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Inter-organ regulation of adipose tissue browning

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Abstract

Adaptive thermogenesis is an important component of energy expenditure. Brown adipocytes are best known for their ability to convert chemical energy into heat. Beige cells are brown-like adipocytes that arise in white adipose tissue in response to certain environmental cues to dissipate heat and improve metabolic homeostasis. A large body of intrinsic factors and external signals are critical for the function of beige adipocytes. In this review, we discuss recent advances in our understanding of neuronal, hormonal, and metabolic regulation of the development and activation of beige adipocytes, with a focus on the regulation of beige adipocytes by other organs, tissues, and cells. Understanding the cellular and molecular mechanisms of inter-organ regulation of adipose tissue browning may provide an avenue for combating obesity and associated diseases.

Keywords

Thermogenesis; beige adipocytes; browning; inter-organ crosstalk; obesity

Introduction

A major type of thermogenic tissue in mammals is brown adipose tissue (BAT). In mice, BAT is located constitutively in the anterior subcutaneous region including the interscapular, axillary and cervical fat (Diaz et al., 2014). Brown adipocytes are characterized by multilocular lipid droplets and a high density of iron-containing mitochondria that give the eponymous appearance (Cinti, 2001). Uncoupling protein 1 (UCP1) is a key thermogenic factor in brown adipocytes. When activated by long-chain fatty acids, UCP1 catalyzes a proton leak across the inner membrane, thus bypasses ATP synthase, dissipates the electrochemical gradient, and generates heat (Bartelt et al., 2011; Krauss et al., 2005).

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Moreover, high vascularization of BAT facilitates sufficient nutrition and oxygen supply as well as efficient heat output to the whole body through circulation.

Recent studies have uncovered another type of thermogenic adipocytes known as beige/brite (brown in white) adipocytes. Beige/brite cells share morphological and functional similarities with brown adipocytes. Beige/brite cells express a key set of brown fat-specific genes including UCP1 and also undergo thermogenesis via uncoupling of oxidative phosphorylation from ATP production (Wu et al., 2015). Although it seems interchangeable between the terms “beige” and “brite” adipocytes, the beige originally refers to those thermogenic adipocytes isolated from subcutaneous WAT depots like inguinal WAT and the brite are from their visceral counterparts such as epididymal and mesenteric depots (Petrovic et al., 2010; Wu et al., 2012). Typically, the inguinal WAT is more prone to browning/beiging (Vitali et al., 2012), but the epididymal WAT also possess bipotent adipogenic precursor cells that can differentiate into both white and UCP1⁺ adipocytes under different conditions (Lee et al., 2012). Hereinafter, all these inducible thermogenic adipocytes will be referred to as beige adipocytes.

The recruitment of beige adipocytes, i.e. the browning process, is potently activated by cold exposure. Chronic cold acclimation of mice induces a substantial amount of beige adipocytes in posterior subcutaneous, retroperitoneal and perigonadal fat depots (Vitali et al., 2012; Young et al., 1984). Moreover, cold-induced formation of beige adipocytes in mice can be reversed within 5 weeks of warm adaptation, suggesting that browning is a reversible and dynamic process (Rosenwald et al., 2013).

Distinct from brown adipocytes, beige adipocytes have certain unique features. A majority of brown adipocytes arise from multipotent cells of the dermomyotome (Kajimura et al., 2015; Seale et al., 2008), whereas beige adipocytes are thought to originate from mesenchymal precursors that also give rise to smooth muscle or smooth muscle-like cells (Lee et al., 2012; Long et al., 2014). It has been further demonstrated that RhoA signaling controls the fate of mesenchyme stem cells (MSCs) to an adipogenic versus smooth muscle-like lineage (McDonald et al., 2015). In addition, it is generally believed that most cold-induced beige adipocytes originate from de novo differentiated adipocytes (Wang et al., 2013). However, beige adipocytes may also derive from the conversion of mature white adipocytes in response to cold or β 3-adrenergic stimuli (Himms-Hagen et al., 2000; Lee et al., 2012; Long et al., 2014; Rosenwald et al., 2013; Wang et al., 2013; Wu et al., 2012). The latter is corroborated by a recent study showing that most UCP1⁺ adipocytes in inguinal WAT upon cold exposure stem from pre-existing mature adipocytes (Lee et al., 2015b).

So far, many intrinsic transcription factors and cofactors have been identified that robustly trigger beige adipocyte biogenesis (Emont et al., 2015; Kajimura et al., 2015; Wu et al., 2013). One of these regulators is PRDM16 that is highly expressed in inguinal white fat relative to other white fat depots in mice and plays a key role in regulating the determination and activation of beige adipocytes (Chi and Cohen, 2016; Kajimura et al., 2008; Ohno et al., 2012; Seale et al., 2011). Moreover, PRDM16-binding partners such as PPAR γ coactivator 1 α (PGC1 α), C/EBP- β , Euchromatic histone-lysine N-methyltransferase 1 (EHMT1), and

Zfp516 serve as powerful transcriptional activators (Dempersmier et al., 2015; Kleiner et al., 2012; Ohno et al., 2013).

Human thermogenic fat

It has long been known that classical brown adipocytes exist in the interscapular regions of human infants and diminish with age (Aherne and Hull, 1966; Heaton, 1972). The existence of brown adipocytes has been detected in adult human samples from both the periadrenal region of benign adrenal tumor patients and the supraclavicular region of healthy individuals (Lidell et al., 2013).

Although brown adipocytes have been identified in multiple BAT depots of adult humans ranging from supraclavicular area, posterior mediastinum, retroperitoneal and intraabdominal regions to mesenteric depots, their identity is still controversial. Several reports suggest that these brown adipocytes in adult humans resemble murine beige adipocytes (Sharp et al., 2012; Wu et al., 2012). This view is further supported by the analysis of molecular signatures of clonally derived adipocytes from superclavicular BAT in adult humans (Shinoda et al., 2015). However, the other study indicates that cold-induced BAT from adult human neck area consists of classical brown adipocytes (Cypess et al., 2013). In addition, it has also been shown that activated thermogenic fat in the supraclavicular region are composed of both classical brown and beige adipocytes (Jespersen et al., 2013).

WAT browning can exert a significant impact on whole-body metabolism in humans. Evidence shows that white adipocytes in patients with pheochromocytoma undergo direct transformation into brown adipocytes, which is associated with elevated thermogenesis and lower BMI in patients (Frontini et al., 2013). Body weight reduction has also been reported in patients with hibernoma due to ectopic de novo development of brown adipocytes (Allegra et al., 1983). However, the extent to which WAT browning contributes to weight loss is not clear until recently. According to one study on three young individuals, mathematical analysis with a modest assumption suggests a decrease in approximately 4.1 kg of adipose tissue over the course of one year, if human BAT were fully activated (Virtanen et al., 2009). Recent studies indicate that BAT activation in humans minimally contributes to the increase in energy expenditure which is only about 15–25 kcal/day, resulting in an estimated weight loss of 1 kg/year (Muzik et al., 2012; Porter et al., 2015). Furthermore, it is still unclear how much white fat can be converted into beige fat in adult humans. In addition to the effects on human body weight, increased activation of thermogenic fat induced by cold acclimation can potentially enhance energy metabolism and insulin sensitization (Chondronikola et al., 2014; Lee et al., 2014). It will be of clinical significance to induce white-to-brown transformation in the treatment of obesity and type 2 diabetes.

Cellular and physiological functions of brown and beige adipocytes have been extensively reviewed recently (Diaz et al., 2014; Kajimura et al., 2015; Pfeifer and Hoffmann, 2015). A growing number of studies indicate that the recruitment of beige adipocytes relies on various extrinsic factors such as hormones and secreted molecules derived from various tissues and

organs. In this review, we will summarize recent advances in understanding how different organs and systems contribute to the development and function of beige adipocytes.

Central nervous system (CNS)

A recent emphasis has been placed on the role of the hypothalamus of the CNS in beige adipocyte development and function (Dodd et al., 2015; Ruan et al., 2014; Yang and Ruan, 2015). The hypothalamus not only senses body temperature fluctuation in cold, but also responds to peripheral signals including hormones and nutrients to modulate sympathetic outputs (Plum et al., 2007; Rezai-Zadeh and Munzberg, 2013). The arcuate nucleus (ARC) of the hypothalamus is one of the important nodes where these peripheral signals converge to regulate browning (Commins et al., 2000; Morrison et al., 2014). The AgRP/NPY neurons are hunger-promoting neurons expressing agouti-related protein and neuropeptide Y, while POMC/CART neurons are satiety neurons expressing proopiomelanocortin and cocaine-amphetamine-regulated transcript. These two major sets of neurons in the ARC respond, generally in opposite directions, to hormones such as leptin, insulin, and ghrelin, as well as nutrients such as glucose, amino acids, and fatty acids (Belgardt et al., 2009; Dietrich and Horvath, 2013; Stefanidis et al., 2014). Previous studies have implicated the role of central leptin in the regulation of WAT browning. Supported by direct genetic evidence leptin-stimulated phosphatidylinositol 3-kinase (PI3K) signaling in the CNS has been shown to modulate energy expenditure via activation of sympathetic nerve activity to perigonadal WAT resulting in BAT-like differentiation of WAT in mice (Plum et al., 2007). But more efforts will be required to identify the exact anatomical site and nature of the hypothalamic leptin-responsive neurons responsible for mediating sympathetic nerve activity in WAT. In addition to hormones, the effects of these two neuronal populations on WAT browning are closely correlated with the body's energy state. In the fed state, insulin and leptin act synergistically on POMC neurons to stimulate beige adipocyte activation in inguinal WAT (Dodd et al., 2015). Genetic ablation of two phosphatases PTP1B and TCPTP that negatively regulate insulin and leptin pathways in POMC neurons leads to increased WAT browning (Dodd et al., 2015). In the fasting state, the hunger-promoting hormone ghrelin activates AgRP neurons, which inhibits browning in retroperitoneal WAT. O-GlcNAc transferase (OGT) is enriched in AgRP neurons, and its expression is increased in response to fasting and ghrelin (Ruan et al., 2014). OGT knockout in AgRP neurons inhibits neuronal excitability and abrogates the suppression of WAT browning by fasting and ghrelin. These studies demonstrate that AgRP and POMC neurons regulate WAT browning through directly modulating sympathetic nerve activity; however, neural circuits linking these neurons to sympathetic innervation onto different WAT depots need to be further explored (Harlan et al., 2011; Shi et al., 2013).

Enriched environment (EE) abundant with complex physical and social stimulations is important for increased neurogenesis, improved cognitive performance and resistance to cerebral insults (Cao et al., 2004; Monteiro et al., 2014). Recently EE has also been found to trigger beige adipocyte induction (Cao et al., 2011). EE induces hypothalamic expression of the brain-derived neurotrophic factor (BDNF), which subsequently increases β -adrenergic receptor (β -AR) and norepinephrine (NE) levels in WAT, and this SNS outflow in WAT ultimately results in browning of retroperitoneal and epididymal WAT and decreased

adiposity in mice (Cao et al., 2011). It has also been reported that the ventromedial nucleus (VMH) and the paraventricular nucleus (PVN) are vital sites of BDNF action (Wang et al., 2007; Wang et al., 2010). Moreover, hypothalamic BDNF also regulates VEGF signaling in retroperitoneal WAT that is required for angiogenesis and browning induced by diverse physiological and pharmacological approaches (During et al., 2015). Although growing evidence demonstrates that acute exercise induces a significant increase in the BDNF level, which might benefit brain cognition, it has yet to be determined whether exercise-induced BDNF has effects on browning of WAT (Etnier et al., 2016; Ieraci et al., 2016; Tsai et al., 2016).

Recent studies show that central serotonin neurons are indispensable for sympathetic activation of brown and beige adipocytes in inguinal WAT in response to cold (McGlashon et al., 2015). In fact, our knowledge of neuronal circuits that control the browning process is still fragmentary. More studies are needed to expand our understanding of how the CNS modulates WAT browning.

Sympathetic nervous system (SNS)

The SNS is believed to be a master regulator of both the recruitment and activation of beige adipocytes (Diaz et al., 2014; Romanovsky, 2007; van Marken Lichtenbelt and Schrauwen, 2011). Either physiological stimuli such as chronic cold exposure or pharmacological agents such as β 3-adrenergic receptor (β 3-AR) agonists, thiazolidinedione (TZDs) and other PPAR γ agonists can activate sympathetic nerve fibers in WATs (Harms and Seale, 2013). Since most sympathetic nerve fibers are actually noradrenergic, the propensity of WAT depots to undergo browning is accompanied by enhanced density of noradrenergic parenchymal nerve fibers (Murano et al., 2009). Of note, prolonged cold exposure induces WAT browning via eliciting a significant increase in the total number of sympathetic noradrenergic fibers as well as macrophage activation. This leads to the release of catecholamine, particularly norepinephrine (NE), to act on β 3-AR and activate mitochondrial biogenesis in adipocytes (Bartness et al., 2014; Collins, 2011; Granneman et al., 2005). Moreover, chronic stimulation of WAT by β 3-AR agonists results in white adipocytes transformation into a brown phenotype (Himms-Hagen et al., 2000; Murano et al., 2009). It has also been suggested that a major physiological action of PPAR γ agonists is to induce UCP1 expression in both BAT and WAT (Sell et al., 2004). Interestingly, the use of TZDs and other PPAR γ agonists may influence the central regulation so as to indirectly reduce sympathetic activity, but additional treatment of β 3-AR agonists overcomes this situation and synergizes with PPAR γ agonism to increase thermogenic energy expenditure in WAT (Sell et al., 2004; Wilson-Fritch et al., 2004). Overall, sympathetic activities vary between different WAT depots under the basal, cold-induced, and fasting-induced conditions (Brito et al., 2008; Ruan et al., 2014). However, the mechanisms by which the SNS differentially regulates browning in different WAT depots remain to be characterized.

Immune cells

Upon cold exposure, in addition to the sympathetic nerves, eosinophil-derived interleukin (IL)-4 has been found to induce catecholamine synthesis from alternatively activated

macrophages (AAMs) that recruits and activates beige adipocyte development in inguinal WAT (Nguyen et al., 2011; Qiu et al., 2014). In response to epithelial cytokines or microbe infection, group 2 innate lymphoid cells (ILC2s) promote eosinophil and AAMs via releasing a large amount of type 2 cytokines (Halim et al., 2014; Molofsky et al., 2013; Moro et al., 2010; Neill et al., 2010). It has been recently identified that activated by IL-33, ILC2s induce beige adipocyte activation in abdominal subcutaneous WAT in humans and epididymal and inguinal WAT in mice (Brestoff et al., 2015; Molofsky et al., 2013). Mechanistically, ILC2s can produce IL-5 and IL-13 to activate eosinophils and AAMs to synthesize catecholamines. Independent of the adaptive immune system, IL-33-elicited ILC2s also drive the browning process by producing methionine-enkephalin (MetEnk) that directly acts on adipocytes to upregulate UCP1 expression (Brestoff et al., 2015). The same group further showed that activated ILC2 cells in thermoneutral mice stimulate the proliferation of PDGFR α ⁺ adipocyte precursor cells, which then commit to the beige adipocyte lineage (Lee et al., 2015a).

Skeletal muscle

Acute and endurance exercise training brings about an increase in brown adipocyte-specific genes expression in WAT of mice (Xu et al., 2011). Skeletal muscle-derived signals such as myokines contribute to the conducive effects of exercise (Bassel-Duby and Olson, 2006). Irisin, a myokine stimulated in muscle upon exercise, has been shown to act on subcutaneous white adipocytes to induce browning in mice at least in part via PPAR α (Bostrom et al., 2012; Jedrychowski et al., 2015). Similar to mice, plasma irisin in humans increases in response to acute exercise and decreases with weight loss after bariatric surgery (Huh et al., 2012; Jedrychowski et al., 2015). Although muscle mass is the strongest predictor of circulating irisin levels, current knowledge of the long-term effects of irisin on browning of WAT in humans are still absent. Meteorin-like (Metrnl), another myokine induced in muscle after exercise and in adipose tissue upon cold exposure, has been observed to induce the cytokines IL4/IL13 and AAM activation to promote production of catecholamine, ultimately leading to browning of both epididymal and subcutaneous WAT in mice (Rao et al., 2014). These observations suggest that muscle-derived myokines might engage type 2 innate immunity to control beige adipocyte activation. The cytokine IL-6, released from contracting skeletal muscle to the circulation (Steensberg et al., 2000), is also required for a full induction of beige cell biogenesis in murine inguinal WAT after exercise and cold exposure (Knudsen et al., 2014). IL-6 induces WAT browning at least partly through increasing PGC-1 α activity (Knudsen et al., 2014).

Recent studies demonstrate that certain metabolites secreted from skeletal muscle after physical activity control WAT browning. Lactate induces thermogenic gene expression in murine and human adipocytes. In mice treated with PPAR γ agonist, lactate triggers beige adipocyte activation in subcutaneous WAT by modifying intracellular redox (Carriere et al., 2014). The ketone body β -hydroxybutyrate (β -HB) that impacts cellular redox state is a robust inducer of browning in inguinal WAT (Carriere et al., 2014). β -aminoisobutyric acid (BAIBA) is a secreted metabolite from PGC-1 α -expressing myocytes and its circulating levels in mice and humans positively correlates with exercise (Roberts et al., 2014). BAIBA is found to be regulated by PGC-1 α and increase brown adipocyte-specific genes

expression. Further mechanistic experiments in rodents demonstrate that BAIBA elicits browning of murine inguinal WAT in a specific PPAR α -dependent manner (Roberts et al., 2014).

Heart

Atrial natriuretic peptides (ANP) and ventricular natriuretic peptides (BNP) are predominantly released from the atria and ventricles, respectively. These two cardiac natriuretic peptides act through the natriuretic peptide receptor A (NPRA), whose intracellular domain possesses a guanylyl cyclase activity to generate the second messenger cGMP. The natriuretic peptide receptor C (NPRC) is the clearance receptor that binds ANP and BNP and removes them from circulation. Cold exposure in mice is associated with an increased ratio of NPRA to NPRC. Infusion of BNP into mice dramatically increases Ucp1 and PGC-1 α levels in WAT via the p38 MAPK pathway, indicating that natriuretic peptides promote WAT browning to boost energy expenditure in mice (Bordicchia et al., 2012). In addition, recent findings show that Roux-en-Y gastric bypass (RYGB) surgery leads to browning of gonadal WAT in female mice and this may be explained in part by the upregulation of ANP and BNP after RYGB (Neinast et al., 2015). Similar observations have been reported in humans undergoing RYGB surgery, although detailed mechanisms by which RYGB surgery promotes beige adipocyte biogenesis in supraclavicular adipose tissue are still unknown (Rachid et al., 2015).

Gut

The gastrointestinal tract is known as the largest endocrine organ that secretes a number of regulatory peptide hormones (Badman and Flier, 2005). The intestinal microbiota develops within the host, and its composition is continuously influenced by different physiological conditions (Koren et al., 2012; Liou et al., 2013; Ridaura et al., 2013). Cold exposure is known to alter microbiota composition, and transplantation of the microbiota from mice under prolonged cold exposure to germ-free mice is sufficient to promote browning of inguinal and perigonadal WAT (Chevalier et al., 2015). There is also the evidence that depletion of microbiota either by means of antibiotic treatment or in germ-free mice promotes beige fat development in inguinal subcutaneous and perigonadal visceral adipose tissues, which is mediated via enhanced type 2 cytokine signaling (Suarez-Zamorano et al., 2015). Re-colonization of antibiotic-treated or germ-free mice with microbiota reverses the browning phenotypes that are induced by microbiota depletion (Suarez-Zamorano et al., 2015). Collectively, these results hold promise for the induction of beige adipocyte in humans through the transplantation of functional microbiota.

Farnesoid X receptor (FXR) is a ligand-activated transcriptional factor expressed in diverse tissues including the intestine. Bile acids act as endogenous ligands for FXR and bile acids released during a meal can selectively activate intestinal FXR (Fang et al., 2015; Fang et al., 2008; Kemper et al., 2009; Lee et al., 2006). In mimicking this tissue-selective effect, gut-restricted FXR agonist fexaramine is able to reduce diet-induced weight gain and activate inguinal WAT browning in mice via enhanced β -adrenergic signaling (Fang et al., 2015).

These results offer insight into intestinal FXR activation, instead of systemic FXR agonism, as a promising approach in the treatment of metabolic morbidities.

Liver

The autocrine/paracrine hormone fibroblast growth factor 21 (FGF21) is a key member of FGF superfamily that is produced mainly from liver and could be induced after fasting (Badman et al., 2007; Inagaki et al., 2007). Pharmacological administration of FGF21 induces browning of inguinal and perirenal WAT, which is evidenced by increased levels of thermogenic genes and histological appearance of increased brown-like adipocytes (Fisher et al., 2012). One possible mechanism is that FGF21 post-transcriptionally regulates PGC-1 α levels in WAT (Fisher et al., 2012). Later, it was reported that intraperitoneal injection of FGF21 normalizes hyperglycemia in diabetic mice independently of insulin action in the liver, but largely due to increased energy expenditure via activation of BAT and browning of subcutaneous WAT (Emanuelli et al., 2014). However, FGF21 has serious limitations in that both genetic and pharmacological gain-of-function of FGF21 are found to severely decrease bone mass in humans (Wei et al., 2012). It has been further demonstrated that FGF21 inhibits osteoblastogenesis but enhances bone marrow adipogenesis by potentiating the activity of peroxisome proliferator-activated receptor γ (PPAR- γ) (Wei et al., 2012). Recent human studies show that circulating FGF21 levels are elevated in lipodystrophy and metabolically unhealthy obesity (Berti et al., 2015; Miehle et al., 2016). Therefore, the clinical application of FGF21 as a potential drug for the treatment of obesity and type 2 diabetes appears less desirable.

Adipose Tissue

Apart from the tissues described above, adipose tissue itself can produce secreted factors that enhance the recruitment of beige adipocytes. A recent study reveals that adenosine released from brown adipocytes during the stimulation of sympathetic nerves plays a critical role in the induction of beige adipocytes (Gnad et al., 2014). The adenosine A_{2A} receptor is the most abundant adenosine receptor in human and murine BAT. Although A_{2A} levels are scarcely expressed in white adipocytes, either pharmacological stimulation of the A_{2A} receptors or injection of lentiviral vectors expressing the A_{2A} receptor into inguinal WAT induces beige adipocyte development (Gnad et al., 2014).

In addition, vascular endothelial growth factor (VEGF)-A secreted by adipocytes plays a pivotal role in adipose tissue angiogenesis (Cao, 2010; Hausman and Richardson, 2004). Up-regulation of VEGF-A in retroperitoneal WAT improves vascularization and leads to browning of WAT (During et al., 2015). Moreover, transgenic overexpression of VEGF in adipose tissue may also directly recruit brown and beige adipocytes and triggers browning of WAT; however, the molecular basis is unclear (Elias et al., 2012; Sun et al., 2012). It is still worth pointing out that cold exposure induces angiogenesis in both brown and white adipose tissues independently of hypoxia (Xue et al., 2009). In inguinal WAT, cold exposure not only results in the browning phenotype with multilocular UCP1-positive adipocytes, but also leads to an increased production of VEGF. However, there is no direct evidence that VEGF-mediated vascularization is sufficient or necessary to induce browning.

Disease-induced browning of WAT

Cancer

Cancer-associated cachexia (CAC) is characterized by systemic inflammation, body weight loss, atrophy of adipose tissue, and skeletal muscle wasting (Fearon et al., 2012). A systematic morphological analysis of WAT depots in the cachectic mouse models of several cancer types such as Kras-pancreatic and lung cancer identified a robust phenotypic switch from white to beige fat in subcutaneous WAT (Petruzzi et al., 2014). WAT browning takes place in the early stages of CAC before skeletal muscle atrophy, whereas inhibiting inflammation or β -adrenergic signaling significantly reduces WAT browning and alleviates the severity of cachexia (Petruzzi et al., 2014). WAT browning is also observed in cancer cachexia patients, characterized by increased UCP1 staining in intestine adipose tissue as well as fat surrounding the liver, kidney and pancreas (Petruzzi et al., 2014). In pursuit of the mechanism underlying WAT browning in CAC mouse models, IL-6 signaling together with β -adrenergic activation was found to jointly trigger and sustain WAT browning in cachexia (Petruzzi et al., 2014). Insight into how tumors induce the development of beige adipocytes is also enriched by a study on tumor-derived parathyroid-hormone-related protein (PTHrP) (Kir et al., 2014). Lewis lung carcinoma-derived PTHrP has been demonstrated to initiate WAT browning and muscle loss, and neutralization of PTHrP is able to prevent tumor-induced browning of WAT (Kir et al., 2014). Collectively, blockage of CAC-induced beige adipocyte biogenesis may underlie the translational value to ameliorate cachexia in cancer patients.

Benign tumors

Several case studies further demonstrate the impact of various benign human tumors on fat browning. Pheochromocytoma is a catecholamine-secreting tumor. In affected patients, omental white adipocytes can transdifferentiate into brown adipocytes due to ectopic adrenergic stimulation (Frontini et al., 2013). Another study in patients with benign adrenal tumors indicates a white-brown plasticity of the white fat in the periadrenal region (Lidell et al., 2013). Similarly, tissue sections from human hibernoma exhibit three different adipocyte morphologies: unilocular, multilocular, and paucilocular. The various intermediate forms of adipocytes suggest a reversible transition between white and brown adipocytes (Manieri et al., 2010).

HIV infection

In addition to cancer, the influence of other diseases on fat browning in adult humans has been documented. HIV-infected subjects with lipodystrophy are characterized by the presence of excessive dorsocervical fat. Dorsocervical fat accumulation is correlated with the down-regulation of brown and beige fat genes in nonlipomatous abdominal subcutaneous fat (Torriani et al., 2016). These observations indicate that WAT browning is impaired in lipodystrophic HIV patients. It is reasonable to speculate that stimulating browning of WAT might improve metabolic health in this population.

Tissue Non-specific Regulators

Beige adipocyte development is regulated by a large variety of intrinsic factors, some of which are not confined to a specific tissue. Such molecules and related signaling pathways important for beige adipocyte activation are highlighted below.

Cyclooxygenase (COX)-2/ and prostaglandin (PG)

COX-2 serves as a rate-limiting enzyme in the synthesis of PG. COX-2 is required for the induction of beige adipocytes in mice as a downstream effector of β -adrenergic signaling in visceral WAT depots under cold exposure (Madsen et al., 2010; Vegiopoulos et al., 2010). Notably, local COX-2 overexpression in intra-abdominal WAT is sufficient for WAT browning. In addition, microsomal prostaglandin E (PGE) synthase-1 (mPGES-1) has recently been shown to be necessary for murine beige adipocyte biogenesis from pre-adipocytes (Garcia-Alonso et al., 2013). Further mechanistic studies suggest that COX-2-PG pathway shifts the differentiation of defined mesenchymal progenitors toward a brown adipocyte phenotype by acting on both the cellular prostacyclin (PGI₂) transmembrane receptor and the nuclear receptor PPAR γ (Garcia-Alonso et al., 2013; Vegiopoulos et al., 2010).

Transforming growth factor (TGF)- β superfamily

Bone morphogenetic protein (BMPs) are the members of the TGF- β superfamily. BMPs have recently been implicated with the ability to stimulate beige adipocyte development. Genetic knockout of the type 1A BMP receptor (Bmpr1a) in brown adipogenic progenitor cells results in a severe paucity of classical brown adipocytes, which in turn increases sympathetic input to WAT with elevated circulating NE, thereby promoting compensatory browning in both inguinal and epididymal WAT (Schulz et al., 2013). Moreover, gain- and loss-of-function experiments show that bone morphogenetic protein 4 (BMP4) recruits beige adipocytes in inguinal WAT by targeting PGC-1 α (Qian et al., 2013). It has also been reported that a subpopulation of adipogenic progenitors (Sca-1+/CD45-/Mac1-; referred to as Sca-1+ progenitor cells, ScaPCs) residing in skeletal muscle and inguinal WAT are highly inducible to differentiation into beige adipocytes upon stimulation with BMP7 (Schulz et al., 2011). In addition, BMP7 suppresses ROCK to facilitate beige adipocyte formation via mediating the G-actin-regulated transcriptional coactivator myocardin-related transcription factor A, MRTFA (McDonald et al., 2015). The mechanisms, however, by which TGF β family members regulate ROCK are still unclear. The role of TGF- β signaling in regulating fat browning is further supported by the pharmacological studies of the activin receptor type IIB (ActRIIB), a type II receptor that binds to multiple ligands from the TGF- β superfamily such as the activin and BMP subgroups (Sako et al., 2010). Administration of a soluble ActRIIB protein comprised of a form of the extracellular domain of ActRIIB fused to a human Fc (ActRIIB-Fc) leads to an induction of beige adipocytes in epididymal WAT, yet the underlying mechanism is poorly defined (Koncarevic et al., 2012).

Concluding remarks

Systemic homeostasis is achieved through coordinated metabolic regulation among multiple tissues/organs. Being no exception, the development and activation of beige adipocytes are also controlled by signals derived from various tissues/organs. Despite the recent explosion in our understanding of such metabolic communication between beige adipocytes and other tissues/organs, it is still a long way to go to fully describe the contribution of each individual tissue or organ to the browning process and how beige adipocytes integrate these signals.

As we are gaining a better understanding of the induction of beige adipocytes, our knowledge concerning the contribution of beige fat cells to energy expenditure and whole-body metabolic homeostasis has also greatly improved.

There is evidence that the function of beige adipocytes in regulation of energy expenditure and thermogenesis may be not entirely mediated by UCP1 (Bal et al., 2012; Cannon and Nedergaard, 2010; Ribeiro et al., 2000). Recently, beige adipocytes are shown to be able to utilize creatine to stimulate mitochondrial respiration when ADP is limiting (Kazak et al., 2015). These data suggest that creatine-driven futile substrate cycle could be another important mechanism of thermoregulation in beige adipocytes independent of UCP1 (Kazak et al., 2015).

In addition to generating heat and mediating energy expenditure, mounting evidence suggests that beige adipocytes also contribute to whole-body glucose and lipid homeostasis. Adipocyte-specific expression of PRDM16 in obese mice not only leads to increased beige fat mass and significantly reduced adipose mass, but also greatly improves glucose tolerance (Seale et al., 2011). Apart from subcutaneous adiposity, hepatic steatosis turns out to be the major phenotype in mice with adipocyte specific deletion of PRDM16 (Cohen et al., 2014). Beige fat may also secrete molecules into the circulation to improve glucose homeostasis. Recent study reveals that mice transplanted with inguinal WAT from exercise-trained mice show increased glucose and fatty acid uptake than those receiving inguinal WAT from sedentary or sham-treated mice (Stanford et al., 2015). These findings indicate a potentially direct function for beige adipocytes in reducing circulating glucose and fatty acids, independently on its regulation of body weight. We need future studies to address new functions of beige adipocytes and their regulatory circuits apart from thermogenesis.

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Figure 1. The inter-organ regulation of adipose tissue browning

The schematic illustrates the cellular and molecular mechanisms of inter-organ regulation of adipose tissue browning in mice, human or both. A number of organs, tissues and cells have been found to either act alone or in concert to promote browning of white adipose tissue. This simplified overview delineates the regulation of beige adipocyte induction by central nervous system (CNS), sympathetic nervous system (SNS), immune cells, skeletal muscle, heart, gut, liver, adipose tissue, disease-associated, or tissue non-specific factors (for details, see the text).