

Adipose tissue in control of metabolism

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Abstract

Adipose tissue plays a central role in regulating whole-body energy and glucose homeostasis through its subtle functions at both organ and systemic levels. On one hand, adipose tissue stores energy in the form of lipid and controls the lipid mobilization and distribution in the body. On the other hand, adipose tissue acts as an endocrine organ and produces numerous bioactive factors such as adipokines that communicate with other organs and modulate a range of metabolic pathways. Moreover, brown and beige adipose tissue burn lipid by dissipating energy in the form of heat to maintain eutheria, and have been considered as a new way to counteract obesity. Therefore, adipose tissue dysfunction plays a prominent role in the development of obesity and its related disorders such as insulin resistance, cardiovascular disease, diabetes, depression and cancer. In this review, we will summarize the recent findings of adipose tissue in the control of metabolism, focusing on its endocrine and thermogenic function.

Key Words

- ▶ adipocytes
- ▶ adipose tissue
- ▶ adipogenesis
- ▶ adipokines
- ▶ thermogenesis

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Introduction

Adipose tissue, which is primarily composed of adipocytes as well as pre-adipocytes, macrophages, endothelial cells, fibroblasts, and leucocytes, has been increasingly recognized as a major player of systemically metabolic regulation. As the fuel reservoir, adipose tissue conserves the heat of the body and controls the lipid mobilization (Sethi & Vidal-Puig 2007). The surplus energy is efficiently deposited in the form of neutral triglycerides (TGs) in adipose tissue through the lipogenic pathway. However, the storage of neutral TGs in adipocytes increases the lipid droplet size, which results in adipose expansion and subsequent obesity (Tan & Vidal-Puig 2008). By contrast, TGs reserved in adipocytes are broken down into glycerol and fatty acids through lipolytic pathway when food is

scarce, energy expenditure requirements are stimulated or the storage of neutral TGs exceeds the capacity of adipocytes (Lafontan & Langin 2009). The released glycerol and fatty acids from adipose tissue can then be transported in the blood and subsequently infiltrate into muscle, liver and other organs, which drives lipid distribution and modulates whole-body energy balance (Frayn 2002).

Adipose tissue is not only a passive fuel reservoir, but also an endocrine organ. Extensive effort has been made to understand adipose tissue-derived factors and their physiological functions in the past two decades (Zhang *et al.* 1994, Friedman & Halaas 1998, Scherer 2006, Giralt *et al.* 2016). These bioactive factors secreted

from adipose tissue circulate and relay information to other metabolically active organs such as muscle, liver, pancreas and brain via endocrine mechanisms, thereby modulating systemic metabolism (Scherer 2006, Rosen & Spiegelman 2014, Parimisetty *et al.* 2016). Among these factors, adipokines-cytokines produced by adipose tissue including leptin, adiponectin, visfatin, apelin, vaspin, hepcidin, chemerin and omentin are implicated in obesity and obesity-related metabolic disorders (Lago *et al.* 2009, Andrade-Oliveira *et al.* 2015). Adipokine action is mainly mediated by binding to their respective receptors on the membrane of target cells and triggering particular intracellular signalling pathways. An enormous amount of evidence has demonstrated that impaired biosynthesis, assembly, secretion and signalling transduction of adipokines are associated with the development of obesity and its related disorders (Deng & Scherer 2010).

Adipose tissue can be classified into two subtypes: white adipose tissue (WAT) and brown adipose tissue (BAT). BAT, different from WAT which stores extra energy as TGs, dissipates chemical energy as heat via high levels of uncoupling protein 1 (UCP1) and combats hypothermia and obesity by burning lipid. Interestingly, it has been known for several years that there is another type of WAT called beige or brite (brown-like-in-white) fat, in which UCP1 expression can be stimulated by cold stress or β 3-adrenoceptor agonists that mimic cold stress (Barbatelli *et al.* 2010, Petrovic *et al.* 2010, Bostrom *et al.* 2012). Both brown and beige fat have thermogenic characteristics and offer a new way to battle obesity and other metabolic disorders (Ishibashi & Seale 2010, Harms & Seale 2013, Cohen *et al.* 2014). In this summary, we will focus on the endocrine and thermogenic function of adipose tissue and its potential therapeutic application for the treatment of obesity-associated metabolic diseases.

Characteristics of adipocytes

Adipocytes, also called adipose cells or fat cells, are the predominant cell type in adipose tissue. In mammals, there are three types of adipocytes: white, brown and beige (brite). They differ in origin, morphology, abundance of mitochondria and thermogenic genes expression. White adipocytes are mainly present in WAT with variable size (25–200 μ m) and have a unilocular lipid droplet, few mitochondria and a low oxidative rate (Jeanson *et al.* 2015). In line with this, white adipocytes have high capacity of storing energy in the form of TGs, and protect organs such as muscle and liver from lipotoxicity (Tan & Vidal-Puig 2008). Although white adipocytes arise

from resident cells of mesenchymal origin in white fat, subcutaneous adipocytes have distinct developmental origins and metabolic properties from visceral adipocytes in rodents and humans (Laviola *et al.* 2006, Ibrahim 2010, Berry *et al.* 2013, Chau *et al.* 2014). Visceral fat including mesenteric, gonadal, epicardial, retroperitoneal, omental and peri-renal fat pad is thought to be more deleterious, while subcutaneous WAT is protective in the development of obesity and related metabolic disease in rodents (Foster *et al.* 2011, Seale *et al.* 2011). In support of this, transplantation of subcutaneous but not visceral adipose tissue improves glucose tolerance and insulin sensitivity in rodents (Tran *et al.* 2008, Foster *et al.* 2013). Although there is still a controversy about metabolic function of subcutaneous and visceral fat in humans (Thorne *et al.* 2002, Fabbrini *et al.* 2010), the fat distribution, rather than total fat mass, most likely plays an important role in the development of obesity and its associated diseases. More studies are urgently needed to elucidate whether transplantation of subcutaneous fat in humans is as efficient as that in rodents.

Brown adipocytes were originally thought to be a skeletal muscle-like lineage arising from Myf5⁺ precursors (Seale *et al.* 2008, Lepper & Fan 2010). However, the complexity of adipocyte origin and identity has been considered recently. First, brown adipocytes are not only from Myf5⁺ precursors. Although interscapular and subscapular BAT are derived from Myf5⁺ lineage, cervical BAT are partially and peri-renal and peri-aortic BAT are completely from Myf5⁻ precursors (Sanchez-Gurmaches & Guertin 2014). In addition, Myf5⁺ precursors have been shown to be present in interscapular and retroperitoneal WAT and are capable of giving rise to some white/brite adipocytes (Sanchez-Gurmaches *et al.* 2012, Sanchez-Gurmaches *et al.* 2016). Brown adipocytes are specialized cells with multilocular morphology, abundant mitochondria and enrichment of UCP1, and dissipate stored energy in the form of heat (Aherne & Hull 1966, Cannon & Nedergaard 2004). UCP1 is located in the inner mitochondrial membrane and uncouple fuel oxidation from ATP synthesis (Fedorenko *et al.* 2012). Brown adipocyte clusters mainly exist in the interscapular and peri-renal regions of rodents and in abdominal sites, like peri-renal region of human infants, where they are richly innervated and vascularized (Blaza 1983, Bamshad *et al.* 1999, Bartness *et al.* 2010). The adult human BAT was recently identified in the lower neck and supraclavicular areas by 18F-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scanning (Nedergaard *et al.* 2007, Cypess *et al.* 2009, van Marken

Lichtenbelt *et al.* 2009, Virtanen *et al.* 2009, Zingaretti *et al.* 2009). However, the characteristics of newly identified brown fat in human adults is unclear. Wu and coworkers found that human brown fat has similar features as mouse beige adipocytes because it expresses beige marker CD137, TMEM26 and TBX1, and UCP1 is greatly induced by cAMP stimulation (Wu *et al.* 2012). Whereas another study from Jespersen and coworkers showed that in addition to beige markers, brown markers including miR-206, miR133b, LHX8 and ZIC1 are expressed in the supraclavicular BAT, suggesting the presence of both brown and beige adipocytes in adult humans (Jespersen *et al.* 2013). In addition, the validity of brown and beige markers has not been well documented. A recent study shows that only ZIC1 but not LHX8 proves to be the marker of brown fat as well as brown adipocytes (de Jong *et al.* 2015). Therefore, more studies are needed to define and characterize the human BAT, a potential therapeutic target for the treatment of obesity.

Beige adipocytes are a distinct type of brown-like thermogenic adipocytes with multilocular morphology and UCP1 positive expression, mainly arising from Myf5⁻ progenitor cells as white adipocytes (Wu *et al.* 2012). Beige adipocytes exist mainly in subcutaneous white fat and are found in a small portion in visceral fat as well. The recruitment and activation of beige adipocytes are markedly induced by cold stress or by a β 3-adrenoceptor agonist that mimics cold stress, a process known as browning or beiging of WAT (Young *et al.* 1984, Cousin *et al.* 1992, Harms & Seale 2013). However, it has also been postulated that beige adipocytes develop in adipose tissue through two distinct pathways. On one hand, beige adipocytes arise from Myf5⁻ adipocyte lineage through *de novo* generation in adipose tissue (Seale *et al.* 2008, Petrovic *et al.* 2010, Wu *et al.* 2012, Wang *et al.* 2013). In support of this, PDGFR α ⁺ adipocyte precursors as bipotential progenitor cells exist in fat. They are able to be differentiated into either beige or white adipocytes, and the commitment of adipocyte progenitors to beige adipocytes precursors is promoted by interleukin 4 receptor α (IL4R α) signalling (Lee *et al.* 2012, Wang *et al.* 2014, Lee *et al.* 2015a). Alternatively, Sca1⁺ progenitor cells (a subpopulation of adipogenic progenitors) can be induced and differentiated into brown-like adipocytes with bone morphogenetic protein 7 (BMP7) stimulation in the skeletal muscle and subcutaneous white fat (Schulz *et al.* 2011). On the other hand, studies have shown that beige adipocytes can be derived from interconversion from white adipocytes or through transdifferentiation of matured white adipocytes in WAT (Himms-Hagen *et al.*

2000, Barbatelli *et al.* 2010, Rosenwald *et al.* 2013), given that PDGFR α ⁺ preadipocytes are not recruited and do not significantly contribute to cold-induced WAT browning (Lee *et al.* 2015b, Vishvanath *et al.* 2016). In addition, Lee and coworkers show that the newly observed UCP1 positive cells derived from adiponectin⁺ unilocular white adipocytes rather than PDGFR α ⁺ preadipocytes in inguinal WAT (Lee *et al.* 2015b). Taken together, beige adipocytes can be derived from beige progenitor lineage, transdifferentiated from mature white adipocytes, or differentiated from other origins. However, the molecular mechanisms underlying the commitment of beige progenitor lineage and transdifferentiation remain to be established.

Adipogenesis and its regulation

Adipogenesis is a cell process of differentiation from committed preadipocytes into mature adipocytes, and plays an important role in adipose development and systemic energy homeostasis (Lefterova & Lazar 2009, Ali *et al.* 2013). As a result, the transcriptional regulation of adipogenesis has been well studied. Peroxisome proliferator-activated receptor γ (PPAR γ), a member of nuclear-receptor superfamily, has been shown to act as the master regulator of adipogenesis (Rosen *et al.* 2000). Overexpressing PPAR γ is sufficient to induce adipocyte differentiation in fibroblasts, and deficiency of PPAR γ fails to promote adipogenic programmes and results in lipodystrophy (Tontonoz *et al.* 1994, Hegele *et al.* 2002, Koutnikova *et al.* 2003). Moreover, other factors or pathways including pro-adipogenic factors such as C/EBPs, and Krüppel-like factors (KLFs) and anti-adipogenic factors such as GATA transcription factors regulate adipogenesis via PPAR γ -dependent mechanisms (Rosen *et al.* 2000, Farmer 2006). Furthermore, PPAR γ is not only crucial for adipogenesis but is also required for the maintenance of differentiation (Rosen *et al.* 2000, Farmer 2006). In support of this, impairing PPAR γ function by overexpression of a dominant-negative form downregulates the expression of key genes in lipid metabolism and insulin signalling and decreases the cell size and lipid content in 3T3-L1 differentiated adipocytes (Tamura *et al.* 2002). In line with this, selective ablation of PPAR γ in mature white and brown adipocytes leads to adipocyte death, while having little effect on the preadipocyte differentiation (Imai *et al.* 2004). Therefore, PPAR γ has been considered as a therapeutic target for the treatment of obesity-related disorders. To this end, extensive effort has been placed on studying the regulation of PPAR γ expression and its

activity (Farmer 2005, Lee & Ge 2014). Thiazolidinediones (TZDs) as the synthetic full agonists of PPAR γ have been shown to improve insulin sensitivity and glucose control by activating PPAR γ . However, their use has been hampered because of severe side effects. Partial agonists have been identified as selective PPAR γ modulators with great promise for the treatment of type 2 diabetes (Higgins & Depaoli 2010, Taygerly *et al.* 2013, Kroker & Bruning 2015). INT131 (previously AMG131) acts as one of the selective PPAR γ modulators to partially activate transcriptional output, enhances insulin sensitivity with decreased side effects in preclinical models and has been tested in phase II clinic trial (Kintscher & Goebel 2009, Higgins & Depaoli 2010, Taygerly *et al.* 2013, DePaoli *et al.* 2014).

C/EBPs are a type of transcription factors homologous to CCAAT/enhancer-binding protein including C/EBP α , C/EBP β , C/EBP γ , C/EBP δ and CHOP (Rosen & Spiegelman 2000). C/EBPs are induced during adipogenesis and coordinate with PPAR γ to regulate adipocyte differentiation (El-Jack *et al.* 1999, Wu *et al.* 1999, Rosen *et al.* 2002, Zuo *et al.* 2006). The expression of C/EBP α is upregulated by PPAR γ , which in turn promotes PPAR γ transcription and substantially induces the expression of other adipogenic genes (Rosen *et al.* 2002, Lefterova *et al.* 2008, Cho *et al.* 2009). As a result, C/EBP α deficiency leads to WAT loss and impaired development of BAT, suggesting a critical role of C/EBP α in adipogenesis (Wang *et al.* 1995). Two other C/EBP family members C/EBP β and C/EBP δ also play important roles in regulating adipogenesis by activating the transcription of C/EBP α and PPAR γ , particularly in early state of adipocyte differentiation (Tanaka *et al.* 1997, Tang *et al.* 2004, Zhang *et al.* 2004).

PRDM16, a zinc-finger transcriptional co-regulator, has been shown to drive brown adipocyte differentiation and repress myogenesis (Seale *et al.* 2008, Kajimura *et al.* 2009). Unlike PPAR γ and C/EBPs, the key transcriptional factors of all types of adipocytes, PRDM16, functions as a key driver of brown adipocytes (Rosen & MacDougald 2006). PRDM16 selectively initiates the switch of myoblasts to brown adipocytes by forming a transcriptional complex with C/EBP β . PRDM16 concurrently suppresses white adipocyte-specific genes by forming complexes with C-terminal binding proteins CTBP1 and CTBP2 (Kajimura *et al.* 2009). On the other hand, CTBPs can be displaced through the recruitment of PPAR γ co-activators PGC1 α and PGC1 β , which leads to activation of brown fat-specific genes (Kajimura *et al.* 2008). Although both PRDM16 and PGC1 α are the main regulators of brown and beige

adipocytes, PGC1 α is required for the expression of mitochondrial biogenesis and thermogenic genes but not for differentiation genes, indicating that PGC1 α is essential for thermogenesis rather than adipogenesis (Uldry *et al.* 2006). Furthermore, adipogenesis is regulated by multiple other factors including positive regulators such as BMPs and early B-cell factor (O/E1), and negative regulators such as transforming growth factor β (TGF- β) and preadipocyte factor 1 (Pref1) (Choy & Derynck 2003, Wang *et al.* 2006, Jimenez *et al.* 2007, Margoni *et al.* 2012). In addition, recent studies have also shown that miRNAs and long noncoding RNA (lncRNA) play important roles in regulating adipogenesis (Park *et al.* 2015). However, the intracellular mechanisms underlying the role of these factors in regulating adipogenesis remain to be fully understood.

Adipose tissue as an energy storage organ

As an energy storage organ, adipose tissue stores TGs and releases fatty acids through lipogenesis and lipolysis, respectively. Systemically, feeding stimulates the lipogenic pathway and storage of TGs in the adipose tissue, while fasting induces the activation of lipolytic pathway and promotes the breakdown of TGs and release of fatty acids from adipose tissue. Lipogenesis is the process that encompasses *de novo* fatty acid synthesis from acetyl-coenzyme A (acetyl-CoA) and TG biosynthesis. Glucose provides its own metabolite acetyl-CoA as the substrate for *de novo* synthesis of fatty acids, induces the expression of acetyl-CoA carboxylase (ACC), the rate-limiting enzyme of lipogenesis and stimulates the release of pancreatic insulin which promotes lipogenesis (Fig. 1). As a result, insulin stimulates glucose uptake in the adipocytes, activates glycolytic and lipogenic enzymes, and stimulates the expression of lipogenic gene sterol regulatory element-binding protein 1 (SREBP1) that controls the expression of genes required for cholesterol, fatty acids, TG and phospholipid synthesis (Assimacopoulos-Jeannet *et al.* 1995, Ferre & Fofelle 2007). In addition to SREBP1, another transcriptional factor carbohydrate response element-binding protein (ChREBP) promotes *de novo* lipogenesis (DNL) gene expression and has been shown to modulate both lipid and glucose metabolism in adipose tissue and substantial whole-body insulin sensitivity (Herman *et al.* 2012, Eissing *et al.* 2013). However, under normal conditions, DNL is relatively low in WAT compared with liver and BAT in rodents and even lower in humans (Swierczynski *et al.* 2000, Letexier *et al.* 2003). The fatty acids used for TGs biosynthesis in adipocytes are

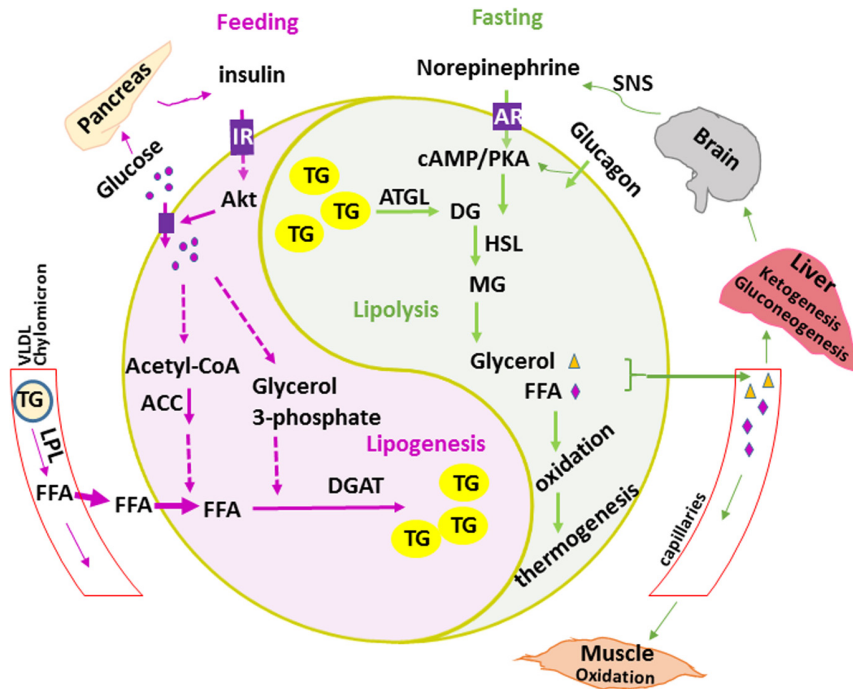


Figure 1

Lipid metabolism and mobilization controlled by adipose tissue. Lipogenesis is a process by which carbohydrate is converted into fatty acids, and promotes the biosynthesis of TG and expansion of lipid droplet in adipocytes. Lipolysis, in an opposite way, breaks down TG to free fatty acid (FFA) and glycerol that can be either oxidized or released. The uptake of circulating FFA by liver, muscle and other tissues is a main pathway of lipid mobilization. Both lipogenic and lipolytic pathways are sensitive to nutrition as well as hormones such as insulin, norepinephrine and glucagon. Thus, a subtle regulation of lipogenesis and lipolysis is required for systemic energy homeostasis and insulin sensitivity. AR, adrenergic receptor; cAMP, cyclic adenosine monophosphate; IR, insulin receptor; PKA, protein kinase A.

actually mainly from circulating, while glucose provides glycerol for esterifying fatty acids taken up from the circulating TGs in chylomicrons and very low-density lipoproteins (VLDL). Lipoprotein lipase (LPL), the key enzyme hydrolyzing one fatty acid from circulating TGs, plays a critical role in facilitating entry of fatty acids into adipocytes (Kersten 2014). LPL is secreted from adipocytes, translocates to the lumen of WAT capillaries and releases fatty acids from circulating TGs (Fielding & Frayn 1998, Frayn 2002) (Fig. 1). The regulation of LPL expression is modulated by multiple factors at the posttranslational level (Kersten 2014). Angiopoietin-like 4 (Angptl4) has been demonstrated to inhibit LPL activity by regulating its conformation and/or intracellular degradation during fasting (Sukonina *et al.* 2006, Dijk *et al.* 2016). During the sequential esterification processes of fatty acids, diacylglycerol acyltransferase (DGAT) catalyzes the final and critical step in the TGs synthesis pathway, and plays an important role in lipid deposition in adipocytes (Smith *et al.* 2000, Harris *et al.* 2011). Insulin, as a predominant stimulus, promotes fatty acid uptake and esterification through multiple mechanisms including activation of LPL, induction of translocation of fatty acid transport protein and upregulation of related gene expression in adipocytes (Raben & Hollenberg 1960, O'Brien & Granner 1996, Picard *et al.* 1999, Dimitriadis *et al.* 2011). In addition, growth hormone (GH) and acylation stimulating protein (ASP) produced by adipose tissue have an important influence on regulation of lipogenesis. GH

suppresses lipogenesis by regulating insulin sensitivity or Stat5 signalling (Teglund *et al.* 1998, Yin *et al.* 1998, Etherton 2000). ASP has been shown to increase TGs synthesis by activating DGAT and induce subcutaneous fat storage in females (Haagsman *et al.* 1982, Yasruel *et al.* 1991, Saleh *et al.* 2011). Taken together, adipose tissue as a fuel reservoir, plays a vital role in buffering fluxes of fatty acids, lipotoxicity and insulin resistance as well as regulating clearance of plasma TGs and keeping it from being deposited in other tissues (Frayn 2002). In other words, the storage capacity of lipid in adipose tissue is a determinant of systemic insulin resistance and lipid infiltration into other tissues such as liver and muscle.

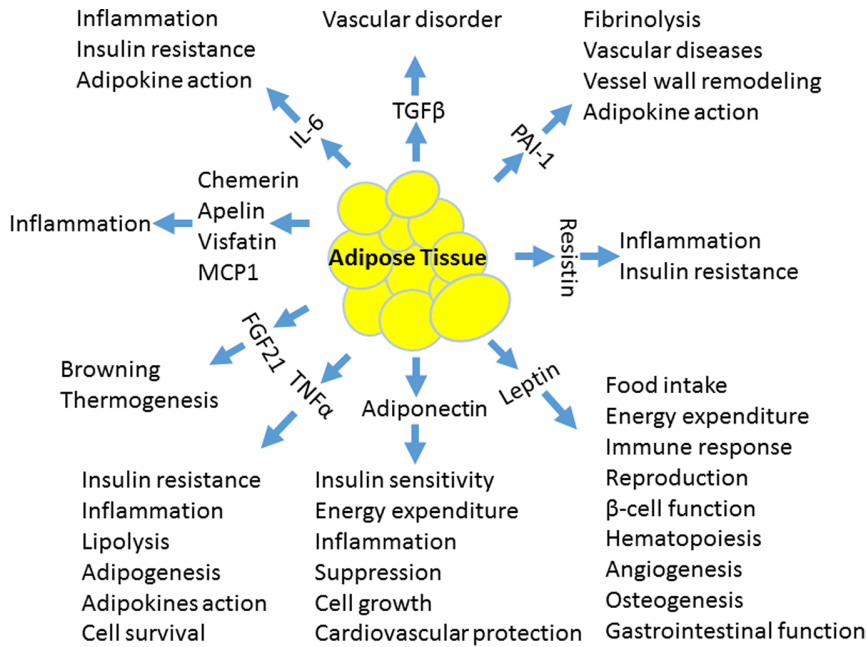
Opposite to lipogenesis, lipolysis is the catabolic process leading to the breakdown of TGs stored in adipocytes and subsequently the release of free fatty acids and glycerol (Zechner *et al.* 2005, Carmen & Victor 2006, Langin 2006) (Fig. 1). Lipolysis is induced by fasting and supplies glycerol for hepatic gluconeogenesis and free fatty acids for oxidation according to energy needs in other organs (Kuriyama *et al.* 2002). Importantly, glycerol but not fatty acids can be used as a substrate for gluconeogenesis in the liver. In the state of high fatty acid and diminished carbohydrate availability, fatty acids can be further broken down to produce a group of substances collectively known as ketone bodies providing for the brain, which is the process called ketogenesis in the liver. Several hormones have been shown to regulate

the lipolytic pathway. During fasting, decreased circulating levels of insulin result in suppression of lipogenesis as well as activation of the lipolytic pathway. Consistently, elevated circulating glucagon during fasting is also responsible for the activation of cAMP-dependent protein kinase A (PKA) pathway and lipolysis in adipocytes. Meanwhile, catecholamine released by sympathetic nervous system (SNS) is also stimulated by fasting, binds to β -adrenoceptor, then activates PKA and lipolytic pathways (Carmen & Victor 2006). Lipolysis consists of lipase-based breakdown of tri-, di- and monoacylglycerides (MGs) into individual fatty acids. Adipocyte triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) are the first two primary lipases for lipolysis and separately responsible for the conversion of TGs to diglycerides (DGs) and hydrolysis of DGs to MGs (Haemmerle *et al.* 2002, Zimmermann *et al.* 2004). Lipid droplet-associated proteins such as perilipin is polyphosphorylated by PKA and then translocates HSL to the lipid droplets for lipolysis (Marcinkiewicz *et al.* 2006, Brasaemle 2007, Lafontan & Langin 2009). Furthermore, recent studies also show that cell death-inducing DNA fragmentation factor 45-like effector family proteins (Cides), including Cidea, Cideb and Cidec (Fsp27) play critical roles in the control of lipid droplet morphology and have a distinct function in adipocytes and hepatocytes (Gong *et al.* 2009). In line with this, both Cidea and Cidec localize on the surface of lipid droplets, particular LD-LD contact sites, and promote atypical LD fusion and growth by lipid exchange and transfer in adipocytes (Gong *et al.* 2011, Wu *et al.* 2014, Barneda *et al.* 2015). Although some studies show that ATGL and HSL are responsible for basal lipolysis and PKA-stimulated lipolysis, respectively, in adipocytes, the physiological function of ATGL and HSL remains controversial (Birnbaum 2003, Langin & Arner 2006). It has been shown that global deficiency of ATGL leads to impaired lipolysis, mild obesity and cold intolerance (Haemmerle *et al.* 2006). Consistent with this, adipose-specific desnutrin/ATGL knockout mice display decreased lipolysis, thermogenesis and fatty acid oxidation despite increased fat mass and improved hepatic insulin sensitivity (Ahmadian *et al.* 2011). However, global HSL-deficient mice display slightly decreased TGs hydrolysis and increased BAT mass, while exhibiting similar WAT mass, body mass and cold tolerance, suggesting that the compensatory effects of other lipases may exist when HSL is lacking (Osuga *et al.* 2000). Given that adiposity-induced mobilization of fatty acids from adipose tissue to other organs is a main

cause of insulin resistance, inhibition of lipolysis has been considered for the treatment of insulin resistance (Guilherme *et al.* 2008). However, lipolysis is also closely linked to thermogenesis and energy expenditure by supplying fatty acids for β -oxidation (Haemmerle *et al.* 2006, Mottillo *et al.* 2012, Chondronikola *et al.* 2016). On the other hand, inhibiting adipose lipogenesis by fatty acid synthase deficiency promotes energy expenditure and protects from diet-induced obesity and insulin resistance (Lodhi *et al.* 2012). These findings suggest that the balance between lipogenesis and lipolysis is critical for maintaining systemic energy homeostasis and insulin sensitivity.

The endocrine function of adipose tissue

In addition to storing energy, adipose tissue exerts an extremely active endocrine function and produces a variety of factors which circulate and regulate systemic metabolism and inflammation (Maury & Brichard 2010, Fasshauer & Bluher 2015) (Fig. 2). Among these factors, adipokines are defined as those cytokines secreted by adipose tissue. Leptin was the first adipokine to be discovered in 1994 (Zhang *et al.* 1994), followed by the cloning of adiponectin in 1995 (Scherer *et al.* 1995). Many other adipokines including resistin, chemerin, apelin, visfatin, plasminogen activator inhibitor 1 (PAI1), monocyte chemoattractant protein 1 (MCP1), tumour necrosis factor alpha (TNF α) and interleukin 6 (IL6) were later discovered (Fasshauer & Bluher 2015). Leptin as well as adiponectin is the adipokine mainly secreted from adipocytes, known as adipocyte hormone, and plays an important role in regulating energy homeostasis (Bluher & Mantzoros 2015). Leptin is also produced or present in other non-adipose organs like stomach, muscle and intestine (Bado *et al.* 1998, Wang *et al.* 1998, Sobhani *et al.* 2000, Hansen *et al.* 2008). Although resistin was originally described as adipocyte-specific hormone linking obesity and insulin resistance, increasing evidence indicates that resistin is also expressed moderately in mononuclear leucocytes, macrophages and bone marrow cells in humans (Jamaluddin *et al.* 2012). Similar to resistin, chemerin was thought to be an adipocyte hormone and regulate adipocyte differentiation and lipolysis. However, it is also found in other cell types such as endothelial cells (Goralski *et al.* 2007, Mattern *et al.* 2014). Adipose-resident immune cells and endothelial cells are the main sources of other adipokines including apelin, visfatin, PAI1, MCP1, TNF α and IL6 (Loskutoff &

**Figure 2**

The physiological functions of adipokines. Adipokines, the cytokines derived from adipose tissue, act to regulate insulin sensitivity, inflammation, cardiovascular function, behaviour and cell growth, resulting in the development of obesity-induced metabolic diseases. ASP, acylating simulation protein; FGF21, fibroblast growth factor 21; IL6, interleukin 6; MCP1, monocyte chemoattractant protein 1; PAI1, plasminogen activator inhibitor 1; TNF α , tumour necrosis factor alpha.

Samad 1998, Weisberg *et al.* 2003, Boucher *et al.* 2005, Kanda *et al.* 2006, Saddi-Rosa *et al.* 2010). Dysregulated production or secretion of these adipokines causes adipose tissue dysfunction and is implicated in obesity-induced inflammation and insulin resistance.

Leptin

Leptin, a satiety hormone of 16-kDa peptide encoded by the obesity (*ob*) gene regulates energy balance by inhibiting hunger (Zhang *et al.* 1994, Halaas *et al.* 1995, Caro *et al.* 1996). The satiety effect of leptin is achieved by passing the blood–brain barrier and targeting the hypothalamus, a primary hunger centre regulating food intake and body weight to regulate adipose tissue mass by decreasing food intake and modulating glucose and fat metabolism (Zhang *et al.* 1994, Trayhurn *et al.* 1998, Dieguez *et al.* 2011, Morton & Schwartz 2011). In support of this, mice with deficiency of leptin expression (*ob/ob*) or receptor function (*db/db*) display increased food intake/hyperplasia, decreased energy expenditure and severe early onset obesity (Coleman 1978, Zhang *et al.* 1994, Lee *et al.* 1996). Along this line, administration of recombinant leptin in rodents suppresses food intake and promotes energy expenditure and weight loss, despite the fact that humans do not demonstrate the same dramatic results (Halaas *et al.* 1995, Pelleymounter *et al.* 1995, Heymsfield *et al.* 1999, Westerterp-Plantenga *et al.* 2001).

Leptin action in hypothalamus is mediated by leptin receptor and downstream signalling pathways including JAK2/STAT3 pathway (Sahu 2003). By binding to its receptors, leptin inhibits orexigenic neurons such as neuropeptide Y (NPY)/agouti-related protein (AgRP) neurons (Schwartz *et al.* 1996, Arvaniti *et al.* 2001). Moreover, leptin controls feeding by regulating multiple orexigenic neuropeptides including NPY, AgRP, melanin-concentrating hormone (MCH), galanin, orexin and galanin-like peptide (Schwartz *et al.* 1996, Sahu 1998, Lopez *et al.* 2000, Meister 2000, Arvaniti *et al.* 2001, Kumano *et al.* 2003). In addition, the satiety effect of leptin is also mediated by regulation of anorexigenic peptides such as POMC, cocaine- and amphetamine-regulated transcript, neurotensin, corticotropin-releasing hormone and brain-derived neurotrophic factor (BDNF) (Golden *et al.* 1997, Sahu 1998, Meister 2000, Liao *et al.* 2012). Although the central effect of leptin has been well studied, accumulating studies show that leptin also plays an important role in directly regulating the function of peripheral organs like reproductive organs (Moschos *et al.* 2002, Perez-Perez *et al.* 2015). Leptin targets pancreatic β -cell to modulate glucose homeostasis through producing effects on β -cell mass and insulin expression and secretion (Marroqui *et al.* 2012). Moreover, leptin regulates the immune response including both adaptive and innate immune cells that links to metabolic adaption (Naylor & Petri 2016). Furthermore, some studies show that leptin increases energy expenditure given that *ob/ob* mice display hypo-metabolic rate and decreased oxygen

consumption, and leptin administration increased energy expenditure when normalized to body weight (Trayhurn *et al.* 1977, Pelleymounter *et al.* 1995). However, some of later studies do not support this and argue that the hypometabolism in leptin-deficient mice is only the effect of normalization (Himms-Hagen 1997, Kaiyala *et al.* 2015, Fischer *et al.* 2016). When the energy expenditure is not normalized, leptin deficiency leads to increase of oxygen consumption and hyper-metabolism (Himms-Hagen 1997, Kaiyala *et al.* 2015). However, some groups found that leptin administration has little effect on the energy expenditure without normalization (Ukropec *et al.* 2006, Fischer *et al.* 2016). Moreover, other two studies show that leptin treatment has little effect on energy expenditure even when the data is normalized with body mass (Doring *et al.* 1998, Hogberg *et al.* 2006). This controversy needs to be further clarified.

As leptin inhibits appetite and promotes weight loss, it has been widely considered as a therapeutic target for the treatment of obesity and its associated disorders. The recombinant leptin has been developed and applied in clinical treatment. However, majority of obese patients exhibit leptin resistance. Thus, treatment with classical leptin may not be of therapeutic potential in the general population (Farooqi *et al.* 1999, Savage & O'Rahilly 2002, Chou & Perry 2013). Alternatively, the drugs improving leptin sensitivity offer a new way to treat obese patients. Amylin (pramlintide), a potential leptin sensitizer, has been shown to exert a weight-lowering effect together with leptin or leptin analog metreleptin. However, a recent clinical trial suggests that amylin administration causes multiple adverse effects such as antibody generation and skin reactions (Moon *et al.* 2013, Bluher 2014). Thus, the development of safe leptin analogs/sensitizers is urgently needed for leptin-based therapeutic purpose.

Adiponectin

Adiponectin, a member of the complement 1q family, is a 30-kDa adipokine and exerts multiple beneficial effects including an insulin sensitizing effect, cardiovascular protection and anti-inflammation (Tomas *et al.* 2002, Gil-Campos *et al.* 2004, Haluzik *et al.* 2004, Hoffstedt *et al.* 2004, Hui *et al.* 2012). The circulating levels of adiponectin are ~10–30 µg/mL or about 0.01% of plasma proteins and remarkably higher compared with other conventional hormones such as insulin and leptin (Pajvani *et al.* 2003). Adiponectin is present primarily in three species: a low-molecular-weight (LMW) trimer

of approximately 67 kDa, a hexamer of ~120 kDa and a high-molecular-weight (HMW) multimer of >300 kDa. The HMW adiponectin has been shown to possess the most potent insulin sensitizing activity (Tsao *et al.* 2002, Waki *et al.* 2003, Pajvani *et al.* 2004).

Circulating adiponectin is capable of targeting multiple tissues and regulating insulin sensitivity as well as energy homeostasis. Liver is a primary target tissue of adiponectin, and the action of adiponectin in liver contributes predominantly in its insulin sensitizing effect. It has been shown that adiponectin activates AMP-activated protein kinase (AMPK) and reduces the expression of gluconeogenic enzymes such as phosphoenolpyruvate carboxylase and glucose-6-phosphatase, leading to the suppression of gluconeogenesis (Combs *et al.* 2004, Nawrocki *et al.* 2006). In addition, adiponectin is able to enhance the ceramidase activity and suppress hepatic ceramide content by which it improves hepatic and whole-body insulin sensitivity independent of AMPK (Holland *et al.* 2011). Moreover, adiponectin also exerts its insulin sensitizing effects through modulating the biological actions of growth factors such as platelet-derived growth factor, fibroblast growth factor (FGF) and heparin-binding epidermal growth factor-like growth factor (HB EGF) (Wang *et al.* 2005). In addition to targeting liver, the globular form of adiponectin (gAd) has been shown to activate the AMPK pathway in skeletal muscle, leading to increased phosphorylation of ACC, fatty acid oxidation and glucose uptake (Tomas *et al.* 2002, Yamauchi *et al.* 2002). Besides insulin sensitizing, another functional role of adiponectin is to regulate thermogenesis and energy homeostasis (Masaki *et al.* 2003, Qi *et al.* 2004, Kubota *et al.* 2007, Kajimura *et al.* 2013, Hui *et al.* 2015). However, it remains controversial whether adiponectin promotes or suppresses energy homeostasis and thermogenesis. The physiological function and underlying mechanisms of adiponectin in the regulation of energy expenditure need to be clarified in the future.

Adiponectin exerts multiple beneficial effects by binding to its receptors, adiponectin receptor 1 and receptor 2 (AdipoR1 and AdipoR2) (Yamauchi *et al.* 2003, Kadowaki *et al.* 2006, Yamauchi *et al.* 2007). In addition, T-cadherin, a cell surface-anchored glycoprotein, is effective in binding adiponectin and mediates adiponectin signalling, while it falls short of being a receptor that binds to both ligands and transduces intracellular signalling pathways (Denzel *et al.* 2010). There is accumulating evidence showing that adiponectin exhibits insulin sensitizing effect through multiple signalling pathways downstream of adiponectin receptors, such as AMPK, Ca²⁺, PPAR α , ceramide and S1P

(Yamauchi *et al.* 2007, Zhou *et al.* 2009, Iwabu *et al.* 2010, Holland *et al.* 2011). Moreover, as an AdipoR1 and AdipoR2 interactive protein, APPL1 (adaptor protein containing pleckstrin homology domain, phosphotyrosine-binding domain and leucine zipper motif) positively mediates adiponectin signalling and its insulin sensitizing effect in muscle cells (Mao *et al.* 2006, Zhou *et al.* 2009, Fang *et al.* 2010, Cleasby *et al.* 2011, Xin *et al.* 2011). AMPK pathway, downstream of adiponectin receptor signalling, is critical for adiponectin action in the liver, muscle and other organs (Yamauchi *et al.* 2002). However, adiponectin has later been found to suppress hepatic glucose production through an interleukin 6 (IL6)-dependent but AMPK-independent pathway (Awazawa *et al.* 2011, Miller *et al.* 2011). However, whether AMPK is dispensable for the glucose lowering effect of adiponectin in the liver remains to be fully understood.

Resistin

Resistin is a 12-kDa peptide and originally found to be secreted from adipocytes in mice (Savage *et al.* 2001, Stepan *et al.* 2001b). However, whether resistin is a human adipokine has been challenged for a while. Although McTernan *et al.* show that resistin is produced by both human preadipocytes and adipocytes (McTernan *et al.* 2002), Nagaev and coworkers find that the mRNA levels of resistin are relatively low in primary human adipocytes (Nagaev & Smith 2001). In addition, the following studies demonstrate that resistin is mainly produced by human monocytes and macrophages rather than by adipocytes (Patel *et al.* 2003, Curat *et al.* 2006). Resistin circulates in the form of hexamer and LMW complex, and hexamer is an active form (Patel *et al.* 2004). Circulating levels of resistin are significantly increased by obesity and implicated in obesity-induced insulin resistance and type 2 diabetes in rodents (Stepan *et al.* 2001a). Supportively, central administration of resistin induces whole-body insulin resistance by downregulation of adiponectin signalling and induction of fibroblast growth factor 21 (FGF21) resistance (Benomar *et al.* 2016). Furthermore, resistin treatment promotes the production of inflammatory cytokines such as TNF α and IL6 as well as adhesion molecule and chemokines such as ICAM1 and VCAM1 (Verma *et al.* 2003). However, the correlation between resistin and obesity remains controversial. In humans, some studies showed that the circulating levels of resistin are increased during ageing and are elevated in obese and diabetic individuals (Degawa-Yamauchi *et al.* 2003, Oliver *et al.* 2003, Gerber *et al.* 2005) while

others reported that the circulating levels of resistin are not correlated with obesity and insulin resistance (Lee *et al.* 2003, Filippidis *et al.* 2005, Hasegawa *et al.* 2005, Iqbal *et al.* 2005). Besides, several animal studies show that the mRNA levels of resistin in adipose tissue are downregulated in adipose tissue of obese animals, and are not associated with circulating levels of insulin or glucose (Le Lay *et al.* 2001, Milan *et al.* 2002, Lee *et al.* 2005). Thus, the physiological function of resistin needs to be further clarified in the future.

FGF21

Fibroblast growth factor 21 (FGF21) has been defined as a hepatokine, adipokine and myokine and exerts diverse biological functions in metabolism (Hotta *et al.* 2009, Fisher *et al.* 2012, Kim *et al.* 2013). As an adipokine, FGF21 is induced by cold exposure, and in turn promotes thermogenic gene expression in BAT and inguinal WAT (iWAT) (Hondares *et al.* 2010, Fisher *et al.* 2012, Adams *et al.* 2013, Emanuelli *et al.* 2014, Lee *et al.* 2014a). FGF receptor 1c and a coreceptor β -klotho have been suggested to mediate the action of FGF21 in BAT and iWAT (Itoh 2010, Foltz *et al.* 2012). Moreover, FGF21 induces browning effect and thermogenic gene expression by upregulating PGC1 α through paracrine and/or autocrine mechanisms (Hondares *et al.* 2011, 2014, Fisher *et al.* 2012, Lee *et al.* 2014b). However, it remains unknown whether FGF21 regulates metabolic pathways solely dependent on its action in adipose tissue. Some studies suggest that FGF21 action in WAT mediates its beneficial effect on metabolic parameters such as body weight, glucose homeostasis and plasma TGs (Wu *et al.* 2011, Veniant *et al.* 2012). Whereas another study shows that FGF21 requires neither UCP1 nor brite adipocytes to elicit weight loss and improve glucose homeostasis (Veniant *et al.* 2015). In addition, the circulating levels of FGF21 are upregulated in obese and type 2 diabetic patients, suggesting that this paradoxical increase of FGF21 may be a compensatory response or a result from FGF21 resistance (Chen *et al.* 2008, Zhang *et al.* 2008). Although FGF21 has drawn growing attention for its anti-obesogenic and antidiabetic actions, the mechanisms underlying FGF21 action need to be established (Emanuelli *et al.* 2014).

Thermogenic function of brown and beige adipose tissue

Brown and beige fat dissipate energy in the form of heat and offer a new way to battle obesity and its associated

disorders (Lowell & Spiegelman 2000, Cannon & Nedergaard 2004). Different from brown fat with relatively high thermogenic activity and enrichment of UCP1 under thermoneutral condition in rodents, the expression of UCP1 in beige fat is very low under this condition, which may be due to low number of beige adipocytes as well as low expression level of UCP1 in individual beige adipocytes (Wu *et al.* 2012). However, the UCP1 expression in beige fat is markedly induced upon cold exposure or treatment of agonists of the β 3-adrenoceptor or PPAR γ (Young *et al.* 1984, Cousin *et al.* 1992, Petrovic *et al.* 2010, Wu *et al.* 2012). Regardless of cold stimulation, the expression levels of UCP1 protein in beige fat are still relatively lower compared with brown fat where the UCP1 gene is also induced at certain extent (Nedergaard & Cannon 2013). Moreover, the mRNA and protein of UCP1 are differentially altered at some particular conditions, suggesting the importance of protein analysis of UCP1 as a thermogenic marker in the future studies (Nedergaard & Cannon 2013). On the other hand, the thermogenic activity and physical location of brown and beige fat vary in different species. It has been shown that the basal levels of UCP1 in human brown fat is not as enriched as that in rodents under thermoneutral conditions (Wu *et al.* 2012). Moreover, rodent brown and beige fat are physically apart from each other, while they are mixed in humans (Xue *et al.* 2005, Xue *et al.* 2007, Sharp *et al.* 2012, Cypess *et al.* 2013). The SNS plays a predominant role in cold-induced thermogenesis and browning of white fat by releasing norepinephrine (NE). Upon cold, feeding or stress exposure, NE is produced and released from sympathetic fibres innervated in adipose tissue to bind to β 3-adrenoceptor on the cell surface of adipocytes (Ueta *et al.* 2012). This binding results in activation of cAMP/protein kinase A (PKA) pathway which induces lipolysis and thermogenic genes expression and substantially activates brown and beige adipocytes (Cao *et al.* 2004b, Ye *et al.* 2013). In adult humans, BAT activation by prolonged cold exposure appears to increase lipid mobilization from other fat depots to BAT and promotes lipid burning through heat production in mitochondria (Chondronikola *et al.* 2016). Brown and beige fat not only maintains energy balance through non-shivering thermogenesis but also promotes glucose uptake and TGs clearance from the circulation (Bartelt *et al.* 2011). In line with this, ablation of UCP1 results in disruption of diet-induced thermogenesis and exacerbation of diet-induced obesity in mice exempt from thermal stress by living at thermoneutrality (Feldmann *et al.* 2009). Furthermore, the implantation of human

beige adipocyte acquired from beige progenitors into high-fat diet (HFD)-fed mice improves systemic glucose tolerance (Min *et al.* 2016).

The therapeutic potential of brown and beige fat for the treatment of obesity and diabetes

Accumulating data has shown that activation of brown and beige adipocytes protects against obesity and related metabolic diseases in rodents (Kopecky *et al.* 1995, Cederberg *et al.* 2001, Seale *et al.* 2011). Consistent with this, administration of β 3-adrenergic agonist, CL 316,243 that mimics cold stress induces WAT browning and improves obesity-induced metabolic dysregulation in rodents (Ghorbani & Himms-Hagen 1997, Guerra *et al.* 1998). Although BAT was primarily found in infants (Lidell *et al.* 2013), it was unknown whether adult humans possess brown fat until Dr Spiegelman, Kahn, Teule and Nuutila groups identified brown fat in adult humans with PET-CT in 2009 (Cypess *et al.* 2009, van Marken Lichtenbelt *et al.* 2009, Virtanen *et al.* 2009). Nowadays, the BAT has been shown to exist in humans at various ages (Gilsanz *et al.* 2013). The following studies show that BAT is inversely correlated with body mass index, decreased during ageing and induced upon cold stimulation (Cypess *et al.* 2009, Lee *et al.* 2010, Pfannenbergl *et al.* 2010, Jacene *et al.* 2011, Cypess *et al.* 2014). Unlike rodent beige adipocytes physically separated from brown adipocytes, adult human brown adipocytes are found together with beige and white adipocytes (Sharp *et al.* 2012, Wu *et al.* 2012, Lidell *et al.* 2013). Despite this, the activated human brown and beige adipocytes have a therapeutic potential against obesity and diabetes.

The inducible characteristics of human brown adipocytes under cold exposure make them the promising therapeutic targets for the treatment of obesity and type 2 diabetes. Cold training has been studied as a viable anti-obesity therapeutic. It has been shown that mild cold exposure is sufficient to increase human BAT activity and energy expenditure, and prolonged (5–8 h) cold exposure in BAT-positive individuals significantly increases resting energy expenditure, whole-body glucose metabolism and insulin sensitivity (Chen *et al.* 2013, Chondronikola *et al.* 2014). Moreover, BAT recruitment by repeated cold exposure or daily ingestion of capsinoids increases energy expenditure and decreases body fat mass in healthy individuals who have lower BAT activity originally compared with control subjects (Yoneshiro *et al.* 2013). These findings again suggest the potential role of human BAT in the prevention and treatment of obesity.

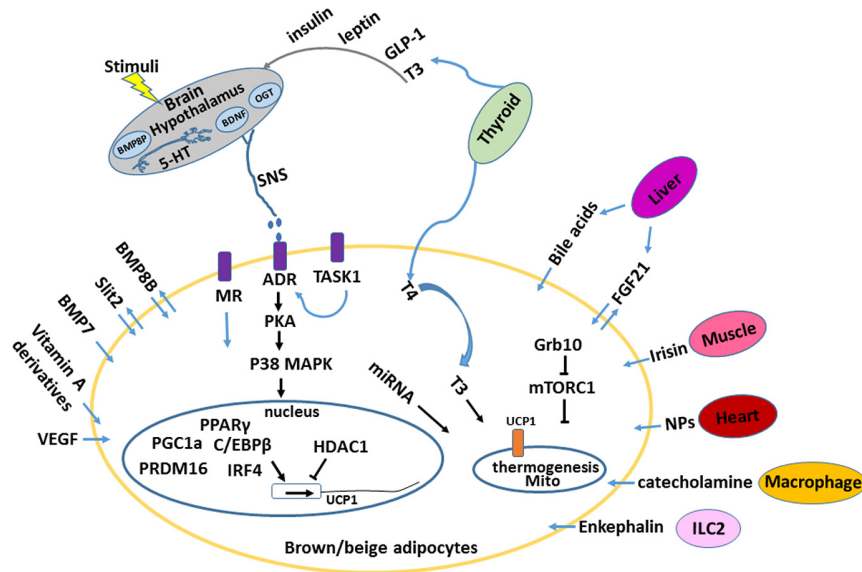
In addition, administration of β 3-adrenoceptor agonists also activates BAT and promotes energy expenditure both in humans and rodents despite low efficacy in humans compared with rodents (Cannon & Nedergaard 2004, Cypess *et al.* 2012, Carey *et al.* 2013, van der Lans *et al.* 2013). However, traditional β 3-adrenoceptor agonists such as CL316,243, L-796568 and TAK-677 were not approved for use in clinical trials due to multiple side effects including the increased heart rate (Arch 2011, Cypess *et al.* 2015). Mirabegron, a new class of β 3-adrenoceptor agonists approved for the treatment of overactive bladder, has been shown to promote human BAT thermogenesis with great therapeutic potential (Cypess *et al.* 2015). Recent studies have also shown that BAT transplantation corrects metabolic phenotypes, and improves type 1 diabetes in streptozotocin-treated mice as well as HFD-induced insulin resistance in mice (Gunawardana & Piston 2012, Stanford *et al.* 2013). Consistently, implantation of human beige adipocytes improves systemic glucose tolerance in HFD-induced glucose-intolerant mice (Min *et al.* 2016). Given that preadipocytes or stem cells are also able to be differentiated into mature brown or beige adipocytes, brown or beige adipocytes transplantation may offer a practicable means for the treatment of obesity and diabetes (Bayindir *et al.* 2015). Therefore, understanding the nature and expansion of human brown or beige adipocytes is urgently needed for BAT-based therapeutics in the future.

Regulation of non-shivering thermogenesis

Thermogenesis and browning of WAT are predominately controlled through SNS (Himms-Hagen *et al.* 1994, Murano *et al.* 2009, Richard *et al.* 2012, Bi & Li 2013) (Fig. 3). Central nervous system (CNS), especially hypothalamic neurons project to the SNS and drive sympathetic outflows to adipose tissue to modulate adaptive thermogenesis (Bamshad *et al.* 1999, Cano *et al.* 2003). Several specific hypothalamic areas or neural circuitries within the hypothalamus have been shown to exert thermoregulation through modulating the activity of SNS (Oldfield *et al.* 2002, Cao *et al.* 2004b, Contreras *et al.* 2015). In line with this, NPY/AgRP signalling derived from the arcuate nucleus (Arc) inhibits sympathetically innervated BAT thermogenesis through regulation of tyrosine hydroxylase neurons in the hypothalamic paraventricular nucleus (PVN), while alpha-melanocyte-stimulating hormone (α -MSH) from POMC neurons increases SNS activity and BAT thermogenesis (Yasuda *et al.* 2004, Shi *et al.* 2013). Furthermore, Ruan *et al.*

reported that O-GlcNAc transferase (OGT), a rate-limiting enzyme for O-linked β -N-acetylglucosamine (O-GlcNAc) modification of cytoplasmic and nuclear proteins, suppresses browning of WAT and thermogenesis by regulating neuronal excitability in AgRP neurons (Ruan *et al.* 2014). In addition to sympathetic neurons, serotonin (5-HT) neurons were recently reported to recruit and activate brown and beige adipocytes and subsequently regulate glucose and lipid homeostasis (McGlashon *et al.* 2015). These findings strongly suggest that CNS plays a critical role in sensing cold, feeding and stress and regulating adaptive thermogenesis through SNS. However, the adverse cardiovascular effects of SNS activation have raised a concern for its therapeutic purpose for the treatment of obesity and its associated diseases.

Given that UCP1 is the key marker for browning of WAT and thermogenesis, concerted effort has been focusing on the understanding of the transcriptional regulation of UCP1 expression in the past decade. Several transcriptional factors including PRDM16, PGC1 α , PPAR γ , C/EBP β and interferon regulator factor 4 (IRF4) have been discovered to promote UCP1 expression (Kelly *et al.* 1998, Barbera *et al.* 2001, Seale *et al.* 2007, Kajimura *et al.* 2009, Kong *et al.* 2014) (Fig. 3). PRDM16 drives the cell fate switching from skeletal myoblasts to brown adipocytes and initiates brown adipocyte differentiation by binding to PPAR γ and PGC1 α and β (Seale *et al.* 2008). Interestingly, PRDM16 is an important factor for thermogenic program, while it is dispensable for brown fat development (Seale *et al.* 2011, Harms *et al.* 2014). Kajimura and coworkers also showed that formation of PRDM16/C/EBP β complex is required for the activation of thermogenic program and induction of PPAR γ , PGC1 α and UCP1 expression (Kajimura *et al.* 2009). In support of this, gain- and loss-of-function studies have demonstrated a cell-autonomous and determinant role of PRDM16 in regulating thermogenic programming and the browning effect in subcutaneous adipose tissues, indicating the importance of PRDM16 in driving thermogenic programming (Seale *et al.* 2011, Cohen *et al.* 2014). On the other hand, PGC1 α is induced upon cold exposure and modulates the expression of thermogenic markers such as UCP1 (Kleiner *et al.* 2012). Consistent with this, PGC1 α is upregulated by FGF21 and mediates the prompting effect of FGF21 on browning of WAT (Fisher *et al.* 2012). Moreover, IRF4 as the key thermogenic transcriptional partner of PGC1 α promotes thermogenic genes expression and energy expenditure, suggesting the key role of PGC1 α in regulating thermogenesis and WAT browning (Kong *et al.* 2014). Furthermore, several other intracellular pathways including p38MAPK, mTORC1,

**Figure 3**

The regulation of adaptive thermogenesis. Thermogenic programme and browning of WAT are driven by SNS in response to cold, diet and stress. Several hormones such as insulin, leptin, BMP8B, GLP-1 and T3 control adaptive thermogenesis through regulating SNS. Moreover, several key transcription factors such as PRDM16, PGC1 α , PPAR γ , C/EBP β and IRF4 assemble to form the transitional machinery of UCP1 and promote UCP1 expression. In addition, adaptive thermogenesis has been shown to be regulated by multiple secreted factors including BMP8B, Slit2, BMP7, vitamin A derivatives, VEGF, T3, bile acids, FGF21, irisin, NPs, enkephalin and macrophages-derived catecholamine. In addition, HDAC1 and miRNAs as well as other intracellular pathways such as p38MAPK, mTORC1, Grb10, MR and TASK1 play important roles in regulating thermogenic program. Double arrow means secretion from adipocytes and in turn action on itself. ADR, adrenergic receptor; MR, mineralocorticoid receptor; NPs, natriuretic peptides; TASK1, Twik-related acid-sensitive K (+) channel; 5-HT, 5-hydroxytryptamine or serotonin neurons.

Grb10, mineralocorticoid receptor (MR), and K (+) channel TASK1 have been shown to modulate thermogenic gene expression, browning of WAT and/or lipolysis through β 3-adrenoceptor-dependent or independent mechanisms (Cao *et al.* 2004a, Bordicchia *et al.* 2012, Armani *et al.* 2014, Liu *et al.* 2014, Liu *et al.* 2016, Pisani *et al.* 2016) (Fig. 3). More studies are needed to further determine whether the modulation of WAT browning by these pathways is intrinsic or secondary effects.

In addition, several circulating factors such as insulin, leptin and GLP-1 have been identified to promote thermogenesis through targeting hypothalamus neurons and regulating activity of SNS (Shimizu *et al.* 1987, Rahmouni & Morgan 2007, Sanchez-Alavez *et al.* 2010, Harlan *et al.* 2011, Lockie *et al.* 2012, Beiroa *et al.* 2014, Dodd *et al.* 2015) (Fig. 3). Furthermore, central-derived factors also play important roles in regulating SNS activity and thermogenesis (Fig. 3). Hypothalamic BDNF enhances thermogenesis and energy expenditure by acting on PVN and VMH neurons, while NPY in the dorsomedial hypothalamus (DMH) promotes WAT browning and BAT activity leading to increase of energy expenditure (Wang *et al.* 2007, Wang *et al.* 2010, Chao *et al.* 2011). BMP8B as a factor derived from the hypothalamus promotes energy balance and thermogenesis through activation of AMPK in the key hypothalamic nuclei and subsequent stimulation of sympathetic tone (Whittle *et al.* 2012). Notably, BMP8B

is also produced in BAT and enhances norepinephrine action by regulating p38MAPK/CREB pathway (Whittle *et al.* 2012). However, which type of cells produces BMP8B in BAT is undetermined. Myokine irisin, encoded by *fndc5* gene, is induced by exercise, promotes browning of WAT by increasing beige adipocyte differentiation and UCP1 expression, and augments brown fat thermogenesis in concert with FGF21 in humans upon cold exposure (Bostrom *et al.* 2012, Lee *et al.* 2014a, Jedrychowski *et al.* 2015). However, the induction of irisin by exercise occurs only in a minority of human subjects (Timmons *et al.* 2012, Pekkala *et al.* 2013). Therefore, the role of irisin in regulating metabolism has been questioned. Moreover, multiple secreted factors from adipose and other tissues including Slit2, BMP7, Vitamin A derivatives, VEGF, prostaglandins, bile acids, FGF21, natriuretic peptides, catecholamine, enkephalin, and thyroid hormone (triiodothyronine, T3), and intracellular modulators such as Histone Deacetylase 1 (HDAC1) and miRNAs have been identified to regulate thermogenic programming (Watanabe *et al.* 2006, Tseng *et al.* 2008, Thomas *et al.* 2009, Lopez *et al.* 2010, Nguyen *et al.* 2011, Bordicchia *et al.* 2012, Fisher *et al.* 2012, Kiefer *et al.* 2012, Bagchi *et al.* 2013, Sun *et al.* 2014, Brestoff *et al.* 2015, Park *et al.* 2015, Li *et al.* 2016, Svensson *et al.* 2016) (Fig. 3). However, whether β 3-adrenoceptor/PKA signalling pathway mediates the effect of these factors on thermogenic program remains largely unknown.

Conclusions

Adipose tissue plays a major role in the regulation of systemic metabolic homeostasis via its profound effects on energy storage, endocrine function and adaptive thermogenesis. The dysfunction of adipose tissue as a causal factor is linked to obesity and its related disorders. Therefore, understanding adipose tissue biology and pathology is of great importance for the identification of novel and potential therapeutic targets for the prevention and treatment of obesity-related disorders. In particular, enormous evidence of newly discovered endocrine and thermogenic function of adipose tissue strongly suggests that selectively targeting adipose tissue as the therapeutic approach is feasible and practicable. Supportively, multiple adipokines have been found to be potential therapeutic targets. The deficient mice of adipokine leptin (*ob/ob*) and leptin receptor (*db/db*) have been widely used in the obesity and diabetes research as well as in other fields. Moreover, accumulating studies in rodents have demonstrated that leptin-based therapy may be a promising strategy for the prevention and treatment of obesity, whereas further research is needed to determine if leptin gene therapy is safe and effective in humans. Furthermore, adiponectin has great potential as a therapeutic target for a variety of obesity-associated diseases. However, preclinical manipulation of circulating adiponectin has been quite challenging due to its complicated multimeric structure and high circulating level at about roughly 3 orders of magnitude greater than most other hormones in humans. Although brown and beige fat have provided another therapeutic approach for the treatment of obesity, the efficacy of β 3-adrenoceptor agonists in humans is relatively lower than that in rodents. Therefore, future studies focusing on adipokines and thermogenesis regulation will be urgently needed for adipose tissue-related therapeutic purpose.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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