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REVIEW

Fat poetry: a kingdom for PPARγ

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Adipose tissue is not an inert cell mass contributing only to the storage of fat, but a sophisticated ensemble of cellular components with highly specialized and complex functions. In addition to managing the most important energy reserve of the body, it secretes a multitude of soluble proteins called adipokines, which have beneficial or, alternatively, deleterious effects on the homeostasis of the whole body. The expression of these adipokines is an integrated response to various signals received from many organs, which depends heavily on the integrity and physiological status of the adipose tissue. One of the main regulators of gene expression in fat is the transcription factor peroxisome proliferator-activated receptor γ (PPARγ), which is a fatty acid- and eicosanoid-dependent nuclear receptor that plays key roles in the development and maintenance of the adipose tissue. Furthermore, synthetic PPARγ agonists are therapeutic agents used in the treatment of type 2 diabetes.

This review discusses recent knowledge on the link between fat physiology and metabolic diseases, and the roles of PPARγ in this interplay via the regulation of lipid and glucose metabolism. Finally, we assess the putative benefits of targeting this nuclear receptor with still-to-be-identified highly selective PPARγ modulators.

***Keywords**:* adipose tissue, energy homeostasis, obesity, peroxisome proliferator-activated receptor

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Introduction

In mammals, the ensemble of fat tissues constitutes a multi-depot adipose organ that is highly innervated and rich in blood vessels. It serves metabolic and endocrine functions, which are of critical importance for the integrative physiology of the body. This organ is not only composed of lipid-laden mature adipocytes and adipocyte precursors called preadipocytes, but also comprises a stromal vascular fraction (SVF), which includes blood cells, endothelial cells and macrophages. Although adipocytes have been recognized as secretory cells with endocrine functions for some time, the importance of macrophages and stromal vascular cells within the adipose tissue of obese animals and humans is now well accepted. This knowledge has contributed to a better understanding of the intense cross-talk between the different components of fat tissue, and has led to stimulating speculations about the initiation of pathological conditions. Furthermore, analysis of the sympathetic and parasympathetic innervations of adipose tissue revealed that the autonomic nervous system modulates the fat cell number and other processes, such as adipokine expression levels, lipogenesis/lipolysis, fatty acid uptake, and glucose uptake. These recent findings underscore the integrative role of the brain in long-term energy balance [1]. As part of this interactive and integrated network, the adipose tissue *per se* is involved in the coordination of diverse processes including not only energy metabolism but also endocrine and immune regulatory functions. This review underlines the importance of the functional integrity of the adipose tissue in maintaining health. Both adipose tissue deficiency (lipodystrophy, lipoatrophy) and adipose tissue excess (obesity) have deleterious effects and constitute major medical problems and socioeconomic burdens all around the world today. Obesity, in particular, is associated with prothrombic and proinflammation states, hypertension, dyslipidemia, hyperglycemia, insulin resistance, degenerative diseases, and some cancers [2]. The World Health Organization estimates that over 300 million people are clinically obese, and the dramatic increase in obesity among children underscores the urgent need for increased

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knowledge on adipocytes as regulators of energy balance, which will hopefully contribute to ameliorating the serious public health problem created by obesity.

Adipose tissue: the organ and its functions

The adipose tissue has two main functions. Firstly, it plays an important role in the storage and release of lipids [3], thus managing the energy reserve of the body according to supply and need. Secondly, it is a *bona fide* endocrine organ synthesizing and secreting a large variety of molecules called adipokines, which act both at the local (autocrine/paracrine) and systemic (endocrine) levels, and have an influence on all major organs involved in the physiology of the body [4-6].

There are several visceral (vis) and subcutaneous (sc) fat depots, each playing a specific role (Figure 1) [7]. Some parts of these depots are predominantly white, and thus they form the white adipose tissue (WAT), while a few depots are predominantly brown, owing to a more dense irrigation and high numbers of mitochondria, and these correspond to the brown adipose tissue (BAT). WAT and BAT perform complementary functions *in vivo*. WAT essentially accumulates excess energy as fat and therefore

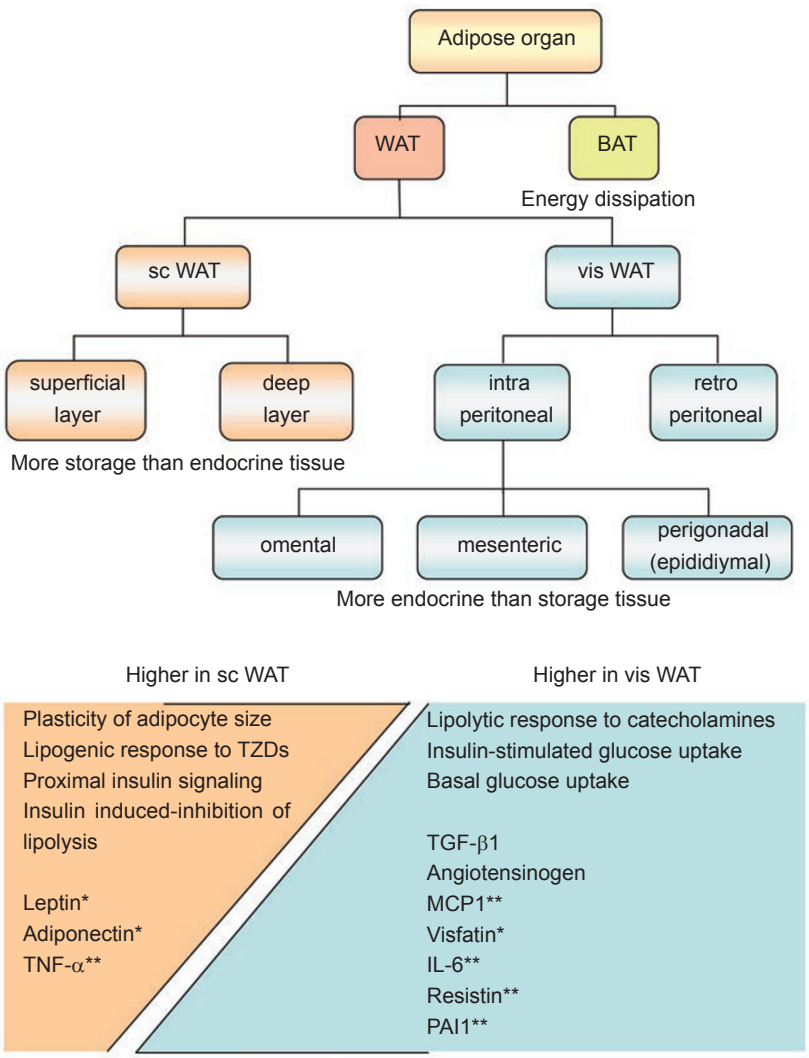

Figure 1 Schematic representation of the human adipose organ, main adipose subtypes and functions. The rodent perigonadal fat, which has no relevance in humans, is depicted here only as a reminder of its broad use as an experimental model of vis fat. Different processes and adipokine expression are indicated with respect to their prevalence in sc WAT or vis WAT. * enhances insulin sensitivity; ** enhances insulin resistance.

constitutes the largest energy reservoir in mammals as a guard against times of food shortage. In contrast, BAT is highly specialized in non-shivering adaptive thermogenesis. Although the role of BAT in rodents and neonates of other mammalian species, including humans, has been extensively studied, the persistence and importance of BAT in adult humans is currently under intense investigation and putative functions remain to be elucidated [8, 9]. In brief, the BAT and WAT closely collaborate in partitioning the energy contained in lipids between thermogenesis and other metabolic functions, respectively. This review will concentrate on the latter only.

WAT subtypes

Mature adipose cells, whose differentiation is controlled by a cascade of specific transcription factors, represent the major component of the adipose tissue. During the differentiation process, morphologically and functionally diverse tissues give birth to the sc and vis adipose tissues [4, 10-13]. Each of them has a different metabolic activity reflected in a different sensitivity to insulin [4, 14, 15]. Different expression profiles in sc and vis WAT of several genes involved in embryonic development and pattern specification suggest different genetically determined developmental programs in preadipocytes for the formation of each depot with its specific functional characteristics [16]. In addition to the main sc and vis depots, WAT is found in small amounts around other organs, such as the heart, kidney and genitalia.

Among these different tissues, the sc deposits are those that undergo the more conspicuous enlargements and retractions without noticeable effects on insulin sensitivity, glucose metabolism, and metabolic profile [17, 18]. In humans, the sc adipose tissue can be subdivided into two distinct layers: the superficial and the deep layers. There is a gender dimorphism in the amount of deep layer sc WAT. Fifty-one percent of a woman's sc WAT is found in this layer, whereas in a man it comprises 66% of the sc WAT. It appears that obesity is associated with a preferential increase in the deep layer, and weight loss in obese people also impacts more on the deep layer, suggesting that the deep layer is metabolically more active than the superficial one [19].

The vis fat is found in both the intraperitoneal and retroperitoneal compartments. Intraperitoneal fat is itself composed of omental and mesenteric adipose tissues, and in rodents perigonadal (epididymal) adipose tissues, the latter being largely used as an experimental model for vis fat. The delimitation between the intraperitoneal and retroperitoneal fat is along the ventral surface of the kidney and the dorsal borderline of the intestines. In humans, the retroperitoneal fat is minor as it represents only 25% of the total vis part [15]. Vis fat is distinct from other adipose regions since it is drained by the portal vein, and therefore has a unique direct connection with the liver. Reduction of vis deposits promotes insulin sensitivity and glucose metabolism. In fact, vis fat mass correlates positively with glucose intolerance, alteration of plasma lipoprotein lipid levels, increased triglyceride (TG) and cholesterol concentrations, hypertension, and dyslipidemia [20, 21]. Moreover, insulin signaling analysis in human vis and sc fat shows that the vis adipose tissue expresses higher levels of specific insulin-signaling proteins and exhibits an earlier and greater response to insulin than the sc WAT [22]. In short, vis fat is more affected by weight reduction than sc fat, is more active metabolically, has a higher lipolytic rate, and produces more adipokines (Figure 1) [15, 23].

These different characteristics of the two fat depots with respect to morphological structure, metabolic activity, and hormonal control suggest a specific role distribution between vis and sc WAT in whole-body energy homeostasis and a differential impact on insulin sensitivity in skeletal muscle and liver. These functions will not be discussed further since the information is already available in two reviews [15, 24].

WAT and energy homeostasis

One of the primary functions of WAT is to store excess energy as lipids, which are then mobilized to other tissues in response to metabolic needs during periods of food scarcity [9].

After copious meals, and in periods of food abundance, the adipose tissue stores the energy ingested in excess as TG (Figure 2A). The adipocyte is able to accumulate astonishingly high amounts of TG, which can be stored anhydrously within intracellular lipid droplets coated with proteins called perilipins, without causing cellular lipotoxicity [25, 26].

Starvation induces the breakdown of these TG into free fatty acids (FFA) and glycerol, which are released into the circulation (Figure 2B). FFA then serve as fuels for metabolically active tissues such as the skeletal muscle where their oxidation to carbon dioxide and water generates ATP. In the liver, most of the acetyl CoA produced by FFA oxidation is used to synthesize ketone bodies (acetoacetate; b-hydroxybutyrate), which are released into the circulation and used as fuels by the peripheral tissues. The glycerol generated by TG hydrolysis serves for the synthesis of glucose, which is reserved for cells depending on it as an energy source (neurons, red blood cells), or participates in the hepatic production of TG [27]. These TG are then packaged within very low-density lipoproteins (VLDL) and released into the circulation from where they can return to WAT. Regulation of the TG stocks is crucial for survival,

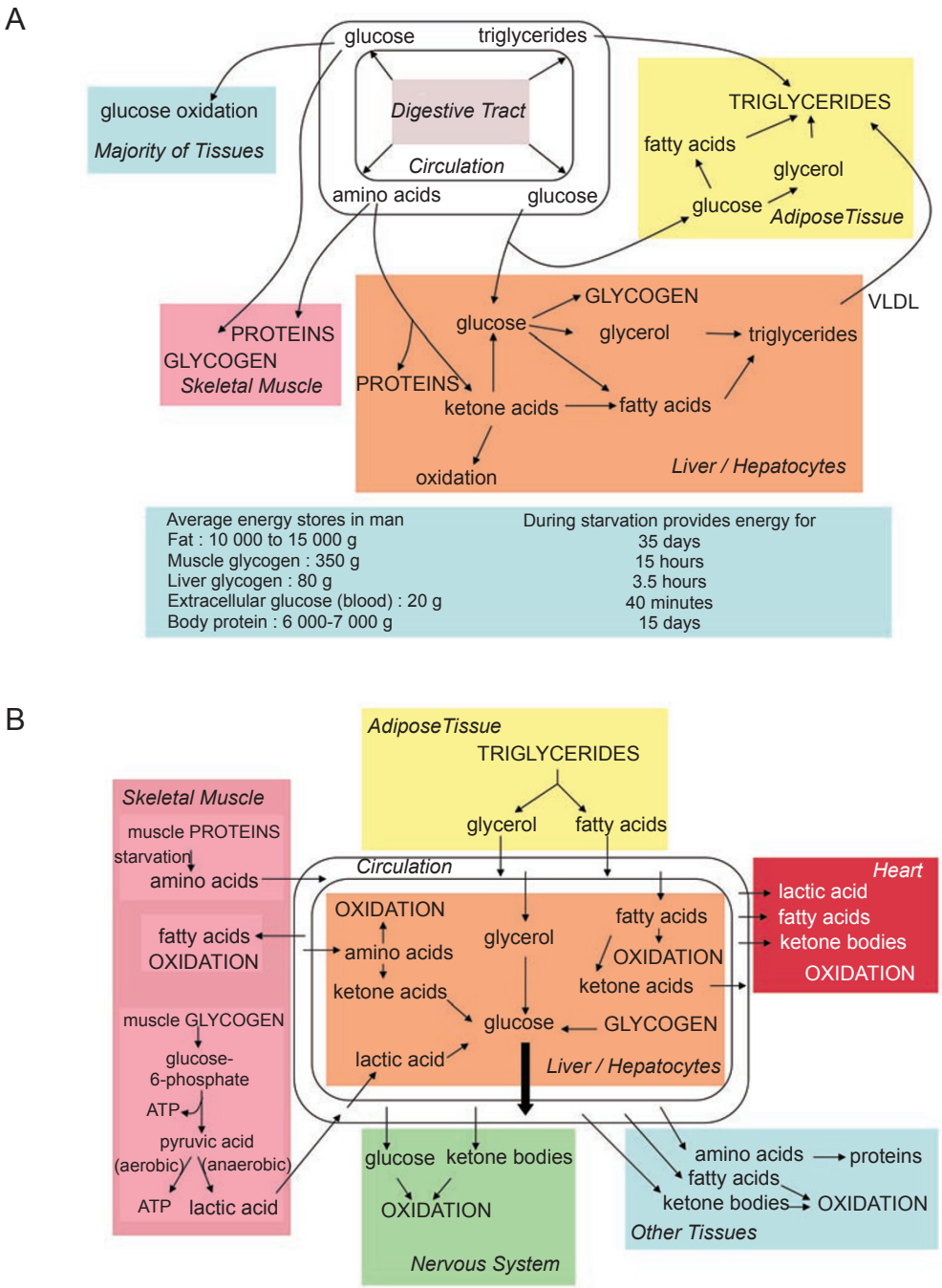

Figure 2 Role of the WAT and peripheral organs in post-prandial **(A)** and fasting **(B)** states. **(A)** In the post-prandial state, the ingested nutrients reach the circulation in the form of triglycerides (in chylomicrons as VLDL), glucose, and amino acids. In this state the main metabolic activities are the oxidation of glucose for the production of ATP in most cells, and the storage of excess fuel molecules in adipocytes as triglycerides, in hepatocytes as proteins, glycogen, and triglycerides, and in skeletal muscle fibers as proteins and glycogen. In fuel-excess conditions, amino acid oxidation increases in proportion to increments in protein intake, regardless of carbohydrate and fat substrate availability. **(B)** Fasting induces breakdown of the triglycerides from WAT into free fatty acids and glycerol, both released into the circulation. Free fatty acids can be directly oxidized by skeletal muscle fibers for the production of ATP. Hepatocytes use glycerol for gluconeogenesis, and free fatty acids for ketone body synthesis. Both glucose and ketone bodies are important fuel molecules for the peripheral organs. In fuel shortage conditions, the extent to which amino acid oxidation rises above the minimum required rate depends on the proportion of the energy needs, which is covered by FFA, glucose, and ketone body oxidation. Stored molecules (triglycerides, glycogen, proteins) are indicated in bold capitals. Adapted in part from [240].

since without WAT and its lipid reserve, animals would have to eat continuously, which is obviously not possible. For well-known reasons, food intake occurs only in distinct episodes underscoring the importance of a control of lipid production or intake, storage, and utilization.

Regulation of lipid metabolism in adipocytes is controlled at three levels: fatty acid uptake, lipogenesis, and lipolysis. Each of these processes is controlled by extracellular stimuli, including insulin, corticoids, catecholamines, natriuretic peptides, and cytokines such as TNF-α, whose levels depend on conditions such as age, gender, physical activity, and nutritional factors [28]. In addition, there are marked differences between the vis and sc adipose tissues in the regulation and levels of lipid metabolic activities. For instance, nearly 80% of fat is in the sc tissue, but the lipolytic effect of catecholamines is more pronounced in the vis fat whereas the antilipolytic effect of insulin is stronger in the sc fat [21].

The adipose tissue participates in the regulation of glucose homeostasis, which depends on the action of other organs as well (pancreas, liver, brain). Firstly, it is involved in glucose disposal, which, via the glycolytic pathway, provides the substrate for the *de novo* synthesis of fatty acids and glycerol (and thus lipogenesis). Too little or too much adiposity is associated with hyperglycemia and insulin resistance. Not surprisingly, by liberating FFA into the circulation, the adipose tissue influences insulin sensitivity and thus glucose metabolism in the muscle and liver. Furthermore, among other functions, FFA serve as a substrate for lipoprotein assembly in the liver, regulate insulin production in the pancreas, and bind to and activate the transcription factors Peroxisome Proliferator-Activated Receptors (PPARs) in all tissues, which in turn results in gene expression changes and their consequences (see below) [10, 28-30]. Thus WAT, by being involved in the regulation of lipid and glucose metabolism, not only in adipocytes but also in the whole body, plays an important integrative role in energy homeostasis especially in extreme conditions when food is available on a very irregular basis and/or is of variable nutritional quality.

In mammals, when excess energy is not directed correctly into sc fat, it will preferentially accumulate in vis WAT, with deleterious effects, a condition often associated with a genetic susceptibility to vis fat obesity, and/or an endocrine-related maladaptive response to stress or smoking [31]. When the adipose tissue is deficient, for instance because it is insulin resistant, or is abnormally distributed (lipodystrophy), the extra TG will be deposited ectopically in muscle, liver and heart, and to some extent also in the pancreas, which will be detrimental to the normal functioning of these now abnormally lipid-loaded tissues. This will impact on whole-body metabolism with the development of features of metabolic syndrome as a consequence (Figure 3) [31].

WAT as an endocrine gland

For long regarded as a mere inert fat store for metabolic demands associated with fasting or exercise, WAT has finally emerged as a *bona fide* endocrine gland able to integrate hormonal signals from different parts of the body and respond by secreting its own signaling polypeptides called adipokines. These mediators have an impact on multiple target organs, such as the liver and skeletal muscle, and directly participate in the general control of the energy balance. Several of these adipokines, such as leptin and adiponectin, mediate some of their effect through activation of neuronal circuits in the hypothalamus and other brain areas with an impact on systemic regulation of energy

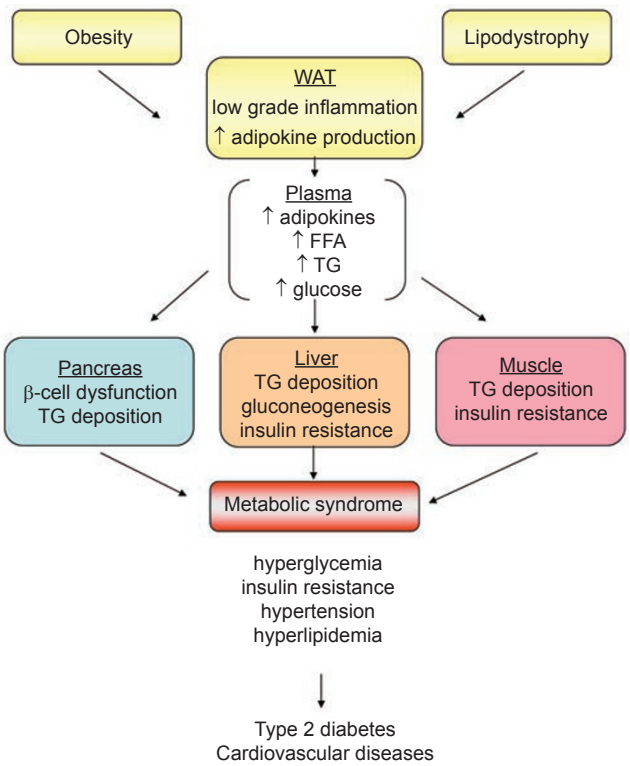

Figure 3 Obesity and lipodystrophy alterations of the WAT induce activation of the innate immune system, which is responsible for a low-grade inflammation of the tissue as well as an increased expression of several deleterious adipokines. Therefore, the plasma levels of adipokines, FFA, TG, and glucose are increased. Ectopic fat accumulation in the liver, skeletal muscle, or the pancreatic beta cells will alter their functioning and in consequence will affect the whole-body energy balance and promote the development of the metabolic syndrome.

expenditure and lipid catabolism [32]. Besides the production of these adipokines, WAT, under stress conditions, also secretes pro- or anti-inflammatory cytokines, with autocrine and/or paracrine effector functions contributing to the control of energy homeostasis. Both the production and secretion of adipokines and pro- or anti-inflammatory cytokines by the WAT are regulated by the overall WAT mass (obesity or lipodystrophy) and the physiological status of the organism [33].

Only a few major adipokines will be considered further, namely those that have been implicated in the direct modulation of metabolism as well as pro/anti-inflammatory cytokines, which are produced under stress conditions and indirectly affect energy homeostasis.

Adipokines directly involved in energy homeostasis

As mentioned previously, adipocytes have a high capacity to produce and secrete adipokines, which act in an autocrine, paracrine or endocrine fashion to control several functions, including lipid and glucose metabolism, and insulin secretion. Deregulation of these processes contributes to the development of the metabolic syndrome. Although several adipokines involved in energy homeostasis were discovered in recent years, the so far most studied ones are leptin, adiponectin, resistin, angiopoietin-like protein 4, and preadipocyte factor 1, on which this section will concentrate. In addition, information on other adipokines is given in Table 1 and Figure 4, or can be found in several review articles [26, 34-38].

Leptin (from the Greek *leptos*, meaning thin) is a small 16 kDa polypeptide of 167 amino acids produced mainly by adipocytes, in direct proportion to adipose tissue mass. Its production is increased by estrogens, glucocorticoids, insulin, TNF-α, and C/EBPα, and decreased by PPARγ agonists, FFA, growth hormone, androgens, and β3-adrenergic activity. It is secreted in higher amounts by sc compared to vis fat (Figure 1). It reduces food intake through a direct effect on the hypothalamus [39]. These observations contributed to viewing leptin as an antiobesity hormone, but it is now thought that it serves primarily as an energy sufficiency signal, whose levels decrease with weight loss or caloric restriction. Reduction in leptin levels during starvation is associated with adaptive responses including decreased energy expenditure and increased appetite. In several obesity models, the role of leptin is less obvious, since there was no improvement in spite of high endogenous leptin levels or treatment with exogenous leptin. Evidently, the target tissues have become resistant to leptin action, but the mechanism of this resistance remains unknown [40]. However, hyperleptinemia induced by overnutrition prevents ectopic lipid deposition by acting on appetite via the hypothalamus, thereby limiting energy surplus storage in the available adipocytes. Furthermore, ectopic lipid deposition is minimized by increasing fatty acid oxidation and decreasing lipogenesis in peripheral tissues [41]. In addition, the WAT itself has a leptin receptor-mediated energy regulating system, which is turned-off during overnutrition allowing the storage of excess calories and thereby diet-induced weight gain. This downregulation of the regulatory mechanism protects the whole organism against toxic ectopic lipid accumulation by permitting lipid accumulation in WAT [42]. The organism appears most leptin sensitive in a range between low levels of the adipokine in situations of food restriction and its increasing levels during re-feeding, rather than in its supraphysiological concentrations such as those occurring in obesity [43]. Exogenous leptin improves glucose homeostasis in *ob*/*ob* and lipodystrophic mice [44, 45]. It also improves glucose homeostasis in humans with congenital leptin deficiency or lipodystrophy, but has little effect on classic obesity [46-48]. In addition to its role in energy homeostasis, leptin has important endocrine functions, including the regulation of the hypothalamic-pituitary-adrenal and gonadal axes, bone development, immune response, angiogenesis, and hematopoiesis, which will not be reviewed here [49, 50].

Adiponectin, also referred to as AdipoQ or adipocyte complement related protein 30 (Acrp30, GBP28, apM1) [51] is a mature adipocyte-specific secretory protein with a molecular weight of approximately 30 kDa, which shares homology with complement C1q, and types VIII and X collagen. Its expression is higher in sc than in vis fat (Figure 1), and post-translational hydroxylation and glycosylation produce multiple isoforms. It circulates in serum at high concentrations (several micrograms per ml) as a hexamer of relatively low molecular weight and a larger multimeric structure of high molecular weight (12-18 subunits). Its biological effects depend both on the circulating concentrations and properties of the different isoforms, and on the tissue-specific expression of the two adiponectin receptors (AdipoR1 and AdipoR2) distantly related to the G protein-coupled receptor [51]. In some cells, T-cadherin may function as a co-receptor to transmit adiponectin metabolic signals [52]. Experimental data suggest that adiponectin has antidiabetic, anti-inflammatory and antiatherogenic effects [37, 53]. Only the former are summarized here, since they play important roles in energy homeostasis, obesity, and insulin sensitivity. In mice, decreased adiponectin is involved in the development of insulin resistance in models of both obesity and lipoatrophy [54]. Adiponectin stimulates phosphorylation and activation of the 5′-AMP-activated protein kinase in skeletal muscle and the liver, thereby regulating insulin sensitivity and glucose metabolism [55]. In muscle, adiponectin stimulates fatty acid oxidation and glucose catabolism, and in the liver it reduces glucose

Table 1 Adipokines involved in energy balance/metabolism

Name	Cell type expression	Metabolic effects	References
Leptin	Adipocytes	Satiety signal with direct effects on the hypothalamus; stimulates lipolysis; inhibits lipogenesis; improves insulin sensitivity; increases glucose metabolism; stimulates fatty acid oxidation (increased leptin plasma concentrations in obese subjects – leptin resistance)	[39, 45]
Adiponectin (Acrp30)	Adipocytes	Increases fatty acid oxidation with reduction in plasma fatty acid levels; decreases plasma glucose levels; increases insulin sensitivity; anti-inflammatory, antiatherogenic (decreased adiponectin plasma concentrations associated with IR)	[37, 53, 54]
Resistin (FIZZ3, ADSF)	Adipocytes	Recombinant resistin promotes systemic IR in mice; induces severe hepatic IR – increased rate of glucose production in rat (increased resistin plasma concentrations in diet-induced obese mice, but reduced mRNA levels in WAT of obese rodents; stimulates lipolysis); function controversial in humans	[59, 62, 124]
Visfatin (PBEF)	Adipocytes	Insulin-mimetic effects; hypoglycaemic effects by stimulating glucose uptake; promotes insulin sensitivity; pro-adipogenic and lipogenic action (increased visfatin plasma concentrations in obesity linked to IR)	[241]
Adipsin	Adipocytes	Stimulates TG storage, inhibits lipolysis	[242]
RBP4	Adipocytes	Promotes IR (increased RBP4 plasma concentrations in obesity)	[243]
Vaspin	Adipocytes	Improves insulin sensitivity; suppresses the production of resistin, leptin and TNF-α	[244]
ANGPTL4/FIAF	Adipocytes	Hypertriglyceridemic effect by LPL inhibition; improves glucose tolerance; induces hepatic steatosis; induces lipolysis (lower ANGPTL4/FIAF plasma concentrations in type 2 diabetes patients)	[72, 74, 75]
Omentin	SVC	Enhances insulin-stimulated glucose transport in sc as well as om adipocytes; modulation of insulin action	[245]
Apelin	Adipose tissue (adipocytes, SVC)	Reduces food intake (?); inhibits glucose-induced insulin secretion (increased plasma levels in obesity associated with IR and hyperinsulinemia)	[16, 246]
Pref-1	Preadipocytes	Inhibits adipogenesis; overexpression in WAT affects glucose tolerance and insulin sensitivity, and induces hypertriglyceridemia	[76]

Abbreviations: IR, insulin resistance; TG, triglycerides; PBEF, pre-B-cell colony-enhancing factor; Vaspin, visceral adipose-tissue-derived serine protease inhibitor; LPL, lipoprotein lipase; FIAF, fasting-induced adipose factor; ANGPTL4, angiopoietin-like protein 4; RBP4, retinol-binding protein 4; sc, subcutaneous; om, omental; SVC, stromal vascular cells; Apelin, APJ endogenous ligand; Acrp30, adipocyte complement-related protein 30; FIZZ3, found in inflammatory zone; ADSF, adipose tissue-specific secretory factor.

output and FFA influx, and increases fatty acid oxidation and insulin sensitivity. In Rhesus monkeys, plasma levels of adiponectin were shown to decrease parallel with reduced insulin sensitivity even before the onset of type 2 diabetes [56], and in Japanese men with type 2 diabetes, hypoadiponectinemia was found to be associated with vis fat accumulation and insulin resistance [57]. In contrast, an increase in adiponectin levels is observed after administration of thiazolidinediones (TZDs), angiotensin-converting enzyme inhibitors, and the angiotensin II receptor blocker (ARB), after weight loss, renal failure, heart failure, or after intake of soy protein or oils [51]. Other effects of adiponectin on monocytes/macrophages, angiogenesis, and nitric oxide production are not discussed here.

Resistin (resistance to insulin, also called FIZZ3 or ADSF) is another small protein (12.5 kDa) and a member of the hormone family of cysteine-rich resistin-like molecules [58], which is mainly produced and secreted by WAT and

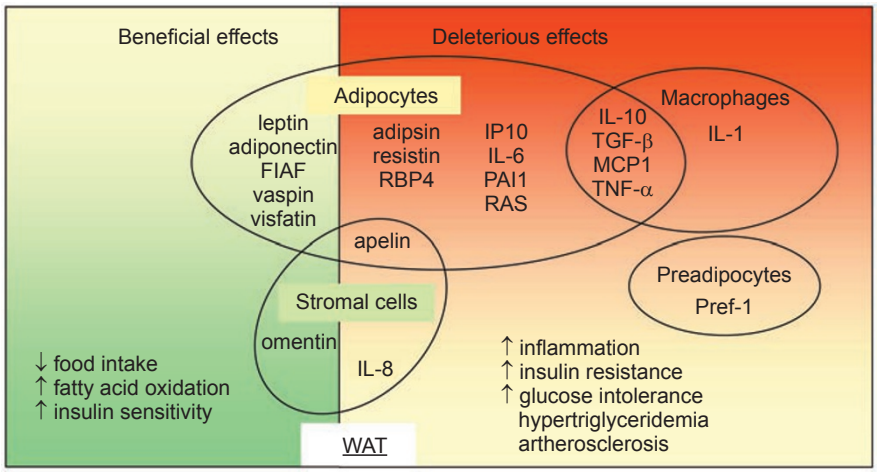

Figure 4 Schematic representation of the cell types that constitute the adipose tissue and the adipokines, chemokines and vascular proteins secreted by each cell type, as well as their beneficial and deleterious effects on whole-body homeostasis.

appears to increase glucose production in the liver by a specific insulin antagonizing action [59]. In rodents, it is expressed 15 times more in vis compared to sc fat (Figure 1) and it is highly upregulated in models of diet-induced obesity, as well as in genetic models of obesity and diabetes. Resistin circulates in multimeric forms, probably corresponding to trimers and hexamers, the conversion of the latter to the trimeric form most likely representing an obligatory step towards activation [60]. Mice treated with recombinant resistin develop insulin resistance and glucose intolerance, while cultured adipocytes receiving the same treatment are impaired in insulin-stimulated glucose uptake, suggesting that resistin affects insulin action. Resistin-null mice have similar fat mass and weight as wild-type (WT) mice and show improved glucose homeostasis associated with a decrease in hepatic gluconeogenesis [59, 61, 62]. In addition, resistin appears to be a pro-inflammatory cytokine. There are substantial inter-species differences between the sites of resistin production, occurring, for example, in adipocytes in rodents, and most likely non-fat cells, macrophages or other stromal cells present in the adipose tissue in humans [63-66]. The role of resistin in humans is not well established, since clinical studies do not show a clear link between obesity and insulin resistance versus resistin levels [67, 68].

Angiopoietin-like proteins (ANGPTLs) are also involved in the regulation of energy homeostasis [69]. One of them, the fasting-induced adipose factor (FIAF), also called ANGPTL4, HFARP and PGAR [70-73], is most highly expressed in the adipose tissue and secreted into the circulation, where it is found associated with plasma lipoproteins. Adenovirus-mediated overexpression of FIAF was found to improve hyperinsulinemia, hyperglycemia and glucose tolerance [74]. Yet it is a powerful signaling molecule that inhibits plasma TG clearance and thus fat storage, and promotes TG mobilization by stimulating adipose tissue lipolysis possibly by the inhibition of lipoprotein lipase activity [75]. Thus, FIAF is efficient in both reducing blood glucose and improving insulin sensitivity, while simultaneously promoting hyperlipidemia and fatty liver. Although much remains to be discovered about this intriguing dual function of FIAF, one can speculate that it connects adipose tissue to the modulation of the levels of plasma lipids. Modification of FIAF production and signaling may contribute to the development of dyslipidemia and possibly type 2 diabetes [75].

Lastly, proteolytic cleavage of the transmembrane protein preadipocyte factor 1 (Pref-1), highly expressed in preadipocytes, but not in adipocytes where it plays the role of an inhibitor of adipogenesis, gives birth to two soluble proteins of 50 and 25 kDa. In transgenic mice, overexpression of Pref-1 specifically in WAT reduces the expression of adipocyte proteins such as leptin and adiponectin, and produces substantial loss of WAT, while these mice suffer from hypertriglycemia, impaired glucose tolerance and decreased insulin sensitivity. These findings demonstrate

that Pref-1-induced impairment of adipocyte functions *in vivo* leads to the development of metabolic abnormalities [76].

Adipokines, chemokines, and vascular proteins involved in pro/anti-inflammatory reactions

Several molecules involved in inflammatory processes are produced by the adipose tissue in situations of stress, such as in obesity or lipodystrophy. Some of these adipokines are synthesized by adipocytes, whereas others are produced by the haematopoietic cell fraction of the WAT (in macrophages, T-cells, B-cells, natural killer cells), or cells from the SVF [36, 77, 78]. A large number of studies suggest that adipose tissue inflammation is associated with metabolic diseases, such as insulin resistance and other obesity-related complications, and lipodystrophy [79-84] (reviewed in [85]). Most of the better-defined adipokines, which are involved in inflammation, are discussed briefly in this section, while a more exhaustive list is given in Table 2 and Figure 4.

The plasmatic levels of TNF-α, a 26-kDa transmembrane protein that is cleaved to a 17-kDa biologically active

Table 2 Adipokines, chemokines and vascular proteins produced in WAT and involved in the inflammatory reactions

Name	Cell type expression	Effects related to the metabolic syndrome	References
Pro-inflammatory adipokines			
TNF-α	Adipocytes/macrophages	Induces IR and increases lipolysis in adipocytes; decreases adiponectin and increases IL-6 expression (increased expression in obese WAT)	[88, 90]
IL-1	Macrophages	Increased expression in obese WAT	[247]
IL-6	Adipocytes	Decreases insulin and leptin signaling; linked to IR (increased plasma concentrations in obesity)	[6, 97]
Anti-inflammatory adipokines			
TGF-β	Adipocytes/macrophages	Increased circulating levels in obesity	[99]
IL-1Ra	Not clearly defined	Produced in response to stress (increased plasma concentrations in IR)	[99, 248]
IL-10	Adipocytes/macrophages	Increased circulating levels in obesity	[36]
Inflammatory chemokines			
MCP1	Adipocytes/macrophages	Increases lipolysis and leptin secretion; decreases insulin-stimulated glucose uptake; (increased plasma concentrations in obesity; disturbs insulin sensitivity)	[101, 103, 104]
IL-8	Non-adipose cells from WAT	Increased expression in vis WAT in obesity	[249]
RANTES	T cells	Increased expression linked to development of type 2 diabetes	[250]
IP10	Adipocytes	Increased plasma concentrations in early stages of diabetes	[251]
Vascular proteins			
PAI1	Adipocytes	Increased circulating levels in obesity; linked to IR	[107]
TF	Not clearly defined	Increased expression in obese WAT; involved in vascular development in WAT (?)	[112]
Angiotensinogen/angiotensin II	Adipocytes	Linked to vascular inflammation (increased plasma levels in obesity)	[252-254]

Abbreviations: IR, insulin resistance; TNF-α, tumor necrosis factor alpha; IL-1, interleukin 1; IL-6, interleukin 6; TGF-β, transforming growth factor beta; IL-1Ra, interleukin 1 receptor antagonist; IL-10, interleukin 10; MCP1, monocyte chemotactic protein 1; IL-8, interleukin 8; RANTES, regulated upon activation, normally T-expressed, and presumably secreted; IP10, interferon gamma inducible protein 10; PAI1, plasminogen activator inhibitor 1; TF, tissue factor.

polypeptide, are relatively low in general. Within WAT, it is expressed in adipocytes and stromovascular cells at higher levels in sc compared to vis adipose tissue (Figure 1). However, the TNF-α produced by the adipocytes has only a local effect since it cannot be secreted. Thus, it is the macrophage-produced TNF-α that is responsible for the systemic effects [86]. Although there is no clear correlation between obesity and insulin resistance versus levels of plasma TNF-α, expression of this cytokine in WAT correlates with these two pathologies [87, 88]. Chronic exposure of mice to TNF-α induces insulin resistance, decreases the expression of genes involved in adipogenesis and lipogenesis in WAT, and promotes lipolysis, while deletion of the *TNF*-α gene improves circulating FFA and insulin sensitivity in mouse obesity [89]. Besides its role in WAT, TNF-α increases the expression of genes involved in the *de novo* synthesis of FA, and decreases that of genes involved in FA oxidation in liver. The autocrine and paracrine effects of TNF-α are responsible for the insulin resistance observed in humans and rats to whom this cytokine has been administrated [90-92]. TNF-α also regulates the expression of other adipokines in WAT. For instance, it downregulates the expression of adiponectin and increases the expression of IL-6, another cytokine involved in the endocrine role of WAT (see below) [93].

IL-6 is found at high levels in the plasma in multiple glycosylated forms ranging from 22 to 27 kDa, a third of which is produced by adipocytes. Its synthesis and secretion are approximately three times greater in vis compared to sc adipose tissue. The plasma levels of IL-6 positively correlate with fat mass, obesity, impaired glucose tolerance and insulin resistance, and thus could be used to predict the development of type 2 diabetes and cardiovascular diseases [6, 94]. IL-6, like TNF-α, modulates the insulin sensitivity of the liver and of skeletal muscle, thereby supporting the notion that cytokines produced by the adipose tissue influence whole-body insulin sensitivity. It is thought that IL-6 increases the expression of Socs-3 (inducing-suppressor of cytokine signaling-3) that negatively regulates insulin and leptin signaling. Central administration of this cytokine in rodents decreases body fat by increasing energy expenditure. In line with this effect, transgenic mice overexpressing IL-6 have reduced fat pad and body weights, which are associated with a growth defect [95-97].

In humans, the circulating levels of TGF-β_1, a homodimer composed of two 12.5-kDa subunits, correlate positively with the body mass index (BMI) [98]. This correlation also exists between the BMI and TGF-β_1 production in WAT, a feature that holds especially for the vis WAT that produces more than two-fold more TGF-β_1 compared to the sc WAT in humans [99, 100]. However, the adipocytes are not the main producers of WAT TGF-β_1, as the non-fat cells in the adipose tissue release more than 90% of it, production of which can be inhibited by TNF-α as well as by IL-1 [99]. In addition to its association with adipogenesis, TGF-β_1 has multiple functions in a wide range of tissues, which will not be discussed here.

Mature monocytes produce monocyte chemotactic protein 1 (MCP1), a non-glycosylated 76 amino-acid polypeptide (8.7 kDa) usually found at low levels. IL-1, TNF-α and LPS rapidly induce its expression and secretion. MCP1 expression in WAT and MCP1 circulating levels are increased in obesity (rodents and humans). Conversely, its circulating levels are reduced parallel to weight loss [101]. In vis WAT especially, MCP1 is not only produced by the infiltrated macrophages but also by adipocytes [102]. In adipocytes, MCP1 influences lipid metabolism by downregulating PPARγ, which regulates lipid accumulation in these cells (the roles of PPARγ will be further discussed later). Moreover, MCP1 also stimulates leptin secretion and decreases insulin-stimulated glucose uptake in adipocytes. Transgenic animals overexpressing MCP1 in WAT only develop a normal adipose depot mass, but the tissue is infiltrated by an increased number of macrophages and produces elevated amounts of TNF-α and IL-6. Furthermore, the plasmatic levels of FFA in these animals are increased, most likely reflecting an increased lipolysis. In addition, the overexpression of MCP1 in WAT influences insulin sensitivity in the liver and especially in skeletal muscle, where it disturbs the insulin signaling pathway [51, 86, 103]. Consistently, these mice become insulin resistant and glucose intolerant. These observations indicate that deregulation of cytokine expression in WAT can affect the overall metabolism of the body, particularly its insulin sensitivity [103, 104]. Furthermore, it suggests that MCP1-mediated macrophage infiltration of fat might contribute to metabolic deregulations associated with insulin resistance and obesity. In rodent obesity, increased circulating levels of MCP1 positively correlate with increased monocytes, a phenotype also seen after peripheral administration of MCP1 to mice. In these animals, accumulation of monocytes in collateral arteries and enhanced neointimal formation might implicate MCP1 in the development of atherosclerosis.

At least two proteins, plasminogen activator inhibitor-1 (PAI1, 45 kDa) and tissue factor (TF, 47 kDa), which are involved in the fibrinolytic system and vascular hemostasis, are secreted by the WAT. PAI1 is a serine protease inhibitor protein (serpin) that is the principal inhibitor of tissue plasminogen activator and urokinase, which activate plasminogen and hence cause the physiological breakdown of blood clots (fribrinolysis). This protein is expressed and secreted in the WAT of rodents (higher in vis compared to sc adipose tissue) and humans, where its expression is regulated by TNF-α and TGF-β_1, themselves produced by

WAT [100, 105]. The circulating levels of PAI1 are correlated with obesity and insulin resistance, and thus predict future risk of type 2 diabetes and cardiovascular disease [106, 107]. The adipose tissue is thought to be an important contributor to the elevated plasmatic PAI1 concentrations in obesity [108, 109], but the mechanisms underlying the association between PAI1 levels and the disturbances found in the metabolic syndrome are not well understood. However, inhibition of fibrinolysis by PAI1 might be responsible for the high incidence of cardiovascular diseases, which is a feature of this syndrome [110].

TF is a protein released from damaged tissue that triggers the clotting cascade. It acts as a cell-surface receptor for the activation of factor VII. Its expression is upregulated in the WAT of *ob/ob* mice [111]. Besides its role in coagulation, TF is thought to be involved in vascular development and integrity [112]. In obesity, where the adipose mass is greatly increased, the need for oxygen supply is dramatically augmented. In this condition, it is likely that TF is involved in the angiogenesis associated with fat mass expansion.

Several proteins of the classic renin angiotensin system (RAS) are synthesized in the WAT. Adipose tissue RAS is considered to be a potential link between hypertension and obesity. The intimate relationship between WAT and RAS may also have a role in the pathophysiology of type 2 diabetes, especially in obese individuals. These points have been addressed in different review articles [43, 113, 114]. Finally, the adipose tissue also expresses a variety of enzymes implicated in the activation, inter-conversion, and inactivation of steroid hormones that are also involved in the regulation of metabolic pathways. This role will not be discussed here as it has been reviewed recently [115]. Similarly, the role of adipokine in the interaction between adipose tissue and immunity has been summarized recently and will not be presented here [34, 77].

Pathologies of the WAT

From the above, it has already become obvious that balanced amounts of adipose tissue are critical for an optimal regulation of lipid and glucose metabolism. Excess adiposity contributes to the development of insulin resistance, dyslipidemia, inflammation, hypertension, and cardiovascular diseases, while selective loss of WAT, called lipodystrophy, also predisposes to the same complications (Figure 3). Both branches of these deregulations, obesity and lipodystrophy, are addressed below.

Obesity

When the energy balance is positive, as often occurs with western diet, the adipose tissue becomes hypertrophic and subsequently hyperplastic. Since the adipocytes cannot expand beyond a "critical size", which is thought to be genetically established for each depot type, the adipocyte number is increased when this critical point is reached [116, 117]. Combined together, cell size and cell number increases lead to an expansion of the adipose tissue, which ultimately results in obesity [7].

Obesity produces what is called a "low-grade" inflammatory reaction in the adipose tissue by a mechanism that remains largely unknown [118]. As presented in a former section, autocrine, paracrine, and endocrine signals from adipocytes, together with increased adipose tissue mass stimulate the synthesis and secretion of adipokines that trigger macrophage infiltration in the WAT. As already mentioned, there is a positive correlation between the adipocyte size and BMI, and the increase in adipokine expression in WAT [101, 119-122]. This low-grade inflammation is thought to result from a chronic activation of the innate immune system [83]. The involvement of obesity in this process was suggested by the decrease of inflammation in the WAT of obese patients after weight loss [101, 123]. Low-grade inflammation in WAT impairs its ability to control plasmatic FFA, promotes its deleterious endocrine function, and ultimately leads to insulin resistance, impaired glucose tolerance, and may result in diabetes and cardiovascular diseases (Figure 3).

It was shown in models of obese rodents as well as in humans that obesity is linked to an increase in adipocyte size. This hyperplasia is associated with an increased number of necrotic-like dead adipocytes surrounded by infiltrated macrophages, and the progressive up-regulation of inflammatory genes, such as TNF-α within the WAT. Moreover, this up-regulation precedes the dramatic increase in the circulating insulin levels, suggesting that the inflammatory reaction in the WAT is responsible for systemic insulin resistance. In addition, the persistence of WAT inflammation is responsible for the maintenance of insulin resistance in obese models [84, 86, 121, 124-126].

The genetics of human obesity unveiled the key role of leptin and melanocortin pathways, but only in rare cases. In fact, it is more a myriad of polymorphisms in genes and candidate regions, which defines the susceptibility of an individual to weight gain, a susceptibility that is accentuated by a permissive environment (diet, sedentarity) [127].

Lipodystrophy

Lipodystrophies are characterized by the absence of fat store development, the altered distribution of these reserves or their loss with, as a consequence, an excess accumulation of lipids in the liver, skeletal muscle and other organs, along with the emergence of insulin resistance (Figure 3) [128]. It was demonstrated recently in mice that the membrane-anchored metalloproteinase MT1-MMP is required for WAT development and function. In its absence, the animals are

lipodystrophic. MT1-MMP governs the interaction between the adipocyte and the extracellular matrix, and hence acts as a three-dimensional-specific adipogenic factor [129].

The different human lipodystrophic syndromes are defined by an altered quantity and/or distribution of adipose tissue (lipoatrophic peripheral sc fat and increased vis fat). In humans, the classification of lipodystrophies is usually made according to their origin, either genetic or acquired. Among the inherited lipodistrophies, some are better characterized, among which are the familial partial lipodystrophy Dunnigan-type (FPLD) and the familial generalized lipoatrophy known as Berardinelli-Seip congenital lipodystrophy (BSCL). FPLD is characterized by a loss of sc fat, while the inter- and intra-muscular fats as well as the abdominal fat are preserved. In adult patients, insulin resistance and type 2 diabetes correlate with an increase in plasma TG and FFA concentrations as well as the presence of C-reactive protein. Several FPLD patients also suffer from dyslipidemia and hypertension. In 50% of the FPLD families, there is a link between FPLD and the *LMNA* (lamin A) gene also associated with premature forms of aging, which codes for the nuclear envelope protein lamin A/C [130]. Different mutations in this gene have been identified as culprits for lipodystrophy, but the mechanism by which it occurs is not known [131-133]. Mutations in the *LMNA* gene are linked to a decrease in the plasma concentrations of adiponectin and leptin, and an increase in circulating TNF-α concentrations, which may cause the insulin resistance observed in FPLD patients [134]. Another gene involved in FPLD encodes PPARγ, a transcription factor involved in adipogenesis.

BSCL is a generalized lipoatrophy characterized by the total loss of WAT, which is associated with insulin resistance and increased plasma TG levels. It is caused by mutations in two genes independently linked to this pathology. These genes encode seipin, a protein of unknown function, and 1-acylglycerol-3-phosphate-acyl transferase, which is involved in TG synthesis [135, 136].

Among the acquired lipodystrophies, the most common is the one associated with the antiretroviral treatments in HIV-infected patients. Fifty percent of these patients suffer from lipoatrophy, often associated with dyslipidemia, impaired glucose tolerance and diabetes. Interestingly, treatment of the patients with protease inhibitors (which are a part of the pharmacopoeia of HIV treatment) markedly alters the expression and secretion of adipokines from WAT. While adiponectin expression and secretion are decreased, IL-6 and TNF-α expression is upregulated in these patients. In WAT, increase in the production of these inflammatory cytokines is correlated to a decrease in adipocyte size, an increase in fibrosis, and infiltration of macrophages [137-140].

Altered metabolism due to the loss of WAT is also observed in mouse models of lipodystrophy. Induced fat-cell apoptosis through targeted activation of caspase 8 causes WAT distrophy, glucose intolerance, and signs of inflammation [81]. The same phenotype of adipocyte death, WAT fibrosis, macrophage infiltration, and increased inflammation is seen in mice with PPARγ specifically deleted from WAT in adult animals (see below) [141].

In conclusion, the study of lipodystrophy resulting from an impaired development of body fat or, alternatively, its altered distribution revealed a link between this pathology and deregulation of lipid and glucose metabolism with insulin resistance. Therefore, lipodystrophic patients, independent of the origin of lipodystrophy, either genetic or acquired, suffer from major complications with a prevalence of diabetes, cardiovascular diseases, pancreatitis, and liver steatosis with an evolution towards cirrhosis. Treatments with hypoglycemic and hypolipidemic drugs are beneficial therapeutic options for these patients, and for those with very low leptin levels, leptin treatment provides a major improvement [142, 143].

Role of the PPARγ in WAT

Adipocyte differentiation is intimately associated with the pathologies linked to WAT such as obesity, lipodystrophy, and inflammation, as described above. PPARs compose a subgroup of three receptors, belonging to the nuclear hormone receptor family, and acting as lipid sensors to modulate gene expression [144, 145]. They are implicated in both major metabolic regulations and processes controlling cellular fate [146]. In this part of the review, we will concentrate on one of the three PPAR isotypes, PPARγ, which is a pivotal coordinator of adipocyte differentiation and fatty acid uptake and storage (Figure 5).

PPARγ and adipocyte differentiation at the cellular level

Both adipocyte number and adipocyte size are major contributors to adipose tissue mass. Therefore, adipocyte differentiation is crucial in the maintenance of adipose tissue integrity. Adipocytes are either derived from resident differentiated preadipocytes or from progenitor cells [147, 148]. PPARγ is a key player in this process (Figure 5). It has been recently shown that activated PPARγ not only stimulates differentiation to adipocytes of resident adipose tissue preadipocytes but also promotes the mobilization of bone marrow-derived circulating progenitor cells to WAT and their subsequent differentiation into adipocytes [149, 150]. These results add an unexpected dimension to the field since they demonstrate, for the first time, that cells that reside outside the adipose tissue can influence and contribute to its fate.

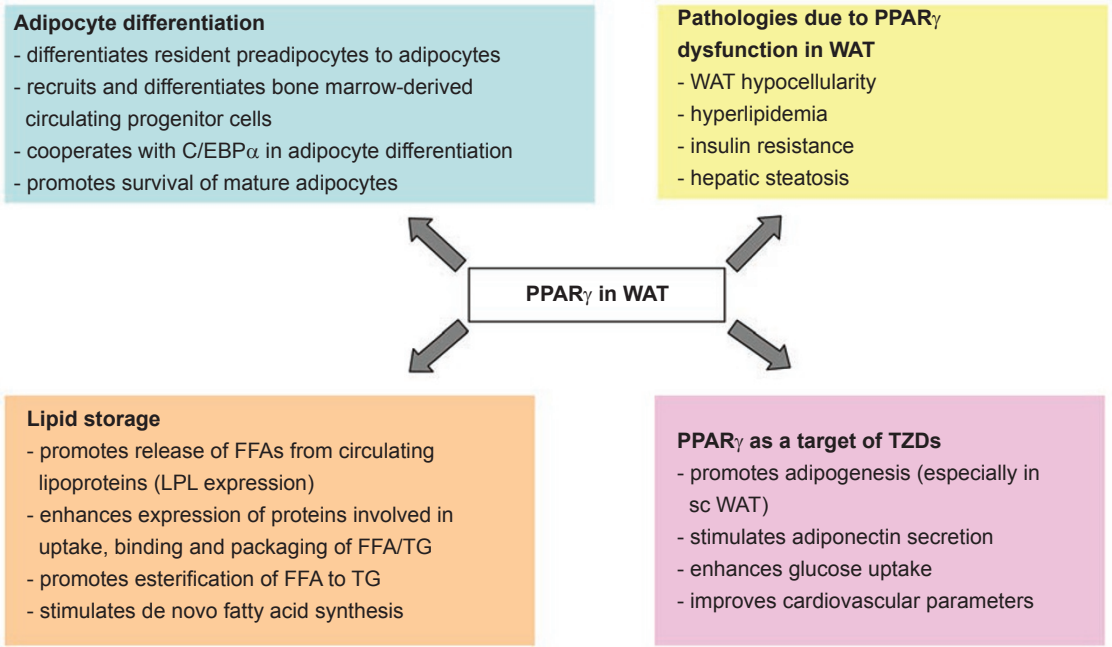

Figure 5 The main functions of PPARγ in the adipose tissue are given with respect to adipocyte differentiation, lipid storage, pathologies induced by its ill-functioning or as a target of TZDs.

Alternative promoter usage gives rise to two PPARγ isoforms. PPARγ$_1$ is the ubiquitous isoform found in all PPARγ-expressing tissues such as WAT, BAT, macrophages, liver, skeletal muscle, kidney, colon, vascular endothelium and others [151, 152]. PPARγ$_2$ has a 30 (rodents) or 28 (human) residue N-terminal extension over that of PPARγ$_1$, and is expressed primarily in adipose tissue [153, 154]. The role of PPARγ$_1$ and PPARγ$_2$ as key regulators of adipocyte differentiation from preadipocytes was shown by several groups [154-156]. Based on cellular studies, the differentiation of preadipocytes to adipocytes can be divided into four steps. First, the preadipocytes are withdrawn from the cell cycle, and genes responsible for the "preadipocyte phenotype" are downregulated. The second step, called the "mitotic clonal expansion", allows a last round of cell division. Next, 48 h after the initiation of differentiation, the cells start to acquire the "early adipocyte phenotype", which represents the third step. Fourth, in the "differentiated adipocytes", genes already expressed at low levels in the early adipocyte phenotype, are now at their maximal expression levels, especially genes involved in energy storage and fat metabolism, such as C/EBPβ and PPARγ [157, 158]. 3T3L1 cells, frequently used as adipocyte differentiation models, which have been manipulated to express small interference RNA (siRNA) against PPARγ or embryonic stem cells (ES cells) deficient for PPARγ (PPARγ–/–), are unable to differentiate into adipocytes. These defects in PPARγ expression reveal the important involvement of the receptor in this differentiation process, especially in the transition between the "mitotic clonal expansion" and the acquisition of the "early adipocyte phenotype" [159, 160]. Conversely, experiments on gain of function, using retroviral expression of PPARγ in cultured fibroblasts, as well as treatment of fibroblasts with PPARγ agonists, were shown to stimulate adipogenesis [161].

Obviously, PPARγ is not the only transcription factor controlling the differentiation of mesenchymal cells to adipocytes, but a major player in a sophisticated network of transcription factors and their co-repressors and co-activators, which respond to specific stimuli to repress or stimulate adipocyte formation. The elegant cascade of transcription factor signaling in the regulation of adiposeness has been reviewed recently [162], and therefore will not be discussed further here.

PPARγ and lipid storage

In addition to being involved in the differentiation of adipocytes, PPARγ participates in the function of the mature cells. Indeed, PPARγ is the major regulator of lipid storage in WAT [163]. It promotes the release of FFA from circulating lipoproteins by regulating lipoprotein lipase expression [164], and stimulates their uptake by enhancing

the expression of the fatty acid translocase CD36, and of the fatty acid transport protein FATP1 [165-167]. Furthermore, PPARγ regulates the intracellular retention/transport of FFA by controlling the expression of fatty acid binding proteins [168]. It also promotes the esterification of FFA into TG and their storage by regulating the expression of enzymes such as phosphoenol pyruvate carboxykinase, glycerol phosphate dehydrogenase, and diacylglycerol O acyltransferase. Expression of perilipin, which is the predominant protein associated with adipocyte lipid droplets and has a key function in regulating adipocyte lipid storage and body fat accumulation, is stimulated, too [167, 169-174]. Finally, PPARγ participates in the *de novo* FFA synthesis by regulating directly or indirectly the expression of enzymes such as fatty acid synthase, acetyl CoA synthetase, and stearoyl CoA desaturase 1 (Figure 5) [163, 166, 167, 175].

Ablation of PPARγ expression and activity in WAT: lessons from mouse models and human genetics

Studies on the role of PPARγ in WAT have been stimulated by the finding that TZDs, now used to treat patients suffering from type 2 diabetes, are specific ligands of PPARγ. Most of the present knowledge on PPARγ functions in energy homeostasis and its deregulations derives from the use of animal models and the investigation of patients bearing variant forms of the *PPARγ* gene (Figure 5).

Mouse models

General ablation of the *PPARγ* gene in mice is lethal due to placental malformation [176]. In a model of generalized *PPARγ* ablation where embryonic lethality is prevented by preserving PPARγ expression in trophoblasts, severe lipodystrophy, insulin resistance and hypotension, probably due to increased vascular relaxation, were observed [177]. On the contrary, the PPARγ+/–heterozygous animals are viable and do not present any major defects except mild growth retardation in males, possibly due to a deregulation of growth hormone signaling in the WAT [178]. The PPARγ+/– mice have normal insulin sensitivity under a standard diet. However, when on a high-fat diet (HFD) and compared to WT animals, they are protected against fat mass increase, which is reflected in smaller adipocytes. Furthermore, they do not develop insulin resistance or liver steatosis, and display a substantial increase in FA oxidation in the liver and in skeletal muscle [179-181].

Specific deletion of PPARγ in WAT has led to a better understanding of pathologies linked directly to PPARγ dysfunction in this tissue. Three different laboratories performed this specific genetic manipulation. In a first study, using mutant animals on a standard diet, adipocyte hypocellularity and hypertrophy were observed, involving an increase in the levels of plasma TG and FFA, and a decrease in leptin and adiponectin levels, which were accompanied by increased hepatic gluconeogenesis and insulin resistance. This latter was reversed by TZD treatment that, however, failed to lower circulating FFA. These animals were more susceptible to HFD-induced steatosis, hyperinsulinemia and associated insulin resistance [182]. A similar phenotype was observed in a "knock in" mouse model using the dominant-negative mutant PPARγL466A, which again showed the relationship between PPARγ function, adipose tissue and typical metabolic syndrome pathologies. Homozygous PPARγL466A mice died *in utero*, similar to *PPARγ*–/– mice [183].

In a second ablation study, mutant mice lacking PPARγ in adipose tissue were fed HFD, following which they presented diminished weight gain and plasma levels of adiponectin and leptin, but, in contrast to the first study, did not develop systemic insulin resistance or glucose intolerance. Furthermore, the mice exhibited diminished glucose uptake in the skeletal muscle, which suggests insulin resistance in this tissue. However, the liver did compensate for this insulin resistance by increasing glucose uptake and utilization, thereby improving the overall systemic insulin sensitivity. This improvement coincided with an increased expression of PPARγ in the liver, where it might have had a protective effect under these conditions [184]. The reason for the difference in insulin resistance between the two studies remains unclear, but different feeding protocols might be the cause. These studies also showed that several genes involved in lipid uptake and lipogenesis were downregulated. The resulting diminution of fat accumulation in the WAT of these animals most likely contributed to the plasmatic increase in FFA and TG concentrations as well as to hepatic steatosis. [182, 184].

In the third study, ablation of *PPARγ* was induced selectively in adipocytes after the animals had reached adulthood. *PPARγ*-null adipocytes died within a few days after ablation of the gene, thus demonstrating that, in addition to its role in adipose differentiation, PPARγ is essential for the survival of mature adipocytes [141]. In the studies discussed above, both isoforms PPARγ1 and PPARγ2 were deleted. When PPARγ2 alone is selectively disrupted, the mutant mice develop normally and are viable. However, they display a reduced WAT mass with smaller and heterogeneous-in-size adipocytes reflecting less lipid accumulation, well in line with a decreased expression of lipogenic genes. However, there was no liver steatosis, and insulin resistance was observed in male mice only. It was corrected by TZD treatment, probably by the effect of this drug on the remaining $PPAR\gamma_1$ in WAT, liver, and skeletal muscle. This model underscores again that the integrity of the adipose tissue is primordial for a good whole-body energy balance as well as for systemic insulin sensitivity.

In addition, it shows that PPARγ_1 alone can sustain development in general and drive adipose tissue formation in particular [185].

Another model in which the expression of PPARγ_2 and γ_1 is blunted in WAT, without affecting PPARγ_1 expression in the liver and skeletal muscle, but in which PPARγ1 was found to increase in BAT, was called the PPARγ hypomorphic mouse (PPAR$\gamma^{hyp/hyp}$) [186]. PPAR $^{hyp/hyp}$ mice present a severe lipodystrophic syndrome and a relatively high neonatal mortality. Even if the surviving mice develop hyperlipidemia, they present only limited metabolic consequences of the severe WAT lipodistrophy most likely because of compensation, particularly by muscles [186].

The site of action of TZDs has been long debated and although not fully clarified yet, significant knowledge has come from the use of the A-ZIP/F1 fatless mouse that lacks WAT. These mice present a phenotype similar to that of humans with lipoatrophic diabetes, fatty liver, hyperlipidemia, and hyperglycemia and insulin resistance. Treatment of these animals with rosiglitazone and troglitazone (two PPARγ agonists; see "PPARγ as a therapeutic target in fat-related diseases") showed that adipose tissue is required for the antidiabetic, but not for the hypolipidemic effect of TZDs [187]. Using the same model, it was shown that rosiglitazone enhances insulin action in skeletal muscle by the distribution of fat away from this organ, contributing at least in part to liver steatosis. Ablation of liver PPARγ in the A-ZIP/F1 mice, while reducing steatosis, aggravates TG clearance problem, hyperlipidemia and, as a consequence, muscle insulin resistance [188, 189].

The results obtained from these different mouse models underscore the link between adipogenesis and the metabolic syndrome [190], and highlight the crucial role of PPARγ for the development, integrity and well-functioning of the WAT. Adipocytes communicate with preadipocytes, monocytes/macrophages and endothelial cells within the adipose tissue and with the liver, skeletal muscle, pancreas and brain at the systemic level. Most importantly, it shows that deregulation of the WAT function and integrity, which often interferes with the production of secreted adipokines and other signaling proteins by the different cell types comprised in the WAT, ultimately affects the homeostasis of the whole body. A disturbance of this balance contributes to the development of the metabolic syndrome and associated risks [31].

Human genetic studies

As highlighted by the animal models, PPARγ is a determining factor for fat-related pathologies. Similarly, arrays of polymorphisms and mutations have been identified in the human *PPARγ* gene, which are linked to metabolic phenotypes. Only mutations particularly informative on the role of PPARγ in WAT will be discussed below, with regard to adipose mass (obesity and lipodystrophy), energy balance, insulin resistance, and low-grade inflammation.

PPARγ loss of function mutations

Familial partial lipodystrophy (FPL) is associated with mutations in the *PPARγ* gene in a few patients. This partial lipodystrophy affects limbs and buttocks, but spares abdominal sc fat that might be increased, causing insulin resistance, diabetes, high plasma TG levels, hypertension, and in some cases liver steatosis and polycystic ovarian syndrome.

A study of the *PPARγ* gene in seven FPL patients revealed a heterozygous change of the highly conserved arginine 425 to cysteine, in exon 6, in one of the patients, a non-Hispanic white woman who developed type 2 diabetes and hypertriglyceridemia, and later lipodystrophy, of the extremities and face, while sc truncal fat was slightly increased [143]. Since arginine 425 might be involved in a salt bridge that maintains the PPARγ protein in a proper configuration, it was speculated that this PPARγR425C mutation represents the molecular basis of one of the FPL phenotypes.

Another mutation, PPARγP467L, was found in two adult patients (man and woman) as well as a PPARγV290M mutation in a female patient. These adults also suffered from lipodystrophy at the extremities, elevated plasma TG concentrations, hyperinsulinemia, and fat accumulation in the liver. However, there was no difference in the circulating levels of leptin and TNF-α but a decrease in adiponectin levels in the two PPARγP467L patients [191]. *In vitro* studies of both mutations suggest a destabilization of the PPARγ configuration more favorable for receptor-co-repressor interactions with dominant-negative properties. Interestingly, a PPARγ ligand stabilizes the receptor structure in the active conformation and promotes co-repressor release, which most likely explains the improvement of these patients' condition after TZD treatment [192].

In addition, four members of a same family were identified, who suffered from a transactivation deficient mutant PPARγ, namely PPARγF388L, which changes a highly conserved residue of helix 8 of the ligand-binding pocket [193]. All four patients were heterozygous carriers and presented partial lipodystrophy as well as hyperinsulinemia. Moreover, the older patients suffered from type 2 diabetes and hypertension. In transactivation assays, the basal transcriptional activity of the mutant receptor was three-fold lower compared to the WT molecule in the absence of an exogenous ligand. However, in the presence of TZD, its activity increased, comparable to the WT receptor only at high rosiglitazone concentrations. It is noteworthy that the proband, when treated with pharmacological doses of

rosiglitazone, in combination with metformin, had a good glycemic control [193].

Another well-studied variant is the PPARγ_2P12A [70, 73, 194, 195]. This is the only well-described change found so far in the N-terminal domain of PPARγ_2. The initial study of Finnish and second-generation Japanese populations concluded that the less common 12A allele promotes insulin sensitivity and confers protection against type 2 diabetes [70, 73, 194, 195]. *In vitro* studies showed that this allele reduces PPARγ DNA binding affinity and transcriptional activity [70, 73, 194, 195]. Although some additional studies did not support a statistically significant role for the PPARγ_2P12A polymorphism in the etiology of type 2 diabetes [196-198], a more recent meta-analysis of all published data, comprising more than 25 000 cases of diabetes, showed an association of P12A with type 2 diabetes [199]. The large population that was necessary in order to demonstrate the association between P12A and type 2 diabetes is due to the weak effect of the risk allele, since individuals that are homozygous for the higher risk P12 allele have only a 25% increase in diabetes risk. However, because the frequency of the P12 allele is high in Europeans, it has a substantial effect at the level of this population, since the disease would be reduced significantly if the risk factor were not present [199]. Data from a recent study support the idea that additional PPARγ variants, besides the one just described, most likely contribute to PPARγ effects on metabolic traits in African-Americans and whites [200].

In brief, the mutations found in the human PPARγ receptor show that, in general, as in mice, the level of PPARγ activity correlates with adiposity. Loss of PPARγ function is linked to partial lipodystrophy, which in turn is associated with severe metabolic dysfunctions. This connection highlights once more the role of PPARγ in the control of both lipid and glucose metabolism. Interestingly, a mild reduction in PPAR activity, as seen above with the 12A in humans, or with a partial antagonist in mice, promotes insulin sensitivity. In mice it also decreases fat depots, and brings the metabolic parameters to the levels seen in PPARγ heterozygous mice [73, 178, 180]. These heterozygous mice are partially protected from high-fat diet or mono sodium glutamate-induced weight gain and insulin resistance. It is not known whether treatment of human diabetic patients with a partial PPARγ antagonist would inhibit TG accumulation in fat tissue without redistribution to muscle and liver, thus promoting insulin sensitivity [201].

PPARγ gain of function mutations

The PPARγP115Q mutation, which was found in four unrelated patients, is the only one in humans that was found to increase PPARγ activity. 115Q prevents the adjacent S114 from being phosphorylated (phosphorylation of this residue inactivates the receptor). All four patients were severely obese, lending additional support to the notion that increased PPARγ activity promotes increase in fat mass. It is noteworthy that in a nation-wide German epidemiological field survey, no individual homozygote or heterozygote for the 115Q allele was found, showing that this mutation is unlikely to have a significant epidemiological impact on morbid obesity [202]. However, it certainly contributes to a better understanding of the role of PPARγ activity on fat mass in humans.

Taken together, data from the mouse models and human genetic studies underscore a direct and positive correlation between PPARγ and adiposity. Such a correlation appears less obvious between PPARγ activity and insulin sensitivity. It may suggest that insulin sensitivity is achieved mainly by a modulation of PPARγ activity within the WAT, possibly through its transcriptional effects on adipokine expression and secretion, as well as on lipogenic gene expression. Maintaining the integrity of the adipose tissue may fulfill this function. In fact, obese and lipodystrophic animals and humans both develop insulin resistance and associated pathologies.

PPARγ as a therapeutic target in fat related diseases

To become transcriptionally active, PPARγ depends on an indispensable partner, the Retinoid X Receptor, which is also a member of the nuclear hormone receptor family, with which it forms a heterodimer. This heterodimer binds to specific sequence elements in the regulatory regions of target genes, called Peroxisome Proliferator Response Elements (PPRE) and, in the presence of ligands, activates transcription. Fatty acids and prostaglandin J derivatives are natural ligands of PPARγ [4, 10].

Before even being identified formally as PPARγ ligands, TZDs were shown to stimulate adipogenesis and to improve insulin sensitivity [203, 204]. It is only more recently that TZDs were described as selective ligands for the receptor, bridging the gap between PPARγ and insulin sensitivity (Figure 5) [205, 206].

Supraphysiological activation of PPARγ by TZDs stimulates adipogenesis by increasing the number of newly differentiated adipocytes, especially in the sc WAT. Increasing the storage capacity of WAT decreases ectopic lipid accumulation. The result is a decrease in liver and skeletal muscle TG content and an amelioration of insulin sensitivity at the expense of increased sc WAT mass. However, TZD amelioration of insulin sensitivity in skeletal muscle appears to be independent of the lipid profile of this organ, since the TZD treatment was shown to increase lipid ac-

cumulation in skeletal muscle [207]. Lessons learned from the PPARγ+/– mouse model, as mentioned above, as well as from clinical observations of obese patients after weight loss, which correlated with reduced PPARγ levels, suggest that a moderate decrease in PPARγ activity might have beneficial effects on the TG content of WAT, liver and skeletal muscle. In fact, diminution of PPARγ transcriptional activity reduces the expression of the lipogenic program and promotes the β-oxidation pathway in the liver and muscle, with an improvement of plasma lipidic parameters as well as insulin sensitivity [179, 208, 209].

Use of synthetic PPARγ agonists in the treatment of lipodystrophies and type 2 diabetes

The effects of the TZD rosiglitazone were investigated in acquired or genetic lipodystrophies, including those caused by mutations in the *PPARγ* gene (see above). In patients with inherited or HIV-induced lipodystrophies, treatment with rosiglitazone increases the sc fat mass, and augments insulin sensitivity and adipokine secretion, probably by increasing the lipogenic program in WAT [175, 210, 211].

With respect to type 2 diabetes, several drugs have been introduced during the past decade, which are effective in lowering blood glucose and in reducing diabetes-related end-organ diseases. The two TZDs, rosiglitazone and pioglitazone, currently approved as antidiabetic drugs, are selective PPARγ agonists. Troglitazone, the first agent of this class, effective in controlling glycaemia, was removed from the market because of serious liver toxicity.

In addition to improving insulin signaling, rosiglitazone and pioglitazone improve cardiovascular parameters, such as lipids (increase in sc WAT, influx of FFA), blood pressure, inflammatory biomarkers (inhibition of adipokine expression and action), endothelial function, and fibrinolytic status [212-214]. Furthermore, pioglitazone treatment shifts fat from the vis to the sc compartment in obese patients, a fat redistribution thought to improve insulin sensitivity since sc WAT confers less insulin resistance than vis WAT [208]. These observations are consistent with recent data from a report on the treatment of male rats with a PPARγ agonist. Redistribution of fat by stimulation of the potential for lipid uptake and esterification in sc WAT was obtained, but only a minimal effect on uptake was achieved in vis WAT. More significantly, energy expenditure was strongly increased in vis fat with a consequent reduction in fat accumulation [215].

Despite the efficacy and beneficial effects of TZDs, a number of undesired side effects have been noted, including increased weight gain due to both increased adiposity and fluid retention (edema) [216, 217]. The latter, which can be explained by PPARγ stimulation of ENaC-mediated renal salt absorption [218], might be the cause of an increased incidence of congestive heart failure [219], an outcome also observed in rats where rosiglitazone treatment is associated with increased post-myocardial infarction mortality [220]. However, this issue is still under debate as the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) showed recently that treatment of type 2 diabetic patients with pioglitazone, another TZD drug, improved their cardiovascular outcome [113].

At the present time, substantial effort has been concentrated on generating novel selective PPARγ modulators that retain the beneficial clinical effects while avoiding the unwanted side effects.

Are PPARγ antagonists candidate drugs for type 2 diabetes?

As mentioned above, PPARγ activation reduces insulin resistance, but also increases fat mass by promoting adipocyte hypertrophy and hyperplasia. Since lasting enhanced adiposity is associated with increased insulin resistance, it was hypothesized that reducing PPARγ activity would result in less fat mass and improved insulin sensitivity. In fact, mice treated with PPARγ partial antagonists such as SR202, GW9662, or BADGE (bisphenol A diacylycidyl ether) showed decreased TG content in WAT, liver and skeletal muscle, decreased adipocyte size, increased resistance to HFD-induced obesity, and decreased expression and secretion of leptin and TNF-α. However, insulin sensitivity under HFD conditions depends on the type of antagonist that was administrated to the animals. SR202- and BADGE-treated mice presented an increased sensitivity to insulin, whereas GW9662 had no effect on insulin sensitivity [221]. Especially for SR202, the effect is comparable to the improved sensitivity recorded in untreated *PPARγ*+/– mice, in which PPARγ levels were reduced by half compared with WT animals. [221-224].

Several lines of evidence discussed above suggest that WAT dysfunctions resulting from lipodystrophies or experimentally induced loss of adiposity in animal models can also be linked to insulin resistance, possibly due to excessive levels of circulating FFA that could be lipotoxic for the liver, skeletal muscle and even for the pancreas (by affecting beta cell action). In addition, experimental disruption of the WAT in mice induces a low-grade inflammation, as in obese patients. Associated with adipokine and pro-inflammatory cytokine expression and secretion from the dysfunctional WAT, this inflammatory condition may affect insulin sensitivity. In line with this possibility, treatment of *PPARγ*+/– mice (where the activity of the receptor is decreased by half) with the PPARγ antagonist BADGE causes re-emergence of the lipotoxic effect of TG in liver and skeletal muscle, and insulin resistance [223].

It would appear, therefore, that the use of PPARγ an-

tagonists over long periods of time might interfere with the integrity of the adipose tissue and trigger unexpected and undesired effects on whole-body metabolism, including insulin sensitivity.

Selective PPARγ modulators: a better alternative?

To overcome side effects associated with the use of TZDs, a novel approach consists in developing new PPARγ ligands that have insulin-sensitizing properties, via selective action on beneficial pathways, without exacerbating fluid retention and obesity. Such compounds are called "selective PPARγ-modulators" (SPPARγMs) analogous to selective estrogen receptor modulators (SERMs) such as raloxifen, which spares the uterus functions, but acts as a partial ER agonist in bones [225]. SPPARγMs would separate the effects of PPARγ on lipid and glucose metabolisms as well as on different organ systems (gastrointestinal, immune, cardiovascular). The selective action of such compounds is thought to depend on different structural configurations induced in the ligand-binding domain by their interaction with the receptor, allowing recruitment of different complexes of cofactors that impact on the activation or repression of specific sets of target genes in different tissues [146, 218, 226-231].

A variety of such new PPARγ ligands with differential pharmacological affinities for PPARγ have been reported in recent years. One of the first SPPARγMs that was tested, and which validated this idea, is FMOC-L-Leucine (F-L-Leu), which separates insulin sensitivity from adipogenesis *in vivo* [232].

The non-TZD-selective PPARγ modulator (nTZDpa) was also shown to alter the conformational stability of the receptor when compared to TZDs. Chronic treatment of fat-fed C57BL/6J mice with nTZDpa improved hyperglycemia and hyperinsulinemia, and promoted reductions in weight gain and adipose depot size, without causing cardiac hypertrophy. In WAT, nTZDpa produced a different *in vivo* expression pattern of a panel of PPAR target genes when compared to a full agonist [227]. Similarly, a series of metabolically robust *N*-benzyl-indole partial PPARγ agonists, with either a 3-benzoyl or 3-benzisoxazoyl moiety, also produced potent glucose reduction in *db/db* mice and attenuated increases in heart weight and BAT mass, which are typically observed in rodents upon treatment with PPARγ full agonists [233, 234]. In addition, halofenate, one of the recently discovered SPPARγMs, displays the characteristics of an optimized modulator, retaining an insulin sensitization potential with minimal adipogenic activity *in vitro* and with less weight gain *in vivo* (*ob/ob* mouse and *fa/fa* Zucker rat models). At the molecular level, the partial agonism of halofenic acid may be explained in part by effective displacement of the corepressors NCoR and SMRT, coupled with inefficient recruitment of co-activators, such as p300, CBP, and TRAP 220 [235]. Further characterization of SPPARγMs will most likely yield novel agents for the treatment of type 2 diabetes, which are as effective as current pharmacological compounds but without their side effects. These findings should encourage mechanism-based screens [225], which would capitalize on a still very incomplete knowledge of the ensemble of PPARγ co-activators and co-repressors and their expression profile in tissues that are pivotal for PPARγ action.

At this point, the emergence of novel potential therapeutic targets is worth mentioning, for the treatment of metabolic-related diseases, among which is the cofactor sirutin 1 (SIRT1), a protein lysine deacectylase. The human SIRT1 regulates several transcription factors that govern metabolism among which is PPARγ. SIRT1 is induced by fasting in several tissues, such as the WAT where it represses PPARγ activity thus decreasing the amount of fat storage. Its activation by resveratrol was shown to improve mitochondrial function and to protect against metabolic related diseases [236-239].

Conclusion

As described herein, the adipose tissue has been promoted within only a few years from a lipid storage bag to the most sophisticated, in terms of functions, and more importantly, in terms of mass, endocrine organ of the body. It participates in the control of energy balance in two ways: firstly by managing the energy depot of the body via the timely appropriate fine-tuned uptake, storage and release of lipids, and, secondly, by communicating with many organs via an incredibly rich array of endocrine signals that are emitted or received. With this in mind, it becomes clear why the functional integrity of this organ is primordial to whole-body homeostasis as a prerequisite for good health. Treatment of metabolic disorders through modulation of PPARγ activity appears to have a promising future once knowledge has been acquired, enabling an activation/repression mechanism-based identification of PPAR isotype-selective modulators with the required characteristics. Ablation of the adipose tissue function by a selective full PPARγ antagonist is obviously not a solution. Indeed, as discussed above, animal and human models of lipodystrophy, some of which were caused by complete or partial loss of PPARγ activity, illustrate the deleterious and potentially dangerous outcome of such an approach. Supraphysiological stimulation of PPARγ activity, such as that achieved by TZDs, triggers unwanted side effects. Based on present knowledge, the demanding path of highly selective SPPARγM identification with respect to functional outcome appears to be the most promising way forward in

terms of potential therapeutic benefits. Such compounds may in fact open the route to preferred therapies for type 2 diabetes, obesity, and various manifestations of the metabolic syndrome.

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