Front. Med. 2015, 9(2): 162–172
DOI 10.1007/s11684-015-0382-2

REVIEW

Brown and beige fat: the metabolic function, induction, and therapeutic potential

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Abstract **Adipose tissue is an important organ for energy homeostasis. White adipose tissue stores energy in the form of triglycerides, whereas brown adipocytes and recently identified beige adipocytes are specialized in dissipating energy by thermogenesis or contribution to dispose glucose and clear triglycerides in blood. The inverse correlation between the brown adipose tissue activity and body mass suggests its protective role against body fat accumulation. Thus, recruitment and activation of brown or beige adipose tissue become particularly appealing targets for increasing energy expenditure. Angiogenesis and sympathetic nerve signals are the fundamental determinants for brown and beige adipose tissue development, as well as for their metabolic functions. Secretary factors including BMPs can induce the development, the activation of brown or beige adipose tissue, which seem to be promising for therapeutic development.**

Keywords brown adipocyte; beige adipocyte; metabolism; obesity

Introduction

The prevalence of overweight and obesity has been considered as a global pandemic. Worldwide, the proportion of adults with a body mass index (BMI) of 25 kg/m^2 or greater increased between 1980 and 2013 from 28.8% to 36.9% in men, and from 29.8% to 38.0% in women. In China, the number of overweighted and obese adult individuals increased dramatically over the past 30 years, reaching 46 million of obesity and 300 million of overweight in 2013 [1]. Obesity, the excessive accumulation of fat mass, is associated with an increased risk of developing insulin resistance, type 2 diabetes, hyperglycemia, hypertension and many types of cancers [2,3]. There is thus an urgent need for novel treatments for this condition.

Although obesity is characterized with increased fat mass, not all fat depots are the same. There are two types of adipose tissue, namely white adipose tissue (WAT) and brown adipose tissue (BAT). The main function of WAT is to store excess energy in the form of triacylglycerols (TAGs), whereas BAT is specialized to dissipate energy as heat. Recently, another kind of adipocytes named inducible "brown-like" adipocytes or beige cells are discovered in white fat depots in response to various activators. The activation of brown and beige fat cells increases energy expenditure and thereby reduces obesity in mice, and is also correlated with leanness in humans. As a result, the brown or beige fat cells would be the promising therapeutic targets for metabolic disease.

Received July 15, 2014; accepted October 16, 2014
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WAT

WAT develops in multiple anatomical sites with major intra-abdominal depots around the omentum, mesentery, gonad, and perirenal areas, as well as in subcutaneous depots of buttocks, thighs, and abdomen [4]. White adipocytes are round and oval in shape, containing a single large lipid droplet and a few mitochondria that are elongated and have less defined cristae [5]. White adipocytes are 25–200 μm in diameter with visceral adipocytes generally larger than subcutaneous adipocytes, suggesting the different capacity of enlargement for individual adipocyte at different sites. WAT is also known as an active endocrine organ, releasing free fatty acid and adipokines such as leptin, adiponectin, tumor necrosis factor α (TNFα), and interleukin-6 (IL-6), which act on distant tissue including brain, liver, muscles to

regulate food intake, energy homeostasis, and insulin sensitivity [6].

BAT

BAT is an indispensible organ in small mammals and infants to defend against temperature decline. In rodents, BAT is composed of only one major depot that is concentrated in interscapular area. Most brown adipocytes are polygonal with a variable diameter from 15 to 50 μm in range. Brown adipocytes contain multilocular lipid droplets and mounts of functional mitochondria which are large, spherical and with dense cristae. Other than energy storage, the most important role of BAT is to burn energy by non-shirvering thermogenesis. At cellular level, BAT regulates energy expenditure through mitochondria and the expression of uncoupling protein 1 (UCP-1), which uncouples oxidative phosphorylation from synthesis of ATP, leading to heat generation. BAT is also thought to be an endocrine organ. Several endocrine factors have been found to be released by BAT, such as insulin-like growth factor 1 (IGF1), IL-6 and fibroblast growth factor 21 (FGF21), contributing to the metabolic effects of BAT [7,8].

Beige fat

It was reported almost 30 years ago that some multilocular UCP-1 positive fat cells existed within certain WAT in mice, rats and cats [9–12]. In 2007, some researchers identified brown adipocytes admixed with WAT and interspersed among bundles of skeletal muscle in rodents [13]. The amount of this kind of brown adipocytes is increased by cold exposure, decreased with age and nutrition overload and also affected by genetic variability [14,15]. Similar phenomena were observed when rodents were treated with β3-adrenergic receptor agonists such as BRL26830A, CGP-12177, and CL 316243 [15–18]. In human infants, BAT is abundant and predominantly located in interscapular depot. BAT gradually disappears with aging, and in normal adult humans BAT is proportionally smaller and was believed to be functionally less important. However, the view was challenged by unexpected findings during positron-emission tomography and computed tomography (PET/CT) with tracer [18F]-2-fluoro-D-2-deoxy-D-glucose (FDG) for cancer staging or surveillance, that collections of adipose tissue with high uptake of [18F]-FDG were found in the neck and shoulder area of patients [19]. In 2009, five independent groups used [18F]-FDG PET/CT to identify and characterized the presence and relevance of BAT in adult humans [20–24]. The major metabolically active fat depots are in the cervical, supraclavicular, axillary, and paravertebral regions, which were defined as BAT because the adipocytes were found to have UCP-1 expression and share other histological characteristics of brown adipocytes. The human BAT was also shown to express type II iodothyroninedeiodinase (DIO2) and β3-adrenergic receptor, indicating its potential responsiveness to cold or pharmacological stimuli. As a matter of fact, there is an inverse correlation between BAT activity and average outdoor temperature. In addition, the percentage of adult humans with BAT that can be activated and detected may be quite high, as 96% of younger people have functional BAT whose activity increases following cold exposure or treatment with antidiabetic drugs, thiazolidinediones or adrenergic activators. Indeed, the human BAT depots were demonstrated to consist of an admixture of UCP-1 positive adipocytes in WAT. These brown-like adipocytes at WAT depots in both human and the rodent have recently been demonstrated to be derived from lineages different from classical brown fat cell precursors, and designated as "beige" or "brite" cells [25–27].

The molecular signature of brown and beige adipocytes

Defining cell types within fat depots lays the basis for exploring the mechanism of brown and beige adipocytes development and activation. The classical brown and white adipocytes have different development origins (Fig. 1): brown preadipocytes express skeletal muscle gene signature but their white counterparts do not [26]. Lineage tracing experiments in mice have demonstrated that classical brown adipocytes derive from precursor cells that express myogenic factor 5 (myf5), a key regulator of myogenesis, while beige adipocytes in subcutaneous WAT derive from myf5 negative progenitors [27]. Immortalized beige cell lines from mouse white fat depots have low basal expression of UCP-1, but respond to cyclic AMP stimulation with high UCP-1 expression. They also have distinct gene expression pattern from either white fat cells or brown fat cells, i.e., expression of CD137, TMEM 26 (transmembrane protein 26), Slc27a1 (fatty acid transport protein-1), and TBX1 (T-box transcription factor), etc. [28]. Waldén examined gene expression pattern in different adipose depots of mice, and identified depots specific gene markers: Zic1 for the classical BAT depots, Hoxc9 (homeobox C9) for the brite depots, Hoxc8 for the brite and white in contrast to the brown, and Tcf21 (transcription factor 21) for the white depots [29](Fig. 1). By applying transcriptional data from murine adipose tissue to human's, the molecular signature of BAT isolated from multiple adipose tissue was examined, and the results indicated that adult human BAT may be primarily composed of beige cells [30]. Recently, however, a combination of high-resolution imaging techniques and histological and

biochemical analyses showed the existence of an anatomically distinguishable interscapular BAT (iBAT) depot in human infants that consists of classical brown adipocytes [31,32]. Studies by two individual groups also showed that some adipose depots in adult humans contained classical brown adipocytes. Cypess examined the gene expression of neck BAT in both superficial and deeper compartments of adult human. They found that the deeper adipose tissue depots displayed higher expression levels of the two classic BAT marker genes Zic1 (Zic family member 1) and LHX8 (LIM homeobox 8), as compared with the superficial WAT [33]. Jespersen assessed gene expression of BAT from the supraclavicular region, and found that a classical brown expression signature, including upregulation of miR-206, miR-133b, LHX8, and Zic1 and downregulation of HOXC8 and HOXC9, coexists with an upregulation of two established beige markers, TBX1 and TMEM26 [34].

Metabolic function of brown and beige adipocytes

Brown adipose tissue (BAT) is an organ for non-shivering thermogenesis and diet induced thermogenesis [35]. In rodents, the thermogenesis capacity of BAT is enormous. In cold-acclimatized rat weighting 350–400 g, oxygen consumption by 3 g of BAT is approximately twice the basal metabolic rate [36]. In human, it has been estimated that as little as 50 g of BAT could utilize up to 20% of basal caloric needs if maximally stimulated [37]. Due to its known function in the dissipation of chemical energy in response to cold or excess feeding, BAT has the capacity to modulate energy balance. BAT induction in mice promotes energy expenditure, reduces adiposity and protects mice from diet-induced obesity [15,38]. Conversely, BAT ablation reduces energy expenditure and increases obesity in response to high fat diet [39].

Since brown fat comprises such a small percentage of total body weight, the stored lipid can sustain thermogenesis for only a short time, and further energy supplies must come from circulation. Recent data showed that the capacity of BAT to uptake and combust triglycerides from circulation. Increased BAT activity induced by short-term cold exposure drastically accelerated plasma clearance of triglycerides as a result of the increased uptake by BAT, a process crucially dependent on local LPL activity and transmembrane receptor CD36. BAT is also a major organ for glucose disposal, as a large fraction of ingested glucose is channeled to BAT, where glucose will be combusted. Glut1 (glucose transporter 1) and Glut4 activity and expression are increased by cold and norepinephrine may also be directly involved in stimulated uptake [40,41]. BAT transplanted to recipient mice had

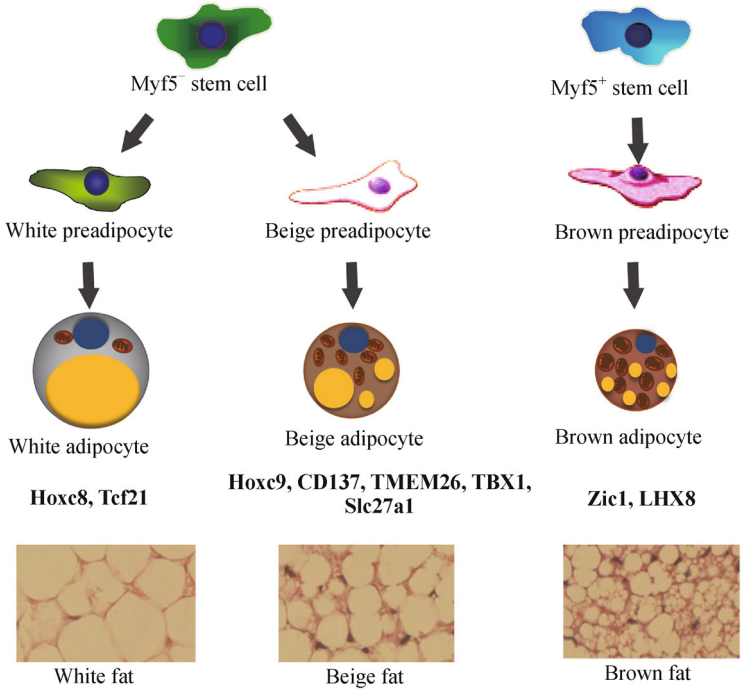

Fig. 1 Origin and molecular signature of adipocytes: classical brown adipocytes derive from myf5^{+} precursors. White and beige adipocytes derive from myf5^{-} precursors, but may come from two distinct population of precursors. Some molecular markers express in different kind of adipocytes or fat depots.

improved glucose tolerance, increased insulin sensitivity. BAT transplantation increased insulin-stimulated glucose uptake *in vivo* by endogenous BAT, WAT, and heart muscle [42].

Classic experiments in rodents have shown that BAT proliferation and/or activation contribute to limiting excess weight gain and improving insulin sensitivity by thermogenesis or increased glucose and triglycerides combustion. The central question that must be addressed is whether BAT function significantly impacts energy balance and human obesity. Recent studies have demonstrated the existence of metabolically active BAT composed of mainly beige adipocytes in adult humans [20–24]. Moreover, the amount of BAT detected in human inversely correlated with age, BMI and diabetic status [21,43]. With the recognition that human BAT can be activated, targeting BAT or beige fat proliferation and activation may be viewed as two appealing ways to prevent or treat obesity and its associated diseases.

Angiogenesis contribution of brown and beige adipose tissue to metabolic function and fat pad expansion

BAT is metabolically active and therefore possesses a higher vascular density. As early as in embryogenesis, adipose tissue development is spatially and temporally associated with microvessel growth [44]. Endothelial dysfunction in obese individuals makes an important contribution to the development and progression of type 2 diabetes [45]. Adipose tissue secrets factors, such as vascular endothelial growth factor A (VEGF-A), fibroblast growth factor (FGF), leptin, adiponectin, thrombospondin 1 and plasminogen activator inhibitor (PAI-1), to regulate angiogenesis [46–51]. Among them VEGF-A is the only *bona fide* endothelial cell growth factor, and accounts for most of the pro-angiogenic activity in adipose tissue [52,53]. VEGF-A stimulates vascular endothelial activation, proliferation, migration and vessel permeability [51,54]. VEGF-A is highly expressed in BAT. Recently, by way of deletion or overexpression of VEGF-A in adipose tissue, the effect of angiogenesis on adipose function and metabolic consequences were studied by several groups [55–58]. Obesity causes capillary rarefaction in BAT with mitochondrial dysfunction and decreased expression of VEGF-A. Deletion of VEGF-A results in a similar phenotype in BAT to obesity. Conversely, introduction of VEGF-A into BAT of obese mice restores vascularity, ameliorated brown adipocyte dysfunction and improved insulin sensitivity [58]. VEGF-A in WAT also has significant effects on its metabolic function, which may be associated with the browning of WAT [56,57]. In inguinal fat depot, cold exposure resulted in browning of WAT. Meanwhile, angiogenesis was also activated and VEGF-A was upregulated [59]. Upregulation of VEGF-A in adipocytes improves vascularization and causes a browning of WAT, which is associated with an increase in energy expenditure and resistance to high fat diet-mediated metabolic insults [56,57]. VEGFR2 blockage abolished the cold induced angiogenesis and impaired non-shivering thermogenesis capacity [59].

What is more, VEGF-A stimulated vascularization also participates in regulation of inflammation in adipose tissue. Obesity causes capillary rarefaction, leading to adipose tissue hypoxia, which is correlated with inflammatory macrophage or T cell infiltration and inflammatory cytokine expression [56–58]. VEGF-A overexpression in adipose tissue increases macrophage infiltration with a higher number of M2 anti-inflammatory and fewer M1 proinflammatory macrophages than wild type mice, and thus influences insulin sensitivity [55].

Adipose vasculature participates in modulating adipose tissue development and growth in various ways (Fig. 2). Angiogenic vessels deliver nutrients and oxygen from the blood to adipocytes. More importantly, angiogenic vessels transport stem cells derived from bone marrow [60], or provide stem cells derived from themselves [61–65]. Recent studies show that mural cells including vascular pericytes have stem cell features and can differentiate into adipocytes under proper inducement. Lineage tracing experiments using the VE-cadherin promoter revealed localization of reporter genes in both preadipocytes and adipocytes of white and brown fat depots [63]. The data suggested endothelial cells in neoangiogenesis might contribute to the stem cell pool of adipogenesis. Adipocytes produce various growth factors and cytokines that communicate with endothelial cells in a paracrine fashion to promote their growth [47], which seems to form a forward circuit. In cold acclimation, BAT-like changes in inguinal fat pad is induced with adipocyte hyperplasia [66]. These changes are accompanied by switching on an angiogenesis, as demonstrated by the increased vasculatures with CD31 staining [59].

Sympathetic signaling control of brown and beige fat

The metabolic function of BAT is facilitated by extremely high mitochondrial content and dense vascular vessels. It is also promoted by extensive nerve supply to this tissue. Brown fat thermogenesis and UCP1 gene transcription are mainly controlled by norepinephrine released from the sympathetic terminals innervating the tissue. It has also been suggested that catecholamines secreted by a certain subtype of macrophages can activate brown and beige fat in mice [67]. More recently, the efferent beige fat thermogenic circuit, consisting of eosinophils, type 2 cytokines interleukin (IL)-4/13, and alternatively activated

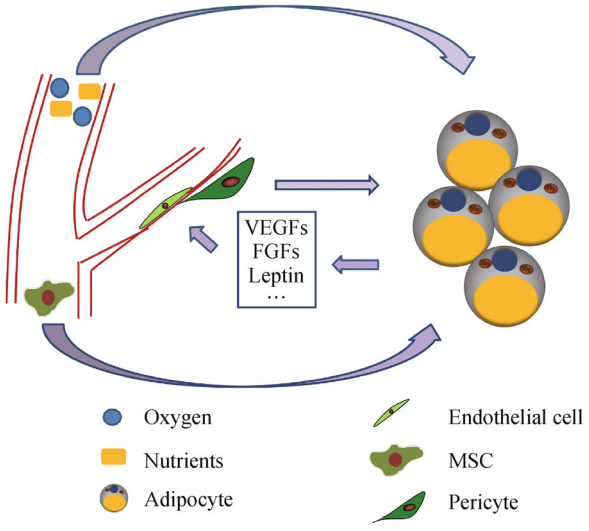

Fig. 2 Vasculature contributes to adipose expansion in variety of ways. Angiogenic vessels supply nutrients and oxygen in the blood to adipocytes. Angiogenic vessels transport mesenchymal stem cells (MSC) from bone marrow, or provide stem cells derived from themselves. Adipocytes produce various growth factors and cytokines that communicate with endothelial cells in a paracrine fashion to promote their growth.

macrophages, was identified [68]. Sympathetic norepinephrine acts through β3-adrenergic and cAMP-dependent pathway. Norepinephrine binds to β3-adrenergic receptors on the membrane of adipocytes and thereby activates adenylatecyclase (AC), resulting in an increased cAMP level in cytosol and protein kinase activation. On the one hand, phosphorylated hormone sensitive lipase (HSL) by PKA releases glycerol and fatty acid from lipid to fuel thermogenesis. It is noteworthy that free fatty acid itself is an activator of UCP-1 by increasing proton leak through UCP-1 [69,70]. On the other hand, the PKA activates UCP-1 transcription through p38 mitogen-activated protein kinase (MAPK) dependent or independent way [71–73]. Sympathetic signaling is activated in the cold, and prolonged cold exposure stimulates the proliferation and differentiation of brown precursor cells to expand BAT mass [74]. Conversely, at warmer housing temperatures or in surgically denervated BAT, the expression of UCP-1 and other thermogenic factors are substantially reduced in mice [35,75].

Cold exposure is also a classic activator of beige adipocyte development and function, indicating the involvement of sympathetic signaling. The propensity of WAT depots to develop beige adipocytes is highly correlated with their density of sympathetic nerve fibers [76]. Treating mice with β3-adrenergic activators, such as CL316,214, led to the expression of UCP1 in inguinal WAT [15–17]. The β3-adrenergic receptor knockout decreased the levels of UCP1 mRNA and protein as well as the density of multilocular cells after cold exposure at 24 °C or an elongated cold exposure for 10 days, but did not affect the UCP1 expression in classic brown fat [77]. These results revealed that β3-adrenergic receptors play a major role in the appearance of beige adipocytes in white fat. However, other factors must also be involved, as systemic β3-agonist administration or β3-adrenergic receptor knockout mice exhibit fat deposit difference in affecting UCP1 expression. Cold exposure or β3-adrenergic receptor agonist increased miR-196a level in WAT. The fat-specific forced expression of miR-196a in mice induced the recruitment of brown adipocyte-like cells in WAT, and enhanced energy expenditure and resistance to obesity. miR-196a induces functional brown adipocytes in WAT through the suppression of Hoxc8 [78,79]. Cyclooxygenase (COX)-2, a rate-limiting enzyme in prostaglandin (PG) synthesis, is a downstream effector of β-adrenergic signaling in WAT and is required for the induction of BAT in WAT depots [80,81]. Foxc2 (forkhead box C2) induces beige fat cell development, drives mitochondrial biogenesis and promotes angiogenesis in adipose tissue [82–84]. Foxc2 functions in fat cells to a large extent by driving the expression of the R1α regulatory subunit of protein kinase A (PKA, encoded by Prkar1a), thus sensitizing adipocytes to the effects of catecholamines [85,86].

BMPs that activate BAT or induce beiging in WAT

While sympathetic signaling undoubtedly plays a role in regulating brown or beige fat function *in vivo*, many other hormones and factors such as Irisin, retinaldehyde dehydrogenase (Raldh), thyroid hormone, natriuretic peptides (NP) have been shown to regulate energy expenditure in adipose tissue and have been discussed comprehensively in other reviews [87,88]. Morphogens of vertebrate embryonic patterning and evolution of mesodermal tissue, including hedgehog [89,90], wingless (Wnt) [91,92], bone morphogenetic proteins (BMPs), and fibroblast growth factors 21 (FGF21) [93–96] have been linked to adipocyte lineage determination. They are also involved in regulating brown or beige fat function. Here we describe some of the BMPs that affect brown and beige fat and seem to be particularly promising for therapeutic development.

BMP7 promotes differentiation of brown preadipocytes and induction of mitochondrial biogenesis via p38 mitogen-activated protein (MAP) kinase and PGC-1-dependent pathways. BMP7 knockout embryos show a marked paucity of brown fat and an almost complete absence of UCP1. Adenoviral mediated expression of BMP7 in mice results in a significant increase in brown, but not white fat mass and leads to an increase in energy

expenditure and a reduction in weight gain [97]. BMP7 was also found to have a role in appetite regulation through central mTOR pathway [98].

BMP8B is produced by mature brown fat cells when stimulated by nutritional and thermogenic factors. BMP8B amplifies the thermogenic response of brown adipocytes to adrenergic activators through enhanced p38MAPK/CREB signaling and increased lipase activity. BMP8B knockout mice exhibit impaired thermogenesis and reduced metabolic rate, causing weight gain. Interestingly, BMP8B is also expressed in the hypothalamus, and BMP8B knockout mice display altered neuropeptide levels and reduced phosphorylation of AMP-activated protein kinase (AMPK). Central BMP8B treatment increases sympathetic activation of BAT and leads to weight loss in mice [99].

BMP7 and BMP8B function in BAT to stimulate BAT development and thermogenesis respectively. BMP4 is thought to regulate WAT development. BMP4 induces multipotent mouse C3H10T1/2 stem cells to commit to preadipocytes in culture, and BMP4 treated C3H10T1/2 cells develop into adipocytes if implanted subcutaneously into nude mice [100]. Preadipocyte cell line A33, subcloned from C3H10T1/2, with 5-azacytidine treatment expresses and secretes BMP4, indicating BMP4's important role in the commitment stage [101]. BMP4-induced commitment is mostly depended on activation of Smad rather than p38/MAPK pathway [102]. The induction of EMT (epithelial-mesenchymal transition)-like response by BMP4 via upregulation of lysyloxidase is required for adipocyte lineage commitment [103]. Although the robust effect of BMP4 on commitment of multipotent stem cells is undoubted, the characteristic of differentiated adipocytes in culture was not well defined. Further *in vivo* data showed that BMP4 can induce brown-like changes in WAT [104]. Forced expression of BMP4 in adipocytes of mice gives rise to reduced white adipocyte and lipid droplet size, along with an enhanced mitochondrial biogenesis. The inguinal white fat pad also expressed some of the marker genes of beige adipocytes. These changes correlate closely with increased energy expenditure, improved insulin-sensitivity and protection against diet-induced obesity and diabetes, suggesting that the adipocytes were metabolic active. Conversely, BMP4-deficient mice exhibit enlarged white adipocyte morphology and impaired insulin sensitivity. Mechanically, the BMP4-p38MAPK-ATF2-PGC1α pathway was required for the BMP4-induced brown-fat like changes in WAT. This effect of BMP4 on WAT appears to extend to human adipose tissue, since the level of expression of BMP4 in WAT correlates inversely with body mass index.

Therapeutic perspectives and challenges

Adipose tissue is an important organ for energy homeostasis. When energy intake exceeds the storage capacity of WAT, the fat will accumulate in non-adipose tissue such as pancreatic beta cells, liver, skeletal muscle, leading to metabolic disorders. The anti-obesity methods involve either reducing energy intake or increasing energy expenditure. Due to their ability to dissipate energy, enhancement of the function of brown adipocytes or beige adipocytes, or/and increase its mass could be very effective in treating type 2 diabetes and obesity. Since the reports that normal adult humans possess brown active adipocytes [20–24], it is accepted that such kind of adipocytes might be the therapeutic targets.

However, the key point is whether human brown or beige adipocytes can be physically recruited and activated. This would seem to be the case, at least by cold exposure. But it would seem difficult to increase exposure to cold in daily life. Moreover, it is to be noted that mice exposed to a cold setting at 4 °C show increased cardiovascular risk such as atherosclerotic plaque growth or instability [105], although human BAT can be activated and recruited by rather mild cold conditions at 10–19 °C [106,107]. It is known that the stimulatory effects of cold exposure on BAT are initiated by peripheral stimulation of transient receptor potential (TRP) channels in sensory neurons [108,109]. TRP vanilloid (TRPV) is a subfamily of TRP channels. TRPV1 is activated by some pungent compounds in chili peppers such as capsaicin or its non-pungent analogs — capsinoids. Acute effects of capsinoids on energy expenditure are quite similar to those of cold exposure in humans [110–112]. In addition, energy expenditure after only 2 h cold exposure at 19 °C increased in human individuals with the daily ingestion of capsinoids for 6 weeks [107]. Capsinoids treatment along with mild and short time cold stimuli via activation of TRP could be a promising way to treat obesity and related metabolic diseases.

It is interesting to pharmacologically expand and activate brown or beige fat in human. However, so far, treatments using β3-adrenergic receptor agonists have been unsuccessful in humans. The discoveries of circulating secreted factors, such as BMPs that enhance brown and beige fat function in mice have garnered tremendous interest [97,99,104]. BMP8B increases the sensitivity of brown fat cells to adrenergic stimuli and activates it. In our laboratory, we found that BMP4 acquired WAT with BAT activity along with increased number of both stromal vascular cells and adipocytes, indicating that BMP4 both recruits and activates the beige adipocytes. Although the findings in mice are valuable, very few studies have been done to explore whether these BMPs have similar function in human fat depots. Given the high variety among human fat depots, defining the fat cells within human fat depots that can be efficiently recruited and thermogenically activated, and exploring which pathways promote this process will be meaningful for future research. Moreover, since BMPs also involve in angiogenesis and bone

formation, their specificity of action will need to be carefully examined and monitored.

Acknowledgements

This article based on research that was funded partially by National Basic Research Program of China (Grant No. 2011CB910201; for Q. Q.T.), and National Natural Science Foundation of China (Grant No. 81200621; for S.W.Q).

Compliance with ethics guidelines

Shuwen Qian, Haiyan Huang, and Qiqun Tang declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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