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.

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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, compelling 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
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, glucokininase and phosphoenolpyruvate 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 adipocytes 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-stimulated 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 intron 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 adenosine-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 adenosine-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 hyperinsulinemia [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 secretory 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 dimer 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 adipokytone, 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


