Brown adipocytes are specialized cells capable of undergoing thermogenesis, a phenomenon regulated by the sympathetic nervous system, due to the presence of uncoupling protein 1 (UCP1). The recent demonstrations of their presence in adult humans, and the discovery that brown adipocytes can be derived from distinct precursors and express specific genes depending on their anatomic location, have sparked intense interest in enhancing the current understanding of their biology and relevance to human energy homeostasis. We provide an overview of the latest advances related to the developmental origins of brown adipocytes, discuss their regulation and function in both rodents and humans, and offer a critical perspective on the relevance of brown adipocyte-mediated thermogenesis in human physiology.

Brown adipocytes and thermogenesis
In mammals, adipocytes can be either white or brown in appearance. Whereas white adipocytes are involved in the storage of lipids, brown adipocytes possess the unique capacity of undergoing thermogenesis (see Glossary) upon stimulation. Recruited in an adaptive manner, brown adipocytes carry tremendous thermogenic capacity that allows small mammals to maintain euthermia even at ambient temperatures close to freezing, without relying on muscle-mediated shivering thermogenesis [1,2]. The brown adipocyte owes its thermogenic capacity to the presence of UCP1, an inner mitochondrial membrane protein that is capable of dissociating oxidative phosphorylation from ATP production [3,4]. Fuel oxidation in brown adipocytes thus primarily results in heat production, as opposed to ATP generation in other metabolically active cells, thereby promoting energy expenditure. The thermogenic function of a brown adipocyte is supported by its hallmark cellular properties such as the presence of numerous spherical mitochondria surrounded by accessible lipid vacuoles [5]. In addition, brown adipocyte clusters are favorably vascularized to permit the dissipation of generated heat and are highly innervated by abundant sympathetic nerve efferent fibers which ensure central control of thermogenesis [5–7].

Classic brown versus brite adipocytes
Anatomic considerations
In rodents, brown adipocytes are found in discrete areas such as interscapular, cervical, peri-aortic, peri-renal, intercostal, and mediastinal depots [5], which are referred as classic brown adipose tissue (BAT) depots. In addition,
brown adipocytes can be found scattered within white adipose tissue (WAT), especially upon cold exposure [8,9], treatment with β-adrenergic agonists [10], or peroxisome-proliferator-activated receptor-γ (PPAR-γ) agonists [11]. These brown-like adipocytes have interchangeably been called 'recruitable' [12,13], 'beige' [14–16] or 'brite' [11,17], in contrast to the brown fat cells found in the classic BAT depots. Considering that the brown-like fat cells in WAT essentially exhibit the properties of classic brown adipocytes upon stimulation, we prefer to use the term 'brite' (derived from the designation 'brown-in-white' – championed by Cannon and Nedergaard [11,18]) to define them, while the BAT depot containing these cells has been labeled 'beige', reflecting the likely color of a fat depot that contains a mixture of brown and white cells. It has been demonstrated that, in rodents, different genetic loci regulate the number of classic brown and brite adipocytes in classic BAT and beige depots, respectively [9,19]. In addition, classic brown and brite adipocytes exhibit distinct molecular signatures, developmental origins, and plausibly distinct physiological roles.

Developmental considerations

Owing to their ability to undergo the typical CCAAT/enhancer binding protein (CEBP)- and PPARγ-driven transcriptional cascade of terminal differentiation, and their lipid storage capacity, classic brown adipocytes have historically been considered close relatives of white adipocytes. However, recent evidence has clearly demonstrated their developmental kinship to myocytes as opposed to the white adipocytes [20–22]. Lineage-tracing studies showed that brown adipocytes in classic BAT are derived from en- grailed-1 (En1) expressing cells of the central dermomyotome [23], and myogenic factor 5 (Myf5)-positive progenitor cells similar to skeletal myocytes, whereas brown adipocyte precursors were reported to share their gene expression and microRNA profile with myotubes [21]. In addition, the mitochondrial proteome signature of classic BAT was found to be closer to skeletal muscle than to WAT [22], supporting the notion of their close association with myocytes.

Among the factors that determine the fate of a mesenchymal stem cell, the transcriptional coregulator PR domain-containing 16 (PRDM16) has been identified as an important player capable of regulating bidirectional cellular fate of classic brown adipocytes and myocytes [20]. Depletion of PRDM16 from cultured brown adipocyte precursors derived from interscapular BAT caused a near-total loss of brown fat characteristics, while prompting overt skeletal muscle differentiation. Correspondingly, ectopic expression of PRDM16 in committed myoblasts was associated with the development of brown cell phenotype upon exposure to pro-adipogenic stimuli [20]. In addition to PRDM16, a variety of regulatory factors capable of altering the cellular fate of adipocyte precursors have also been identified, such as forkhead box C2 (FOXC2), PPARγ coactivator 1a (PGC1α), and its repressors like pRB and RIP40, as reviewed elsewhere [24]. However, the exact involvement and plausible overlap among these factors has not been fully established so far.

In contrast to the classic brown adipocytes, brite adipocytes have been shown to originate from Myf5-negative (Myf5−) progenitor cells, much like the white adipocytes [11]. In addition, PRDM16 was demonstrated to be a cell-autonomous factor required for the development of brite adipocytes in murine subcutaneous WAT [25]. The factors and pathways involved in the determination of brite adipocyte fate, however, remain largely unknown. Considering the anatomic location and recruitable nature of brite adipocytes, it has been proposed that brite adipocytes (i) are derived either from the maturation of a brown adipocyte precursor present within WAT [11], (ii) differentiate from a white adipocyte precursor [26,27], or (iii) trans-differentiate from an existing mature white adipocyte [28,29]. However, convincing evidence to support any of above hypotheses is still awaited. Notably, murine brite adipocytes were recently demonstrated to exhibit a molecular signature, such as the expression of TBX1, TMEM26, and CD137, that was not shared by either classic brown adipocytes or white adipocytes [14], pointing to their distinct identity. Whether brite adipocytes descend from unique precursors, or share progenitors with either white or classic brown adipocytes, remains to be established. However, the observations of Wu et al. [14] certainly question the validity of the trans-differentiation hypothesis. Future work is necessary to understand the developmental origins of brite adipocytes.

Physiological considerations

The anatomic and developmental distinction between the classic brown and brite adipocytes has also been argued to reflect their physiological relevance. Although brown adipocytes in classic BAT have been associated with the protection of optimum core body temperature during cold stress, the induction of brite adipocytes has been proposed to be associated with the maintenance of energy balance and improved metabolic phenotypes in rodents, especially under nutritionally replete conditions [30,31]. However, there is no convincing evidence to indicate that the classic BAT or beige depots work in isolation to fulfill these roles. Most rodent studies reporting improvements in the metabolic phenotype upon burning of WAT depots have also reported phenotypic or molecular changes in their interscapular BAT [32–36]. Similarly, cold exposure is usually associated with proliferation of both classic BAT and beige depots [37], together with an improvement of metabolic phenotype in mice [38]. Thus, conclusive experimental evidence to prove the hypothesis of distinct physiological roles for classic brown adipocytes versus brite adipocytes is still awaited.

Despite the above-described differences in the anatomic, developmental, and molecular properties of classic brown and brite adipocytes, it is important to acknowledge that these cells retain functional similarity and undergo thermogenesis upon stimulation [11,31,39]. Whether the central regulation of thermogenic activation differs between classic brown and brite adipocytes, however, remains to be determined.

Brown adipocyte activation via the sympathetic nervous system (SNS)

It is well established that the activation of brown adipocytes is critically controlled by the SNS [7,40]. Indeed, a variety of brain centers and neuronal circuitries
Box 1. SNS-mediated control of brown adipocyte thermogenesis

During thermoregulatory thermogenesis, cold temperature information is relayed to the median preoptic area (POA) of the hypothalamus via cutaneous cold receptors such as transient receptor potential cation channel, subfamily M, member 8 (TRPM8) [125,126]. The median POA then relays its tonic inhibition of SNS premotor neurons in the dorsomedial hypothalamus (DMH), which leads to an excitation of the SNS premotor neurons in the rostral RPa projecting directly to the intermediolateral cell column (IML) of the spinal cord. IML contains the SNS preganglionic neurons that project to the stellate ganglion containing post-ganglionic SNS neurons that ultimately project to the interscapular BAT [125] (Figure 1). In addition to the cold-activated pathways, several brain centers involved in the regulation of energy homeostasis, including the paraventricular hypothalamus (PVN), arcuate nucleus (ARC), lateral hypothalamus (LH), and ventromedial hypothalamus (VMH), have been implicated in the regulation of BAT thermogenesis in rodents because direct stimulatory or inhibitory effects on BAT thermogenesis for these hypothalamic nuclei have been indicated [4]. However, based on the observations that very few pseudorabies virus (PRV)-labeled neurons are found in the VMH when PRV is injected in the interscapular BAT during trans-synaptic retrograde tract-tracing studies in rodents, a direct role for VMH in the regulation of BAT thermogenesis has been questioned [40,127]. Nonetheless, VMH specific knockout of steroidogenic factor-1-expressing neurons, a subset of which also express brain-derived neurotrophic factor, have been associated with reduced energy expenditure and blunted expression of UCP1 in BAT, pointing towards its involvement in the regulation of BAT thermogenesis [128,129]. In addition, VMH was reported to play an important role in the thyroid hormone-mediated regulation of BAT thermogenesis [130]. Although the exact neuroanatomical pathways linking the brain centers involved in energy homeostasis with interscapular BAT have yet to be identified, previous studies have demonstrated that RPa receives multiple direct projections, as well as strong tonic inhibitory and stimulatory synaptic inputs, from the ARC, PVN, LH, and DMH, in addition to median POA [46–48,125,131]. Moreover, the neuroanatomical proximity of these centers to the thermoregulatory centers within the hypothalamus raises the question of whether these pathways interact or overlap to integrate the peripheral signals to stimulate BAT thermogenesis in response to thermal and metabolic changes (Figure 1). Considering that the brain has access to a common set of metabolic processes and anatomic substrates for thermogenesis in response to various stimuli, an overlap of these pathways would be expected. At least one candidate providing such a link is proposed to be the brain melanocortin system (Box 2).

Participant in regulating the SNS tone to brown adipocytes, as discussed below. Norepinephrine (NE) released from postganglionic SNS fibers stimulates the β-adrenergic receptors (β-AR), including β3-adrenergic receptors (ADRB3) present on brown adipocytes, to increase the intracellular cAMP levels, which in turn stimulate lipolysis via induction of adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacylglycerol lipase (MGL). ATGL, HSL, and MGL exhibit preferential hydrolytic activity towards triglycerides (TG), diacylglycerols, and monoacylglycerols, respectively, leading to stepwise hydrolysis of intracellular TG into free fatty acids (FFA) and glycerol within brown adipocytes [41,42]. These intracellularly derived FFA serve dual roles by allosterically activating UCP1 and, additionally, undergoing β-oxidation to fuel thermogenesis [6]. Stimulation of β-ARs can also upregulate UCP1 gene expression downstream of a cAMP/protein kinase A (PKA)/p38 mitogen-activated protein kinase (MAPK) pathway. Alternatively, lipolysis and thermogenesis can be activated by natriuretic peptides using the cGMP/protein kinase G (PKG)/p38 MAPK pathway, as demonstrated recently in cultured human adipocytes [43]. In addition to direct stimulation, chronic infusion of NE resulting in very high levels of circulating NE has also been shown to elevate UCP1 expression and the metabolic activity of brown adipocytes in rodents [44,45].

Neuronal regulators of brown adipocyte thermogenesis

Brown adipocyte thermogenesis is conceivably involved in the regulation of optimum body temperature and maintenance of energy homeostasis. Thus, neural centers involved in thermoregulation and control of energy homeostasis have been shown to regulate SNS outflow to BAT and WAT in rodents [46]. In particular, the raphe pallidus (RPa) has been proposed to be a major site of convergence in the circuits regulating interscapular BAT thermogenesis [47,48] (Box 1 and Figure 1). In addition, the brain melanocortin system is proposed to serve as a plausible integrator of the thermal and metabolic changes in the regulation of BAT thermogenesis (Box 2 and Figure 1). Recent work in rodents has further indicated that interscapular BAT has sensory innervations [49]. Using anterograde transneuronal viral tract-tracing analyses, Vaughan et al. [49] reported that sensory neuronal circuits from interscapular BAT project to the paraventricular nucleus of the hypothalamus (PVN), periaqueductal grey (PAG), and RPa, brain nuclei known to participate in the SNS outflow to interscapular BAT, suggesting a likely involvement of brown adipocyte–sensory neuron–SNS feedback circuits in the control of BAT thermogenesis (Figure 1). Whether other classic BAT and beige depots have similar sensory feedback loops remains to be ascertained; however, an enhanced understanding of the various circuits involved in the regulation of BAT thermogenesis and their neurochemical characteristics could allow the identification of novel pharmaceutical targets aimed at the central activation of BAT thermogenesis in humans.

Endocrine factors affecting brown adipocytes

In addition to the SNS, a variety of circulating factors have been identified in rodents that stimulate the thermogenic capacity and activity of classic brown adipocytes, as well as the recruitment of brite adipocytes.

Thyroid hormones

Thyroid hormones [i.e., local 3,3′,5′-triiodothyronine (T3) levels] have been shown to exhibit direct stimulatory effects on UCP1 gene expression [50,51] in addition to enhancing adrenergic signaling in brown adipocytes. Mice with targeted disruption of deiodinase iodothyronine type 2 (DIO2), an enzyme responsible for converting inactive thyroxine (T4) to the active T3, within the classic brown adipocytes, exhibit impaired BAT function, reduced CAMP levels in response to various adrenergic stimuli, defects in adaptive thermogenesis, and hypothermia upon cold-exposure [52,53], indicating the importance of thyroid–SNS synergism for maintaining thermal homeostasis and BAT thermogenesis.
**Natriuretic peptides (NP)**

Atrial natriuretic peptide (ANP), brain-derived natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) are the most commonly studied members of the NP family of polypeptide hormones. Secreted from the heart and vascular system, NPs are known to primarily regulate body fluid homeostasis [54]; however, recent studies have indicated a role for NPs in the control of food intake and energy expenditure, and especially in BAT thermogenesis [43,55]. Using knockout mice models and human adipocytes, Bordichia et al. [43] showed that both ANP and BNP could induce the appearance of brite adipocytes in WAT, and thermogenic activation of classic BAT, via induction of PGC-1α and UCP1 in a cGMP/PKG/p38 MAPK-dependent fashion. Furthermore, cold-exposure was associated with increased circulating levels of NPs in mice during this study, whereas coadministration of ANP and β-adrenergic agonists resulted in additive browning effects, indicating that NPs may work in concert with SNS to regulate BAT thermogenesis [43]. By contrast, CNP was previously shown to inhibit thermogenesis by attenuating SNS activity to interscapular BAT [55].

**Fibroblast growth factor-21 (FGF-21)**

Mainly produced in liver, FGF-21, a member of the FGF superfamily of proteins involved in the regulation of glucose and lipid metabolism, has emerged as an important player in the regulation of BAT thermogenesis. Hepatic release of FGF21 in response to nutritional signals during the early neonatal period was shown to activate classic BAT thermogenesis in rodents [56]. In addition, interscapular BAT was reported to express and secrete FGF-21 in response to cold exposure and β-adrenergic agonist treatment [57,58], reflecting the endocrine capacity of classic BAT in rodents. A recent study further reported that mice deficient in FGF21 exhibited a lower core body temperature during cold exposure in association with diminished presence of brite adipocytes in their subcutaneous WAT depot [59]. Mild cold exposure was also recently reported to be associated with increased levels of circulating FGF21 in healthy humans [60]. Circulating FGF21 levels further predicted greater lipolysis and cold-induced thermogenesis in these subjects, independent of age, gender, fat mass, and lean mass [60], indicating a plausible role for FGF21 in cold adaptation in humans.

**Bone morphogenetic proteins (BMP)**

BMPs belong to the transforming growth factor superfamily, known to control multiple key steps during embryonic development and differentiation. Although some members of the BMP family (i.e., BMP2 and 4) participate in white adipogenesis, BMP7 has been recognized as a singular factor capable of initiating a full program of brown adipogenesis, including the induction of PREDM16, PGC-1α, mitochondrial biogenesis, and enhanced expression of UCP1 in brown pre-adipocytes [12], as well as enhancing mitochondrial activity in mature brown adipocytes [61]. In addition, BMP7 was able to trigger the commitment of multipotent mesenchymal stem cells into brown adipocyte lineage in both *in vivo* and *ex vivo* settings [12]. The role of BMP7 in the recruitment and differentiation of brite adipocytes, however, remains to be established. Genetic ablation of BMP receptor 1A (BMPRIA) from brown adipogenic progenitor cells was recently shown to result in stunted development of classic or constitutive BAT, while simultaneously inducing browning of WAT depots in a mouse model [13]. Impairment of classic BAT development was associated with enhanced SNS drive to WAT and a compensatory increase in brite adipocytes, which was further shown to maintain normal temperature homeostasis and resistance to diet-induced obesity in these mice [13]. This study indicates an important role for BMP signaling in the regulation of BAT thermogenesis, as well as highlights the crosstalk between classic BAT and beige depots that plausibly contributes to the control of systemic thermogenesis.
Irisin

Recently identified in mice and humans [36], irisin is a hormone that represents the cleaved and secreted form of a membrane protein, FNDC5, which is expressed in muscle under the control of PGC-1α and as a result of exercise. Highly conserved in all sequenced mammalian species, irisin, when used even in nanomolar concentrations, was able to recruit bricate adipocytes in the mouse subcutaneous WAT in both in vitro and in vivo settings [36]. Only a modest increase in the circulating levels of irisin was associated with a 10–20-fold increase in UCP1 expression, enhanced energy expenditure, and improvement of glucose tolerance in mice fed a high-fat diet, reflecting the therapeutic potential of this hormone [36]. Irisin expression was also reported in muscle, subcutaneous, and visceral fat depots in a human cohort recently [62]. Although both adipose tissue and muscle expressed FNDC5, its expression was significantly decreased in the muscle of obese participants with type 2 diabetes [62]. In addition, muscle FNDC5 expression was associated with FNDC5 and UCP1 gene expression in visceral adipose tissue and body mass index (BMI) of these participants, whereas circulating irisin levels were associated with FNDC5 gene expression in adipose tissue [62]. Circulating irisin levels were further shown to associate negatively with the incidence of obesity and insulin resistance in this cohort, thereby supporting a role for irisin in the regulation of thermogenesis and body-weight regulation [62].

Acknowledging that most of the above-described factors have only been identified recently, our understanding of these factors is only beginning to develop. Indeed, much work would be required to ensure a complete understanding of their specific roles in the regulation of BAT thermogenesis. It would also be of interest to understand if these factors interact with SNS to regulate BAT thermogenesis. Initial data indicate that thyroid hormones and NPs work in concert with SNS to execute their control on the recruitment and activation of brown adipocytes; however, a plausible interaction between PFG21, irisin, and SNS remains to be determined. Identification of these circulating and regulatory factors has, nonetheless, provided alternative routes for the stimulation and recruitment of classic brown and white adipocytes, at least in mice. In addition, recognition of these factors could affect our future view of the regulation of BAT thermogenesis. As summarized in Figure 2, it seems plausible that, in addition to the brain, most metabolically important organs such as the heart, liver, and skeletal muscle are involved in crosstalk with classic brown and white adipocytes to execute the regulation of whole-body energy homeostasis, both under cold-stress and metabolically challenging situations. Future work is necessary to extend this view because an enhanced understanding may prove beneficial for the activation of BAT thermogenesis in humans.

Human BAT

Despite the availability of anatomic evidence since 1972 for the presence of brown adipocytes in humans during all stages of life, the notion that human BAT was solely apparent during neonatal stages prevailed for decades [63,64]. The earliest indication for revisiting this notion came from investigations on cancer patients undergoing combined positron emission tomography/computed tomography (PET/CT) screening, when the enigmatic symmetrical uptake of 18F-fluorodeoxyglucose (18F-FDG) in the supraclavicular area of these patients, also referred as the ‘uptake in the supraclavicular area’ fat (USA Fat) phenomenon, was ascribed to the presence of definite clusters of brown adipocytes in this area [64–66]. Following this, a number of seminal studies involving retrospective, prospective, and gene expression analyses of various cohorts revealed that these clusters of brown adipocytes were involved in the non-stimulated and cold-stimulated (18F-FDG) uptake activities of the cervical, supraclavicular, paravertebral, mediastinal, para-aortic, and suprarenal regions in adult humans [67–71]. UCP1 expression has also been documented in the human epicardial adipose

<table>
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<th>Box 2. The brain homeostatic melanocortin system</th>
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| The brain homeostatic melanocortin system consists of neurons that express (i) proopiomelanocortin (POMC), the precursor of α-melanocyte stimulating hormone (α-MSH), (ii) the melanocortin receptors MC3R and MC4R, and (iii) the MC3R and MC4R endogenous inhibitor agouti-related protein (AgRP) [132]. The melanocortin system plays a significant role in energy-balance regulation because loss-of-function mutations of key players such as POMC and MC4R have been associated with massive obesity in rodents [133] and humans [134]. The melanocortin system is also considered to be one of the ultimate physiological mediators of leptin actions, a WAT-derived hormone that controls energy intake and expenditure [108]. Leptin governs SNS outflow to peripheral organs including BAT [135]. In accordance, the synthetic MC3R and MC4R agonist melanin il (MT2) has been shown to increase SNS discharge to both BAT and WAT, as well as BAT thermogenesis, when injected either into the 3rd ventricle [93] or into specific brain regions such as the PVH [136]. Additionally, central MT2 injections were shown to associate with differential activation of SNS drive (measured as NE turnover rate or NETO) to various fat depots, being significantly higher in interscapular BAT than most WAT depots, and being higher in inguinal and dorsosubcutaneous WAT than the epidymal and retroperitoneal WAT [93]. Considering that basal SNS innervation of various WAT depots does not differ significantly, these observations reflect the ability of the melanocortin system to differentially modulate peripheral fat depots, plausibly via its association with diverse brain circuits. Recent observations that various brain regions, such as the PVH, POA, and PAG that are polysynaptically connected with interscapular BAT and WAT, also coexpress MC4R mRNA would support this notion [136,137]. However, the phenotypes of the MC4R neurons connected to BAT and WAT remain to be established. It has been suggested that the PVH MC4R neurons connected to BAT and WAT might be the oxytocin or cannabinoid receptor 1 (CB1)-expressing neurons that directly project to IML in the spinal cord to control BAT thermogenesis [138,139]. Furthermore, the PAG MC4R neurons could be those projecting from ventrolateral division to the PPa, where 5-hydroxytryptamine (serotonin) neurons have been found to project to IML [140–142]. Similarly, the POA MC4R neurons could be the γ-amino butyric acid (GABA) neurons that project to DMH and regulate the premotor neurons of the brainstem that ultimately govern the activity of SNS efferent neurons to interscapular BAT [125,143]. Indeed, these observations can form the basis of targeting specific stimulation of BAT thermogenesis using melanocortin system, provided that specific neuronal connections between the melanocortin system and BAT depots can be characterized.

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| Recently identified in mice and humans [36], irisin is a hormone that represents the cleaved and secreted form of a membrane protein, FNDC5, which is expressed in muscle under the control of PGC-1α and as a result of exercise. Highly conserved in all sequenced mammalian species, irisin, when used even in nanomolar concentrations, was able to recruit bricate adipocytes in the mouse subcutaneous WAT in both in vitro and in vivo settings [36]. Only a modest increase in the circulating levels of irisin was associated with a 10–20-fold increase in UCP1 expression, enhanced energy expenditure, and improvement of glucose tolerance in mice fed a high-fat diet, reflecting the therapeutic potential of this hormone [36]. Irisin expression was also reported in muscle, subcutaneous, and visceral fat depots in a human cohort recently [62]. Although both adipose tissue and muscle expressed FNDC5, its expression was significantly decreased in the muscle of obese participants with type 2 diabetes [62]. In addition, muscle FNDC5 expression was associated with FNDC5 and UCP1 gene expression in visceral adipose tissue and body mass index (BMI) of these participants, whereas circulating irisin levels were associated with FNDC5 gene expression in adipose tissue [62]. Circulating irisin levels were further shown to associate negatively with the incidence of obesity and insulin resistance in this cohort, thereby supporting a role for irisin in the regulation of thermogenesis and body-weight regulation [62].

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tissue (EAT), adding a further potential site for the presence of brown adipocytes in humans [72,73].

In terms of BAT prevalence, most of the retrospective studies report a low occurrence (5–10%) among adults. However, the likely inactive state of brown fat during PET/CT scanning has been argued to contribute to its minimal detection, and hence the low reported prevalence of brown fat in these studies [74]. Prospective and dedicated analyses using standardized conditions with healthy subjects have, by contrast, provided data that reveal near 100% prevalence of fat taking up 18F-FDG in response to cold in adults [68,71]. In addition, highly metabolically active areas of 18F-FDG uptake in humans have been shown to exhibit (i) the histological signature of brown adipocytes, in other words cells with numerous small lipid vacuoles and spherical mitochondria; (ii) UCP1 mRNA and protein expression; (iii) increased ADRB3, PRDM16, DIO2, and PGC-1α mRNA expression relative to WAT; (iv) increased blood flow; and (v) increased sympathetic innervation, thereby undeniably demonstrating the presence of true BAT in adult humans [69,70].

The brown adipocytes found in the supraclavicular area of adult humans, collected from two independent cohorts, exhibited some of the gene signatures of murine brite adipocytes mentioned earlier [14]. Additionally, brown adipocytes obtained from multiple fat depots of a pediatric cohort, including cervical supraclavicular, posterior mediastinal, retroperitoneal, intra-abdominal, and mesenteric fat depots, were reported to exhibit the gene signatures of brite adipocytes that were identified separately during this study [75]. By contrast, two recent studies further demonstrated the presence of classic brown adipocytes in the interscapular fat depot of infants [76] and neck fat depots of adult humans [77], respectively. The current evidence thus points to the presence of both classic brown and brite adipocytes in humans from infancy until adulthood. Future evidence from multiple cohorts across the spectrum of age, sex, and various metabolic conditions would, nevertheless, be required to consolidate the nature of human brown fat (which we will continue to refer as BAT or brown fat in this article), and to further determine if the prevalence of classic brown versus brite adipocytes is affected by these factors in humans.

**Sympathetic control of human BAT**

As in small mammals and rodents, BAT thermogenesis in humans is also under the control of the SNS, as demonstrated by the observations of reduced 18F-FDG uptake in human BAT with the use of β-blockers, and increased BAT activity in humans with pheochromocytomas [78,79]. It is noteworthy that systemic non-selective β-AR activation, using the β-adrenergic agonist isoprenaline or sympathomimetics, did not result in enhanced BAT activity in healthy adults, plausibly due to low dosage [80,81] because an increase in BAT activity of healthy lean adults was observed upon oral administration of relatively higher dosage of ephedrine [82]. Ephedrine administration, however, was still unable to enhance BAT activity to the degree usually seen during cold exposure, despite an increase in circulating NE levels [81,82]. Enhanced SNS tone specifically to brown fat, which likely occurs during cold exposure, thus seems essential for appreciable stimulation of BAT thermogenesis in humans [81].

**Factors affecting the detection and activity of human BAT**

Despite the limitations of retrospective analyses, these studies have proven to be of great significance for the identification of BAT in adults, and for the recognition of factors that affect detection as well as the activity of BAT in humans, revealed as positive scans, and increased 18F-FDG uptake during PET/CT scanning, respectively. Because retrospective investigations allow the analyses of much larger sample sizes, such studies have led to the recognition of factors that influence BAT detection, as well as to the identification of complex interactions among these factors. However, it is acknowledged that indications derived from retrospective studies need to be further qualified using prospective analyses before conclusive
information can be drawn. As discussed in the following sections, both retrospective and prospective analyses have identified outdoor temperature, age, BMI, and sex as common factors affecting the detection of BAT in humans [67,68,70,83]. In addition, there is some evidence suggesting that diabetes [83], β-blocker use [79], and hypothyroidism are also associated with lower 18F-FDG uptake in human BAT [84].

Outdoor temperature
Colder outdoor temperatures were associated with histochcmical detection of multilocular adipocytes in the neck of outdoor Finnish workers in an autopsy study conducted as early as in 1981 [85]. More recent reports, although retrospective in nature, corroborated the positive associations between colder outdoor temperatures and increased activity of BAT using PET/CT scanning [67,83,86]. A dedicated analysis confirmed these observations and further revealed that seasonal variation can affect BAT detection in humans [68]. By repeating 18F-FDG uptake analyses of eight subjects during winter and summer months, Saito et al. [68] identified four additional BAT-positive subjects during winter scanning, whereas only two such subjects were identified during summer scanning. Using retrospective analyses, Au-Yong et al. [87] observed that seasonal variation in the prevalence of BAT in humans was more closely related to photoperiod than to outdoor temperature. However, this observation was recently challenged when multivariate analyses of a separate cohort identified only outdoor temperature, and not photoperiod, as an independent predictor of BAT detection, mass, and activity in humans [83]. Interestingly, this retrospective study also demonstrated that outdoor temperature on the day of scanning was a better predictor of BAT detection than the temperatures on days 2, 3, 7 and 1 month before scanning [83]. Considering that cold enhances SNS activity, these observations point to the impact of acute as well as chronic stimulation of SNS activity on BAT detection in humans. Whether chronic cold exposure (that probably occurs during winter months) induces the recruitment of brown adipocytes or if short- or long-term cold exposures only increase the metabolic activity of pre-existing BAT (resulting in its enhanced detection in humans) remains to be fully explored.

Age
Increasing age has been associated with reduced BAT prevalence among adults in several studies [67,83,88], including an autopsy study where age-related decrease in the presence of multilocular brown adipocytes was observed in humans from infancy to late adulthood [63]. In a retrospectively analyzed large cohort study, where subjects were divided into age tertiles of <50, 50–64, and >64 years, the likelihood of detecting BAT was estimated to be 3-fold lower in older subjects (i.e., >64 years of age) relative to the youngest subjects (i.e., <50 years of age) [67]. Similarly, an impact of age on BAT mass and activity was reported in a retrospectively analyzed cohort of patients aged 12–83 years [88]. Age-associations were also observed in a retrospectively analyzed pediatric cohort with an age range of 0–21 years, where children in the age group of 13–15 years exhibited the highest (~40%) prevalence of BAT [89]. This study further emphasized that the detection of BAT was higher in adolescents (40%) than in adults (5–10%), especially under non-stimulated conditions [89]. Recently, some prospective studies also analyzed the impact of age on BAT detection [68,71,90]. In a dedicated study of younger males (age 18–32 years) [71], enhanced 18F-FDG uptake upon cold exposure was reported in 17 of 32 younger subjects and, in another study, in only 2 of 24 elderly subjects [68]. The mean age of the BAT-positive subjects in this cohort was also found to be significantly lower than the mean age of subjects showing no 18F-FDG uptake activity [68]. A further investigation reported that upon cold exposure BAT detection decreased from 50% in humans in their 20s to 10% in the 50s and 60s age bands [90]. It can thus be concluded that, in humans, the presence of BAT declines from infancy/adolescence to young adulthood, followed by a steeper decline during older ages. This decline has been proposed to occur as a result of an initial reduction in the amount of active BAT during adolescence, which is followed by a reduction in the function and sensitivity of existing brown fat during adulthood [91]. One plausible physiological mechanism explaining these proposals may involve a selective reduction in the SNS activity/sensitivity of brown adipocytes with aging, even though aging is associated with a progressive and general increase in the SNS activity in humans [92]. Indeed, the proposal of a selective reduction in SNS activity to BAT is supported by observations that selective neuronal circuits controlling SNS-mediated interscapular BAT thermogenesis are present in rodents [7,46,93]. Meanwhile, one cannot exclude the possibility that there is a reduction in the amount of functional brown adipocytes with age, regardless of changes in SNS activity to the BAT depots [94].

Biological sex/gender
Gender has been identified as yet another factor affecting the presence and activity of BAT in humans during retrospective studies [66,67,83]. The USA Fat phenomenon was shown to be higher in women than men [66]. Similarly, greater fat mass, increased 18F-FDG-uptake activity, as well as 2-fold higher prevalence of active BAT was reported in women, compared to men, in a retrospectively analyzed large cohort [67]. However, no gender effect on BAT prevalence was observed in a prospective study involving cold-exposed subjects [68]. In addition, the association between human gender and the detection of BAT further seems to be confounded by age. In one retrospectively analyzed cohort [88], females exhibited higher BAT mass and 18F-FDG-uptake activity than did males, but only in older subjects (43–82 years of age) and not in younger subjects (11–43 years). In addition, a consistent, although statistically non-significant, trend for higher BAT prevalence was observed in girls aged 15–21 years compared to boys, which was not seen for children aged between 5–15 years, in a retrospectively analyzed pediatric cohort [89]. It is not yet clear why BAT may be more easily detectable in women than in men. It has been proposed that, at any given temperature, females exhibit higher cold-sensativity than males, likely contributing to enhanced BAT
Factors affecting activity, including sex hormones, have been observed to affect the density and functional properties of the cutaneous cold receptor TRPM8 [95], thereby supporting sex-associated differences in cold-sensitivity that are observed in both rodents and humans. Indeed, generally enhanced cold-sensitivity would promote higher mass and activity of brown adipocyte depots in association with female sex. However, the probability of a true association between biological sex and brown adipocyte thermogenesis cannot be denied entirely. In rodents, sexual dimorphism has been observed in mitochondrial structure and adrenergic responsiveness of classic BAT that likely translates into higher thermogenic capacity and activity in females [96]. Direct effects of sex hormones are plausible, especially considering that classic BAT in mice and cultured brown adipocytes express sex steroid receptors such as estrogen, progesterone and androgen receptors [97]. Moreover, estrogens have been proposed to alter leptin–melanocortin system mediated regulation of SNS activity to brown adipocytes [98,99].

**Body weight and adiposity**

An important issue of whether the presence of brown adipocytes can affect obesity or the propensity of an individual to obesity has been tackled by various retrospective studies that have consistently reported significant inverse associations between BMI and the presence of BAT in adults and adolescents [67,83,89]. In addition to BMI, 18F-FDG uptake in BAT has been inversely correlated with both percent body fat mass and central obesity, in retrospective as well as in dedicated studies involving cold-exposed subjects [67,71,100]. The association between BMI and BAT detection, however, is complicated by other factors such as age and sex that can interact with body adiposity. One retrospective study reported negative associations between BMI and BAT mass as well as with activity, but only in younger male subjects (aged 12–43 years) and not in older subjects (43–82 years), whereas females of all age groups (11–43 years) exhibited significant negative associations between BMI and BAT mass/activity, leading to the conclusion that the presence of BAT is an important regulator of adiposity, particularly in younger male subjects [88]. By contrast, a negative association between BMI and BAT presence became significant only with increasing age in another retrospectively analyzed cohort [67]. Similarly, Yoneshiro et al. [90] reported that presence of brown fat could protect the BAT positive subjects from age-associated increase in body adiposity because positive associations between age, BMI, and body fat mass were observed only for BAT-negative subjects in a prospective study. Independent associations observed between BMI and the presence of BAT in both retrospective and prospective settings would, however, support the notion that presence of brown fat is a negative regulator of adiposity in humans [83,89,101].

The relationship between obesity and human BAT, in terms of whether obesity induces BAT atrophy or lack of brown fat induces obesity, remains to be clarified at this point. Nonetheless, a recent study reported increased 18F-FDG-uptake activity in BAT of morbidly obese patients upon weight loss after gastric bypass surgery [102]. Alternatively, it has been suggested that increased thermal insulation and reduced surface area/volume ratio associated with obesity may reduce the need for cold-induced thermogenesis and hence contribute to a lower detection/activity of BAT in humans [103]. By contrast, however, rodent studies have clearly pointed towards a causal role for diminished brown adipocyte thermogenesis in the development of obesity. While genetic rodent models of obesity exhibit reduced capacity and activity of interscapular BAT thermogenesis [104,105], UCP1-ablated mice kept at thermoneutrality become obese even on chow diet [106]. Moreover, body fat accumulation in these UCP1-ablated mice is further pronounced under an obesogenic dietary environment [106], which can be paralleled with individual propensity to develop obesity during modern times, if having less or no BAT. In addition, reports of low SNS activity [107], lower thermogenic response to NE administration [105], and increased SNS stimulation of interscapular BAT in ob/ob mice [108] further suggest that defects in SNS-mediated control of BAT thermogenesis are causal for the development of obesity, at least in animal models. Considering that reduced SNS activity and lower thermic response to NE administration during obesity have also been documented in humans [109,110], defective SNS control of brown adipocyte thermogenesis and hence reduced activity of BAT may represent a plausible mechanism for the development of obesity even in humans.

**Insulin sensitivity**

Similarly to BMI, negative associations between the presence of brown fat and plasma insulin levels as well as diabetes status have also been observed in adult humans in retrospective studies [67,83], supporting a role for BAT thermogenesis in glucose regulation, and simultaneously supporting a plausible role for insulin in regulating the presence and activity of BAT in humans. Insulin-stimulated glucose uptake was demonstrated in human BAT recently [111]; however, this uptake was not associated with increased blood flow to BAT. By contrast, in view of the enhanced glucose uptake in human BAT upon cold exposure, coupled with observations that brown adipocytes are major contributors to glucose disposal in mice [112] and in resting humans [64], a plausible role for BAT thermogenesis in regulating basal and adaptive glucose metabolism can be proposed. Indeed, lack of NE-stimulated glucose uptake in the interscapular BAT of UCP1-ablated mice demonstrates that glucose disposal by classic BAT is dependent upon active thermogenesis [113]. In addition, BAT-mediated glucose disposal was found to be less than 1% of whole-body glucose turnover in healthy male subjects [83], thereby casting a doubt about a direct role of BAT in the impairment of glucose disposal that is usually observed in diabetic humans. However, an indirect role through chronic regulation of energy balance remains to be elucidated.

**Brown adipocyte thermogenesis, regulation of energy balance, and associated metabolic benefits in humans**

The current interest in BAT is fuelled by its significant energy-expending capacity derived from burning fat, together with circulating glucose and NEFA, as seen in...
rodents. However, a potential role for BAT thermogenesis that is physiologically relevant to the energy-balance equation in humans is only beginning to be appreciated.

Rothwell and Stock [114] predicted that 40–50 g of maximally stimulated BAT in humans could contribute to 20% of daily energy expenditure, based on rodent studies, as early as in 1979. These projections were not revisited until recently, when van Marken Lichtenbelt [115] questioned these estimates for the allometric differences between mice and humans and the likely sub-maximal activity state of BAT in physiological settings, leading to the proposal that 50 g of active brown fat in humans could contribute to 2.7–5% of basal metabolic rate (BMR). Virtanen et al. [70] reached similar conclusions using glucose-uptake estimates made during PET/CT scanning in a study, where brown fat activity contributed to 4.5% of BMR in cold-exposed subjects. It was further estimated that 63 g of active brown fat could burn 4.1 kg of fat per year in humans [70]. Recent studies have further reported a 28% increase on 2 h of cold exposure [116], and an 80% increase on 3 h cold exposure [117], in the total energy expenditure of healthy young subjects, part of which could be attributed to enhanced BAT activity [117]. Cold exposure has also been shown to increase blood perfusion to BAT that correlated positively with whole-body energy expenditure in healthy adults [111].

Using a radiolabeled acetate technique, Ouellet et al. [117] further provided the first evidence to indicate that cold exposure associates with significantly enhanced oxidative metabolism of BAT in humans. Although the fuel for increased metabolic activity of BAT upon cold exposure in this study was primarily obtained from intracellular TG stored within BAT, circulating glucose and NEFA were also taken up by BAT in relatively smaller fractions [117]. In addition, cold exposure was associated with increased circulating NEFA levels in these subjects, indicating enhanced peripheral VAT lipolysis [117]. Considering that the 3 h of cold exposure employed during this study was rather short and only acutely stimulated BAT, it is likely that continued stimulation and hence sustained activity of brown fat may result in exhaustion of intracellular TG stored within BAT, thereby shifting the fuel source to circulating glucose, NEFA, and TG. This could not only contribute to VAT reduction but may also lead to a rapid clearance of circulating TG-rich lipoproteins such as chylomicrons (CM) and very low density lipoproteins (VLDL) [118]. Indeed, this was recently demonstrated in a rodent study where cold exposure was associated with clearance of circulating CM and VLDL specifically by interscapular BAT [38]. In support of this view, a positive correlation between UCP1 expression in epicardial adipose tissue and circulating HDL cholesterol was recently observed in a cohort of patients undergoing coronary artery bypass grafting [73]. In addition to UCP1, genes involved in the lipolysis and β-oxidation of fatty acids correlated positively with circulating HDL-cholesterol and negatively with circulating TG in this cohort, which points to a functional association, likely indirect, between the presence of brown adipocytes in epicardial adipose tissue and circulating lipids in humans [73]. Furthermore, although it is highly likely that various brown fat depots differ in their activity and stimulation, if epicardial expression of UCP1 could be considered as a proxy for the plausible cumulative activity of all BAT depots in human body, then it may be suggested that, in addition to total energy expenditure, clearance of circulating glucose and NEFA, brown fat activity favors a beneficial lipoprotein metabolism even in humans.

Concluding remarks
Despite the fact that BAT possesses significant energy-expending capacity, appreciation of its physiological relevance has historically often been restricted solely to its role in maintaining thermal homeostasis in rodents and in human neonates [6]. Recent demonstrations of the presence and activity of BAT in humans, as well as its relevance to the energy-balance equation, have rejuvenated our interest in deciphering the true thermogenic role of BAT. Although the question of whether brown adipocytes evolved to burn off excess calories in a state of positive energy balance to maintain normal body weight relative to the regulation of body temperature under cold stress has been strongly debated [119], there is no doubt about the effects of cold-induced thermogenesis on body weight loss in rodents [120,121]. In addition, genetically modified mice have consistently shown that an increase in the amount of brown adipocytes not only protects against body weight gain and metabolic dysregulation, but can also ameliorate disturbances in glucose homeostasis and insulin sensitivity associated with diet-induced obesity [25,32]. Furthermore, active brown adipocytes were also shown to correct the hyperlipidemic lipid profile of mice [38]. BAT thermogenesis thus undoubtedly represents an attractive candidate for both prevention as well as treatment of obesity and its related comorbidities, provided it can be recruited and maintained in an active state (Figure 3).

Achieving either the recruitment or chronic activation of BAT-mediated thermogenesis in humans, however, may not be as straightforward. Although a recent study reported that morbidly obese humans enhanced cold-induced [18F-FDG uptake activity or recruited brown fat upon weight loss after gastric bypass surgery [102], this approach is not feasible for the general population. The SNS-mediated control of BAT thermogenesis can be targeted as an alternative pathway for activating human brown fat. Systemic infusion of a non-selective β-adrenergic agonist, however, was unable to activate brown fat in healthy adults, despite an increase in circulating NE levels and an increase in metabolic activity similar in extent to that seen during cold exposure [80]. Likewise, although cold exposure has consistently been shown to induce the activity of BAT in humans, the feasibility of its use remains limited considering that modern-day humans are habituated to thermoneutral living conditions [122]. The central circuitries involved in the control of brown adipocyte activity thus represent important avenues for pharmaceutical interventions aimed at the activation of human brown fat. In addition, use of dietary means to activate brown adipocyte-mediated thermogenesis seems plausible, especially when dietary menthol and capsaicin have been associated with induction of classic BAT thermogenesis in mice [123] and humans [124], respectively.
Moreover, although debated, the phenomenon of diet-induced thermogenesis remains to be explored in human studies [119].

The applicability of brown adipocyte thermogenesis as an anti-obesity tool for humans is further questioned by the observations that seemingly not all humans possess BAT, as evident from the 18F-FDG uptake studies. Acknowledging that the current state of knowledge on human BAT is based on a mix of retrospective, observational, and prospective studies, where data are not usually derived in a consistent fashion and ‘cold exposure’ conditions are loosely defined, the presence and detection of BAT still seem to depend upon a variety of factors such as age, sex, BMI, and metabolic health in humans. It is not known whether these factors cause the involution of developed BAT or interfere with the development and activation of existing BAT per se. Moreover, with the possibility that humans carry both classic brown and brite adipocytes [14,78,79], a need to focus on the differentiation and regulation of the thermogenic capacity and activity of these adipocytes in humans has now emerged. Reversibility of the loss or induction of both classic brown and brite adipocytes should thus be investigated in humans. Despite these challenges, unlocking the thermogenic potential of brown fat unquestionably provides a novel paradigm in our fight against the current obesity epidemic.

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