Adipose tissue in control of metabolism

Liping Luo[1] and **Meilian Liu**[1,2]

[1]Department of Metabolism and Endocrinology, Metabolic Syndrome Research Center, Key Laboratory of Diabetes Immunology, National Clinical Research Center for Metabolic Diseases, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China
[2]Department of Biochemistry and Molecular Biology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA

Correspondence should be addressed to M Liu
Email
meilianliu@salud.unm.edu

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 euthermia, 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

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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 β3-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 μm) 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

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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 β3-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, PDGFRα$^+$ 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 (IL4Rα) signalling (Lee *et al*. 2012, Wang *et al*. 2014, Lee *et al*. 2015*a*). 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 PDGFRα$^+$ preadipocytes are not recruited and do not significantly contribute to cold-induced WAT browning (Lee *et al*. 2015*b*, 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 PDGFRα$^+$ preadipocytes in inguinal WAT (Lee *et al*. 2015*b*). 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 (PPARγ), a member of nuclear-receptor superfamily, has been shown to act as the master regulator of adipogenesis (Rosen *et al*. 2000). Overexpressing PPARγ is sufficient to induce adipocyte differentiation in fibroblasts, and deficiency of PPARγ 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 PPARγ-dependent mechanisms (Rosen *et al*. 2000, Farmer 2006). Furthermore, PPARγ 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 PPARγ 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 (Tamori *et al*. 2002). In line with this, selective ablation of PPARγ in mature white and brown adipocytes leads to adipocyte death, while having little effect on the preadipocyte differentiation (Imai *et al*. 2004). Therefore, PPARγ 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 PPARγ expression and its

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activity (Farmer 2005, Lee & Ge 2014). Thiazolidinediones (TZDs) as the synthetic full agonists of PPARγ have been shown to improve insulin sensitivity and glucose control by activating PPARγ. However, their use has been hampered because of severe side effects. Partial agonists have been identified as selective PPARγ 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 PPARγ 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/EBPα, C/EBPβ, C/EBPγ, C/EBPδ and CHOP (Rosen & Spiegelman 2000). C/EBPs are induced during adipogenesis and coordinate with PPARγ 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/EBPα is upregulated by PPARγ, which in turn promotes PPARγ 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/EBPα deficiency leads to WAT loss and impaired development of BAT, suggesting a critical role of C/EBPα in adipogenesis (Wang *et al*. 1995). Two other C/EBP family members C/EBPβ and C/EBPδ also play important roles in regulating adipogenesis by activating the transcription of C/EBPα and PPARγ, 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 PPARγ 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/EBPβ. 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 PPARγ co-activators PGC1α and PGC1β, which leads to activation of brown fat-specific genes (Kajimura *et al*. 2008). Although both PRDM16 and PGC1α are the main regulators of brown and beige adipocytes, PGC1α is required for the expression of mitochondrial biogenesis and thermogenic genes but not for differentiation genes, indicating that PGC1α 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 & Foufelle 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

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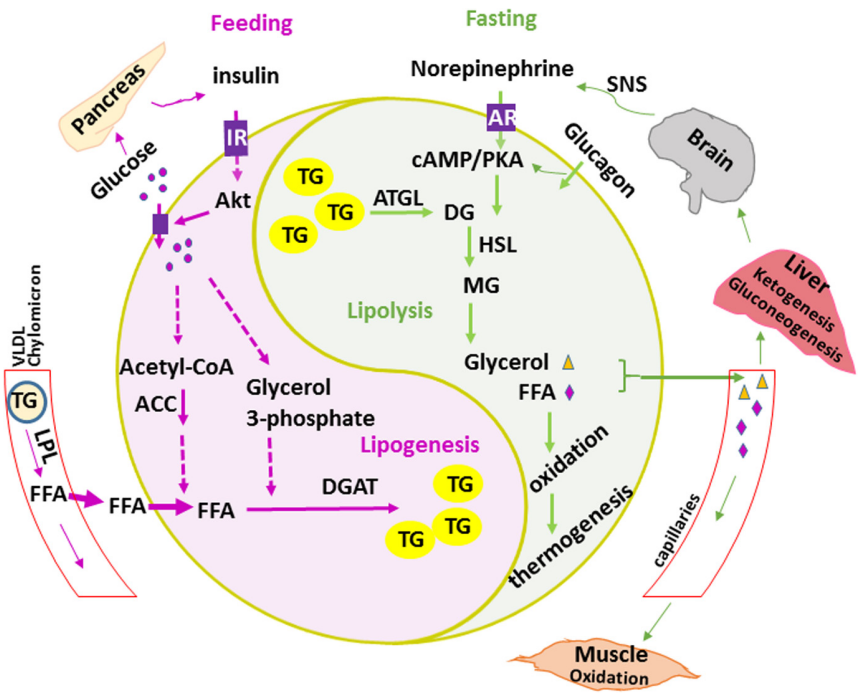

Figure 1
Lipid metabolism and mobilization controlled by adipose tissue. Lipogenesis is a process by which carbohydrate is converted into fatty acids, and promotes the biosynthesis of TG and expansion of lipid droplet in adipocytes. Lipolysis, in an opposite way, breaks down TG to free fatty acid (FFA) 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

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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 (TNFα) 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, TNFα and IL6 (Loskutoff &

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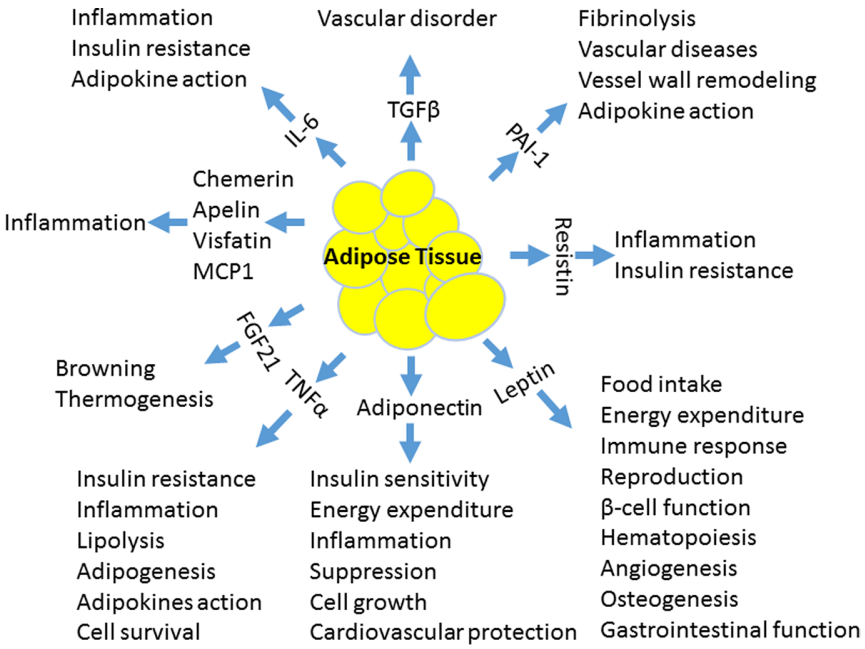

Figure 2
The physiological functions of adipokines. Adipokines, the cytokines derived from adipose tissue, act to regulate insulin sensitivity, inflammation, cardiovascular function, behaviour and cell growth, resulting in the development of obesity-induced metabolic diseases. ASP, acylating simulation protein; FGF21, fibroblast growth factor 21; IL6, interleukin 6; MCP1, monocyte chemoattractant protein 1; PAI1, plasminogen activator inhibitor 1; TNFα, 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

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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, Ca^{2+}, PPARα, ceramide and S1P

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(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, Steppan *et al*. 2001*b*). 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 (Steppan *et al*. 2001*a*). 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 TNFα 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*. 2014*a*). 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 PGC1α through paracrine and/or autocrine mechanisms (Hondares *et al*. 2011, 2014, Fisher *et al*. 2012, Lee *et al*. 2014*b*). 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

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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 β3-adrenoceptor or PPARγ (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 β3-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*. 2004*b*, 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 β3-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, Pfannenberg *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.

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In addition, administration of β3-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 β3-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 β3-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*. 2004*b*, 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, PGC1α, PPARγ, C/EBPβ 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 PPARγ and PGC1α 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/EBPβ complex is required for the activation of thermogenic program and induction of PPARγ, PGC1α 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 programing and the browning effect in subcutaneous adipose tissues, indicating the importance of PRDM16 in driving thermogenic programing (Seale *et al*. 2011, Cohen *et al*. 2014). On the other hand, PGC1α is induced upon cold exposure and modulates the expression of thermogenic markers such as UCP1 (Kleiner *et al*. 2012). Consistent with this, PGC1α 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 PGC1α promotes thermogenic genes expression and energy expenditure, suggesting the key role of PGC1α in regulating thermogenesis and WAT browning (Kong *et al*. 2014). Furthermore, several other intracellular pathways including p38MAPK, mTORC1,

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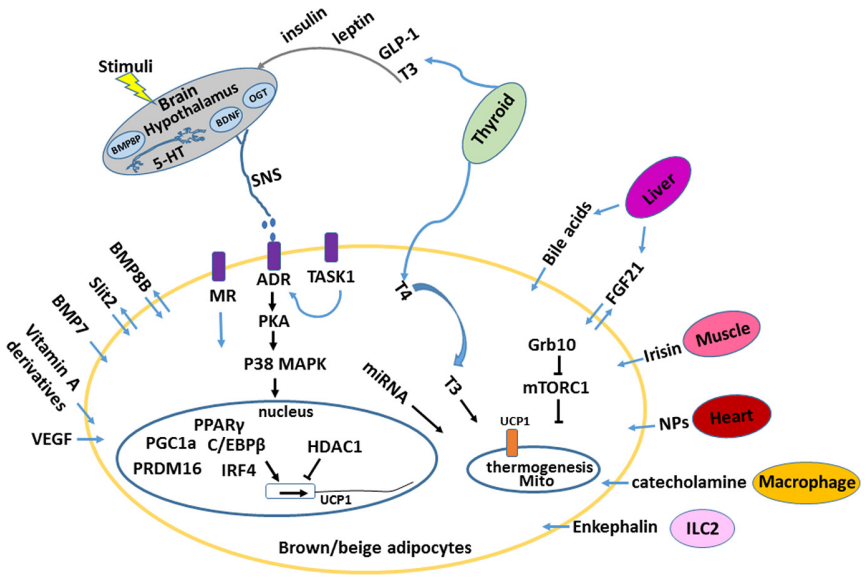

Figure 3
The regulation of adaptive thermogenesis. Thermogenic programme and browning of WAT are driven by SNS in response to cold, diet and stress. Several hormones such as insulin, leptin, BMP8B, GLP-1 and T3 control adaptive thermogenesis through regulating SNS. Moreover, several key transcription factors such as PRDM16, PGC1α, PPARγ, C/EBPβ 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 β3-adrenoceptor-dependent or independent mechanisms (Cao *et al*. 2004*a*, 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*. 2014*a*, 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 programing (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 β3-adrenoceptor/PKA signalling pathway mediates the effect of these factors on thermogenic program remains largely unknown.

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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 β3-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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References

Adams AC, Coskun T, Cheng CC, LS OF, Dubois SL & Kharitonenkov A 2013 Fibroblast growth factor 21 is not required for the antidiabetic actions of the thiazoladinediones. *Molecular Metabolism* **2** 205–214. (doi:10.1016/j.molmet.2013.05.005)

Aherne W & Hull D 1966 Brown adipose tissue and heat production in the newborn infant. *Journal of Pathology and Bacteriology* **91** 223–234. (doi:10.1002/path.1700910126)

Ahmadian M, Abbott MJ, Tang T, Hudak CS, Kim Y, Bruss M, Hellerstein MK, Lee HY, Samuel VT, Shulman GI, *et al.* 2011 Desnutrin/ATGL is regulated by AMPK and is required for a brown adipose phenotype. *Cell Metabolism* **13** 739–748. (doi:10.1016/j.cmet.2011.05.002)

Ali AT, Hochfeld WE, Myburgh R & Pepper MS 2013 Adipocyte and adipogenesis. *European Journal of Cell Biology* **92** 229–236. (doi:10.1016/j.ejcb.2013.06.001)

Andrade-Oliveira V, Camara NO & Moraes-Vieira PM 2015 Adipokines as drug targets in diabetes and underlying disturbances. *Journal of Diabetes Research* **2015** 681612. (doi:10.1155/2015/681612)

Arch JR 2011 Challenges in beta(3)-adrenoceptor agonist drug development. *Therapeutic Advances in Endocrinology and Metabolism* **2** 59–64. (doi:10.1177/2042018811398517)

Armani A, Cinti F, Marzolla V, Morgan J, Cranston GA, Antelmi A, Carpinelli G, Canese R, Pagotto U, Quarta C, *et al.* 2014 Mineralocorticoid receptor antagonism induces browning of white adipose tissue through impairment of autophagy and prevents adipocyte dysfunction in high-fat-diet-fed mice. *FASEB Journal* **28** 3745–3757. (doi:10.1096/fj.13-245415)

Arvaniti K, Huang Q & Richard D 2001 Effects of leptin and corticosterone on the expression of corticotropin-releasing hormone, agouti-related protein, and proopiomelanocortin in the brain of ob/ob mouse. *Neuroendocrinology* **73** 227–236. (doi:10.1159/000054639)

Assimacopoulos-Jeannet F, Brichard S, Rencurel F, Cusin I & Jeanrenaud B 1995 In vivo effects of hyperinsulinemia on lipogenic enzymes and glucose transporter expression in rat liver and adipose tissues. *Metabolism* **44** 228–233. (doi:10.1016/0026-0495(95)90270-8)

Awazawa M, Ueki K, Inabe K, Yamauchi T, Kubota N, Kaneko K, Kobayashi M, Iwane A, Sasako T, Okazaki Y, *et al.* 2011 Adiponectin enhances insulin sensitivity by increasing hepatic IRS-2 expression via a macrophage-derived IL-6-dependent pathway. *Cell Metabolism* **13** 401–412. (doi:10.1016/j.cmet.2011.02.010)

Bado A, Levasseur S, Attoub S, Kermorgant S, Laigneau JP, Bortoluzzi MN, Moizo L, Lehy T, Guerre-Millo M, Le Marchand-Brustel Y, *et al.* 1998 The stomach is a source of leptin. *Nature* **394** 790–793. (doi:10.1038/29547)

Bagchi M, Kim LA, Boucher J, Walshe TE, Kahn CR & D'Amore PA 2013 Vascular endothelial growth factor is important for brown adipose tissue development and maintenance. *FASEB Journal* **27** 3257–3271. (doi:10.1096/fj.12-221812)

Bamshad M, Song CK & Bartness TJ 1999 CNS origins of the sympathetic nervous system outflow to brown adipose tissue. *American Journal of Physiology* **276** R1569–R1578.

Barbatelli G, Murano I, Madsen L, Hao Q, Jimenez M, Kristiansen K, Giacobino JP, De Matteis R & Cinti S 2010 The emergence of cold-induced brown adipocytes in mouse white fat depots is determined predominantly by white to brown adipocyte transdifferentiation. *American Journal of Physiology: Endocrinology and Metabolism* **298** E1244–E1253. (doi:10.1152/ajpendo.00600.2009)

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Barbera MJ, Schluter A, Pedraza N, Iglesias R, Villarroya F & Giralt M 2001 Peroxisome proliferator-activated receptor alpha activates transcription of the brown fat uncoupling protein-1 gene. A link between regulation of the thermogenic and lipid oxidation pathways in the brown fat cell. *Journal of Biological Chemistry* **276** 1486–1493. (doi:10.1074/jbc.M006246200)

Barneda D, Planas-Iglesias J, Gaspar ML, Mohammadyani D, Prasannan S, Dormann D, Han GS, Jesch SA, Carman GM, Kagan V, *et al*. 2015 The brown adipocyte protein CIDEA promotes lipid droplet fusion via a phosphatidic acid-binding amphipathic helix. *eLife* **4** e07485. (doi:10.7554/elife.07485)

Bartelt A, Bruns OT, Reimer R, Hohenberg H, Ittrich H, Peldschus K, Kaul MG, Tromsdorf UI, Weller H, Waurisch C, *et al*. 2011 Brown adipose tissue activity controls triglyceride clearance. *Nature Medicine* **17** 200–205. (doi:10.1038/nm.2297)

Bartness TJ, Vaughan CH & Song CK 2010 Sympathetic and sensory innervation of brown adipose tissue. *International Journal of Obesity* **34** (Supplement 1) S36–S42. (doi:10.1038/ijo.2010.182)

Bayindir I, Babaeikelishomi R, Kocanova S, Sousa IS, Lerch S, Hardt O, Wild S, Bosio A, Bystricky K, Herzig S, *et al*. 2015 Transcriptional pathways in cPGI2-induced adipocyte progenitor activation for browning. *Frontiers in Endocrinology* **6** 129. (doi:10.3389/fendo.2015.00129)

Beiroa D, Imbernon M, Gallego R, Senra A, Herranz D, Villarroya F, Serrano M, Ferno J, Salvador J, Escalada J, *et al*. 2014 GLP-1 agonism stimulates brown adipose tissue thermogenesis and browning through hypothalamic AMPK. *Diabetes* **63** 3346–3358. (doi:10.2337/db14-0302)

Benomar Y, Amine H, Crepin D, Al Rifai S, Riffault L, Gertler A & Taouis M 2016 Central resistin/TLR4 impairs adiponectin signaling contributing to insulin and FGF21 resistance. *Diabetes* **65** 913–926. (doi:10.2337/db15-1029)

Berry DC, Stenesen D, Zeve D & Graff JM 2013 The developmental origins of adipose tissue. *Development* **140** 3939–3949. (doi:10.1242/dev.080549)

Bi S & Li L 2013 Browning of white adipose tissue: role of hypothalamic signaling. *Annals of the New York Academy of Sciences* **1302** 30–34. (doi:10.1111/nyas.12258)

Birnbaum MJ 2003 Lipolysis: more than just a lipase. *Journal of Cell Biology* **161** 1011–1012. (doi:10.1083/jcb.200306008)

Blaza S 1983 Brown adipose tissue in man: a review. *Journal of the Royal Society of Medicine* **76** 213–216.

Bluher M 2014 Adipokines – removing road blocks to obesity and diabetes therapy. *Molecular Metabolism* **3** 230–240. (doi:10.1016/j.molmet.2014.01.005)

Bluher M & Mantzoros CS 2015 From leptin to other adipokines in health and disease: facts and expectations at the beginning of the 21st century. *Metabolism* **64** 131–145. (doi:10.1016/j.metabol.2014.10.016)

Bordicchia M, Liu D, Amri EZ, Ailhaud G, Dessi-Fulgheri P, Zhang C, Takahashi N, Sarzani R & Collins S 2012 Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes. *Journal of Clinical Investigation* **122** 1022–1036. (doi:10.1172/JCI59701)

Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, Rasbach KA, Bostrom EA, Choi JH, Long JZ, *et al*. 2012 A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* **481** 463–468. (doi:10.1038/nature10777)

Boucher J, Masri B, Daviaud D, Gesta S, Guigne C, Mazzucotelli A, Castan-Laurell I, Tack I, Knibiehler B, Carpene C, *et al*. 2005 Apelin, a newly identified adipokine up-regulated by insulin and obesity. *Endocrinology* **146** 1764–1771. (doi:10.1210/en.2004-1427)

Brasaemle DL 2007 Thematic review series: adipocyte biology. The perilipin family of structural lipid droplet proteins: stabilization of lipid droplets and control of lipolysis. *Journal of Lipid Research* **48** 2547–2559. (doi:10.1194/jlr.R700014-JLR200)

Brestoff JR, Kim BS, Saenz SA, Stine RR, Monticelli LA, Sonnenberg GF, Thome JJ, Farber DL, Lutfy K, Seale P, *et al*. 2015 Group 2 innate lymphoid cells promote beiging of white adipose tissue and limit obesity. *Nature* **519** 242–246. (doi:10.1038/nature14115)

Cannon B & Nedergaard J 2004 Brown adipose tissue: function and physiological significance. *Physiological Reviews* **84** 277–359. (doi:10.1152/physrev.00015.2003)

Cano G, Passerin AM, Schiltz JC, Card JP, Morrison SF & Sved AF 2003 Anatomical substrates for the central control of sympathetic outflow to interscapular adipose tissue during cold exposure. *Journal of Comparative Neurology* **460** 303–326. (doi:10.1002/cne.10643)

Cao W, Daniel KW, Robidoux J, Puigserver P, Medvedev AV, Bai X, Floering LM, Spiegelman BM & Collins S 2004*a* p38 mitogen-activated protein kinase is the central regulator of cyclic AMP-dependent transcription of the brown fat uncoupling protein 1 gene. *Molecular and Cellular Biology* **24** 3057–3067. (doi:10.1128/MCB.24.7.3057-3067.2004)

Cao WH, Fan W & Morrison SF 2004*b* Medullary pathways mediating specific sympathetic responses to activation of dorsomedial hypothalamus. *Neuroscience* **126** 229–240. (doi:10.1016/j.neuroscience.2004.03.013)

Carey AL, Formosa MF, Van Every B, Bertovic D, Eikelis N, Lambert GW, Kalff V, Duffy SJ, Cherk MH & Kingwell BA 2013 Ephedrine activates brown adipose tissue in lean but not obese humans. *Diabetologia* **56** 147–155. (doi:10.1007/s00125-012-2748-1)

Carmen GY & Victor SM 2006 Signalling mechanisms regulating lipolysis. *Cellular Signalling* **18** 401–408. (doi:10.1016/j.cellsig.2005.08.009)

Caro JF, Sinha MK, Kolaczynski JW, Zhang PL & Considine RV 1996 Leptin: the tale of an obesity gene. *Diabetes* **45** 1455–1462. (doi:10.2337/diab.45.11.1455)

Cederberg A, Gronning LM, Ahren B, Tasken K, Carlsson P & Enerback S 2001 FOXC2 is a winged helix gene that counteracts obesity, hypertriglyceridemia, and diet-induced insulin resistance. *Cell* **106** 563–573. (doi:10.1016/S0092-8674(01)00474-3)

Chao PT, Yang L, Aja S, Moran TH & Bi S 2011 Knockdown of NPY expression in the dorsomedial hypothalamus promotes development of brown adipocytes and prevents diet-induced obesity. *Cell Metabolism* **13** 573–583. (doi:10.1016/j.cmet.2011.02.019)

Chau YY, Bandiera R, Serrels A, Martinez-Estrada OM, Qing W, Lee M, Slight J, Thornburn A, Berry R, McHaffie S, *et al*. 2014 Visceral and subcutaneous fat have different origins and evidence supports a mesothelial source. *Nature Cell Biology* **16** 367–375. (doi:10.1038/ncb2922)

Chen KY, Brychta RJ, Linderman JD, Smith S, Courville A, Dieckmann W, Herscovitch P, Millo CM, Remaley A, Lee P, *et al*. 2013 Brown fat activation mediates cold-induced thermogenesis in adult humans in response to a mild decrease in ambient temperature. *Journal of Clinical Endocrinology and Metabolism* **98** E1218–1223. (doi:10.1210/jc.2012-4213)

Chen WW, Li L, Yang GY, Li K, Qi XY, Zhu W, Tang Y, Liu H & Boden G 2008 Circulating FGF-21 levels in normal subjects and in newly diagnose patients with Type 2 diabetes mellitus. *Experimental and Clinical Endocrinology and Diabetes* **116** 65–68. (doi:10.1055/s-2007-985148)

Cho YW, Hong S, Jin Q, Wang L, Lee JE, Gavrilova O & Ge K 2009 Histone methylation regulator PTIP is required for PPARgamma and C/EBPalpha expression and adipogenesis. *Cell Metabolism* **10** 27–39. (doi:10.1016/j.cmet.2009.05.010)

Chondronikola M, Volpi E, Borsheim E, Porter C, Annamalai P, Enerback S, Lidell ME, Saraf MK, Labbe SM, Hurren NM, *et al*. 2014 Brown adipose tissue improves whole-body glucose homeostasis and insulin sensitivity in humans. *Diabetes* **63** 4089–4099. (doi:10.2337/db14-0746)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-16-0211

Published by Bioscientifica Ltd.

Chondronikola M, Volpi E, Borsheim E, Porter C, Saraf MK, Annamalai P, Yfanti C, Chao T, Wong D, Shinoda K, *et al*. 2016 Brown adipose tissue activation is linked to distinct systemic effects on lipid metabolism in humans. *Cell Metabolism* **23** 1200–1206. (doi:10.1016/j.cmet.2016.04.029)

Chou K & Perry CM 2013 Metreleptin: first global approval. *Drugs* **73** 989–997. (doi:10.1007/s40265-013-0074-7)

Choy L & Derynck R 2003 Transforming growth factor-beta inhibits adipocyte differentiation by Smad3 interacting with CCAAT/enhancer-binding protein (C/EBP) and repressing C/EBP transactivation function. *Journal of Biological Chemistry* **278** 9609–9619. (doi:10.1074/jbc.M212259200)

Cleasby ME, Lau Q, Polkinghorne E, Patel SA, Leslie SJ, Turner N, Cooney GJ, Xu A & Kraegen EW 2011 The adaptor protein APPL1 increases glycogen accumulation in rat skeletal muscle through activation of the PI3-kinase signalling pathway. *Journal of Endocrinology* **210** 81–92. (doi:10.1530/JOE-11-0039)

Cohen P, Levy JD, Zhang Y, Frontini A, Kolodin DP, Svensson KJ, Lo JC, Zeng X, Ye L, Khandekar MJ, *et al*. 2014 Ablation of PRDM16 and beige adipose causes metabolic dysfunction and a subcutaneous to visceral fat switch. *Cell* **156** 304–316. (doi:10.1016/j.cell.2013.12.021)

Coleman DL 1978 Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. *Diabetologia* **14** 141–148. (doi:10.1007/BF00429772)

Combs TP, Pajvani UB, Berg AH, Lin Y, Jelicks LA, Laplante M, Nawrocki AR, Rajala MW, Parlow AF, Cheeseboro L, *et al*. 2004 A transgenic mouse with a deletion in the collagenous domain of adiponectin displays elevated circulating adiponectin and improved insulin sensitivity. *Endocrinology* **145** 367–383. (doi:10.1210/en.2003-1068)

Contreras C, Gonzalez F, Ferno J, Dieguez C, Rahmouni K, Nogueiras R & Lopez M 2015 The brain and brown fat. *Annals of Medicine* **47** 150–168. (doi:10.3109/07853890.2014.919727)

Cousin B, Cinti S, Morroni M, Raimbault S, Ricquier D, Penicaud L & Casteilla L 1992 Occurrence of brown adipocytes in rat white adipose tissue: molecular and morphological characterization. *Journal of Cell Science* **103** 931–942.

Curat CA, Wegner V, Sengenes C, Miranville A, Tonus C, Busse R & Bouloumie A 2006 Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. *Diabetologia* **49** 744–747. (doi:10.1007/s00125-006-0173-z)

Cypess AM, Chen YC, Sze C, Wang K, English J, Chan O, Holman AR, Tal I, Palmer MR, Kolodny GM, *et al*. 2012 Cold but not sympathomimetics activates human brown adipose tissue in vivo. *PNAS* **109** 10001–10005. (doi:10.1073/pnas.1207911109)

Cypess AM, Haft CR, Laughlin MR & Hu HH 2014 Brown fat in humans: consensus points and experimental guidelines. *Cell Metabolism* **20** 408–415. (doi:10.1016/j.cmet.2014.07.025)

Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, *et al*. 2009 Identification and importance of brown adipose tissue in adult humans. *New England Journal of Medicine* **360** 1509–1517. (doi:10.1056/NEJMoa0810780)

Cypess AM, Weiner LS, Roberts-Toler C, Franquet Elia E, Kessler SH, Kahn PA, English J, Chatman K, Trauger SA, Doria A, *et al*. 2015 Activation of human brown adipose tissue by a beta3-adrenergic receptor agonist. *Cell Metabolism* **21** 33–38. (doi:10.1016/j.cmet.2014.12.009)

Cypess AM, White AP, Vernochet C, Schulz TJ, Xue R, Sass CA, Huang TL, Roberts-Toler C, Weiner LS, Sze C, *et al*. 2013 Anatomical localization, gene expression profiling and functional characterization of adult human neck brown fat. *Nature Medicine* **19** 635–639. (doi:10.1038/nm.3112)

de Jong JM, Larsson O, Cannon B & Nedergaard J 2015 A stringent validation of mouse adipose tissue identity markers. *American Journal of Physiology: Endocrinology and Metabolism* **308** E1085–E1105. (doi:10.1152/ajpendo.00023.2015)

Degawa-Yamauchi M, Bovenkerk JE, Juliar BE, Watson W, Kerr K, Jones R, Zhu Q & Considine RV 2003 Serum resistin (FIZZ3) protein is increased in obese humans. *Journal of Clinical Endocrinology and Metabolism* **88** 5452–5455. (doi:10.1210/jc.2002-021808)

Deng Y & Scherer PE 2010 Adipokines as novel biomarkers and regulators of the metabolic syndrome. *Annals of the New York Academy of Sciences* **1212** E1–E19. (doi:10.1111/j.1749-6632.2010.05875.x)

Denzel MS, Scimia MC, Zumstein PM, Walsh K, Ruiz-Lozano P & Ranscht B 2010 T-cadherin is critical for adiponectin-mediated cardioprotection in mice. *Journal of Clinical Investigation* **120** 4342–4352. (doi:10.1172/JCI43464)

DePaoli AM, Higgins LS, Henry RR, Mantzoros C, Dunn FL & Group INTS 2014 Can a selective PPARgamma modulator improve glycemic control in patients with type 2 diabetes with fewer side effects compared with pioglitazone? *Diabetes Care* **37** 1918–1923. (doi:10.2337/dc13-2480)

Dieguez C, Vazquez MJ, Romero A, Lopez M & Nogueiras R 2011 Hypothalamic control of lipid metabolism: focus on leptin, ghrelin and melanocortins. *Neuroendocrinology* **94** 1–11. (doi:10.1159/000328122)

Dijk W, Beigneux AP, Larsson M, Bensadoun A, Young SG & Kersten S 2016 Angiopoietin-like 4 (ANGPTL4) promotes intracellular degradation of lipoprotein lipase in adipocytes. *Journal of Lipid Research* **57** 1670–1683. (doi:10.1194/jlr.M067363)

Dimitriadis G, Mitrou P, Lambadiari V, Maratou E & Raptis SA 2011 Insulin effects in muscle and adipose tissue. *Diabetes Research and Clinical Practice* **93** (Supplement 1) S52–S59. (doi:10.1016/S0168-8227(11)70014-6)

Dodd GT, Decherf S, Loh K, Simonds SE, Wiede F, Balland E, Merry TL, Munzberg H, Zhang ZY, Kahn BB, *et al*. 2015 Leptin and insulin act on POMC neurons to promote the browning of white fat. *Cell* **160** 88–104. (doi:10.1016/j.cell.2014.12.022)

Doring H, Schwarzer K, Nuesslein-Hildesheim B & Schmidt I 1998 Leptin selectively increases energy expenditure of food-restricted lean mice. *International Journal of Obesity and Related Metabolic Disorders* **22** 83–88. (doi:10.1038/sj.ijo.0800547)

Eissing L, Scherer T, Todter K, Knippschild U, Greve JW, Buurman WA, Pinnschmidt HO, Rensen SS, Wolf AM, Bartelt A, *et al*. 2013 De novo lipogenesis in human fat and liver is linked to ChREBP-beta and metabolic health. *Nature Communications* **4** 1528. (doi:10.1038/ncomms2537)

El-Jack AK, Hamm JK, Pilch PF & Farmer SR 1999 Reconstitution of insulin-sensitive glucose transport in fibroblasts requires expression of both PPARgamma and C/EBPalpha. *Journal of Biological Chemistry* **274** 7946–7951. (doi:10.1074/jbc.274.12.7946)

Emanuelli B, Vienberg SG, Smyth G, Cheng C, Stanford KI, Arumugam M, Michael MD, Adams AC, Kharitonenkov A & Kahn CR 2014 Interplay between FGF21 and insulin action in the liver regulates metabolism. *Journal of Clinical Investigation* **124** 515–527. (doi:10.1172/JCI67353)

Etherton TD 2000 The biology of somatotropin in adipose tissue growth and nutrient partitioning. *Journal of Nutrition* **130** 2623–2625.

Fabbrini E, Tamboli RA, Magkos F, Marks-Shulman PA, Eckhauser AW, Richards WO, Klein S & Abumrad NN 2010 Surgical removal of omental fat does not improve insulin sensitivity and cardiovascular risk factors in obese adults. *Gastroenterology* **139** 448–455. (doi:10.1053/j.gastro.2010.04.056)

Fang X, Palanivel R, Cresser J, Schram K, Ganguly R, Thong FS, Tuinei J, Xu A, Abel ED & Sweeney G 2010 An APPL1-AMPK signaling axis mediates beneficial metabolic effects of adiponectin in the heart. *American Journal of Physiology: Endocrinology and Metabolism* **299** E721–E729. (doi:10.1152/ajpendo.00086.2010)

Farmer SR 2005 Regulation of PPARgamma activity during adipogenesis. *International Journal of Obesity* **29** (Supplement 1) S13–S16. (doi:10.1038/sj.ijo.0802907)

Farmer SR 2006 Transcriptional control of adipocyte formation. *Cell Metabolism* **4** 263–273. (doi:10.1016/j.cmet.2006.07.001)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-16-0211

Published by Bioscientifica Ltd.

Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, Hughes IA, McCamish MA & O'Rahilly S 1999 Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *New England Journal of Medicine* **341** 879–884. (doi:10.1056/NEJM199909163411204)

Fasshauer M & Bluher M 2015 Adipokines in health and disease. *Trends in Pharmacological Sciences* **36** 461–470. (doi:10.1016/j.tips.2015.04.014)

Fedorenko A, Lishko PV & Kirichok Y 2012 Mechanism of fatty-acid-dependent UCP1 uncoupling in brown fat mitochondria. *Cell* **151** 400–413. (doi:10.1016/j.cell.2012.09.010)

Feldmann HM, Golozoubova V, Cannon B & Nedergaard J 2009 UCP1 ablation induces obesity and abolishes diet-induced thermogenesis in mice exempt from thermal stress by living at thermoneutrality. *Cell Metabolism* **9** 203–209. (doi:10.1016/j.cmet.2008.12.014)

Ferre P & Foufelle F 2007 SREBP-1c transcription factor and lipid homeostasis: clinical perspective. *Hormone Research* **68** 72–82. (doi:10.1159/000100426)

Fielding BA & Frayn KN 1998 Lipoprotein lipase and the disposition of dietary fatty acids. *British Journal of Nutrition* **80** 495–502.

Filippidis G, Liakopoulos V, Mertens PR, Kiropoulos T, Stakias N, Verikouki C, Patsidis E, Koukoulis G & Stefanidis I 2005 Resistin serum levels are increased but not correlated with insulin resistance in chronic hemodialysis patients. *Blood Purification* **23** 421–428. (doi:10.1159/000088017)

Fischer AW, Hoefig CS, Abreu-Vieira G, de Jong JM, Petrovic N, Mittag J, Cannon B & Nedergaard J 2016 Leptin raises defended body temperature without activating thermogenesis. *Cell Reports* **14** 1621–1631. (doi:10.1016/j.celrep.2016.01.041)

Fisher FM, Kleiner S, Douris N, Fox EC, Mepani RJ, Verdeguer F, Wu J, Kharitonenkov A, Flier JS, Maratos-Flier E, *et al.* 2012 FGF21 regulates PGC-1alpha and browning of white adipose tissues in adaptive thermogenesis. *Genes and Development* **26** 271–281. (doi:10.1101/gad.177857.111)

Foltz IN, Hu S, King C, Wu X, Yang C, Wang W, Weiszmann J, Stevens J, Chen JS, Nuanmanee N, *et al.* 2012 Treating diabetes and obesity with an FGF21-mimetic antibody activating the betaKlotho/FGFR1c receptor complex. *Science Translational Medicine* **4** 162ra153. (doi:10.1126/scitranslmed.3004690)

Foster MT, Shi H, Seeley RJ & Woods SC 2011 Removal of intra-abdominal visceral adipose tissue improves glucose tolerance in rats: role of hepatic triglyceride storage. *Physiology and Behavior* **104** 845–854. (doi:10.1016/j.physbeh.2011.04.064)

Foster MT, Softic S, Caldwell J, Kohli R, de Kloet AD & Seeley RJ 2013 Subcutaneous adipose tissue transplantation in diet-induced obese mice attenuates metabolic dysregulation while removal exacerbates it. *Physiological Reports* **1** e00015. (doi:10.1002/phy2.15)

Frayn KN 2002 Adipose tissue as a buffer for daily lipid flux. *Diabetologia* **45** 1201–1210. (doi:10.1007/s00125-002-0873-y)

Friedman JM & Halaas JL 1998 Leptin and the regulation of body weight in mammals. *Nature* **395** 763–770. (doi:10.1038/27376)

Gerber M, Boettner A, Seidel B, Lammert A, Bar J, Schuster E, Thiery J, Kiess W & Kratzsch J 2005 Serum resistin levels of obese and lean children and adolescents: biochemical analysis and clinical relevance. *Journal of Clinical Endocrinology and Metabolism* **90** 4503–4509. (doi:10.1210/jc.2005-0437)

Ghorbani M & Himms-Hagen J 1997 Appearance of brown adipocytes in white adipose tissue during CL 316,243-induced reversal of obesity and diabetes in Zucker fa/fa rats. *International Journal of Obesity and Related Metabolic Disorders* **21** 465–475. (doi:10.1038/sj.ijo.0800432)

Gil-Campos M, Canete RR & Gil A 2004 Adiponectin, the missing link in insulin resistance and obesity. *Clinical Nutrition* **23** 963–974. (doi:10.1016/j.clnu.2004.04.010)

Gilsanz V, Hu HH & Kajimura S 2013 Relevance of brown adipose tissue in infancy and adolescence. *Pediatric Research* **73** 3–9. (doi:10.1038/pr.2012.141)

Giralt M, Cereijo R & Villarroya F 2016 Adipokines and the endocrine role of adipose tissues. *Handbook of Experimental Pharmacology* **233** 265–282. (doi:10.1007/164_2015_6)

Golden PL, Maccagnan TJ & Pardridge WM 1997 Human blood–brain barrier leptin receptor. Binding and endocytosis in isolated human brain microvessels. *Journal of Clinical Investigation* **99** 14–18. (doi:10.1172/JCI119125)

Gong J, Sun Z & Li P 2009 CIDE proteins and metabolic disorders. *Current Opinion in Lipidology* **20** 121–126. (doi:10.1097/MOL.0b013e328328d0bb)

Gong J, Sun Z, Wu L, Xu W, Schieber N, Xu D, Shui G, Yang H, Parton RG & Li P 2011 Fsp27 promotes lipid droplet growth by lipid exchange and transfer at lipid droplet contact sites. *Journal of Cell Biology* **195** 953–963. (doi:10.1083/jcb.201104142)

Goralski KB, McCarthy TC, Hanniman EA, Zabel BA, Butcher EC, Parlee SD, Muruganandan S & Sinal CJ 2007 Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. *Journal of Biological Chemistry* **282** 28175–28188. (doi:10.1074/jbc.M700793200)

Guerra C, Koza RA, Yamashita H, Walsh K & Kozak LP 1998 Emergence of brown adipocytes in white fat in mice is under genetic control. Effects on body weight and adiposity. *Journal of Clinical Investigation* **102** 412–420. (doi:10.1172/JCI3155)

Guilherme A, Virbasius JV, Puri V & Czech MP 2008 Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nature Reviews Molecular Cell Biology* **9** 367–377. (doi:10.1038/nrm2391)

Gunawardana SC & Piston DW 2012 Reversal of type 1 diabetes in mice by brown adipose tissue transplant. *Diabetes* **61** 674–682. (doi:10.2337/db11-0510)

Haagsman HP, de Haas CG, Geelen MJ & van Golde LM 1982 Regulation of triacylglycerol synthesis in the liver. Modulation of diacylglycerol acyltransferase activity in vitro. *Journal of Biological Chemistry* **257** 10593–10598.

Haemmerle G, Lass A, Zimmermann R, Gorkiewicz G, Meyer C, Rozman J, Heldmaier G, Maier R, Theussl C, Eder S, *et al.* 2006 Defective lipolysis and altered energy metabolism in mice lacking adipose triglyceride lipase. *Science* **312** 734–737. (doi:10.1126/science.1123965)

Haemmerle G, Zimmermann R, Hayn M, Theussl C, Waeg G, Wagner E, Sattler W, Magin TM, Wagner EF & Zechner R 2002 Hormone-sensitive lipase deficiency in mice causes diglyceride accumulation in adipose tissue, muscle, and testis. *Journal of Biological Chemistry* **277** 4806–4815. (doi:10.1074/jbc.M110355200)

Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK & Friedman JM 1995 Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* **269** 543–546. (doi:10.1126/science.7624777)

Haluzik M, Parizkova J & Haluzik MM 2004 Adiponectin and its role in the obesity-induced insulin resistance and related complications. *Physiological Research* **53** 123–129.

Hansen GH, Niels-Christiansen LL & Danielsen EM 2008 Leptin and the obesity receptor (OB-R) in the small intestine and colon: a colocalization study. *Journal of Histochemistry and Cytochemistry* **56** 677–685. (doi:10.1369/jhc.2008.950782)

Harlan SM, Morgan DA, Agassandian K, Guo DF, Cassell MD, Sigmund CD, Mark AL & Rahmouni K 2011 Ablation of the leptin receptor in the hypothalamic arcuate nucleus abrogates leptin-induced sympathetic activation. *Circulation Research* **108** 808–812. (doi:10.1161/CIRCRESAHA.111.240226)

Harms M & Seale P 2013 Brown and beige fat: development, function and therapeutic potential. *Nature Medicine* **19** 1252–1263. (doi:10.1038/nm.3361)

Harms MJ, Ishibashi J, Wang W, Lim HW, Goyama S, Sato T, Kurokawa M, Won KJ & Seale P 2014 Prdm16 is required for the maintenance of brown adipocyte identity and function in adult mice. *Cell Metabolism* **19** 593–604. (doi:10.1016/j.cmet.2014.03.007)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-16-0211

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Harris CA, Haas JT, Streeper RS, Stone SJ, Kumari M, Yang K, Han X, Brownell N, Gross RW, Zechner R, *et al*. 2011 DGAT enzymes are required for triacylglycerol synthesis and lipid droplets in adipocytes. *Journal of Lipid Research* **52** 657–667. (doi:10.1194/jlr.M013003)

Hasegawa G, Ohta M, Ichida Y, Obayashi H, Shigeta M, Yamasaki M, Fukui M, Yoshikawa T & Nakamura N 2005 Increased serum resistin levels in patients with type 2 diabetes are not linked with markers of insulin resistance and adiposity. *Acta Diabetologica* **42** 104–109. (doi:10.1007/s00592-005-0187-x)

Hegele RA, Cao H, Frankowski C, Mathews ST & Leff T 2002 PPARG F388L, a transactivation-deficient mutant, in familial partial lipodystrophy. *Diabetes* **51** 3586–3590. (doi:10.2337/diabetes.51.12.3586)

Herman MA, Peroni OD, Villoria J, Schon MR, Abumrad NA, Bluher M, Klein S & Kahn BB 2012 A novel ChREBP isoform in adipose tissue regulates systemic glucose metabolism. *Nature* **484** 333–338. (doi:10.1038/nature10986)

Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, Lubina JA, Patane J, Self B, Hunt P, *et al*. 1999 Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. *JAMA* **282** 1568–1575. (doi:10.1001/jama.282.16.1568)

Higgins LS & Depaoli AM 2010 Selective peroxisome proliferator-activated receptor gamma (PPARgamma) modulation as a strategy for safer therapeutic PPARgamma activation. *American Journal of Clinical Nutrition* **91** 267S–272S. (doi:10.3945/ajcn.2009.28449E)

Himms-Hagen J 1997 On raising energy expenditure in ob/ob mice. *Science* **276** 1132–1133. (doi:10.1126/science.276.5315.1132)

Himms-Hagen J, Cui J, Danforth E Jr, Taatjes DJ, Lang SS, Waters BL & Claus TH 1994 Effect of CL-316,243, a thermogenic beta 3-agonist, on energy balance and brown and white adipose tissues in rats. *American Journal of Physiology* **266** R1371–R1382.

Himms-Hagen J, Melnyk A, Zingaretti MC, Ceresi E, Barbatelli G & Cinti S 2000 Multilocular fat cells in WAT of CL-316243-treated rats derive directly from white adipocytes. *American Journal of Physiology: Cell Physiology* **279** C670–C681.

Hoffstedt J, Arvidsson E, Sjolin E, Wahlen K & Arner P 2004 Adipose tissue adiponectin production and adiponectin serum concentration in human obesity and insulin resistance. *Journal of Clinical Endocrinology and Metabolism* **89** 1391–1396. (doi:10.1210/jc.2003-031458)

Hogberg H, Engblom L, Ekdahl A, Lidell V, Walum E & Alberts P 2006 Temperature dependence of O2 consumption; opposite effects of leptin and etomoxir on respiratory quotient in mice. *Obesity* **14** 673–682. (doi:10.1038/oby.2006.76)

Holland WL, Miller RA, Wang ZV, Sun K, Barth BM, Bui HH, Davis KE, Bikman BT, Halberg N, Rutkowski JM, *et al*. 2011 Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. *Nature Medicine* **17** 55–63. (doi:10.1038/nm.2277)

Hondares E, Gallego-Escuredo JM, Flachs P, Frontini A, Cereijo R, Goday A, Perugini J, Kopecky P, Giralt M, Cinti S, *et al*. 2014 Fibroblast growth factor-21 is expressed in neonatal and pheochromocytoma-induced adult human brown adipose tissue. *Metabolism* **63** 312–317. (doi:10.1016/j.metabol.2013.11.014)

Hondares E, Iglesias R, Giralt A, Gonzalez FJ, Giralt M, Mampel T & Villarroya F 2011 Thermogenic activation induces FGF21 expression and release in brown adipose tissue. *Journal of Biological Chemistry* **286** 12983–12990. (doi:10.1074/jbc.M110.215889)

Hondares E, Rosell M, Gonzalez FJ, Giralt M, Iglesias R & Villarroya F 2010 Hepatic FGF21 expression is induced at birth via PPARalpha in response to milk intake and contributes to thermogenic activation of neonatal brown fat. *Cell Metabolism* **11** 206–212. (doi:10.1016/j.cmet.2010.02.001)

Hotta Y, Nakamura H, Konishi M, Murata Y, Takagi H, Matsumura S, Inoue K, Fushiki T & Itoh N 2009 Fibroblast growth factor 21 regulates lipolysis in white adipose tissue but is not required for ketogenesis and triglyceride clearance in liver. *Endocrinology* **150** 4625–4633. (doi:10.1210/en.2009-0119)

Hui X, Gu P, Zhang J, Nie T, Pan Y, Wu D, Feng T, Zhong C, Wang Y, Lam KS, *et al*. 2015 Adiponectin enhances cold-induced browning of subcutaneous adipose tissue via promoting M2 macrophage proliferation. *Cell Metabolism* **22** 279–290. (doi:10.1016/j.cmet.2015.06.004)

Hui X, Lam KS, Vanhoutte PM & Xu A 2012 Adiponectin and cardiovascular health: an update. *British Journal of Pharmacology* **165** 574–590. (doi:10.1111/j.1476-5381.2011.01395.x)

Ibrahim MM 2010 Subcutaneous and visceral adipose tissue: structural and functional differences. *Obesity Reviews* **11** 11–18. (doi:10.1111/j.1467-789X.2009.00623.x)

Imai T, Takakuwa R, Marchand S, Dentz E, Bornert JM, Messaddeq N, Wendling O, Mark M, Desvergne B, Wahli W, *et al*. 2004 Peroxisome proliferator-activated receptor gamma is required in mature white and brown adipocytes for their survival in the mouse. *PNAS* **101** 4543–4547. (doi:10.1073/pnas.0400356101)

Iqbal N, Seshadri P, Stern L, Loh J, Kundu S, Jafar T & Samaha FF 2005 Serum resistin is not associated with obesity or insulin resistance in humans. *European Review for Medical and Pharmacological Sciences* **9** 161–165.

Ishibashi J & Seale P 2010 Medicine. Beige can be slimming. *Science* **328** 1113–1114. (doi:10.1126/science.1190816)

Itoh N 2010 Hormone-like (endocrine) Fgfs: their evolutionary history and roles in development, metabolism, and disease. *Cell and Tissue Research* **342** 1–11. (doi:10.1007/s00441-010-1024-2)

Iwabu M, Yamauchi T, Okada-Iwabu M, Sato K, Nakagawa T, Funata M, Yamaguchi M, Namiki S, Nakayama R, Tabata M, *et al*. 2010 Adiponectin and AdipoR1 regulate PGC-1alpha and mitochondria by Ca(2+) and AMPK/SIRT1. *Nature* **464** 1313–1319. (doi:10.1038/nature08991)

Jacene HA, Cohade CC, Zhang Z & Wahl RL 2011 The relationship between patients' serum glucose levels and metabolically active brown adipose tissue detected by PET/CT. *Molecular Imaging and Biology* **13** 1278–1283. (doi:10.1007/s11307-010-0379-9)

Jamaluddin MS, Weakley SM, Yao Q & Chen C 2012 Resistin: functional roles and therapeutic considerations for cardiovascular disease. *British Journal of Pharmacology* **165** 622–632. (doi:10.1111/j.1476-5381.2011.01369.x)

Jeanson Y, Carriere A & Casteilla L 2015 A new role for browning as a redox and stress adaptive mechanism? *Frontiers in Endocrinology* **6** 158. (doi:10.3389/fendo.2015.00158)

Jedrychowski MP, Wrann CD, Paulo JA, Gerber KK, Szpyt J, Robinson MM, Nair KS, Gygi SP & Spiegelman BM 2015 Detection and quantitation of circulating human irisin by tandem mass spectrometry. *Cell Metabolism* **22** 734–740. (doi:10.1016/j.cmet.2015.08.001)

Jespersen NZ, Larsen TJ, Peijs L, Daugaard S, Homoe P, Loft A, de Jong J, Mathur N, Cannon B, Nedergaard J, *et al*. 2013 A classical brown adipose tissue mRNA signature partly overlaps with brite in the supraclavicular region of adult humans. *Cell Metabolism* **17** 798–805. (doi:10.1016/j.cmet.2013.04.011)

Jimenez MA, Akerblad P, Sigvardsson M & Rosen ED 2007 Critical role for Ebf1 and Ebf2 in the adipogenic transcriptional cascade. *Molecular and Cellular Biology* **27** 743–757. (doi:10.1128/MCB.01557-06)

Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K & Tobe K 2006 Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *Journal of Clinical Investigation* **116** 1784–1792. (doi:10.1172/JCI29126)

Kaiyala KJ, Ogimoto K, Nelson JT, Schwartz MW & Morton GJ 2015 Leptin signaling is required for adaptive changes in food intake, but not energy expenditure, in response to different thermal conditions. *PLoS ONE* **10** e0119391. (doi:10.1371/journal.pone.0119391)

Kajimura D, Lee HW, Riley KJ, Arteaga-Solis E, Ferron M, Zhou B, Clarke CJ, Hannun YA, DePinho RA, Guo XE, *et al*. 2013 Adiponectin regulates bone mass via opposite central and peripheral mechanisms through FoxO1. *Cell Metabolism* **17** 901–915. (doi:10.1016/j.cmet.2013.04.009)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-16-0211

Published by Bioscientifica Ltd.

Kajimura S, Seale P, Kubota K, Lunsford E, Frangioni JV, Gygi SP & Spiegelman BM 2009 Initiation of myoblast to brown fat switch by a PRDM16-C/EBP-beta transcriptional complex. *Nature* **460** 1154–1158. (doi:10.1038/nature08262)

Kajimura S, Seale P, Tomaru T, Erdjument-Bromage H, Cooper MP, Ruas JL, Chin S, Tempst P, Lazar MA & Spiegelman BM 2008 Regulation of the brown and white fat gene programs through a PRDM16/CtBP transcriptional complex. *Genes and Development* **22** 1397–1409. (doi:10.1101/gad.1666108)

Kanda H, Tateya S, Tamori Y, Kotani K, Hiasa K, Kitazawa R, Kitazawa S, Miyachi H, Maeda S, Egashira K, *et al*. 2006 MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *Journal of Clinical Investigation* **116** 1494–1505. (doi:10.1172/JCI26498)

Kelly LJ, Vicario PP, Thompson GM, Candelore MR, Doebber TW, Ventre J, Wu MS, Meurer R, Forrest MJ, Conner MW, *et al*. 1998 Peroxisome proliferator-activated receptors gamma and alpha mediate in vivo regulation of uncoupling protein (UCP-1, UCP-2, UCP-3) gene expression. *Endocrinology* **139** 4920–4927. (doi:10.1210/en.139.12.4920)

Kersten S 2014 Physiological regulation of lipoprotein lipase. *Biochimica et Biophysica Acta* **1841** 919–933. (doi:10.1016/j.bbalip.2014.03.013)

Kiefer FW, Vernochet C, O'Brien P, Spoerl S, Brown JD, Nallamshetty S, Zeyda M, Stulnig TM, Cohen DE, Kahn CR, *et al*. 2012 Retinaldehyde dehydrogenase 1 regulates a thermogenic program in white adipose tissue. *Nature Medicine* **18** 918–925. (doi:10.1038/nm.2757)

Kim KH, Jeong YT, Oh H, Kim SH, Cho JM, Kim YN, Kim SS, Kim do H, Hur KY, Kim HK, *et al*. 2013 Autophagy deficiency leads to protection from obesity and insulin resistance by inducing Fgf21 as a mitokine. *Nature Medicine* **19** 83–92. (doi:10.1038/nm.3014)

Kintscher U & Goebel M 2009 INT-131, a PPARgamma agonist for the treatment of type 2 diabetes. *Current Opinion in Investigational Drugs* **10** 381–387.

Kleiner S, Mepani RJ, Laznik D, Ye L, Jurczak MJ, Jornayvaz FR, Estall JL, Chatterjee Bhowmick D, Shulman GI & Spiegelman BM 2012 Development of insulin resistance in mice lacking PGC-1alpha in adipose tissues. *PNAS* **109** 9635–9640. (doi:10.1073/pnas.1207287109)

Kong X, Banks A, Liu T, Kazak L, Rao RR, Cohen P, Wang X, Yu S, Lo JC, Tseng YH, *et al*. 2014 IRF4 is a key thermogenic transcriptional partner of PGC-1alpha. *Cell* **158** 69–83. (doi:10.1016/j.cell.2014.04.049)

Kopecky J, Clarke G, Enerback S, Spiegelman B & Kozak LP 1995 Expression of the mitochondrial uncoupling protein gene from the aP2 gene promoter prevents genetic obesity. *Journal of Clinical Investigation* **96** 2914–2923. (doi:10.1172/JCI118363)

Koutnikova H, Cock TA, Watanabe M, Houten SM, Champy MF, Dierich A & Auwerx J 2003 Compensation by the muscle limits the metabolic consequences of lipodystrophy in PPAR gamma hypomorphic mice. *PNAS* **100** 14457–14462. (doi:10.1073/pnas.2336090100)

Kroker AJ & Bruning JB 2015 Review of the structural and dynamic mechanisms of PPARgamma partial agonism. *PPAR Research* **2015** 816856. (doi:10.1155/2015/816856)

Kubota N, Yano W, Kubota T, Yamauchi T, Itoh S, Kumagai H, Kozono H, Takamoto I, Okamoto S, Shiuchi T, *et al*. 2007 Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. *Cell Metabolism* **6** 55–68. (doi:10.1016/j.cmet.2007.06.003)

Kumano S, Matsumoto H, Takatsu Y, Noguchi J, Kitada C & Ohtaki T 2003 Changes in hypothalamic expression levels of galanin-like peptide in rat and mouse models support that it is a leptin-target peptide. *Endocrinology* **144** 2634–2643. (doi:10.1210/en.2002-221113)

Kuriyama H, Shimomura I, Kishida K, Kondo H, Furuyama N, Nishizawa H, Maeda N, Matsuda M, Nagaretani H, Kihara S, *et al*. 2002 Coordinated regulation of fat-specific and liver-specific glycerol channels, aquaporin adipose and aquaporin 9. *Diabetes* **51** 2915–2921. (doi:10.2337/diabetes.51.10.2915)

Lafontan M & Langin D 2009 Lipolysis and lipid mobilization in human adipose tissue. *Progress in Lipid Research* **48** 275–297. (doi:10.1016/j.plipres.2009.05.001)

Lago F, Gomez R, Gomez-Reino JJ, Dieguez C & Gualillo O 2009 Adipokines as novel modulators of lipid metabolism. *Trends in Biochemical Sciences* **34** 500–510. (doi:10.1016/j.tibs.2009.06.008)

Langin D 2006 Adipose tissue lipolysis as a metabolic pathway to define pharmacological strategies against obesity and the metabolic syndrome. *Pharmacological Research* **53** 482–491. (doi:10.1016/j.phrs.2006.03.009)

Langin D & Arner P 2006 Importance of TNFalpha and neutral lipases in human adipose tissue lipolysis. *Trends in Endocrinology and Metabolism* **17** 314–320. (doi:10.1016/j.tem.2006.08.003)

Laviola L, Perrini S, Cignarelli A, Natalicchio A, Leonardini A, De Stefano F, Cuscito M, De Fazio M, Memeo V, Neri V, *et al*. 2006 Insulin signaling in human visceral and subcutaneous adipose tissue in vivo. *Diabetes* **55** 952–961. (doi:10.2337/diabetes.55.04.06.db05-1414)

Le Lay S, Boucher J, Rey A, Castan-Laurell I, Krief S, Ferre P, Valet P & Dugail I 2001 Decreased resistin expression in mice with different sensitivities to a high-fat diet. *Biochemical and Biophysical Research Communications* **289** 564–567. (doi:10.1006/bbrc.2001.6015)

Lee GH, Proenca R, Montez JM, Carroll KM, Darvishzadeh JG, Lee JI & Friedman JM 1996 Abnormal splicing of the leptin receptor in diabetic mice. *Nature* **379** 632–635. (doi:10.1038/379632a0)

Lee JE & Ge K 2014 Transcriptional and epigenetic regulation of PPARgamma expression during adipogenesis. *Cell and Bioscience* **4** 29. (doi:10.1186/2045-3701-4-29)

Lee JH, Bullen JW Jr, Stoyneva VL & Mantzoros CS 2005 Circulating resistin in lean, obese, and insulin-resistant mouse models: lack of association with insulinemia and glycemia. *American Journal of Physiology: Endocrinology and Metabolism* **288** E625–E632. (doi:10.1152/ajpendo.00184.2004)

Lee JH, Chan JL, Yiannakouris N, Kontogianni M, Estrada E, Seip R, Orlova C & Mantzoros CS 2003 Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. *Journal of Clinical Endocrinology and Metabolism* **88** 4848–4856. (doi:10.1210/jc.2003-030519)

Lee MW, Odegaard JI, Mukundan L, Qiu Y, Molofsky AB, Nussbaum JC, Yun K, Locksley RM & Chawla A 2015*a* Activated type 2 innate lymphoid cells regulate beige fat biogenesis. *Cell* **160** 74–87. (doi:10.1016/j.cell.2014.12.011)

Lee YH, Petkova AP, Konkar AA & Granneman JG 2015*b* Cellular origins of cold-induced brown adipocytes in adult mice. *FASEB Journal* **29** 286–299. (doi:10.1096/fj.14-263038)

Lee P, Greenfield JR, Ho KK & Fulham MJ 2010 A critical appraisal of the prevalence and metabolic significance of brown adipose tissue in adult humans. *American Journal of Physiology: Endocrinology and Metabolism* **299** E601–E606. (doi:10.1152/ajpendo.00298.2010)

Lee P, Linderman JD, Smith S, Brychta RJ, Wang J, Idelson C, Perron RM, Werner CD, Phan GQ, Kammula US, *et al*. 2014*a* Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. *Cell Metabolism* **19** 302–309. (doi:10.1016/j.cmet.2013.12.017)

Lee P, Werner CD, Kebebew E & Celi FS 2014*b* Functional thermogenic beige adipogenesis is inducible in human neck fat. *International Journal of Obesity* **38** 170–176. (doi:10.1038/ijo.2013.82)

Lee YH, Petkova AP, Mottillo EP & Granneman JG 2012 In vivo identification of bipotential adipocyte progenitors recruited by beta3-adrenoceptor activation and high-fat feeding. *Cell Metabolism* **15** 480–491. (doi:10.1016/j.cmet.2012.03.009)

Lefterova MI & Lazar MA 2009 New developments in adipogenesis. *Trends in Endocrinology and Metabolism* **20** 107–114. (doi:10.1016/j.tem.2008.11.005)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-16-0211

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Lefterova MI, Zhang Y, Steger DJ, Schupp M, Schug J, Cristancho A, Feng D, Zhuo D, Stoeckert CJ Jr, Liu XS, *et al*. 2008 PPARgamma and C/EBP factors orchestrate adipocyte biology via adjacent binding on a genome-wide scale. *Genes and Development* **22** 2941–2952. (doi:10.1101/gad.1709008)

Lepper C & Fan CM 2010 Inducible lineage tracing of Pax7-descendant cells reveals embryonic origin of adult satellite cells. *Genesis* **48** 424–436. (doi:10.1002/dvg.20630)

Letexier D, Pinteur C, Large V, Frering V & Beylot M 2003 Comparison of the expression and activity of the lipogenic pathway in human and rat adipose tissue. *Journal of Lipid Research* **44** 2127–2134. (doi:10.1194/jlr.M300235-JLR200)

Li F, Wu R, Cui X, Zha L, Yu L, Shi H & Xue B 2016 Histone deacetylase 1 (HDAC1) negatively regulates thermogenic program in brown adipocytes via coordinated regulation of histone H3 lysine 27 (H3K27) deacetylation and methylation. *Journal of Biological Chemistry* **291** 4523–4536. (doi:10.1074/jbc.M115.677930)

Liao GY, An JJ, Gharami K, Waterhouse EG, Vanevski F, Jones KR & Xu B 2012 Dendritically targeted Bdnf mRNA is essential for energy balance and response to leptin. *Nature Medicine* **18** 564–571. (doi:10.1038/nm.2687)

Lidell ME, Betz MJ, Dahlqvist Leinhard O, Heglind M, Elander L, Slawik M, Mussack T, Nilsson D, Romu T, Nuutila P, *et al*. 2013 Evidence for two types of brown adipose tissue in humans. *Nature Medicine* **19** 631–634. (doi:10.1038/nm.3017)

Liu D, Bordicchia M, Zhang C, Fang H, Wei W, Li JL, Guilherme A, Guntur K, Czech MP & Collins S 2016 Activation of mTORC1 is essential for beta-adrenergic stimulation of adipose browning. *Journal of Clinical Investigation* **126** 1704–1716. (doi:10.1172/JCI83532)

Liu M, Bai J, He S, Villarreal R, Hu D, Zhang C, Yang X, Liang H, Slaga TJ, Yu Y, *et al*. 2014 Grb10 promotes lipolysis and thermogenesis by phosphorylation-dependent feedback inhibition of mTORC1. *Cell Metabolism* **19** 967–980. (doi:10.1016/j.cmet.2014.03.018)

Lockie SH, Heppner KM, Chaudhary N, Chabenne JR, Morgan DA, Veyrat-Durebex C, Ananthakrishnan G, Rohner-Jeanrenaud F, Drucker DJ, DiMarchi R, *et al*. 2012 Direct control of brown adipose tissue thermogenesis by central nervous system glucagon-like peptide-1 receptor signaling. *Diabetes* **61** 2753–2762. (doi:10.2337/db11-1556)

Lodhi IJ, Yin L, Jensen-Urstad AP, Funai K, Coleman T, Baird JH, El Ramahi MK, Razani B, Song H, Fu-Hsu F, *et al*. 2012 Inhibiting adipose tissue lipogenesis reprograms thermogenesis and PPARgamma activation to decrease diet-induced obesity. *Cell Metabolism* **16** 189–201. (doi:10.1016/j.cmet.2012.06.013)

Lopez M, Seoane L, Garcia MC, Lago F, Casanueva FF, Senaris R & Dieguez C 2000 Leptin regulation of prepro-orexin and orexin receptor mRNA levels in the hypothalamus. *Biochemical and Biophysical Research Communications* **269** 41–45. (doi:10.1006/bbrc.2000.2245)

Lopez M, Varela L, Vazquez MJ, Rodriguez-Cuenca S, Gonzalez CR, Velagapudi VR, Morgan DA, Schoenmakers E, Agassandian K, Lage R, *et al*. 2010 Hypothalamic AMPK and fatty acid metabolism mediate thyroid regulation of energy balance. *Nature Medicine* **16** 1001–1008. (doi:10.1038/nm.2207)

Loskutoff DJ & Samad F 1998 The adipocyte and hemostatic balance in obesity: studies of PAI-1. *Arteriosclerosis, Thrombosis, and Vascular Biology* **18** 1–6. (doi:10.1161/01.ATV.18.1.1)

Lowell BB & Spiegelman BM 2000 Towards a molecular understanding of adaptive thermogenesis. *Nature* **404** 652–660.

Mao X, Kikani CK, Riojas RA, Langlais P, Wang L, Ramos FJ, Fang Q, Christ-Roberts CY, Hong JY, Kim RY, *et al*. 2006 APPL1 binds to adiponectin receptors and mediates adiponectin signalling and function. *Nature Cell Biology* **8** 516–523. (doi:10.1038/ncb1404)

Marcinkiewicz A, Gauthier D, Garcia A & Brasaemle DL 2006 The phosphorylation of serine 492 of perilipin a directs lipid droplet fragmentation and dispersion. *Journal of Biological Chemistry* **281** 11901–11909. (doi:10.1074/jbc.M600171200)

Margoni A, Fotis L & Papavassiliou AG 2012 The transforming growth factor-beta/bone morphogenetic protein signalling pathway in adipogenesis. *International Journal of Biochemistry and Cell Biology* **44** 475–479. (doi:10.1016/j.biocel.2011.12.014)

Marroqui L, Gonzalez A, Neco P, Caballero-Garrido E, Vieira E, Ripoll C, Nadal A & Quesada I 2012 Role of leptin in the pancreatic beta-cell: effects and signaling pathways. *Journal of Molecular Endocrinology* **49** R9–R17. (doi:10.1530/JME-12-0025)

Masaki T, Chiba S, Yasuda T, Tsubone T, Kakuma T, Shimomura I, Funahashi T, Matsuzawa Y & Yoshimatsu H 2003 Peripheral, but not central, administration of adiponectin reduces visceral adiposity and upregulates the expression of uncoupling protein in agouti yellow (Ay/a) obese mice. *Diabetes* **52** 2266–2273. (doi:10.2337/diabetes.52.9.2266)

Mattern A, Zellmann T & Beck-Sickinger AG 2014 Processing, signaling, and physiological function of chemerin. *IUBMB Life* **66** 19–26. (doi:10.1002/iub.1242)

Maury E & Brichard SM 2010 Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. *Molecular and Cellular Endocrinology* **314** 1–16. (doi:10.1016/j.mce.2009.07.031)

McGlashon JM, Gorecki MC, Kozlowski AE, Thirnbeck CK, Markan KR, Leslie KL, Kotas ME, Potthoff MJ, Richerson GB & Gillum MP 2015 Central serotonergic neurons activate and recruit thermogenic brown and beige fat and regulate glucose and lipid homeostasis. *Cell Metabolism* **21** 692–705. (doi:10.1016/j.cmet.2015.04.008)

McTernan PG, McTernan CL, Chetty R, Jenner K, Fisher FM, Lauer MN, Crocker J, Barnett AH & Kumar S 2002 Increased resistin gene and protein expression in human abdominal adipose tissue. *Journal of Clinical Endocrinology and Metabolism* **87** 2407. (doi:10.1210/jcem.87.5.8627)

Meister B 2000 Control of food intake via leptin receptors in the hypothalamus. *Vitamins and Hormones* **59** 265–304. (doi:10.1016/s0083-6729(00)59010-4)

Milan G, Granzotto M, Scarda A, Calcagno A, Pagano C, Federspil G & Vettor R 2002 Resistin and adiponectin expression in visceral fat of obese rats: effect of weight loss. *Obesity Research* **10** 1095–1103. (doi:10.1038/oby.2002.149)

Miller RA, Chu Q, Le Lay J, Scherer PE, Ahima RS, Kaestner KH, Foretz M, Viollet B & Birnbaum MJ 2011 Adiponectin suppresses gluconeogenic gene expression in mouse hepatocytes independent of LKB1-AMPK signaling. *Journal of Clinical Investigation* **121** 2518–2528. (doi:10.1172/JCI45942)

Min SY, Kady J, Nam M, Rojas-Rodriguez R, Berkenwald A, Kim JH, Noh HL, Kim JK, Cooper MP, Fitzgibbons T, *et al*. 2016 Human 'brite/beige' adipocytes develop from capillary networks, and their implantation improves metabolic homeostasis in mice. *Nature Medicine* **22** 312–318. (doi:10.1038/nm.4031)

Moon HS, Dalamaga M, Kim SY, Polyzos SA, Hamnvik OP, Magkos F, Paruthi J & Mantzoros CS 2013 Leptin's role in lipodystrophic and nonlipodystrophic insulin-resistant and diabetic individuals. *Endocrine Reviews* **34** 377–412. (doi:10.1210/er.2012-1053)

Morton GJ & Schwartz MW 2011 Leptin and the central nervous system control of glucose metabolism. *Physiological Reviews* **91** 389–411. (doi:10.1152/physrev.00007.2010)

Moschos S, Chan JL & Mantzoros CS 2002 Leptin and reproduction: a review. *Fertility and Sterility* **77** 433–444. (doi:10.1016/S0015-0282(01)03010-2)

Mottillo EP, Bloch AE, Leff T & Granneman JG 2012 Lipolytic products activate peroxisome proliferator-activated receptor (PPAR) alpha and delta in brown adipocytes to match fatty acid oxidation with supply. *Journal of Biological Chemistry* **287** 25038–25048. (doi:10.1074/jbc.M112.374041)

Murano I, Barbatelli G, Giordano A & Cinti S 2009 Noradrenergic parenchymal nerve fiber branching after cold acclimatisation

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DOI: 10.1530/JOE-16-0211

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correlates with brown adipocyte density in mouse adipose organ. *Journal of Anatomy* **214** 171–178. (doi:10.1111/j.1469-7580.2008.01001.x)

Nagaev I & Smith U 2001 Insulin resistance and type 2 diabetes are not related to resistin expression in human fat cells or skeletal muscle. *Biochemical and Biophysical Research Communications* **285** 561–564. (doi:10.1006/bbrc.2001.5173)

Nawrocki AR, Rajala MW, Tomas E, Pajvani UB, Saha AK, Trumbauer ME, Pang Z, Chen AS, Ruderman NB, Chen H, *et al*. 2006 Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. *Journal of Biological Chemistry* **281** 2654–2660. (doi:10.1074/jbc.M505311200)

Nedergaard J, Bengtsson T & Cannon B 2007 Unexpected evidence for active brown adipose tissue in adult humans. *American Journal of Physiology: Endocrinology and Metabolism* **293** E444–E452. (doi:10.1152/ajpendo.00691.2006)

Nedergaard J & Cannon B 2013 UCP1 mRNA does not produce heat. *Biochimica et Biophysica Acta* **1831** 943–949. (doi:10.1016/j.bbalip.2013.01.009)

Nguyen KD, Qiu Y, Cui X, Goh YP, Mwangi J, David T, Mukundan L, Brombacher F, Locksley RM & Chawla A 2011 Alternatively activated macrophages produce catecholamines to sustain adaptive thermogenesis. *Nature* **480** 104–108. (doi:10.1038/nature10653)

O'Brien RM & Granner DK 1996 Regulation of gene expression by insulin. *Physiological Reviews* **76** 1109–1161.

Oldfield BJ, Giles ME, Watson A, Anderson C, Colvill LM & McKinley MJ 2002 The neurochemical characterisation of hypothalamic pathways projecting polysynaptically to brown adipose tissue in the rat. *Neuroscience* **110** 515–526. (doi:10.1016/S0306-4522(01)00555-3)

Oliver P, Pico C, Serra F & Palou A 2003 Resistin expression in different adipose tissue depots during rat development. *Molecular and Cellular Biochemistry* **252** 397–400. (doi:10.1023/A:1025500605884)

Osuga J, Ishibashi S, Oka T, Yagyu H, Tozawa R, Fujimoto A, Shionoiri F, Yahagi N, Kraemer FB, Tsutsumi O, *et al*. 2000 Targeted disruption of hormone-sensitive lipase results in male sterility and adipocyte hypertrophy, but not in obesity. *PNAS* **97** 787–792. (doi:10.1073/pnas.97.2.787)

Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, Engel J, Brownlee M & Scherer PE 2003 Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin. Implications fpr metabolic regulation and bioactivity. *Journal of Biological Chemistry* **278** 9073–9085. (doi:10.1074/jbc.M207198200)

Pajvani UB, Hawkins M, Combs TP, Rajala MW, Doebber T, Berger JP, Wagner JA, Wu M, Knopps A, Xiang AH, *et al*. 2004 Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. *Journal of Biological Chemistry* **279** 12152–12162. (doi:10.1074/jbc.M311113200)

Parimisetty A, Dorsemans AC, Awada R, Ravanan P, Diotel N & Lefebvre d'Hellencourt C 2016 Secret talk between adipose tissue and central nervous system via secreted factors-an emerging frontier in the neurodegenerative research. *Journal of Neuroinflammation* **13** 67. (doi:10.1186/s12974-016-0530-x)

Park JH, Hur W & Lee SB 2015 Intricate transcriptional networks of classical brown and beige fat cells. *Frontiers in Endocrinology* **6** 124. (doi:10.3389/fendo.2015.00124)

Patel L, Buckels AC, Kinghorn IJ, Murdock PR, Holbrook JD, Plumpton C, Macphee CH & Smith SA 2003 Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. *Biochemical and Biophysical Research Communications* **300** 472–476. (doi:10.1016/S0006-291X(02)02841-3)

Patel SD, Rajala MW, Rossetti L, Scherer PE & Shapiro L 2004 Disulfide-dependent multimeric assembly of resistin family hormones. *Science* **304** 1154–1158. (doi:10.1126/science.1093466)

Pekkala S, Wiklund PK, Hulmi JJ, Ahtiainen JP, Horttanainen M, Pollanen E, Makela KA, Kainulainen H, Hakkinen K, Nyman K, *et al*. 2013 Are skeletal muscle FNDC5 gene expression and irisin release regulated by exercise and related to health? *Journal of Physiology* **591** 5393–5400. (doi:10.1113/jphysiol.2013.263707)

Pelleymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T & Collins F 1995 Effects of the obese gene product on body weight regulation in ob/ob mice. *Science* **269** 540–543. (doi:10.1126/science.7624776)

Perez-Perez A, Sanchez-Jimenez F, Maymo J, Duenas JL, Varone C & Sanchez-Margalet V 2015 Role of leptin in female reproduction. *Clinical Chemistry and Laboratory Medicine* **53** 15–28.

Petrovic N, Walden TB, Shabalina IG, Timmons JA, Cannon B & Nedergaard J 2010 Chronic peroxisome proliferator-activated receptor gamma (PPARgamma) activation of epididymally derived white adipocyte cultures reveals a population of thermogenically competent, UCP1-containing adipocytes molecularly distinct from classic brown adipocytes. *Journal of Biological Chemistry* **285** 7153–7164. (doi:10.1074/jbc.M109.053942)

Pfannenberg C, Werner MK, Ripkens S, Stef I, Deckert A, Schmadl M, Reimold M, Haring HU, Claussen CD & Stefan N 2010 Impact of age on the relationships of brown adipose tissue with sex and adiposity in humans. *Diabetes* **59** 1789–1793. (doi:10.2337/db10-0004)

Picard F, Naimi N, Richard D & Deshaies Y 1999 Response of adipose tissue lipoprotein lipase to the cephalic phase of insulin secretion. *Diabetes* **48** 452–459. (doi:10.2337/diabetes.48.3.452)

Pisani DF, Beranger GE, Corinus A, Giroud M, Ghandour RA, Altirriba J, Chambard JC, Mazure NM, Bendahhou S, Duranton C, *et al*. 2016 The K+ channel TASK1 modulates beta-adrenergic response in brown adipose tissue through the mineralocorticoid receptor pathway. *FASEB Journal* **30** 909–922. (doi:10.1096/fj.15-277475)

Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, Scherer PE & Ahima RS 2004 Adiponectin acts in the brain to decrease body weight. *Nature Medicine* **10** 524–529. (doi:10.1038/nm1029)

Raben MS & Hollenberg CH 1960 Effect of glucose and insulin on the esterification of fatty acids by isolated adipose tissue. *Journal of Clinical Investigation* **39** 435–439. (doi:10.1172/JCI104055)

Rahmouni K & Morgan DA 2007 Hypothalamic arcuate nucleus mediates the sympathetic and arterial pressure responses to leptin. *Hypertension* **49** 647–652. (doi:10.1161/01.HYP.0000254827.59792.b2)

Richard D, Monge-Roffarello B, Chechi K, Labbe SM & Turcotte EE 2012 Control and physiological determinants of sympathetically mediated brown adipose tissue thermogenesis. *Frontiers in Endocrinology* **3** 36. (doi:10.3389/fendo.2012.00036)

Rosen ED, Hsu CH, Wang X, Sakai S, Freeman MW, Gonzalez FJ & Spiegelman BM 2002 C/EBPalpha induces adipogenesis through PPARgamma: a unified pathway. *Genes and Development* **16** 22–26. (doi:10.1101/gad.948702)

Rosen ED & MacDougald OA 2006 Adipocyte differentiation from the inside out. *Nature Reviews Molecular Cell Biology* **7** 885–896. (doi:10.1038/nrm2066)

Rosen ED & Spiegelman BM 2000 Molecular regulation of adipogenesis. *Annual Review of Cell and Developmental Biology* **16** 145–171. (doi:10.1146/annurev.cellbio.16.1.145)

Rosen ED & Spiegelman BM 2014 What we talk about when we talk about fat. *Cell* **156** 20–44. (doi:10.1016/j.cell.2013.12.012)

Rosen ED, Walkey CJ, Puigserver P & Spiegelman BM 2000 Transcriptional regulation of adipogenesis. *Genes and Development* **14** 1293–1307.

Rosenwald M, Perdikari A, Rulicke T & Wolfrum C 2013 Bi-directional interconversion of brite and white adipocytes. *Nature Cell Biology* **15** 659–667. (doi:10.1038/ncb2740)

Ruan HB, Dietrich MO, Liu ZW, Zimmer MR, Li MD, Singh JP, Zhang K, Yin R, Wu J, Horvath TL, *et al*. 2014 O-GlcNAc transferase enables

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-16-0211

Published by Bioscientifica Ltd.

AgRP neurons to suppress browning of white fat. *Cell* **159** 306–317. (doi:10.1016/j.cell.2014.09.010)

Saddi-Rosa P, Oliveira CS, Giuffrida FM & Reis AF 2010 Visfatin, glucose metabolism and vascular disease: a review of evidence. *Diabetology and Metabolic Syndrome* **2** 21. (doi:10.1186/1758-5996-2-21)

Sahu A 1998 Evidence suggesting that galanin (GAL), melanin-concentrating hormone (MCH), neurotensin (NT), proopiomelanocortin (POMC) and neuropeptide Y (NPY) are targets of leptin signaling in the hypothalamus. *Endocrinology* **139** 795–798. (doi:10.1210/endo.139.2.5909)

Sahu A 2003 Leptin signaling in the hypothalamus: emphasis on energy homeostasis and leptin resistance. *Frontiers in Neuroendocrinology* **24** 225–253. (doi:10.1016/j.yfrne.2003.10.001)

Saleh J, Al-Wardy N, Farhan H, Al-Khanbashi M & Cianflone K 2011 Acylation stimulating protein: a female lipogenic factor? *Obesity Reviews* **12** 440–448. (doi:10.1111/j.1467-789X.2010.00832.x)

Sanchez-Alavez M, Tabarean IV, Osborn O, Mitsukawa K, Schaefer J, Dubins J, Holmberg KH, Klein I, Klaus J, Gomez LF, *et al*. 2010 Insulin causes hyperthermia by direct inhibition of warm-sensitive neurons. *Diabetes* **59** 43–50. (doi:10.2337/db09-1128)

Sanchez-Gurmaches J & Guertin DA 2014 Adipocytes arise from multiple lineages that are heterogeneously and dynamically distributed. *Nature Communications* **5** 4099. (doi:10.1038/ncomms5099)

Sanchez-Gurmaches J, Hung CM & Guertin DA 2016 Emerging complexities in adipocyte origins and identity. *Trends in Cell Biology* **26** 313–326. (doi:10.1016/j.tcb.2016.01.004)

Sanchez-Gurmaches J, Hung CM, Sparks CA, Tang Y, Li H & Guertin DA 2012 PTEN loss in the Myf5 lineage redistributes body fat and reveals subsets of white adipocytes that arise from Myf5 precursors. *Cell Metabolism* **16** 348–362. (doi:10.1016/j.cmet.2012.08.003)

Savage DB & O'Rahilly S 2002 Leptin: a novel therapeutic role in lipodystrophy. *Journal of Clinical Investigation* **109** 1285–1286. (doi:10.1172/JCI0215326)

Savage DB, Sewter CP, Klenk ES, Segal DG, Vidal-Puig A, Considine RV & O'Rahilly S 2001 Resistin/Fizz3 expression in relation to obesity and peroxisome proliferator-activated receptor-gamma action in humans. *Diabetes* **50** 2199–2202. (doi:10.2337/diabetes.50.10.2199)

Scherer PE 2006 Adipose tissue: from lipid storage compartment to endocrine organ. *Diabetes* **55** 1537–1545. (doi:10.2337/db06-0263)

Scherer PE, Williams S, Fogliano M, Baldini G & Lodish HF 1995 A novel serum protein similar to C1q, produced exclusively in adipocytes. *Journal of Biological Chemistry* **270** 26746–26749. (doi:10.1074/jbc.270.45.26746)

Schulz TJ, Huang TL, Tran TT, Zhang H, Townsend KL, Shadrach JL, Cerletti M, McDougall LE, Giorgadze N, Tchkonia T, *et al*. 2011 Identification of inducible brown adipocyte progenitors residing in skeletal muscle and white fat. *PNAS* **108** 143–148. (doi:10.1073/pnas.1010929108)

Schwartz MW, Seeley RJ, Campfield LA, Burn P & Baskin DG 1996 Identification of targets of leptin action in rat hypothalamus. *Journal of Clinical Investigation* **98** 1101–1106. (doi:10.1172/JCI118891)

Seale P, Bjork B, Yang W, Kajimura S, Chin S, Kuang S, Scime A, Devarakonda S, Conroe HM, Erdjument-Bromage H, *et al*. 2008 PRDM16 controls a brown fat/skeletal muscle switch. *Nature* **454** 961–967. (doi:10.1038/nature07182)

Seale P, Conroe HM, Estall J, Kajimura S, Frontini A, Ishibashi J, Cohen P, Cinti S & Spiegelman BM 2011 Prdm16 determines the thermogenic program of subcutaneous white adipose tissue in mice. *Journal of Clinical Investigation* **121** 96–105. (doi:10.1172/JCI44271)

Seale P, Kajimura S, Yang W, Chin S, Rohas LM, Uldry M, Tavernier G, Langin D & Spiegelman BM 2007 Transcriptional control of brown fat determination by PRDM16. *Cell Metabolism* **6** 38–54. (doi:10.1016/j.cmet.2007.06.001)

Sethi JK & Vidal-Puig AJ 2007 Thematic review series: adipocyte biology. Adipose tissue function and plasticity orchestrate nutritional adaptation. *Journal of Lipid Research* **48** 1253–1262. (doi:10.1194/jlr.R700005-JLR200)

Sharp LZ, Shinoda K, Ohno H, Scheel DW, Tomoda E, Ruiz L, Hu H, Wang L, Pavlova Z, Gilsanz V, *et al*. 2012 Human BAT possesses molecular signatures that resemble beige/brite cells. *PLoS ONE* **7** e49452. (doi:10.1371/journal.pone.0049452)

Shi YC, Lau J, Lin Z, Zhang H, Zhai L, Sperk G, Heilbronn R, Mietzsch M, Weger S, Huang XF, *et al*. 2013 Arcuate NPY controls sympathetic output and BAT function via a relay of tyrosine hydroxylase neurons in the PVN. *Cell Metabolism* **17** 236–248. (doi:10.1016/j.cmet.2013.01.006)

Shimizu I, Hirota M, Ohboshi C & Shima K 1987 Identification and localization of glucagon-like peptide-1 and its receptor in rat brain. *Endocrinology* **121** 1076–1082. (doi:10.1210/endo-121-3-1076)

Smith SJ, Cases S, Jensen DR, Chen HC, Sande E, Tow B, Sanan DA, Raber J, Eckel RH & Farese RV Jr 2000 Obesity resistance and multiple mechanisms of triglyceride synthesis in mice lacking Dgat. *Nature Genetics* **25** 87–90. (doi:10.1038/75651)

Sobhani I, Bado A, Vissuzaine C, Buyse M, Kermorgant S, Laigneau JP, Attoub S, Lehy T, Henin D, Mignon M, *et al*. 2000 Leptin secretion and leptin receptor in the human stomach. *Gut* **47** 178–183. (doi:10.1136/gut.47.2.178)

Stanford KI, Middelbeek RJ, Townsend KL, An D, Nygaard EB, Hitchcox KM, Markan KR, Nakano K, Hirshman MF, Tseng YH, *et al*. 2013 Brown adipose tissue regulates glucose homeostasis and insulin sensitivity. *Journal of Clinical Investigation* **123** 215–223. (doi:10.1172/JCI62308)

Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS & Lazar MA 2001*a* The hormone resistin links obesity to diabetes. *Nature* **409** 307–312. (doi:10.1038/35053000)

Steppan CM, Brown EJ, Wright CM, Bhat S, Banerjee RR, Dai CY, Enders GH, Silberg DG, Wen X, Wu GD, *et al*. 2001*b* A family of tissue-specific resistin-like molecules. *PNAS* **98** 502–506. (doi:10.1073/pnas.98.2.502)

Sukonina V, Lookene A, Olivecrona T & Olivecrona G 2006 Angiopoietin-like protein 4 converts lipoprotein lipase to inactive monomers and modulates lipase activity in adipose tissue. *PNAS* **103** 17450–17455. (doi:10.1073/pnas.0604026103)

Sun K, Kusminski CM, Luby-Phelps K, Spurgin SB, An YA, Wang QA, Holland WL & Scherer PE 2014 Brown adipose tissue derived VEGF-A modulates cold tolerance and energy expenditure. *Molecular Metabolism* **3** 474–483. (doi:10.1016/j.molmet.2014.03.010)

Svensson KJ, Long JZ, Jedrychowski MP, Cohen P, Lo JC, Serag S, Kir S, Shinoda K, Tartaglia JA, Rao RR, *et al*. 2016 A secreted Slit2 fragment regulates adipose tissue thermogenesis and metabolic function. *Cell Metabolism* **23** 454–466. (doi:10.1016/j.cmet.2016.01.008)

Swierczynski J, Goyke E, Wach L, Pankiewicz A, Kochan Z, Adamonis W, Sledzinski Z & Aleksandrowicz Z 2000 Comparative study of the lipogenic potential of human and rat adipose tissue. *Metabolism* **49** 594–599. (doi:10.1016/S0026-0495(00)80033-5)

Tamori Y, Masugi J, Nishino N & Kasuga M 2002 Role of peroxisome proliferator-activated receptor-gamma in maintenance of the characteristics of mature 3T3-L1 adipocytes. *Diabetes* **51** 2045–2055. (doi:10.2337/diabetes.51.7.2045)

Tan CY & Vidal-Puig A 2008 Adipose tissue expandability: the metabolic problems of obesity may arise from the inability to become more obese. *Biochemical Society Transactions* **36** 935–940. (doi:10.1042/BST0360935)

Tanaka T, Yoshida N, Kishimoto T & Akira S 1997 Defective adipocyte differentiation in mice lacking the C/EBPbeta and/or C/EBPdelta gene. *EMBO Journal* **16** 7432–7443. (doi:10.1093/emboj/16.24.7432)

Tang QQ, Zhang JW & Daniel Lane M 2004 Sequential gene promoter interactions by C/EBPbeta, C/EBPalpha, and PPARgamma during adipogenesis. *Biochemical and Biophysical Research Communications* **318** 213–218. (doi:10.1016/j.bbrc.2004.04.017)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-16-0211

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Taygerly JP, McGee LR, Rubenstein SM, Houze JB, Cushing TD, Li Y, Motani A, Chen JL, Frankmoelle W, Ye G, *et al*. 2013 Discovery of INT131: a selective PPARgamma modulator that enhances insulin sensitivity. *Bioorganic and Medicinal Chemistry* **21** 979–992. (doi:10.1016/j.bmc.2012.11.058)

Teglund S, McKay C, Schuetz E, van Deursen JM, Stravopodis D, Wang D, Brown M, Bodner S, Grosveld G & Ihle JN 1998 Stat5a and Stat5b proteins have essential and nonessential, or redundant, roles in cytokine responses. *Cell* **93** 841–850. (doi:10.1016/S0092-8674(00)81444-0)

Thomas C, Gioiello A, Noriega L, Strehle A, Oury J, Rizzo G, Macchiarulo A, Yamamoto H, Mataki C, Pruzanski M, *et al*. 2009 TGR5-mediated bile acid sensing controls glucose homeostasis. *Cell Metabolism* **10** 167–177. (doi:10.1016/j.cmet.2009.08.001)

Thorne A, Lonnqvist F, Apelman J, Hellers G & Arner P 2002 A pilot study of long-term effects of a novel obesity treatment: omentectomy in connection with adjustable gastric banding. *International Journal of Obesity and Related Metabolic Disorders* **26** 193–199. (doi:10.1038/sj.ijo.0801871)

Timmons JA, Baar K, Davidsen PK & Atherton PJ 2012 Is irisin a human exercise gene? *Nature* **488** E9–E10; discussion E10–E11. (doi:10.1038/nature11364)

Tomas E, Tsao TS, Saha AK, Murrey HE, Zhang Cc C, Itani SI, Lodish HF & Ruderman NB 2002 Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation. *PNAS* **99** 16309–16313. (doi:10.1073/pnas.222657499)

Tontonoz P, Hu E & Spiegelman BM 1994 Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. *Cell* **79** 1147–1156. (doi:10.1016/0092-8674(94)90006-X)

Tran TT, Yamamoto Y, Gesta S & Kahn CR 2008 Beneficial effects of subcutaneous fat transplantation on metabolism. *Cell Metabolism* **7** 410–420. (doi:10.1016/j.cmet.2008.04.004)

Trayhurn P, Duncan JS, Hoggard N & Rayner DV 1998 Regulation of leptin production: a dominant role for the sympathetic nervous system? *Proceedings of the Nutrition Society* **57** 413–419. (doi:10.1079/PNS19980060)

Trayhurn P, Thurlby PL & James WP 1977 Thermogenic defect in pre-obese ob/ob mice. *Nature* **266** 60–62. (doi:10.1038/266060a0)

Tsao TS, Murrey HE, Hug C, Lee DH & Lodish HF 2002 Oligomerization state-dependent activation of NF-kappa B signaling pathway by adipocyte complement-related protein of 30 kDa (Acrp30). *Journal of Biological Chemistry* **277** 29359–29362. (doi:10.1074/jbc.C200312200)

Tseng YH, Kokkotou E, Schulz TJ, Huang TL, Winnay JN, Taniguchi CM, Tran TT, Suzuki R, Espinoza DO, Yamamoto Y, *et al*. 2008 New role of bone morphogenetic protein 7 in brown adipogenesis and energy expenditure. *Nature* **454** 1000–1004. (doi:10.1038/nature07221)

Ueta CB, Fernandes GW, Capelo LP, Fonseca TL, Maculan FD, Gouveia CH, Brum PC, Christoffolete MA, Aoki MS, Lancellotti CL, *et al*. 2012 beta(1) Adrenergic receptor is key to cold- and diet-induced thermogenesis in mice. *Journal of Endocrinology* **214** 359–365. (doi:10.1530/JOE-12-0155)

Ukropec J, Anunciado RV, Ravussin Y & Kozak LP 2006 Leptin is required for uncoupling protein-1-independent thermogenesis during cold stress. *Endocrinology* **147** 2468–2480. (doi:10.1210/en.2005-1216)

Uldry M, Yang W, St-Pierre J, Lin J, Seale P & Spiegelman BM 2006 Complementary action of the PGC-1 coactivators in mitochondrial biogenesis and brown fat differentiation. *Cell Metabolism* **3** 333–341. (doi:10.1016/j.cmet.2006.04.002)

van der Lans AA, Hoeks J, Brans B, Vijgen GH, Visser MG, Vosselman MJ, Hansen J, Jorgensen JA, Wu J, Mottaghy FM, *et al*. 2013 Cold acclimation recruits human brown fat and increases nonshivering thermogenesis. *Journal of Clinical Investigation* **123** 3395–3403. (doi:10.1172/JCI68993)

van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, Schrauwen P & Teule GJ 2009 Cold-activated brown adipose tissue in healthy men. *New England Journal of Medicine* **360** 1500–1508. (doi:10.1056/NEJMoa0808718)

Veniant MM, Hale C, Helmering J, Chen MM, Stanislaus S, Busby J, Vonderfecht S, Xu J & Lloyd DJ 2012 FGF21 promotes metabolic homeostasis via white adipose and leptin in mice. *PLoS ONE* **7** e40164. (doi:10.1371/journal.pone.0040164)

Veniant MM, Sivits G, Helmering J, Komorowski R, Lee J, Fan W, Moyer C & Lloyd DJ 2015 Pharmacologic effects of FGF21 are independent of the 'browning' of white adipose tissue. *Cell Metabolism* **21** 731–738. (doi:10.1016/j.cmet.2015.04.019)

Verma S, Li SH, Wang CH, Fedak PW, Li RK, Weisel RD & Mickle DA 2003 Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction. *Circulation* **108** 736–740. (doi:10.1161/01.CIR.0000084503.91330.49)

Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto NJ, Enerback S, *et al*. 2009 Functional brown adipose tissue in healthy adults. *New England Journal of Medicine* **360** 1518–1525. (doi:10.1056/NEJMoa0808949)

Vishvanath L, MacPherson KA, Hepler C, Wang QA, Shao M, Spurgin SB, Wang MY, Kusminski CM, Morley TS & Gupta RK 2016 Pdgfrbeta(+) mural preadipocytes contribute to adipocyte hyperplasia induced by high-fat-diet feeding and prolonged cold exposure in adult mice. *Cell Metabolism* **23** 350–359. (doi:10.1016/j.cmet.2015.10.018)

Waki H, Yamauchi T, Kamon J, Ito Y, Uchida S, Kita S, Hara K, Hada Y, Vasseur F, Froguel P, *et al*. 2003 Impaired multimerization of human adiponectin mutants associated with diabetes. Molecular structure and multimer formation of adiponectin. *Journal of Biological Chemistry* **278** 40352–40363. (doi:10.1074/jbc.M300365200)

Wang C, Bomberg E, Billington C, Levine A & Kotz CM 2007 Brain-derived neurotrophic factor in the hypothalamic paraventricular nucleus increases energy expenditure by elevating metabolic rate. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology* **293** R992–R1002. (doi:10.1152/ajpregu.00516.2006)

Wang C, Bomberg E, Billington CJ, Levine AS & Kotz CM 2010 Brain-derived neurotrophic factor (BDNF) in the hypothalamic ventromedial nucleus increases energy expenditure. *Brain Research* **1336** 66–77. (doi:10.1016/j.brainres.2010.04.013)

Wang J, Liu R, Hawkins M, Barzilai N & Rossetti L 1998 A nutrient-sensing pathway regulates leptin gene expression in muscle and fat. *Nature* **393** 684–688. (doi:10.1038/31474)

Wang ND, Finegold MJ, Bradley A, Ou CN, Abdelsayed SV, Wilde MD, Taylor LR, Wilson DR & Darlington GJ 1995 Impaired energy homeostasis in C/EBP alpha knockout mice. *Science* **269** 1108–1112. (doi:10.1126/science.7652557)

Wang QA, Tao C, Gupta RK & Scherer PE 2013 Tracking adipogenesis during white adipose tissue development, expansion and regeneration. *Nature Medicine* **19** 1338–1344. (doi:10.1038/nm.3324)

Wang W, Kissig M, Rajakumari S, Huang L, Lim HW, Won KJ & Seale P 2014 Ebf2 is a selective marker of brown and beige adipogenic precursor cells. *PNAS* **111** 14466–14471. (doi:10.1073/pnas.1412685111)

Wang Y, Kim KA, Kim JH & Sul HS 2006 Pref-1, a preadipocyte secreted factor that inhibits adipogenesis. *Journal of Nutrition* **136** 2953–2956.

Wang Y, Lam KS, Xu JY, Lu G, Xu LY, Cooper GJ & Xu A 2005 Adiponectin inhibits cell proliferation by interacting with several growth factors in an oligomerization-dependent manner. *Journal of Biological Chemistry* **280** 18341–18347. (doi:10.1074/jbc.M501149200)

Watanabe M, Houten SM, Mataki C, Christoffolete MA, Kim BW, Sato H, Messaddeq N, Harney JW, Ezaki O, Kodama T, *et al*. 2006 Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature* **439** 484–489. (doi:10.1038/nature04330)

Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL & Ferrante AW Jr 2003 Obesity is associated with macrophage

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-16-0211

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accumulation in adipose tissue. *Journal of Clinical Investigation* **112** 1796–1808. (doi:10.1172/JCI200319246)

Westerterp-Plantenga MS, Saris WH, Hukshorn CJ & Campfield LA 2001 Effects of weekly administration of pegylated recombinant human OB protein on appetite profile and energy metabolism in obese men. *American Journal of Clinical Nutrition* **74** 426–434.

Whittle AJ, Carobbio S, Martins L, Slawik M, Hondares E, Vazquez MJ, Morgan D, Csikasz RI, Gallego R, Rodriguez-Cuenca S, *et al*. 2012 BMP8B increases brown adipose tissue thermogenesis through both central and peripheral actions. *Cell* **149** 871–885. (doi:10.1016/j.cell.2012.02.066)

Wu AL, Kolumam G, Stawicki S, Chen Y, Li J, Zavala-Solorio J, Phamluong K, Feng B, Li L, Marsters S, *et al*. 2011 Amelioration of type 2 diabetes by antibody-mediated activation of fibroblast growth factor receptor 1. *Science Translational Medicine* **3** 113ra126. (doi:10.1126/scitranslmed.3002669)

Wu J, Bostrom P, Sparks LM, Ye L, Choi JH, Giang AH, Khandekar M, Virtanen KA, Nuutila P, Schaart G, *et al*. 2012 Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell* **150** 366–376. (doi:10.1016/j.cell.2012.05.016)

Wu L, Zhou L, Chen C, Gong J, Xu L, Ye J, Li D & Li P 2014 Cidea controls lipid droplet fusion and lipid storage in brown and white adipose tissue. *Science China Life Sciences* **57** 107–116. (doi:10.1007/s11427-013-4585-y)

Wu Z, Rosen ED, Brun R, Hauser S, Adelmant G, Troy AE, McKeon C, Darlington GJ & Spiegelman BM 1999 Cross-regulation of C/EBP alpha and PPAR gamma controls the transcriptional pathway of adipogenesis and insulin sensitivity. *Molecular Cell* **3** 151–158. (doi:10.1016/S1097-2765(00)80306-8)

Xin X, Zhou L, Reyes CM, Liu F & Dong LQ 2011 APPL1 mediates adiponectin-stimulated p38 MAPK activation by scaffolding the TAK1-MKK3-p38 MAPK pathway. *American Journal of Physiology: Endocrinology and Metabolism* **300** E103–E110. (doi:10.1152/ajpendo.00427.2010)

Xue B, Coulter A, Rim JS, Koza RA & Kozak LP 2005 Transcriptional synergy and the regulation of Ucp1 during brown adipocyte induction in white fat depots. *Molecular and Cellular Biology* **25** 8311–8322. (doi:10.1128/MCB.25.18.8311-8322.2005)

Xue B, Rim JS, Hogan JC, Coulter AA, Koza RA & Kozak LP 2007 Genetic variability affects the development of brown adipocytes in white fat but not in interscapular brown fat. *Journal of Lipid Research* **48** 41–51. (doi:10.1194/jlr.M600287-JLR200)

Yamauchi T, Hara K, Kubota N, Terauchi Y, Tobe K, Froguel P, Nagai R & Kadowaki T 2003 Dual roles of adiponectin/Acrp30 in vivo as an anti-diabetic and anti-atherogenic adipokine. *Current Drug Targets: Immune, Endocrine and Metabolic Disorders* **3** 243–254. (doi:10.2174/1568008033340090)

Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, Yamashita S, Noda M, Kita S, Ueki K, *et al*. 2002 Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nature Medicine* **8** 1288–1295. (doi:10.1038/nm788)

Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, Okada-Iwabu M, Kawamoto S, Kubota N, Kubota T, *et al*. 2007 Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nature Medicine* **13** 332–339. (doi:10.1038/nm1557)

Yasruel Z, Cianflone K, Sniderman AD, Rosenbloom M, Walsh M & Rodriguez MA 1991 Effect of acylation stimulating protein on the triacylglycerol synthetic pathway of human adipose tissue. *Lipids* **26** 495–499. (doi:10.1007/BF02536592)

Yasuda T, Masaki T, Kakuma T & Yoshimatsu H 2004 Hypothalamic melanocortin system regulates sympathetic nerve activity in brown adipose tissue. *Experimental Biology and Medicine* **229** 235–239.

Ye L, Wu J, Cohen P, Kazak L, Khandekar MJ, Jedrychowski MP, Zeng X, Gygi SP & Spiegelman BM 2013 Fat cells directly sense temperature to activate thermogenesis. *PNAS* **110** 12480–12485. (doi:10.1073/pnas.1310261110)

Yin D, Clarke SD, Peters JL & Etherton TD 1998 Somatotropin-dependent decrease in fatty acid synthase mRNA abundance in 3T3-F442A adipocytes is the result of a decrease in both gene transcription and mRNA stability. *Biochemical Journal* **331** 815–820. (doi:10.1042/bj3310815)

Yoneshiro T, Aita S, Matsushita M, Kayahara T, Kameya T, Kawai Y, Iwanaga T & Saito M 2013 Recruited brown adipose tissue as an antiobesity agent in humans. *Journal of Clinical Investigation* **123** 3404–3408. (doi:10.1172/JCI67803)

Young P, Arch JR & Ashwell M 1984 Brown adipose tissue in the parametrial fat pad of the mouse. *FEBS Letters* **167** 10–14. (doi:10.1016/0014-5793(84)80822-4)

Zechner R, Strauss JG, Haemmerle G, Lass A & Zimmermann R 2005 Lipolysis: pathway under construction. *Current Opinion in Lipidology* **16** 333–340. (doi:10.1097/01.mol.0000169354.20395.1c)

Zhang JW, Klemm DJ, Vinson C & Lane MD 2004 Role of CREB in transcriptional regulation of CCAAT/enhancer-binding protein beta gene during adipogenesis. *Journal of Biological Chemistry* **279** 4471–4478. (doi:10.1074/jbc.M311327200)

Zhang X, Yeung DC, Karpisek M, Stejskal D, Zhou ZG, Liu F, Wong RL, Chow WS, Tso AW, Lam KS, *et al*. 2008 Serum FGF21 levels are increased in obesity and are independently associated with the metabolic syndrome in humans. *Diabetes* **57** 1246–1253. (doi:10.2337/db07-1476)

Zhang Y, Proenca R, Maffei M, Barone M, Leopold L & Friedman JM 1994 Positional cloning of the mouse obese gene and its human homologue. *Nature* **372** 425–432. (doi:10.1038/372425a0)

Zhou L, Deepa SS, Etzler JC, Ryu J, Mao X, Fang Q, Liu DD, Torres JM, Jia W, Lechleiter JD, *et al*. 2009 Adiponectin activates AMP-activated protein kinase in muscle cells via APPL1/LKB1-dependent and phospholipase C/Ca^{2+}/Ca^{2+}/calmodulin-dependent protein kinase kinase-dependent pathways. *Journal of Biological Chemistry* **284** 22426–22435. (doi:10.1074/jbc.M109.028357)

Zimmermann R, Strauss JG, Haemmerle G, Schoiswohl G, Birner-Gruenberger R, Riederer M, Lass A, Neuberger G, Eisenhaber F, Hermetter A, *et al*. 2004 Fat mobilization in adipose tissue is promoted by adipose triglyceride lipase. *Science* **306** 1383–1386. (doi:10.1126/science.1100747)

Zingaretti MC, Crosta F, Vitali A, Guerrieri M, Frontini A, Cannon B, Nedergaard J & Cinti S 2009 The presence of UCP1 demonstrates that metabolically active adipose tissue in the neck of adult humans truly represents brown adipose tissue. *FASEB Journal* **23** 3113–3120. (doi:10.1096/fj.09-133546)

Zuo Y, Qiang L & Farmer SR 2006 Activation of CCAAT/enhancer-binding protein (C/EBP) alpha expression by C/EBP beta during adipogenesis requires a peroxisome proliferator-activated receptor-gamma-associated repression of HDAC1 at the C/ebp alpha gene promoter. *Journal of Biological Chemistry* **281** 7960–7967. (doi:10.1074/jbc.M510682200)

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