Chapter 5
White Adipose Tissue

Stephane Gesta and C. Ronald Kahn

Abstract White adipose tissue (WAT) is one of the most abundant tissues in mammals, exhibiting numerous complex functions. The primary purpose of WAT is to store excess energy in the form of fat for future use by other cells of the organism during periods of energy deprivation. In order to do this, white adipocytes acquire the expression of specific enzymes during their differentiation, which enable both the accumulation and mobilization of fat. Fat accumulation is achieved by de novo synthesis of fatty acids (lipogenesis) as well as fatty acid uptake, while fat mobilization is accomplished during lipolysis. Both processes are regulated by various hormones including insulin and catecholamines. In addition, WAT secretes various factors, known as adipokines, which can act locally or distally on other tissues. These adipokines, which include leptin, adiponectin, RBP4, and others, are involved in the regulation of whole body energy homeostasis. In mammals, WAT is distributed throughout the body in two main depots, located subcutaneously and intra-abdominally. In obesity, intra-abdominal fat accumulation is strongly associated with the development of related diseases, including type 2 diabetes, while accumulation of subcutaneous fat exhibits no correlation. This phenomenon is the result of differences in anatomical location and developmental intrinsic properties of subcutaneous and intra-abdominal white adipose depots. In this chapter, we discuss how the developmental origins of fat may play a role in the heterogeneity of WAT distribution and function and the impact of fat distribution on obesity-related diseases.

Keywords White adipose tissue • Anatomy • Metabolism • Adipokines

5.1 Introduction

Every organism must have the ability to acquire and use energy to live. While simple organisms, like bacteria, acquire energy only in response to their immediate needs and are therefore highly dependent on the constant presence of energy sources in their ecosystem for survival, higher organisms have developed mechanisms to

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store excess energy which can be used as fuel when external energy sources are limited. For this, in virtually all animal species, from *Caenorhabditis elegans* to *Homo sapiens*, the major form of energy storage is fat. In most higher animal species, this is done in a specialized tissue – adipose tissue.

In mammals, adipose tissue exists in two forms, white adipose tissue (WAT) and brown adipose tissue (BAT), each performing different functions. The primary role of BAT is to store only small amounts of fat that can be used, when needed, to produce heat and maintain body temperature (Nicholls and Locke 1984). WAT, on the other hand, is designed to store large amounts of excess energy in the form of triglycerides for use during periods of food deprivation. This requires the process of lipogenesis as well as triglyceride uptake for accumulation of fat, and the mobilization of this energy for use by other cells of the organism through the process of lipolysis. In addition, WAT has an endocrine function which contributes to the regulation of whole body energy homeostasis through the secretion of various adipose-derived hormones or adipokines.

WAT is the most abundant tissue in mammals, and its bodily distribution varies greatly among species, as well as between individuals from the same species. Generally, WAT is considered to exist in two main depots: the subcutaneous adipose tissue located beneath the skin and the intra-abdominal adipose tissue, which is present surrounding the intestine, kidneys, and in rodents, the gonads. These depots harbor major differences in their properties and function. When excessive fat accumulation occurs in obesity, whether it is deposited in the subcutaneous or intra-abdominal depots has a very different impact on the development of obesity-related diseases.

5.2 Development of WAT: Adipocyte Differentiation

The major lipid storage cell in WAT is the white adipocyte which conducts the primary functions of WAT, e.g., lipid and glucose transport, fatty acid synthesis and mobilization, regulation of insulin sensitivity, and endocrine function. These cells are derived from undifferentiated preadipocytes, which undergo terminal differentiation through a complex process orchestrated by a transcriptional cascade involving the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) and members of the CCAAT/enhancer-binding protein (C/EBP) family (Farmer 2006). Over the past 3 decades, these transcriptional events have been extensively studied using 3T3-L1 and 3T3-F442A preadipocyte cell lines (Rosen and Spiegelman 2000; Rosen and MacDougald 2006). In these cultured preadipocytes, induction of adipocyte differentiation is under the control of hormonal stimuli including glucocorticoids, cyclic adenosine monophosphate (cAMP), and the insulin/IGF-1 pathways. In culture, this induction occurs during the first 2 days of differentiation and involves a sequential transciptional cascade beginning with a transient high expression of C/EBPβ and C/EBPδ, which in turn promotes the expression of the transcription factors involved in terminal adipocyte differentiation, C/EBPα and PPARγ. These two

latter transcription factors cooperate to induce terminal differentiation by increasing the expression of genes involved in the acquisition of adipocyte function, such as the glucose transporter (GLUT) 4, the fatty acid transporter aP2, the insulin receptor, and the enzymes involved in triglyceride synthesis (e.g., fatty acid synthase [FAS]) and lipolysis (e.g., hormone sensitive lipase [HSL]) (Rosen and Spiegelman 2000; Farmer 2006). A similar transcriptional cascade and pattern of differentiation is observed with brown preadipocytes in culture (Tseng et al. 2008).

In order to understand the relative importance of these transcription factors in controlling adipocyte differentiation, the role played by PPARγ and the C/EBPs has been carefully dissected using gain and loss of function studies both in vitro and in vivo. PPARγ plays a critical role in the control of adipogenesis and has been demonstrated to be necessary and sufficient for adipocyte differentiation. Indeed, forced expression of PPARγ is sufficient to induce adipocyte differentiation of non-adipogenic fibroblastic cells (Tontonoz et al. 1994b). Conversely, loss of function of PPARγ reduces or eliminates adipogenesis in vivo and in vitro (Barak et al. 1999; Rosen et al. 1999; Kubota et al. 1999). PPARγ also appears to be required for maintenance of the terminal differentiated state of adipocytes, and expression of a dominant negative PPARγ in differentiated 3T3-L1 cells induces dedifferentiation with loss of lipid accumulation and decreased expression of adipocytes markers (Tamori et al. 2002). Likewise, an inducible knockout of PPARγ in mature adipocytes in vivo leads to death of both brown and white adipocytes followed by generation of new adipocytes (Imai et al. 2004). However, mice with adipocyte-specific inactivation of the *Pparg* gene still develop some WAT, suggesting some mechanism of escape from this genetic manipulation (He et al. 2003).

There are two isoforms of PPARγ, PPARγ1 and PPARγ2, that are generated by alternative splicing and alternative promoter usage of the *Pparg* gene (Fajas et al. 1997; Tontonoz et al. 1994a). While both are expressed in the adipocyte, PPARγ2 is more specific to white and brown adipocytes and has been regarded as a specific marker of these cell types (Tontonoz et al. 1994a). However, mice with germline knockout of PPARγ2 still have some WAT, suggesting that PPARγ1 has the ability to compensate for many of the adipogenic functions of PPARγ2 (Zhang et al. 2004; Medina-Gomez et al. 2005). Interestingly, mice with PPARγ2 knockout develop whole body insulin resistance, suggesting a specific role for PPARγ2 in the control of insulin sensitivity, independent of its effects on adipogenesis (Medina-Gomez et al. 2005). Together, these studies have led to the now commonly used characterization of PPARγ as the "master regulator" of adipogenesis.

However, it is important to note that PPARγ expression during adipocyte differentiation is partly under the control of the C/EBP transcription factors. Indeed, the transient expression of C/EBPβ and C/EBPδ during early adipocyte differentiation has been shown to promote the expression of C/EBPα and PPARγ (Farmer 2006). Indeed, forced expression of C/EBPβ in 3T3-L1 cells can promote adipocyte differentiation even in the absence of the required hormonal inducers (Yeh et al. 1995). Overexpression of C/EBPδ, on the other hand, accelerates the process of differentiation after it is triggered by these agents (Yeh et al. 1995). Although expression of C/EBPβ and C/EBPδ appears earlier than PPARγ during the progression of adipocyte

differentiation, it seems that these two factors are not absolutely required for WAT development. Mice deficient in the *Cebpb* gene have a reduced WAT mass; however, mesenchymal embryonic fibroblasts (MEFs) derived from these mice are still able to differentiate into adipocytes in vitro, albeit with reduced efficiency (Tanaka et al. 1997). Furthermore, mice with deletion of both C/EBPβ and C/EBPδ still develop some WAT (Tanaka et al. 1997).

The transcription factor C/EBPα, like PPARγ, appears to be essential for adipocyte differentiation in vitro. MEFs derived from C/EBPα deficient mice lose their capacity to differentiate into adipocytes. Interestingly, although forced expression of PPARγ in these cells restores their adipogenic capacity, these cells present several defects in triglyceride storage and insulin-stimulated glucose transport capacitiy. In addition, while forced overexpression of PPARγ in *C/ebpa*$^{-/-}$ MEFs can restore adipocyte differentiation, forced expression of C/EBPα in *Pparg*$^{-/-}$ MEFs is unable to restore the adipocyte differentiation capacity of these cells, suggesting that PPARγ is a dominant factor controlling adipocyte differentiation. In vivo, C/EBPα has been shown to be essential for the development of only certain adipose depots. Although germline deletion of the *C/ebpa* gene is postnatal lethal due to the critical role played by C/EBPα in the control of gluconeogenesis in liver (Wang et al. 1995), re-expression of *C/ebpa* in the liver rescues these mice from death and these animals present with an absence of subcutaneous, perirenal, and epididymal WAT, but near normal WAT in the mammary gland (Linhart et al. 2001). Furthermore, in these mice, BAT is actually somewhat hypertrophied. These observations indicate a depot-specific importance played by C/EBPα in the development of adipose tissue, as well as intrinsic developmental differences which exist in the formation of the various adipose depots in mice.

5.3 Functions of WAT

5.3.1 Metabolic Function of WAT

One of the main characteristics of the energy metabolism in mammals is that energy utilization by cells is continuous, whereas energy intake is discontinuous. Therefore, to maintain energy balance and address the needs of all cells, the organism must be able to store and quickly mobilize excess energy sources. This requires two closely related energetic compartments. The first is a circulating compartment, i.e., the blood, which continuously provides energy to the cells. The second is the WAT, which constitutes a storage compartment constantly exchanging substrates with the circulating compartment. Only glucose and fatty acids, which are the two principal energy sources of the organism, can be stored in WAT in the form of triglycerides. For this, WAT can take up and transform the glucose into fatty acids, through the process of lipogenesis. Following this, intracellular glycerol is esterified with fatty acids derived from the circulation or lipogenesis, to form triglycerides (Fig. 5.1).

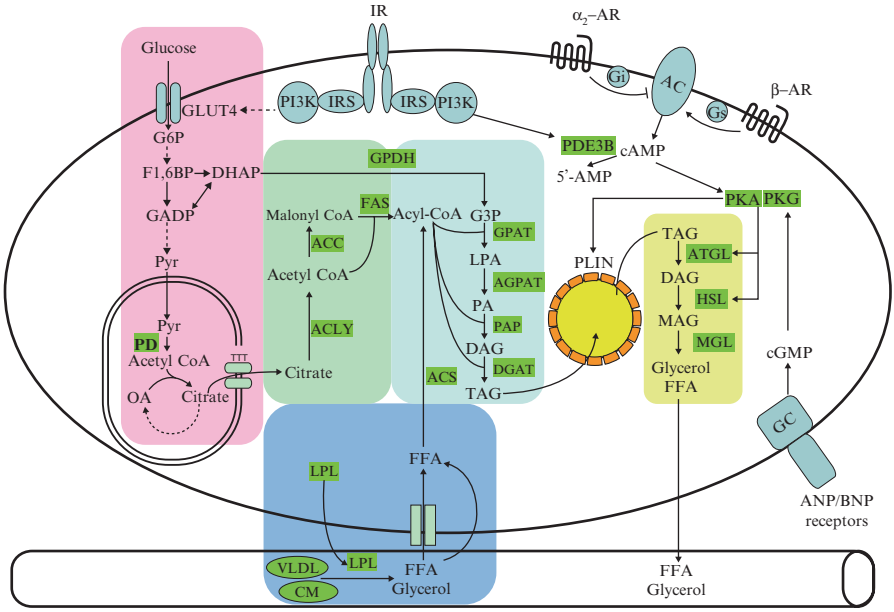

Fig. 5.1 Metabolic functions of WAT. The main metabolic functions of WAT are the storage of energy in the form of triglycerides and the mobilization of this energy when it is required by the body. In WAT, triglycerides can be synthesized (*turquoise box*) following the uptake and metabolism of glucose (*pink box*) by the process of de novo lipogenesis (*green box*) and/or after the uptake of free fatty acids from the circulation (*blue box*). The triglycerides stored in the adipocyte can be hydrolyzed by the process of lipolysis (*yellow box*), which delivers free fatty acids to the circulation. These processes are regulated by the insulin pathway, the adrenergic pathway and the atrial natriuetic hormone pathways. *α2-AR* α2-adrenergic receptor; *β-AR* β-adrenergic receptor; *5′-AMP 5′-adenosine monophosphate*; *AC* adenylate cyclase; *ACC* acetyl-CoA carboxylase; *ACLY* ATP citrate lyase; *ACS* acyl-CoA synthetase; *AGPAT* 1-acylglycerol-3-phosphate *O*-acyltransferase; *ANP* atrial natriuretic peptide; *ATGL* adipose triglyceride lipase; *BNP* brain natriuretic peptide; *cAMP* cyclic adenosine monophosphate; *cGMP* cyclic guanosine monophosphate; *CM* chylomicron; *DAG* diacylglycerol; *DGAT* diacylglycerol acyltransferase; *DHAP* dihydroxyacetone phosphate; *F1,6BP* fructose 1,6 bisphosphate; *FAS* fatty acid synthase; *FFA* free fatty acid; *G3P* glycerol-3-phosphate; *G6P* glucose 6 phosphate; *GADH* glyceraldehyde 3-phosphate; *GC* guanylate cyclase; *Gi* Gαi protein; *GLUT4* glucose transporter 4; *GPAT* glycerol 3-phosphate acyltransferase; *GPDH* glycerol-3-phosphate dehydrogenase; *Gs* Gαs protein; *HSL* hormone sensitive lipase; *IR* insulin receptor; *IRS* insulin receptor substrate; *LPA* lysophosphatidic acid; *LPL* lipoprotein lipase; *MAG* monoacylglycerol; *MGL* monoacylglycerol lipase; *OA* oxaloacetate; *PA* phosphatidic acid; *PAP* phosphatidic acid phosphatase; *PDE3B* phosphodiesterase 3B; *PI3K* phosphatidylinositol 3-kinase; *PKA* cAMP-dependent protein kinase; *PKG* cGMP-dependent protein kinase; *PLIN* perilipin; *Pyr* pyruvate; *PD* pyruvate dehydrogenase; *TAG* triacylglycerol; *TTT* tripartite tricarboxylate transporter; *VLDL* very low density lipoprotein

5.3.1.1 Adipose Tissue Lipogenesis

Lipogenesis ensures the de novo synthesis of fatty acids from glucose for storage. This occurs in WAT and liver. While lipogenesis in rodents is considered to generate an important amount of the triglycerides stored in WAT, lipogenesis only minimally contributes to the total body lipid storage in humans (Hellerstein

1999). De novo fatty acid synthesis requires the production of cytoplasmic acetyl-coenzyme A (CoA) from metabolism of glucose. For this, glucose enters the cells through specific GLUTs and is then metabolized to pyruvate via glycolysis. Under aerobic conditions, pyruvate enters the mitochondria and is transformed by pyruvate dehydrogenase into acetyl-CoA which then enters the tricarboxylic acid cycle to be condensed with oxaloacetate to form citrate. Citrate is then able to leave the mitochondria and enter the cytoplasm, through the mitochondrial tricarboxylate transporter (Kaplan et al. 1993). This cytoplasmic citrate is then broken down by citrate lyase to give cytoplasmic acetyl-CoA, which is the mainstay of de novo fatty acid synthesis.

Fatty acid synthesis is carried out by the sequential action of two cytosolic enzymatic systems: acetyl-CoA carboxylase (ACC), which mediates the formation of malonyl-CoA from acetyl-CoA, and the multi-enzyme complex referred to as FAS, which mediates elongation of malonyl-CoA to acyl-CoAs with various carbon chain lengths by the successive addition of acetyl-CoA molecules.

Key enzymes of de novo fatty acid synthesis can be controlled by hormones, especially insulin, or metabolites. Thus, glucose uptake in adipocytes is increased after insulin stimulation by its transfer across the plasma membrane by GLUT4 (James et al. 1988). This process is reduced by high intracellular levels of ATP (Begum et al. 1993). Pyruvate dehydrogenase is also activated by insulin through dephosphorylation of its alpha subunit (Macaulay and Jarett 1985), and can be inactivated when the ratio of ATP/ADP, NADH/NAD+ or acetyl-CoA/CoA are increased (Pettit et al. 1975). FAS and ACC gene expression have both been shown to be upregulated by insulin, but this regulation is dependent on the presence of glucose, as insulin alone has no effect on these genes. Thus, insulin indirectly increases the gene expression of FAS and ACC by stimulating glucose metabolism through the regulation of glucose transport (Foufelle et al. 1992). In addition, insulin activates ACC, via activation of protein phosphatases which dephosphorylate the enzyme (Witters et al. 1988).

Deletion of the insulin receptor in adipose tissue of mice (the fat insulin receptor knockout (FIRKO)) leads to a 90% decrease in insulin-stimulated glucose uptake and a corresponding decrease in insulin-stimulated incorporation of glucose into triglycerides, lactate, and carbon dioxide (Bluher et al. 2002). These mice have a ~50% reduction in WAT mass and are protected against diet-induced obesity. Unexpectedly, histological examination of FIRKO fat tissue also reveals that a small subset of adipocytes (~45%) are protected from excessive triglyceride load, whereas a second subset maintains normal triglyceride storage capacity, despite a 90% decrease in insulin-stimulated lipogenesis. This adipocyte knockout unveils intrinsic differences of adipocytes within a given WAT depot.

5.3.1.2 Fatty Acid Uptake

As noted above, de novo lipogenesis in adipose tissue makes only a minor contribution to total lipid storage in humans. In fact, in humans, most de novo lipogenesis and triglyceride synthesis occurs in the liver, after which triglycerides are

transported in the circulation by very low density lipoproteins (VLDL) to peripheral tissues including WAT. The main source of fat accumulation in human WAT, therefore, comes from the uptake of circulating triglycerides and fatty acids from VLDL produced in the liver and chylomicrons produced by absorption of fat in the small intestine. In order for fatty acids to be stored in the WAT, triglycerides from chylomicrons and VLDL must first be processed in the extracellular space by the enzyme lipoprotein lipase (LPL). This enzyme is produced by various tissues, including WATs and BATs, skeletal muscle, heart, mammary gland, brain, and macrophages (Camps et al. 1990; Goldberg et al. 1989; Khoo et al. 1981). Low levels of LPL activity can also be found in liver, spleen, and lung, where it is found in Kupffer cells and infiltrating macrophages (Camps et al. 1991; Neuger et al. 2004).

In adipose tissue, LPL is secreted by the adipocytes and released into the lumen of capillaries where it becomes anchored to endothelial cells. Here, this enzyme interacts with chylomicrons and VLDL to liberate fatty acids and monoacylglycerol (MAG), facilitating their uptake (Seo et al. 2000). LPL activity depends on its interaction with the co-factor apoC-II (Kinnunen et al. 1977) and in adipocytes apoC-II expression and activity is increased by insulin (Semenkovich et al. 1989). Interestingly, this regulation appears to be both depot and gender dependent. In humans, regulation of LPL expression and activity by insulin is observed in subcutaneous, but not omental, adipose tissue (Fried et al. 1993). However, after stimulation by glucocorticoids, both depots show an increase in LPL expression and activity in response to insulin, but this is still more marked in subcutaneous adipose tissue of women (Fried et al. 1993). Although LPL plays an important role in the fatty acid uptake by adipose tissue, mice with LPL deficiency in adipose tissue are able to maintain normal fat mass by increasing de novo lipogenesis in adipose tissue (Weinstock et al. 1997). In addition, patients with LPL deficiency also exhibit normal fat mass (Ullrich et al. 2001). However, there is a change in the fatty acid composition of their adipose tissue with an increase in 16:1 and decrease in 18:0, 18:2, and 18:3 fatty acids. The reduction in essential fatty acids, which cannot be synthesized by cells, associated with the increase in non-essential fatty acids, which can be synthesized, suggests that fat mass is maintained in these subjects primarily through an increase in adipocyte de novo lipogenesis (Ullrich et al. 2001).

The fatty acids generated by the action of LPL on lipoproteins are rapidly taken up by the adipocytes. The mechanisms for fatty acid uptake are still a subject of debate and may include passive diffusion across the membrane and active transport facilitated by a membrane transporter (Kampf and Kleinfeld 2007). Fatty acids can diffuse passively across the membrane through a mechanism called "flip-flop." This mechanism was first tested using an in vitro model membrane (small unilamellar vesicle [SUV]) by measuring pH gradients across a protein-free phospholipid membrane bilayer in response to free fatty acid (FFA) (Kamp and Hamilton 1992). Addition of long-chain fatty acids to this model membrane causes their absorption within the outer leaflet of SUV, and 50% of these absorbed fatty acids are then ionized. Unionized fatty acids "flip" from the outer to the inner leaflet of the SUV. This is associated with a release of protons creating a proton gradient which is then slowly dissipated. On the other hand, addition of albumin to the external buffer extracts fatty acids from the external leaflet. Unionized fatty acids "flop" from the

inner to outer leaflet of the SUV rapidly to restore the concentration equilibrium in the bilayer. This theory has been proven using isolated adipocytes incubated with FFAs or treated with a lipolytic agent, which cause a rapid intracellular acidification that can be reversed by addition of albumin (Civelek et al. 1996). Conversely, stimulation with insulin, which promotes fatty acid esterification, leads to alkalization of the cells (Civelek et al. 1996). However, this passive diffusion of fatty acids across the phospholipid bilayer can be accelerated by certain membrane proteins, including fatty acid translocase (CD36/FAT) (Abumrad et al. 1993), caveolin (Trigatti et al. 1999), fatty acid transport protein (FATP) (Schaffer and Lodish 1994), and fatty acid binding protein plasma membrane (FABPpm) (Schwieterman et al. 1988), implicating these proteins in facilitated fatty acid uptake by adipocytes.

The fatty acid translocase CD36/FAT is highly expressed in adipose tissue (Abumrad et al. 1993), where its role in regulating fatty acid uptake has been clearly demonstrated (Harmon and Abumrad 1993; Baillie et al. 1996). Mice with a whole body deletion of CD36/FAT have higher levels of circulating FFAs and triglycerides (Febbraio et al. 1999). Injection of labeled fatty acid analogs in these mice revealed a 60–70% reduction in the uptake of these analogs by adipose tissues (Coburn et al. 2000). Isolated adipocytes of CD36/FAT null mice exhibit a 60% reduction in ^{3}H-labeled palmitate (Coburn et al. 2000) and oleate (Febbraio et al. 1999) uptake, consistent with the in vivo observations. This impairment in fatty acid uptake results in a decrease in triglyceride accumulation in adipose tissue of CD36/FAT null mice (Coburn et al. 2000). In 3T3-L1 adipocytes, CD36/FAT is located in lipid rafts, along with caveolin-1 (Pohl et al. 2004a). Disruption of these lipid rafts by beta-cyclodextrin reduces the uptake of ^{3}H-labeled oleate in these cells (Pohl et al. 2004a). Furthermore, the presence of caveolin-1 appears to be required for FAT/CD36 localization and function at the plasma membrane (Ring et al. 2006).

The FATP family is comprised of six members, FATP1–6, of which two, FATP1 and FATP4, are present in adipose tissue (Pohl et al. 2004b). The transport activity of FATPs appears to be specific for long-chain fatty acids (Schaffer and Lodish 1994; Stahl et al. 1999); however, no specific binding sites have yet been identified. In fact, these FATPs appear to differ from other fatty acid binding proteins, in that they possess an acyl-CoA synthetase activity conveyed by an AMP-binding motif (DiRusso et al. 2005). This acyl-CoA synthetase activity has been reported for FATP1, and there is strong evidence suggesting that the uptake of fatty acids by FATP1 requires the conversion of fatty acids to fatty acyl-CoA within the intracellular leaflet of the plasma membrane (Schaffer and Lodish 1994). In addition, a constitutive interaction between FATP1 and acyl CoA synthetase 1 contributes to the efficient cellular uptake of long-chain fatty acids in adipocytes through vectorial acylation (Richards et al. 2006). The expression of FABP1 and FABP4 is induced during adipocyte differentiation of 3T3-L1 cells, and a peroxisome proliferator-activated receptor response element has been described in the promoter of the murine FATP1 gene (Frohnert et al. 1999). In addition, positive regulation of the expression of these transporters has been observed in response to activators of PPARα and PPARγ (Martin et al. 1997).

FATP1 and FATP4 appear to have a distinct and complementary role in the regulation of long-chain fatty acid uptake by adipocytes (Lobo et al. 2007). FATP4 has been shown to be involved in fatty acid re-uptake and re-esterification after stimulation of lipolysis (Stahl et al. 2002), whereas FATP1 appears to play a major role in the uptake of fatty acids in response to insulin, which induces its translocation from an intracellular perinuclear compartment to the plasma membrane (Stahl et al. 2002; Lobo et al. 2007). This critical role of FATP1 in fatty acid uptake regulated by insulin has also been demonstrated in vivo. Indeed, mice with inactivation of the FATP1 gene are protected against long-term high fat diet (HFD) induced-obesity, and their fatty acid uptake in response to insulin is completely abolished in isolated adipocytes (Wu et al. 2006b). However, when exposed to a short-term HFD or lipid infusion, these mice have no alteration of whole body adiposity but exhibit a decrease in intramuscular accumulation of fatty acyl-CoA associated with improved insulin sensitivity in skeletal muscle (Kim et al. 2004). Interestingly, these mice also fail to maintain their body temperature under cold exposure, indicating a critical role of FATP1 in BAT in the regulation of non-shivering thermogenesis (Wu et al. 2006a). While there is strong evidence for a role of CD36/FAT, caveolin 1, fatty FATPs and FABPpm in the regulation of fatty acid influx and efflux in adipocytes, in preadipocytes, a different and still unknown membrane protein pump has been proposed to regulate fatty acid uptake (Kampf et al. 2007).

5.3.1.3 Triglyceride Synthesis

In adipocytes, fatty acid esterification with CoA followed by acylation of the glycerol backbone represent the last steps in the formation of triglycerides (Coleman and Lee 2004). This requires the formation of glycerol 3-phosphate from glycolysis. For this, fructose 1,6-bisphosphate is broken down to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate by the fructose bisphosphate aldolase. In adipocytes, the dihydroxyacetone phosphate is then reduced into glycerol 3-phosphate by the glycerol-3-phosphate dehydrogenase (Schlossman and Bell 1976). As mentioned above, esterification of fatty acid with CoA can occur through the acyl-CoA synthetase activity of the FATPs during fatty acid uptake, but also through a long-chain fatty acyl-CoA synthetase which acts in synergy with FATPs (Gargiulo et al. 1999). Subsequently, the acylation of the glycerol backbone occurs by action of glycerol 3-phosphate acyltransferase (GPAT) which catalyzes the addition of acyl-CoA on position 1 of glycerol 3-phosphate to give 1-acyl-*sn*-glycerol-3-phosphate, also known as lysophosphatidic acid or LPA. Two different GPAT isoforms have been characterized based on their subcellular localization and biochemical properties (Saggerson et al. 1980). In adipocytes, the major isoform is microsomal and is the product of two separate genes, *Gpat3* and *Gpat4* (previously named *Agpat6*) (Cao et al. 2006; Shan et al. 2010). Expression of these two genes is regulated during adipocyte differentiation, but only GPAT3 knockdown leads to profound inhibition of triglyceride accumulation, suggesting a critical role of this gene in triglyceride synthesis in adipocytes (Shan et al. 2010). Interestingly, in vivo studies have

suggested that GPAT4 has an important role in triglyceride accumulation in certain fat depots, as GPAT4/AGPAT6-deficient mice have been reported to exhibit a mild decrease in intra-abdominal epididymal fat and subcutaneous inguinal fat mass, but an almost complete absence of subdermal adipose tissue (Vergnes et al. 2006).

The addition of a second fatty acid on position 2 of LPA occurs through the action of the 1-acylglycerol-3-phosphate *O*-acyltransferase (AGPAT) (also called lysophosphatidate acyltransferase) which produces the 1,2-diacyl-sn-glycerol 3-phosphate (also called phosphatidic acid or PA). To date, ten different AGPATs have been reported (AGPAT1–10), but only AGPAT1 and AGPAT2 have been implicated in the regulation of triglyceride synthesis (Takeuchi and Reue 2009). Both enzymes are expressed in WAT, but AGPAT2 is the major isoform and is the only AGPAT which has been associated with a human disease. Several different mutations of *Agpat2* gene have been associated with congenital generalized lipodystrophy (Agarwal et al. 2002; Magre et al. 2003), and mice deficient in AGPAT2 have a generalized lipodystrophy demonstrating that this enzyme has a non-redundant function in adipose tissue triglyceride synthesis (Cortes et al. 2009). In vitro in 3T3-L1 adipocytes, overexpression of AGPAT1 increases oleate uptake and incorporation into triglycerides (Ruan and Pownall 2001). In addition, this overexpression leads to an increase in insulin-stimulated glucose transport and a suppression of FFA released during basal and stimulated lipolysis occurring without changes in glycerol release, suggesting a normal rate of lipolysis with increased re-esterification of FFAs (Ruan and Pownall 2001).

PA generated by the action of the AGPATs can serve as a precursor for the synthesis of acidic phospholipids, or be dephosphorylated by a phosphatidic acid phosphatase (PAP) to produce diacylglycerol (DAG), the last intermediate before the production of triglyceride. Two types of PAP enzyme have been described: PAP1 which is dependent of Mg^{2+} and PAP2 which is independent of Mg^{2+}. Only PAP1 appears to be involved in triglyceride synthesis (Coleman and Lee 2004). PAP1 activity in mammals is determined by the lipin family of proteins, lipin-1 (LPN1), lipin-2, and lipin-3, which have a distinct tissue expression pattern (Donkor et al. 2007). LPN1 accounts for all of the PAP1 activity in adipose tissue and was initially identified through the study of a spontaneous mouse mutation known as fatty liver dystrophy (*fld*) (Peterfy et al. 2001). In addition to other defects in lipid homeostasis, these mice have severe lipodystrophy indicating the critical role played by LPN1 in adipose tissue triglyceride synthesis. Interestingly, in addition to its PAP activity, LPN1 has been shown to act as a transcriptional co-activator for a number of transcription factors including PPARα, PPARδ, PPARγ, HNF 4α, and the glucocorticoid receptor (Finck et al. 2006). Thus, mouse embryonic fibroblasts from *fld* mice exhibit defects in the expression of key adipogenic genes PPARγ and C/EBPα suggesting that LPN1 plays a critical role in the regulation of adipocyte differentiation (Phan et al. 2004). More importantly, LPN1 is required for the maintenance of adipocytes and has been shown to be specifically recruited to the PPARγ-response elements of the phosphoenolpyruvate carboxykinase gene through a direct physical interaction with PPARγ (Koh et al. 2008).

Acylation of a third fatty acid on DAG to produce triglyceride can be catalyzed by several enzymatic activities, including those of the diacylglycerol acyltransferases (DGATs), which has been shown to be a critical step in vivo in transgenic mice. Two different DGAT enzymes have been characterized, encoded by two distinct genes, *Dgat1* and *Dgat2* (Cases et al. 1998, 2001; Lardizabal et al. 2001). Both enzymes are highly expressed in adipose tissue, and their levels increase with adipocyte differentiation, but they exhibit different biochemical properties and substrate selectivity (Yen et al. 2005). Mice lacking expression of DGAT1 have a normal body weight, enhanced insulin sensitivity, and are resistant to diet-induced obesity, due to increased energy expenditure and activity (Smith et al. 2000). Conversely, adipose tissue specific overexpression of DGAT1 in mice leads to an increase in adipose tissue mass when on a regular diet and a greater susceptibility to diet-induced obesity without impaired glucose tolerance (Chen et al. 2002). This last observation is consistent with results obtained in human adipose tissue, where DGAT1 expression has been reported to be strongly positively correlated with insulin sensitivity (Ranganathan et al. 2006). In addition, these studies demonstrate that DGAT1 is not essential for triglyceride synthesis in adipose tissue, but can be considered as a potential therapeutic target for obesity control. Unlike DGAT1, mice deficient in DGAT2 have a severe reduction of lipid in both blood and tissues and die shortly after birth due to a lack of sufficient substrates to maintain energy homeostasis. These studies demonstrate the fundamental role played by DGAT2 in mammalian triglyceride synthesis and the non-redundancy between DGAT1 and DGAT2 in vivo (Stone et al. 2004).

5.3.1.4 Lipolysis and Its Regulation

During lipolysis, the hydrolysis of triglycerides results in the efflux of non-esterified fatty acids (NEFA) and glycerol in the blood stream which can then be used as substrates by other tissues. For this, each fatty acid moiety is sequentially removed from triglyceride to produce successively DAG, MAG, and finally glycerol itself. In WAT, this lipolytic cascade is catalyzed by at least three different lipases, adipose triglyceride lipase (ATGL), HSL, and monoacylglycerol lipase (MGL), which have been proposed to act sequentially in the conversion of triglyceride to glycerol and three NEFAs (Jaworski et al. 2007). Since its cloning in 1988, HSL has been thought to be responsible for the first two steps of triglyceride hydrolysis (Holm et al. 1988). However, the characterization of mice deficient in this enzyme revealed a substantial residual triacylglycerol lipase activity in WAT (Osuga et al. 2000) which was associated with accumulation of DAG rather than triglyceride (Haemmerle et al. 2002), suggesting the presence of an additional unidentified triacylglycerol lipase. These unexpected observations led to the identification of a triacylglycerol lipase in adipose tissue by several groups, which has been called ATGL, desnutrin, TTS2.2, PNPLA2, or iPLA2ζ (Zimmermann et al. 2004; Villena et al. 2004; Jenkins et al. 2004). This enzyme, which is predominantly expressed in adipose tissue, exhibits high substrate specificity for triglyceride and is induced under conditions that favor

lipolysis, such as fasting. Mice deficient in ATGL have increased WAT mass and ectopic triglyceride storage in several tissues, including the heart, leading to heart failure and shortened lifespan (Haemmerle et al. 2006).

It is well accepted now that ATGL is responsible for the first step of the lipolytic cascade, hydrolyzing triglycerides to form DAG and releasing a NEFA. A second fatty acid is then removed by HSL to generate MGA. Finally, MGL hydrolyzes MGA, producing glycerol and a third NEFA. Recently, a hypothetical model for the regulation of basal and stimulated lipolysis has been proposed based on studies of the different components involved in the lipolytic cascade (Bezaire and Langin 2009). Under basal conditions, lipid droplets are coated with perilipin, a protein relatively specific to adipocytes (Greenberg et al. 1991). ATGL is found in the cytosol and on the surface of lipid droplets, associated with a co-factor named comparative gene identification 58 (CGI-58), which also interacts with perilipin (Subramanian et al. 2004; Yamaguchi et al. 2004). This complex has been shown to be required for ATGL activation (Lass et al. 2006; Schweiger et al. 2008). In this state, ATGL and CGI-58 facilitate the hydrolysis of triglyceride, delivering DAG to the cytosol. HSL, which is exclusively located in the cytosol under basal conditions (Egan et al. 1992), hydrolyzes the DAG produced by ATGL to give monoacylglycerol. Hormones which stimulate lipolysis, such as catecholamines, lead to the activation of protein kinase A (PKA), which phosphorylates perilipin (Miyoshi et al. 2007). This promotes the fragmentation of the lipid droplet and the release of CGI-58 and ATGL, which form a highly active complex around the small fragmented lipid droplets (Granneman et al. 2007). At the same time, phosphorylation of HSL by PKA increases its activity (Huttunen et al. 1970), promotes its association with fatty acid binding protein 4 (FABP4), and stimulates its translocation to the lipid droplet where it hydrolyzes the DAG produced by ATGL (Smith et al. 2004). In both basal and stimulated conditions, monoglycerol lipase completes this lipolytic cascade by hydrolyzing MAG and releasing a fatty acid and glycerol. FABP4 ensures the intracellular trafficking of NEFA from lipid droplets to the plasma membrane.

Regulation of intracellular cAMP levels in adipocytes allows rapid and precise regulation of PKA activity and subsequently lipolysis. Adenylyl cyclase is the enzyme responsible for the production of cAMP in adipocytes (Mendes et al. 1978). Its activity is tightly controlled by several membrane receptors including adrenergic receptors (Langin 2006). Catecholamines (epinephrine and norepinephrine) exert a bimodal regulation of lipolysis through their interaction with different adrenergic receptors (Lafontan et al. 1997). Binding of catecholamines to β-adrenergic receptors (β_1-, β-$_2$, and β_3-), acting through Gαs protein, stimulates adenylyl cyclase and induces cAMP production leading to the activation of lipolysis. This is counteracted by binding of catecholamines to the α_2-adrenergic receptor, which is coupled to the inhibitory Gαi protein, leading to inhibition of adenylyl cyclase and subsequently to inhibition of lipolysis. The regulation of lipolysis in response to catecholamine results in a balance between the affinity of α_2- and β-adrenergic receptors for catecholamines and their presence and number at the cell membrane. In humans, catecholamines have a higher affinity for the α_2-adrenergic receptor than for β-adrenergic receptors. More importantly, adipose tissue depots are heterogeneous

with regard to their response to catecholamine-stimulated lipolysis due to expression differences of these two receptors.

Although, catecholamines are able to stimulate lipolysis in both intra-abdominal and subcutaneous abdominal WAT in human, intra-abdominal WAT is more responsive to catecholamine-stimulated lipolysis than subcutaneous abdominal WAT, due to a greater presence of β-adrenergic receptors than α_2-adrenergic receptors on the cell membrane (Hellmer et al. 1992; Mauriege et al. 1987). By contrast, catecholamines have a very small lipolytic effect in gluteal subcutaneous WAT of normal and obese women and subcutaneous abdominal WAT of obese men, due to a concomitant increase in α_2-adrenergic and decrease in β-adrenergic responsiveness (Mauriege et al. 1991). Adipocyte hypertrophy strongly affects this functional balance between β- and α_2-adrenergic receptors (Arner et al. 1987). In addition to the role of G protein-coupled receptors in controlling adenylyl cyclase production of cAMP to regulate lipolysis, insulin can inhibit lipolysis through the activation of phosphodiesterase 3B which hydrolyzes cAMP and reduces PKA activity (Hagstrom-Toft et al. 1995). This regulation is critical in the postprandial state where insulin not only favors substrate uptake and storage but also limits hydrolysis of triglyceride in adipocytes. Interestingly, the anti-lipolytic effect of insulin is greater in subcutaneous than in visceral WAT, due to an increased insulin receptor autophosphorylation and signal transduction through the insulin-receptor substrate 1-associated phosphatidylinositol 3-kinase pathway in subcutaneous adipose tissue (Meek et al. 1999; Lafontan and Berlan 2003).

An alternative pathway in the regulation of lipolysis which does not involve PKA is starting to emerge. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), which are secreted by the heart, have been reported to stimulate lipolysis in human adipocytes through a cGMP/PKG-signaling pathway leading to the phosphorylation and activation of HSL (Sengenes et al. 2000, 2003). Although the physiological relevance for this regulation is still debated, it has been proposed that the secretion of ANP/BNP by the heart during and after strenuous endurance exercise contributes, in part, to the regulation of WAT lipolysis (Moro et al. 2004).

5.3.2 Endocrine Function of WAT

Classically, the role of WAT was viewed as limited to energy storage in the form of triglyceride. However, in 1953, Kennedy hypothesized that adipose tissue might make a circulating lipostatic factor that coordinated fat mass and food intake (Kennedy 1953). A decade later, LPL was the first protein characterized as being secreted by the adipocyte (Rodbell 1964). In 1994, the first adipocyte hormone was discovered with the cloning of leptin (Zhang et al. 1994). Since that time, the list of factors secreted from WAT, which influence metabolic homeostasis, has increased exponentially, leading to the notion of WAT as an endocrine organ (Mohamed-Ali et al. 1998). Indeed, WAT produces a large number of peptides (hormones, growth factors, cytokines, etc.), proteins (enzymes, extracellular matrix components), and

lipids (fatty acids and derived products) which affect metabolism. Many of these factors act locally within the WAT through autocrine/paracrine mechanisms, but others act systemically to influence the function of distant tissues like the brain, skeletal muscle, liver, pancreas, and heart.

More recently, proteomic screening approaches have been used to characterize the complete secretome of WAT. Using these approaches, over 250 proteins secreted by human visceral adipose tissue have been identified (Varez-Llamas et al. 2007). Using a similar technique, thus far only 84 proteins from isolated rat adipocytes have been identified (Chen et al. 2005). This may represent a species difference, but more likely indicates that many of the proteins secreted by the adipose tissue come from cells types others than adipocytes. Several studies have shown that macrophages contained in the stromovascular fraction of adipose tissue are responsible for many of the proteins secreted by WAT (Fain et al. 2004, 2006). Among the large number of factors secreted by the WAT, leptin, adiponectin, retinol binding protein 4 (RBP4), resistin, tumor necrosis factor α (TNFα), and interleukin-6 (IL-6) have been the most studied for their role and effect on metabolism homeostasis. Of these, leptin and adiponectin are the only two proteins recognized as being secreted almost exclusively by adipocytes (Fain et al. 2004), whereas the other proteins are also secreted by other tissues and other cell types within the fat pad. In addition, regional differences in the secretory capacity of the different adipose depots have been reported. Thus recently, a quantitative analysis of the secretomes comparing visceral and subcutaneous WAT showed that visceral WAT has a higher secretory capacity than subcutaneous WAT, and that this difference was an intrinsic feature of its cellular components (Hocking et al. 2010).

5.3.2.1 Leptin

In 1959, Hervey carried out a series of parabiotic experiments between rats which had hypothalamic lesions leading to hyperphagia-induced obesity and normal control rats (Hervey 1959). In these experiments, he noted that while the obese rats maintained their hyperphagia, the control rats stop eating, suggesting the presence of a circulating factor controlling food intake and coming from the obese rats. This hypothesis was further supported by the work of Coleman at the Jackson Laboratory in which mice carrying genetic lesions leading to obesity, the *ob/ob* and *db/db* mice, were subjected to parabiosis (Ingalls et al. 1950; Hummel et al. 1966). These experiments led to the conclusion that *ob/ob* mice are hyperphagic because they lack a satiety factor, and that *db/db* mice are hyperphagic because they are insensitive to this factor (Coleman 1973). Positional cloning revealed that the *ob* and *db* genes were leptin and its receptor, respectively (Zhang et al. 1994; Tartaglia et al. 1995).

Leptin is a 16 kDa hormone secreted by adipocytes which acts at the hypothalamus to control appetite and energy expenditure. The plasma concentration of leptin correlates with the size of the fat mass and nutritional state. Obesity is associated with an increase in the plasma levels of leptin, whereas subjects with lipodystrophies exhibit almost undetectable levels (Maffei et al. 1995). In addition, in the

postprandial state, plasma levels of leptin increase, at least in rodents (Saladin et al. 1995; Korbonits et al. 1997). In humans, high-fat meals also provoke a postprandial elevation of plasma leptin concentration (Poppitt et al. 2006). In both rodents and humans, fasting strongly decreases circulating leptin levels. In accordance with these results, insulin has been reported to regulate the expression or secretion of leptin in vitro and in vivo (Saladin et al. 1995; Kolaczynski et al. 1996; Rentsch and Chiesi 1996). Several other factors have been reported to regulate the expression and secretion of leptin including glucose, glucocorticoids (Kolaczynski et al. 1996), thiazolidinedione (De Vos et al. 1996; Kallen and Lazar 1996), TNFα (Zhang et al. 2000), fatty acids (Deng et al. 1997), estrogens (Shimizu et al. 1997), interleukin-1 (Janik et al. 1997), growth hormone (Isozaki et al. 1999), and several endotoxins (Grunfeld et al. 1996).

Leptin mediates its action through the activation of its transmembrane receptor termed ObR (Tartaglia et al. 1995). To date, six ObR isoforms have been identified (ObRa to ObRf) which are the result of alternative splicing of ObR messenger RNA (mRNA). These isoforms are categorized in three classes: long, short, and secreted (Myers 2004). Among these receptors, the long isoform ObRb, which contains an intracellular domain of 306 amino acids, is mainly expressed in the hypothalamus and is regarded as the signaling form of the receptor. Thus, *db/db* mice, which only lack the ObRb isoform (Lee et al. 1996), have a phenotype indistinguishable from that of mice lacking all isoforms of ObR (Lee et al. 1997; Cohen et al. 2001). The principal target of leptin in the hypothalamus is the arcuate nucleus which contains two populations of neurons, orexigenic, and anorexigenic that are involved in the control of energy homeostasis. Leptin inhibits orexigenic neuropeptide Y (NPY) and agouti-related protein (AgRP) neurons while it activates anorexigenic pro-opiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART) neurons. ObRb is expressed in other tissues including cells of the immune system and pancreas. In the immune system, ObRb plays a critical role in regulating proliferation of naive and memory T lymphocytes (Lord et al. 1998), and its specific disruption in pancreas affects β-cell growth and function (Morioka et al. 2007).

Depot-specific variation in leptin secretion has been observed in WAT and appears to be determined by intrinsic factors. Thus, leptin expression and secretion are higher in subcutaneous than in visceral WAT in humans (Van Harmelen et al. 1998). In addition, β-adrenergic stimulation can inhibit leptin expression and production (Slieker et al. 1996; Gettys et al. 1996; Hardie et al. 1996). As noted above, the highest β-adrenergic responsiveness observed in visceral vs. subcutaneous WAT could explain these regional differences in leptin secretion.

5.3.2.2 Adiponectin

Adiponectin is a protein of 30 kDa (also called adipocyte complement-related protein of 30 kDa [ACRP30] or AdipoQ) which is specifically secreted by adipose tissue (Scherer et al. 1995; Maeda et al. 1996). However, the expression of adiponectin is reduced with obesity in rodents and humans (Hu et al. 1996). Adiponectin

is found in the plasma as a monomer, trimer, hexamer, and in higher molecular weight structures consisting of the assembly of up to six trimers (Pajvani et al. 2003; Tsao et al. 2003). In addition to these multimeric assemblies, a circulating globular form derived from the proteolysis of the C-terminal domain of adiponectin has been postulated to exist in vivo (Fruebis et al. 2001). Adiponectin exhibits insulin-sensitizing and anti-atherosclerotic properties (Fruebis et al. 2001; Yamauchi et al. 2001; Berg et al. 2001; Funahashi et al. 1999). Although mice deficient for adiponectin have normal body weight, these mice present all the characteristics of the metabolic syndrome including insulin resistance, glucose intolerance, hyperglycemia, and hypertension (Kubota et al. 2002; Maeda et al. 2002; Ouchi et al. 2003). Transgenic mice with overexpression of adiponectin show decreased weight gain and fat accumulation, due to inhibition of adipocyte differentiation, associated with an increase in life span and resistance to premature death induced by a high-calorie diet (Otabe et al. 2007; Bauche et al. 2007). Adiponectin mediates its effects through the activation of two unique seven transmembrane receptors, AdipoR1 and AdipoR2, which are ubiquitously expressed (Yamauchi et al. 2003). AdipoR1 has a high level of expression in skeletal muscle whereas AdipoR2 is most highly expressed in liver. These receptors have opposite functions in the control of metabolism. Mice deficient in AdipoR1 exhibit decreased energy expenditure and are obese and glucose intolerant, whereas AdipoR2 deficient mice are lean, exhibit increased energy expenditure, and do not become obese on a HFD (Bjursell et al. 2007).

In humans, a sexual dimorphism has been reported for the plasma concentration of adiponectin with higher levels being observed in women (Nishizawa et al. 2002). These differences are the consequence of a regulation of adiponectin by androgens. Indeed, while ovariectomy does not affect adiponectin plasma levels, castrated mice have higher levels of circulating adiponectin, which can be reduced by testosterone treatment (Nishizawa et al. 2002). Studies on differences in adiponectin expression and secretion between subcutaneous and visceral adipose tissue have produced somewhat conflicting results. Most studies have reported higher adiponectin expression or secretion in subcutaneous WAT than in visceral WAT in both rodents and humans (Lihn et al. 2004; Fisher et al. 2002), although this has not been observed in all studies (Atzmon et al. 2002; Motoshima et al. 2002; Perrini et al. 2008). While in general, adiponectin levels are low in obese individuals, the association between subcutaneous WAT, visceral WAT, and adiponectin levels is less clear. Some studies have reported a positive correlation between subcutaneous WAT and serum adiponectin (van der Poorten et al. 2008; Hanley et al. 2007), while other have reported a negative correlation (Fujikawa et al. 2008; Farvid et al. 2005). What is clear, however, in all of these studies is the negative correlation between visceral WAT and serum adiponectin. A recent study in young Danish men reported that abdominal subcutaneous fat, rather than intra-abdominal/visceral fat, is negatively associated with adiponectin levels, whereas fat in the thighs and lower extremities is positively associated with serum adiponectin levels (Frederiksen et al. 2009). As with leptin, stimulation of the β-adrenergic receptor decreases the expression and release of adiponectin by adipose tissue and may explain these depot-specific differences (Fu et al. 2007; Fasshauer et al. 2001; Delporte et al. 2002).

5.3.2.3 Other Adipocyte Secreted Factors

RBP4 belongs to the lipocalin family and is the principal transport protein for retinol (vitamin A) in the circulation (Yang et al. 2005). Production of RBP4 by adipose tissue was originally identified in mice with deletion of Glut4 in adipose tissue (AG4KO) (Yang et al. 2005). These mice are insulin resistant and glucose intolerant and have increased expression of RBP4 in adipose tissue and elevated circulating RBP4. High circulating levels of RBP4 have been found in insulin-resistant mice models and humans with obesity and type 2 diabetes, and in mice can be normalized by the insulin sensitizing agent rosiglitazone (Yang et al. 2005; Graham et al. 2006). In addition, injection of recombinant RBP4 in normal mice is sufficient to cause insulin resistance (Yang et al. 2005). In humans, serum RBP4 concentration has been reported to be negatively associated with insulin sensitivity and onset of type 2 diabetes (Graham et al. 2006; Stefan et al. 2007; Gavi et al. 2007; Kloting et al. 2007; Cho et al. 2006), although some studies observed no correlations (Promintzer et al. 2007; Broch et al. 2007). Circulating levels of RBP4 show a strong association with fat distribution. Thus, in healthy subjects, serum RBP4 is positively correlated with percentage of fat in the trunk, but not with percentage of total body fat (Gavi et al. 2007). RBP4 is also a strong measure of visceral fat accumulation in women (Lee et al. 2007).

At the level of mRNA expression, RBP4 is higher in visceral WAT than subcutaneous WAT. Furthermore, RBP4 expression in visceral adipose shows a stronger correlation with circulating RBP4 levels than expression in subcutaneous WAT (Kloting et al. 2007). Like adiponectin, plasma levels of RBP4 exhibit a sexual dimorphism; however, in this case, higher levels of circulating RBP4 are found in men (Cho et al. 2006). Although the mechanisms by which RBP4 might induce insulin resistance are not well understood, systemic and paracrine regulations have been described. Thus, RBP4 can act on the liver and the skeletal muscle to increase expression of phosphoenolpyruvate carboxykinase and decrease insulin signaling, respectively (Yang et al. 2005).

Resistin is a member of a family of resistin-like molecules, also known as the FIZZ family (Holcomb et al. 2000; Steppan et al. 2001b). When first discovered, this adipokine was proposed to be the link between obesity, insulin resistance, and diabetes, and hence the name resistin (Steppan et al. 2001a). Although initial reports indicated adipocytes as a main source of resistin, resistin mRNA is present in hypothalamus (Morash et al. 2002; Wilkinson et al. 2005; Tovar et al. 2005), pituitary (Morash et al. 2002, 2004), and pancreatic β-cells (Minn et al. 2003) in mice. Resistin expression in adipose tissue is increased in diet-induced and genetic mice models of obesity and is down-regulated by the insulin sensitizing agent rosiglitazone (Steppan et al. 2001a). In addition, treatment of normal mice with recombinant resistin impairs glucose tolerance and insulin action (Steppan et al. 2001a). Somewhat contrary to the view of an insulin resistance factor, resistin mRNA expression increases during differentiation of murine preadipocytes into adipocytes (Kim et al. 2001). In mice, resistin expression in adipose tissue decreases in response to fasting and greatly increases after refeeding (Kim et al. 2001). In addition, resistin expression is strongly upregulated in adipose tissue of streptozotocin-diabetic mice after insulin injection (Kim et al. 2001).

In humans, the role of resistin in insulin sensitivity is less clear. Human adipose tissue expresses only low levels of resistin, and adipocytes seem to contribute very little to its production (Nagaev and Smith 2001; Pagano et al. 2005; McTernan et al. 2002, 2003; Yang et al. 2003; Fain et al. 2003; Savage et al. 2001). In fact, in human WAT, the major source of resistin expression and secretion is the stromal-vascular fraction containing preadipocytes, vascular endothelial, smooth muscle cells, and inflammatory cells (Fain et al. 2003; Savage et al. 2001). In this fraction, macrophages have been identified as the primary source of resistin production (Savage et al. 2001; Curat et al. 2006). In addition, studies of the association between serum levels of resistin and obesity or type 2 diabetes in humans have yielded divided opinions. While many studies have reported a positive correlation between circulating resistin levels and obesity (Lee et al. 2005; Vendrell et al. 2004; Gawa-Yamauchi et al. 2003) or insulin resistance and type 2 diabetes (Fujinami et al. 2004; Silha et al. 2003; Smith et al. 2003; McTernan et al. 2003), others have observed no correlation (Heilbronn et al. 2004; Lee et al. 2003; Savage et al. 2001). Interestingly, there is growing evidence that resistin could be involved in other diseases, including atherosclerosis, non-alcoholic fatty liver, cancer, inflammatory bowel disease, chronic kidney disease, and asthma (Filkova et al. 2009).

TNFα was discovered in 1975 as a cytotoxic factor in the serum of mice infected with bacillus Calmette-Guerin and was given its name because it was able to induce necrosis of tumors (Carswell et al. 1975). TNFα is produced as a 26 kDa transmembrane protein and after cleavage by a metalloproteinase is released in the circulation as a 17 kDa soluble molecule (Black et al. 1997; Moss et al. 1997). TNFα was the first factor secreted by adipose proposed to represent a link between obesity and insulin resistance (Hotamisligil and Spiegelman 1994). TNFα expression is increased in adipose tissue of obese mice models and in human obese individuals (Hotamisligil and Spiegelman 1994; Hotamisligil et al. 1995; Kern et al. 1995; Yamakawa et al. 1995; Hofmann et al. 1994). Although adipocytes can make TNFα, it appears that infiltrating proinflammatory (M1) macrophages are responsible for almost all of the TNFα expression in adipose tissue (Weisberg et al. 2003). TNFα mediates its effects through the activation of two distinct receptors TNFR1 and TNFR2 which homodimerize in the presence of TNFα (Tartaglia and Goeddel 1992; Smith et al. 1990). While TNFR1 is ubiquitously expressed, TNFR2 is found only in cells of the immune system. Both receptors are found in a soluble form in the circulation and can block TNFα effects in vitro and in vivo (Van Zee et al. 1992).

A large number of studies have reported the multiple effects of TNFα on metabolism homeostasis. Thus, TNFα has been shown to impair insulin sensitivity in vitro and in vivo (Hotamisligil 1999). TNFα has also been shown to affect fatty acid metabolism by reducing LPL expression and activity (Hauner et al. 1995; Cornelius et al. 1988; Semb et al. 1987), decreasing expression of fatty acid transporter (Memon et al. 1998a), ACC and FAS (Doerrler et al. 1994; Pape and Kim 1988) acyl-CoA synthetase (Memon et al. 1998b), and increasing lipolytic activity (Green et al. 1994; Feingold et al. 1992; Hauner et al. 1995). TNFα is able to block adipocyte differentiation by preventing the induction of C/EBPα and PPARγ expression (Kurebayashi et al. 2001; Xing et al. 1997; Zhang et al. 1996), and to induce the dedifferentiation

of mature adipocytes (Petruschke and Hauner 1993; Torti et al. 1989; Xing et al. 1997). Finally, TNFα can induce apoptosis of preadipocytes and adipocytes (Qian et al. 2001; Prins et al. 1997). The regulation of metabolism homeostasis by TNFα is not limited to its action on adipose tissue. Indeed, TNFα can impair insulin sensitivity in muscle (Li and Reid 2001) and liver (Tilg and Moschen 2008).

IL-6 is a cytokine with pleiotropic biological effects in multiple organs (Kamimura et al. 2003). A large number of tissues and cell types, including WAT, secrete IL-6. Adipose tissue has been estimated to account for 10–35% of circulating IL-6 in healthy humans (Mohamed-Ali et al. 1997) and slightly more in obese individuals (Hoene and Weigert 2008; Bastard et al. 2002). Omental WAT releases 2–3 times more IL-6 than subcutaneous WAT (Fried et al. 1998). Although several studies have reported positive correlations between IL-6 levels and the presence of insulin resistance or type 2 diabetes (Pradhan et al. 2001; Fernandez-Real et al. 2001; Pickup et al. 1997), other studies have demonstrated that plasma IL-6 levels and increased fat mass are not independent risk factors for the development of insulin resistance (Corpeleijn et al. 2005; Carey et al. 2004; Kopp et al. 2003). Furthermore, whether IL-6 induces or has a beneficial effect on insulin sensitivity is still actively debated (Pedersen and Febbraio 2007; Mooney 2007; Spangenburg et al. 2007).

5.4 Depot-Specific Differences of WAT

5.4.1 Anatomical Distribution of Adipose Tissues

With evolution, the adipose organ has become more anatomically dispersed (Gesta et al. 2007). In vertebrates, the two major divisions of WAT are in subcutaneous and intra-abdominal locations. These were described as being distinct as early as 1871 by Flemming (1871). Today, this simple dichotomization of WAT is still referred to in a large number of metabolic studies, due to the different impacts of these depots on metabolism. However, this is an over-simplification and often leads to discordant observations due to an important heterogeneity within these two divisions. Additional difficulty in attempting to categorize WAT resides in the fact that fat distribution varies considerably between species and also between individuals from the same species. In this review, we will discuss only WAT distribution in mice and the corresponding depots in humans (Fig. 5.2).

5.4.1.1 Subcutaneous Adipose Tissue

In mice, subcutaneous WAT is referred to as the tissue that is located beneath the skin and outside the peritoneal cavity. It consists of two main depots, one which is anterior and the other posterior (Cinti 2005). The anterior depot lies in the interscapular region between and under the scapulae and projects into the axillary and

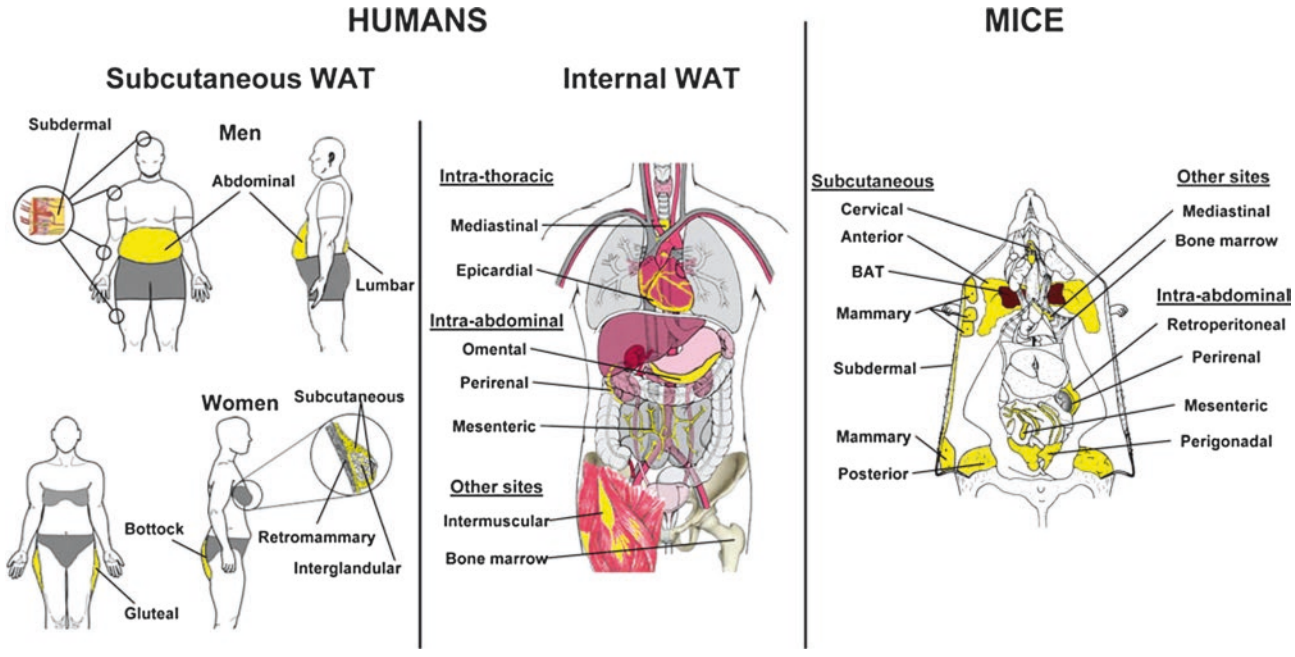

Fig. 5.2 White adipose tissue distribution in humans and mice. White adipose tissue is distributed throughout the body in both humans and mice. The two major compartments of WAT are located subcutaneously and intra-abdominally, although WAT can be found in other regions, such as the intra-thoracic region. While these two species share most of their WAT depots, some depots are species specific, such as the epicardial WAT in humans and the perigonadal WAT in mice

proximal regions of the forelimbs and the cervical area (Cinti 2005). BAT is also located within this interscapular region, the majority being embedded in the WAT. BAT also projects anteriorly into a deep cervical depot and laterally into subscapular and axillo-thoracic depots. Small amounts of BAT are also visible in the mediastinal and perirenal regions (Cinti 2005). Interestingly, although these two tissues share an intimate location, they are diametrically opposite in their function and their developmental origin (Yamamoto et al. 2010). In human fetuses and newborns, BAT can be found in this interscapular location in addition to axillary, perirenal, and periadrenal regions. In humans, these BAT depots decrease shortly after birth (Cannon and Nedergaard 2004), and in adults, only cervical, supraclavicular, axillary, and paravertebral BATs remain (Nedergaard et al. 2007; Cypess et al. 2009). In humans, enlargement of the subcutaneous WAT in these neck and upper back regions has been described as being part of Cushing's syndrome. In this disease, hypercorticism leads to an increase in fat mass forming a so-called "buffalo-hump," indicating the higher glucocorticoid responsiveness of this depot (Nieman et al. 1985). An increase in fat accumulation in these regions has also been observed in the acquired form of lipodystrophy that is associated with treatment for human immunodeficiency virus (Miller et al. 1998).

The posterior WAT of mice (also called inguinal or flank) consists of a long strip of tissue located around the hind legs. This tissue can be dissociated in three portions, starting from the dorsum at the lumbar level (dorso-lumbar portion). It then extends into the inguino-crural region (inguinal portion) up to the pubic level and into the gluteal region (gluteal portion). At the pubic level, this depot joins the contralateral depot (Cinti 2005). In humans, the distribution of subcutaneous fat is similar with large WAT depositions in the posterior lumbar, epidural, buttock, gluteal, and thigh regions. In lean subjects, these regions are dissociated from one other, whereas as obesity develops, especially lower body obesity, these regions appear to join. In addition, humans have a subcutaneous abdominal adipose depot which is absent in mice. This abdominal subcutaneous depot has a great expansion capacity and exhibits important differences in several biochemical pathways compared to other subcutaneous depots (Lafontan and Berlan 2003; Arner 1995). In addition to these two main subcutaneous depots in mice, some adipose tissue can be found at the root of the limb and at the level of the join in the middle of the limbs (Cinti 2005). This latter depot is called the popliteal adipose depot and is well-known by radiologists who try to suppress its lingering signal observed during magnetic resonance imaging (Moriya et al. 2010).

Besides these well-delimited subcutaneous depots, a subdermal layer of fat is present in both mice and humans throughout the body. Unfortunately, this layer of fat has been poorly studied in mice, as it cannot be easily dissected. However, this tissue seems to present properties which differ from the other subcutaneous depots. Indeed, as mentioned above, a recent genetic engineering study showed that deletion of the gene encoding for GAPT4 (also called AGPAT6) in mice leads to complete absence of subdermal adipose tissue, whereas the posterior (inguinal) subcutaneous fat pad was modestly reduced (Vergnes et al. 2006). In humans, increased fat accumulation in this subdermal adipose tissue causes skin dimpling

and nodularity, better known as cellulite. Although this fat accumulation has been of limited interest to metabolic researchers, its cosmetic interest is significant.

Recently, Sbarbati et al. defined three different types of subcutaneous WAT in humans, based on their structural and ultrastructural features (Sbarbati et al. 2010). Type 1 WAT or deposit WAT (dWAT) is a non-lobulated organized WAT with low collagen content and large adipocytes which tend to adhere to one other in parallel membrane plates. dWAT is considered as a metabolic depot due to its high lipid content. It mainly corresponds to the abdominal subcutaneous depot. Type 2 WAT or structural WAT (sWAT) is more polymorphous and variable from site to site. It is defined as a stromal depot with a non-lobular structure and smaller adipocytes. sWAT is located in limited adipose areas, usually rich in muscular tissue, including around trochanters, suprapubic, axillae, inner faces of the knees, thighs, hips, arms, pectoral, and mammary areas. Type 3 WAT or fibrous WAT (fWAT) has an important fibrous component and can be found in areas where a severe mechanic stress occurs. Adipocytes of fWAT are the smallest and surrounded by a thick collagen layer. fWAT is divided into two subtypes: lobular and non-lobular. Lobular fWAT can be found in the calcaneal region where mechanical constraint is important. It is organized into micro- and macro-chambers delimited by connective septae. Non-lobular fWAT is a hard adipose tissue with a major degree of fibrosis and low lipid content.

5.4.1.2 Intra-Abdominal Adipose Tissue

Internal adipose tissue is located in the thoracic and abdominal cavities. Mice and humans share the large majority of intra-abdominal adipose depots, but also have distinct depots. In the abdominal cavity, large amounts of adipose tissue accumulate around the digestive system in two main depots, namely mesenteric and omental adipose tissues. Mesenteric adipose tissue (often called visceral adipose tissue) is present in both species and is located in the connective tissue of the intestine, along with blood and lymph vessels. In mice, this connective tissue also contains the pancreas, which is diffuse and irregular, often leading to cross contamination during dissection (Caesar and Drevon 2008). Omental adipose tissue is hardly detectable in mice; however, in humans, this depot can be substantial. This adipose tissue develops in the greater omentum, a serous membrane hanging from the greater curvature of the stomach. This depot can enlarge in obese humans to cover the entire intestine and form a pannus, or apron, of fat.

Two other adipose tissues are present in the intra-abdominal cavity and present in both humans and mice: the retroperitoneal and the perirenal adipose tissue. In mice, the retroperitoneal adipose tissue lies in the paravertebral position between the spine and the posterior abdominal wall. Perirenal adipose tissue is found around the kidney and can be separated from the retroperitoneal adipose tissue by a peritoneal fold (Cinti 2005). In humans, in addition to the perirenal adipose tissue, also called the adipose capsule of the kidney, there is an additional depot located superficially to the renal fascia termed the pararenal adipose tissue (or paranephric body).

The last adipose depot present in the intra-abdominal cavity is found surrounding reproductive organs and is called perigonadal adipose tissue. This is only present in mice. In females, this tissue surrounds the uterus, bladder, and ovaries and is called periovarian adipose tissue. In males, this tissue surrounds the epididymis, projecting anteriorly in the intra-abdominal cavity along the peritoneum and is termed epididymal adipose tissue. Interestingly, although this tissue is absent in humans, it has been the most studied WAT depot because of its easy access and dissectability in mice. However, this does raise some questions about the relevance of certain physiological and pathophysiological studies in mice to humans (Harris and Leibel 2008).

Two adipose tissues have been described in the thoracic cavity: epicardial and mediastinal adipose tissues. Epicardial WAT develops at different sites around the heart: on the free wall of the right ventricle, on the left ventricular apex, around the atria, from the epicardial surface into the myocardium, following the adventitia of the coronary artery branches and around the two appendages (Iacobellis et al. 2005). Epicardial WAT is usually found only in large mammals, such as humans, and is almost absent in mice or rats (Marchington et al. 1989), which explains why epicardial adipose tissue has been so poorly studied. However, in humans, the size of epicardial adipose tissue has been related to left ventricular mass and other features of the metabolic syndrome (Iacobellis et al. 2005). Indeed, increases in epicardial adipose tissue are strongly associated with abdominal obesity and visceral adiposity as opposed to overall adiposity (Iacobellis et al. 2003a, b; Silaghi et al. 2008). The mediastinal adipose tissue is located in the superior and posterior mediastinum in both mice and humans. Although the presence of this tissue in humans during android obesity was observed almost 250 years ago by Joannes Baptista Morgagni, this tissue has also been poorly studied in mice (Morgagni 1765). Interestingly, in rats, this tissue appears to be a mixture of WAT and BAT (Osculati et al. 1989; Giordano et al. 2004).

5.4.1.3 Mammary Adipose Tissue

In mice, there are five pairs of mammary glands, three of which are located in the thoracic region and two in the inguinal region. All are surrounded by subdermal adipose tissue. In the lipodystrophic mouse model A-ZIP/F-1 transgenic mice, rudimentary mammary anlagen were able to form, but were unable to grow and branch normally (Couldrey et al. 2002). However during gestation, even in the absence of adipocytes, a tremendous amount of epithelial cell division and alveolar cell formation occurred, illustrating that adipose tissue was not required for mammary gland differentiation (Couldrey et al. 2002). Adipose tissue represents an important component of the human breast. Using ultrasound imaging, Ramsay et al. have calculated that in non-lactating women, the ratio of glandular tissue to adipose tissue is 1:1, and this rises to 2:1 during lactation (Ramsay et al. 2005). Although the distribution of adipose tissue shows a wide variation between women, they identified several adipose tissue sub-depots within the breast: one located directly under the skin (subcutaneous fat), another within the glandular tissue (intraglandular fat) and

a third behind the glandular tissue in front of the pectoral muscle (retromammary fat) (Ramsay et al. 2005). Mammary adipose tissue represents an important source for the synthesis of many diverse molecules involved in the development and the function of mammary glands (Hovey et al. 1999). In addition, several studies have implicated mammary adipose tissue in the metastatic progression of breast tumors (Elliott et al. 1992; Chamras et al. 1998; Manabe et al. 2003). Interestingly, over 350 unique proteins have been identified in the interstitial fluid of mammary adipose tissue from high-risk breast cancer patients (Celis et al. 2005).

5.4.1.4 Intermuscular Adipose Tissue

Lipid deposition is present in muscle and can be separated into two compartments: intermuscular and intramuscular. Intramuscular fat is the result of ectopic lipid accumulation within myocytes and therefore by definition cannot be considered as adipose tissue. However, intermuscular fat is the visible muscle fat marbling resulting in infiltration of adipose tissue between the muscle fibers that can be observed in mice, human and other mammals. In mice, this depot has been poorly studied, but it has been reported to increase in mice deficient in CC chemokine receptor 2 following ischemic injury (Contreras-Shannon et al. 2007) and decrease in mice overexpressing the mitochondrial uncoupling protein-3 (Changani et al. 2003). In addition, a BAT depot, with regulatable expression of the uncoupling protein-1, has been recently observed within the muscles of a strain of mouse that is resistant to diet-induced obesity and metabolic disorders, providing a genetically based mechanism for this protection (Almind et al. 2007). In humans, intermuscular adipose tissue has been well documented to increase with age and obesity, with higher levels found in women than in men (Ryan and Nicklas 1999; Kelley et al. 1999). Its function is not clear, but a high amount of intermuscular adipose tissue appeared to be associated with muscle weakness in the elderly (Katsiaras et al. 2005; Goodpaster et al. 2001).

5.4.1.5 Bone Marrow Adipose Tissue

Bone marrow is the site of production of red blood cells, platelets, and most white blood cells. While bone marrow usually has a red color due to its high content in hematopoietic cells, the color changes from red to yellow when adipose tissue develops in the bone marrow. Adipose tissue-rich marrow (also called yellow marrow) increases with age and in patients with osteoporosis, but unlike the other adipose depots, it does not increase with obesity (Justesen et al. 2001; Kugel et al. 2001). The function of adipose tissue in the bone marrow is still unclear and subject to controversy. It has been suggested to serve simply as a passive space filler, to be an active participant in lipid metabolism, energy storage, or even contribute to cell differentiation within the bone marrow (Gimble et al. 1996). Interestingly, thiazolidinediones have been reported to increase adipocyte and decrease osteoblast

formation in the bone marrow of mice (Rzonca et al. 2004) and diabetic women, but not men (Schwartz et al. 2006). A recent study reported that bone marrow adipocytes are negative regulators of the hematopoietic microenvironment, suggesting that antagonizing bone marrow adipogenesis may enhance hematopoietic recovery after bone-marrow transplantation (Naveiras et al. 2009).

5.4.2 Fat Distribution and Associated Risks

As noted above, adipose tissue is distributed throughout the body in humans, but this distribution can vary considerably from one individual to another. In lean individuals, when body fat accumulation increases leading to overweight and/or obesity, fat deposition can be exacerbated in specific regions of the body, leading to altered fat distribution. These changes have an important impact on metabolism and lead to the development of metabolic disorders such as type 2 diabetes and metabolic syndrome. This has resulted in several classifications of different types of obesity.

At the end of the 1940s, a French physician from Marseille, Jean Vague, noted that "fat excess is dangerous because of its metabolic complications and a woman normally has twice a man's fat mass, i.e., the mass of an obese man. Though she is often as obese as a man or is fatter, she dies later and less often from metabolic complications of obesity." He then proposed in *La presse medicale* the existence of sexual dimorphism as a determining factor for two different patterns of fat distribution in obese patients (Vague 1947). He classified these two patterns of obesity as android (or upper-body) vs. gynoid (or lower-body) obesity using the brachio-femoral adipo-muscular ratio, which was based on ratios of skinfolds and circumferences of the arms and thighs. In 1956, he reported that a high brachio-femoral adipo-muscular ratio in obese individuals (android obesity) was associated with an increased risk of type 2 diabetes, atherosclerosis, and gout, whereas gynoid obesity was not (Vague 1956). Three decades later, a new classification was made based on the calculated ratio between the waist circumference (WC) (measured midway between the lowest rib and the iliac crest) and the hip circumference (measured at the level of the great trochanters with the legs together) (Kissebah et al. 1982; Bjorntorp 1987). In a 12-year longitudinal study, Larson et al. reported that abdominal obesity, determined by a high waist–hip ratio (WHR), was associated with an increased risk of myocardial infarction, stroke, and premature death, whereas no association was found when indices of generalized obesity, such as body mass index (BMI), were used (Larsson et al. 1984). Interestingly, in this study, individuals with a low BMI but high WHR exhibited the highest risk of developing myocardial infarction and premature death, indicating the deleterious consequences of "pure" abdominal fat accumulation (Larsson et al. 1984).

Since that time, an impressive number of studies have recognized that abdominal obesity, assessed by WHR or simply WC, is associated with adverse health risks,

including insulin resistance, type 2 diabetes mellitus, dyslipidemia, hypertension, atherosclerosis, hepatic steatosis, cholesterol gallstones, several cancers (esophagus, pancreas, colorectum, breast, endometrium, cervix, and kidney), and overall mortality (Carey et al. 1997; Wang et al. 2005; Zhang et al. 2008; Baik et al. 2000; Pischon et al. 2008; Seidell 2010). The most common cutoffs used for WC are 102 cm for men and 88 cm for women, while those for WHR are 0.95 for men and 0.80 for women. However, concerns have been raised about using the same upper limits of these indicators in all ethnic groups. Strong evidence has been presented that lower WC cutoffs should be used for Asians (85 and 80 cm for men and women, respectively) for assessment of diabetes and hypertension risk, whereas the normal limits for WHR may be similar. In addition, the use of specific cutoffs for African–American, Hispanic, and Middle Eastern populations has been recommended (Lear et al. 2010).

Fat distribution is determined by multiple factors in addition to ethnicity. Gonadal steroids have been shown to affect adipose tissue mass and distribution in humans. For example, a decrease in intra-abdominal adipose tissue and increase in subcutaneous adipose tissue mass are observed in men that have been treated with testosterone. Interestingly, this adipose tissue redistribution has been shown to be associated with increased insulin sensitivity (Mayes and Watson 2004). In addition, while premenopausal women often have increased amounts of subcutaneous WAT (Lear et al. 2010; Loomba-Albrecht and Styne 2009; Wells 2007), postmenopausal women are prone to increases in intra-abdominal fat (Turgeon et al. 2006), and this is attenuated by hormone replacement therapy (Mayes and Watson 2004). In ovariectomized mice, adipose tissue mass and adipocyte size increase in both subcutaneous and perigonadal depots, and this has been associated with impaired glucose uptake and insulin sensitivity (Macotela et al. 2009). In male mice, castration has no effect on fat mass in either depots (Macotela et al. 2009).

In addition, genetics play an important role in both obesity and distribution of WAT. Twin and population studies have revealed that both BMI and WHR are heritable traits, with genetics accounting for 30–70% of the variability (Nelson et al. 2000). Such genetic control of body fat distribution is most evident in Hottentot/Khoisan women, who have a marked accumulation of fat in the buttocks (steatopygia) (Krut and Singer 1963). Striking differences in WAT distribution can also be observed in individuals with heritable forms of partial lipodystrophy (Agarwal and Garg 2006). For example, in congenital generalized lipodystrophy (Berardinelli-Seip Syndrome), adipose tissue is almost completely absent from subcutaneous depots, intra-abdominal depots, intra-thoracic region, and bone marrow. However, these individuals still have a relatively normal amount of adipose tissue in the buccal region, palms, soles, and other areas. By contrast, individuals with familial partial lipodystrophy of the Dunnigan type have a marked loss of subcutaneous adipose tissue in the extremities and trunk, but no loss of visceral, neck, or facial adipose tissue. These partial lipodystrophies, which are the result of mutations in different genes, indicate the developmental heterogeneity of the different adipose depots.

5.4.3 Causes for the Deleterious Impact of Abdominal Obesity

Several theories have been proposed to explain the link between intra-abdominal/visceral adipose tissue and the increased risk for metabolic complications, such as insulin resistance, glucose intolerance, and dyslipidemia. Historically, the "Portal circulation Theory" has been the most actively discussed. In this theory, it has been noted that intra-abdominal/visceral adipose tissue drains into the portal vein, allowing preferential access of FFA to the liver (Bjorntorp 1990). This high level of FFA could stimulate hepatic gluconeogenesis and reduce hepatic insulin sensitivity by decreasing the number of insulin receptors and altering intracellular insulin signaling through activation of protein kinase C and other pathways. This theory was also supported by the fact that intra-abdominal adipose depots possess higher lipolytic rates than subcutaneous adipose tissue, and therefore release more FFA directly into the portal vein to feed the liver. Indeed, it is now well-established that in humans, intra-abdominal adipose tissue depots show a significantly greater lipolytic activity when stimulated by catecholamines than subcutaneous adipose depots. This difference is due primarily to the presence of a higher level of lipolytic β-adrenergic receptors and a much lower level of anti-lipolytic α_2-adrenergic receptors on the surface of adipocytes from intra-abdominal adipose depots compared to those from subcutaneous depots.

This theory of FFA being released in the portal vein as the major mechanism to explain the association between intra-abdominal fat accumulation and metabolic disorders has been subject to challenge. One major argument against the theory is that any adipose depot with a high continuous rate of FFA release should ultimately disappear, and presumably the metabolic disorders associated with it would also disappear. However, in reality the converse is true. Thus, as central obesity develops, fat accumulation in intra-abdominal adipose depot tends to increase rather than disappear and the metabolic disorders worsen rather than improve. One possibility to explain the increase in intra-abdominal WAT as obesity develops would be the presence of a high FFA turnover such that at certain times of the day, e.g., postprandially, there would be high triglyceride accumulation, whereas during periods of fasting or stress, this would be followed by episodes of high lipolysis. Interestingly, in healthy individuals, intra-abdominal WAT has a 30% higher FFA uptake rate per gram of tissue than abdominal subcutaneous WAT (Hannukainen et al. 2010). However, when tissue FFA uptake per gram of fat is multiplied by the total tissue mass, total FFA uptake is almost 1.5 times higher in abdominal subcutaneous WAT than in visceral WAT, indicating that subcutaneous rather than visceral fat storage plays a more direct role in systemic FFA availability (Hannukainen et al. 2010). In addition, measurement of FFA in the portal vein has been found to be very close to those in arterial plasma (Hagenfeldt et al. 1972; Bjorkman et al. 1990; Blackard et al. 1993). Finally, it appears that in central obesity, the higher level of FFAs delivered to the liver originate from upper-body, non-splanchnic adipose depots (probably the subcutaneous abdominal depot), but not a visceral depot (Guo et al. 1999).

In addition to FFAs, adipokines and cytokines, such as interleukin-1, IL-6, TNFα, resistin, and others, which have been associated with reduced insulin sensitivity, are also potential mediators for the portal mechanism of insulin resistance

(Lafontan and Girard 2008; Girard and Lafontan 2008). These cytokines, whose secretion from adipose tissue is increased in obese individuals, are produced at higher levels from intra-abdominal than subcutaneous adipose depots. From this observation, a cell biological theory has emerged based on the concept that fat cells in different depots possess different intrinsic properties, and possibly have a different developmental origin, causing them to be more or less associated with metabolic alterations. This hypothesis is supported by the fact that at a molecular level, significant differences in expression of hundreds of genes have been reported between distinct adipose tissue depots in both rodents and humans, and these depot-specific variations in gene expression appear to be intrinsic (Gesta et al. 2007). Therefore, although there is no doubt that the anatomical location of intra-abdominal adipose depots draining into the portal circulation plays a critical role, the intrinsic properties of these depots are also one of the causes for the association between central obesity and metabolic disorders.

5.5 Adipogenic Lineage of Different WAT Depots

Intrinsic property differences between adipocytes from various WAT depots have recently lead to theories about the existence of different adipogenic lineages that are responsible for the development of the various WAT depots. Indeed, substantial evidence supporting the theory that different white adipose depots may be derived from distinct precursors exists (Vohl et al. 2004; Cantile et al. 2003; Gesta et al. 2006; Tchkonia et al. 2007). In rodents, the different WAT depots appear after birth. The first depots to develop are the intra-abdominal perigonadal and the anterior and posterior subcutaneous, while the intra-abdominal mesenteric, retroperitoneal, and perirenal depots usually develop later. In humans, although the development of subcutaneous and intra-abdominal WAT starts during early to mid-gestation, at birth, newborn babies have greater amounts of subcutaneous than intra-abdominal WAT. In healthy newborns, only 10% of the total WAT mass is intra-abdominal, whereas 90% is subcutaneous, with 70% being non-abdominal subcutaneous WAT (Modi et al. 2009). In addition, several intrinsic properties have been observed in cells taken from different white adipose depots. Thus, cloned human preadipocytes from subcutaneous adipose tissue exhibit a greater ability to differentiate and accumulate lipids in culture than those from mesenteric or omental adipose depots. These attributes are associated with differences in expression of C/EBPα, PPARγ, and many other adipocyte-related genes (Tchkonia et al. 2002). Furthermore, these inter-depot differences have been shown to be conserved after multiple generations of cell replication in culture (Tchkonia et al. 2006). Similarly, intrinsic variations in gene expression have been observed in adipocyte and preadipocyte fractions taken from different intra-abdominal and subcutaneous adipose tissue depots in mice (Gesta et al. 2006). In addition, Wu et al. have shown that administration of monoclonal antibodies raised against adipocyte plasma membranes in chick embryos significantly reduces abdominal adipose tissue weight without affecting femoral or

pectoral fat depots (Wu et al. 2000), suggesting that the adipocytes in these depots have different membrane protein antigens. Together, these observations indicate that the adipogenic lineage for the development of WAT differs from one depot to another (Fig. 5.3).

Recent gene expression profiling approaches have provided insights into the molecular mechanisms involved in the early development and patterning of the different adipose depots. Thus, using this approach, several fundamental developmental genes have been found to be differentially expressed between intra-abdomi-

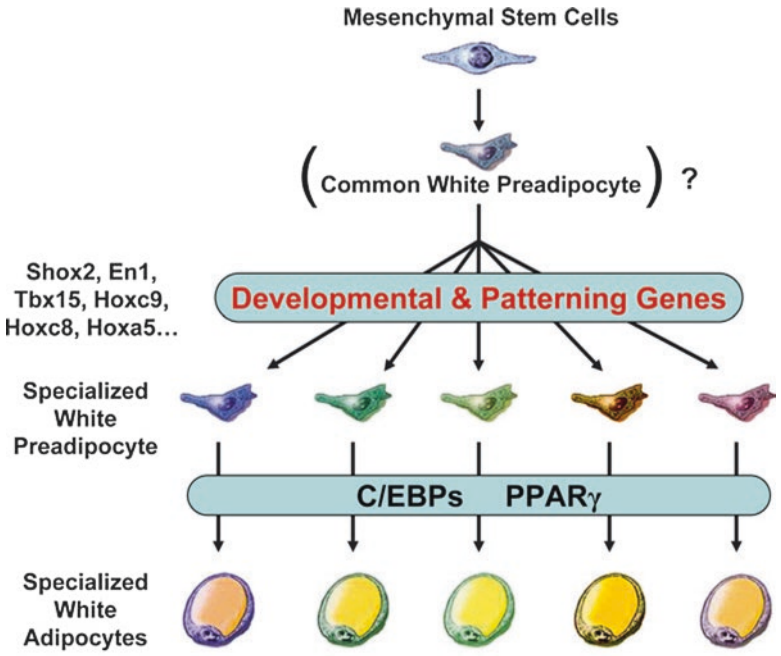

Fig. 5.3 Hypothetical scheme of the adipogenic lineage of the different WAT depots. Under the influence of developmental and patterning genes including *Shox2*, *En1*, *Tbx15*, *HoxC9*, *HoxC8*, and *HoxA5*, mesenchymal stem cells or a pool of common white preadipocyte precursors give rise to different specialized white preadipocytes which will form the various WAT depots. The adipocytes in these depots have specialized functions which are at least in part, therefore, cell autonomous. Thus, WAT depots develop as separate mini-organs with different functions and a specific developmental signature

nal and subcutaneous adipose depots in both humans and mice (Vohl et al. 2004; Cantile et al. 2003; Gesta et al. 2006; Tchkonia et al. 2007). Among those genes, intra-abdominal WAT of rodents expressed higher levels of several members of the homeobox gene family HOX, including *HoxA5*, *HoxA4*, *HoxC8*, as well as other developmental genes including, *Glypican 4* (*Gpc4*) and *nuclear receptor subfamily 2 group F member 1* (*Nr2f1* also known as Coup-TF1). Conversely, subcutaneous WAT has been shown to express higher levels of other members of the HOX family, including *HoxA10*, *HoxC9*, and the developmental genes *Twist1* (twist homolog 1), *Tbx15* (T-box15), *Shox2* (Short stature homeobox 2), *En1* (Engrailed 1), and *Sfpr2* (Secreted frizzled-related protein 2). Interestingly, a recent study in mice demonstrated that this profile of expression is not simply dichotomized between intra-abdominal and subcutaneous WAT depots, as these developmental genes have specific patterns of expression when one compares multiple depots throughout the body (Yamamoto et al. 2010).

The precise role played by these developmental genes in adipose tissue is still unclear; however, in humans, *HoxA5*, *Gpc4*, and *Tbx15* expression has been shown to be highly correlated with both obesity (measured by BMI) and fat distribution (measured by WHR) (Gesta et al. 2006). The most striking correlations were observed with *Tbx15*, for which in visceral adipose tissue, a robust exponential negative relationship is observed, with *Tbx15* expression exhibiting a marked decrease as BMI progressed from normal to overweight or obese levels. In addition, a strong exponential negative relationship between *Tbx15* expression and WHR in this tissue has been found, with markedly lower levels of expression observed when WHR is above 1.05 in males and above 0.95 in females. In contrast, *Tbx15* expression in subcutaneous adipose tissue shows a modest, but significant positive correlation with both BMI and WHR in subcutaneous adipose tissue of both males and females (Gesta et al. 2006). Recently, a study in human subjects also reported differential expression of *Tbx15* between subcutaneous (gluteal) and visceral (omental) fat depots. In this study, the authors performed a meta-analysis of genome-wide association studies and observed a single nucleotide polymorphism in the *Tbx15* allele to be strongly associated with WHR in men and women (Heid et al. 2010). Interestingly, another recent study has reported that overexpression of *Tbx15* in murine preadipocytes impairs adipocyte differentiation and mitochondrial mass and respiration, suggesting that differential expression of *Tbx15* between WAT depots plays an important role in controlling both adipocyte development and function that may contribute to the risk of diabetes and metabolic disease (Gesta et al. 2011).

5.6 Is There a Good Fat: An Alternative View

The anatomical location and biological intrinsic properties of intra-abdominal omental and mesenteric WAT both appear to be responsible for their deleterious effects on health. Consistent with this notion, removal of WAT from these depots should therefore be sufficient to improve metabolic dysfunction associated with central obesity. The impact of surgical removal of omental WAT (omentectomy) on

several metabolic parameters has been tested in humans, however, with mixed results. Thorne et al. observed that omentectomy leads to an improvement in glucose tolerance and insulin sensitivity in individuals undergoing adjustable gastric banding. However, in addition to these metabolic improvements, these subjects lost more weight than the group of individuals with adjustable gastric banding alone, complicating conclusions regarding the specific effects of omentectomy (Thorne et al. 2002). Two other studies have reported that omentectomy in addition to a Roux-en-Y gastric bypass procedure in humans exerted no beneficial effects on various metabolic parameters (plasma glucose, plasma insulin, plasma adiponectin, plasma C-reactive protein, lipid profile, blood pressure and glucose tolerance) (Csendes et al. 2009; Herrera et al. 2010). However, these studies are also limited, since weight loss induced by Roux-en-Y gastric bypass surgery could have masked any potential therapeutic effects of the omentectomy (Klein 2010).

Several experiments employing WAT transplantation in mice have provided further insights. Indeed, a recent study demonstrated that transplantation of intra-abdominal WAT into the mesentery (conferring a portal venous drainage) leads to the development of glucose intolerance and hepatic insulin resistance, whereas transplantation of intra-abdominal WAT into the parietal peritoneum (conferring a caval/systemic venous drainage) has no effect (Rytka et al. 2011). These deleterious effects of portally drained intra-abdominal transplantation appeared to be mediated by the production of IL-6, as these effects are abolished when transplants are derived from IL-6 knockout mice. Several studies involving the transplantation of subcutaneous WAT into the visceral cavity have provided some novel perspectives. Indeed, in contrast to intra-abdominal WAT, transplantation of subcutaneous WAT leads to a decrease in total adipose tissue mass, improved glucose tolerance, and improved whole body and hepatic insulin sensitivity (Tran et al. 2008; Hocking et al. 2008). These results strongly suggest that the nature of the WAT rather than the anatomical location per se appears to have a major influence on whole body metabolic homeostasis. Although the mechanisms mediating these beneficial effects remain unknown it seems likely that one or more factors are secreted specifically from subcutaneous adipose tissue which can act on nearby tissues, such as the liver, to improve insulin sensitivity. Whether these interesting findings can be extrapolated to humans remains to be determined.

5.7 Conclusions

WAT is a complex heterogeneous organ with multiple compartments (e.g., intra-abdominal WAT, subcutaneous WAT) and with multiple functions (e.g., metabolic and endocrine). Recent advances in the understanding of these heterogeneities have led to the conclusion that the different WAT depots should be considered as separate mini-organs which most likely arise from different developmental lineages and have different metabolic functions. These intrinsic differences have clearly shown that intra-abdominal and subcutaneous WAT have diametrical consequences on the risk of developing metabolic complications during obesity. The discovery of molecular

mediators of these effects, together with a better characterization of the different developmental lineages of the various WAT depots, will be the next challenge in the development of new therapeutics to fight obesity and its adverse complications.

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