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REVIEWS: CURRENT TOPICS

Role of adipocytokines in obesity-associated insulin resistance

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Abstract

The rapid increase of obese population in the United States has made obesity into epidemic proportion. Obesity is a strong risk factor for metabolic syndrome, type 2 diabetes mellitus, cardiovascular diseases, cancer and other diseases. Compelling evidence has demonstrated that increased adipose tissue mass is not only the consequence of obesity, but also plays a central role in the development of obesity-associated diseases. Recent studies have profoundly changed the concept of adipose tissue from being an energy depot to an active endocrine organ. The development of obesity alters adipocyte-derived hormones or cytokines expression, which provide a link between obesity and impaired insulin sensitivity and metabolic defects in other tissues. This review summarizes the current knowledge on how major adipose-derived hormones or adipocytokines influence insulin sensitivity.

Keywords: Obesity; Adipose tissue; Insulin resistance; Diabetes mellitus; Adipocytokine

1. Introduction

Over the last two decades, the prevalence of overweight or obesity in the United States has increased at an accelerating and alarming rate. Now more than 60% of the adults in the United States are overweight or obese, and morbidly obese individuals number in the millions [1]. Virtually, obesity affects both developed and undeveloped countries [2,3]. Apart from the heightened genetic susceptibility of certain ethnic groups, environmental and behavioral factors such as sedentary lifestyle and nutrition are clearly important [4].

Epidemiological studies indicate a strong link between the increased food intake and the dramatic rise in the incidence and prevalence of obesity [5]. From a thermodynamic perspective, body weight and composition and the storage of energy as triglyceride in adipose tissue are results of the imbalance between energy intake (feeding) and energy expenditure (thermal and physical activity) [6].

Obesity is closely linked to a wide array of pathophysiologic consequences including insulin resistance (IR), type 2 diabetes mellitus (T2D), hypertension, hyperlipidemia and atherosclerosis. The association of obesity with T2D has been recognized for decades, and the major basis for this link is the ability of obesity to engender IR [7]. Circulating free fatty acids (FFAs) derived from adipocytes are elevated in many insulin-resistant states and have been suggested to be a main underlying mechanism of IR in obesity-associated T2D [8,9]. However, compeling evidence demonstrates that several adipocyte-derived cytokines or hormones are also involved in obesity-induced IR.

The adipocyte is unique among cells in that one "organelle," the lipid droplet, encompasses greater than 95% of the entire cell body. It is now clear that the adipocyte has additional roles with the remaining 5% of its cellular mass [10]. The significance of adipose tissue as an endocrine organ first surfaced in 1995 with the groundbreaking discovery of leptin [11]. Since then, a group of adipocyte-derived cytokines (adipocytokines) or proteins highly

Abbreviations: IR, insulin resistance; T2D, type 2 diabetes mellitus; FFA, free fatty acid; PEPCK, phospho*enol*pyruvate carboxykinase; IRS-1, insulin receptor substrate-1; PI3-kinase, phosphatidylinositol 3-kinase; HMW, high molecular weight; BMI, body mass index; Akt, protein kinase B; MAPK, mitogen-activated protein kinase; AMPK, AMP-activated protein kinase; AdipoR, adiponectin receptor; PPAR, peroxisome proliferator-activated receptor; TNF-α, tumor necrosis factor-α; GLUT, glucose-transporting protein; IL-6, interleukin-6; TZD, thiazolidinedione; RBP4, retinol-binding protein 4.

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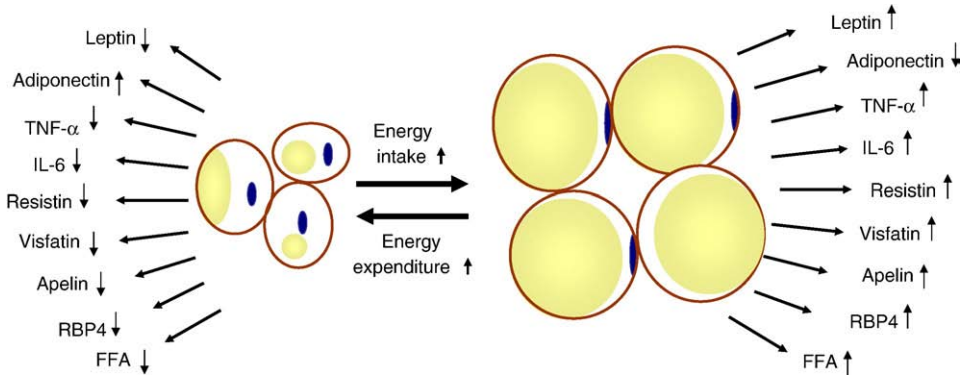

Fig. 1. An overview of secretion of adipocytokines in adipose tissue under normal and obesity conditions.

expressed in adipose tissue has been discovered with a variety of biological functions, including energy balance, glucose homeostasis, lipid metabolism or inflammation (Fig. 1). Therefore, in addition to energy storage, adipose tissue is a very active endocrine organ. Here, we review some important research progress in the context of these adipocyte-derived proteins and their roles in obesity-associated IR.

2. Leptin

Leptin was named from the Greek root "leptos" because it suppresses food intake and decreases body weight in mice. Leptin was originally cloned as the protein product of the *ob* gene [11]. The murine *ob* gene encodes a 4.5-kb messenger RNA (mRNA) transcript with a highly conserved 167-amino-acid open reading frame. Detailed information on the leptin gene, its protein structure and biological functions, has been summarized in a recent review [12].

Circulating leptin is mainly synthesized and secreted by adipose tissue. Leptin is also expressed, albeit at lower levels, in other tissues, such as gastric epithelium, muscle and placenta [13–15]. Adipocytes secrete leptin in direct proportion to adipose tissue mass as well as nutritional status. Plasma leptin concentrations positively correlate with subcutaneous, rather than intra-abdominal, fat tissue mass [16]. Leptin expression and protein levels in circulation are increased during the development of obesity [17]. Obese persons have higher leptin mRNA and protein levels than lean individuals [18]. Leptin expression is stimulated upon feeding [12]; plasma leptin level declines rapidly during fasting [19]. Insulin is a potent activator of leptin mRNA expression and protein secretion and is the major mediator of increased postprandial leptin concentration [20,21]. Potential modifiers of leptin concentrations are energy-yielding nutrients such as fatty acids, carbohydrates, proteins and alcohol [22]. Leptin is also regulated by steroid hormones. Chronic exposure to glucocorticoids and estrogens increases leptin synthesis and release [23,24].

Leptin plays a very important role in maintaining energy homeostasis. Leptin acts both centrally and peripherally, with a major role in the regulation of food intake, body weight and energy balance [25]. Leptin inhibits appetite and weight gain by decreasing orexigenic and increasing anorexigenic peptide expression in the hypothalamus [26] and reduces the level of intracellular lipid in skeletal muscle and liver [27]. Reduced leptin levels promote energy intake and limit the high-energy cost of reproduction, thyroid thermogenesis and immune response [28]. The mutation of the *ob* gene leads to massive obesity in *ob/ob* mice [29]. While the leptin-mediated adaptation to energy deficiency is likely to have been beneficial in times of food shortage, this tendency towards efficient energy metabolism may have contributed to the current epidemic of obesity in an environment where food is abundant [28].

Well-documented discoveries have also raised the possibility that leptin pathways act in concert with insulin to control glucose and lipids, aside from regulating food intake and metabolic rate, linking this hormone to IR and T2D. Leptin can act through some of the components of the insulin signaling cascade, such as insulin receptor substrate (IRS)-1 and IRS-2, mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3-kinase), suggesting that there are cross-talks of insulin and leptin signaling pathways [30]. Leptin pretreatment transiently enhances insulin-induced tyrosine phosphorylation and PI3-kinase binding to IRS-1 while producing an inhibition of tyrosine phosphorylation and PI3-kinase binding to IRS-2 [30]. Leptin alone also induces serine phosphorylation of protein kinase B (Akt) and glycogen synthase kinase 3α/β but to a lesser extent than insulin [30]. Intravenous infusion of leptin in mice increases glucose turnover, stimulates glucose uptake in skeletal muscle and brown adipose tissue and causes a decrease in hepatic glycogen content [17]. Leptin has also been reported to enhance insulin's action on the gene expression for two key metabolic enzymes, glucokinase and phospho*enol*pyruvate carboxykinase (PEPCK) [31,32]. However, the role of elevated leptin in obesity-associated IR is still controversial, and direct

cross-talk between leptin and the insulin signaling system remains unclear [30]. For example, one study reported that leptin impairs insulin signaling by increasing IRS-1 phosphorylation at the serine 318 site [33]. In HepG2 human hepatoma cells, leptin antagonizes insulin-induced down-regulation of PEPCK expression and decreases insulin-stimulated tyrosine phosphorylation of IRS-1 but enhances IRS-1-associated PI3-kinase activity [34]. But in C2C12 muscle cells, leptin stimulates a non-IRS-1-associated PI3-kinase and mimics insulin action on glucose transport and glycogen synthesis [35].

3. Adiponectin

Adiponectin is a 30-kDa protein that was first cloned from adipose tissue in 1995 [36]. Later, three independent groups cloned the same gene in adipose tissue [37–39].

The adiponectin gene is located on chromosome 3q27. Adiponectin protein is composed of an N-terminal signal sequence, a hypervariable domain, 15 collagenous repeats and a C-terminal globular domain [40]. Circulating adiponectin forms several different complexes in adipocyte before being secreted into the serum [41]. The most basic form is the trimer. Aside from forming free trimers, adiponectin also forms two higher ordered structures through the noncovalent binding of two trimers (hexamers) and six trimers (18 mers). These higher ordered complexes are described as medium molecular weight (hexamers) and high molecular weight (12–18 mers) forms of adiponectin [36,42]. Studies have suggested that high molecular weight adiponectin may be biologically active and critical for enhancing insulin sensitivity [43].

Both *in vivo* and *in vitro* studies have demonstrated that adiponectin enhances insulin sensitivity, increases fatty acid oxidation, glucose uptake and suppresses hepatic glucose production [44–48]. Studies in humans showed that adiponectin levels correlate with basal and insulin-suppressed endogenous glucose production and not with β-oxidation [49,50]. These studies strongly indicated that adiponectin acts through multiple tissues to enhance insulin sensitivity. Thus, adiponectin is referred to as an insulin sensitizer. A recent study indeed showed that adiponectin enhances insulin-stimulated IRS-1 tyrosine phosphorylation and Akt phosphorylation [51]. The study also revealed that activation of the serine/threonine kinase 11/AMP-activated protein kinase (AMPK)/TSC1/2 pathway alleviates the p70S6 kinase-mediated negative regulation of insulin signaling, providing a mechanism by which adiponectin increases insulin sensitivity in cells [51].

Adiponectin is abundant in plasma, with concentrations ranging from 5 to 30 μg/ml, thus accounting for approximately 0.01% of total plasma protein [40]. This is three orders of magnitude higher than concentrations of most other hormones [52]. Plasma adiponectin also has a rapid turn over [41]. The expression and secretion of adiponectin are inhibited by tumor necrosis factor (TNF)-α, interleukin-6 (IL-6), and dexamethasone [53,54]. The effects of insulin on adiponectin gene expression and secretion are still controversial [36,55–59]. Low plasma adiponectin concentrations have been observed in obese and insulin-resistant human subjects and obese animal models [37,52,60]. Plasma adiponectin concentrations are inversely correlated to body mass index (BMI) [52]. Most important, a longitudinal study in monkeys has found that plasma adiponectin level started to drop at an early phase, prior to the onset of frank hyperglycemia, glucose intolerance and maximal level of obesity [60]. In contrast to obesity, reduction of body weight in obese subjects increases plasma adiponectin concentrations [61,62]. These studies suggest that obesity-associated hypoadiponectinemia is reversible.

Adiponectin gene expression can be regulated at both transcription and posttranscription level. Studies have suggested that posttranscriptional regulation is another mechanism that determines the circulated adiponectin protein level [63]. Unfortunately, no detailed information regarding adiponectin transcript stability, protein translation, modification and clearance has been systemically reported. Adiponectin is predominantly expressed in adipocyte. Adipogenic master transcription factor C/EBPα and peroxisome proliferator-activated receptor (PPAR)γ play a key role in controlling adiponectin transcription [54,64]. In addition, SREBP1c responding element has been identified in adiponectin promoter [55]. However, studies have indicated that adiponectin promoter is a basal promoter without significant tissue specificity [65]. Our study further demonstrated that C/EBPα regulates human adiponectin gene transcription through an intronic enhancer, which is responsible for adipocyte specificity of adiponectin gene transcription [64]. Our recent study revealed that C/EBPα and Foxo1 interact and form a transcriptional complex and up-regulate adiponectin transcription through two Foxo1 binding sites [66]. Furthermore, silent information regulator 2 mammalian orthology SIRT1 enhances Foxo1–C/EBPα complex formation and up-regulates adiponectin expression, providing a molecular mechanism for calorie-restriction-induced adiponectin gene expression [66].

Three membrane proteins have been reported as adiponectin receptors [67,68]. The biological function and downstream signal of adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2) have been described [68]. AdipoR1 is expressed ubiquitously, with the most abundant expression occurring in skeletal muscle [68]. AdipoR2 is most abundantly expressed in the liver [68]. Recent studies showed that the APPL1 adaptor protein binds to the intracellular domain of adiponectin receptors and mediates some of adiponectin's actions [69,70]. AMPK can be activated by adiponectin and is another downstream protein in the adiponectin signal cascade [68,71,72].

The biological functions of AdipoR1 and AdipoR2 have been further studied by using gain- or loss-of-function approaches. Surprisingly, AdipoR2-deficient mice are

resistant to obesity induced by a high-fat diet [73,74]. AdipoR2 deficiency improves glucose tolerance and diminishes IR induced by a high-fat diet in mice [73,74]. In contrast, AdipoR1-deficient mice show increased adiposity and impaired glucose tolerance without alteration of AMPK activity and PPARα expression [74]. Interestingly, Yamauchi et al. [75] reported that AdipoR1− or AdipoR2-deficient and AdipoR1/R2 double knockout mice were insulin resistant. The study also showed that adenovirus-mediated overexpression of AdipoR1 or AdipoR2 in liver improves glucose metabolism in *db/db* diabetic mice by increasing AMPK activity and PPARα expression [75]. However, our study showed that although AdipoR1 or AdipoR2 mRNA levels were increased over 200-fold by adenovirus-mediated gene transduction in liver, neither significant change of glucose tolerance nor AMPK phosphorylation in liver tissues was observed in C57BL/6J mice (Qiao, L., Zou, C., and Shao, J., unpublished data). So far, there is no explanation for these discrepancies, which may be caused by the difference of animal models. Therefore, more studies are warranted to further determine the functions of adiponectin receptor in glucose and lipid metabolism.

4. Tumor necrosis factor-α

TNF-α, expressed as a 26-kDa cell surface transmembrane protein that undergoes cleavage to produce a 17-kDa soluble, biologically active form [76], was originally identified as a proinflammatory cytokine produced by macrophages and lymphocytes [77]. Further study has demonstrated that adipose tissue can also express and secrete this cytokine [78]. However, recent studies indicated that infiltrated macrophage is the main source of TNF-α in adipose tissue [79,80].

TNF-α was recognized as the first cytokine that could induce IR [76] and was proposed to represent a molecular link between obesity and IR [78]. Both human and animal studies showed that TNF-α expression in adipose tissue is highly induced by obesity [78,81]. Expression of TNF-α mRNA was increased and was strongly correlated to the degree of obesity and the level of IR in obese animal models and humans [82,83]. Therefore, TNF-α may partially contribute to IR in obesity.

In obese individuals and subjects with IR and T2D, TNF-α levels are raised and correlated with high plasma insulin levels and decreased insulin sensitivity. In adipose tissue of obese humans, there is a strong inverse correlation between secretion of TNF-α and insulin-stimulated glucose metabolism [84,85]. TNF-α attenuates insulin receptor signaling pathway through its ability to decrease the tyrosine kinase activity of the insulin receptor. Treatment of cultured murine adipocytes with TNF-α was shown to induce serine phosphorylation of IRS-1 and convert IRS-1 into an inhibitor of the insulin receptor tyrosine kinase activity and then increase IRS-1 degradation [86]. In adipocytes, TNF-α down-regulates the expression of several proteins implicated in the insulin signaling pathway, including GLUT 4 and PPARγ [87,88]. A recent study by Gao et al. [89] demonstrated that TNF-α inhibits PPARγ activity through two mechanisms: inhibition of PPARγ expression and suppression of the transcriptional activity of PPARγ by nuclear corepressor. TNF-α can also induce IR in many ways such as by stimulation of adipocyte lipolysis so that the circulating fatty acid level increases, which, in turn, alters insulin action. Studies also suggest that elevated levels of TNF-α in obesity suppress adiponectin expression locally by autocrine or paracrine mechanisms, then impair insulin sensitivity of other tissues through the down-regulation of circulating adiponectin [58,90].

In vivo studies have shown that the inhibitory effects of TNF-α on insulin action are, at least in part, antagonized by thiazolidinedione (TZD) [88]. Further support comes from studies of obese rats, where neutralization of TNF-α or employment of a replication-incompetent adenovirus-5 vector to endogenously express a TNF inhibitor gene improved insulin sensitivity [91]. However, administration of TNF-α antibody did not improve insulin sensitivity in obese patients with T2D [92]. In summary, the role of TNF-α in the development of IR in humans has not been conclusive and additional human studies are needed.

5. Interleukin-6

IL-6 has originally been cloned as a variably glycosylated 22- to 27-kDa leucocyte-derived proinflammatory protein and binds to a transmembrane receptor, gp130, which initiates a signal transduction cascade [93]. It is a pleiotropic circulating cytokine with effects ranging from inflammation to host defense to tissue injury [94] and it is one of several proinflammatory cytokines that have been associated with IR.

IL-6 is secreted by many types of cells. IL-6 is also produced by fat cells and stromal-vascular cells in adipose tissue [95]. Since about 30% of systemic IL-6 is secreted by adipose tissue, this protein is also an adipocytokine [96].

Elevated plasma levels of IL-6 are strongly linked to IR [84,85]. IL-6 concentrations at baseline independently predict future risk of developing T2D [97]. Weight loss significantly decreases IL-6 levels in both adipose tissue and serum [98]. IL-6 has direct effects on insulin signaling in adipocytes and hepatocytes [99,100]. It impairs insulin signaling in primary mouse hepatocytes and 3T3-L1 adipocytes with decreased activation of IRS-1 and PI3-kinase, as well as impaired insulin-induced glycogenesis in hepatocytes [100]. Administration of recombinant IL-6 in rodent models and humans induces hepatic gluconeogenesis that, in turn, leads to hyperglycaemia and compensatory hyperinsulinaemia [101]. IL-6 exerts its adverse effects on insulin sensitivity by increasing circulating FFA [102]. *In vivo* administration of IL-6 stimulates whole-body

lipolysis and inhibits glucose metabolism in man [103]. IL-6 may also induce IR, at least in part, by decreasing adiponectin secretion [53]. TNF-α potently induces IL-6 gene transcription and protein secretion in differentiated 3T3-L1 adipocytes [104].

Although much evidence implicates IL-6 in IR, there is some conflicting evidence. Transgenic mice overexpressing IL-6 have a generalized defect in growth, which includes reduced body weight and decreased fat pad weights [105]. On the other hand, mice with a targeted deletion of IL-6 develop mature-onset obesity and associated metabolic abnormalities, which are reversed by IL-6 replacement, suggesting that IL-6 is involved in preventing rather than causing these conditions [106].

All these observations suggest that IL-6 might act in a local and systemic fashion to influence body weight, energy homeostasis and insulin sensitivity.

6. Resistin

Resistin is an approximately 12-kDa polypeptide that belongs to a unique family of cysteine-rich C-terminal domain proteins called resistin-like molecules. It was discovered as a novel mRNA induced during adipocyte differentiation but down-regulated by TZDs *in vitro* [107]. Resistin was subsequently identified by other groups. It is also known as ADSF (adipose tissue-specific secretary factory) and FIZZ3 (found in inflammatory zone 3). The resistin polypeptide is expressed and secreted by mature adipocytes [108]. However, human resistin is also expressed in macrophage at a much higher level compared with adipocyte [109].

The resistin mRNA encodes a 114-amino-acid polypeptide containing a 20-amino-acid signal sequence [110]. Resistin contains 11 cysteine (Cys) residues, and is secreted as a disulfide-linked dimmer through Cys26. The remaining 10 Cys residues are probably involved in intramolecular disulfide bonding, which determines the structure of the monomeric polypeptide [111].

Initial studies suggested that resistin had significant effects on insulin action, potentially linking obesity with IR [112]. It was found that serum resistin concentrations are raised in high-fat-induced obese, leptin gene mutant (*ob/ob*), or leptin receptor mutant (*db/db*) diabetic and obese mice models [107]. Furthermore, administration of antiresistin antibody improves insulin action and glucose metabolism in mice with diet-induced obesity [107]. Treatment of normal mice with recombinant resistin impairs glucose tolerance and insulin action [107]. Resistin suppresses insulin-stimulated glucose uptake in 3T3-L1 adipocytes, and the inhibitory effect is prevented by antiresistin antibody [107]. Infusion of recombinant resistin to rats rapidly induces hepatic IR and increases hepatic glucose production [113]. Ablation of the resistin gene in mice decreases fasting glucose through reducing gluconeogenesis, while resistin administration in these resistin-deficient mice increases hepatic glucose production [114]. Moreover, overexpression of resistin impairs glucose transport in skeletal muscle in rats, while treatment with recombinant resistin decreases insulin-mediated glucose transport in myotubes [115]. Three studies have further explored the physiological functions and the role or mechanisms of resistin in the development of IR in rodents [116–118]. These studies show that chronic hyperresistinemia impairs insulin signaling pathway in all three insulin target tissues: muscle, liver and fat. All these studies indicate that resistin impairs insulin sensitivity and may contribute to the development of IR or diabetes in obese rodents.

However, the physiological role of resistin has been proven to be more challenging to figure out than originally anticipated. A study shows that while resistin mRNA is indeed suppressed in obese mice, the circulating resistin protein level is significantly elevated and positively correlated with insulin, glucose and lipids [116]. The role of endogenous resistin in the development of IR or T2D also remains controversial, especially in human subjects. Some studies have observed significant low resistin mRNA levels in adipose tissue in different obese mouse models, such as *db/db*, or high-fat-diet-induced obesity, and in rat models characterized by IR [119–121]. Although in both humans and rodents serum resistin protein concentrations are positively associated with adiposity, resistin mRNA in humans does not correlate with BMI [122]. Resistin mRNA levels and protein expression are initially reported to be low in isolated subcutaneous and omental adipocytes [122,123]. However, Vozarova de Courten et al. [124] reported that in nondiabetic Pima Indians serum resistin levels were positively associated with percent body fat and 2-h blood glucose, respectively. However, serum resistin levels were not associated with fasting glucose and insulin levels and hepatic glucose output [124]. They concluded that high serum resistin levels were cross-sectionally associated with adiposity, but not with whole-body or hepatic IR.

Most mouse studies, but not all, support the notion that resistin is an adipokine regulator of insulin action. However, most human studies show an entirely different picture. Human fat cells, unlike those of mice, do not produce resistin [123], although segments of human adipose tissue do release it [125]. Resistin was originally thought to be an adipokine because it is produced by fat cells and causes IR in rodent models. However, subsequent human studies failed to link resistin to IR. In addition, the protein is not produced by human fat cells but by some yet unidentified cell in the stroma of human adipose tissue, which might be the macrophage [126]. In humans, it appears that peripheral blood mononuclear cells and macrophages are the major source of resistin rather than adipocyte [127]. This may explain why resistin mRNA expression is relatively low in human adipocytes [128]. Moreover, as resistin levels do not consistently correlate with IR or obesity [129], the role of human resistin in the pathogenesis of IR is unclear.

Obviously, identifying the similarities and differences between mouse and human resistin will shed light on the role and underlying mechanisms of resistin in obesity-related IR in these two species.

7. Visfatin

A protein termed visfatin was recently reported as an adipocyte-derived hormone [130]. This protein was previously identified as a growth factor for early B-lymphocytes termed pre-B cell colony-enhancing factor [131].

Visfatin is highly enriched in the visceral fat of both humans and mice, and plasma protein level increases during the development of obesity [132]. However, visfatin is not specifically expressed in adipose tissue, and the visceral depot-specific expression of visfatin has recently been questioned as well [132]. Serum visfatin concentrations are positively correlated with serum triglyceride and down-regulated by overfeeding in healthy young men [133].

Visfatin was described with putative antidiabetogenic properties [130]. This protein has insulinlike effects in cultured cells and lowers plasma glucose in mice [130]. Like insulin, visfatin stimulates glucose uptake in cultured adipocytes and muscle cells and suppresses glucose release by cultured hepatocytes [130]. Visfatin also induces phosphorylation of signal transduction proteins that operated downstream of the insulin receptor [130]. Most intriguing of all, it was shown that visfatin binds to the insulin receptor but does not compete with insulin, suggesting that the two proteins bind to different sites [130].

However, the role of visfatin in obesity-associated IR still remains unclear. Several clinical studies have failed to demonstrate any association of the circulating visfatin with insulin sensitivity [134–137]. Exercise-induced increase in adipose tissue visfatin was, however, not accompanied by elevated levels of plasma visfatin [138]. The lower serum levels of visfatin, compared to those of insulin, and the fact that visfatin levels do not change after feeding imply that the hypoglycemic effects of visfatin may not be of physiological importance [139].

8. Apelin

Apelin is a novel bioactive peptide identified as the endogenous ligand of the orphan G-protein-coupled receptor [140]. It has been shown to be expressed in a variety of tissues, including stomach, brain, heart, skeletal muscle and white adipose tissue [141–145].

Apelin expression in adipose tissue is markedly influenced *in vivo* by nutritional status, being strongly reduced by fasting and rescued by refeeding [146]. A strong relationship exists between apelin and insulin [146]. Insulin exerts a direct positive action on adipocyte apelin production both *in vivo* and *in vitro* by the stimulation of PI3-kinase, protein kinase C and MAPK and may influence plasma apelin levels in obese humans [146]. Indeed, adipocyte apelin mRNA levels as well as plasma apelin concentrations are increased in various mouse models of obesity associated with hyperinsulinemia, but obesity or high-fat feeding are not the main determinants of the rise of apelin expression [146]. Accordingly, insulin-deficient mice (streptozotocin-treated) had low apelin mRNA levels in adipose tissue [147]. Administration of apelin reduced adiposity and serum insulin and triglyceride levels in both C57BL/6J normal and high-fat-diet-induced obese mice [148]. Interestingly, apelin treatment increased serum adiponectin and energy expenditure in mice [148].

9. Retinol-binding protein 4

Defects of glucose transport in adipocyte are linked to IR in muscle and liver [149]. Retinol-binding protein 4 (RBP4) now emerges as a new adipocytokine, linking glucose uptake in adipocytes with systemic insulin sensitivity [150].

RBP4 was reported by Yang et al. [150] as a factor derived from fat cells that can impair insulin sensitivity throughout the body. Then, RBP4 was added to the list of fat-derived peptides that modulate glucose homeostasis.

By using DNA microarrays, RBP-4 was discovered to be regulated reciprocally in adipose tissue of mice with overexpressed glucose-transporting protein (GLUT)4 and those lacking GLUT4 [149]. Mice lacking GLUT4 could normalize insulin sensitivity by lowering circulating RBP4 levels [149]. It was also shown that treatment of mice with the synthetic retinoid fenretinide, which increased the excretion of RBP4, can lower its levels in the blood and ameliorate IR caused by high-fat feeding [149]. Overexpression of RBP4 or injection of recombinant RBP4 in wild-type mice induced IR [149]. These results demonstrate that RBP4 is an adipokine involved in obesity-induced IR.

RBP4, a protein whose only function was thought to be the delivery of retinol to tissues, was increased in adipose tissue of mice with adipocyte-specific ablation of GLUT4 [151]. Circulating RBP4 levels were substantially increased not only in several obesity and IR mouse models, but also in obese human subjects with IR [150, 152]. Recent human studies showed that plasma RBP4 correlated with the magnitude of IR and age [152,153]. Women tend to have low plasma RBP4 [152]. Plasma RBP4 levels were positively associated with serum triglyceride, systolic blood pressure, BMI and other components of metabolic syndrome [153]. In addition, increased plasma RBP4 levels in obese children were correlated not only with indices of obesity and IR but also with inflammatory factors [154].

10. Summary

The discovery of the endocrine property of white adipose tissue enriches our understanding of the role of adipose in energy metabolism. Although long-term energy imbalance

or surplus is the main mechanism of obesity, adipose tissue-derived cytokines play an active role in this process. The increase of adipose tissue mass not only provides a depot for the excessive energy, but also alters adipocyte-derived hormones or cytokines synthesis. The studies from the recent two decades have demonstrated that adipocyte-derived hormones and cytokines regulate energy metabolism in other tissues. These studies reveal new mechanisms of obesity-associated IR and type 2 diabetes.

References

[1] Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 2006;29:1549–55.

[2] World Health Organization. Obesity: preventing and managing the global epidemic; 1997 [Geneva].

[3] Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. JAMA 2002;288: 1723–7.

[4] Zimmet P, Alberti KGMM, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001;414:782–7.

[5] Spiegelman BM, Flier JS. Obesity and the regulation of energy balance. Cell 2001;104:531–43.

[6] Pilch PF, Bergenhem N. Pharmacological targeting of adipocytes/fat metabolism for treatment of obesity and diabetes. Mol Pharmacol 2006;70:779–85.

[7] Kahn BB, Flier JS. Obesity and insulin resistance. J Clin Invest 2000;106:473–81.

[8] Bergman RN, Ader M. Free fatty acids and pathogenesis of type 2 diabetes mellitus. Trends Endocrinol Metab 2000;11:351–6.

[9] Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. Nature 2001;414:799–806.

[10] Trujillo ME, Scherer PE. Adipose tissue-derived factors: impact on health and disease. Endocr Rev 2006:2006–33.

[11] Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. Science 1995;269:543–6.

[12] Ahima RS, Flier JS. Adipose tissue as an endocrine organ. Trends Endocrinol Metab 2000;11:327–32.

[13] Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, et al. Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. Nat Med 1997;3:1029–33.

[14] Yura S, Sagawa N, Ogawa Y, Masuzaki H, Mise H, Matsumoto T, et al. Augmentation of leptin synthesis and secretion through activation of protein kinases A and C in cultured human trophoblastic cells. J Clin Endocrinol Metab 1998;83:3609–14.

[15] Wang J, Liu R, Hawkins M, Barzilai N, Rossetti L. A nutrient-sensing pathway regulates leptin gene expression in muscle and fat. Nature 1998;393:684–8.

[16] Cnop M, Landchild MJ, Vidal J, Havel PJ, Knowles NG, Carr DR, et al. The concurrent accumulation of intra-abdominal and subcutaneous fat explains the association between insulin resistance and plasma leptin concentrations : distinct metabolic effects of two fat compartments. Diabetes 2002;51:1005–15.

[17] Kamohara S, Burcelin R, Halaas JL, Friedman JM, Charron MJ. Acute stimulation of glucose metabolism in mice by leptin treatment. Nature 1997;389:374–7.

[18] Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med 1995;1: 1155–61.

[19] Ahima RS, Kelly J, Elmquist JK, Flier JS. Distinct physiologic and neuronal responses to decreased leptin and mild hyperleptinemia. Endocrinology 1999;140:4923–31.

[20] Vicennati V, Vottero A, Friedman C, Papanicolaou DA. Hormonal regulation of interleukin-6 production in human adipocytes. Int J Obes Relat Metab Disord 2002;26:905–11.

[21] Rentsch J, Chiesi M. Regulation of ob gene mRNA levels in cultured adipocytes. FEBS Lett 1996;379:55–9.

[22] Perusse L, Collier G, Gagnon J, Leon AS, Rao DC, Skinner JS, et al. Acute and chronic effects of exercise on leptin levels in humans. J Appl Physiol 1997;83:5–10.

[23] Ahima RS, Osei SY. Leptin signaling. Physiol Behav 2004;81: 223–41.

[24] Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004;89:2548–56.

[25] Friedman JM. Modern science versus the stigma of obesity. Nat Med 2004;10:563–9.

[26] Trayhurn P, Hoggard N, Mercer JG, Rayner DV. Leptin: fundamental aspects. Int J Obes Relat Metab Disord 1999;23(Suppl 1):22–8.

[27] Shimabukuro M, Koyama K, Chen G, Wang M-Y, Trieu F, Lee Y, et al. Direct antidiabetic effect of leptin through triglyceride depletion of tissues. PNAS 1997;94:4637–41.

[28] Flier JS. What's in a name? In search of leptin's physiologic role. J Clin Endocrinol Metab 1998;83:1407–13.

[29] Ahima RS. Body fat, leptin, and hypothalamic amenorrhea. N Engl J Med 2004;351:959–62.

[30] Szanto I, Kahn CR. Selective interaction between leptin and insulin signaling pathways in a hepatic cell line. PNAS 2000;97:2355–60.

[31] Rossetti L, Massillon D, Barzilai N, Vuguin P, Chen W, Hawkins M, et al. Short term effects of leptin on hepatic gluconeogenesis and in vivo insulin action. J Biol Chem 1997;272:27758–63.

[32] Liu L, Karkanias GB, Morales JC, Hawkins M, Barzilai N, Wang J, Rossetti L. Intracerebroventricular leptin regulates hepatic but not peripheral glucose fluxes. J Biol Chem 1998;273:31160–7.

[33] Hennige AM, Stefan N, Kapp K, Lehmann R, Weigert C, Beck A, et al. Leptin down-regulates insulin action through phosphorylation of serine-318 in insulin receptor substrate 1. FASEB J 2006;20: 1206–8.

[34] Cohen B, Novick D, Rubinstein M. Modulation of insulin activities by leptin. Science 1996;274:1185–8.

[35] Berti L, Kellerer M, Capp E, Haring HU. Leptin stimulates glucose transport and glycogen synthesis in C2C12 myotubes: evidence for a P13-kinase mediated effect. Diabetologia 1997;40:606–9.

[36] Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem 1995;270:26746–9.

[37] Hu E, Liang P, Spiegelman BM. AdipoQ is a novel adipose-specific gene dysregulated in obesity. J Biol Chem 1996;271:10697–703.

[38] Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (dioseost Abundant Gene Transcript 1). Biochem Biophys Res Commun 1996;221:286–9.

[39] Nakano Y, Tobe T, Choi-Miura N-H, Mazda T, Tomita M. Isolation and characterization of GBP28, a novel gelatin-binding protein purified from human plasma. J Biochem (Tokyo) 1996;120:803–12.

[40] Berg AH, Combs TP, Scherer PE. ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. Trends Endocrinol Metab 2002;13:84–9.

[41] Pajvani UB, Du X, Combs TP, Berg AH, Rajala MW, Schulthess T, et al. Structure–function studies of the adipocyte-secreted hormone acrp30/adiponectin. Implications for metabolic regulation and bioactivity. J Biol Chem 2003;278:9073–85.

[42] Tsao T-S, Murrey HE, Hug C, Lee DH, Lodish HF. Oligomerization state-dependent activation of NF-kappa B signaling pathway by adipocyte complement-related protein of 30 kDa (Acrp30). J Biol Chem 2002;277:29359–62.

[43] Pajvani UB, Hawkins M, Combs TP, Rajala MW, Doebber T, Berger JP, et al. Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. J Biol Chem 2004;279:12152–62.

[44] Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. Nat Med 2001;7:947–53.
[45] Fruebis J, Tsao T-S, Javorschi S, Ebbets-Reed D, Erickson MRS, Yen FT, et al. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. PNAS 2001;98:2005–10.
[46] Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med 2001;7:941–6.
[47] Wu X, Motoshima H, Mahadev K, Stalker TJ, Scalia R, Goldstein BJ. Involvement of AMP-activated protein kinase in glucose uptake stimulated by the globular domain of adiponectin in primary rat adipocytes. Diabetes 2003;52:1355–63.
[48] Combs TP, Berg AH, Obici S, Scherer PE, Rossetti L. Endogenous glucose production is inhibited by the adipose-derived protein Acrp30. J Clin Invest 2001;108:1875–81.
[49] Stefan N, Stumvoll M, Vozarova B, Weyer C, Funahashi T, Matsuzawa Y, et al. Plasma adiponectin and endogenous glucose production in humans. Diabetes Care 2003;26:3315–9.
[50] Stefan N, Vozarova B, Funahashi T, Matsuzawa Y, Ravussin E, Weyer C, et al. Plasma adiponectin levels are not associated with fat oxidation in humans. Obes Res 2002;10:1016–20.
[51] Wang C, Mao X, Wang L, Liu M, Wetzel MD, Guan K-L, et al. Adiponectin sensitizes insulin signaling by reducing p70 S6 kinase-mediated serine phosphorylation of IRS-1. J Biol Chem 2007;282: 7991–6.
[52] Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, J.-i. Miyagawa K, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999;257: 79–83.
[53] Fasshauer M, Kralisch S, Klier M, Lossner U, Bluher M, Klein J, et al. Adiponectin gene expression and secretion is inhibited by interleukin-6 in 3T3-L1 adipocyte. Biochem Biophys Res Commun 2003;301:1045–50.
[54] Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, et al. PPAR{gamma} ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. Diabetes 2001;50:2094–9.
[55] Seo JB, Moon HM, Noh MJ, Lee YS, Jeong HW, Yoo EJ, et al. Adipocyte determination-and differentiation-dependent factor 1/sterol regulatory element-binding protein 1c regulates mouse adiponectin expression. J Biol Chem 2004;279:22108–17.
[56] Motoshima H, Wu X, Sinha MK, Hardy VE, Rosato EL, Barbot DJ, et al. Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. J Clin Endocrinol Metab 2002;87:5662–7.
[57] Halleux CM, Takahashi M, Delporte ML, Detry R, Funahashi T, Matsuzawa Y, et al. Secretion of adiponectin and regulation of apM1 gene expression in human visceral adipose tissue. Biochem Biophys Res Commun 2001;288:1102–7.
[58] Fasshauer M, Klein J, Neumann S, Eszlinger M, Paschke R. Hormonal regulation of adiponectin gene expression in 3T3-L1 adipocytes. Biochem Biophys Res Commun 2002;290:1084–9.
[59] Bluher M, Michael MD, Peroni OD, Ueki K, Carter N, Kahn BB, et al. Adipose tissue selective insulin receptor knockout protects against obesity and obesity-related glucose intolerance. Dev Cell 2002;3:25–38.
[60] Hotta K, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, Hansen BC, et al. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes 2001;50:1126–33.
[61] Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595–9.
[62] Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, et al. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. J Clin Endocrinol Metab 2001;86:3815–9.
[63] Rasouli N, Yao-Borengasser A, Miles LM, Elbein SC, Kern PA. Increased plasma adiponectin in response to pioglitazone does not result from increased gene expression. Am J Physiol Endocrinol Metab 2006;290:E42–6.
[64] Qiao L, MacLean PS, Schaack J, Orlicky DJ, Darimont C, Pagliassotti M, et al. C/EBP{alpha} regulates human adiponectin gene transcription through an intronic enhancer. Diabetes 2005;54:1744–54.
[65] Das K, Lin Y, Widen E, Zhang Y, Scherer PE. Chromosomal localization, expression pattern, and promoter analysis of the mouse gene encoding adipocyte-specific secretory protein Acrp30. Biochem Biophys Res Commun 2001;280:1120–9.
[66] Qiao L, Shao J. SIRT1 regulates adiponectin gene expression through Foxo1-C/enhancer-binding protein {alpha} transcriptional complex. J Biol Chem 2006;281:39915–24.
[67] Hug C, Wang J, Ahmad NS, Bogan JS, Tsao T-S, Lodish HF. T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. PNAS 2004;101:10308–13.
[68] Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 2003;423:762–9.
[69] Mao X, Kikani CK, Riojas RA, Langlais P, Wang L, Ramos FJ, et al. APPL1 binds to adiponectin receptors and mediates adiponectin signalling and function. Nat Cell Biol 2006;8:516–23.
[70] Cheng KKY, Lam KSL, Wang Y, Yu H, Carling D, Wu D, et al. Adiponectin-induced eNOS activation and nitric oxide production are mediated by APPL1 in endothelial cells. Diabetes 2007;56(5): 1387–94.
[71] Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med 2002;8: 1288–95.
[72] Tomas E, Tsao T-S, Saha AK, Murrey HE, Zhang Cc, Itani SI, et al. Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation. PNAS 2002;99:16309–13.
[73] Liu Y, Michael MD, Kash S, Bensch WR, Monia BP, Murray SF, et al. Deficiency of adiponectin receptor 2 reduces diet-induced insulin resistance but promotes type 2 diabetes. Endocrinology 2007;148: 683–92.
[74] Bjursell M, Ahnmark A, Bohlooly-Y M, William-Olsson L, Rhedin M, Peng X-R, et al. Opposing effects of adiponectin receptors 1 and 2 on energy metabolism. Diabetes 2007;56:583–93.
[75] Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 2007;13: 332–9.
[76] Moller DE. Potential role of TNF-alpha in the pathogenesis of insulin resistance and type 2 diabetes. Trends Endocrinol Metab 2000;11: 212–7.
[77] Kriegler M, Perez C, De Fay K, Albert I, Lu SD. A novel form of TNF/cachectin is a cell surface cytotoxic transmembrane protein: ramifications for the complex physiology of TNF. Cell 1988;53: 45–53.
[78] Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259:87–91.
[79] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel Jr RL, Ferrante Jr AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112:1796–808.
[80] Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003;112:1821–30.

[81] Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995;95:2409–15.
[82] Kern PA, Di G, Gregorio B, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-{alpha} expression. Diabetes 2003;52:1779–85.
[83] Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab 2001;280:E745–51.
[84] Arner P. Insulin resistance in type 2 diabetes — role of the adipokines. Curr Mol Med 2005;5:333–9.
[85] Vozarova B, Weyer C, Hanson K, Tataranni PA, Bogardus C, Pratley RE. Circulating interleukin-6 in relation to adiposity insulin action, and insulin secretion. Obes Res 2001;9:414–7.
[86] Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science 1996;271:665–8.
[87] Stephens JM, Lee J, Pilch PF. Tumor necrosis factor-alpha-induced insulin resistance in 3T3-L1 adipocytes is accompanied by a loss of insulin receptor substrate-1 and GLUT4 expression without a loss of insulin receptor-mediated signal transduction. J Biol Chem 1997;272:971–6.
[88] Peraldi P, Xu M, Spiegelman BM. Thiazolidinediones block tumor necrosis factor-alpha-induced inhibition of insulin signaling. J Clin Invest 1997;100:1863–9.
[89] Gao Z, He Q, Peng B, Chiao PJ, Ye J. Regulation of nuclear translocation of HDAC3 by I{kappa}B{alpha} is required for tumor necrosis factor inhibition of peroxisome proliferator-activated receptor {gamma} function. J Biol Chem 2006;281:4540–7.
[90] Kappes A, Loffler G. Influences of ionomycin, dibutyryl-cycloAMP and tumour necrosis factor-alpha on intracellular amount and secretion of apM1 in differentiating primary human preadipocytes. Horm Metab Res 2000;32:548–54.
[91] Cheung AT, Ree D, Kolls JK, Fuselier J, Coy DH, Bryer-Ash M. An in vivo model for elucidation of the mechanism of tumor necrosis factor-{alpha} (TNF-{alpha})-induced insulin resistance: evidence for differential regulation of insulin signaling by TNF-{alpha}. Endocrinology 1998;139:4928–35.
[92] Sethi JK, Hotamisligil GS. The role of TNF alpha in adipocyte metabolism. Semin Cell Dev Biol 1999;10:19–29.
[93] Pittas AG, Joseph NA, Greenberg AS. Adipocytokines and insulin resistance. J Clin Endocrinol Metab 2004;89:447–52.
[94] Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP. The pathophysiologic roles of interleukin-6 in human disease. Ann Intern Med 1998;128:127–37.
[95] Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab 1998;83:847–50.
[96] Mohamed-Ali V, Goodrick S, Bulmer K, Holly JMP, Yudkin JS, Coppack SW. Production of soluble tumor necrosis factor receptors by human subcutaneous adipose tissue in vivo. Am J Physiol Endocrinol Metab 1999;277:E971–5.
[97] Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327–34.
[98] Bastard J-P, Jardel C, Bruckert E, Blondy P, Capeau J, Laville M, et al. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. J Clin Endocrinol Metab 2000;85:3338–42.
[99] Rotter V, Nagaev I, Smith U. 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 2003;278:45777–84.
[100] Senn JJ, Klover PJ, Nowak IA, Mooney RA. Interleukin-6 induces cellular insulin resistance in hepatocytes. Diabetes 2002;51:3391–9.
[101] Tsigos C, Papanicolaou DA, Kyrou I, Defensor R, Mitsiadis CS, Chrousos GP. Dose-dependent effects of recombinant human interleukin-6 on glucose regulation. J Clin Endocrinol Metab 1997; 82:4167–70.
[102] Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. Eur J Clin Invest 2002;3:14–23.
[103] Petersen EW, Carey AL, Sacchetti M, Steinberg GR, Macaulay SL, Febbraio MA, Pedersen BK. Acute IL-6 treatment increases fatty acid turnover in elderly humans in vivo and in tissue culture in vitro. Am J Physiol Endocrinol Metab 2005;288:E155–62.
[104] Fasshauer M, Klein J, Lossner U, Paschke R. Interleukin (IL)-6 mRNA expression is stimulated by insulin, isoproterenol, tumour necrosis factor alpha, growth hormone, and IL-6 in 3T3-L1 adipocytes. Horm Metab Res 2003;35:147–52.
[105] De Benedetti F, Alonzi T, Moretta A, Lazzaro D, Costa P, Poli V, et al. Interleukin 6 causes growth impairment in transgenic mice through a decrease in insulin-like growth factor-I. A model for stunted growth in children with chronic inflammation. J Clin Invest 1997;99:643–50.
[106] Wallenius V, Wallenius K, Ahren B, Rudling M, Carlsten H, Dickson SL, et al. Interleukin-6-deficient mice develop mature-onset obesity. Nat Med 2002;8:75–9.
[107] Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. Nature 2001;409: 307–12.
[108] Steppan CM, Lazar MA. Resistin and obesity-associated insulin resistance. Trends Endocrinol Metab 2002;13:18–23.
[109] Patel L, Buckels AC, Kinghorn IJ, Murdock PR, Holbrook JD, Plumpton C, et al. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. Biochem Biophys Res Commun 2003;300:472–6.
[110] Meier U, Gressner AM. Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin ghrelin, adiponectin, and resistin. Clin Chem 2004;50:1511–25.
[111] Banerjee RR, Lazar MA. Dimerization of resistin and resistin-like molecules is determined by a single cysteine. J Biol Chem 2001;276: 25970–3.
[112] Banerjee RR, Lazar MA. Resistin: molecular history and prognosis. J Mol Med 2003;81:218–26.
[113] Rajala MW, Obici S, Scherer PE, Rossetti L. Adipose-derived resistin and gut-derived resistin-like molecule-{beta} selectively impair insulin action on glucose production. J Clin Invest 2003; 111:225–30.
[114] Banerjee RR, Rangwala SM, Shapiro JS, Rich AS, Rhoades B, Qi Y, et al. Regulation of fasted blood glucose by resistin. Science 2004; 303:1195–8.
[115] Pravenec M, Kazdova L, Landa V, Zidek V, Mlejnek P, Jansa P, et al. Transgenic and recombinant resistin impair skeletal muscle glucose metabolism in the spontaneously hypertensive rat. J Biol Chem 2003;278:45209–15.
[116] Rajala MW, Qi Y, Patel HR, Takahashi N, Banerjee R, Pajvani UB, et al. Regulation of resistin expression and circulating levels in obesity. Diabetes, and Fasting, Diabetes 2004;53:1671–9.
[117] Rangwala SM, Rich AS, Rhoades B, Shapiro JS, Obici S, Rossetti L, et al. Abnormal glucose homeostasis due to chronic hyperresistinemia. Diabetes 2004;53:1937–41.
[118] Satoh H, Nguyen MTA, Miles PDG, Imamura T, Usui I, Olefsky JM. Adenovirus-mediated chronic "hyper-resistinemia" leads to in vivo insulin resistance in normal rats. J Clin Invest 2004;114:224–31.
[119] Way JM, Gorgun CZ, Tong Q, Uysal KT, Brown KK, Harrington WW, et al. Adipose tissue resistin expression is severely suppressed in obesity and stimulated by peroxisome proliferator-activated receptor gamma agonists. J Biol Chem 2001;276:25651–3.
[120] Moore GB, Chapman H, Holder JC, Lister CA, Piercy V, Smith SA, et al. Differential regulation of adipocytokine mRNAs by

rosiglitazone in db/db mice. Biochem Biophys Res Commun 2001; 286:735–41.
[121] Le Lay S, Boucher J, Rey A, Castan-Laurell I, Krief S, Ferre P, et al. Decreased resistin expression in mice with different sensitivities to a high-fat diet. Biochem Biophys Res Commun 2001;289:564–7.
[122] Savage DB, Sewter CP, Klenk ES, Segal DG, Vidal-Puig A, Considine RV, et al. Resistin/Fizz3 expression in relation to obesity and peroxisome proliferator-activated receptor-{gamma} action in humans. Diabetes 2001;50:2199–202.
[123] Nagaev I, Smith U. Insulin resistance and type 2 diabetes are not related to resistin expression in human fat cells or skeletal muscle. Biochem Biophys Res Commun 2001;285:561–4.
[124] Vozarova de Courten B, Degawa-Yamauchi M, Considine RV, Tataranni PA. High serum resistin is associated with an increase in adiposity but not a worsening of insulin resistance in Pima Indians. Diabetes 2004;53:1279–84.
[125] Fain JN, Cheema PS, Bahouth SW, Lloyd Hiler M. Resistin release by human adipose tissue explants in primary culture. Biochem Biophys Res Commun 2003;300:674–8.
[126] Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. J Immunol 2005;174:5789–95.
[127] Lehrke M, Reilly MP, Millington SC, Iqbal N, Rader DJ, Lazar MA. An inflammatory cascade leading to hyperresistinemia in humans. PLoS Med 2004;1:e45.
[128] Yang RZ, Huang Q, Xu A, McLenithan JA, Eisen AR, Alkan S, et al. Comparative studies of resistin expression and phylogenomics in human and mouse. Biochem Biophys Res Commun 2003;310: 927–35.
[129] Janke J, Engeli S, Gorzelniak K, Luft FC, Sharma AM. Resistin gene expression in human adipocytes is not related to insulin resistance. Obes Res 2002;10:1–5.
[130] Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science 2005;307:426–30.
[131] Samal B, Sun Y, Stearns G, Xie C, Suggs S. Cloning and characterization of the cDNA encoding a novel human pre-B-cell colony-enhancing factor. Mol Cell Biol 1994;14:1431–7.
[132] Stephens JM, Vidal-Puig AJ. An update on visfatin/pre-B cell colony-enhancing factor, an ubiquitously expressed, illusive cytokine that is regulated in obesity. Curr Opin Lipidol 2006;17:128–31.
[133] Sun G, Bishop J, Khalili S, Vasdev S, Gill V, Pace D. Serum visfatin concentrations are positively correlated with serum triacylglycerols and down-regulated by overfeeding in healthy young men. Am J Clin Nutr 2007;85:399–404.
[134] Fernandez-Real JM, Moreno JM, Chico B, Lopez-Bermejo A, Ricart W. Circulating visfatin is associated with parameters of iron metabolism in subjects with altered glucose tolerance. Diabetes Care 2007;30:616–21.
[135] Berndt J, Kloting N, Kralisch S, Kovacs P, Fasshauer M, Schon MR, et al. Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. Diabetes 2005;54:2911–6.
[136] Arner P. Visfatin — a true or false trail to type 2 diabetes mellitus. [editorial]. J Clin Endocrinol Metab 2006;91:28–30.
[137] Varma V, Yao-Borengasser A, Rasouli N, Bodles AM, Phanavanh B, Lee M-J. Human visfatin expression: relationship to insulin sensitivity, intramyocellular lipids, and inflammation. J Clin Endocrinol Metab 2007;92:666–72.
[138] Frydelund-Larsen L, Akerstrom T, Nielsen S, Keller P, Keller C. Visfatin mRNA expression in human subcutaneous adipose tissue is regulated by exercise. Am J Physiol Endocrinol Metab 2007;292: E24–E31.
[139] Hug C, Lodish HF. Visfatin: a new adipokine. Science 2005;307: 366–7.
[140] Tatemoto K, Hosoya M, Habata Y, Fujii R, Kakegawa T, et al. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. Biochem Biophys Res Commun 1998;251:471–6.
[141] Kawamata Y, Habata Y, Fukusumi S, Hosoya M, Fujii R, Hinuma S, et al. Molecular properties of apelin: tissue distribution and receptor binding. Biochim Biophys Acta 2001;1538:162–71.
[142] Lee DK, Cheng R, Nguyen T, Fan T, Kariyawasam AP, Liu Y, et al. Characterization of apelin, the ligand for the APJ receptor. J Neurochem 2000;74:34–41.
[143] Hosoya M, Kawamata Y, Fukusumi S, Fujii R, Habata Y, Hinuma S, et al. Molecular and functional characteristics of APJ. Tissue distribution of mRNA and interaction with the endogenous ligand apelin. J Biol Chem 2000;275:21061–7.
[144] O'Carroll A-M, Selby TL, Palkovits M, Lolait SJ. Distribution of mRNA encoding B78/apj, the rat homologue of the human APJ receptor, and its endogenous ligand apelin in brain and peripheral tissues. Biochimica et Biophysica Acta (BBA) — Gene Struct Expr 2000;1492:72–80.
[145] Medhurst AD, Jennings CA, Robbins MJ, Davis RP, Ellis C, Winborn KY. Pharmacological and immunohistochemical characterization of the APJ receptor and its endogenous ligand apelin. J Neurochem 2003;84:1162–72.
[146] Boucher J, Masri B, Daviaud D, Gesta S, Guigne C, Mazzucotelli A, et al. Apelin, a newly identified adipokine up-regulated by insulin and obesity. Endocrinology 2005;146:1764–71.
[147] Castan-Laurell I, Boucher J, Dray C, Daviaud D, Guigne C, Valet P. Apelin, a novel adipokine over-produced in obesity: friend or foe? Mol Cell Endocrinol 2005;245:7–9.
[148] Higuchi K, Masaki T, Gotoh K, Chiba S, Katsuragi I, Tanaka K, et al. Apelin, an APJ receptor ligand, regulates body adiposity and favors the mRNA expression of uncoupling proteins in mice. Endocrinology 2007.
[149] Tamori Y, Sakaue H, Kasuga M. RBP4, an unexpected adipokine. Nat Med 2006;12:30–1 [discussion 31].
[150] Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature 2005;436:356–62.
[151] Abel ED, Peroni O, Kim JK, Kim YB, Boss O, Hadro E, et al. Adipose-selective targeting of the GLUT4 gene impairs insulin action in muscle and liver. Nature 2001;409:729–33.
[152] Gavi S, Stuart LM, Kelly P, Melendez MM, Mynarcik DC, Gelato MC, et al. Retinol-binding protein 4 is associated with insulin resistance and body fat distribution in non-obese subjects without type 2 diabetes. J Clin Endocrinol Metab 2007;92(5):1886–90.
[153] Graham TE, Yang Q, Bluher M, Hammarstedt A, Ciaraldi TP, Henry RR, et al. Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. N Engl J Med 2006;354:2552–63.
[154] Balagopal P, Graham TE, Kahn BB, Altomare A, Funanage V, George D. Reduction of elevated serum retinol binding protein (RBP4) in obese children by lifestyle intervention: association with sub-clinical inflammation. J Clin Endocrinol Metab 2007:2006–712.