

WJSC 6th Anniversary Special Issues (2): Mesenchymal stem cells**Distinction of white, beige and brown adipocytes derived from mesenchymal stem cells**

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Abstract

Adipose tissue is a major metabolic organ, and it has been traditionally classified as either white adipose tissue (WAT) or brown adipose tissue (BAT). WAT and BAT are characterized by different anatomical locations, morphological structures, functions, and regulations. WAT and BAT are both involved in energy balance. WAT is mainly involved in the storage and mobilization of energy in the form of triglycerides, whereas BAT specializes in dissipating energy as heat during cold- or diet-induced thermogenesis. Recently, brown-like adipocytes were discovered in WAT. These brown-like adipocytes that appear in WAT are called beige or brite adipocytes. Interestingly, these beige/brite cells resemble white fat cells in the basal state, but they respond to thermogenic stimuli with increased levels of thermogenic genes and increased respiration rates. In addition, beige/brite cells have a gene expression

pattern distinct from that of either white or brown fat cells. The current epidemic of obesity has increased the interest in studying adipocyte formation (adipogenesis), especially in beige/brite cells. This review summarizes the developmental process of adipose tissues that originate from the mesenchymal stem cells and the features of these three different types of adipocytes.

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Key words: White adipocytes; Brown adipocytes; Beige/brite adipocytes; Mesenchymal stem cells; Adipogenesis; Thermogenesis; Browning

Core tip: Here, we summarize the characteristic differences of the white, brown and beige adipocytes derived from mesenchymal stem cells, including their anatomical location. In particular, we focus on the newly discovered brown-like adipocytes called beige/brite adipocytes. A deeper understanding of the molecular mechanism of these adipocytes may provide clues for overcoming obesity and its associated metabolic diseases.

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INTRODUCTION

Obesity is a worldwide challenge and not unique to any one country. Furthermore, obesity is closely connected to many metabolic diseases. Essentially, obesity and overweight are caused by the energy imbalance between the calories consumed and calories expended. Adipose tissue,

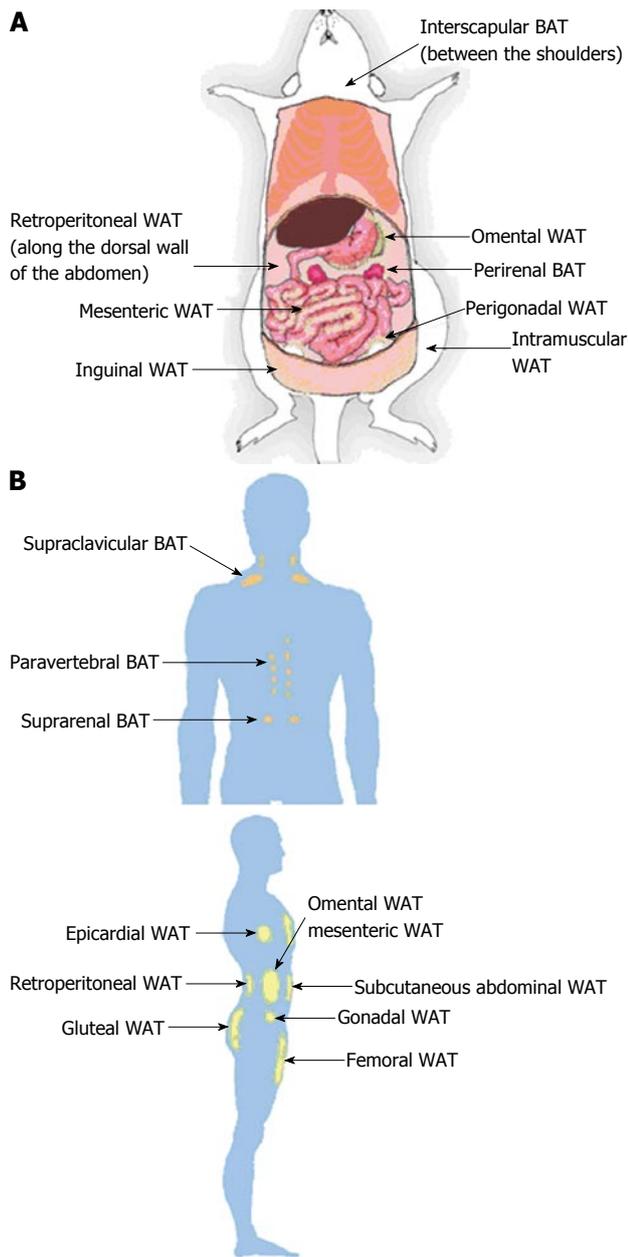


Figure 1 Locations of adipose tissue depots in a mouse (A) and an adult human (B). A: Subcutaneous (inguinal and intramuscular), visceral (mesenteric, omental, perigonadal and retroperitoneal) and brown (interscapular and perirenal) adipose tissue depots are shown in a mouse model; B: Subcutaneous (abdominal, femoral and gluteal), visceral (epicardial, gonadal, mesenteric, omental and retroperitoneal) and brown (paravertebral, supraclavicular and suprarenal) adipose tissue depots are shown in a human model. WAT: White adipose tissue; BAT: Brown adipose tissue.

which is composed mostly of adipocytes, is a major endocrine organ and plays a key role in energy homeostasis. Two types of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT), have been identified^[1]. In practice, obesity does not depend on body weight but depends on either the number of white adipocytes or the amount of WAT. WAT functions primarily to store excess energy in the form of triglycerides (TGs). In contrast, BAT oxidizes fuels and dissipates energy in the form of heat, which suggests that BAT plays a natural anti-obesity

role. Therefore, a deeper understanding of the regulation mechanisms of adipose tissues can potentially open the way to treating obesity-associated metabolic diseases. In this review, we describe the recent advances in studying the characteristics of white, brown, and beige/brite adipocytes (a third class of adipocytes). Additionally, we review the molecular mechanisms involved in the development of adipocytes and suggest possible future therapeutic approaches.

ANATOMICAL LOCATIONS OF ADIPOSE TISSUES

Adipose tissue depots are distinguished by their different anatomical locations. WAT is distributed throughout the body, and there are two representative types: visceral WAT (vWAT) and subcutaneous WAT (sWAT). vWAT is distributed around organs and provides protective padding. sWAT is located under the skin and provides insulation from heat or cold. vWAT, or abdominal fat, is located inside the peritoneum and is distributed around internal organs (*e.g.*, stomach, liver, intestines, and kidneys). Depending on the location, vWAT is sub-classified roughly into mesenteric, retroperitoneal, perigonadal and omental adipose tissue. Mesenteric adipose tissue resembles a web that supports the intestines, and the paired perigonadal adipose tissue is attached to the uterus and ovaries in females and the epididymis and testis in males. The paired retroperitoneal depots are found along the dorsal wall of the abdomen. Lastly, omental depots are located around the stomach and spleen and extend into the ventral abdomen (Figure 1A). The locations of sWAT differ from those of vWAT; sWAT is located inside the abdominal cavity and can be found underneath the skin as well as in the intramuscular fat that is interspersed amongst skeletal muscles. A typical example of sWAT is inguinal WAT, which is found anterior to the upper site of the hind limbs and underneath the skin. In humans, sWAT is typically distributed around the hips, thighs, and buttocks (Figure 1B).

Because beige/brite adipocyte cells were recently defined^[2], brown adipocytes are sometimes termed “classical”, “constitutive”, or “developmentally programmed” brown adipocytes to distinguish them from brown-like cells in WAT. Classical brown fat is primarily distributed around interscapular BAT (iBAT), axillary, paravertebral, and perirenal sites. The most classical brown fat depots are located in interscapular (in the upper back region) and perirenal (around the kidney) sites in rodents and large mammals. iBAT is distributed subcutaneously between the shoulders and can be easily removed. In contrast, it is difficult to selectively remove perirenal BAT from the whole pad without removing the kidney. In humans, small areas of iBAT are found in the thorax region (supraclavicular), chest and abdomen^[3]. In humans and other large mammalian species, BAT was traditionally thought to be restricted to the neonatal and early childhood periods^[3,4]. However, positron emission tomography (PET)

Table 1 Differences amongst the three types of adipocytes

	Brown	White	Beige (Brown-like)
Location	Interscapular, perirenal, axillary, paravertebral	Inguinal (sWAT), mesenteric, retroperitoneal, perigonadal, omental (vWAT)	Within inguinal WAT, other sWAT?
Morphology	Multilocular/small lipid droplets	Unilocular/large lipid droplets	Unilocular large/multiple small lipid droplets
Function	Heat production	Storage of energy as triglycerides	Adaptive thermogenesis
Mitochondria	(+++)	(+)	Upon stimulation (++)
Iron content	Abundant	Low	Upon stimulation (Abundant)
Correlation with insulin resistance	Negative	Positive	Negative
UCP1	(+++)	Nearly undetectable	Upon stimulation (++)
Vascularization/ Capillaries	Abundant	Low	Cold stimulation led to increase of angiogenesis in sWAT ^[66]
α -, β -Adrenergic receptors	β 3 (+++)	β 3 (++), α 2 (+)	β 3/ α 2?
Obesity	Negative effect	Positive effect	Negative effect
Enriched markers	UCP1, Eva1, Pdk4, Ebf3, Hspb7 ^[2,9]	Ang, Resistin ^[13] , LPL, G3PDH ^[14]	Tmem26, Tbx1 ^[2] , Cited1 ^[9] , Shox2 ^[67]
Activators	Cold, thyroid hormone, thiazolidinediones, FGF21, Bmp7, Bmp8b, natriuretic peptide	HFD	Cold, thiazolidinediones, natriuretic peptide, FGF21, irisin, catecholamines, β -adrenergic receptor agonists

WAT: White adipose tissue; vWAT: Visceral WAT; sWAT: Subcutaneous WAT; UCP1: Uncoupling protein 1; FGF21: Fibroblast growth factor-21; HFD: High fat diet.

scanning technology was recently adapted for detecting metabolically active sites for oncology diagnosis; this application is based on the uptake of radiolabeled non-metabolizable glucose derivatives. The results obtained from a scanning experiment using PET to analyze BAT clearly demonstrated that active BAT is present in adult humans at discrete anatomical sites, especially in the upper trunk, such as cervical, supraclavicular, paravertebral, pericardial, and to some extent, mediastinal and mesenteric areas^[5-8] (Figure 1B).

Recently, a new type of brown-like adipocyte was discovered that shows distinct gene expression patterns from those of white or brown adipocytes. These novel brown-like cells that reside within WAT, especially inguinal WAT, were termed beige/brite adipocytes or inducible brown adipocytes^[2]. Adult human neck fat depots are composed of classical BAT, and these depots have the molecular features of classical BAT. However, unexpectedly and interestingly, some studies analyzed the gene expressed in the BAT areas of neonate and adult humans and found beige/brite cell-selective genes^[9]. In contrast, Cypess *et al.*^[10] identified and more precisely analyzed the anatomical sites of adult human BAT around neck fat depots. The researchers isolated samples of neck fat from superficial and deep depots and then compared the gene expression patterns. The results showed that human superficial neck fat had an expression pattern similar to that of mouse sWAT; however, the expression pattern from human deep neck fat was more similar to that of mouse iBAT. Overall, these reports indicate that more extensive analysis is necessary in human BAT studies. Finding beige/brite cells, which were once roughly classified as BAT, requires us to now further distinguish BAT as either classical BAT or beige/brite adipose tissue. It is highly

probable that the tissue that was previously assumed to be BAT in some of the above mentioned studies may in fact be beige/brite adipose tissue.

FEATURES AND FUNCTIONS OF ADIPOCYTES

Traditionally, two different types of adipose tissues, WAT and BAT, have been identified in human and other mammals. These adipose tissues have different colors, morphology, metabolic functions, biochemical features, and gene expression patterns. WAT is the main storage organ of energy in the form of lipids for the organism, whereas BAT plays a role in regulating body temperature by generating heat *via* the consumption of stored energy.

WAT generally constitutes as much as 20% of the body weight of normal adult humans. The development of WAT begins *in utero* but primarily occurs after birth when specialized fat storage cells are needed to provide fuel during fasting periods. WAT is normally characterized by an ivory or yellowish color as well as unilocular/large lipid droplets. The primary function of WAT is to store excess energy as TGs to regulate energy homeostasis. Although the expression of uncoupling protein 1 (UCP1), which is known to be a unique selective marker of BAT^[11], is nearly undetectable, the isoform UCP2 has been reported to be expressed in parts of WAT^[12]. Furthermore, some genes, such as those for Adiponectin, Resistin^[13], LPL, and G3PDH^[14], are known selective markers of WAT (Table 1).

Mitochondria play an essential role in adipose tissue because mature adipocytes require a large amount of ATP to maintain processes such as lipolysis, β -oxidation of fatty acids, and fatty acid synthesis. Mature brown

adipocytes have a relatively high mitochondrial content and contain a specialized mitochondrial protein called UCP1^[15]. Lipolysis occurs during cold exposure, which activates sympathetic nervous system signaling in brown adipocytes; the resulting free fatty acids are used to generate heat using the UCP1 protein. Therefore, in comparison to white adipocytes, brown adipocytes have significantly higher levels of mitochondria that contain red-brownish iron and consequently appear brown in color. They also contain many multilocular/small lipid droplets. As mentioned above, the main function of BAT is to regulate the non-shivering thermogenesis that dissipates energy as heat in response to cold exposure^[16-18]. The thermogenic process of brown adipocytes is activated by UCP1, also known as thermogenin, in their mitochondria. The UCP1 expressed in the inner membrane of mitochondria is mainly regulated by adrenergic signaling through sympathetic innervations, and this signaling is responsible for the production of heat *via* the respiratory uncoupling reaction. UCP1 causes a proton leak across the inner membrane of mitochondria, thereby converting chemical energy into the heat. UCP1 is responsible for the main function of BAT and is a representative marker of brown adipocytes^[15,18]. Additionally, BAT is highly vascularized and innervated, which likely allows BAT to respond to sympathetic nerve activity and dissipate the generated heat throughout the body through blood vessels. In addition to UCP1, *Eva1*, *Pdk4*, *Ebf3*, and *Hspb7* have also been reported to be BAT-specific markers^[3,4] (Table 1).

Previous evidences have supported the idea that white and brown adipocytes coexist within the same depot, which suggests that white adipocytes transdifferentiate into brown adipocytes *via* several factors that normally regulate BAT development or activity^[19-21]. However, a new type of brown-like adipocyte within WAT called beige/brite cells was recently discovered, and this transdifferentiation process is referred to as the “browning” or “briteening” of WAT. Researchers have also reported the differential expression of several genes that can be used to distinguish beige/brite adipocytes from brown adipocytes. These genes encode proteins with very distinct cellular functions, including transcription factors (*e.g.*, *Tbx15*), metabolism-related proteins (*e.g.*, *Slc27a1*), and proteins associated with inflammatory pathways (*e.g.*, *CD40* and *CD137*)^[2,9,22]. Interestingly, beige/brite adipocytes have the characteristics of both white and brown adipocytes. They display unilocular/large lipid morphology as well as gene expression patterns similar to those of white adipocytes during basal states. However, upon cold stimulation, beige/brite adipocytes change into an “intermediate cell morphology” in which multilocular lipid droplets surround large ones; this change ultimately results in UCP1 expression and a transformation into the multilocular/small lipid morphology characteristic of brown adipocytes^[2,9,22]. Moreover, the inducible browning processes are reversible reactions. In other words, when mice were rewarmed at room temperature after

cold stimulation, the former beige/brite adipocytes reconverted into white adipocytes with decreased expression of brown-selective marker genes approximately 6 wk after the warm adaptation^[23]. This result suggests that browning and whitening are reversible processes and depend on environmental conditions.

It is unclear whether the beige/brite fat cells arise through the transdifferentiation of pre-existing white adipocytes or by *de novo* adipogenesis from a subgroup of precursor cells. Previously, several reports suggested that beige/brite adipocytes arise from pre-existing white adipocytes. Himms-Hagen *et al.*^[19] observed that mature adipocytes transform into beige/brite adipocytes without dividing, and Cinti^[24] showed that large unilocular white adipocytes convert into beige/brite adipocytes in response to cold or 3-adrenergic agonists. However, new research has recently shown conflicting results. During the writing of this paper, Wang *et al.*^[25] suggested that most beige/brite adipocytes stem from a subgroup of precursors in WAT. In that study, the researchers developed a system for inducible, permanent labeling of mature adipocytes. Although cold induced the formation of beige/brite adipocytes, the researchers observed large areas of beige/brite fat cells with multiple small lipid droplets that were not labeled in the subcutaneous white fat.

DIFFERENTIATION OF ADIPOCYTES

BAT develops and differentiates before birth because its function is to protect a newborn against cold. In contrast, the formation of WAT commences shortly after birth. Mesenchymal stem cells (MSCs), which are multipotent stem cells, become adipoblasts and subsequently differentiate into preadipocytes. Under certain types of stimulation, preadipocytes are converted into mature adipocytes in the final phase of differentiation^[26].

The initial phase of adipogenesis is characterized by the proliferation of preadipocytes. Preadipocytes progress through multiple rounds of mitosis until they reach growth arrest, the G₁ phase of the cell cycle. At this point, the preadipocytes must re-enter the cell cycle, undergo mitotic clonal expansion until they eventually exit the cell cycle, acquire the metabolic features of mature adipocytes, change their morphology, and accumulate cytoplasmic TGs^[27]. Mature adipocytes are believed to have lost the ability to divide following the completion of terminal differentiation^[28]. Thus, inducing differentiation in cells isolated from the stromal vascular fraction of adipose tissue depots requires the specific contents of a “differentiation cocktail”. The differentiation induction cocktail contains fetal bovine serum, insulin, dexamethasone (a glucocorticoid), and 3-isobutyl-1-methylxanthine (IBMX). Insulin is an adipogenesis-inducing hormone that promotes cell cycle reentry and synchronous cell division (mitotic clonal expansion). This process is dependent on the induction of two members of CCAAT/enhancer-binding protein (C/EBP) family: C/EBP-β

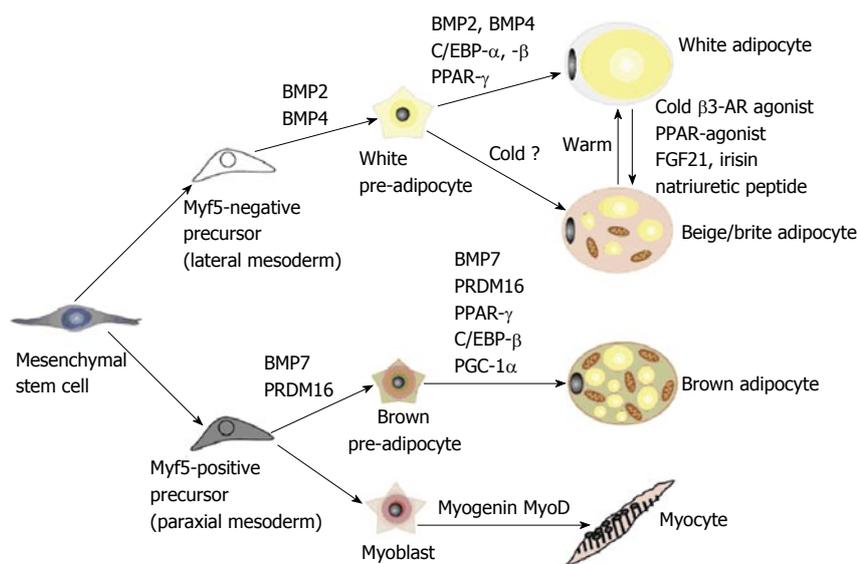


Figure 2 Differentiation into white, beige or brown adipocytes. Previously, white and brown adipocytes were thought to be derived from the same precursor cell. However, recent studies demonstrated that brown fat shares a progenitor cell (Myf5+) with skeletal muscle and not with white adipocytes. The Myf5+ precursors are induced to transform into mature brown adipocytes by bone morphogenetic protein 7 (BMP7), peroxisome proliferator-activated receptor- γ (PPAR- γ) and CCAAT/enhancer-binding proteins (C/EBPs) in cooperation with the transcriptional co-regulator PR domain-containing 16 (PRDM16) and PGC-1 α . White adipocytes can also be transformed to brown-like adipocytes, called beige/brite adipocytes, by cold exposure, a β -adrenergic agonist or a PPAR- γ agonist. AR: adrenergic receptor; FGF21: Fibroblast growth factor 21; PGC-1 α : Peroxisome proliferator activated receptor gamma coactivator 1 alpha.

and C/EBP- δ . Dexamethasone treatment is important for inducing differentiation because it activates the transcription factor C/EBP- β . IBMX is a phosphodiesterase inhibitor that increases intracellular cyclic AMP (cAMP) levels, leading to the activation of the transcription factor C/EBP- δ .

Both white and brown adipocytes originate from the mesoderm, but they are believed to be derived from different precursor cells (Figure 2). MSCs can be committed to either an adipogenic lineage of Myf5-negative cells or a myogenic lineage of Myf5-positive cells^[29,30]. Myf5 is known to be a key myogenic regulatory factor. White adipocytes are derived from the adipogenic lineage, whereas brown adipocytes are derived from the myogenic lineage. Although the adipocytes originate from different lineages, the subsequent adipogenic differentiation shares common transcriptional cascades that mainly involve peroxisome proliferator-activated receptor- γ (PPAR- γ), the dominant regulator of fat cell development, and C/EBPs^[26,28].

Differentiation into white adipocytes from progenitor cells

C/EBP family members are important for adipocyte differentiation, whereby the early induction of C/EBP- β and C/EBP- δ leads to the induction of C/EBP- α and PPAR- γ . Immediately after the induction of differentiation, the cAMP response element binding protein becomes phosphorylated and then induces the expression of C/EBP- β ^[31]. In a relatively early stage of differentiation, mitogen-activated protein kinase and GSK3 β phosphorylate C/EBP- β , which induces the dimerization of two monomers of C/EBP- β , thereby creating a DNA-binding domain. The binding of C/EBP- β to DNA allows preadipocytes to re-enter the cell cycle, that is, C/EBP- β plays a role in mitotic clonal expansion. Furthermore, the functions of C/EBP- β and C/EBP- δ may be redundant^[32]. A knockout of C/EBP- β in mice has little effect on adipose tissue accumulation, whereas C/EBP- β and C/EBP- δ double-knockout mice show considerably

reduced adipose tissue accumulation. The binding of C/EBP- β to DNA leads to increased levels of C/EBP- α and PPAR- γ , which act together as transcriptional activators^[26,33]. C/EBP- α functions to maintain PPAR- γ expression. Upon expression, PPAR- γ and C/EBP- α exert positive feedback on each other, and this stage is regarded as a key step in acquiring the adipocyte phenotype in mature adipocytes. In addition, PPAR- γ is essential for regulating gene transcription to promote and maintain the differentiated state of adipocytes (*i.e.*, lipid metabolism, glucose metabolism, and insulin sensitivity). The dominant negative form of PPAR- γ leads to de-differentiation and the loss of lipid accumulation in differentiated 3T3-L1 cells^[34]. Furthermore, the absence of C/EBP- α in mice impairs the development of WAT, but interestingly, it has no effect on BAT. Thus, some researchers have speculated that the lack of C/EBP- α can be compensated for in brown fat development by C/EBP- β ^[35].

Differentiation of into brown adipocytes from progenitor cells

In contrast to white adipocytes, brown adipocytes originate from the myogenic lineage of Myf5-positive progenitor cells. The differentiation of brown preadipocytes into brown adipocytes is controlled by transforming growth factor- β family proteins, such as bone morphogenetic protein (BMP)-7^[36] and myostatin^[37]. However, Wnt signaling is known to suppress the differentiation of the preadipocytes into brown adipocytes^[38]. C/EBP- β and PR domain containing 16 (PRDM16) have been shown to act as key transcriptional factors in the differentiation of brown adipocytes^[32,39,40]. When PRDM16 was suppressed in brown precursor cells using an shRNA system, the cells differentiated into skeletal muscle cells. Additionally, the myoblasts that ectopically expressed PRDM16 were converted into brown fat cells^[40]. PRDM16, together with C/EBP- β , operates as a critical switch factor in determining the fate of BAT from the myogenic lineage^[41]. In the Myf5-positive myogenic lineage, the PRDM16 and C/

EBP- β transcriptional complex induces the expression of PPAR- γ and peroxisome proliferator activated receptor gamma coactivator 1 alpha (PGC-1 α), which subsequently induces the differentiation of brown adipocytes^[42]. In particular, PGC-1 α also cooperates with PPAR- γ and PPAR- α and regulates mitochondrial biogenesis and oxidative metabolism^[43,44]. In addition, C/EBP- β has been reported to be a key transcriptional activator of UCP1 expression and the thermogenesis process^[32,41]. Interestingly, overexpression of C/EBP- β alone induces a brown fat cell-like phenotype in white adipocytes^[45].

Formation of beige/brite adipocytes (Browning)

After the completion of adipocyte differentiation, some differential processes are sometimes still observed. Interestingly, white adipose depots have the ability to switch between energy storage and expenditure. Thus, these depots can shift from a WAT phenotype to a BAT-like phenotype in terms of features such as morphology, gene expression pattern, and mitochondrial respiratory activity under some specific stimuli^[46]. As mentioned above, this induction of the brown adipocyte-like phenotype in WAT is called “browning” and the beige/brite cells of WAT are capable of this transformation. The beige/brite cells in WAT are derived from precursor cells that are different from classical brown adipocytes and are closer to the white adipocyte cell lineage^[47]. These beige/brite cells show a white adipocyte-like phenotype, including large lipid droplets and the lack of UCP1 expression, under basal conditions. However, in response to certain stimuli (cold exposure^[21] or β 3-adrenergic activators^[19]), beige/brite cells transform into cells having BAT-like characteristics, such as multilocular/small lipid droplets and UCP1 expression.

Recently, in an *in vivo* lineage-tracing study using transgenic mice^[23], brown and beige adipocytes were either transiently or permanently labeled, thereby allowing the tracing of current and past UCP1-expressing cells. After the first cold stimulation, the beige/brite adipocytes expressed both the permanent and transient labels in inguinal WAT. Additionally, when returned to warm conditions, the former beige/brite adipocytes were permanently retained but lost the transient label. The second round of cold stimulation resulted in the re-browning of the whitened former beige/brite adipocytes, as well as the formation of new beige/brite adipocytes within inguinal white fat depots. This experiment strongly suggests that inter-conversion between white and beige/brite adipocytes is possible. Considering these results, we speculate that beige/brite cells can regulate the adaptive thermogenesis against cold in sWAT because the primary function of BAT is non-shivering thermogenesis. In general, classical BAT protects an organism from decreasing temperatures during the neonatal period when the organism is not yet sufficiently capable of adapting to a change in environment; in adults, classical BAT is still present and increases energy expenditure in response to cold or an excess energy state. We think that the classical BAT has

already been set up to control energy homeostasis and is thus a fixed mechanism. Meanwhile, beige/brite cells provide a more flexible means to regulate body temperature and energy balance.

Several factors that can lead to WAT browning have been reported. One of strong inducer of beige/brite cells is cold exposure. Chronic cold exposure induces remarkable changes in metabolism as well as gene expression. In addition, it stimulates the differentiation of precursors into beige/brite adipocytes within one week of exposure^[23]. Although recent report assumed that a cool temperature (27-33 °C, *in vitro* cells) can directly activate the thermogenic gene process in a cell-autonomous manner in sWAT but not in classical BAT, the detailed mechanism is not yet clear. Traditionally, it has been accepted that thermogenic activity is regulated by a canonical β -adrenergic receptor pathway *via* the sympathetic nervous system. Catecholamines, such as norepinephrine, activate β -adrenergic receptor (there are three subtypes, 1, 2, and 3, in humans, but mainly 3 and 1 are involved) that are coupled to a G-protein and increase the intracellular cAMP level. In a subsequent process, this signal leads to fatty acid mobilization and induces the UCP1 expression in mitochondria related to non-shivering thermogenesis. Thus, catecholamines or β -adrenergic receptor agonists mimic the majority of thermogenic effects, as demonstrated using CL316243^[48-51]. Other agents, such as the PPAR- γ activator thiazolidinediones, can also promote WAT browning^[52]. In addition, multiple novel nonadrenergic soluble molecules that are capable of inducing BAT activity and WAT browning have been identified^[53]. Although some of these molecules act indirectly by modulating sympathetic activation and the subsequent noradrenergic pathways, several agents [*e.g.*, fibroblast growth factor-21 (FGF21) and the cardiac peptides (ANP/BNP)] appear to have direct effects on brown adipocytes and the browning process^[54-56]. Recently, the Spiegelman group identified irisin^[57], a novel hormonal factor that converts white fat into the more thermogenic beige fat. Irisin is secreted and released from muscle during exercise and appears to affect the browning process in WAT but not classical BAT activation (Figure 3). Other stimuli are able to enhance the recruitment of beige cells; these stimuli include prostaglandins, which are locally generated by cyclooxygenase-2-mediated production, Bmp8b, the transcription factor FOXC2, and cyclic guanosine monophosphate^[24,58-60]. A recent study suggested that the overexpression of BMP-4 promotes the browning of WAT^[61].

THERAPEUTIC POTENTIAL

sWAT and BAT have intrinsic beneficial metabolic properties, whereas vWAT is the main cause of insulin resistance and type II diabetes mellitus. Obesity and its related metabolic diseases are worldwide challenges. Many strategies to address the problems have been attempted, but there are still no clear solutions. Recently, however, the rediscovery of BAT in human adults led to many

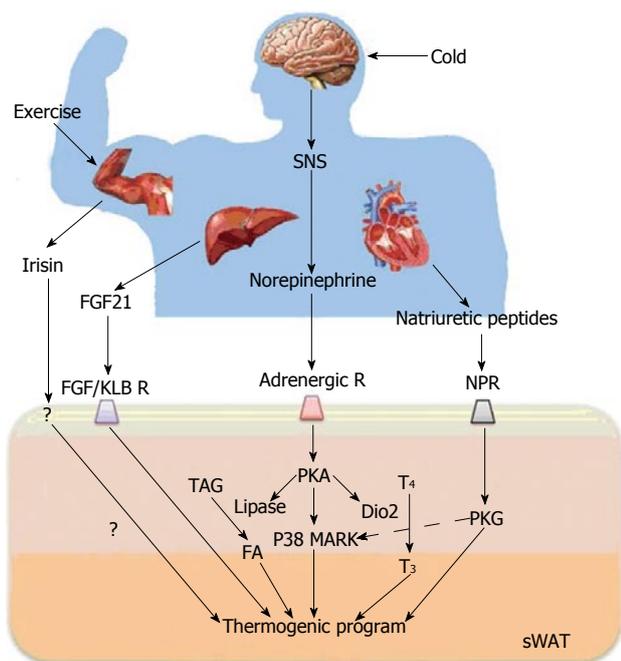


Figure 3 Key regulators of the browning process and their action mechanisms. Browning is induced by sympathetic nervous system (SNS)-independent or SNS-dependent signals. These signals sometimes synergistically or competitively influence the activation of browning of subcutaneous white adipose tissue (sWAT). Irisin is a newly discovered myokine and is released by skeletal muscle during exercise. Irisin induces the browning process of sWAT. Fibroblast growth factor-21 (FGF21), a hormonal factor from the liver, directly activates the thermogenic process via interaction with the FGF receptor/ β -Klotho (KLB) complex. The norepinephrine secreted by the SNS in response to thermogenic stimuli induces the activation of adrenergic receptor(s). The adrenergic receptor-mediated signal increases the level of intracellular cAMP and activates cAMP-dependent protein kinase A (PKA). Subsequently, PKA activates p38 MAP kinase (p38 MAPK) and 5'-deiodinase 2 (Dio2), which catalyzes the conversion of thyroxine (T4) into the active form 3,5,3'-tri-iodothyronine (T3). Then, it ultimately induces the gene process for thermogenic activation. Natriuretic peptides (NPs) originating from the heart activate the thermogenic process through binding to the NP receptor, activation of protein kinase G (PKG) and the subsequent activation of p38 MAPK and NPR. NPR: Natriuretic peptides receptor; TAG: Triacylglycerol; FA: Fatty acid.

investigations of BAT for anti-obesity treatments. Some of the experimental evidence suggests that BAT could be a new therapeutic tool as well as a precise regulator of energy homeostasis. People who have adapted to cold environments show some resistance to the development of diabetes, possibly due to the maintenance of a larger amount of BAT^[62]. In addition, the extent of human BAT activity in patients is inversely associated with obesity, age and type II diabetes^[63]. In mouse experiments, the mouse strains with higher thermogenic gene expression in WAT depots tended to be more resistant to obesity and insulin resistance than those with lower levels^[64]. Based on these results, many molecules (such as irisin^[57], FGF21^[55], and natriuretic peptides^[56]) that induce BAT activation or WAT browning have been studied as potential drugs. Of course, these molecules also create side effects; nevertheless, these molecules may be an important key to address many challenges if the side effects can be mitigated.

CONCLUSION

WAT is an important endocrine organ that maintains body homeostasis by storing excess energy and secreting hormones. However, the excessive accumulation of fat in the organ causes obesity and obesity-associated metabolic disorders. Thus, developing treatments for obesity is important for maintaining public health. Interestingly, a potential solution to the problem of obesity-associated diseases has been found in brown fat, a type of adipose tissue that dissipates energy through a thermogenesis process. Previous studies showed that activated BAT is inversely correlated with BMI^[65], adipose tissue mass and insulin resistance. Thus, BAT is one of the best targets for creating strategies to treat obesity and obesity-associated diseases. However, the transdifferentiation of white adipocytes into brown adipocytes is difficult because each type of adipose tissue is derived from a different progenitor lineage. The recent discovery of beige/brite adipocytes within WAT that are derived from the same lineage provides the possibility to overcome this challenge. Moreover, beige/brite cells are distributed throughout the human body, and they are highly activated in response to a variety of factors, including endogenous hormones. Therefore, WAT browning as well as BAT activation may contribute to an important strategy for treating obesity. A deeper understanding of the biological mechanisms that regulate the conversion within adipocytes will help in developing browning-inducing strategies for suppressing obesity.

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