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REVIEW

Structural and biochemical characteristics of various white adipose tissue depots

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Abstract

It is now widely accepted that white adipose tissue (WAT) is not merely a fuel storage organ, but also a key component of metabolic homoeostatic mechanisms. Apart from its major role in lipid and glucose metabolism, adipose tissue is also involved in a wide array of other biological processes. The hormones and adipokines, as well as other biologically active agents released from fat cells, affect many physiological and pathological processes. WAT is neither uniform nor inflexible because it undergoes constant remodelling, adapting the size and number of adipocytes to changes in nutrients' availability and hormonal milieu. Fat depots from different areas of the body display distinct structural and functional properties and have disparate roles in pathology. The two major types of WAT are visceral fat, localized within the abdominal cavity and mediastinum, and subcutaneous fat in the hypodermis. Visceral obesity correlates with increased risk of insulin resistance and cardiovascular diseases, while increase of subcutaneous fat is associated with favourable plasma lipid profiles. Visceral adipocytes show higher lipogenic and lipolytic activities and produce more pro-inflammatory cytokines, while subcutaneous adipocytes are the main source of leptin and adiponectin. Moreover, adipose tissue associated with skeletal muscles (intramyocellular and intermuscular fat) and with the epicardium is believed to provide fuels for skeletal and cardiac muscle contraction. However, increased mass of either epicardial or intermuscular adipose tissue correlates with cardiovascular risk, while the presence of the intramyocellular fat is a risk factor for the development of insulin resistance. This review summarizes results of mainly human studies related to the differential characteristics of various WAT depots.

Keywords adipocyte, fat depots, subcutaneous, visceral, white adipose tissue.

During the past 20 years, the fat tissue, that is white and brown fat adipose tissue (WAT and BAT, respectively), has become the subject of intensive research. The first spur for studies came with the discovery of leptin and next adiponectin secretion by adipocytes. These discoveries dramatically changed our view on adipose tissue, from a simple storage depot to an endocrine organ. Adipose tissue thus participates in the extremely intricate network of signalling for maintenance of systemic homoeostasis. Another stimulus for the logarithmic increase in adipose tissue research comes from the rapidly increasing numbers of overweight people (Pijl 2011). The growing prevalence of obesity, even designated as the 'obesity epidemic' by the World Health Organisation (WHO), calls for more efficient measures to cope with excess fat and its

adverse consequences on the body. While studies on factors and mechanisms that control lipid metabolism in health and disease continue, it is relatively less known that WAT, similarly to skeletal muscles, shows profound functional differences dependent on its localization. In this short review, we present some relevant data, derived mainly from human-centred research, on the structural and functional differences between various WAT depots. However, first, we shortly summarize the general structure and functions of WAT.

Structure and functions of adipocytes

General structure of white adipose tissue

WAT is composed primarily of tightly packed, large spherical adipocytes (also called unilocular fat cells as opposed to multilocular adipocytes present in BAT), supported by a richly vascularized loose connective tissue (Fig. 1a). Adipocytes' size varies in relation to the cell lipid content, ranging from about 30–130 μm in diameter. The volume of an adipocyte is a determinant of cell's functionality, with larger adipocytes generally exhibiting higher metabolic activity and secreting more chemoattractants for immune cells (Skurk *et al.* 2007). In mature adipocytes, a large lipid droplet fills almost entire cell volume, being bounded only by a lipid monolayer enhanced with a range of structural proteins (Ohsaki *et al.* 2009). A strong external connective tissue framework is thus a prerequisite for maintaining appropriate fat cell and tissue structure.

Adipocyte's exoskeleton is composed of a meshwork of collagen 1 and reticular fibres, forming the 'collagenic peri-adipocyte basket' (Sbarbati *et al.* 2010) that functions to protect the cell from mechanical disruption. Each cell produces a basal lamina of a typical composition (Divoux & Clément 2011). Adipocytes and other cell populations present in WAT synthesize collagens type 1, 3 and 4 as well as substantial amounts of collagen type 6a1, which may interact with collagen type 4 in mediating the attachment of the basal lamina to fat cells (Khan *et al.* 2009). The scaffold provided by adipocytes' basal laminas and a multitude of extracellular matrix (ECM) proteins and proteoglycans (e.g. fibronectin, decorin, tenascin C, osteonectin, osteopontin, matrix metalloproteinases) reduces external forces and ensures structural and functional integrity of the adipose tissue (Mariman & Wang 2010, Divoux & Clément 2011). Apart from the ECM, the other non-adipocyte component of WAT, the stromal vascular fraction, comprises multipotent stem cells, preadipocytes, fibroblasts, pericytes and endothelial cells of blood and lymphatic vessels, macrophages and other infiltrating immune cells (Fig. 1a) (Ouchi *et al.* 2010). All of these cells also contribute to the production of ECM components (Divoux & Clément 2011). Adipose

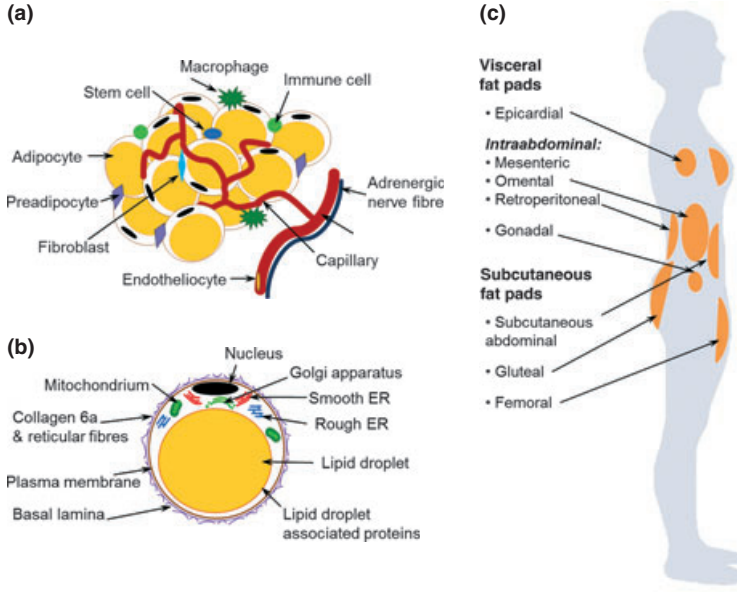

Figure 1 White adipose tissue structure and distribution in human body. (a) Cell types present in WAT. (b) Structure of a unilocular (white) adipocyte. Only some organelles are depicted, not drawn to scale. Cytoskeleton elements (e.g. microtubules and cortical actin filaments) were omitted for better clarity of the picture. (c) Localization of the major WAT depots in human body. ER, endoplasmic reticulum; WAT, white adipose tissue.

tissue contains stem cells with a capacity to differentiate not only into cells of mesodermal lineage, such as adipocytes, but also non-mesodermal cells (neurons, hepatocytes and other) (Yarak & Okamoto 2010). Preadipocytes, which account for 15–50% of all WAT cells, display different proliferative potentials within various WAT depots (Walker *et al.* 2008). WAT is infiltrated by varying counts of immune cells such as macrophages, lymphocytes (natural killer, T helper, T regulatory and B lymphocytes) and mast cells (Anderson *et al.* 2010, Ouchi *et al.* 2010). Alternatively activated (M2) macrophages predominate in WAT of lean subjects, whereas in obesity, the adipose tissue becomes markedly infiltrated by macrophages polarized towards the classically activated, pro-inflammatory M1 phenotype (Anderson *et al.* 2010).

A dense network of capillaries in adipose tissue provides adequate delivery of substrates and oxygen and ensures sufficient routes for the release of hormones, cytokines and a multitude of other biological agents, which act in an endocrine fashion (Sbarbati *et al.* 2010). The expansion of the adipose tissue that accompanies the early phase of overfeeding in humans depends on the remodelling of its stromal compartment with enhanced angiogenesis and increased density of microvessels (Alligier *et al.* 2011). However, in pathological states such as obesity or insulin resistance, decreased density of capillaries and increased density of larger vessels were observed (Spencer *et al.* 2011). WAT contains also lymphatic vessels that provide an important transport route for many of the secreted adipokines (Miller *et al.* 2011).

WAT is innervated mainly by the sympathetic nervous system (SNS) with nerve fibres accompanying arteries and arterioles (Bartness & Song 2007). However, the use of anterograde tracing technique in Siberian hamster revealed the existence of sensory nerve fibres originating in inguinal WAT (Song *et al.* 2009), which provide the brain information on the lipolytic activity of the adipose tissue depots, and by affecting SNS output may provide negative feedback control of lipid mobilization (Bartness *et al.* 2010). The reports of parasympathetic innervation of the adipose tissue (Kreier *et al.* 2002) have been recently questioned (Bartness *et al.* 2010).

Morphology of unilocular adipocytes

A fat cell of the WAT (Fig. 1b) contains a single large lipid droplet in its cytoplasm and is therefore referred to as a unilocular adipocyte. The lipid droplet in each cell is centrally positioned, occupying most of the cell volume. It is surrounded by a phospholipid monolayer enhanced by a cage-like structure of vimentin network, perilipin and CIDE proteins (Ohsaki *et al.* 2009). Newly synthesized lipids initially form small droplets in the cytoplasm's peripheral layer. They are transported along microtubules and eventually fuse with the central droplet (Verstraeten *et al.* 2011). Adipocytes also have a profound actin cortical network (Verstraeten *et al.* 2011). Both actin and microtubule networks play important roles in insulin-dependent glucose transporter type 4 (GLUT4) redistribution. While microtubules mediate basal subcellular distribution of GLUT4 storage vesicles, insulin stimulation leads to dynamic remodelling of filamentous actin cortical meshwork via phosphoinositide 3-kinase signalling (Balamatsias *et al.* 2011). In effect, the vesicles undergo translocation, tethering, docking and fusion with plasma membrane. Cortical actin organization depends on plasma membrane microdomains called caveolae, as well as a multitude of proteins involved in insulin signal transduction (Hoffman & Elmendorf 2011).

A cup-shaped nucleus is displaced to the periphery of the cell, and its nuclear lamina is coupled to the vimentin network (Verstraeten *et al.* 2011). Near the nucleus the cytoplasm gets thicker and contains a Golgi apparatus, smooth and rough endoplasmic reticulum, free ribosomes, and large, elongated mitochondria with densely packed transverse cristae (Fig. 1b) (Sato *et al.* 2005). The amount of mitochondria and their enzymatic equipment varies between different fat depots, contributing to the diverse physiology of the adipose tissue (Deveaud *et al.* 2004). Adipocyte's surface is covered by glycocalyx, which can be observed by transmission electron microscopy as a textured coating (Sato *et al.* 2005). The plasma membrane contains many types of receptors for hormones, neurotransmitters (mainly noradrenalin), cytokines and other signalling molecules (Ouchi *et al.* 2010). Adipocytes express Toll-like receptors, responsible for the recognition of pathogen-associated molecular patterns and other signalling molecules of innate and adaptive immunity (Suganami & Ogawa 2010).

Remodelling of white adipose tissue

Adipose tissue's ECM undergoes constant remodelling to accommodate for changing amounts of fuels to store (Lee *et al.* 2010). The changes encompass hypertrophy, that is enlargement, and hyperplasia, that is proliferation of adipocytes, remodelling of the ECM, angiogenesis and alterations of immune cell subsets' counts. In adults, mature adipocytes constitute a terminally differentiated cell population; however, because of the presence of mesenchymal stem cells and preadipocytes, the turnover rate of human adipocytes is high at all ages, both in lean and obese subjects (Arner *et al.* 2011). Calculations based on the

incorporation of atmospheric C into adipocyte DNA revealed that approx. 10% of total adipocytes become renewed every year (Spalding *et al.* 2008).

Because WAT remodelling is an energetically costly process, it is tightly modulated by insulin, leptin and other factors regulating energy metabolism, as well as by mechanical forces (Mariman & Wang 2010). Abdominal obesity is accompanied by a moderate increase of fat cell counts and substantial enlargement of individual adipocytes (Skurk *et al.* 2007), which may lead to ECM instability. Both in humans and in rodent models, obesity was associated with higher expansion of fibrotic tissue in various WAT depots as compared to lean subjects (Mariman & Wang 2010). Expression of collagen type 6a1, matrix metalloproteinases, thrombospondins, osteonectin, osteopontin, connective tissue growth factor, decorin, tenascin C and other ECM components becomes elevated during prolonged positive energy balance (Mariman & Wang 2010). Moreover, these changes may underlie local inflammation with a subsequent release of various types of pro-inflammatory mediators (Suganami & Ogawa 2010), including plasminogen activator inhibitor 1 and monocyte chemotactic protein 1 (MCP-1), which are also potent inducers of fibrosis (Sell & Eckel 2010). Progressive fibrosis and ECM expansion in the WAT of obese subjects may pose mechanical limits to adipocytes' hypertrophy and thus promote storage of lipids in ectopic fat (Szendroedi & Roden 2009).

White adipose tissue functions

WAT functions primarily as a key regulatory centre of energy metabolism and a site for fuel storage. It also influences other biological processes such as angiogenesis, blood pressure control, blood clotting and immunity. WAT performs its regulatory functions by secreting hormones and cytokines, referred to as adipokines, that act locally or at systemic level. Moreover, adipose tissue provides thermal insulation of the body and cushions internal organs against mechanical damage.

During times of excessive dietary nutrient intake or decreased energy expenditure, WAT stores surplus fuel in the form of neutral triacyliglycerides (TG). In response to insulin stimulation, adipocytes incorporate glucose and utilize it to produce TG for storage. Lipoprotein lipase (LPL) attached to the endothelial lining of blood vessels hydrolyses TG of chylomicrons and very low-density lipoproteins (VLDL), releasing fatty acids that can be transported into adipocytes. Alternatively, free fatty acids (FFA) from blood plasma can be taken up by fat cells and reesterified to form TG. In humans, re-esterification of fatty acids appears to have greater significance in TG storage than *de novo* lipogenesis (Virtue & Vidal-Puig 2010). In case of nutrient scarcity or increased energy requirements, TG undergo lipolysis, that is, they are hydrolysed by adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL). The resultant fatty acids can then be transported via blood or lymph vessels to other locations, where they serve as energy substrates for β-oxidation in mitochondria.

WAT is also involved in the regulation of whole-body glucose homoeostasis and insulin sensitivity. Adipocytes take up glucose through GLUT4 transporters. Insulin sensitivity of peripheral tissues is modulated both by adipokines and by the FFA flux (Miyazaki *et al.* 2002). Moreover, WAT regulates homoeostasis and the body's nutritional status by secreting cytokines with pro-inflammatory and anti-inflammatory properties (Ouchi *et al.* 2010). WAT's endocrine function depends on the activity of both adipocytes and cells of the stromal vascular fraction (Fain *et al.* 2004). Adipocytes are the main source of leptin and adiponectin, while M2 macrophages secrete pro-inflammatory cytokines such as tumour necrosis factor α (TNFα) and interleukin 6 (IL-6) (Fain *et al.* 2004). The most important biological processes affected by adipokines involve regulation of energy homoeostasis (including satiety signalling, lipid and carbohydrate metabolism), adipocyte proliferation and differentiation, angiogenesis, immune responses, reproduction, blood clotting and blood pressure regulation. In obesity, dysregulation of the balance between pro- and anti-inflammatory cytokines released from WAT results in a state of chronic low-grade systemic inflammation and contributes to metabolic and cardiovascular disorders (Ouchi *et al.* 2010, Xu *et al.* 2010).

Hormonal and nervous regulation of white adipose tissue functions

As the key source of fuels, WAT is required to respond adequately to changes in the body's nutritional status and energy requirements. Its functions are thus acutely regulated by both endocrine signals and SNS.

Energy metabolism in adipocytes is controlled by hormones produced by other organs and by WAT itself. Storage and utilization of TG is regulated primarily by insulin, catecholamines and leptin (Lafontan & Langin 2009). Insulin not only promotes the uptake and utilization of glucose in fat cells but also activates lipogenic enzymes such as acyl-CoA carboxylase and fatty acid synthase and simultaneously diminishes lipolysis by inhibiting the activity of HSL (Ahmadian *et al.* 2010). Leptin counteracts insulin's effects on

adipocytes. It reduces glucose uptake and lipogenesis, while promoting lipolysis and oxidation of glucose and fatty acids (Ceddia 2005).

Glucocorticoids counteract insulin's effects on glucose utilization in the liver and peripheral tissues. Glucocorticoids stimulate lipolysis by increasing the activity of adipocyte's intracellular lipases (HSL, ATGL) and WAT's intravascular lipase (LPL), thus modulating both the release and uptake of fatty acids (Macfarlane *et al.* 2008).

Catecholamines belong to key lipolytic agents. Binding of noradrenaline to β1-, β2- and β3-adrenergic receptors on adipocytes activates HSL, which results in increased fuel delivery to tissues (Lafontan & Langin 2009). However, activation of adipocytes' α-adrenergic receptors inhibits lipolysis (Bartness *et al.* 2010). Although under basal conditions, noradrenaline is released in WAT from postganglionic sympathetic neurons synapsing at adipocytes, during stress or strenuous physical activity, adrenal medulla becomes the major source of catecholamines (Arner 2005).

Neurotransmitters and neuropeptides were also shown to affect preadipocyte proliferation and adipose tissue expansion. Noradrenaline inhibited the proliferation of preadipocytes, and denervation of inguinal WAT increased adipocyte proliferation (Foster & Bartness 2006). Neuropeptide Y (NPY), a potent orexigenic co-transmitter released centrally from the hypothalamic neurons and peripherally from sympathetic nerve terminals, stimulates proliferation of preadipocytes (Yang *et al.* 2010). It was shown that under stressful conditions, increased NPY release and its Y1 receptor expression in abdominal WAT led to enhanced fat deposition in mice and in 3T3-L1 cell cultures (Yang *et al.* 2010).

Intercellular communication between different cell populations of WAT not only modulates the tissue's functions, but also influences other systems. A notable example is the macrophage–adipocyte interaction (Suganami & Ogawa 2010). M1 macrophages infiltrating adipose tissue secrete TNFα, which induces in adipocytes pro-inflammatory cytokine production as well as lipolysis. In turn, saturated fatty acids released by hypertrophied adipocytes activate macrophages via their Toll-like receptor 4 complexes (Suganami & Ogawa 2010). In the obese, such cross-talk aggravates systemic chronic inflammation.

Tissue specificity of adipocytes from various fat depots

Since the last 20 years, our understanding of the physiology and pathology of various fat depots has immensely increased. An emerging view is that fat distribution in various body locations affects the development and progression of metabolic diseases more than total fat mass does. Different roles of regional adipose tissue depots in pathology result from the differences in their structure, expression profiles, responsiveness to endocrine and nervous stimuli, as well as local supply of oxygen, nutrients and hormones.

Two types of adipose tissue with substantially different functions and cell ultrastructure coexist in mammals. The primary function of WAT is energy storage, as discussed above. In contrast, BAT is specialized in thermogenesis to maintain energy balance and protect the organism from hypothermia via energy expenditure. Heterogeneous developmental origins have been reported not only for WAT and BAT, but also for different WAT depots (Billon & Dani 2011). Transdifferentiation of unilocular white adipocytes into multilocular cells functionally and morphologically resembling brown adipocytes (Karamanlidis *et al.* 2007, Toh *et al.* 2008) and the discovery of inducible brown adipocyte progenitors residing in human subcutaneous adipose tissue (SAT) (and skeletal muscles) (Schulz *et al.* 2011) pose a promising new target for antiobesity and antidiabetes therapies based on increasing energy expenditure (Cypess & Kahn 2010).

Body distribution of WAT may be divided into two major depots: subcutaneous and visceral fat. The visceral adipose tissue surrounds inner organs in the abdominal cavity and mediastinum, while the SAT forms a fat layer under the skin, that is in hypodermis. Visceral abdominal WAT can be divided into three major depots, that is omental fat surrounding the intestines superficially, mesenteric fat that is more deeply buried around the intestines and retroperitoneal fat near the kidneys, at the dorsal side of the abdominal cavity (Fig. 1c). Additionally, smaller amounts of visceral WAT are also localized in the mediastinum (intrathoracic or paracardial fat) and around specific organs, such as the heart (epicardial WAT), stomach (epigastric fat tissue) and blood vessels (perivascular adipose tissue) (Iozzo 2011). In women, adipose tissue forming mammary fat pad plays an important role in the development of the mammary gland and after puberty in the regulation of epithelial cell proliferation and function (Hovey & Aimo 2010). In pathological states, lipids can also accumulate within non-adipose tissues forming ectopic fat depots, especially in the liver, skeletal muscles, heart, pancreas and within blood vessel wall. Organ function may be altered by the surrounding fat deposits, as the mechanical compression may impair its function. Furthermore, local fat depots may also affect the surrounding structures through secreted

factors, such as hormones, cytokines and other biologically active agents.

Differences between abdominal and subcutaneous WAT depots arise from the different genetic differentiation programs of preadipocytes and influence of the local microenvironment (Tchkonia *et al.* 2007, Yamamoto *et al.* 2010). Tchkonia and coworkers found that human subcutaneous, mesenteric and omental preadipocytes isolated from the same subjects and cultured under identical conditions maintained fat depot-specific characteristics even after many population doublings *ex vivo* (Tchkonia *et al.* 2002, 2005). They demonstrated the existence of two major subtypes of preadipocytes with different capacities for replication and differentiation. Although the two subtypes may convert one to another, their ratios vary among fat depots (Tchkonia *et al.* 2005). Subcutaneous fat is rich in preadipocytes of the rapidly replicating and differentiating subtype, whereas the slowly replicating and differentiating subtype is abundant in omental depot (Tchkonia *et al.* 2005). Differences in preadipocyte cell dynamic properties and in preadipocyte subtype abundance among regional fat stores could affect the capacity of various WAT depots to alter in size and function in response to ageing and changes in nutritional, paracrine and hormonal states.

Besides the recently revealed genetic programming of adipocyte progenitor cells in various regional fat depots, the distribution of adipose tissue in the body depends on other important factors such as sex, nutrition, age and individual genetic background (Wolfs *et al.* 2010, Bjørndal *et al.* 2011).

Visceral adipose tissue

Relative to the location of WAT within the abdominal cavity, mesenteric, omental, retroperitoneal and gonadal visceral fat depots can be distinguished (Fig. 1c). Among these, blood from omental and mesenteric WAT drains into the portal vein, while from retroperitoneal and gonadal fat tissue does not. Because of its anatomical location in humans, the mesenteric fat is the most difficult to access, while the omental fat is more easily accessible during abdominal surgery. The retroperitoneal fat surrounds the kidneys at the dorsal side of the abdominal cavity. Gonadal fat depots, that is epididymal, peritesticular, periovarian and periuterine, are well developed in rodents and their mass increases with age (Bjørndal *et al.* 2011).

The results of animal WAT studies do not always correspond to the data obtained from human studies. For example, there are discrepant observations regarding the relative size of visceral fat cells, partially resulting from different measurement methods. In humans, omental fat cells were reported to be smaller (Ray *et al.* 2009, Kraunsoe *et al.* 2010) than subcutaneous adipocytes; however, in rat, visceral adipocytes were significantly larger (Deveaud *et al.* 2004). Examples of the structural and functional characteristics of rat and human visceral and subcutaneous WAT are presented in Tables 1–3.

Both in rat and human studies, significant functional differences were found between regional depots of the visceral WAT. For example, in rat, the retroperitoneal WAT displays higher expression of key lipolytic enzymes, HSL and ATGL, than the mesenteric and inguinal depots (Palou *et al.* 2009). Generally, in rat, visceral adipocytes show higher basal expression of genes related to lipogenesis, lipolysis and fatty acid oxidation and display faster metabolic response to fasting than subcutaneous fat cells (Table 1).

The interpretation of human studies is more difficult because adipose tissue depots in lean persons were very often compared with those in obese subjects. The regional distribution of fat in humans varies as a function of gender, hormonal status and genetic predisposition. Some authors found that the regional differences in adipocyte size were more pronounced in women (Tchernof *et al.* 2006). Men generally deposit fat preferentially in intraabdominal (visceral) and upper-body subcutaneous fat depots, while women store more fat in subcutaneous areas, especially in the gluteal and femoral depots (Shay *et al.* 2010). Thus, upper-body obesity is more common in men, and lower-body obesity occurs more often in women. For technical reasons, in men, the omental fat tissue has to be regarded as the 'representative' of the visceral WAT, whereas in women, both the omental depot and the adipose tissue present in lower abdomen are accessible during gynaecological surgery. Besides direct studies on isolated adipocytes, investigations of human WAT have also been carried out by indirect methods like computed tomography, positron emission tomography, dual-energy x-ray absorptiometry, magnetic resonance imaging (MRI), magnetic resonance spectroscopy, echography or selective perfusion of regional fat depots, to name the most important. Results of these whole-body studies provide valuable data that, however, are more difficult to interpret than the results of *in vitro* investigations. These considerations have to be taken into account when analysing characteristics of the two major types of WAT in healthy non-obese humans (Table 2) and comparing them in non-obese and obese subjects (Table 3).

In humans of both genders, preadipocytes from visceral depots, as compared to subcutaneous preadipocytes, show lower responsiveness to the induction of differentiation via the peroxisome proliferator-

Table 1 Comparison of the characteristics of visceral and SAT in rat

Variable	Visceral* (VS) vs. SAT	References
Adipocyte size	Retroperitoneal adipocytes larger than mesenteric and SAT adipocytes	Deveaud *et al.* (2004), Palou *et al.* (2009)
Mitochondria	Epididymal adipocytes have more mitochondria, higher cyt c oxidase and citric synthase activities, higher respiration rate	Deveaud *et al.* (2004)
Expression of lipogenesis-related genes	In retroperitoneal WAT higher mRNA levels of PPARγ2, SREBP1c, ACC1, GPAT, LPL, CD36, GLUT4 and HK2 than in inguinal SAT	Palou *et al.* (2009)
Expression of lipolysis-related genes	In retroperitoneal WAT higher levels of HSL and ATGL mRNAs vs. mesenteric and SAT	Palou *et al.* (2009)
Expression of fatty acid oxidation-related genes	In retroperitoneal WAT lower levels of PPARα and CPT1 mRNAs than in SAT	Palou *et al.* (2009)
Fasting-induced expression of lipid metabolism genes	Faster response in retroperitoneal WAT than in SAT	Palou *et al.* (2010)
Basal and catechol-amine-induced lipolysis	Higher in VS fat vs. SAT	Lafontan & Langin (2009)

ACC1, acetyl-CoA carboxylase 1; ATGL, adipose triglyceride lipase; CD36, cluster of differentiation 36; CPT1, carnitine palmitoyltransferase 1; cyt c oxidase, cytochrome c oxidase; GLUT4, glucose transporter type 4; HK2, hexokinase 2; HSL, hormone-sensitive lipase; LPL, lipoprotein lipase; PPAR, peroxisome proliferator-activated receptor; SAT, subcutaneous adipose tissue; SREBP1c, sterol regulatory element-binding protein 1c; VS, visceral adipose tissue; WAT, white adipose tissue.
*In animal studies, various visceral fat depots such as retroperitoneal, mesenteric, omental or epididymal adipose tissue were analysed.

activated receptor γ (PPARγ) pathway (Tchkonia *et al.* 2002). Only in women, higher glucocorticoid receptor expression in subcutaneous preadipocytes further contributes to higher differentiation potential of SAT preadipocytes than visceral ones (Joyner *et al.* 2000). This gender-related difference can partially account for women's propensity to accumulate more fat subcutaneously. Moreover, subcutaneous WAT's greater expandability can result from its higher responsiveness to thyroid hormones, especially in obese subjects (Ortega *et al.* 2009).

Adipose tissue expansion depends also on angiogenesis. However, studies on depot-specific angiogenic potential of adipose tissue provide controversial results. Formation of new blood vessels starts with endothelial proliferation, controlled by growth factors including vascular endothelial growth factor (VEGF), followed by tube formation and maturation of the capillaries, regulated by a different set of cytokines (Ye 2011). Adipocyte expression of VEGF was higher in visceral than in subcutaneous fat in mice (Miyazawa-Hoshimoto *et al.* 2005, Ye 2011), while in humans the amount of serum VEGF correlated positively with visceral fat mass (Ledoux *et al.* 2008). However, contrary to what might have been inferred from these data, the angiogenic potential of human visceral fat was demonstrated to be lower than of subcutaneous fat in a model of capillary branch formation from tissue explants embedded in Matrigel (Gealekman *et al.* 2011). Interestingly, the angiogenic capacity of adipose tissue is decreased in severe obesity (Gealekman *et al.* 2011).

Human visceral adipocytes have higher basal and catecholamine-induced lipolytic activity as compared to subcutaneous WAT (Ahmadian *et al.* 2010). Accordingly, a larger fraction of circulating FFA is derived from the visceral fat. The 'portal hypothesis' implicates that hyperglycaemia, hyperinsulinemia and eventually insulin resistance result from high levels of FFA in blood plasma (Heilbronn *et al.* 2004). It has been suggested that excess visceral fat, because of both its high lipolytic activity and its drainage into the portal system, can raise hepatic FFA uptake, as well as glucose and VLDL output, which altogether lead to impaired insulin responsiveness of the liver (Miyazaki *et al.* 2002). Along with the portal hypothesis, it was shown that the mass of visceral adipose tissue correlated with the development of insulin resistance, in contrast to total body fat mass and subcutaneous fat mass (Yang *et al.* 2008).

As compared to subcutaneous fat cells, visceral adipocytes display decreased expression of adiponectin

Table 2 Differences between omental (OM) and SAT in non-obese humans

Variable	Omental* (OM) vs. SAT	References
Adipocyte size	Smaller in OM fat than in SAT depots	Tchernof *et al.* (2006)†
β-agonists-stimulated lipolysis in preadipocytes‡	Higher in OM than in SAT-differentiated preadipocytes, higher levels of β1 and β3, lower level of β2-adrenoceptors' mRNA	Dicker *et al.* (2009)
Basal and β-agonists-stimulated lipolysis§	Lower rates in OM than SAT adipocytes	Tchernof *et al.* (2006)†
LPL activity§	Lower activity in OM fat than SAT adipose tissue	Tchernof *et al.* (2006)†
	Higher in OM fat than in SAT depots	Ruge *et al.* (2006)†¶
LPL mRNA levels	Lower in OM fat compared with SAT	Panarotto *et al.* (2000)†¶
	Higher in OM fat than in SAT	Ruge *et al.* (2006)†¶
GLUT4 and IRS-1 mRNA and protein expression	Lower mRNA levels in OM fat than in SAT; GLUT4 protein expression higher in OM fat than in SAT	Veilleux *et al.* (2009)†
Leptin secretion and mRNA expression	Lower in OM fat vs. SAT	Van Harmelen *et al.* (1998)†
Adiponectin secretion	Lower in OM fat vs. SAT	Drolet *et al.* (2009)†
VEGF, PAI-1 and IL-6 production‡	Higher in VS vs. SAT	Fain *et al.* (2004)†¶
FPA uptake	Higher in VS than in SAT; however, total FFA uptake was 1.5 times higher in SAT than VS fat	Hannukainen *et al.* (2010)¶, Bonen *et al.* (2006)†¶
PPARγ-agonist-stimulated preadipocyte differentiation	Higher in SAT vs. VS	Walker *et al.* (2008)†¶
Glucocorticoid receptor expression on preadipocytes‡	Lower glucocorticoid receptor density in VS vs. SAT preadipocytes in women but not men	Joyner *et al.* (2000)†,¶

GLUT4, glucose transporter type 4; IL-6, interleukin 6; IRS-1, insulin receptor substrate 1 LPL, lipoprotein lipase; PAI-1, plasminogen activator inhibitor 1; PPARγ, peroxisome proliferator-activated receptor γ; SAT, subcutaneous adipose tissue; VS, visceral; VEGF, vascular endothelial growth factor; FFA, free fatty acids.
*In human studies, omental white adipose tissue (WAT) was the most often used type of visceral WAT.
†Women.
‡In cell culture.
§Expressed as a function of cell number.
¶Men.

(Yang *et al.* 2008) and adiponectin's receptor (AdipoR1) genes (Rasmussen *et al.* 2006). Similarly, leptin mRNA expression and protein secretion was lower in omental WAT of both lean and obese women (Van Harmelen *et al.* 1998). Generally, visceral WAT secretes more pro-inflammatory cytokines, such as IL-6, than the subcutaneous fat depot (Fontana *et al.* 2007). Such expression profile contributes to systemic inflammation associated with visceral obesity and obesity-associated metabolic disorders like insulin resistance and cardiovascular diseases (Fontana *et al.* 2007, Torres-Leal *et al.* 2010).

Subcutaneous adipose tissue

The SAT is distributed over the body's surface in the hypodermal layer of the skin. In most regions of the human body, there are two anatomically and histologically distinct layers within the subcutaneous fat, that is the superficial and the deep SAT (dSAT) (Smith *et al.* 2001, Miyazaki *et al.* 2002, Walker *et al.* 2007, Sbarbati *et al.* 2010). In humans, SAT of the abdomen, described often as subcutaneous abdominal adipose tissue, is routinely subjected to medical examination, and it is commonly used in both *in vivo* and *in vitro* studies because of its relatively easy accessibility (Fain *et al.* 2004).

The well-known gender differences in the body's distribution of adipose tissue are best exemplified by excessive SAT accumulation in hips and thighs of women, forming the gluteofemoral fat depot. The amount of gluteofemoral fat can be estimated in a simple way by measuring hip or thigh circumference (Canoy 2008).

As stated before, comparative analyses of fat cell size gave discrepant results dependent on the measuring method. Nevertheless, as compared to visceral adipose tissue, subcutaneous fat is more cellularized, that is, it has a higher proportion of smaller cells because of the higher differentiation potential of subcutaneous adipocytes (Walker *et al.* 2007). Subcutaneous fat is more densely vascularized than visceral fat, and it

Table 3 Properties of various white adipose tissue depots in non-obese and obese humans

Variable	Non-obese	Obese	References
Adipocyte size	Not determined	Smaller in OM fat than SAT in women	Fried *et al.* 1993*†
Mitochondrial number and respiration rate	Not determined	More mitochondria and higher respiration rates in OM than SAT adipocytes	Kraunsoe *et al.* 2010*†
Lipolysis rate	No differences between OM and SAT adipocytes	Higher in OM fat than SAT fat	Hoffstedt *et al.* 1997†
Basal and NA-induced lipolysis in adipocytes	Not determined	Lower in OM adipocytes Lower in OM adipocytes	Ray *et al.* 2009* Fried *et al.* 1993*†
HSL mRNA and protein levels	mRNA expression lower in OM fat vs. SAT; similar HSL protein content in both depots	Similar as in lean subjects; in both depots mRNA amount 3× higher than in lean women	Ray *et al.* 2009*
Perilipin mRNA and protein levels	mRNA expression similar in OM fat vs. SAT; twofold higher protein level in OM fat vs. SAT	Twofold lower mRNA level in OM fat vs. SAT; similar protein level in both fat locations	Ray *et al.* 2009*
Fatty acid transporter FAT/CD36 protein expression	Higher by 50% in VS vs. SAT	Similar in VS and SAT depots	Bonen *et al.* 2006*†
Lipogenesis: DGAT activity	2× higher in OM fat vs. SAT	Similar in OM fat and SAT	Hou *et al.* 2009*†
Insulin-stimulated glucose uptake	Higher in VS vs. SAT	Similar as in non-obese men	Virtanen *et al.* 2002†
Adiponectin release by isolated adipocytes	Similar in OM and SAT adipocytes	Reduced in OM and unchanged in SAT fat cells	Drolet *et al.* 2009*
Expression of thyroid hormone receptors	Similar in OM and SAT adipocytes	TRα and TRα1 mRNA increased in SAT vs. OM fat	Ortega *et al.* 2009*
Expression of growth hormone receptor (GHR)	Higher GHR mRNA levels in OM fat than in SAT	Lower GHR mRNA in OM fat and SAT than in lean subjects	Erman *et al.* 2011*

DGAT, diacylglycerol acyltransferase; FAT/CD36, fatty acid transporter/cluster of differentiation 36; GHR, growth hormone receptor; HSL, hormone-sensitive lipase; NA, noradrenaline; OM, omental; SAT, subcutaneous adipose tissue; TRα, thyroid receptor α; VS, visceral.
*Women.
†Men.

retains higher angiogenic potential (Gealekman *et al.* 2011). SAT is regarded as less metabolically active than visceral adipose tissue. It was shown that gluteofemoral fat presented lower lipolytic activity than subcutaneous abdominal fat (Lafontan & Langin 2009) and preferentially picked up recycled lipids in the form of VLDL and FFA, rather than chylomicrons derived from dietary lipids (McQuaid *et al.* 2011). High gluteofemoral fat mass was associated with elevated high-density lipoproteins and decreased low-density lipoproteins blood serum levels in aged people (Snijder *et al.* 2005, Buemann *et al.* 2006). Subcutaneous fat is characterized by smaller rate of macrophage infiltration, which partly accounts for its lower production of pro-inflammatory cytokines in comparison to visceral WAT (Cancello *et al.* 2006). It was shown that SAT was responsible for most of the body's leptin synthesis (Van Harmelen *et al.* 1998). The amount of gluteofemoral fat also correlates positively with adiponectin serum levels (Buemann *et al.* 2006). From these data, a protective role of the gluteofemoral fat depot against diabetes and cardiovascular diseases has been inferred. Furthermore, in accordance with the 'overflow hypothesis', the high potential of subcutaneous fat for expansion may partly explain its protective effect against lipotoxicity. The 'overflow hypothesis' states that adipose tissue has limited capacity for fuel storage, and thus prolonged positive energy balance may eventually result in an 'overspill' of excess lipids to non-adipose tissues and disruption of their functions (Heilbronn *et al.* 2004).

However, subcutaneous adipose fat is a heterogeneous tissue – there are differences in the histological structure and metabolic properties of superficial SAT (sSAT) and dSAT, as well as SAT of different regions in the body (Sbarbati *et al.* 2010). While sSAT was not associated with the risk of type 2 diabetes, the size of dSAT depots correlated with fasting insulin serum concentration and insulin-stimulated glucose utilization (Smith *et al.* 2001, Miyazaki *et al.* 2002).

SAT, thanks to its relative metabolic inertia, serves primarily as a long-term triglyceride storage organ. It has been suggested that the role of SAT is to act as a metabolic buffer against excess of energy substrates during consumption of surplus dietary lipids as well as against shortage of energy substrates during periods of fasting, starvation and strenuous exercise (McQuaid *et al.* 2010). Therefore, it can be concluded that SAT, especially of the gluteofemoral region, indirectly protects the body against lipotoxicity and ectopic fat deposition.

Ectopic sites of fat accumulation

Surplus nutrients can be accommodated for by oxidizing them or depositing as energy stores in adipocytes. When nutrients' quantity exceeds adipose tissue's handling capacity, the overload of fuels is transferred to other organs. In states of nutritional overload, certain genetic programmes for the transport and storage of fatty acids can be induced in non-adipose tissues, leading to ectopic fat deposition. Sethi & Vidal-Puig (2007) demonstrated ectopic induction of PPARγ2 in peripheral organs of overnourished animals. This response might enhance the transport and storage of fatty acids and thus result in the accommodation for the fuel surplus. However, excessive fat accumulation impairs the functionality of such organs as the liver, skeletal muscles, pancreas, epicardium and wall of blood vessels (Heilbronn *et al.* 2004, Szendroedi & Roden 2009).

Lipid droplets can also be found in the sarcoplasm of skeletal muscle fibres in direct contact with mitochondria as so-called 'intramyocellular lipids' (IMCL) (Schrauwen-Hinderling *et al.* 2006). It has been hypothesized that these lipids provide fuel for mitochondrial oxidation, because fatty acids contribute significantly to energy requirements of skeletal muscles during endurance exercise (Bergman *et al.* 2010). On the other hand, in obese men, low intracellular lipid oxidation and turnover resulted in IMCL accumulation, which was correlated to a pre-diabetic state of insulin resistance (Perreault *et al.* 2010). It was shown that intermediates of fatty acid metabolism, for example diacylglycerols, may activate protein kinase C and subsequently inhibit insulin signal transduction in muscles (Samuel *et al.* 2010).

Apart from the intracellular lipids, skeletal muscles contain 'intermuscular adipose tissue' (IMAT) located between muscle bundles, which can be measured using whole-body MRI. It was found that the amount of IMAT was strongly associated with cardiovascular risk, similarly but independently of the visceral adipose tissue content (Yim *et al.* 2007). The involvement of IMAT in the development of insulin resistance can be inferred from its negative correlation with glucose infusion rates (Boettcher *et al.* 2009) as well as fasting glucose and total cholesterol levels (Yim *et al.* 2007). The amount of IMAT was shown to be associated with little physical activity and old age (Marcus *et al.* 2010).

Although epicardial adipose tissue, located just below the visceral layer of pericardium, is typically found also in lean people, its expansion in subjects with increased body mass index contributes to cardiovascular disorders. The epicardial fat is believed to act as a metabolic buffer in providing fatty acids to the coronary arteries and thus energy substrates for the myocardium. High expression of uncoupling protein 1 involved in heat generation suggests that the epicardial fat protects the heart against hypothermia (Sacks *et al.* 2009). The epicardial WAT secretes adiponectin, which protects the heart against metabolic or mechanical damage, as well as a variety of pro-inflammatory cytokines, which may contribute to coronary atherosclerosis (Vlasova *et al.* 2010). The amount of epicardial fat was demonstrated to correlate with insulin resistance and metabolic syndrome in obese adults (Mazur *et al.* 2010) as well as with carotid stiffness in hypertensive obese patients (Natale *et al.* 2009).

Perivascular adipose tissue is often present within the adventitia of large arteries, and thus, adipokines may directly affect their function. In particular, vessel tonicity may be regulated by renin-angiotensin system components produced by adipocytes, adiponectin, which has pleiotropic antihypertensive activities, and WAT-derived pro-inflammatory cytokines (Li *et al.* 2011). The anti-contractile effects of perivascular adipose tissue (Vlasova *et al.* 2010) may be suppressed in obesity (Aghamohammadzadeh *et al.* 2011), which adds another factor contributing to the development of hypertension in overweight people.

During advanced ageing, the total fat amount shows a tendency to decline or remains stable. However, a marked redistribution of adipose tissue from subcutaneous to intraabdominal and ectopic, mainly intramuscular depots, occurs (Garg & Agarwal 2009). These ageing-associated changes are accompanied by an increased risk of metabolic syndrome, adipose tissue chronic inflammation and decreased proliferation of preadipocytes (Sepe *et al.* 2011).

Conclusions

The emerging view on WAT biology encompasses the heterogeneity of WAT in relation to its localization. Some crucial aspects of the differences in the physiology of various fat depots, for example the association of metabolic syndrome-like complications with abdominal, but not peripheral obesity, have first arisen from clinical observations. Many authors have shown that visceral adipose tissue mass correlates with insulin resistance, while total or subcutaneous tissue mass does not. Animal studies allow to investigate the cellular and molecular mechanisms underlying the observed differences between various fat depots. The results of both animal and human investigations have apprehended the higher metabolic activity of the visceral depots and their role as a nutrient buffer, as opposed to long-term storage in the less metabolically active subcutaneous fat. Further studies will elucidate disparate roles of WAT depots in the development of diabetes, atherosclerosis and other obesity-associated diseases. It may be hoped that better understanding of regional differences in adipose tissue physiology will be applied to design more effective therapies against metabolic disorders and diseases.

Conflict of interest

The authors have no conflicts of interest to disclose.

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References

Aghamohammadzadeh, R., Withers, S., Lynch, F., Greenstein, A., Malik, R. & Heagerty, A. 2011. Perivascular adipose tissue from human systemic and coronary vessels: the emergence of a new pharmacotherapeutic target. *Br J Pharmacol* **13**, 1476–5381.

Ahmadian, M., Wang, Y. & Sul, H. 2010. Lipolysis in adipocytes. *Int J Biochem Cell Biol* **42**, 555–559.

Alligier, M., Meugnier, E., Debard, C., Lambert-Porcheron, S., Chanseaume, E., Sothier, M., Loizon, E., Ait Hssain, A., Brozek, J., Scoazec, J.Y., Morio, B., Vidal, H. & Laville, M. 2011. Subcutaneous adipose tissue remodeling during the initial phase of weight gain induced by overfeeding in humans. *J Clin Endocrinol Metab* doi: 10.1210/jc.2011-2314. [Epub ahead of print].

Anderson, E., Gutierrez, D. & Hasty, A. 2010. Adipose tissue recruitment of leukocytes. *Curr Opin Lipidol* **21**, 172–177.

Arner, P. 2005. Human fat cell lipolysis: biochemistry, regulation and clinical role. *Best Pract Res Clin Endocrinol Metab* **19**, 471–482.

Arner, P., Bernard, S., Salehpour, M., Possnert, G., Liebl, J., Steier, P., Buchholz, B., Eriksson, M., Arner, E., Hauner, H., Skurk, T., Rydén, M., Frayn, K. & Spalding, K. 2011. Dynamics of human adipose lipid turnover in health and metabolic disease. *Nature* **478**, 110–113.

Balamatsias, D., Kong, A., Waters, J., Sriratana, A., Gurung, R., Bailey, C., Rasko, J., Tiganis, T., Macaulay, S. & Mitchell, C. 2011. Identification of P-Rex1 as a novel Rac1-guanine nucleotide exchange factor (GEF) that promotes actin remodeling and GLUT4 protein trafficking in adipocytes. *J Biol Chem* **286**, 43229–43240.

Bartness, T.J. & Song, C.K. 2007. Brain-adipose tissue neural crosstalk. *Physiol Behav* **91**, 343–351.

Bartness, T., Shrestha, Y., Vaughan, C., Schwartz, G. & Song, C. 2010. Sensory and sympathetic nervous system control of white adipose tissue lipolysis. *Mol Cell Endocrinol* **318**, 34–43.

Bergman, B., Perreault, L., Hunerdosse, D., Koehler, M., Samek, A. & Eckel, R. 2010. Increased intramuscular lipid synthesis and low saturation relate to insulin sensitivity in endurance-trained athletes. *J Appl Physiol* **108**, 1134–1141.

Billon, N. & Dani, C. 2011. Developmental origins of the adipocyte lineage: new insights from genetics and genomics studies. *Stem Cell Rev* doi: 10.1007/s12015-011-9242-x. [Epub ahead of print].

Bjørndal, B., Burri, L., Staalesen, V., Skorve, J. & Berge, R. 2011. Different adipose depots: their role in the development of metabolic syndrome and mitochondrial response to hypolipidemic agents. *J Obes* doi: 10.1155/2011/490650. [Epub ahead of print].

Boettcher, M., Machann, J., Stefan, N., Thamer, C., Häring, H., Claussen, C., Fritsche, A. & Schick, F. 2009. Intermuscular adipose tissue (IMAT): association with other adipose tissue compartments and insulin sensitivity. *J Magn Reson Imaging* **29**, 1340–1345.

Bonen, A., Tandon, N., Glatz, J., Luiken, J. & Heigenhauser, G. 2006. The fatty acid transporter FAT/CD36 is upregulated in subcutaneous and visceral adipose tissues in human obesity and type 2 diabetes. *Int J Obes* **30**, 877–883.

Buemann, B., Astrup, A., Pedersen, O., Black, E., Holst, C., Toubro, S., Echwald, S., Holst, J., Rasmussen, C. & Sørensen, T. 2006. Possible role of adiponectin and insulin sensitivity in mediating the favorable effects of lower body fat mass on blood lipids. *J Clin Endocrinol Metab* **91**, 1698–1704.

Cancello, R., Tordjman, J., Poitou, C., Guilhem, G., Bouillot, J., Hugol, D., Coussieu, C., Basdevant, A., Bar Hen, A., Bedossa, P., Guerre-Millo, M. & Clement, K. 2006. Increased infiltration of macrophages in omental adipose tissue is associated with marked hepatic lesions in morbid human obesity. *Diabetes* **55**, 1554–1561.

Canoy, D. 2008. Distribution of body fat and risk of coronary heart disease in men and women. *Curr Opin Cardiol* **23**, 591–600.

Ceddia, R. 2005. Direct metabolic regulation in skeletal muscle and fat tissue by leptin: implications for glucose and fatty acids homeostasis. *Int J Obes* **29**, 1175–1183.

Cypess, A. & Kahn, C. 2010. Brown fat as a therapy for obesity and diabetes. *Curr Opin Endocrinol Diabetes Obes* **17**, 143–149.

Deveaud, C., Beauvoit, B., Salin, B., Schaeffer, J. & Rigoulet, M. 2004. Regional differences in oxidative capacity of rat

white adipose tissue are linked to the mitochondrial content of mature adipocytes. *Mol Cell Biochem* **267**, 157–166.

Dicker, A., Aström, G., Wåhlén, K., Hoffstedt, J., Näslund, E., Wirén, M., Rydén, M., Arner, P. & van Harmelen, V. 2009. Primary differences in lipolysis between human omental and subcutaneous adipose tissue observed using in vitro differentiated adipocytes. *Horm Metab Res* **41**, 350–355.

Divoux, A. & Clément, K. 2011. Architecture and the extracellular matrix: the still unappreciated components of the adipose tissue. *Obes Rev* **12**, e494–e503.

Drolet, R., Bélanger, C., Fortier, M., Huot, C., Mailloux, J., Légaré, D. & Tchernof, A. 2009. Fat depot-specific impact of visceral obesity on adipocyte adiponectin release in women. *Obesity (Silver Spring)* **17**, 424–430.

Erman, A., Veilleux, A., Tchernof, A. & Goodyer, C. 2011. Human growth hormone receptor (GHR) expression in obesity: I. GHR mRNA expression in omental and subcutaneous adipose tissues of obese women. *Int J Obes* **35**, 1511–1519.

Fain, J., Madan, A., Hiler, M., Cheema, P. & Bahouth, S. 2004. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. *Endocrinology* **145**, 2273–2282.

Fontana, L., Eagon, J., Trujillo, M., Scherer, P. & Klein, S. 2007. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes* **56**, 1010–1013.

Foster, M. & Bartness, T. 2006. Sympathetic but not sensory denervation stimulates white adipocyte proliferation. *Am J Physiol Regul Integr Comp Physiol* **291**, R1630–R1637.

Fried, S., Russell, C., Grauso, N. & Brolin, R. 1993. Lipoprotein lipase regulation by insulin and glucocorticoid in subcutaneous and omental adipose tissues of obese women and men. *J Clin Invest* **92**, 2191–2198.

Garg, A. & Agarwal, A. 2009. Lipodystrophies: disorders of adipose tissue biology. *Biochim Biophys Acta* **1791**, 507–513.

Gealekman, O., Guseva, N., Hartigan, C., Apotheker, S., Gorgoglione, M., Gurav, K., Tran, K., Straubhaar, J., Nicoloro, S., Czech, M., Thompson, M., Perugini, R. & Corvera, S. 2011. Depot-specific differences and insufficient subcutaneous adipose tissue angiogenesis in human obesity. *Circulation* **123**, 186–194.

Hannukainen, J., Kalliokoski, K., Borra, R., Viljanen, A., Janatuinen, T., Kujala, U., Kaprio, J., Heinonen, O., Viljanen, T., Haaparanta, M., Iozzo, P., Parkkola, R. & Nuutila, P. 2010. Higher free fatty acid uptake in visceral than in abdominal subcutaneous fat tissue in men. *Obesity (Silver Spring)* **18**, 261–265.

Heilbronn, L., Smith, S. & Ravussin, E. 2004. Failure of fat cell proliferation, mitochondrial function and fat oxidation results in ectopic fat storage, insulin resistance and type II diabetes mellitus. *Int J Obes Relat Metab Disord* **28**, S12–S21.

Hoffman, N. & Elmendorf, J. 2011. Signaling, cytoskeletal and membrane mechanisms regulating GLUT4 exocytosis. *Trends Endocrinol Metab* **22**, 110–116.

Hoffstedt, J., Amer, P., Hellers, G. & Lonnqvist, F. 1997. Variation in adrenergic regulation of lipolysis between omental and subcutaneous adipocytes from obese and non-obese men. *J Lipid Res* **38**, 795–804.

Hou, X., Moser, S., Sarr, M., Thompson, G., Que, F. & Jensen, M. 2009. Visceral and subcutaneous adipose tissue diacylglycerol acyltransferase activity in humans. *Obesity (Silver Spring)* **17**, 1129–1134.

Hovey, R. & Aimo, L. 2010. Diverse and active roles for adipocytes during mammary gland growth and function. *J Mammary Gland Biol Neoplasia* **15**, 279–290.

Iozzo, P. 2011. Myocardial, perivascular, and epicardial fat. *Diabetes Care* **34**, S371–S379.

Joyner, J., Hutley, J. & Cameron, D. 2000. Glucocorticoid receptors in human preadipocytes: regional and gender differences. *Endocrinol Metab* **284**, E1140–E1148.

Karamanlidis, G., Karamitri, A., Docherty, K., Hazlerigg, D. & Lomax, M. 2007. C/EBPbeta reprograms white 3T3-L1 preadipocytes to a brown adipocyte pattern of gene expression. *J Biol Chem* **282**, 24660–24669.

Khan, T., Muise, E., Iyengar, P., Wang, Z., Chandalia, M., Abate, N., Zhang, B., Bonaldo, P., Chua, S. & Scherer, P. 2009. Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI. *Mol Cell Biol* **29**, 1575–1591.

Kraunsoe, R., Boushel, R., Neigaard Hansen, C., Schjerling, P., Qvortrup, K., Støckel, M., Mikines, K. & Dela, F. 2010. Mitochondrial respiration in subcutaneous and visceral adipose tissue from patients with morbid obesity. *J Physiol* **588**, 2023–2032.

Kreier, F., Fliers, E., Voshol, P., Van Eden, C., Havekes, L., Kalsbeek, A., Van Heijningen, C., Sluiter, A., Mettenleiter, T., Romijn, J., Sauerwein, H. & Buijs, R. 2002. Selective parasympathetic innervation of subcutaneous and intra-abdominal fat–functional implications. *J Clin Invest* **110**, 1243–1250.

Lafontan, M. & Langin, D. 2009. Lipolysis and lipid mobilization in human adipose tissue. *Prog Lipid Res* **48**, 275–297.

Ledoux, S., Queguiner, I., Msika, S., Calderari, S., Rufat, P., Gasc, J., Corvol, P. & Larger, E. 2008. Angiogenesis associated with visceral and subcutaneous adipose tissue in severe human obesity. *Diabetes* **57**, 3247–3257.

Lee, M.-J., Wu, Y. & Fried, S. 2010. Adipose tissue remodeling in pathophysiology of obesity. *Curr Opin Clin Nutr Metab Care* **13**, 371–376.

Li, F., Cheng, K., Lam, K., Vanhoutte, P. & Xu, A. 2011. Cross-talk between adipose tissue and vasculature: role of adiponectin. *Acta Physiol (Oxf)* **203**, 167–180.

Macfarlane, D., Forbes, S. & Walker, B. 2008. Glucocorticoids and fatty acid metabolism in humans: fuelling fat redistribution in the metabolic syndrome. *J Endocrinol* **197**, 189–204.

Marcus, R., Addison, O., Kidde, J., Dibble, L. & Lastayo, P. 2010. Skeletal muscle fat infiltration: impact of age, inactivity, and exercise. *J Nutr Health Aging* **14**, 362–366.

Mariman, E. & Wang, P. 2010. Adipocyte extracellular matrix composition, dynamics and role in obesity. *Cell Mol Life Sci* **67**, 1277–1292.

Mazur, A., Ostanski, M., Telega, G. & Malecka-Tendera, E. 2010. Is epicardial fat tissue a marker of metabolic syndrome in obese children? *Atherosclerosis* **211**, 596–600.

McQuaid, S., Humphreys, S., Hodson, L., Fielding, B., Karpe, F. & Frayn, K. 2010. Femoral adipose tissue may accumulate the fat that has been recycled as VLDL and nonesterified fatty acids. *Diabetes* **59**, 2465–2473.

McQuaid, S., Hodson, L., Neville, M., Dennis, A., Cheeseman, J., Humphreys, S., Ruge, T., Gilbert, M., Fielding, B., Frayn, K. & Karpe, F. 2011. Downregulation of adipose tissue fatty acid trafficking in obesity: a driver for ectopic fat deposition? *Diabetes* **60**, 47–55.

Miller, N.E., Michel, C.C., Nanjee, M.N., Olszewski, W.L., Miller, I.P., Hazell, M., Olivecrona, G., Sutton, P., Humphreys, S.M. & Frayn, K.N. 2011. Secretion of adipokines by human adipose tissue in vivo: partitioning between capillary and lymphatic transport. *Am J Physiol Endocrinol Metab* **301**, E659–E667.

Miyazaki, Y., Glass, L., Triplitt, C., Wajcberg, E., Mandarino, L. & DeFronzo, R. 2002. Abdominal fat distribution and peripheral and hepatic insulin resistance in type 2 diabetes mellitus. *Am J Physiol* **283**, E1135–E1143.

Miyazawa-Hoshimoto, S., Takahashi, K., Bujo, H., Hashimoto, N., Yagui, K. & Saito, Y. 2005. Roles of degree of fat deposition and its localization on VEGF expression in adipocytes. *Am J Physiol Endocrinol Metab* **288**, E1128–E1136.

Natale, F., Tedesco, M., Mocerino, R., de Simone, V., Di Marco, G., Aronne, L., Credendino, M., Siniscalchi, C., Calabrò, P., Cotrufo, M. & Calabrò, R. 2009. Visceral adiposity and arterial stiffness: echocardiographic epicardial fat thickness reflects, better than waist circumference, carotid arterial stiffness in a large population of hypertensives. *Eur J Echocardiogr* **10**, 549–555.

Ohsaki, Y., Cheng, J., Suzuki, M., Shinohara, Y., Fujita, A. & Fujimoto, T. 2009. Biogenesis of cytoplasmic lipid droplets: from the lipid ester globule in the membrane to the visible structure. *Biochim Biophys Acta* **1791**, 399–407.

Ortega, F., Moreno-Navarrete, J., Ribas, V., Esteve, E., Rodriguez-Hermosa, J., Ruiz, B., Peral, B., Ricart, W., Zorzano, A. & Fernández-Real, J. 2009. Subcutaneous fat shows higher thyroid hormone receptor-α1 gene expression than omental fat. *Obesity* **17**, 2134–2141.

Ouchi, N., Parker, J., Lugus, J. & Walsh, K. 2010. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* **11**, 85–97.

Palou, M., Priego, T., Sánchez, J., Rodriguez, A., Palou, A. & Pico, C. 2009. Gene expression patterns in visceral and subcutaneous adipose depots in rats are linked to their morphologic features. *Cell Physiol Biochem* **24**, 547–556.

Palou, M., Sanchez, J., Priego, T., Rodriguez, A., Pico, C. & Palou, A. 2010. Regional differences in the expression of genes involved in lipid metabolism in adipose tissue in response to short- and medium-term fasting and refeeding. *J Nutr Biochem* **21**, 23–33.

Panarotto, D., Poisson, J., Devroede, G. & Maheux, P. 2000. Lipoprotein lipase steady-state mRNA levels are lower in human omental versus subcutaneous abdominal adipose tissue. *Metabolism* **49**, 1224–1227.

Perreault, L., Bergman, B., Hunerdosse, D. & Eckel, R. 2010. Altered intramuscular lipid metabolism relates to diminished insulin action in men, but not women, in progression to diabetes. *Obesity (Silver Spring)* **18**, 2093–2100.

Pijl, H. 2011. Obesity: evolution of a symptom of affluence. *Neth J Med* **69**, 159–166.

Rasmussen, M., Lihn, A., Pedersen, S., Bruun, J., Rasmussen, M. & Richelsen, B. 2006. Adiponectin receptors in human adipose tissue: effects of obesity, weight loss, and fat depots. *Obesity* **14**, 28–35.

Ray, H., Pinteur, C., Frering, V., Beylot, M. & Large, V. 2009. Depot-specific differences in perilipin and hormone-sensitive lipase expression in lean and obese. *Lipids Health Dis* **18**, 8–58.

Ruge, T., Sukonina, V., Myrnäs, T., Lundgren, M., Eriksson, J. & Olivecrona, G. 2006. Lipoprotein lipase activity/mass ratio is higher in omental than in subcutaneous adipose tissue. *Eur J Clin Invest* **36**, 16–21.

Sacks, H., Fain, J., Holman, B., Cheema, P., Chary, A., Parks, F., Karas, J., Optican, R., Bahouth, S., Garrett, E., Wolf, R., Carter, R., Robbins, T., Wolford, D. & Samaha, J. 2009. Uncoupling protein-1 and related messenger ribonucleic acids in human epicardial and other adipose tissues: epicardial fat functioning as brown fat. *J Clin Endocrinol Metab* **94**, 3611–3615.

Samuel, V., Petersen, K. & Shulman, G. 2010. Lipid-induced insulin resistance: unravelling the mechanism. *Lancet* **375**, 2267–2277.

Sato, K., Umeno, H. & Nakashima, T. 2005. Histological investigation of liposuctioned fat for injection laryngoplasty. *Otolaryngol Head Neck Surg* **26**, 219–225.

Sbarbati, A., Accorsi, D., Benati, D., Marchetti, L., Orsini, G., Rigotti, G. & Panettiere, P. 2010. Subcutaneous adipose tissue classification. *Eur J Histochem* **54**, e48.

Schrauwen-Hinderling, V., Hesselink, M., Schrauwen, P. & Kooi, M. 2006. Intramyocellular lipid content in human skeletal muscle. *Obesity (Silver Spring)* **14**, 357–367.

Schulz, T.J., Huang, T.L., Tran, T.T., Zhang, H., Townsend, K.L., Shadrach, J.L., Cerletti, M., McDougall, L.E., Giorgadze, N., Tchkonia, T., Schrier, D., Falb, D., Kirkland, J.L., Wagers, A.J. & Tseng, Y.H. 2011. Identification of inducible brown adipocyte progenitors residing in skeletal muscle and white fat. *Proc Natl Acad Sci U S A* **108**, 143–148.

Sell, H. & Eckel, J. 2010. Adipose tissue inflammation: novel insight into the role of macrophages and lymphocytes. *Curr Opin Clin Nutr Metab Care* **13**, 366–370.

Sepe, A., Tchkonia, T., Thumou, T., Zamboni, M. & Kirkland, J.L. 2011. Aging and regional differences in fat cell progenitors - a mini-review. *Gerontology* **57**, 66–75.

Sethi, J. & Vidal-Puig, A. 2007. Thematic review series: adipocyte biology. Adipose tissue function and plasticity orchestrate nutritional adaptation. *J Lipid Res* **48**, 1253–1262.

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Shay, C., Secrest, A., Goodpaster, B., Kelsey, S., Strotmeyer, E. & Orchard, T. 2010. Regional adiposity and risk for coronary artery disease in type 1 diabetes: does having greater amounts of gluteal-femoral adiposity lower the risk? *Diabetes Res Clin Pract* **89**, 288–295.

Skurk, T., Alberti-Huber, C., Herder, C. & Hauner, H. 2007. Relationship between adipocyte size and adipokine expression and secretion. *J Clin Endocrinol Metab* **92**, 1023–1033.

Smith, S., Lovejoy, J., Greenway, F., Ryan, D., de Jonge, L., de la Bretonne, J., Volafova, J. & Bray, G. 2001. Contributions of total body fat, abdominal subcutaneous adipose tissue compartments, and visceral adipose tissue to the metabolic complications of obesity. *Metabolism* **50**, 425–435.

Snijder, M., Visser, M., Dekker, J., Goodpaster, B., Harris, T., Kritchevsky, S., De Rekeneire, N., Kanaya, A., Newman, A., Tylavsky, F., Seidell, J.; Health ABC Study. 2005. Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. The Health ABC Study. *Diabetologia* **48**, 301–308.

Song, C.K., Schwartz, G.J. & Bartness, T.J. 2009. Anterograde transneuronal viral tract tracing reveals central sensory circuits from white adipose tissue. *Am J Physiol Regul Integr Comp Physiol* **296**, R501–R511.

Spalding, K., Arner, E., Westermark, P., Bernard, S., Buchholz, B., Bergmann, O., Blomqvist, L., Hoffstedt, J., Näslund, E., Britton, T., Concha, H., Hassan, M., Rydén, M., Frisén, J. & Arner, P. 2008. Dynamics of fat cell turnover in humans. *Nature* **453**, 783–787.

Spencer, M., Unal, R., Zhu, B., Rasouli, N., McGehee, R., Peterson, C. & Kern, P. 2011. Adipose tissue extracellular matrix and vascular abnormalities in obesity and insulin resistance. *J Clin Endocrinol Metab* **96**, E1990–E1998.

Suganami, T. & Ogawa, Y. 2010. Adipose tissue macrophages: their role in adipose tissue remodeling. *J Leukoc Biol* **88**, 33–39.

Szendroedi, J. & Roden, M. 2009. Ectopic lipids and organ function. *Curr Opin Lipidol* **20**, 50–56.

Tchernof, A., Bélanger, C., Morisset, A., Richard, C., Mailloux, J., Laberge, P. & Dupont, P. 2006. Regional differences in adipose tissue metabolism in women: minor effect of obesity and body fat distribution. *Diabetes* **55**, 1353–1360.

Tchkonia, T., Giorgadze, N., Pirtskhalava, T., Tchoukalova, Y., Karagiannides, I., Forse, R., DePonte, M., Stevenson, M., Guo, W., Han, J., Waloga, G., Lash, T., Jensen, M. & Kirkland, J. 2002. Fat depot origin affects adipogenesis in primary cultured and cloned human preadipocytes. *Am J Physiol Regul Integr Comp Physiol* **282**, R1286–R1296.

Tchkonia, T., Tchoukalova, Y.D., Giorgadze, N., Pirtskhalava, T., Karagiannides, I., Forse, R.A., Koo, A., Stevenson, M., Chinnappan, D., Cartwright, A., Jensen, M. & Kirkland, J. 2005. Abundance of two human preadipocyte subtypes with distinct capacities for replication, adipogenesis, and apoptosis varies among fat depots. *Am J Physiol* **288**, E267–E277.

Tchkonia, T., Lenburg, M., Thomou, T., Giorgadze, N., Frampton, G., Pirtskhalava, T., Cartwright, A., Cartwright, M., Flanagan, J., Karagiannides, I. *et al.* 2007. Identification of depot specific human fat cell progenitors through distinct expression profiles and developmental gene patterns. *Am J Physiol* **292**, E298–E307.

Toh, S., Gong, J., Du, G., Li, J., Yang, S., Ye, J., Yao, H., Zhang, Y., Xue, B., Li, Q., Yang, H., Wen, Z. & Li, P. 2008. Up-regulation of mitochondrial activity and acquirement of brown adipose tissue-like property in the white adipose tissue of *Fsp27* deficient mice. *PLoS ONE* **3**, e2890.

Torres-Leal, F.L., Fonseca-Alaniz, M.H., Rogero, M.M. & Tirapegui, J. 2010. The role of inflamed adipose tissue in the insulin resistance. *Cell Biochem Funct* **28**, 623–631.

Van Harmelen, V., Reynisdottir, S., Eriksson, P., Thorne, A., Hoffstedt, J., Lonnqvist, F. & Arner, P. 1998. Leptin secretion from subcutaneous and visceral adipose tissue in women. *Diabetes* **47**, 913–917.

Veilleux, A., Blouin, K., Rhéaume, C., Daris, M., Marette, A. & Tchernof, A. 2009. Glucose transporter 4 and insulin receptor substrate–1 messenger RNA expression in omental and subcutaneous adipose tissue in women. *Metabolism* **58**, 624–631.

Verstraeten, V., Renes, J., Ramaekers, F., Kamps, M., Kuijpers, H., Verheyen, F., Wabitsch, M., Steijlen, P., van Steensel, M. & Broer, J. 2011. Reorganization of the nuclear lamina and cytoskeleton in adipogenesis. *Histochem Cell Biol* **135**, 251–261.

Virtanen, K., Lonnroth, P., Parkkola, R., Peltoniemi, P., Asola, M., Viljanen, T., Tolvanen, T., Knuuti, J., Ronnemaa, T., Huupponen, R. & Nuutila, P. 2002. Glucose uptake and perfusion in subcutaneous and visceral adipose tissue during insulin stimulation in nonobese and obese humans. *J Clin Endocrinol Metab* **87**, 3902–3910.

Virtue, S. & Vidal-Puig, A. 2010. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome - an allostatic perspective. *Biochim Biophys Acta* **1801**, 338–349.

Vlasova, M., Purhonen, A., Jarvelin, M., Rodilla, E., Pascual, J. & Herzig, K. 2010. Role of adipokines in obesity-associated hypertension. *Acta Physiol (Oxf)* **200**, 107–127.

Walker, G., Verti, B., Marzullo, P., Savia, G., Mencarelli, M., Zurleni, F., Liuzi, A. & Di Blasio, A. 2007. Cellular and molecular deep subcutaneous adipose tissue: a distinct abdominal adipose depot. *Obesity* **15**, 1933–1943.

Walker, G., Marzullo, P., Verti, B., Guzzaloni, G., Maestrini, S., Zurleni, F., Liuzzi, A. & Di Blasio, A. 2008. Subcutaneous abdominal adipose tissue subcompartments: potential role in rosiglitazone effects. *Obesity* **16**, 1983–1991.

Wolfs, M., Rensen, S., Bruin-Van Dijk, E., Verdam, F., Greve, J., Sanjabi, B., Bruinenberg, M., Wijmenga, C., van Haeften, T., Buurman, W., Franke, L. & Hofker, M. 2010. Co-expressed immune and metabolic genes in visceral and subcutaneous adipose tissue from severely obese individuals are associated with plasma HDL and glucose levels: a microarray study. *BMC Med Genomics* **5**, 3–34.

Xu, A., Wang, Y., Lam, K. & Vanhoutte, P. 2010. Vascular actions of adipokines: molecular mechanisms and therapeutic implications. *Adv Pharmacol* **60**, 229–255.

Yamamoto, Y., Gesta, S., Lee, K., Tran, T., Saadatirad, P. & Kahn, C. 2010. Adipose depots possess unique developmental gene signatures. *Obesity (Silver Spring)* **18**, 872–878.

Yang, Y., Chen, M., Clements, R., Abrams, J., Aprahamian, C. & Harmon, C. 2008. Human mesenteric adipose tissue plays unique role versus subcutaneous and omental fat in obesity related diabetes. *Cell Physiol Biochem* **22**, 531–538.

Yang, K., Guan, H., Arany, E., Hill, D. & CaoYarak, X. 2010. Neuropeptide Y is produced in visceral adipose tissue and promotes proliferation of adipocyte precursor cells via the Y1 receptor. *FASEB J* **22**, 2452–2464.

Yarak, S. & Okamoto, O. 2010. Human adipose-derived stem cells: current challenges and clinical perspectives. *An Bras Dermatol* **85**, 647–656.

Ye, J. 2011. Adipose tissue vascularization: its role in chronic inflammation. *Curr Diab Rep* **11**, 203–210.

Yim, J., Heshka, S., Albu, J., Heymsfield, S., Kuznia, P., Harris, T. & Gallagher, D. 2007. Intermuscular adipose tissue rivals visceral adipose tissue in independent associations with cardiovascular risk. *Int J Obes* **31**, 1400–1405.

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