Anna Fenzl and Florian W. Kiefer*

Brown adipose tissue and thermogenesis

Abstract: The growing understanding of adipose tissue as an important endocrine organ with multiple metabolic functions has directed the attention to the (patho)physiology of distinct fat depots. Brown adipose tissue (BAT), in contrast to bona fide white fat, can dissipate significant amounts of chemical energy through uncoupled respiration and heat production (thermogenesis). This process is mediated by the major thermogenic factor uncoupling protein-1 and can be activated by certain stimuli, such as cold exposure, adrenergic compounds or genetic alterations. White adipose tissue (WAT) depots, however, also possess the capacity to acquire brown fat characteristics in response to thermogenic stimuli. The induction of a BAT-like cellular and molecular program in WAT has recently been termed “browning” or “beiging”. Promotion of BAT activity or the browning of WAT is associated with in vivo cold tolerance, increased energy expenditure, and protection against obesity and type 2 diabetes. These preclinical observations have gained additional significance with the recent discovery that active BAT is present in adult humans and can be detected by 18fluor-deoxy-glucose positron emission tomography coupled with computed tomography. As in rodents, human BAT can be activated by cold exposure and is associated with increased energy turnover and lower body fat mass. Despite the tremendous progress in brown fat research in recent years, pharmacological concepts to harness BAT function therapeutically are currently still lacking.

Keywords: brown adipose tissue; obesity; thermogenesis; uncoupling protein-1.

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Introduction

The prevalence of obesity is increasing at an alarming rate worldwide, and already affects one-third of the world population [1]. Obese people are at high risk for developing complications such as type 2 diabetes, cardiovascular disease, and the metabolic syndrome [2, 3]. Obesity is a consequence of altered energy balance and develops when energy intake exceeds total energy expenditure [4], which is dictated by the basal metabolic rate, physical activity, and thermogenesis [5]. Excess nutrient-derived energy is mainly stored in white adipose tissue (WAT) and leads to the expansion of total body mass [6]. Adipose tissue depots exert distinct local and systemic effects. Due to its unique metabolic function, brown adipose tissue (BAT) has recently been in the focus of metabolism research. BAT, in contrast to WAT, dissipates energy through a process called uncoupled respiration mediated by uncoupling protein-1 (UCP1), resulting in increased fatty acid oxidation and heat production (thermogenesis) [7, 8]. The thermogenic capacity of brown fat has been appreciated particularly in small mammals and infants, where it serves a vital role in maintaining core body temperature [8]. Notably, promoting brown fat function or the acquisition of BAT characteristics within white adipose depots (referred to as “browning” or “beiging”) has been shown to protect against obesity and related metabolic complications in animal studies [9–15]. Evidence for a clinical relevance provided the recent discovery of active BAT in adult humans, detected by 18fluor-deoxy-glucose positron emission tomography coupled with computed tomography (FDG-PET/CT) [16–21]. Importantly, active BAT in humans appears to be negatively correlated with body mass index, body fat mass [22–25], blood glucose levels [25, 26] and diabetes status [27].

In this review we will summarize the function of brown and beige adipocytes, their putative developmental origin and their role in energy metabolism. We will highlight recent advances in translational human studies and discuss potential therapeutic approaches for the treatment of obesity.

Body of review

Different types of fat: white, beige and brown

The functional importance of different adipose depots in energy metabolism and nutritional homeostasis mainly
depends on the composition of the various types of adipocytes, classified as white, beige or brown (Table 1).

WAT mainly consists of mature white adipocytes, which contain a single cytoplasmic lipid droplet (unilocular) and a peripherally-located nucleus. White fat can store excess energy in the form of triglycerides that can be released as free fatty acids into the circulation in times of high energy demand [28]. Moreover, WAT serves as a thermal insulator, protects organs against mechanical damage [29] and secretes adipokines that are implicated in inflammation, angiogenesis, and metabolism [30, 31]. WAT can be found at various anatomic locations and possesses distinct metabolic functions. For example, expansion of the visceral WAT is closely associated with inflammation, insulin resistance, and type 2 diabetes [29]; whereas subcutaneous WAT has been shown to be less inflammatory [32–35] but more susceptible to acquiring brown fat characteristics [9, 10, 14, 36–38].

BAT, the major site of non-shivering thermogenesis, was first discovered in hibernating animals and infants, where it helps maintain an adequate core body temperature [39–42]. BAT also differs morphologically from WAT, containing multiple small (multilocular) cytoplasmic lipid droplets, a central nucleus, and a large number of mitochondria [8]. In contrast to WAT, BAT lipids serve primarily as fuel for oxidative phosphorylation and heat production [43], the latter process primarily depends on UCP1 activity [7, 44]. Briefly, free fatty acids released into the cytoplasm by lipolysis of fat droplets are channeled towards the mitochondria via the general activation/carnitine shuttle system. As a result, free fatty acids are β-oxidized to generate NADH, FADH₂, and acetyl coenzyme A. Acetyl coenzyme A enters the tricarboxylic acid cycle (TCA) where it produces additional electron carriers (NADH and FADH₂) that subsequently donate electrons to the complexes of the electron transport chain, located in the inner mitochondrial membrane. The terminal electron acceptor is molecular oxygen, which is reduced to water. An electrochemical gradient is generated as protons are pumped through the mitochondrial respiratory chain complexes. Finally, ATP is synthesized by the ATP synthase complex, which is driven by the energy of the proton gradient. UCP1, located in the inner mitochondrial membrane of brown adipocytes, acts as a transmembrane protein allowing protons to re-enter the mitochondrial matrix, thereby dissipating the electrochemical gradient that drives ATP synthesis. This process results in the release of significant amounts of chemical energy in the form of heat [8, 45, 46] (see Figure 1).

In addition to classic brown adipocytes, which are typically located in distinct brown fat depots, it has previously been noted that brown adipocytes can also emerge in white adipose depots in response to prolonged cold exposure or β-adrenergic stimulation [8, 12, 13, 47–50]. This phenomenon has recently been termed “browning” or “beiging.” Depending upon the stimulus, these recruitable brown adipocytes [51] display the molecular and metabolic characteristics of either white or brown adipocytes.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>White adipose tissue</th>
<th>Beige adipose tissue</th>
<th>Brown adipose tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rodents</td>
<td>Subcutaneous, intra-abdominal</td>
<td>Predominantly subcutaneous (inguinal, axillary)</td>
<td>Interscapular, perivascular</td>
</tr>
<tr>
<td>Humans</td>
<td>Subcutaneous, intra-abdominal</td>
<td>Cervical, parasternal, supraclavicular, para- and prevetebral</td>
<td>Cervical, parasternal, supraclavicular, para- and prevetebral</td>
</tr>
<tr>
<td><strong>Developmental origin</strong></td>
<td>Myf5-negative</td>
<td>Myf5-negative</td>
<td>Myf5-positive</td>
</tr>
<tr>
<td>Lipid droplets</td>
<td>Unilocular</td>
<td>Uni/multilocular</td>
<td>Multilocular</td>
</tr>
<tr>
<td>Mitochondrial content</td>
<td>Low</td>
<td>Low to high</td>
<td>High</td>
</tr>
<tr>
<td>Vascularization</td>
<td>Low</td>
<td>Basal: low</td>
<td>Abundant</td>
</tr>
<tr>
<td><strong>UCP1 expression</strong></td>
<td>Low</td>
<td>Basal: low</td>
<td>High</td>
</tr>
<tr>
<td>Adaptive thermogenesis</td>
<td>Negative</td>
<td>Basal: low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Marker genes</strong></td>
<td>Leptin, TCF21</td>
<td>CD137 (TNFRSF9), TMEM26, Tbx1</td>
<td>Lhx8, Zic1</td>
</tr>
<tr>
<td>Energy metabolism</td>
<td>Energy storage</td>
<td>Stimulated: energy dissipation</td>
<td>Energy dissipation</td>
</tr>
<tr>
<td>Obesity and diabetes</td>
<td>Positive correlation</td>
<td>Negative correlation (in animal models)</td>
<td>Negative correlation</td>
</tr>
<tr>
<td>Activators</td>
<td>High fat diet</td>
<td>Cold, catecholamines, β-adrenergic receptor agonists, FGF21, irisin, METRLN, vitamin A derivatives, BMP4, BMP7, BMP8b, BMP9, etc.</td>
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and are therefore also named beige [52] or brite adipocytes [53]. These cells possess a high thermogenic capacity and thus significantly contribute to energy expenditure in various in vivo models [9, 12, 35]. In addition to cold and β-adrenergic stimulation, multiple genetic factors have recently been identified to regulate the browning of WAT, highlighting the transcriptional complexity underlying this process [32, 38, 54–58].

Developmental origin of brown and beige adipocytes

The adipogenesis of white and brown adipocytes includes the development of pre-adipocytes from mesenchymal stem cells that further differentiate to mature adipocytes. Adipose mesenchymal stem cells can be committed to either Myf5-negative cells, which differentiate to white adipocytes, or Myf5-positive cells, giving rise to brown adipocytes and skeletal myoblasts [59, 60]. The bi-directional cell fate switch between brown fat and muscle cells has been attributed to the transcriptional regulator PR domain containing 16 (PRDM16) [60]. Although, beige adipocytes derive from Myf5-positive cells, their origin remains a matter of debate and includes two major theories. One implies that brown adipocytes in WAT arise from transdifferentiation or transformation of white adipocytes [10, 48, 61–63]. This theory is supported by lineage tracing of transiently- or permanently-labeled brown and beige adipocytes in transgenic mice showing bi-directional conversion between white and beige adipocytes upon cold or warm conditions [63]. Alternatively, beige adipocytes may arise from distinct progenitor cells by de novo formation [14, 64–66]. These progenitor cells, which express the surface markers CD34, stem cell antigen 1 (SCA1), and platelet-derived growth factor receptor alpha (PDGFRα) were found to give rise to either white or beige adipocytes depending upon the stimuli [65, 67, 68]. Regardless of their exact developmental origin, beige adipocytes constitute a new competent thermogenic cell type [63].
Genetic signature of brown and beige adipocytes

In order to ease the distinction between white, beige, and brown adipocytes, researchers have set out to compare the genetic signature of these three cell types. Combined efforts have revealed a number of “marker” genes for each fat cell type. However, most of this work has been done in mice and it turned out that the expression of these marker genes was far less consistent in human adipocytes. Some genes identified from rodent studies include TCF21 and Leptin for white adipocytes [69]; CD137 (TNFRSF9), TMEM26, and TBX1 for beige [14]; and LHX8 and ZIC1 for brown adipocytes [70]. Using a combination of gene expression analysis and imaging techniques it has been shown that human infants possess classical brown fat in their interscapular and supraclavicular region [71]. However, the genetic profiling of adult BAT has been more challenging and largely depends on the anatomical location of the fat depot. Characterization of human deep neck fat biopsies (a preferred location of BAT in adults) revealed conflicting results, with some authors arguing that human BAT resembles bona fide interscapular brown fat in mice and others suggesting it may express the genetic signatures of both, beige and brown adipocytes [14, 21, 70–73]. Possible explanations for such inconsistent reports may be the large inter-individual variability as well as the heterogeneous distribution of brown/beige adipocytes throughout white fat depots in humans. Nonetheless, all authors agree that UCP1-expressing adipocytes do exist in distinct human fat depots, but their presence may depend on various factors including anatomical location, sex, age, environmental conditions, and metabolic state.

Metabolic implications of brown/beige fat activity

The therapeutic potential of both, brown and beige adipocyte activation in the treatment of obesity and diabetes is now essentially settled science, at least in animal models [38, 56, 57]. Numerous genetic factors have been identified that regulate a thermogenic phenotype in mice [74]. Most of these mouse models are characterized by the browning of WAT or promotion of classic BAT function and they share a number of common features: mitochondria density and/or mitochondrial activity is increased and the expression of brown fat markers including UCP1 is augmented. Substrate utilization is shifted towards fatty acid oxidation and energy expenditure is enhanced. This phenotype can be unmasked under cold conditions or in response to high-fat diet feeding, where mice display cold tolerance and protection against diet-induced obesity, respectively. Consequently glucose metabolism is improved in these models and diabetes progression can be halted [11, 12, 14, 32, 38, 56–58, 75–80].

Transcriptional regulators of brown/beige fat function

Expression of a thermogenic program in adipose tissue is orchestrated by a sophisticated transcriptional machinery that involves a plethora of transcription factors, co-activators, and co-repressors. Several dozen transcriptional regulators have already been identified and the list is constantly growing. The following is a selection of some prototypical factors that have been demonstrated to be potent mediators of brown fat thermogenesis.

PGC1α–PPARγ complex

One of the first identified transcriptional regulators of adaptive thermogenesis was peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1-alpha (PGC1α) [81]. PGC1α is induced upon cold exposure, exercise or fasting, and exerts its function on adaptive thermogenesis mainly through the nuclear receptor PPARγ but also through the thyroid hormone receptor [81–83]. Overexpression of PGC1α in white adipocytes induces the expression of UCP1 and key mitochondrial enzymes of the respiratory chain [81]. In contrast, fat-specific deletion of PGC1α in mice results in a blunted thermogenic response following cold exposure with decreased core body temperature and attenuated thermogenic gene expression in adipose depots. Although PGC1α is not required for BAT development, it is indispensable for cold- or β-agonist-induced activation of brown adipocytes [84, 85] as well as for the browning of WAT [86]. In addition, adipose PGC1α seems to be critical for glucose and lipid metabolism under obese conditions in mice [86] and defective PGC1α may be linked to an increased susceptibility to insulin resistance and type 2 diabetes in humans [87–89]. This notion is further supported by the observation of reduced PGC1α expression in the adipose tissue of patients with type 2 diabetes [90, 91].
PRDM16

PRDM16 is a recently-identified transcriptional co-regulator that controls the fate between muscle and brown fat cell development. In an elegant study by Bruce Spiegelman’s group, overexpression of PRDM16 in myogenic precursor cells was sufficient to reprogram these cells towards brown adipogenesis whereas PRDM16 knockdown forced brown preadipocytes towards muscle cell differentiation [60]. During brown fat development, PRDM16 interacts with PPARα/PPARγ and the CCAAT/enhancer-binding protein beta (C/EBPβ) family [38, 92, 93] leading to the induction of brown-fat genes as well as the repression of selective VAT or skeletal muscle markers [94–96]. Notably, PRDM16 also contributes to the browning of VAT. Transgenic expression of PRDM16 in adipose tissue strongly induces a thermogenic program in subcutaneous but not in visceral VAT, with potent effects on energy expenditure and glucose metabolism. Likewise, transplantation of PRDM16- and C/EBPβ-expressing embryonic fibroblasts into the fat pads of nude mice results in increased thermogenic activity of these fat depots as determined by FDG-PET scans [92]. PRDM16 is also required for PPARγ agonist-mediated white-to-brown fat conversion. The PPARγ agonist rosiglitazone exerts its thermogenic effects in adipocytes through binding and activation of various white fat depots. The observation that media from PGC1α-expressing myocytes induces the transcription of several brown-fat-specific genes in primary subcutaneous fat cells led to the assumption that a muscle-derived secreted factor, under the control of PGC1α, controls a BAT-like program in white adipocytes. Using a combination of gene expression arrays and bioinformatics approaches, Bruce Spiegelman’s laboratory identified a protein called fibronectin type III domain-containing protein 5 (FNDC5) as a putative candidate driving brown-fat activation whereas PRDM16 knockdown forced brown adipogenesis towards muscle cell differentiation [56].

Secreted proteins and browning

Recently an interorgan crosstalk between skeletal muscle and VAT was shown to promote browning via a muscle-secreted factor called irisin. Exercise is known to increase the expression of PGC1α in skeletal muscle. Mice with transgenically-increased muscle PGC1α are resistant to diet-induced obesity and diabetes largely due to browning of various white fat depots. The observation that media from PGC1α-expressing myocytes induces the transcription of several brown-fat-specific genes in primary subcutaneous fat cells led to the assumption that a muscle-derived secreted factor, under the control of PGC1α, controls a BAT-like program in white adipocytes. Using a combination of gene expression arrays and bioinformatics approaches, Bruce Spiegelman’s laboratory identified a protein called fibronectin type III domain-containing protein 5 (FNDC5) as a putative candidate driving brown-fat activation whereas PRDM16 knockdown forced brown adipogenesis towards muscle cell differentiation [56].

Retinoids

Another group of potent transcriptional activators of brown fat activation are vitamin A metabolites or retinoids. The main metabolite, retinoic acid, strongly induces UCP1 expression in adipocytes through binding and activation of the nuclear receptors retinoic acid receptor and retinoid X receptor [102–107]. Respective retinoic acid receptor response elements have been identified at the enhancer region of the UCP1 promoter. The in vivo relevance of the vitamin A pathway for energy metabolism has been supported by the observations that retinoid administration in mice is associated with increased adipose UCP1 expression and reduced body weight on a high-fat diet [102, 104, 107, 108]. We have recently shown that retinaldehyde-dehydrogenase 1, the rate-limiting enzyme of retinoid conversion, regulates a thermogenic program in VAT. Retinaldehyde-dehydrogenase 1 deficiency in mice induces a BAT-like transcriptional program, particularly in the visceral VAT which results in cold tolerance, limited body weight gain, and improved insulin sensitivity in response to high-fat diet feeding [56].
to contribute to the thermogenic activation of neonatal BAT [120, 122, 124]. These preclinical observations have been further supported by reports that circulating FGF21 is increased in humans in response to cold exposure and exercise. Stimulation with recombinant FGF21 enhances a thermogenic program in human neck adipocytes and shows synergistic effects with FNDC5. It has therefore been suggested that FGF21 may act in concert with irisin to augment cold- and exercise-mediated brown fat thermogenesis [125]. In summary, FGF21 is now considered a promising new anti-obesity agent based on its beneficial effects on body weight, energy expenditure, lipid mobilization, hepatic and peripheral insulin sensitivity, and hepatic steatosis [122, 126–129].

Bone morphogenetic proteins (BMPs) are a family of secreted molecules that play a role in the differentiation of mesenchymal stem cells and drive the formation and thermogenic activation of BAT [64, 130, 131]. BMP7 activates brown pre-adipocytes in vitro and promotes brown adipocyte differentiation and thermogenesis in vivo [131]. BMP8b is a thermogenic protein that directly regulates energy balance by increasing the cellular response to noradrenaline [130]. Another BMP family member, BMP9, drives brown adipogenesis of human adipose tissue-derived stem cells. In vivo, BMP9 treatment results in browning of subcutaneous WAT, improved glucose tolerance and reduced weight gain [132]. Finally, BMP4 transgenic mice display BAT-like changes in WAT and are therefore protected against diet-induced obesity and diabetes [133].

Immune cells and browning

Adipose tissue is a rich source of immune cells, which play important roles in the metabolic function of distinct fat depots. Depending upon their immunological and metabolic function, two broad classes of immune cells can be distinguished in fat. Neutrophils, mast cells, M1 macrophages, B lymphocytes, CD8+ and CD4+ T-lymphocytes are predominantly pro-inflammatory and thus have detrimental effects on insulin sensitivity and glucose metabolism. The other group includes regulatory T-cells, alternatively activated (M2) macrophages, eosinophil and innate lymphoid cells, which act to contain the inflammatory response, contribute to tissue repair, and ultimately have beneficial effects on insulin sensitivity and the metabolic state [134]. Recently, two cell types among the latter group have been implicated in the regulation of thermogenic processes in WAT, thus linking immune responses to adaptive thermogenesis and energy expenditure. These two cell types are eosinophils and M2 macrophages. Eosinophils are the major source of interleukin-4 (IL-4) in adipose tissue. IL-4 helps polarize macrophages towards the alternatively activated type (M2). Interestingly, cold exposure has recently been shown to promote M2 macrophage activation in adipose tissue in an IL-4/IL-13 dependent manner. Cold-activated macrophages then release catecholamines and induce a local BAT-like phenotype in WAT with effects on whole-body energy metabolism [35]. In contrast, mouse models lacking alternatively activated macrophages or macrophage recruitment due to disrupted chemokine receptor signaling, show a blunted thermogenic response as a result of impaired browning of WAT [33, 35, 135, 136]. The involvement of eosinophil-derived signals in the browning of WAT is further supported by the identification of the circulating factor meteorin-like that is induced in adipose tissue upon cold exposure and in muscle after exercise [33]. Overexpression or the administration of recombinant meteorin-like in mice drives expression of IL-4/IL-13 in adipose tissue together with alternative activation of adipose tissue macrophages, which promote a thermogenic and anti-inflammatory gene program in fat.

Brown adipose tissue in humans

While BAT has long been appreciated as an important player in cold defense in human infants, BAT thermogenesis was thought to be completely blunted during adulthood. This view changed in 2009 when three groups reported independently that active BAT was present in adults and could be activated via cold exposure [16, 18, 20]. Only moderate cold stimulation (14–17°C) for a short period of time (1–2 h) is sufficient to augment glucose uptake in BAT accompanied by enhanced fatty acid oxidation and increased energy expenditure [22, 137, 138]. The observations that BAT activity is negatively associated with human obesity and type 2 diabetes have further propelled clinical research in this field [16, 17, 20, 22, 25–27]. FDG-PET/CT is currently considered the gold standard for measuring BAT activity in humans, which correlates positively with intracellular glucose uptake. However, other techniques including magnetic resonance imaging (MRI) are being investigated as alternative approaches for BAT detection [16, 17, 71, 137, 139–142]. Using FDG-PET/CT scans a typical anatomical pattern of BAT distribution has been identified in humans. Most active BAT is located in the cervical, parasternal, para- and pre-vertebral region [16,
Reports that short-term cold exposure can trigger glucose uptake in distinct fat depots provided the first evidence that thermogenically-active BAT pre-exists in adult humans and that the observed cold-mediated alterations are not dependent on de novo brown fat formation. However, several case studies suggest that the recruitment of brown adipocytes into white fat depots can occur in humans like in rodents. In patients with untreated pheochromocytoma, significant amounts of active brown/beige adipocytes have been found in visceral adipose tissue, which is most likely due to a chronic over-stimulation with catecholamines [143, 144]. A few months after resection of the tumor, FDG positivity of the visceral fat depot was no longer present, consistent with a regression of thermogenically-active brown/beige fat [144]. Some controversy exists regarding the molecular signature of human BAT, with reports demonstrating a gene expression pattern that resembles the classic interscapular brown fat in mice, while others argue that human BAT also displays characteristics of inducible beige fat cells [14, 15, 70–72, 145]. Nonetheless, all authors agree that the promotion of BAT activity drives energy expenditure in humans and thus may counteract obesity. Despite such evidence, recent attempts to harness BAT thermogenesis therapeutically have had little success. Administration of β-adrenergic compounds such as ephedrine or isoproterenol has only shown modest effects on glucose uptake in BAT as determined by FDG-PET scans [144, 146–149]. Irrespectively, the use of such substances is of very limited therapeutic value, given their known side effects on the cardiovascular system. In contrast, moderate cold exposure (17°C) for 6 weeks, 2 h daily significantly enhanced BAT activity and energy expenditure accompanied by a decrease in body fat mass [22]. Nonetheless, effective pharmacological approaches to counteract obesity are still lacking, therefore the search for novel therapeutic strategies targeting brown fat continues.

In contrast to such efforts, two recent studies suggest that beige fat thermogenesis may also have deleterious effects under certain circumstances. Increased browning of white fat seems to be a major trigger of tumor cachexia in some cancer models. The pro-inflammatory state (particularly IL-6) along with tumor-derived factors such as parathyroid-hormone-related protein have been discussed as possible mediators of adipose tissue browning that contributes to tumor cachexia [150, 151]. It remains to be shown whether the induction of WAT thermogenesis also plays a part in cachexia associated with other catabolic diseases, such as congestive heart failure, chronic kidney disease or critically ill patients.

**Expert opinion**

The metabolic effects of thermogenically-active brown fat are indisputable. The important role that brown/beige fat cells play in the regulation of total energy expenditure has now been evidenced in countless preclinical and an increasing number of human studies. With the rise of the obesity and diabetes prevalence, new scientific challenges have evolved and a new era of research, focused on the regulation of energy pathways, has begun. Less than 20 years ago the major thermogenic factor UCP1 was yet to be discovered. A lot has happened since and the entire
field of metabolism research has been heavily influenced by the tremendous progress that has been made over the last decade. Brown/beige fat has lately been the center of attention and due to its metabolic properties it is a legitimate candidate for novel anti-obesity concepts. The impact that brown fat thermogenesis will have on future therapeutic regimens in metabolic diseases is still up in the air but we dare to offer a potential outlook.

**Outlook**

The incredible developments in brown fat research in the past years are a strong indicator of what we can expect in the near future. The primary goal of many researchers (and of pharmaceutical companies) is the discovery of novel drug candidates that promote brown/beige fat function, energy expenditure, and body weight loss in humans. Despite the fact that a lot more studies will be needed to gain a better understanding of how beige fat conversion and induction of thermogenic responses are regulated in human fat depots, it would not be surprising if the first clinical trials evaluating the effects of novel substances that promote BAT activity will soon be presented. It will be interesting to see whether increased energy expenditure due to enhanced thermogenesis will be associated with increased food intake that may partially counteract the effects on body weight. In such a case, a combination of BAT activity enhancers together with appetite regulators might be the most powerful pharmacological approach to target obesity. In terms of BAT detection in humans, significant progress can be expected involving new imaging techniques. In particular, functional MRI, PET/MRI, dual-energy computed tomography and single-photon emission computed tomography are currently being investigated as alternative approaches to FDG-PET/CT [139, 141, 152]. Also new radiotracers could be developed to improve the sensitivity of PET-based imaging strategies.

**Key points**

- Brown adipocytes are capable of dissipating energy in the form of heat (thermogenesis) and thus exhibit anti-obesity and anti-diabetic properties.
- Uncoupling protein-1 is the central regulator of thermogenic processes.
- Beige adipocytes can emerge in white fat depots upon certain stimuli (genetic factors, cold or adrenergic stimulation, and exercise).
- Active brown adipose tissue is present in humans, it can be activated by cold, and correlates negatively with obesity.
- Currently no therapeutic agents are available for the activation of brown/beige fat in humans.

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