,51–53]. This trend was seen also in studies of BAT in rodents [54]. This difference might be explained by the influence of the hormonal environment and differences in cold sensation between genders.

The association between BAT and environmental temperature is also well described. Activation of BAT is more frequent during the cooler seasons of the year [53], and seasonal variations and outdoor temperature appear to be related to detection of BAT by PET/CT scans [33,35,55]. In a recent review of 9 studies of BAT, it was found that the prevalence of activated BAT decreased by 1 % for each increase of 5 °C in average outdoor temperature and that the prevalence is lower in neutral ambient temperature and rare in tropical areas [56].

Origins and Recruitment of BAT

In the past, it was accepted that brown and white adipocytes had a common origin because of morphological analogy and the fact that both adipocytes store triglycerides in intracellular lipid droplets. However, it became apparent in recent years that BAT and WAT have different developmental origins. There are 2 independent pathways for the development of BAT. Classic BAT originates from muscle progenitor cells in the fetus, which leads to functional brown adipocyte cells that are located at typical brown fat pads. Muscles and brown fat cells have a common lineage, and both express myogenic factors such as myf5 [57]. It was demonstrated in rodents that brown fat cells derived from myf5 + cells were located at "classic" brown fat locations. In contrast, brown adipocytes induced by adrenergic stimuli were negative for the myf5 marker, and these cells were interspersed in WAT and might have been activated from dormant precursor cells [58]. Accordingly, the second origin of BAT is brown-like adipocytes that transiently emerge in traditional white fat depots, which are induced upon cold or adrenergic stimulation. These brown cells are typically called "recruitable" BAT and may be transdifferentiated from WAT (**Fig. 1**). This process is often termed development of "brite" (brown-in-white cells) or the cells are called "beige" cells [59–61].

Recent investigational experiments suggest that beige adipocytes are a separate subtype of adipocytes with a developmental origin, molecular characteristics and unique gene expression profile that distinguish them from WAT or classical BAT [62,63]. Although these cells are distinct from the classical brown adipocytes and have different expression pattern of various genes, they display the functional characteristics of brown adipocytes. These experiments, in different from the transdifferentiation theory, support the notion that beige cells progress directly from distinct precursor cells in the undifferentiated state into the brown adipocyte-like appearance, without transition through a phase of being true white adipocytes [62,63] (**Fig. 1**).

A recent report showed that beige cells are not a rare cell type in the subcutaneous tissue of mice. They have a very low level of UCP1 gene expression, comparable to that of WAT, in basal conditions. However, when activated by exposure to cold or beta-adrenergic stimulation, these cells go through phenotypic transdifferentiation and morphological browning and express UCP1 at levels that are similar to those of classic BAT [63]. This research group further demonstrated that BAT previously identified in adult humans resembles murine beige cells more than classic brown fat. Recent data further indicate that human BAT may be primarily composed of beige/brite cells [64]. Increasing BAT recruitment and activation have potential therapeutic implications, and may be targets for pharmacological therapies for obesity and type 2 diabetes.

Investigators identified brown adipocyte stem cells which are CD34 + in skeletal muscle, showing in adult humans the existence in skeletal muscle of a reservoir of progenitor cells with a high potential for brown adipogenic differentiation and UCP1 expression [65]. Human multipotent adipose-derived stem cells were also shown to be able to differentiate into "brite" (brown-in-white) adipocytes [66]. Recent experiments established protocols to generate white and brown adipocytes from human pluripotent stem cells, showing distinct morphology, functional properties, and gene expression for each type of adipose cell. Moreover, transplantation of the cells into mice yielded ectopic fat pads with a morphology and function characteristic of primary BAT and WAT [67]. Nishio et al. recently suggested a high-efficiency method to produce functional BAT from differentiation of human pluripotent stem cells. The generation of functional classical brown adipose pluripotent stem cells was accomplished without exogenous gene transfer, and resulted in lipid and glucose metabolic improvements [68].

Transplantation procedures for BAT progenitors may be a future therapeutic tool for the treatment of patients with obesity and metabolic derangements. A recent experiment in diabetic mice showed that subcutaneous transplants of embryonic BAT can cure type 1 diabetes, resulting in euglycemia, normalized glu-

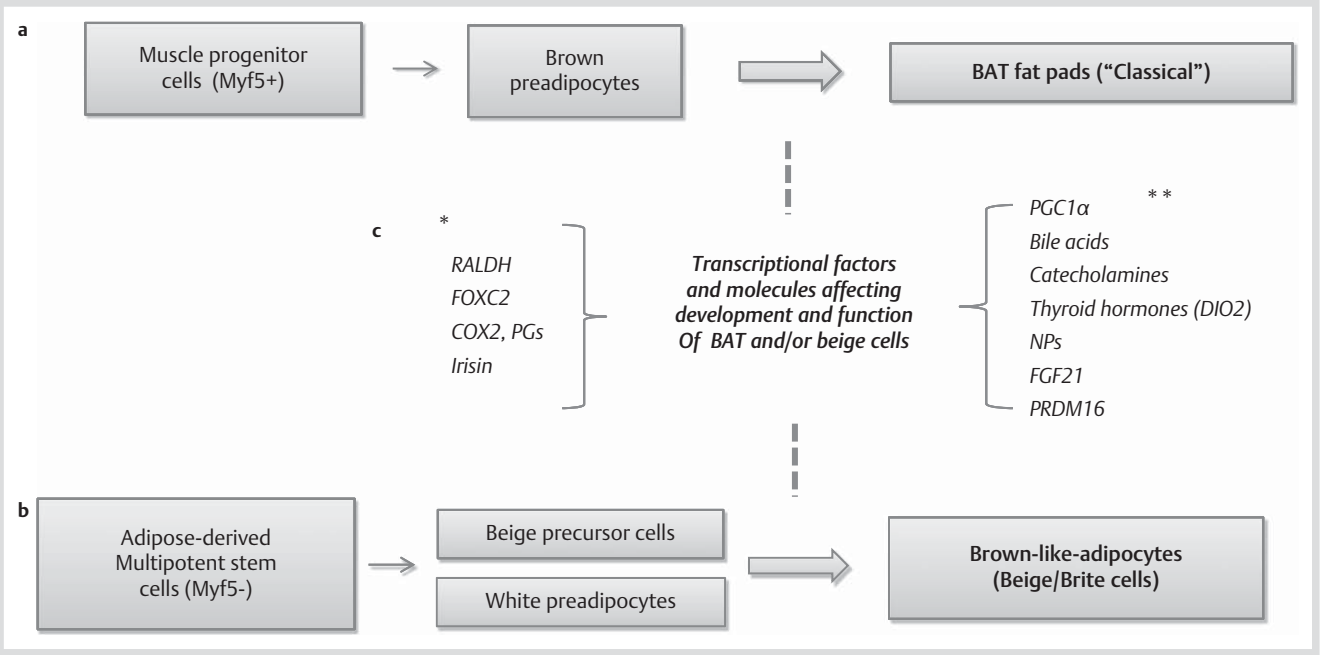

Fig. 1 Recruitment and differentiation of brown adipocytes: **a** Depots of discrete brown adipocytes are differentiated from myf5 (+) expressing embryonic precursors that also give rise to skeletal muscle. **b** White pre/adipocytes, and/or myf5 (−) beige precursor cells, may be recruited to BAT in response to factors such as cold or adrenergic stimulation. It has been suggested that brown-in-white adipocytes (brite cells) are "transdifferentiated" from white fat cells. However, recent evidence supports the existence of subset of beige precursor cells within subcutaneous adipose tissue, which are distinct from white or classical brown adipocytes, and give rise to beige cells. **c** Various transcriptional factors and secreted molecules regulate and promote differentiation and function of brown adipocytes. Some molecules were reported to affect only development of beige adipocytes (*), whereas others influence the development of both brown adipocytes and beige cells (**).

cose tolerance, reduced tissue inflammation, and reversal of clinical diabetic markers [69]. Researchers have also recently demonstrated that transplantation of BAT from donor mice into the visceral cavity of matched recipient mice, resulted in significantly decreased body weight and improved glucose metabolism and insulin sensitivity [70]. The mechanism for this effect involved BAT-derived IL-6. Transplantation of BAT from IL6-knockout mice failed to significantly improve glucose homeostasis and insulin sensitivity.

Stimulation and Activation of BAT

Adaptive cold-induced nonshivering thermogenesis

As explained in the previous text, exposure to cold stimulates nonshivering thermogenesis derived from the activity of UCP1 in BAT, a process that has been demonstrated and confirmed in numerous investigations in both small mammals and humans. Cold sensations signal neurons up to the pre-optic area of the hypothalamus, further activating the sympathetic nervous system to release norepinephrine, which induces UCP1 and BAT activity. This activity is also manifested in BAT during seasonal variations and increases during the winter months.

Sympathetic nervous system

Physiological regulation of BAT occurs via the sympathetic nervous system, mainly through activation of beta3-adrenergic receptors, which are expressed in brown adipocytes. The adrenergic stimulation increases intracellular levels of cyclic adenosine monophosphate (AMP), which activates protein kinase A, mediating transcriptional factors for the induction of thermogenic gene expression. As mentioned previously in this review, pheochromocytoma, a catecholamine-producing tumor of the adrenal gland, significantly increases the thermogenic activity of BAT and provides an example of the long-term sympathetic regulation favoring thermogenesis and reduced body weight. Drugs that increase sympathetic nerve activity, such as ephedrine and sibutramine, have also been targeted to increase thermogenesis, metabolic rate, and weight loss. However, wide-range adrenergic drugs cause overstimulation of adrenergic receptors in the cardiovascular system, increasing the risk of vascular events. In addition, beta3-adrenergic agonists had an insufficient long-term effect on energy balance in human studies [71, 72]. A recent study demonstrated consistent stimulation of BAT in healthy humans by exposure to cold, but not ephedrine, which even at doses with broad sympathetic activation was unable to appreciably affect BAT [73]. However, additional study using a higher dose (2.5 mg/kg) of acute oral administration of ephedrine, displayed activation of BAT in the majority of lean, but not obese humans, although the degree of activation was lower than that observed for cold exposure [74].

Central control by the hypothalamus and the thyroid axis

Changes in temperature are sensed by hypothalamic areas, which coordinate response through vasoactivity, and sympathetic nervous system regulation of BAT and thermogenesis. Recent studies imply that various hypothalamic peptides participate in the control of function and development of BAT. In addition, the hypothalamus responds to dynamic changes in metabolic state and nutrition through AMP-activated protein kinase (AMPK), which is an intracellular energy sensor that affects appetite and energy metabolism. It has also been suggested that hypothalamic inflammation and dysfunction are fac-

tors contributing to the development of obesity through the effect on the control of BAT activity [75]. A recent review by Whittle et al. summarized the evidence on mechanisms of central regulation of thermogenesis [76].

Thyroid hormones are involved in the long-term regulation of energy balance and act coincidently with the sympathetic nervous system, enhancing adrenergic effects. Increasing the activity of the thyroid axis may lead to increased BAT activity. BAT expresses high levels of type 2 iodothyronine deiodinase, an enzyme that converts thyroxine (T4) to triiodothyronine (T3). Induction of type 2 iodothyronine deiodinase enhances local thyroid hormone signaling and energy expenditure during activation of BAT by exposure to cold. Recent data mark the role of thyroid hormones in the regulation of energy expenditure and BAT thermogenesis through the modulation of hypothalamic fat metabolism and AMPK activity [77]. Hyperthyroidism or central administration of T3 decreased the activity of AMPK, increasing sympathetic nervous system activity and upregulating thermogenic BAT markers. Inhibition of the lipogenic pathway in the hypothalamus nuclei or the thyroid hormone receptors prevented central nervous system-mediated activation of BAT and reversed the weight loss associated with hyperthyroidism. Thus, thyroid hormone-induced modulation of AMPK activity and lipid metabolism in the hypothalamus may be an important regulator of energy homeostasis.

Diet-induced thermogenesis

In rodents, feeding of a high-calorie diet in the presence of thermoneutral conditions results in increased BAT mass and thermogenic capacity, generating heat in response to cold but not through nonshivering thermogenesis [46]. This phenomenon was termed "diet-induced thermogenesis" in rodents [78]. Expression of UCP1 in BAT is increased in response to a high-fat diet in rodents, but the size effect is heterogeneous in different studies and seems to be independent of dietary fat content and duration of the feeding trial [79]. Enabling this mechanism in humans could be used for weight control and treatment of metabolic dysregulation. However, there is disagreement among studies concerning the possibility of diet-induced thermogenesis in humans [80]. A study comparing thermogenesis of human subjects exposed to both mild cold and overfeeding showed that the changes in energy expenditure during mild cold and overfeeding were significantly correlated [81]. Indirect evidence for involvement of BAT in diet-induced thermogenesis comes also from results from recent research in humans showing that insulin increases the metabolism of BAT, stimulating the rate of glucose uptake in BAT and suggesting that food that similarly elevates insulin levels may activate BAT as well [38]. However, to date, there are no direct intervention studies in humans showing a relation between overfeeding and BAT activity.

Exercise

Exercise is an effective way to maintain stable weight, aiding in the prevention of obesity. Physical activity results in an increase in activation of the sympathetic nervous system. However, previous data concerning the influence of exercise training on BAT recruitment and thermogenic activity displayed contradictory results. Nevertheless, recent studies suggest that exercise could be an effective stimulus to browning of WAT. A study evaluating the effects of exercise training in rats on a high-fat diet found that exercise increased mitochondrial number and brown adipocyte gene expression in WAT and BAT and enhanced the population of brown adipocyte progenitor cells and brown adipogenesis [82]. In an additional investigation on the effect of exercise training on BAT in rats, browning of the visceral fat was observed by an apparently white-to-brown transdifferentiation, suggesting that exercise could be a physiological stimulus to counteract weight gain by an adrenergic-regulated brown recruitment of adipocytes [83]. Furthermore, a myokine called irisin, which is released to the circulation during exercise, was recently shown to stimulate UCP1 expression and brown fat-like development. Irisin was induced by exercise in both mice and humans [84]. We will discuss this in more detail in the next section.

Physiology of BAT: Regulation, Differentiation, and Transcriptional Control

Knowledge of the development and regulation of BAT has increased significantly in recent years, and a considerable number of transcriptional regulators, proteins, and hormones influencing the differentiation and function of BAT have been discovered, mostly in rodent investigations. Representative examples of milestone research developments in recent years are explained in the following text.

PGC-1α

PPARγ coactivator 1α (PGC-1α) is a transcriptional coactivator that exerts its function by increasing the expression and activation of peroxisome proliferator-activated receptors (PPARs) and other transcriptional factors. PGC-1α is expressed in BAT, especially during exposure to cold. Induced expression of PGC-1α in WAT stimulates mitochondrial biogenesis and induces the expression of genes involved in oxidative phosphorylation and thermogenesis, such as UCP1. Mice deficient in PGC-1α develop hypothermia during exposure to cold as a result of decreased nonshivering thermogenesis [60, 85], and it has been shown that beta-adrenergic stimulation cannot induce UCP1 in BAT that lack PGC-1α activity [86]. A recent investigation found that loss of PGC-1α in white fat resulted in reduced expression of thermogenic and mitochondrial genes, influencing regulation of glucose homeostasis and insulin resistance [87].

PRDM16 and BMP

The PR domain containing 16 (PRDM16) is a transcriptional regulator expressed at a high level in BAT. It has been shown to control a bidirectional cell fate switch between skeletal myoblasts and brown fat cells in mice. Loss of PRDM16 from brown fat precursors caused a loss of brown fat characteristics and promoted muscle differentiation. Conversely, ectopic expression of PRDM16 in myoblasts induced their differentiation into brown fat cells [58]. PPARα induced PGC-1α gene transcription in brown adipocytes through mechanisms involving PRDM16. In addition, activation of PPARα in human WAT led to the appearance of brown adipocyte gene expression [88]. These results suggest that PPARα acts as a key component of brown fat thermogenesis by regulating gene expression via induction of PGC-1α and PRDM16.

Bone morphogenetic protein (BMP-7) is a member of the transforming growth factor β family. It is secreted at an early phase of BAT differentiation and was shown to induce regulators of BAT such as PRDM16 and PGC1α and the expression of the brown fat-defining protein UCP1 [89]. Recently, investigators described

a role of BMP-8B in the direct regulation of thermogenesis, suggesting that this protein regulates energy balance by a coordinated activity in both the hypothalamus and mature BAT [90]. In addition, researchers have recently shown in a mouse model a role for BMP in the physiological cross-talk between constitutive and recruitable brown fat cells [91]. Genetic ablation of BMP receptors in BAT progenitor cells led to severe paucity of constitutive BAT, but compensatory increase in sympathetic input to WAT, promoting the formation of recruitable BAT within white fat depots. The purpose of this regulatory mechanism may be to restore total brown-fat mediated thermogenic capacity in the body and maintain normal temperature homeostasis.

FOXC2

FOXC2 is a member of the forkhead transcription factor family. Its overexpression in adipose tissue in mice led to browning of white fat pads and protected mice against diet-induced obesity and insulin resistance [92]. Enhanced expression of FOXC2 in adipocytes increases upregulation of genes encoding respiratory complexes and brown fat-related genes [93].

FGF21

Fibroblast growth factors (FGFs) have been implied in the physiology of BAT. Circulating FGF21 originates mostly from the liver and is a metabolic regulator of glucose and lipid homeostasis. Systemic administration of FGF21 in obese mice resulted in reduction in adiposity, increased energy expenditure, and improved glycemic control [94]. FGF21 is induced by cold exposure and adrenergic stimulation, and injection of FGF21 into mice induced genes involved in BAT thermogenesis [95]. A recent investigation reported that FGF21 has a physiological role in the thermogenic recruitment of WAT. Mice deficient in FGF21 displayed an impaired ability to adapt to long-term exposure to cold, with diminished browning of WAT. Adipose-derived FGF21 acted to increase expression of UCP1 and the appearance of brown-like adipocytes in subcutaneous WAT. Moreover, FGF21 enhanced PGC-1α protein levels (a key regulatory protein in adipose tissue) independently of messenger RNA expression [96].

VEGF

Vascular endothelial growth factor (VEGF), a potent angiogenic factor, was found in the past to be expressed abundantly in the BAT of rodents when exposed to cold. The cold-induced increase in VEGF messenger RNA was abolished by sympathetic denervation but was elevated by administration of catecholamines [97]. Recently, researchers demonstrated that overexpression of VEGF resulted in increased blood vessel number and size in both WAT and BAT and protection against high-fat-diet-induced obesity. This increase was associated with increased thermogenesis and energy expenditure, increased insulin sensitivity and glucose tolerance, and an increased number of anti-inflammatory macrophages, suggesting that overexpression of VEGF in adipose tissue is a potential therapeutic strategy for the prevention of obesity and insulin resistance [98]. Another recent study showed that repression of VEGF-A induced development of brown-like adipocytes in WAT and upregulation of BAT-specific genes including PRDM16 and UCP-1 [99]. VEGF-A-repressed mice presented a lean phenotype and resistance to high-fat diet-induced body weight gain. The investigators suggested that repression of VEGF-A upregulated expression of VEGF-B and its downstream fatty acid transport proteins and that those relative levels of VEGF-A/VEGF-B might be important in energy metabolism.

COX2

Cyclooxygenase (COX) 2 is a rate-limiting enzyme in prostaglandin synthesis. COX2 activity and prostaglandin E_2 were reported to be involved in induction of UCP1 expression in inguinal white adipocytes but not in classic intercapsular BAT [100]. Cold-induced expression of UCP1 in WAT was repressed in COX2-deficient mice and by administration of a COX inhibitor (indomethacin), whereas injection of a prostaglandin E_2 analogue induced expression of UCP1 in WAT. These findings support evidence that induction of UCP1 expression in WAT, but not in classic interscapular BAT, is dependent on COX activity, suggesting a role for COX in the control of energy balance and development of obesity. Other researchers have additionally shown that catecholamines induced COX2 activity in WAT and that overexpression of COX2 resulted in de novo BAT recruitment in WAT and increased systemic energy expenditure, which protected mice against high-fat diet-induced obesity [101].

Myokines

Myokines are peptides that are expressed and released by muscle fibers, enabling a secretory function of bioactive proteins. In recent years, it has been shown that myokines participate in endocrine "cross talk" with other tissues, including adipocytes [102]. Bostrom and colleagues recently identified in mice a new myokine hormone, irisin (a cleavage product of FNDC5), which is released to the circulation during exercise and acts on white adipose cells in culture and in vivo to stimulate UCP1 expression and brown fat-like development [84]. The same group recently showed that irisin preferentially activates beige fat cells [63].

The transcriptional coactivator PGC-1α is expressed in muscle and is known to be increased during exercise and reduced with a sedentary lifestyle and diabetes. Increased levels of PGC-1α in muscle stimulated an increase in the amount of irisin, acting on white adipocytes to stimulate expression of UCP1 and programming of brown fat-like development [84]. Irisin was induced by exercise in mice and humans and showed an increase in expression of UCP1 when injected in adenoviral particles to mice, resulting in an increase in energy expenditure and improvement in obesity and glucose homeostasis. These findings suggest that exercise, through the influence of irisin, has the capacity to turn on a phenotype similar to that of BAT and may have therapeutic implications for metabolic diseases.

Retinoid metabolism in BAT

Retinoids are vitamin A metabolites that stimulate various essential biological functions. They have been linked to an effect on obesity and diabetes [103]. A recent investigation showed a specific role for retinoid metabolism in BAT [104]. A deficiency of retinaldehyde dehydrogenase enzyme in mice (converting retinaldehyde to retinoic acid), which is predominantly expressed in WAT, induced a BAT-like transcriptional program in WAT, promoting UCP1 and PGC-1α expression, activating a thermogenic program, and limiting weight gain in obese mice, with improved glucose homeostasis.

Macrophages and BAT

Macrophage responses are broadly classified through 2 distinct activation programs, termed classical (M1; proinflammatory) and alternative (M2; anti-inflammatory). A transition from M2 to M1 predominance occurs in adiposity states, promotes metabolic inflammation and insulin resistance [105].

Recent data support macrophages as BAT regulators. Researchers reported that interlukin-4 (IL4), which is a direct inducer of

M2 macrophages, stimulated a program of alternative macrophage activation required in adaptive thermogenesis [106]. In the absence of activated macrophages, impaired metabolic adaptations to cold were observed. Furthermore, administration of IL4 increased thermogenic gene expression and raised energy expenditure. Under cold stress conditions the alternatively activated macrophages (M2) coordinated thermogenic response by noradrenaline secretion, suggesting that macrophages secrete cathecholamines to sustain BAT activation.

BAT and the Cardiometabolic Link

Cardiac NPs and BAT

The cardiac natriuretic peptides (NPs) are hormones produced in the heart that serve an important role in hemodynamic and fluid homeostasis. NPs act by binding to NP receptor A (NPRA), which possesses guanylyl cyclase activity, increasing cyclic guanosine monophosphate (GMP) levels and thus activating cyclic GMP-dependent protein kinase (PKG). Another NP receptor (NPRC) is a clearance receptor that removes the NPs from the circulation. These NP actions are parallel to the process of thermogenesis mediated by beta-adrenoreceptors, which act by cyclic AMP-dependent protein kinase (PKA) signaling. Both exert their effect through the p38α-MAPK pathway, enhancing transcriptional effects. NP receptors are expressed in adipose tissue, and the increase in circulating NPs is associated with lipolysis and weight loss, suggesting a role for NPs as metabolic regulators [107]. A recent novel work by Bordicchia and colleagues demonstrated that atrial NPs and beta-adrenoreceptor agonists can act synergistically to promote adipocyte functions [108]. In both human-derived adipocyte cell lines and mice, cardiac NPs through NPRA and PKG signaling activated p38α-MAPK to increase mitochondrial biogenesis as well as PGC-1α and UCP1 expression, similar and additive to the response to beta-agonists. NRPC-deficient mice increased the expression of BAT markers, whereas NRPA-deficient mice showed the opposite. Cold exposure increased NP levels, with an increase in the expression of NPRA and a decrease in NPRC, favoring lipolysis and thermogenesis. Furthermore, infusing brain NP into mice stimulated the appearance of brown-like adipocytes, expressing thermogenesis markers in WAT and BAT, associated with increased oxygen consumption and energy expenditure. These results suggest that NPs promote browning of WAT to increase energy expenditure and raise the possibility of achieving greater activation of BAT from an existing level of adrenergic stimulation while avoiding the adverse effects associated with increasing sympathetic nervous tone [109]. Overall, there is increasing recognition that the heart may play an active role in the defense against metabolic diseases.

Studies consistently show an inverse correlation between NP levels and BMI in humans, demonstrating lower levels of NPs in obese individuals. In parallel, there is also a significant inverse correlation between BMI and BAT activity. It is suggested that increased clearance of NPs by NRPC within adipose tissue may have a role in the lower plasma NP levels observed in obese patients. In addition, development of weight loss in patients with advanced heart failure (cardiac cachexia) could be associated with high circulating levels of NPs and catecholamine levels, which may affect the increase in brown fat activity and energy expenditure [108].

Epicardial fat

Epicardial fat is located between the myocardium and visceral pericardium and shares the same microcirculation of the myocardium. It is active in lipid and energy homeostasis and has endocrine and paracrine effects [110]. In recent years, it was suggested that epicardial fat has a role in the development and progression of atherosclerosis, mediated through oxidative stress and inflammatory signals. Imaging techniques such as echocardiography and CT/MRI can reliably measure epicardial fat thickness, which was shown in several clinical studies to correlate with metabolic syndrome and cardiovascular risk [110–112] and to be affected by changes in body weight and exercise [113,114]. To better understand the thermogenic function of epicardial fat, investigators analyzed fat samples taken during open-heart surgeries in humans with coronary artery disease. They showed that the expression of UCP1 and transcriptional factors marking BAT activity were apparent in epicardial fat in a significantly higher amount compared with other fat depots, raising the possibility that epicardial fat functions like BAT and suggesting that it may have a role in defending the myocardium and coronary vessels from hypothermia [115]. A recent study supported these results, showing an abundance of UCP1 protein in epicardial fat relative to other fat depots and the capability of epicardial fat to alter circulating lipid levels [116].

Lipoprotein metabolism and BAT

In an obese state, the calories consumed often overpower the ability of the adipose tissue to store lipids, resulting in metabolic and inflammatory derangements leading to ectopic lipid deposition and a risk of developing diabetes. The role of lipoproteins in energy delivery to BAT is not definitely understood. Stimulation of BAT results in efficient uptake of fatty acids and utilization of triglycerides for producing heat. Thus, clearance of triglyceride-rich lipoproteins by BAT may protect not only against the cold but also against conditions such as obesity, dyslipidemia, and cardiovascular disease [117]. Indeed, a recent investigation in mice showed that the triglyceride concentration in triglyceride-rich lipoproteins was markedly reduced after exposure to cold [118]. Radioactive scans revealed a selective increase in organ uptake of fatty acids into BAT, a process that was facilitated by the transmembrane receptor CD36 and the enzyme lipoprotein lipase. The exposure to cold shifted the clearance of lipoproteins from the liver into BAT. Impaired glucose tolerance was shown in the obese mice and was normalized on exposure to cold. Uptake of triglyceride-rich lipoproteins was independent of insulin levels and resistance. These results support that BAT after exposure to cold regulates triglyceride-rich lipoprotein clearance and is dependent on lipoprotein lipase activity. They also suggest that significant activation of BAT may potentially correct dyslipidemia and improve the metabolic consequences of obesity [119]. Finding ways to increase the mass and activity of BAT may enable promotion of triglyceride clearance and weight loss in order to fight dyslipidemia, obesity, and type 2 diabetes.

Summary and Future Considerations

There have been significant advances in recent years in the understanding of the role of BAT in human thermogenesis, uncovering essential knowledge of the origin, differentiation, distribution, activators, and regulation of BAT. The accumulating data suggest that BAT-mediated thermogenesis may be an

important player in human energy balance. Activating brown fat-mediated thermogenesis may have therapeutic potential in the treatment of patients with obesity, diabetes, and metabolic syndrome, providing new options for interventional therapy. However, parallel to these exciting developments, important issues still need to be solved. Will we find novel ways to stimulate and recruit brown adipocytes and sustain BAT activity? Will targeting BAT thermogenesis be sufficient, tissue specific, and proven safe in humans? How effective and clinically significant will be the recruitment of BAT thermogenesis in reducing obesity and improving insulin resistance, particularly in light of the evidence of reduced mass and activity of BAT in obese individuals? Finally, will physiological compensating and counter-regulatory mechanisms reduce the benefits of BAT activation?

New sites of involvement of BAT, such as epicardial fat, and recognition of novel metabolic influences, such as cardiac NPs, will further contribute to the development and implementation of new perspectives in research on BAT.

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Conflict of Interest

The author declares no potential conflicts of interest with respect to the authorship and/or publication of this article.

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