Molecular and Cellular Endocrinology 316 (2010) 129–139

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

Adipose tissue as an endocrine organ

Sandra Galic[a], Jon S. Oakhill[a], Gregory R. Steinberg[a,b,*]

[a] St. Vincent's Institute of Medical Research and Department of Medicine, University of Melbourne, Melbourne, Victoria, 3065, Australia
[b] McMaster University, Department of Medicine, 1200 Main Street West, Hamilton, Ontario, Canada, L8N 3Z5

ARTICLE INFO

Article history:
Received 12 December 2008
Received in revised form 5 August 2009
Accepted 25 August 2009

Keywords:
Leptin
Adiponectin
TNFα
IL-6
Resistin
RBP4
Nutrient signaling
Innate immunity
Cytokines
Insulin sensitivity
Obesity

ABSTRACT

Obesity is characterized by increased storage of fatty acids in an expanded adipose tissue mass and is closely associated with the development of insulin resistance in peripheral tissues such as skeletal muscle and the liver. In addition to being the largest source of fuel in the body, adipose tissue and resident macrophages are also the source of a number of secreted proteins. Cloning of the obese gene and the identification of its product, leptin, was one of the first discoveries of an adipocyte-derived signaling molecule and established an important role for adipose tissue as an endocrine organ. Since then, leptin has been found to have a profound role in the regulation of whole-body metabolism by stimulating energy expenditure, inhibiting food intake and restoring euglycemia, however, in most cases of obesity leptin resistance limits its biological efficacy. In contrast to leptin, adiponectin secretion is often diminished in obesity. Adiponectin acts to increase insulin sensitivity, fatty acid oxidation, as well as energy expenditure and reduces the production of glucose by the liver. Resistin and retinol binding protein-4 are less well described. Their expression levels are positively correlated with adiposity and they are both implicated in the development of insulin resistance. More recently it has been acknowledged that macrophages are an important part of the secretory function of adipose tissue and the main source of inflammatory cyokines, such as TNFα and IL-6. An increase in circulating levels of these macrophage-derived factors in obesity leads to a chronic low-grade inflammatory state that has been linked to the development of insulin resistance and diabetes. These proteins commonly known as adipokines are central to the dynamic control of energy metabolism, communicating the nutrient status of the organism with the tissues responsible for controlling both energy intake and expenditure as well as insulin sensitivity.

Contents

* Corresponding author at: McMaster University, Department of Medicine, 1200 Main Street West, Hamilton, Ontario, Canada, L8N 3Z5. Tel.: +1 905 521 2100x21691; fax: +1 905 777 7856.
E-mail address: gsteinberg@mcmaster.ca (G.R. Steinberg).

0303-7207/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.mce.2009.08.018

1. Introduction

The rapid rise in the rate of obesity is a critically important health issue for the developed world. Obesity is associated with a number of health problems that are often summarized together as the metabolic syndrome and involves the development of insulin resistance, type 2 diabetes, cardiovascular disease and fatty liver disease. Both obesity and type 2 diabetes are causally linked through their association with the development of insulin resistance. Obesity is characterized by increased storage of fatty acids in an expanded adipose tissue mass and is closely associated with the development of insulin resistance in peripheral tissues such as skeletal muscle and the liver (Fig. 1). Adipose tissue plays a crucial role in the regulation of whole-body fatty acid homeostasis. In periods of calorie abundance it stores free fatty acids (FFAs) in the form of triglycerides through their esterification to glycerol and releases them back into the circulation in times of energy shortage. While the role of adipose tissue as a central source of energy has been recognized for centuries it has been just over 50 years since Kennedy (1953) hypothesized about the presence of a circulating, lipostatic, negative feedback signal acting centrally to alter energy expenditure and food intake. The following decade studies involving genetically obese (*ob*/*ob*) and diabetic (*db*/*db*) mice confirmed the presence of such a circulating factor (Coleman, 1973). While these mutations are on unrelated genes located on separate chromosomes both models were characterized by obesity, hyperphagia, diabetes, infertility and reduced physical activity and thermoregulation. Parabiosis experiments explained the identical syndromes by suggesting the existence of a humoral factor that is absent in the *ob*/*ob* mouse and present but ineffective in *db*/*db* mice. However, the identity of this lipostatic signal remained elusive. In 1994, using positional cloning in the *ob*/*ob* mouse, Zhang et al. (1994) identified and sequenced the *ob* gene and its protein product, leptin (from *leptos*, for thin). Shortly thereafter, a cohort of studies (Campfield et al., 1995; Halaas et al., 1995; Pelleymounter et al., 1995) demonstrated that daily injections of *ob*/*ob* mice with the 16 kDa peptide leptin rapidly reduced food intake, body mass and percent body fat, while maintaining lean muscle mass. In addition, leptin administration resulted in increased energy expenditure and restored euglycemia and reproductive function, confirming its role as a regulator of energy intake and storage.

Around the same time as the discovery of leptin, Hotamisligil et al. (1993) identified that in addition to proteins involved in metabolic regulation, adipose tissue also secreted tumour necrosis factor-α (TNFα), which they identified to be a negative regulator of insulin signal transduction. Subsequent studies in genetic models of TNFα deficiency confirmed a causal role for this inflammatory cytokine in the development of obesity-induced insulin resistance establishing the now well accepted paradigm that obesity is a chronic condition of low-grade inflammation (Uysal et al., 1997). More recently it has been revealed though that the predominant source of this adipose inflammation is from activated adipose tissue macrophages (Weisberg et al., 2003). These pivotal discoveries established the foundation for the now well accepted idea that adipose tissue is a dynamic endocrine organ that is critical for regulating metabolism in both health and disease, findings, which provided a foundation for the subsequent discovery of many other adipocyte-derived secreted proteins (adipokines) such as adiponectin, resistin, retinol binding protein-4 (RBP4) and interleukin-6 (IL-6). The purpose of this review is to provide a general overview of the above stated adipokines with a focus on their source, whether it is adipose tissue or resident macrophages, structure and function and their effects on whole-body energy metabolism and insulin resistance.

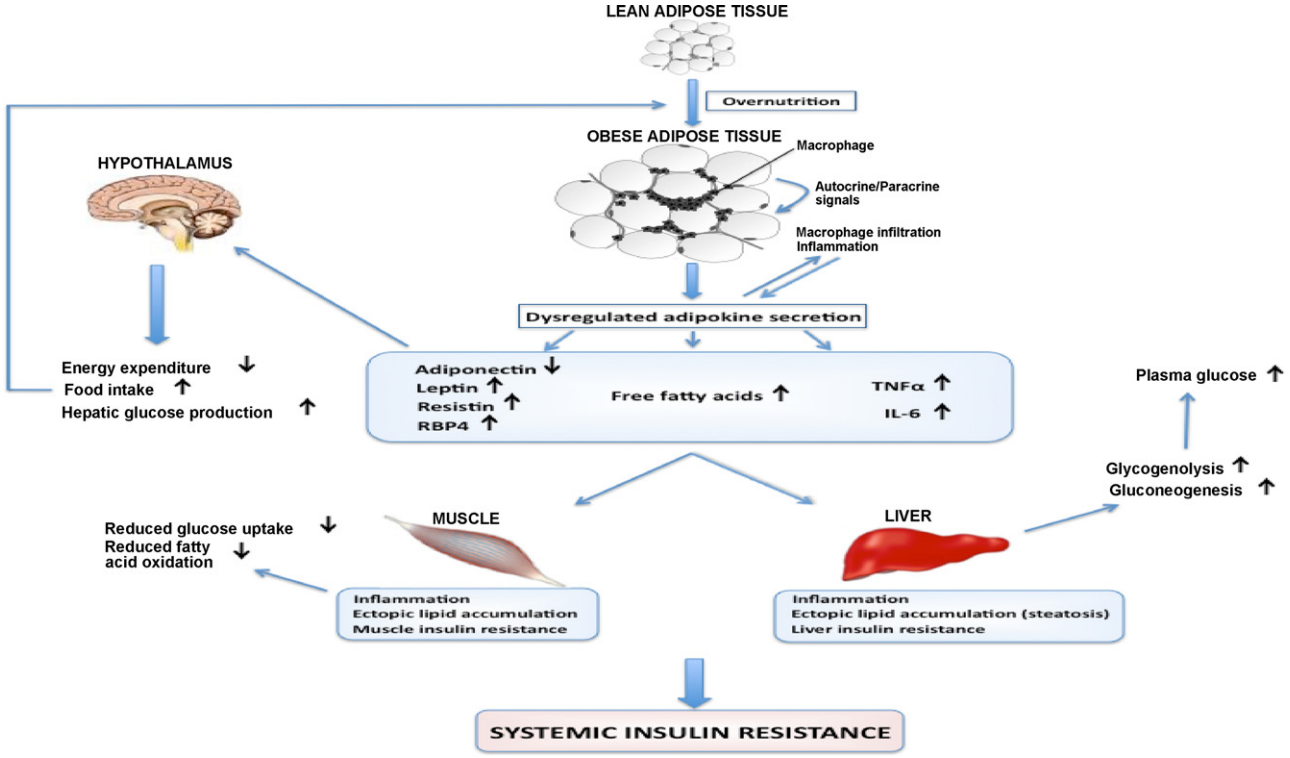

Fig. 1. Obesity-induced changes in adipokine secretion and the development of insulin resistance. Expansion of adipose tissue in obesity leads to increased macrophage infiltration and inflammation with enhanced production of pro-inflammatory cytokines such as TNFα and IL-6. This is accompanied by an increased release of free fatty acids and dysregulated secretion of leptin, adiponectin, resistin and retinol binding protein-4 (RBP4). Together, these adipocyte- and macrophage-derived substances can act in a paracrine or autocrine fashion to further exacerbate adipose tissue inflammation. On the systemic level, altered adipokine secretion can lead to increased food intake and reduced energy expenditure through actions in the hypothalamus and to decreased muscle and liver insulin sensitivity through enhanced ectopic lipid deposition and inflammation.

2. Leptin

In contrast to the *ob*/*ob* mouse which lacks leptin, plasma leptin levels increase with weight gain and decrease with weight loss, consistent with leptin's role as a signal of adipose tissue stores (Havel et al., 1996; Maffei et al., 1995). There is a positive linear correlation ($r = 0.8$) between circulating levels of serum leptin and total body fat mass, which can be explained by increased release of leptin from large compared with small fat cells (Lonnqvist et al., 1997). On average leptin release per gram of adipose tissue is two times greater in obese than in lean subjects. Because fat cell size is usually enlarged 2–4 times in the obese, when expressed per fat cell, leptin secretion is up to seven times higher in obese than in lean subjects (Fried et al., 2000). Serum leptin levels display a diurnal rhythm with the highest levels between 2300 and 0100 h, after which plasma leptin declines until early afternoon (Sinha et al., 1996a; Saladin et al., 1995). This diurnal rhythm is linked to meal timing because a 6-h delay in meals produces a similar phase shift in the plasma leptin profile (Saladin et al., 1995). This pulsatile and periodic nature of leptin production (Sinha et al., 1996a, 1996b) might be due to the ability of adipose tissue to store significant amounts of leptin in intracellular membrane-bound fractions (Russell et al., 2001). The nature of these subcellular compartments is still controversial with recent research pointing to the endoplasmic reticulum and a small hormone-regulated secretory compartment of unknown composition (Roh et al., 2001; Xie et al., 2008). The kidney has been found to be an important site of leptin clearance as total nephrectomy in rats (Cumin et al., 1996, 1997; Meyer et al., 1997) and chronic renal failure in humans (Jensen et al., 1999) results in increased plasma leptin concentrations, however, with obesity increased leptin levels are not due to reduced clearance (Meyer et al., 1997).

2.1. Leptin signaling

The leptin receptor (Ob-R, also known as LEP-R, LR, DR, CD295, HuB219) was first isolated from mouse choroid plexus by expression cloning and is a member of the interleukin-6 receptor family of class I cytokine receptors (Tartaglia et al., 1995). The OB-R gene, encodes five alternatively spliced forms of the leptin receptor; Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd and Ob-Re (Tartaglia et al., 1995; Lee et al., 1996). Ob-Rb is the long form of the leptin receptor (also known as ObR-L) and has a long cytoplasmic region containing several motifs required for signal transduction (discussed below) (Tartaglia, 1997). ObR-L is found in high concentrations (30–40% of total Ob-R) in the brain and more specifically in areas which regulate feeding such as the arcuate, dorsomedial and ventromedial hypothalamic nuclei (Tartaglia, 1997). It is also found in low concentrations (5–8% of total Ob-R) in several peripheral tissues including adipose tissue, ovaries, testis, placenta, adrenal medulla, liver, pancreatic beta-cells, lung, jejunum, peripheral blood mononuclear cells, articular chondrocytes, heart and skeletal muscle (Tartaglia, 1997; Cao et al., 1997; Briscoe et al., 2001; Figenschau et al., 2001; Matteis et al., 1998; Sanchez-Margalet and Martin-Romero, 2001). In comparison to ObR-L, the short forms of the receptor ObR-S (Ob-Ra, Rc, Rd, Re) are present at relatively low concentrations in the hypothalamus but are ubiquitously expressed within the microvessels and choroid plexus of the brain as well as all the peripheral tissues (Tartaglia et al., 1995; Tartaglia, 1997; Chen et al., 1996).

Like other class I cytokine receptors, Ob-R lacks intrinsic tyrosine kinase activity and therefore requires recruitment of the activated receptor-associated kinases of the Janus family (JAKs) (Banks et al., 2000). Activated signal transducers and activators of transcription (STATs) then dimerize and translocate to the nucleus, where specific gene responses are elicited, which in the hypothalamus include suppression of orexigenic gene expression (Ghilardi et al., 1996). Both the long and short forms of the leptin receptor have the ability to activate JAK2 in a leptin dose dependent manner (Bjorbaek et al., 1997) although it is clear that the ObR-L more robustly activates (~5-fold greater) these pathways than does ObR-S. Tyrosine phosphorylation of ObR-L at Tyr1138 within hypothalamic nuclei, has been found to be critical for the regulation of food intake and energy expenditure (Bates et al., 2003). Leptin administration also suppresses the activity of AMP-activated protein kinase (AMPK) in the paraventricular nucleus (PVN) and arcuate nucleus (ARC) of the hypothalamus (Andersson et al., 2004; Steinberg et al., 2006a; Minokoshi et al., 2004). The effects of leptin on AMPK signaling in the brain appear to be downstream of the melanocortin (MC) receptor as intracerebroventricular (icv) administration of the MC4 receptor agonist, MT-II, inhibits AMPK activity in the PVN, while both refeeding and leptin fail to inhibit hypothalamic AMPK activity in MC4 receptor knockout mice (Minokoshi et al., 2004).

Leptin's effects on metabolism are not limited to the hypothalamus as almost all tissues examined express leptin receptors (Tartaglia et al., 1995). Leptin acts directly in isolated skeletal muscle to increase fatty acid oxidation (Muoio et al., 1997) in an AMPK-dependent manner (Minokoshi et al., 2002) and this process appears to involve an increase in the AMP:ATP ratio. In addition to the direct activation of AMPK in skeletal muscle, there is also a delayed action of leptin that requires inputs from the central nervous system (CNS). The CNS-mediated activation of AMPK involves the stimulation of α-adrenergic signaling (Minokoshi et al., 2002) and is dependent on the MC system since icv delivery of an MC4 receptor antagonist inhibits leptin activation of AMPK in skeletal muscle while an MC agonist directly increases AMPK signaling in muscle (Tanaka et al., 2007). Since α-adrenergic receptors couple to G proteins and activate calcium/calmodulin-dependent kinase kinase (CAMKK) signaling, it is possible that the chronic effects of AMPK activation in skeletal muscle are mediated through CAMKK signaling. Conversely, the acute effects of leptin alter the AMP:ATP ratio and may be dependent on reducing protein phosphatase 2C (PP2C) dephosphorylation of Thr172. Future studies are required to delineate the upstream pathways mediating the acute and chronic effects of leptin on AMPK signaling. A second important question is how leptin mediates opposite effects on AMPK, activating in muscle but suppressing in hypothalamus. This effect may be related to different upstream AMPK kinase expression, which in skeletal muscle primarily is dependent on the tumour suppressor and serine–threonine protein kinase LKB1, while in the hypothalamus more likely involves CAMKKβ.

2.2. Genetic mutations in rodents and humans

In *ob*/*ob* mice mutations due to a C → T substitution results in a stop codon at position 105, which leads to the production of a truncated protein that is incapable of being secreted. This results in a phenotype characterized by leptin deficiency, hyperphagia, hypothermia, insulin resistance, reproductive dysfunction and early onset morbid obesity (Zhang et al., 1994). Human ob gene mutations are rare and were first reported in two children from a Pakistani family (Farooqi et al., 1998). In these patients, deletion of a single guanine nucleotide in codon 133 led to a frameshift mutation and synthesis of a truncated leptin protein. A second mutation similar to that seen in the *ob*/*ob* mouse (C → T in codon 105) has been found in three members of a Turkish family (Ozata et al., 1999). Here, the mutation leads to a substitution of Arg with Trp at position 105 and the synthesis of a mutant non-truncated leptin protein that cannot be processed through the secretory pathway. However, physiologic replacement for one year with recombinant leptin leads to substantial weight loss and the reversal of the physiological abnormalities (Ozata et al., 1999). Leptin receptor mutations cause early onset obesity in rodents (Tartaglia et al., 1995; Tartaglia, 1997;

Chen et al., 1996). In humans ObR-L mutations are extremely rare but in three sisters from a Kabilian family a homozygous mutation in the human leptin receptor gene resulted in a truncated leptin receptor lacking both transmembrane and intracellular domains (Clement et al., 1998). More recently, four novel missense mutations were identified after sequencing of the OB-R from 300 patients with severe obesity (Kimber et al., 2008). Ala409Glu leads to the synthesis of a mutant leptin receptor that is expressed at the cell surface and retains the ability to bind leptin, but displays impaired signaling transduction. The Trp664Arg and His684Pro mutations are presumed to interfere with correct folding of the OB-R protein and result in completely abolished signal transduction, whereas receptors with the Arg612His mutation are thought to be unable to reach the cell surface but retain some signaling capability.

2.3. Leptin resistance in obesity

Although leptin administration in *ob*/*ob* mice has been demonstrated to cause a rapid reversal of obesity through a reduction in caloric intake and an increase in basal metabolic rate, the relevance of this genetic model to the treatment of human obesity appears to be minimal. In contrast to the leptin deficient *ob*/*ob* mice high levels of circulating leptin even when normalized per kilogram fat mass characterize human obesity. Therefore, despite the presence of elevated leptin concentrations, which should reduce food intake and body fat, obese persons appear to be insensitive or resistant to leptin and continue to maintain high levels of body fat. In addition, while recombinant leptin injection reduces body fat in obese rodents the effects appear to be minimal in obese humans. In the first clinical trial examining the efficacy of leptin treatment Heymsfield et al. (1999) found that while recombinant leptin injection at high doses (elevated by ~20-fold) resulted in weight loss due to lower energy intake (and no change in energy expenditure) there was considerable variability in the amount of body mass lost between subjects at any given dose. In a follow up study, which used doubly labelled water and a respiration chamber to measure metabolic rate while also assessing food intake and appetite profiles, recombinant leptin injection reduced appetite but had no effect on energy expenditure or basal metabolic rate (Westerterp-Plantenga et al., 2001). These data suggest that the primary site of leptin resistance may be in metabolically important tissues such as skeletal muscle (Westerterp-Plantenga et al., 2001).

Skeletal muscle leptin resistance develops following high-fat feeding in rodents (Steinberg and Dyck, 2000) and is also prevalent in obese humans (Steinberg et al., 2002, 2004a). The development of leptin resistance in obese skeletal muscle is characterized by suppressed rates of leptin stimulated AMPK signaling (Steinberg et al., 2004a, 2006b; Watt et al., 2006; Martin et al., 2006). Similarly, high-fat feeding inhibits the ability of leptin to suppress hypothalamic AMPK signaling (Steinberg et al., 2006a; Martin et al., 2006). Two important mediators of leptin resistance are the suppressor of cytokine signaling 3 (SOCS3) (Bjorbaek et al., 1998) and the protein tyrosine phosphatase 1B (PTP1B) (Cheng et al., 2002; Zabolotny et al., 2002). SOCS3 is a member of a family of proteins (SOCS1–SOCS7, and CIS) in which their central SH2 domains bind to phosphotyrosine residues in cytokine receptors (Wormald and Hilton, 2004). Bjorbaek et al. (1998) demonstrated that inhibition of leptin signaling via the signal transducer and activator of transcription (STAT)-3 in hypothalamic nuclei was mediated by SOCS3 binding of Tyr985 of the leptin receptor (Bjorbaek et al., 1999, 2000). Both SOCS3 hypothalamic specific null mice (Mori et al., 2004) and SOCS3 mice with haploinsufficiency (Howard et al., 2004) have enhanced leptin sensitivity and are resistant to diet-induced obesity. In addition female mice with a point mutation of Tyr985 to Leu are protected against developing diet-induced obesity and insulin resistance (Bjornholm et al., 2007). SOCS3 is also up-regulated in skeletal muscle with high-fat feeding (Steinberg et al., 2004b) and is associated with leptin resistance (Carey et al., 2006). Moreover, the over-expression of SOCS3 via adenovirus-mediated infection in skeletal muscle cells, to a similar degree as observed in skeletal muscle of mice fed a high-fat diet (Steinberg et al., 2004b) or in obese humans (Carey et al., 2006), inhibited leptin but not pharmacological activation of AMPK α2 activity (Carey et al., 2006). These data demonstrate that SOCS3 inhibits leptin activation of AMPK and suggest that the down-regulation of leptin signaling in skeletal muscle may contribute to the aberrant regulation of fatty acid metabolism. This paradigm requires experimental support *in vivo*. It also appears as though blunted leptin signaling to AMPK in the hypothalamus may contribute to hyperphagia as elevated hypothalamic AMPK α2 activity in diabetic rats was associated with elevated NPY and suppressed POMC mRNA, whereas these effects were reversed with pharmacological AMPK inhibition (Namkoong et al., 2005).

The ubiquitously expressed protein tyrosine phosphatase PTP1B has been implicated as another possible mediator of leptin resistance. PTP1B has been shown to negatively regulate hypothalamic leptin signaling by dephosphorylating JAK2, leading to reduced leptin-induced STAT3 phosphorylation (Cheng et al., 2002; Zabolotny et al., 2002). Consistent with this, whole-body and neuron-specific PTP1B knockout mice are resistant to diet-induced obesity and show improved leptin sensitivity (Bence et al., 2006). Recently, physiological conditions associated with leptin resistance, such as high-fat diet or age, in addition to leptin infusion experiments have been shown to result in increased hypothalamic PTP1B protein levels and enzymatic activity raising the possibility that this phosphatase might act as a negative feedback regulator of the leptin signaling pathway (White et al., 2009). However, high-fat diet feeding can also lead to leptin-independent increases in PTP1B expression and leptin resistance through an as yet unidentified mechanism (White et al., 2009). Further studies will be necessary to better understand the full extent of PTP1B's role in the development of leptin resistance.

Recently, endoplasmic reticulum (ER) stress has been suggested in the development of obesity-induced leptin-independent leptin resistance (Ozcan et al., 2009). In certain pathological stress conditions, such as a high-fat diet, elevated levels of free fatty acids and cytokines have been recognized to lead to the accumulation of improperly folded proteins in the ER lumen and to the activation of the unfolded protein response (UPR) pathway (Zhang and Kaufman, 2004). This complex signaling network has already previously been implicated to contribute to the development of obesity-induced insulin resistance through inhibition of the insulin signal transduction process. In recent studies, chemical chaperons with the ability to reduce ER stress effectively increased leptin sensitivity in genetic and diet-induced mouse models of obesity. Furthermore, genetically modified mice with severely increased ER stress in the hypothalamus displayed reduced leptin signaling, leptin resistance, hyperphagia and rapid weight gain without the necessity for prolonged leptin exposure, indicating that excess nutrition might be sufficient for the development of leptin resistance. Interestingly, PTP1B has previously been found to potentiate ER stress signaling pathways, suggesting another possible mechanism for leptin-independent leptin resistance (Gu et al., 2004)

3. Adiponectin

Adiponectin is secreted exclusively from adipose tissue and is an abundant plasma protein (Hu et al., 1996). Structurally, adiponectin is related to the complement 1q family and contains a carboxyl-terminal globular domain and an amino-terminal collagenous domain (Scherer et al., 1995) and also shares extensive

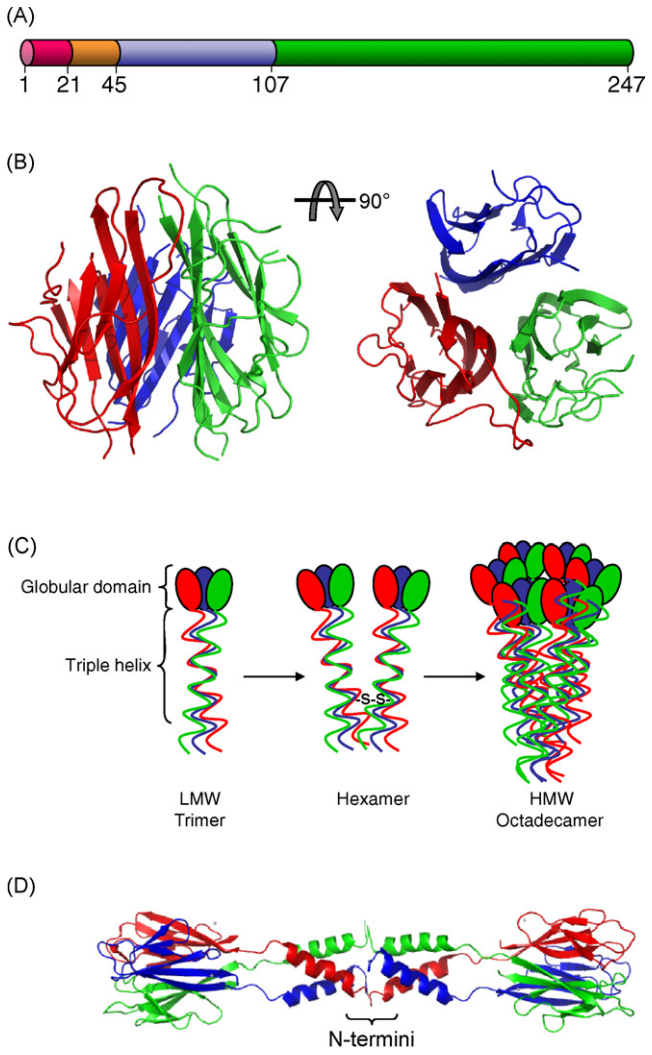

Fig. 2. Adiponectin and resistin structure. (A) Domain organisation of the human adiponectin protomer. Red: signal peptide; orange: variable region; blue: collagen stalk; green globular domain. Numbers indicate region boundaries. (B) Crystal structure of the adiponectin head domain homotrimer. The collagenous domain triple-helix would extend from the bottom of the left-hand orientation. (C) Representation of adiponectin trimeric, hexameric and octadecameric oligomerisation states. The location of the disulphide-bond responsible for trimer association is indicated in the hexamer. (D) Crystal structure of the resistin hexamer. Resistin trimers associate via three disulphide-bonds at their N-termini. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

sequence homology with collagen VIII and X (Hu et al., 1996). Adiponectin circulates in serum as a range of multimers from low-molecular-weight trimers to high-molecular-weight (HMW) dodecamers (Barre et al., 2006). The adiponectin monomer is composed of three domains: a variable N-terminal region, an α-helical collagenous 'stalk' composed of multiple G–X–X repeats, and a distinctive C-terminal globular domain of approximately 140 amino acids (Fig. 2A) (Shapiro and Scherer, 1998). The protein undergoes extensive post-translational modification, particularly within the collagenous domain, such as hydroxylation of seven proline residues and hydroxy-glycosylation of five lysine residues (Wang et al., 2002; Richards et al., 2006). The globular head fragment was crystallised as an asymmetric, bell-shaped homotrimer which is stabilised primarily by extensively buried hydrophobic interfaces at its base. Within the trimer each protomer adopts a 10-stranded β-sandwich jellyroll topology, similar to those of the TNFs (Fig. 2B) (Shapiro and Scherer, 1998). The trimer is further stabilised by non-covalent interactions within a collagenous domain triple-helix to form the low-molecular-mass (LMW) adiponectin complex (90 kDa). Higher-order oligomerisation of adiponectin is enabled via disulphide-bond formations, mediated by Cys-39 at the N-termini of individual homotrimers, resulting in hexamers and high-molecular-mass (HMW) species typically ranging in humans from 12- to 18-mers (Richards et al., 2006; Waki et al., 2003). Analysis of HMW adiponectin suggests that it adopts a conical structure, with the globular head domains forming a tight circular base and the thin collagen stalk orientated to enable disulphide-bond formation (Fig. 2C).

With exception of severe cases of undernutrition (Iwahashi et al., 2003) and in the newborn (Lindsay et al., 2003), there is a strong negative correlation between plasma adiponectin concentration in humans and fat mass (Hu et al., 1996), with obesity reducing adiponectin levels while weight reduction increases adiponectin (Ouchi et al., 1999; Matsubara et al., 2002). These findings are also supported by human genome-wide scans and SNP analysis in multiple ethnic groups which have identified several chromosomal loci with low levels of adiponectin and type 2 diabetes (Wang et al., 2004; Poitou et al., 2005). Although serum adiponectin can be recovered in the full range of oligomeric states, there is now a growing body of evidence to suggest that the HMW complex is the most active form and accounts for the majority of the adipokines' peripheral metabolic effects (for a more comprehensive review see Ref. Schraw et al., 2008). For instance, the decreased serum levels of total adiponectin associated with type 2 diabetes is almost exclusively due to a decrease in levels of the circulating HMW isoform, without an accompanying reduction in levels of the other two oligomeric forms (Kobayashi et al., 2004). Consequently naturally occurring SNPs, such as those giving rise to the mutations Gly84Arg and Gly90Ser that impair oligomerisation through abrogation of Cys-39 disulphide-bond formation, are closely associated with insulin resistance and type 2 diabetes (Waki et al., 2003). Post-translational modification also appears to be an absolute requirement for HMW complex formation since recombinant adiponectin derived from bacterial sources, which lack the ability to perform lysine hydroxylation and glycosylation, only assemble into trimers and hexamers. In addition, the reduction in HMW oligomer levels in type 2 diabetes is accompanied by a decrease in total adiponectin glycosylation when compared with adiponectin from healthy individuals (Wang et al., 2006).

The distribution of circulating adiponectin oligomers is thought to be primarily regulated at the stage of secretion from adipocytes, since interconversion between the different isoforms does not occur once they have been released from the cell (Schraw et al., 2008). The secretion process itself is controlled by the ER chaperone proteins ERp44 and Ero1-Lα, which regulate adiponectin retention and release, respectively. It is believed that newly synthesised adiponectin is trapped inside the cell by disulphide-bond formation between ERp44 and Cys-39 and that this prolonged retention within the ER might facilitate adiponectin maturation and assembly into higher molecular weight forms (Wang et al., 2007a). In contrast, the oxidoreductase Ero1-Lα acts to displace adiponectin from ERp44 and promote its release into the circulation (Qiang et al., 2007). The thiazolidinedione (TZD) class of insulin sensitizers, such as rosiglitazone, act as peroxisome proliferator-activated receptor gamma (PPARγ) agonists and are increasingly believed to promote the selective secretion of the HMW form of adiponectin (Pajvani et al., 2004; Maeda et al., 2001). Growing evidence suggests that this might be due to an up-regulation of Ero1-Lα and decreased expression of ERp44, leading to a higher distribution of HMW adiponectin within the circulation (Phillips et al., 2009).

Adiponectin has been shown to improve whole-body insulin sensitivity in models of genetic and diet-induced obesity (Combs et al., 2001; Ouchi et al., 2001; Yamauchi et al., 2001). In muscle

cells *in vitro* improvements in insulin sensitivity by adiponectin are dependent on the activation of AMPK and a subsequent reduction in mTOR/S6 kinase activity which in turn results in a reduction of insulin receptor substrate 1 inhibitory serine phosphorylation (Wang et al., 2007b). Adiponectin stimulates fatty acid oxidation and glucose uptake in skeletal muscle (Yamauchi et al., 2002; Tomas et al., 2002) and adipose tissue (Wu et al., 2003) effects which are dependent on AMPK signaling. Purification and characterization of adiponectin multimers from human plasma suggests that HMW adiponectin is the most potent oligomer in stimulating AMPK activity, at least in C2C12 cells (Hada et al., 2007). The activation of AMPK is dependent on signaling through the adiponectin receptor 1 (AdipoR1) while the adiponectin receptor 2 (AdipoR2) appears to be essential for regulating PPARα gene expression (Yamauchi et al., 2003). Two reports (Debard et al., 2004; Civitarese et al., 2004) in human skeletal muscle and a recent study in primary myotubes (Staiger et al., 2004) suggest that skeletal muscle contains abundant levels of both AdipoR1 and AdipoR2 but that liver primarily expresses AdipoR2. Adiponectin receptor signaling appears to be dependent on the adaptor protein containing pleckstrin homology domain, phosphotyrosine binding domain and leucine zipper motif (AAPL1), however, it is still unknown if AAPL1 regulates AMPK signaling and if so what mechanisms may be involved (Mao et al., 2006). Adiponectin activation of AMPK signaling is blunted in obesity (Chen et al., 2005; Bruce et al., 2005), despite similar AdipoR1 and AdipoR2 expression, suggesting that defects in AAPL1, or other distal signaling events, may be important in this process.

An important role for adiponectin is the suppression of hepatic glucose output through activation of AMPK (Combs et al., 2001). Adenovirus expressing a dominant negative AMPK (Yamauchi et al., 2002) or the knockout of the AMPK α2 subunit (Andreelli et al., 2006) results in increased hepatic glucose output and glucose intolerance, which can be suppressed by insulin, but no longer by adiponectin. In agreement with these findings, the deletion of the AdipoR1 receptor in liver using siRNA results in reduced AMPK and increased gluconeogenesis and glucose intolerance (Yamauchi et al., 2007). As previously discussed PPARγ ligands increase adiponectin expression. Recent studies (Yamauchi et al., 2007; Nawrocki et al., 2006) have indicated that hepatic insulin sensitization induced by PPARγ ligands is largely dependent on adiponectin as evidenced by findings that hepatic insulin sensitivity is not improved in *Adipo−/− ob/ob* mice an effect also associated with impaired activation of liver AMPK.

Kubota et al. (2007) have shown that adiponectin regulates energy expenditure through activation of AMPK in the hypothalamus. They show that in the hypothalamus, AdipoR1 and AdipoR2 colocalize with the leptin receptor Ob-R and that cerebrospinal fluid (CSF) contains low levels of adiponectin that comes from the blood because intravenous injection of adiponectin raises CSF levels in adiponectin deficient (adipo−/−) mice. The effects of adiponectin to stimulate appetite and reduce energy expenditure were eliminated following the ablation of AdipoR1 (AdipoR1 siRNA) or AMPK signaling (AMPK dominant negative) (Kubota et al., 2007). Although HMW adiponectin is regarded to be the main from of adiponectin responsible for most metabolic actions of this hormone in the periphery, the main forms detectable in the CSF appear to be it's trimer and hexamer forms. The HMW oligomer, consisting of multiple complexes, may be too large to cross the blood–brain barrier. This may be an important point of difference between a previous study which infused HMW recombinant adiponectin into the brain and found it induced weight loss and increased energy expenditure (Qi et al., 2004). In contrast to leptin, which has been suggested to enter the brain via endocytosis through the leptin receptor, the mechanism by which intravenously administered adiponectin trimers and hexamers are able to reach the hypothalamus is unknown. Another critical finding from this study was that leptin sensitivity is markedly increased in adipo−/− mice leading to the proposal that the central actions of leptin and adiponectin have reciprocal functions to provide a homeostatic mechanism to maintain fat levels/energy stores through the suppression or stimulation of appetite and energy expenditure.

4. Resistin

The peptide hormone resistin (or FIZZ3) is an adipocyte-derived secretory factor which was first identified as a novel transcript produced exclusively by adipocytes (Steppan et al., 2001) and has been shown to play a significant role in obesity-induced insulin resistance (Steppan et al., 2001). Resistin is expressed within adipocytes of rodents (Steppan et al., 2001) and macrophages of humans (Patel et al., 2003) and its production is increased with feeding and obesity and decreased by PPARγ ligands (Rajala et al., 2004). The human protein is expressed as a cysteine-rich 108 residue precursor containing a 16 residue N-terminal signal peptide (Steppan et al., 2001). The structure of resistin is strikingly similar to that of adiponectin described above (Patel et al., 2004). It contains an N-terminal helical tail linked to a C-terminal β-sandwich jelly-roll head domain, in this instance containing six β-strands. The head domain contains five intramolecular disulphide-bonds that are conserved amongst species and other resistin family members. In addition resistin monomers also readily trimerise, although complex formation is mediated largely by the parallel alignment of helical regions rather than the large hydrophobic core seen in the adiponectin trimer, allowing the resistin head domains to retain a degree of flexibility. Higher-order oligomerisation is achieved by interdigitation of N-terminal coiled-coils, to form hexamers linked by three highly surface-exposed disulphide-bonds between Cys-6 residues from each monomer (Fig. 2D). Circulating resistin exists predominantly as the hexamer, although our current understanding of the metabolic effects of either complex is limited.

Studies demonstrating a causal role of resistin in glucose homeostasis are based on animal models with altered serum resistin levels. Infusion or over-expression of resistin leads to hyperglycemia, a response which to a large degree can be explained by increased hepatic glucose production (Banerjee et al., 2004; Qi et al., 2006). Conversely, reducing circulating resistin by deleting the resistin gene, infusing resistin antibodies or resistin antisense oligodeoxynucleotides all protect against obesity-induced hyperglycemia primarily by restoring hepatic insulin responsiveness (Steppan et al., 2001; Banerjee et al., 2004; Muse et al., 2004). The importance of resistin in humans is less clear as not all studies report increases in serum resistin in obese type 2 diabetics (Savage et al., 2001; Sentinelli et al., 2002), however, it should be noted that the −420G/G genotype of the resistin promoter region has been associated with elevated resistin gene transcription, increased levels of serum resistin, obesity and insulin resistance (Azuma et al., 2004; Osawa et al., 2004).

Despite the significant interest generated by the discovery of resistin in 2001 (Steppan et al., 2001), very little is known about the intracellular signaling pathways by which resistin induces its metabolic effects although resistin has been shown to be important in regulating metabolic pathways in several tissues and organs including the hypothalamus, adipocytes and the liver. A consistent finding *in vivo* is that resistin suppresses liver and muscle AMPK activation (Banerjee et al., 2004; Qi et al., 2006; Satoh et al., 2004), however, in isolated mouse muscle this does not occur suggesting that the inhibitory effects of resistin on AMPK may require release of an unknown factor from other cell types (Jorgensen et al., 2009). One possibility may be that resistin-induced increases in SOCS3 (Steppan et al., 2005), which does not occur in isolated muscles (Jorgensen et al., 2009), may inhibit leptin signaling through to AMPK.

5. Retinol binding protein-4

Retinol binding protein-4 is an approximately 21 kDa protein, that was first reported to be an adipokine by Kahn and co-workers (Yang et al., 2005) when trying to understand the muscle insulin resistance observed in adipose specific Glut 4 null mice. They found that RBP4 expression was increased in insulin resistant adipose tissue specific Glut 4 null mice and reduced in insulin sensitive adipose specific Glut 4 transgenics. Injection of recombinant human RBP4 into lean mice, resulted in insulin resistance and glucose intolerance, a finding recapitulated in RBP4 transgenic mice while RBP4 null mice were protected from developing HFD induced insulin resistance. RBP4 has been shown to cause systemic insulin resistance, by impairing insulin signaling in muscle (Yang et al., 2005) and adipocytes (Ost et al., 2007) and leading to increased expression of PEPCK and glucose production in liver (Yang et al., 2005). A large number of studies have demonstrated strong correlational evidence in both rodent and human obesity that serum levels of RBP4 are elevated and that this is associated with many aspects of the metabolic syndrome including inflammation, fatty liver disease and insulin resistance (Yang et al., 2005; Kovacs et al., 2007; Graham et al., 2006). Interestingly, recent studies have suggested that one possibility for this correlation may be due to renal insufficiency, which is common in type 2 diabetes (Henze et al., 2008). Future studies determining the mechanisms by which RBP4 induces insulin resistance and whether RBP4 neutralization in humans is effective in reversing insulin resistance will be important to establish the importance of this newly discovered adipokine.

6. Adipose tissue macrophages

Increased adipose mass associated with obesity has been linked with a low-grade, chronic inflammatory response, characterized by altered production of adipokines and increases in biological markers of inflammation, such as tumour necrosis factor-α, interleukin-6 or monocyte-chemoattractant protein-1 (MCP-1) plasminogen activated inhibitor (PAI-1), colony stimulating factor (CSF) or inducible nitric oxide synthase (iNOS) (Neels and Olefsky, 2006). However, studies in recent years have revealed that adipocytes are not the major source of inflammatory cytokine secretion from adipose tissue. Non-adipose cells, that constitute the stromal vascular fraction, which includes preadipocytes, endothelial cells, fibroblasts, leukocytes and macrophages seem to be responsible for the chronic inflammatory response observed in obesity (Weisberg et al., 2003). Macrophages residing in lean adipose tissue are characterized by increased expression of genes such as *Ym-1*, *arginase-1* and the anti-inflammatory cytokine IL10 (Lumeng et al., 2007). They show an increased capacity for tissue repair and angiogenesis and are commonly described as M2 or "alternatively activated" macrophages. However, in recent years it has been found that the expansion of adipose tissue in obesity is associated with an increased infiltration with macrophages of the M1 or "classically activated" phenotype from the circulation (Coenen et al., 2007). These macrophages are usually recruited to sites of tissue damage and have been reported to be in a pro-inflammatory state with increased expression of TNFα and iNOS (Lumeng et al., 2007) (Fig. 3).

The cellular mechanisms responsible for this enhanced macrophage recruitment remain largely unknown, but it has been suggested that dysregulated adipokine production and increased adipocyte size might contribute to this phenomenon in a crosstalk between adipocytes and macrophages (Neels and Olefsky, 2006). Adipocyte-derived factors, such as MCP-1 or CSF-1 are overexpressed in obesity and can promote the recruitment of circulating monocytes (Weisberg et al., 2006). Furthermore, obesity

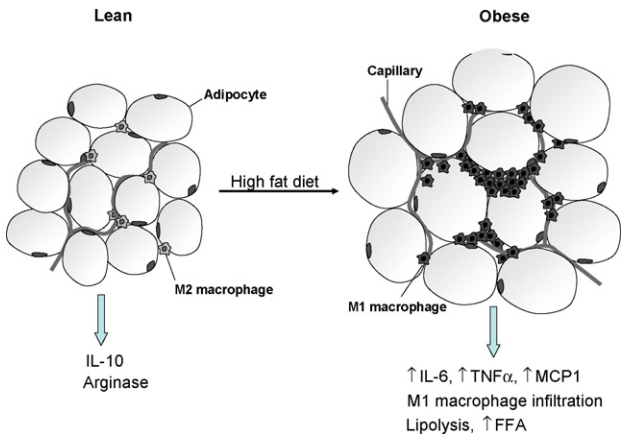

Fig. 3. Obesity-induced changes in macrophage infiltration and polarisation. Adipose tissue macrophages (ATMs) in the lean state show characteristics of "alternative" or M2 activation with increased production of arginase and the anti-inflammatory cytokine IL-10. They are postulated to participate in tissue repair and the attenuation of inflammatory responses. Expansion of adipose tissue leads to adipocyte hypertrophy and the release of chemokines that induce increased recruitment of M1 macrophages from the blood stream. M1 or "classically activated" ATMs are characterized by increased production of the pro-inflammatory cytokines TNFα and IL-6, which promote altered gene expression and insulin resistance in adipocytes. These changes result in altered adipokine secretion, increased lipolysis and excess of circulating nonesterified fatty acids, which may eventually contribute to systemic insulin resistance.

is characterized by decreased secretion of adiponectin, which has been shown to exert anti-inflammatory effects on macrophages, whereas the production of the pro-inflammatory adipokine leptin is increased. Another contributing factor might be the increased levels of free fatty acids released from enlarged adipose tissue in obesity. Recently, it has been demonstrated that saturated fatty acids can act as ligands for TLR-4 and induce the production of inflammatory cytokines from macrophages through the activation of the NF-κB pathway (Shi et al., 2006). In addition, free fatty acids may contribute to the accumulation of bioactive lipids, such as DAGs and ceramides within the macrophage which are also thought to be an upstream activator of NF-κB (Boden et al., 2005; Yu et al., 2002).

7. Tumour necrosis factor-α (TNFα)

TNFα is synthesised as a 26 kDa transmembrane protein that undergoes cleavage by a metalloproteinase to be released into the circulation as a 17 kDa soluble TNFα molecule (Kriegler et al., 1988). Isolated and differentiated adipocytes are capable of producing TNFα and it was originally suggested that adipocytes are the principal source of elevated TNFα levels in obesity. However, more recently it has been recognized that macrophages from the stromal vascular fraction are the primary source of adipose derived TNFα and that the increased levels of this cytokine in obesity are due to the increased infiltration of adipose tissue with M1 macrophages (Weisberg et al., 2003).

TNFα was the first adipose derived factor suggested to represent a link between obesity, inflammation and diabetes. Hotamisligil et al. (1993) reported increased TNFα mRNA expression levels in adipose tissue in obesity and this cytokine has since been strongly implicated in the pathogenesis of insulin resistance. A number of studies have demonstrated that TNFα can impair insulin signaling in hepatocytes and adipose tissue (Stephens et al., 1997; Ruan et al., 2002; Cai et al., 2005). Chronic treatment with TNFα decreases insulin-stimulated glucose uptake in rat skeletal muscle. In addition, studies using a soluble TNFα receptor-IgG chimeric protein restored insulin-induced insulin receptor and IRS-1 phosphoryla-

tion in Zucker rats in fat and skeletal muscle. Furthermore, the targeted deletion of TNFα or its receptors increased insulin sensitivity and glucose tolerance in obese rodents in some (Uysal et al., 1997) but not all studies (Schreyer et al., 1998). In obese type 2 diabetic humans, TNF neutralization does not appear to improve glucose tolerance or insulin sensitivity, however, in individuals without established type 2 diabetes prolonged treatment does improve insulin sensitivity (Tam et al., 2007). The molecular basis for the observed impairment in insulin action involves inhibition of IRS signaling capability through the activation of serine kinases such as the c-Jun-N-terminal kinase (JNK) or inhibitor of NF-κB kinase (IKK) and through increased expression of suppressor of cytokine signaling 3 (SOCS3) (Steinberg et al., 2006b). TNFα also reduces fatty acid oxidation in hepatocytes (Nachiappan et al., 1994) and skeletal muscle (Steinberg et al., 2006c) through effects mediated by the induction of protein phosphatase 2C and suppression of AMPK (Steinberg et al., 2006c). The reduced rates of fatty acid oxidation are accompanied by increased accumulation of bioactive lipids, such as diacyglycerols (Steinberg et al., 2006c), which in turn are known to activate protein kinase C and inhibit IRS function (Yu et al., 2002).

8. Interleukin-6 (IL-6)

Plasma IL-6 levels are increased in type 2 diabetes and are positively correlated with body mass and plasma free fatty acid concentrations (Lazar, 2005). Approximately 1/3 of the IL-6 detected in plasma is attributed to the production from white adipose tissue (Mohamed-Ali et al., 1997). However, most of the adipose derived IL-6 comes from cells of the stromal vascular fraction. In adipocytes and hepatocytes IL-6 has been demonstrated to inhibit the insulin signaling pathway by up-regulating SOCS3 expression, which in turn is known to impair insulin-induced insulin receptor and IRS-1 phosphorylation (Senn et al., 2002, 2003; Rotter et al., 2003). However, studies demonstrating that IL-6 is released from skeletal muscle have shed a different light on the role of IL-6 in the aetiology of insulin resistance since insulin action is known to be enhanced in the period immediately after exercise (Richter et al., 1982; Febbraio and Pedersen, 2002). Furthermore, IL-6 can promote fatty acid oxidation and glucose uptake in skeletal muscle (Carey et al., 2006; Kelly et al., 2004; Petersen et al., 2005; Al-Khalili et al., 2006; Glund et al., 2007) findings which are also observed with the IL-6 family member ciliary neurotrophic factor (CNTF) (Watt et al., 2006; Steinberg et al., 2009). Studies in myotubes have demonstrated that these effects require activation of AMPK-activated protein kinase (Carey et al., 2006; Al-Khalili et al., 2006). However, the exact mechanism by which IL-6 activates AMPK to promote glucose uptake and fatty acid oxidation is not yet understood.

9. Conclusion

Adipose tissue is the primary storage site for excess energy. In the past decade it has become increasingly clear that adipose tissue also displays characteristics of an endocrine organ releasing a number of adipocyte-specific factors known as adipokines. Much of the research in this area has focussed on leptin and adiponectin, the two prototypic adipokines, which show beneficial effects on insulin action and lipid metabolism. In obesity leptin concentrations are elevated while adiponectin levels are reduced. Resistin and RBP4 have also been linked to the development of insulin resistance, however, there are still many discrepancies between findings in rodent models and humans and the molecular mechanisms by which these adipokines potentially exert their detrimental effects on insulin action. More recently, the finding that adipose tissue in the obese state is infiltrated by inflamed macrophages that release TNFα and IL-6 has also helped us understand the link between obesity, inflammation and insulin resistance. The strong correlations between adipose tissue mass and the secretion of many adipokines has led to the suggestion that reducing total adipose mass may be a strategy for the treatment of obesity-related diseases. However, due to the severe metabolic consequences of adipose tissue ablation as observed in lipoatrophic patients, directly modifying adipokine gene expression and release into the circulation may be more viable. Other potentially important strategies may also include targeting the mechanisms involved in macrophage recruitment from the circulation as well as understanding the molecular mechanisms responsible for macrophage polarisation. However, much remains to be determined about the exact cellular reactions within the macrophage as well as the interactions between adipocytes and macrophages that are responsible for the increased inflammation observed in obesity. Lastly, understanding the signaling pathways in target tissues such as the brain, skeletal muscle and liver by which adipokines control metabolism may also reveal novel therapies for obesity-related diseases.

Acknowledgement

GRS is a Canadian Research Chair in Metabolism, Obesity and Type 2 Diabetes.

References

Al-Khalili, L., Bouzakri, K., Glund, S., Lonnqvist, F., Koistinen, H.A., Krook, A., 2006. Signaling specificity of interleukin-6 action on glucose and lipid metabolism in skeletal muscle. Mol. Endocrinol. 20, 3364–3375.
Andersson, U., Filipsson, K., Abbott, C.R., Woods, A., Smith, K., Bloom, S.R., Carling, D., Small, C.J., 2004. AMP-activated protein kinase plays a role in the control of food intake. J. Biol. Chem. 279, 12005–12008.
Andreelli, F., Foretz, M., Knauf, C., Cani, P.D., Perrin, C., Iglesias, M.A., Pillot, B., Bado, A., Tronche, F., Mithieux, G., Vaulont, S., Burcelin, R., Viollet, B., 2006. Liver adenosine monophosphate-activated kinase-alpha2 catalytic subunit is a key target for the control of hepatic glucose production by adiponectin and leptin but not insulin. Endocrinology 147, 2432–2441.
Azuma, K., Oguchi, S., Matsubara, Y., Mamizuka, T., Murata, M., Kikuchi, H., Watanabe, K., Katsukawa, F., Yamazaki, H., Shimada, A., Saruta, T., 2004. Novel resistin promoter polymorphisms: association with serum resistin level in Japanese obese individuals. Horm. Metab. Res. 36, 564–570.
Banerjee, R.R., Rangwala, S.M., Shapiro, J.S., Rich, A.S., Rhoades, B., Qi, Y., Wang, J., Rajala, M.W., Pocai, A., Scherer, P.E., Steppan, C.M., Ahima, R.S., Obici, S., Rossetti, L., Lazar, M.A., 2004. Regulation of fasted blood glucose by resistin. Science 303, 1195–1198.
Banks, A.S., Davis, S.M., Bates, S.H., Myers Jr., M.G., 2000. Activation of downstream signals by the long form of the leptin receptor. J. Biol. Chem. 275, 14563–14572.
Barre, L., Richardson, C., Hirshman, M.F., Brozinick, J.T., Fiering, S., Kemp, B.E., Goodyear, L.J., Witters, L.A., 2006. A genetic model for the chronic activation of skeletal muscle AMP-activated protein kinase leads to glycogen accumulation. Am. J. Physiol. Endocrinol. Metab. 292, E802–E811.
Bates, S.H., Stearns, W.H., Dundon, T.A., Schubert, M., Tso, A.W., Wang, Y., Banks, A.S., Lavery, H.J., Haq, A.K., Maratos-Flier, E., Neel, B.G., Schwartz, M.W., Myers Jr., M.G., 2003. STAT3 signalling is required for leptin regulation of energy balance but not reproduction. Nature 421, 856–859.
Bence, K.K., Delibegovic, M., Xue, B., Gorgun, C.Z., Hotamisligil, G.S., Neel, B.G., Kahn, B.B., 2006. Neuronal PTP1B regulates body weight, adiposity and leptin action. Nat. Med. 12, 917–924.
Bjorbaek, C., Uotani, S., da Silva, B., Flier, J.S., 1997. Divergent signaling capacities of the long and short isoforms of the leptin receptor. J. Biol. Chem. 272, 32686–32695.
Bjorbaek, C., Elmquist, J.K., Frantz, J.D., Shoelson, S.E., Flier, J.S., 1998. Identification of SOCS-3 as a potential mediator of central leptin resistance. Mol. Cell 1, 619–625.
Bjorbaek, C., El-Haschimi, K., Frantz, J.D., Flier, J.S., 1999. The role of SOCS-3 in leptin signaling and leptin resistance. J. Biol. Chem. 274, 30059–30065.
Bjorbaek, C., Lavery, H.J., Bates, S.H., Olson, R.K., Davis, S.M., Flier, J.S., Myers Jr., M.G., 2000. SOCS3 mediates feedback inhibition of the leptin receptor via Tyr985. J. Biol. Chem. 275, 40649–40657.
Bjornholm, M., Munzberg, H., Leshan, R.L., Villanueva, E.C., Bates, S.H., Louis, G.W., Jones, J.C., Ishida-Takahashi, R., Bjorbaek, C., Myers Jr., M.G., 2007. Mice lacking inhibitory leptin receptor signals are lean with normal endocrine function. J. Clin. Invest. 117, 1354–1360.
Boden, G., She, P., Mozzoli, M., Cheung, P., Gumireddy, K., Reddy, P., Xiang, X., Luo, Z., Ruderman, N., 2005. Free fatty acids produce insulin resistance and activate the proinflammatory nuclear factor-kappaB pathway in rat liver. Diabetes 54, 3458–3465.

Briscoe, C.P., Hanif, S., Arch, J.R., Tadayyon, M., 2001. Leptin receptor long-form signalling in a human liver cell line. Cytokine 14, 225–229.
Bruce, C.R., Mertz, V.A., Heigenhauser, G.J., Dyck, D.J., 2005. The stimulatory effect of globular adiponectin on insulin-stimulated glucose uptake and fatty acid oxidation is impaired in skeletal muscle from obese subjects. Diabetes 54, 3154–3160.
Cai, D., Yuan, M., Frantz, D.F., Melendez, P.A., Hansen, L., Lee, J., Shoelson, S.E., 2005. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. Nat. Med. 11, 183–190.
Campfield, L.A., Smith, F.J., Guisez, Y., Devos, R., Burn, P., 1995. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. Science 269, 546–549.
Cao, G.-Y., Considine, R.V., Lynn, R.B., 1997. Leptin receptors in the adrenal medulla of the rat. Am. J. Physiol. 273, E448–E452.
Carey, A.L., Steinberg, G.R., Macaulay, S.L., Thomas, W.G., Holmes, A.G., Ramm, G., Prelovsek, O., Hohnen-Behrens, C., Watt, M.J., James, D.E., Kemp, B.E., Pedersen, B.K., Febbraio, M.A., 2006. Interleukin-6 increases insulin-stimulated glucose disposal in humans and glucose uptake and fatty acid oxidation in vitro via AMP-activated protein kinase. Diabetes 55, 2688–2697.
Chen, H., Charlat, O., Tartaglia, L.A., Woolf, E.A., Weng, X., Ellis, S.J., Lakey, N.D., Culpepper, J., Moore, K.J., Breitbart, R.E., Duyk, G.M., Tepper, R.I., Morgenstern, J.P., 1996. Evidence that the diabetes gene encodes the leptin receptor: identification of a mutation in the leptin receptor gene in *db*/*db* mice. Cell 84, 491–495.
Chen, M.B., McAinch, A.J., Macaulay, S.L., Castelli, L.A., O'Brien, P.E., Dixon, J.B., Cameron-Smith, D., Kemp, B.E., Steinberg, G.R., 2005. Impaired activation of AMP-kinase and fatty acid oxidation by globular adiponectin in cultured human skeletal muscle of obese type 2 diabetics. J. Clin. Endocrinol. Metab. 90, 3665–3672.
Cheng, A., Uetani, N., Simoncic, P.D., Chaubey, V.P., Lee-Loy, A., McGlade, C.J., Kennedy, B.P., Tremblay, M.L., 2002. Attenuation of leptin action and regulation of obesity by protein tyrosine phosphatase 1B. Dev. Cell 2, 497–503.
Civitarese, A.E., Jenkinson, C.P., Richardson, D., Bajaj, M., Cusi, K., Kashyap, S., Berria, R., Belfort, R., DeFronzo, R.A., Mandarino, L.J., Ravussin, E., 2004. Adiponectin receptors gene expression and insulin sensitivity in non-diabetic Mexican Americans with or without a family history of Type 2 diabetes. Diabetologia 47, 816–820.
Clement, K., Vaisse, C., Lahlou, N., Cabrol, S., Pelloux, V., Cassuto, D., Gourmelen, M., Dina, C., Chambaz, J., Lacorte, J.M., Basdevant, A., Bougneres, P., Lebouc, Y., Froguel, P., Guy-Grand, B., 1998. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 392, 398–401.
Coenen, K.R., Gruen, M.L., Chait, A., Hasty, A.H., 2007. Diet-induced increases in adiposity, but not plasma lipids, promote macrophage infiltration into white adipose tissue. Diabetes 56, 564–573.
Coleman, D.L., 1973. Effects of parabiosis of obese with diabetes and normal mice. Diabetologia 9, 294–298.
Combs, T.P., Berg, A.H., Obici, S., Scherer, P.E., Rossetti, L., 2001. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. J. Clin. Invest. 108, 1875–1881.
Cumin, F., Baum, H.-P., Levens, N., 1996. Leptin is cleared from the circulation primarily by the kidney. Int. J. Obes. Relat. Metab. Disord. 20, 1120–1126.
Cumin, F., Baum, H.-P., De Gaspero, M., Levens, N., 1997. Removal of endogenous leptin from the circulation by the kidney. Int. J. Obes. Relat. Metab. Disord. 21, 495–504.
Debard, C., Laville, M., Berbe, V., Loizon, E.C.G., Morio-Liondore, B., Boirie, Y., Vidal, H., 2004. Expression of key genes of fatty acid oxidation, including adiponectin receptors, in skeletal muscle of Type 2 diabetic patients. Diabetaologia 47, 816–820.
Farooqi, S., Rau, H., Whitehead, J., O'Rahilly, S., 1998. *ob* gene mutations and human obesity. Proc. Nutr. Soc. 57, 471–475.
Febbraio, M.A., Pedersen, B.K., 2002. Muscle-derived interleukin-6: mechanisms for activation and possible biological roles. FASEB J. 16, 1335–1347.
Figenschau, Y., Knutsen, G., Shahazeydi, S., Johansen, O., Sveinbjornsson, B., 2001. Human articular chondrocytes express functional leptin receptors. Biochem. Biophys. Res. Commun. 287, 190–197.
Fried, S.K., Ricci, M.R., Russell, C.D., Laferrere, B., 2000. Regulation of leptin production in humans. J. Nutr. 130, 3127S–3131S.
Ghilardi, N.S., Ziegler, S., Wiestner, A., Stoffel, R., Heim, M., Radek, S.C., 1996. Defective STAT signaling by the leptin receptor in diabetic mice. Proc. Natl. Acad. Sci. 93, 6231–6235.
Glund, S., Deshmukh, A., Long, Y.C., Moller, T., Koistinen, H.A., Caidahl, K., Zierath, J.R., Krook, A., 2007. Interleukin-6 directly increases glucose metabolism in resting human skeletal muscle. Diabetes 56, 1630–1637.
Graham, T.E., Yang, Q., Bluher, M., Hammarstedt, A., Ciaraldi, T.P., Henry, R.R., Wason, C.J., Oberbach, A., Jansson, P.A., Smith, U., Kahn, B.B., 2006. Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. N. Engl. J. Med. 354, 2552–2563.
Gu, F., Nguyen, D.T., Stuible, M., Dube, N., Tremblay, M.L., Chevet, E., 2004. Protein-tyrosine phosphatase 1B potentiates IRE1 signaling during endoplasmic reticulum stress. J. Biol. Chem. 279, 49689–49693.
Hada, Y., Yamauchi, T., Waki, H., Tsuchida, A., Hara, K., Yago, H., Miyazaki, O., Ebinuma, H., Kadowaki, T., 2007. Selective purification and characterization of adiponectin multimer species from human plasma. Biochem. Biophys. Res. Commun. 356, 487–493.
Halaas, J.L., Gajiwala, K.S., Maffei, M., Cohen, S.L., Chait, B.T., Rabinowitz, D., Lallone, R.L., Burley, S.K., Friedman, J.M., 1995. Weight reducing effects of the plasma protein encoded by the obese gene. Science 269, 543–546.
Havel, P.J., Kasim-Karakas, S., Mueller, W., Johnson, P.R., Gingerich, R.L., Stern, J.S., 1996. Relationship of plasma leptin to plasma insulin and adiposity in normal weight and overweight women: effects of dietary fat content and sustained weight loss. J. Clin. Endocrinol. Metab. 81, 4406–4413.
Henze, A., Frey, S.K., Raila, J., Tepel, M., Scholze, A., Pfeiffer, A.F., Weickert, M.O., Spranger, J., Schweigert, F.J., 2008. Evidence that kidney function but not type 2 diabetes determines retinol-binding protein 4 serum levels. Diabetes 57, 3323–3326.
Heymsfield, S.B., Greenberg, A.S., Fujioka, K., Dixon, R.M., Kuschner, R., Hunt, T., Lubina, J.A., Patane, J., Self, B., Hunt, P., McCamish, M., 1999. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. JAMA 282, 1568–1575.
Hotamisligil, G., Shargill, N., Spiegelman, B.M., 1993. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 259, 87–91.
Howard, J.K., Cave, B.J., Oksanen, L.J., Tzameli, I., Bjorbaek, C., Flier, J.S., 2004. Enhanced leptin sensitivity and attenuation of diet-induced obesity in mice with haploinsufficiency of Socs3. Nat. Med. 10, 734–738.
Hu, E., Liang, P., Spiegelman, B.M., 1996. AdipoQ is a novel adipose-specific gene dysregulated in obesity. J. Biol. Chem. 271, 10697–10703.
Iwahashi, H., Funahashi, T., Kurokawa, N., Sayama, K., Fukuda, E., Okita, K., Imagawa, A., Yamagata, K., Shimomura, I., Miyagawa, J.I., Matsuzawa, Y., 2003. Plasma adiponectin levels in women with anorexia nervosa. Horm. Metab. Res. 35, 537–540.
Jensen, M.D., Moller, N., Sreekumaran Nair, K., Eisenberg, P., Landt, M., Klein, S., 1999. Regional leptin kinetics in humans. Am. J. Clin. Nutr. 69, 18–21.
Jorgensen, S.B., Honeyman, J., Oakhill, J.S., Fazakerley, D., Stockli, J., Kemp, B.E., Steinberg, G.R., 2009. Oligomeric resistin impairs insulin and AICAR-stimulated glucose uptake in mouse skeletal muscle by inhibiting GLUT4 translocation. Am. J. Physiol. Endocrinol. Metab. 297, E57–E66.
Kelly, M., Keller, C., Aviluea, P.R., Keller, P., Luo, Z., Ziang, X., Giralt, M., Hidalgo, J., Saha, A.K., Pedersen, B.K., Ruderman, N.B., 2004. AMPK activity is diminished in tissues of IL-6 knockout mice: the effect of exercise. Biochem. Biophys. Res. Commun. 320, 449–454.
Kennedy, G.C., 1953. The role of depot fat in the hypothalamic control of food intake in the rat. Proc. R. Soc. 140, 578–592.
Kimber, W., Peelman, F., Prieur, X., Wangensteen, T., O'Rahilly, S., Tavernier, J., Farooqi, I.S., 2008. Functional characterization of naturally occurring pathogenic mutations in the human leptin receptor. Endocrinology 149, 6043–6052.
Kobayashi, H., Ouchi, N., Kihara, S., Walsh, K., Kumada, M., Abe, Y., Funahashi, T., Matsuzawa, Y., 2004. Selective suppression of endothelial cell apoptosis by the high molecular weight form of adiponectin. Circ. Res. 94, e27–e31.
Kovacs, P., Geyer, M., Berndt, J., Kloting, N., Graham, T.E., Bottcher, Y., Enigk, B., Tonjes, A., Schleinitz, D., Schon, M.R., Kahn, B.B., Bluher, M., Stumvoll, M., 2007. Effects of genetic variation in the human retinol binding protein-4 gene (RBP4) on insulin resistance and fat depot-specific mRNA expression. Diabetes 56, 3095–3100.
Kriegler, M., Perez, C., DeFay, K., Albert, I., Lu, S.D., 1988. A novel form of TNF/cachectin is a cell surface cytotoxic transmembrane protein: ramifications for the complex physiology of TNF. Cell 53, 45–53.
Kubota, N., Yano, W., Kubota, T., Yamauchi, T., Itoh, S., Kumagai, H., Kozono, H., Takamoto, I., Okamoto, S., Shiuchi, T., Suzuki, R., Satoh, H., Tsuchida, A., Moroi, M., Sugi, K., Noda, T., Ebinuma, H., Ueta, Y., Kondo, T., Araki, E., Ezaki, O., Nagai, R., Tobe, K., Terauchi, Y., Ueki, K., Minokoshi, Y., Kadowaki, T., 2007. Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. Cell Metab. 6, 55–68.
Lazar, M.A., 2005. How obesity causes diabetes: not a tall tale. Science 307, 373–375.
Lee, G.H., Proenca, R., Montez, J.M., Carroll, K.M., Darishzadeh, J., Lee, J.L., Friedman, J.M., 1996. Abnormal splicing of the leptin receptor in diabetic mice. Nature 379, 632–635.
Lindsay, R.S., Walker, J.D., Havel, P.J., Hamilton, B.A., Calder, A.A., Johnstone, F.D., 2003. Adiponectin is present in cord blood but is unrelated to birth weight. Diabetes Care 26, 2244–2249.
Lonnqvist, F., Nordfors, L., Jansson, M., Thorne, A., Schalling, M., Arner, P., 1997. Leptin secretion from adipose tissue in women: relationship to plasma levels and gene expression. J. Clin. Invest. 99, 2398–2404.
Lumeng, C.N., Bodzin, J.L., Saltiel, A.R., 2007. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J. Clin. Invest. 117, 175–184.
Maeda, N., Takahashi, M., Funahashi, T., Kihara, S., Nishizawa, H., Kishida, K., Nagaretani, H., Matsuda, M., Komuro, R., Ouchi, N., Kuriyama, H., Hotta, K., Nakamura, T., Shimomura, I., Matsuzawa, Y., 2001. PPAR{gamma} ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. Diabetes 50, 2094–2099.
Maffei, M., Halaas, J., Ravussin, E., Pratley, R.E., Lee, G.H., Zhang, Y., Fei, H., Kim, S., Lallone, R., Ranganathan, S., Kern, P.A., Friedman, J.M., 1995. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat. Med. 1, 1155–1161.
Mao, X., Kikani, C.K., Riojas, R.A., Langlais, P., Wang, L., Ramos, F.J., Fang, Q., Christ-Roberts, C.Y., Hong, J.Y., Kim, R.Y., Liu, F., Dong, L.Q., 2006. APPL1 binds to adiponectin receptors and mediates adiponectin signalling and function. Nat. Cell Biol. 8, 516–523.
Martin, T.L., Alquier, T., Asakura, K., Furukawa, N., Preitner, F., Kahn, B.B., 2006. Diet-induced obesity alters AMP kinase activity in hypothalamus and skeletal muscle. J. Biol. Chem. 281, 18933–18941.
Matsubara, M., Maruoka, S., Katayose, S., 2002. Inverse relationship between plasma adiponectin and leptin concentrations in normal-weight and obese women. Eur. J. Endocrinol. 147, 173–180.

Matteis, R.D., Dashtipour, K., Ognibene, A., Cinti, S., 1998. Localization of leptin receptor splice variants in mouse peripheral tissues by immunohistochemistry. Proc. Nutr. Soc. 57, 441–448.
Meyer, C., Robson, D., Rackovsky, N., Nadkarni, V., Gerich, J., 1997. Role of the kidney in human leptin metabolism. Am. J. Physiol. 273, E903–E907.
Minokoshi, Y., Kim, Y.B., Peroni, O.D., Fryer, L.G., Muller, C., Carling, D., Kahn, B.B., 2002. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. Nature 415, 339–343.
Minokoshi, Y., Alquier, T., Furukawa, N., Kim, Y.B., Lee, A., Xue, B., Mu, J., Foufelle, F., Ferre, P., Birnbaum, M.J., Stuck, B.J., Kahn, B.B., 2004. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. Nature 428, 569–572.
Mohamed-Ali, V., Goodrick, S., Rawesh, A., Katz, D.R., Miles, J.M., Yudkin, J.S., Klein, S., Coppack, S.W., 1997. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J. Clin. Endocrinol. Metab. 82, 4196–4200.
Mori, H., Hanada, R., Hanada, T., Aki, D., Mashima, R., Nishinakamura, H., Torisu, T., Chien, K.R., Yasukawa, H., Yoshimura, A., 2004. Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity. Nat. Med. 10, 739–743.
Muoio, D.M., Dohm, G.L., Fiedorek, F.T.J., Tapscott, E.B., Coleman, R.A., 1997. Leptin directly alters lipid partitioning in skeletal muscle. Diabetes 46, 1360–1363.
Muse, E.D., Obici, S., Bhanot, S., Monia, B.P., McKay, R.A., Rajala, M.W., Scherer, P.E., Rossetti, L., 2004. Role of resistin in diet-induced hepatic insulin resistance. J. Clin. Invest. 114, 232–239.
Nachiappan, V., Curtiss, D., Corkey, B.E., Kilpatrick, L., 1994. Cytokines inhibit fatty acid oxidation in isolated rat hepatocytes: synergy among TNF, IL-6, and IL-1. Shock 1, 123–129.
Namkoong, C., Kim, M.-S., Jang, P.-G., Han, S.M., Park, J.-Y., Koh, E.H., Lee, I.-K., Kim, J.Y., Park, I.-S., Lee, K.-U., 2005. Enhanced hypothalamic AMP-activated protein kinase activity contributes to hyperphagia in diabetic rats. Diabetes 54, 63–68.
Nawrocki, A.R., Rajala, M.W., Tomas, E., Pajvani, U.B., Saha, A.K., Trumbauer, M.E., Pang, Z., Chen, A.S., Ruderman, N.B., Chen, H., Rossetti, L., Scherer, P.E., 2006. Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. J. Biol. Chem. 281, 2654–2660.
Neels, J.G., Olefsky, J.M., 2006. Inflamed fat: what starts the fire? J. Clin. Invest. 116, 33–35.
Osawa, H., Yamada, K., Onuma, H., Murakami, A., Ochi, M., Kawata, H., Nishimiya, T., Niiya, T., Shimizu, I., Nishida, W., Hashiramoto, M., Kanatsuka, A., Fujii, Y., Ohashi, J., Makino, H., 2004. The G/G genotype of a resistin single-nucleotide polymorphism at −420 increases type 2 diabetes mellitus susceptibility by inducing promoter activity through specific binding of Sp1/3. Am. J. Hum. Genet. 75, 678–686.
Ost, A., Danielsson, A., Liden, M., Eriksson, U., Nystrom, F.H., Stralfors, P., 2007. Retinol-binding protein-4 attenuates insulin-induced phosphorylation of IRS1 and ERK1/2 in primary human adipocytes. FASEB J. 21, 3696–3704.
Ouchi, N., Kihara, S., Arita, Y., Maeda, K., Kuriyama, H., Okamoto, Y., Hotta, K., Nishida, M., Takahashi, M., Nakamura, T., Yamashita, S., Funahashi, T., Matsuzawa, Y., 1999. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 100, 2473–2476.
Ouchi, N., Kihara, S., Arita, Y., Nishida, M., Matsuyama, A., Okamoto, Y., Ishigami, M., Kuriyama, H., Kishida, K., Nishizawa, H., Hotta, K., Muraguchi, M., Ohmoto, Y., Yamashita, S., Funahashi, T., Matsuzawa, Y., 2001. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. Circulation 103, 1057–1063.
Ozata, M., Ozdemir, I.C., Licinio, J., 1999. Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin and spontaneous correction of leptin-mediated defects. J. Clin. Endocrinol. Metab. 84, 3686–3695.
Ozcan, L., Ergin, A.S., Lu, A., Chung, J., Sarkar, S., Nie, D., Myers Jr., M.G., Ozcan, U., 2009. Endoplasmic reticulum stress plays a central role in development of leptin resistance. Cell Metab. 9, 35–51.
Pajvani, U.B., Hawkins, M., Combs, T.P., Rajala, M.W., Doebber, T., Berger, J.P., Wagner, J.A., Wu, M., Knopps, A., Xiang, A.H., Utzschneider, K.M., Kahn, S.E., Olefsky, J.M., Buchanan, T.A., Scherer, P.E., 2004. Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. J. Biol. Chem. 279, 12152–12162.
Patel, L., Buckels, A.C., Kinghorn, I.J., Murdock, P.R., Holbrook, J.D., Plumpton, C., Macphee, C.H., Smith, S.A., 2003. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. Biochem. Biophys. Res. Commun. 300, 472–476.
Patel, S.D., Rajala, M.W., Rossetti, L., Scherer, P.E., Shapiro, L., 2004. Disulfide-dependent multimeric assembly of resistin family hormones. Science 304, 1154–1158.
Pelleymounter, M.A., Cullen, M.J., Baker, B.M., Hecht, R., Winter, D., Boone, T., Collins, F., 1995. Effects of the obese gene product on body weight regulation in *ob*/*ob* mice. Science 269, 540–543.
Petersen, E.W., Carey, A.L., Sacchetti, M., Steinberg, G.R., Macaulay, S.L., Febbraio, M.A., Pedersen, B.K., 2005. Acute IL-6 treatment increases fatty acid turnover in elderly humans in vivo and in tissue culture in vitro. Am. J. Physiol. 288, E155–E162.
Phillips, S.A., Kung, J., Ciaraldi, T.P., Choe, C., Christiansen, L., Mudaliar, S.R., Henry, R.R., 2009. Selective regulation of cellular and secreted multimeric adiponectin by anti-diabetic therapies in humans. Am. J. Physiol. Endocrinol. Metab..
Poitou, C., Lacorte, J.M., Coupaye, M., Bertrais, S., Bedel, J.F., Lafon, N., Bouillot, J.L., Galan, P., Borson-Chazot, F., Basdevant, A., Coussieu, C., Clement, K., 2005. Relationship between single nucleotide polymorphisms in leptin, IL6 and adiponectin genes and their circulating product in morbidly obese subjects before and after gastric banding surgery. Obes. Surg. 15, 11–23.
Qi, Y., Takahashi, N., Hileman, S.M., Patel, H.R., Berg, A.H., Pajvani, U.B., Scherer, P.E., Ahima, R.S., 2004. Adiponectin acts in the brain to decrease body weight. Nat. Med. 10, 524–529.
Qi, Y., Nie, Z., Lee, Y.S., Singhal, N.S., Scherer, P.E., Lazar, M.A., Ahima, R.S., 2006. Loss of resistin improves glucose homeostasis in leptin deficiency. Diabetes 55, 3083–3090.
Qiang, L., Wang, H., Farmer, S.R., 2007. Adiponectin secretion is regulated by SIRT1 and the endoplasmic reticulum oxidoreductase Ero1-L alpha. Mol. Cell Biol. 27, 4698–4707.
Rajala, M.W., Qi, Y., Patel, H.R., Takahashi, N., Banerjee, R., Pajvani, U.B., Sinha, M.K., Gingerich, R.L., Scherer, P.E., Ahima, R.S., 2004. Regulation of resistin expression and circulating levels in obesity, diabetes, and fasting. Diabetes 53, 1671–1679.
Richards, A.A., Stephens, T., Charlton, H.K., Jones, A., Macdonald, G.A., Prins, J.B., Whitehead, J.P., 2006. Adiponectin multimerization is dependent on conserved lysines in the collagenous domain: evidence for regulation of multimerization by alterations in posttranslational modifications. Mol. Endocrinol. 20, 1673–1687.
Richter, E.A., Garetto, L.P., Goodman, M.N., Ruderman, N.B., 1982. Muscle glucose metabolism following exercise in the rat: increased sensitivity to insulin. J. Clin. Invest. 69, 785–793.
Roh, C., Roduit, R., Thorens, B., Fried, S., Kandror, K.V., 2001. Lipoprotein lipase and leptin are accumulated in different secretory compartments in rat adipocytes. J. Biol. Chem. 276, 35990–35994.
Rotter, V., Nagaev, I., Smith, U., 2003. Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor-alpha, overexpressed in human fat cells from insulin-resistant subjects. J. Biol. Chem. 278, 45777–45784.
Ruan, H., Miles, P.D.G., Ladd, C.M., Ross, K., Golub, T.R., Olefsky, J.M., Lodish, H.F., 2002. Profiling gene transcription in vivo reveals adipose tissue as an immediate target of tumor necrosis factor-{alpha}: implications for insulin resistance. Diabetes 51, 3176–3188.
Russell, C.D., Ricci, M.R., Brolin, R.E., Magill, E., Fried, S.K., 2001. Regulation of the leptin content of obese human adipose tissue. Am. J. Physiol. 280, E399–E404.
Saladin, R., De Vos, P., Guerre-Millo, M., Leturque, A., Girard, J., Staels, B., Auwerx, J., 1995. Transient increase in obese gene expression after food intake or insulin administration. Nature 377, 527–529.
Sanchez-Margalet, V., Martin-Romero, C., 2001. Human leptin signaling in human peripheral blood mononuclear cells: activation of the jak-stat pathway. Cell Immunol. 211, 30–36.
Satoh, H., Nguyen, M.T.A., Miles, P.D.G., Imamura, T., Usui, I., Olefsky, J.M., 2004. Adenovirus-mediated chronic "hyper-resistinemia" leads to in vivo insulin resistance in normal rats. J. Clin. Invest. 114, 224–231.
Savage, D.B., Sewter, C.P., Klenk, E.S., Segal, D.G., Vidal-Puig, A., Considine, R.V., O'Rahilly, S., 2001. Resistin/fizz3 expression in relation to obesity and peroxisome proliferator-activated receptor-gamma action in humans. Diabetes 50, 2199–2202.
Scherer, P.E., Williams, S., Fogliano, M., Baldini, G., Lodish, H.F., 1995. A novel serum protein similar to C1q, produced exclusively in adipocytes. J. Biol. Chem. 270, 26746–26749.
Schraw, T., Wang, Z.V., Halberg, N., Hawkins, M., Scherer, P.E., 2008. Plasma adiponectin complexes have distinct biochemical characteristics. Endocrinology 149, 2270–2282.
Schreyer, S.A., Chua Jr., S.C., LeBoeuf, R.C., 1998. Obesity and diabetes in TNF-alpha receptor-deficient mice. J. Clin. Invest. 102, 402–411.
Senn, J.J., Klover, P.J., Nowak, I.A., Mooney, R.A., 2002. Interleukin-6 induces cellular insulin resistance in hepatocytes. Diabetes 51, 3391–3399.
Senn, J.J., Klover, P.J., Nowak, I.A., Zimmers, T.A., Koniaris, L.G., Furlanetto, R.W., Mooney, R.A., 2003. Suppressor of cytokine signaling-3 (SOCS-3), a potential mediator of interleukin-6-dependent insulin resistance in hepatocytes. J. Biol. Chem. 278, 13740–13746.
Sentinelli, F., Romeo, S., Arca, M., Filippi, E., Leonetti, F., Banchieri, M., Di Mario, U., Baroni, M.G., 2002. Human resistin gene, obesity, and type 2 diabetes: mutation analysis and population study. Diabetes 51, 860–862.
Shapiro, L., Scherer, P.E., 1998. The crystal structure of a complement-1q family protein suggests an evolutionary link to tumor necrosis factor. Curr. Biol. 8, 335–338.
Shi, H., Kokoeva, M.V., Inouye, K., Tzameli, I., Yin, H., Flier, J.S., 2006. TLR4 links innate immunity and fatty acid-induced insulin resistance. J. Clin. Invest..
Sinha, M., Ohannesian, J.P., Heiman, M., Kriauciunas, A., Stephens, T.W., Magosin, S., Marco, C.C., Caro, J.F., 1996a. Nocturnal rise of leptin in lean, obese, and non-insulin-dependent diabetes mellitus subjects. J. Clin. Invest. 97, 1344–1347.
Sinha, M., Opentanova, I., Ohannesian, J.P., Kolaczynski, J.W., Heiman, M., Hale, J., Becker, G.W., Bowsher, R.R., Stephens, T.W., Caro, J.F., 1996b. Evidence for free and bound leptin in human circulation: studies in lean and obese subjects during short term fasting. J. Clin. Invest. 98, 1277–1282.
Staiger, H., Kaltenbach, S., Staiger, K., Stefan, N., Fritsche, A., Guirguis, A., Peterfi, C., Weisser, M., Machicao, F., Stumvoll, M., Haring, H.-U., 2004. Expression of adiponectin receptor mRNA in human skeletal muscle cells is related to in vivo parameters of glucose and lipid metabolism. Diabetes 53, 2195–2201.
Steinberg, G.R., Dyck, D.J., 2000. Development of leptin resistance in rat soleus muscle in response to high-fat diets. Am. J. Physiol. 279, E1374–E1382.

Steinberg, G.R., Parolin, M.L., Heigenhauser, G.J., Dyck, D.J., 2002. Leptin increases FA oxidation in lean but not obese human skeletal muscle: evidence of peripheral leptin resistance. Am. J. Physiol. Endocrinol. Metab. 283, E187–E192.

Steinberg, G.R., Smith, A.C., van Denderen, B.J.W., Chen, Z., Murthy, S., Campbell, D.J., Heigenhauser, G.J.F., Dyck, D.J., Kemp, B.E., 2004a. AMP-activated protein kinase is not down-regulated in human skeletal muscle of obese females. J. Clin. Endocrinol. Metab. 89, 4575–4580.

Steinberg, G.R., Smith, A.C., Wormald, S., Malenfant, P., Collier, C., Dyck, D.J., 2004b. Endurance training partially reverses dietary-induced leptin resistance in rodent skeletal muscle. Am. J. Physiol. Endocrinol. Metab. 286, E57–E63.

Steinberg, G.R., Watt, M.J., Fam, B.C., Proietto, J., Andrikopoulos, S., Allen, A.M., Febbraio, M.A., Kemp, B.E., 2006a. Ciliary neurotrophic factor suppresses hypothalamic AMP-kinase signaling in leptin-resistant obese mice. Endocrinology 147, 3906–3914.

Steinberg, G.R., McAinch, A.J., Chen, M.B., O'Brien, P.E., Dixon, J.B., Cameron-Smith, D., Kemp, B.E., 2006b. The suppressor of cytokine signaling 3 inhibits leptin activation of AMP-kinase in cultured skeletal muscle of obese humans. J. Clin. Endocrinol. Metab. 91, 3592–3597.

Steinberg, G.R., Michell, B.J., van Denderen, B.J., Watt, M.J., Carey, A.L., Fam, B.C., Andrikopoulos, S., Proietto, J., Gorgun, C.Z., Carling, D., Hotamisligil, G.S., Febbraio, M.A., Kay, T.W., Kemp, B.E., 2006c. Tumor necrosis factor alpha-induced skeletal muscle insulin resistance involves suppression of AMP-kinase signaling. Cell Metab. 4, 465–474.

Steinberg, G.R., Watt, M.J., Ernst, M., Birnbaum, M.J., Kemp, B.E., Jorgensen, S.B., 2009. Ciliary neurotrophic factor stimulates muscle glucose uptake by a PI3-kinase-dependent pathway that is impaired with obesity. Diabetes 58, 829–839.

Stephens, J.M., Lee, J.L., Pilch, P.F., 1997. Tumor necrosis factor alpha induced insulin resistance in 3T3-L1 adipocytes is accompanied by a loss of insulin receptor substrate-1 and GLUT4 expression with a loss of insulin receptor-mediated signal transduction. J. Biol. Chem. 272, 971–976.

Steppan, C.M., Bailey, S.T., Bhat, S., Brown, E.J., Banerjee, R.R., Wright, C.M., Patel, H.R., Ahima, R.S., Lazar, M.A., 2001. The hormone resistin links obesity to diabetes. Nature 409, 307–312.

Steppan, C.M., Wang, J., Whiteman, E.L., Birnbaum, M.J., Lazar, M.A., 2005. Activation of SOCS-3 by resistin. Mol. Cell Biol. 25, 1569–1575.

Tam, L.S., Tomlinson, B., Chu, T.T., Li, T.K., Li, E.K., 2007. Impact of TNF inhibition on insulin resistance and lipids levels in patients with rheumatoid arthritis. Clin. Rheumatol. 26, 1495–1498.

Tanaka, T., Masuzaki, H., Yasue, S., Ebihara, K., Shiuchi, T., Ishii, T., Arai, N., Hirata, M., Yamamoto, H., Hayashi, T., Hosoda, K., Minokoshi, Y., Nakao, K., 2007. Central melanocortin signaling restores skeletal muscle AMP-activated protein kinase phosphorylation in mice fed a high-fat diet. Cell Metab. 5, 395–402.

Tartaglia, L.A., 1997. The leptin receptor. J. Biol. Chem. 272, 6093–6096.

Tartaglia, L., Dembski, M., Weng, X., Deng, N., Culpepper, J., Devos, R., Richards, G.J., Campfield, L.A., Clark, F.T., Deeds, J., Muir, C., Sanker, S., Moriarty, A., Moore, K.J., Smutko, J.S., Mays, G.G., Woolf, E.A., Monroe, C.A., Tepper, R.I., 1995. Identification and expression cloning of a leptin receptor, OB-R. Cell. 83, 1263–1271.

Tomas, E., Tsao, T.-S., Saha, A.K., Murrey, H.E., Zhang, C.C., Itani, S.I., Lodish, H.F., Ruderman, N.B., 2002. Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation. Proc. Natl. Acad. Sci. U.S.A. 99, 16309–16313.

Uysal, K.T., Wiesbrock, S.M., Marino, M.W., Hotamisligil, G.S., 1997. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature 389, 610–614.

Waki, H., Yamauchi, T., Kamon, J., Ito, Y., Uchida, S., Kita, S., Hara, K., Hada, Y., Vasseur, F., Froguel, P., Kimura, S., Nagai, R., Kadowaki, T., 2003. Impaired multimerization of human adiponectin mutants associated with diabetes: molecular structure and multimer formation of adiponectin. J. Biol. Chem. 278, 40352–40363.

Wang, Y., Xu, A., Knight, C., Xu, L.Y., Cooper, G.J., 2002. Hydroxylation and glycosylation of the four conserved lysine residues in the collagenous domain of adiponectin. Potential role in the modulation of its insulin-sensitizing activity. J. Biol. Chem. 277, 19521–19529.

Wang, H., Zhang, H., Jia, Y., Zhang, Z., Craig, R., Wang, X., Elbein, S.C., 2004. Adiponectin receptor 1 gene (ADIPOR1) as a candidate for type 2 diabetes and insulin resistance. Diabetes 53, 2132–2136.

Wang, Y., Lam, K.S., Chan, L., Chan, K.W., Lam, J.B., Lam, M.C., Hoo, R.C., Mak, W.W., Cooper, G.J., Xu, A., 2006. Post-translational modifications of the four conserved lysine residues within the collagenous domain of adiponectin are required for the formation of its high molecular weight oligomeric complex. J. Biol. Chem. 281, 16391–16400.

Wang, Z.V., Schraw, T.D., Kim, J.Y., Khan, T., Rajala, M.W., Follenzi, A., Scherer, P.E., 2007a. Secretion of the adipocyte-specific secretory protein adiponectin critically depends on thiol-mediated protein retention. Mol. Cell Biol. 27, 3716–3731.

Wang, C., Mao, X., Wang, L., Liu, M., Wetzel, M.D., Guan, K.-L., Dong, L.Q., Liu, F., 2007b. Adiponectin sensitizes insulin signaling by reducing p70 S6 kinase-mediated serine phosphorylation of IRS-1. J. Biol. Chem. 282, 7991–7996.

Watt, M.J., Dzamko, N., Thomas, W.G., Rose-John, S., Ernst, M., Carling, D., Kemp, B.E., Febbraio, M.A., Steinberg, G.R., 2006. CNTF reverses obesity-induced insulin resistance by activating skeletal muscle AMPK. Nat. Med. 12, 541–548.

Weisberg, S.P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R.L., Ferrante Jr., A.W., 2003. Obesity is associated with macrophage accumulation in adipose tissue. J. Clin. Invest. 112, 1796–1808.

Weisberg, S.P., Hunter, D., Huber, R., Lemieux, J., Slaymaker, S., Vaddi, K., Charo, I., Leibel, R.L., Ferrante Jr., A.W., 2006. CCR2 modulates inflammatory and metabolic effects of high-fat feeding. J. Clin. Invest. 116, 115–124.

Westerterp-Plantenga, M.S., Saris, W.H., Hukshorn, C.J., Campfield, L.A., 2001. Effects of weekly administration of pegylated recombinant human OB protein on appetite profile and energy metabolism in obese men. Am. J. Clin. Nutr. 74, 426–434.

White, C.L., Whittington, A., Barnes, M.J., Wang, Z., Bray, G.A., Morrison, C.D., 2009. HF diets increase hypothalamic PTP1B and induce leptin resistance through both leptin-dependent and -independent mechanisms. Am. J. Physiol. Endocrinol. Metab. 296, E291–E299.

Wormald, S., Hilton, D.J., 2004. Inhibitors of cytokine signal transduction. J. Biol. Chem. 279, 821–824.

Wu, X., Motoshima, H., Mahadev, K., Stalker, T.J., Scalia, R., Goldstein, B.J., 2003. Involvement of AMP-activated protein kinase in glucose uptake stimulated by the globular domain of adiponectin in primary rat adipocytes. Diabetes 52, 1355–1363.

Xie, L., O'Reilly, C.P., Chapes, S.K., Mora, S., 2008. Adiponectin and leptin are secreted through distinct trafficking pathways in adipocytes. Biochim. Biophys. Acta 1782, 99–108.

Yamauchi, T., Kamon, J., Waki, H., Terauchi, Y., Kubota, N., Hara, K., Mori, Y., Ide, T., Murakami, K., Tsuboyama-Kasaoka, N., Ezaki, O., Akanuma, Y., Gavrilova, O., Vinson, C., Reitman, M.L., Kagechika, H., Shudo, K., Yoda, M., Nakano, Y., Tobe, K., Nagai, R., Kimura, S., Tomita, M., Froguel, P., Kadowaki, T., 2001. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat. Med. 7, 941–946.

Yamauchi, T., Kamon, J., Minokoshi, Y., Ito, Y., Waki, H., Uchida, S., Yamashita, S., Noda, M., Kita, S., Ueki, K., Eto, K., Akanuma, Y., Froguel, P., Foufelle, F., Ferre, P., Carling, D., Kimura, S., Nagai, R., Kahn, B.B., Kadowaki, T., 2002. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat. Med. 8, 1288–1295.

Yamauchi, T., Kamon, J., Ito, Y., Tsuchida, A., Yokomizo, T., Kita, S., Sugiyama, T., Miyagishi, M., Hara, K., Tsunoda, M., Murakami, K., Ohteki, T., Uchida, S., Takekawa, S., Waki, H., Tsuno, N.H., Shibata, Y., Terauchi, Y., Froguel, P., Tobe, K., Koyasu, S., Taira, K., Kitamura, T., Shimizu, T., Nagai, R., Kadowaki, T., 2003. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 423, 762–769.

Yamauchi, T., Nio, Y., Maki, T., Kobayashi, M., Takazawa, T., Iwabu, M., Okada-Iwabu, M., Kawamoto, S., Kubota, N., Kubota, T., Ito, Y., Kamon, J., Tsuchida, A., Kumagai, K., Kozono, H., Hada, Y., Ogata, H., Tokuyama, K., Tsunoda, M., Ide, T., Murakami, K., Awazawa, M., Takamoto, I., Froguel, P., Hara, K., Tobe, K., Nagai, R., Ueki, K., Kadowaki, T., 2007. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat. Med. 13, 332–339.

Yang, Q., Graham, T.E., Mody, N., Preitner, F., Peroni, O.D., Zabolotny, J.M., Kotani, K., Quadro, L., Kahn, B.B., 2005. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature 436, 356–362.

Yu, C., Chen, Y., Cline, G.W., Zhang, D., Zong, H., Wang, Y., Bergeron, R., Kim, J.K., Cushman, S.W., Cooney, G.J., Atcheson, B., White, M.F., Kraegen, E.W., Shulman, G.I., 2002. Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate-1 (IRS-1)-associated phosphatidylinositol 3-kinase activity in muscle. J. Biol. Chem. 277, 50230–50236.

Zabolotny, J.M., Bence-Hanulec, K.K., Stricker-Krongrad, A., Haj, F., Wang, Y., Minokoshi, Y., Kim, Y.B., Elmquist, J.K., Tartaglia, L.A., Kahn, B.B., Neel, B.G., 2002. PTP1B regulates leptin signal transduction in vivo. Dev. Cell 2, 489–495.

Zhang, K., Kaufman, R.J., 2004. Signaling the unfolded protein response from the endoplasmic reticulum. J. Biol. Chem. 279, 25935–25938.

Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., Friedman, J.M., 1994. Positional cloning of the mouse obese gene and its human homologue. Nature 372, 425–432.