

# Endocrinology of Adipose Tissue – An Update

## Authors

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## Key words

- obesity
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- RBP-4

## Abstract

Adipose tissue is the body's largest repository of energy and it plays an important role in total energy homeostasis. Moreover, it is now well recognized as an endocrine organ. A wide range of different factors including complex proteins as well as fatty acids, prostaglandins, and steroids are either synthesized *de novo* or converted

in adipose tissue and released into the blood stream. These so-called adipokines contribute to the development of obesity-related disorders, particularly type-2 diabetes (T2D) and cardiovascular disease. In this review, we present an overview on the endocrine functions of adipose tissue with a special focus on discoveries reported within the past 5 years.

## Introduction

For many years, adipose tissue was considered as a passive organ playing a metabolic role in total energy homeostasis. Its only function was believed to be the storage of excess energy as triglycerides, and its release according to need in the form of fatty acids.

Now, there has been a paradigm shift and it becomes increasingly clear that adipose tissue is an endocrine organ secreting a wide range of hormones and other factors [1,2]. These so-called adipokines contribute to the development of obesity-related disorders, particularly type-2 diabetes (T2D) and cardiovascular disease. Thereby, adipose tissue itself participates in the pathogenesis of obesity-associated co-morbidities [1, 2, 3].

In 2002, *Hormone and Metabolic Research* published a special issue on The Endocrinology of Adipose Tissue (Editorial [4]). It summarized the 20th century understanding of the hormonal cross-talk between fat cells and many other tissues such as endothelium, muscle, liver, pancreas, adrenal glands, and central nervous structures. A central message in that issue was that obesity represents a state of chronic inflammation, which may act as common soil for the development of insulin resistance and cardiovascular dysfunction. By then scientists had only preliminary data on the effects of dietary meas-

ures and of specific drugs that may be able to restore the dysregulated endocrine system of adipose tissue. It was hoped that through prevention and intervention the deleterious sequelae of obesity and, in particular, of the visceral accumulation of body fat, might be avoided.

Five years later, more than one hundred adipose tissue secretion products have been described including fatty acids, prostaglandins, and steroids, as well as complex proteins (○ Fig. 1). Some of these factors primarily have local auto- or paracrine effects in adipose tissue, while others are released into the circulation and exert specific effects at target organs or systemic effects. In this review, we present an overview of the endocrine functions of adipose tissue with special focus on findings obtained within the past 5 years.

## Old and new findings of adipose tissue cellularity

Adipose tissue mass is determined by competing processes regulating both the volume and the number of adipocytes. For many years the dogma claimed that the number of adipocytes is fixed during childhood, and remains constant throughout life. According to this model, changes in size of adipose tissue could only be achieved by modulation of adipocyte volume, which in turn is bal-

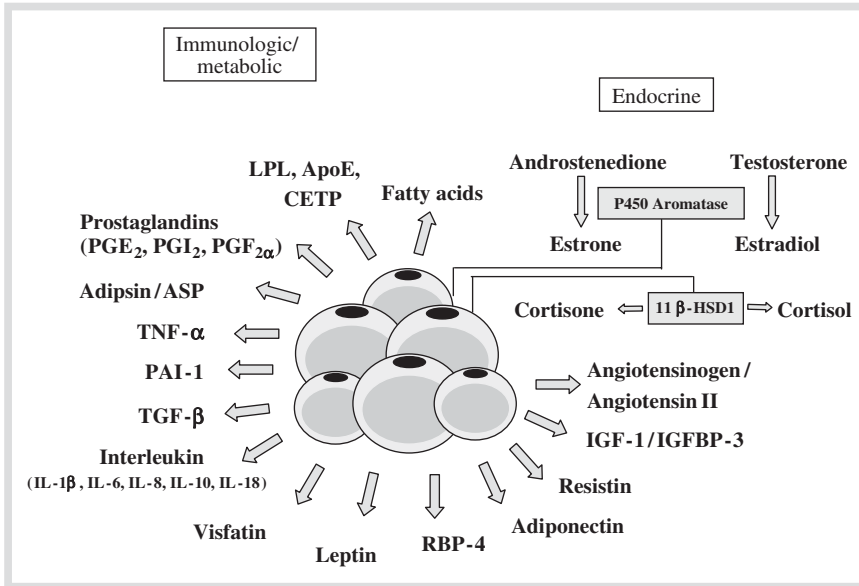
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**Fig. 1** Adipose tissue as an endocrine organ. More than one hundred adipose tissue secretion products have been described. Most factors are synthesized de novo while others are converted from precursor molecules. In mature adipocytes, 11- $\beta$ -hydroxysteroiddehydrogenase type 1 (11 $\beta$ -HSD1) catalyzes conversion of inactive cortisone into cortisol. Activity of P450 aromatase in preadipocytes results in conversion of male sex steroids (androstenedione, testosterone) into female sex steroids (estrone, estradiol). All factors might act locally in an auto-/paracrine manner or might exert systemic effects on metabolism, immunology, and endocrinology.

anced by storage of triglycerides (lipogenesis) and mobilization of fatty acids (lipolysis).

This model does not hold true any longer. In addition to changes in adipocyte volume, modulations of adipocyte number have been shown to occur throughout life [5, 6, 7, 8, 9]. Adipose tissue contains a large pool of precursor cells – multipotent mesenchymal stem cells and pre-determined preadipocytes – which are available for proliferation and differentiation into mature adipocytes upon appropriate stimulation [10]. These precursors can be detected in adipose tissue at all stages of life [9]. A reduction of adipocyte number can be achieved by a de-lipidation and de-differentiation of adipocytes [11]. On the other hand, there is now growing evidence that apoptosis of fat cells occurs in adipose tissue [6, 7, 8]. Therapeutically, an enhancement of adipocyte apoptosis during weight loss would be beneficial since the post-obese state is characterized by vulnerability of the adipose tissue for hyperplasia, associated with lower leptin production – a relative hypoleptinemia [12].

Thus, obesity is characterized by an enlargement of adipose mass by either fat cell hypertrophy or, in severe forms, by a combination of hypertrophy and hyperplasia [13]. Initially, an increase in body weight leads to hypertrophy of existing adipocytes. Once these cells exceed a critical cell size, unknown factors trigger the differentiation of precursor cells into mature adipocytes. Recent findings show that cell size seems to be critical for fat cell function [14, 15]. Thus, large fat cells are less sensitive to the metabolic effects of insulin and exert a higher basal rate of lipolysis in comparison to smaller fat cells [16]. Interestingly, there is also a marked difference in gene expression between small and large human adipocytes [17].

Besides mature, lipid-laden adipocytes and precursor cells, adipose tissue contains endothelial cells, nerve cells, and immune cells [5]. The latter are of special interest since it has become apparent that inflammation may underlie the development of obesity-related disorders. The existence of an inflammatory state of adipose tissue was proposed for the first time by Hotamisligil et al., [18] who showed constitutive production of TNF- $\alpha$  (tumor necrosis factor- $\alpha$ ) by white adipose tissue. Recently, it has been shown that obesity is associated with macrophage accumulation in white adipose tissue [19, 20, 21, 22]. The abundance of macrophages in the adipose tissue is positively

correlated with increased BMI (body mass index) [19, 22], and it has been shown that these macrophages significantly contribute to the secretion of pro-inflammatory cytokines from adipose tissue. At the clinical level, obese subjects show high serum levels of pro-inflammatory adipokines and reactive proteins, which are reversed by weight loss [23]. Thus, the so-called adipokines include not only adipocyte-specific factors but also secretion products derived from other cells types found in adipose tissue, such as preadipocytes or macrophages.

### Recently discovered important adipokines

#### ▼ Leptin

The identification of the leptin gene [24] and its cognate receptor [25, 26, 27] started the endocrine era of the adipocyte. Mice with mutations in the leptin gene (*ob/ob* mice) [24] or the leptin receptor gene (*db/db* mice) [25, 26, 27] are massively obese. These data have been extensively reviewed by Campfield et al. [131] in a special issue of *Hormone Metabolic Research* in 1996. Like in mice, congenital leptin deficiency in humans causes severe obesity, impaired thermogenesis, and insulin resistance; all are reversed by leptin treatment [28]. Although leptin was first regarded as a promising anti-obesity drug, administration of recombinant leptin to overweight and obese subjects was not efficacious in terms of weight loss [29] due to central leptin resistance. Potential mechanisms for leptin resistance have been proposed and include defective transport of leptin across the blood-brain barrier, defects in leptin signaling and central antagonism of leptin physiological actions. In that respect, *Socs3* was reported to be a molecular mediator of leptin resistance, suggesting that strategies to lower or inhibit the action of *Socs3* may be of value in the prevention and treatment of human obesity and associated insulin resistance [30, 31].

Besides its role in regulation of body weight, leptin regulates puberty and reproduction, placental and fetal function, immune response, and insulin sensitivity of muscle and liver. In hypoleptinemic patients with lipodystrophy, leptin replacement therapy resulted in a dramatic improvement in glucose metabolism, dyslipidemia, and hepatic steatosis [32]. An overview on the various

effects of the hormone has been given in a number of recent reviews [33, 34, 35].

Bouret et al. described an unanticipated regulatory role of leptin – that of a neurotrophic growth factor during development of the hypothalamus [36]. Leptin promotes formation of hypothalamic pathways that later convey leptin signals to brain regions regulating food intake and energy consumption. These observations are consistent with the concept that under- and over-nutrition during critical periods of hypothalamic development may induce long-lasting and potentially irreversible effects into adulthood.

### Adiponectin

Adiponectin, also referred to as Acrp30 [37], AdipoQ [38], apM1 [39], or GBP28 [40], was first identified by four independent groups using different approaches. It is specifically expressed in mature adipocytes with higher levels detected in subcutaneous rather than visceral fat [41]. It is released into the blood stream and accounts for ~0.01% of all serum proteins [42]. Adiponectin is a 30 kDa protein with an N-terminal collagen-like domain and a C-terminal globular domain. As such it structurally belongs to the collagen superfamily, which is known to form characteristic multimers [43, 44, 45]. Indeed, after posttranslational modification by glycosylation and hydroxylation [46] it creates, via its collagen domain, 3 major oligomeric forms: a low molecular weight (LMW) trimer, a middle molecular weight (MMW) hexamer, and a high molecular weight (HMW) 12–18-mer [47, 48]. In addition, a smaller, globular fragment of adiponectin has been detected, which accounts for ~1% of total circulating adiponectin [49, 50].

Two receptors for adiponectin, AdipoR1 and AdipoR2 have been cloned [51]. Both contain seven-transmembrane domains, but are functionally and structurally different from G protein-coupled receptors [51]. AdipoR1 is expressed in muscle and binds with high affinity to globular adiponectin and with low affinity to full-length adiponectin. AdipoR2 is expressed primarily in liver and binds full-length adiponectin and, with relatively low affinity, the globular form. Thus, the biological effects of adiponectin not only depend on relative circulating concentrations, but also on tissue-specific expression of its receptor subtypes.

In contrast to other adipokines, serum adiponectin is reduced with obesity, under conditions of insulin resistance and T2D, and cardiovascular disease in correlation with increasing severity [52, 53]. This reduction seems to precede the disorders [54]. Low levels of adiponectin, especially the HMW form, apparently predict the development of T2D and cardiovascular disease [55, 56, 57, 58, 59]. In addition, a close correlation of adiponectin levels has been shown with risk factors and components of the metabolic syndrome [53]. Weight loss results in an increase in adiponectin levels that is accompanied by an improvement in insulin sensitivity [53]. These findings demonstrate the important role of adiponectin in the pathogenesis of the metabolic syndrome. It is further supported by adiponectin gene polymorphisms, which may result in hypoadiponectinemia, insulin resistance, T2D, and cardiovascular disease [60, 61].

Numerous experimental studies have been performed investigating the effect of adiponectin and the underlying molecular mechanisms in several *in vitro* and *in vivo* models, as recently reviewed [49, 62]. An insulin-sensitizing effect of adiponectin was first identified by three independent groups in 2001 [50, 63, 64]. Many subsequent studies rounded up a large picture of adiponectin action in different tissues, as reviewed [49].

Globular, trimeric adiponectin or the HMW multimer binds to AdipoR1, which in turn stimulates interaction of the N-terminal cytoplasmic domain with an intracellular adaptor protein (APPL), containing a pleckstrin homology domain, phosphotyrosine-binding domain, and leucine zipper motif [65]. AdipoR2 is mainly activated by multimers of full-length adiponectin. Binding of adiponectin to its receptors causes activation of specific intracellular pathways, which include p38 MAPK, AMPK, and PPAR $\alpha$ . Subsequently, this leads to a reduction of plasma glucose levels by an increased glucose uptake and increased fatty acid oxidation in muscle, where AdipoR1 is predominantly expressed, and by increased fatty acid oxidation and decreased gluconeogenesis in liver.

As another beneficial aspect, adiponectin has been reported to exert antiatherosclerotic effects. It downregulates the expression of the vascular adhesion molecules: intracellular adhesion molecule-1, vascular cellular adhesion molecule-1, and E-selectin [66]. It inhibits endothelial NF $\kappa$ B signaling which might be a major mechanism for inhibiting monocyte adhesion to the vascular wall [67, 68]. Besides reduction of scavenger receptor class A-1 expression in macrophages [69], adiponectin inhibits proliferation and migration of smooth muscle cells [70].

Several findings suggest that adiponectin plays also an important role in innate and adaptive immunity [71]. It induces the production of important inflammatory cytokines, such as IL-10 and IL-10 receptor antagonist (IL-10 RA) by human monocytes, macrophages, and dendritic cells, and inhibits the generation of interferon- $\gamma$  by lipopolysaccharide (LPS) stimulated macrophages [72]. Adiponectin suppresses Toll-like receptor (TLR)-induced activation of NF $\kappa$ B [73]. It markedly reduces the phagocytic capacity of macrophages, decreased T-cell responses [72], and influences B-cell lymphopoiesis [74]. Taken together, these observations make adiponectin an important suppressor of inflammation, linking the paradoxical decrease of adiponectin levels in obesity to associated diseases such as insulin resistance, T2D, and atherosclerosis.

### Retinol binding protein 4 (RBP4)

In 2001, Abel et al. postulated the existence of an adipocyte-secreted factor that cause insulin resistance when they found that mice with an adipose-specific GLUT4 knockout developed insulin resistance in muscle and liver [75]. On the other hand, mice specifically overexpressing GLUT4 in adipose tissue exhibited an increased efficiency of glucose clearance [76]. DNA arrays of these two mice identified RBP4 [77]. RBP4 is a specific circulating transport protein for retinol (Vitamin A) [78]. RBP4 was upregulated in adipose tissue of adipose-*Glut4*<sup>-/-</sup> mice, and its serum levels were elevated in five independent mouse models of obesity and insulin resistance. Treatment with the insulin sensitizing PPAR $\gamma$  agonist rosiglitazone lowered RBP4 levels and normalized insulin sensitivity in mice lacking GLUT4, and injection of recombinant RBP4 to normal mice, or overexpression of RBP4, induced insulin resistance. On the other hand, mice with a heterozygous or homozygous RBP4 knockout showed increased insulin sensitivity. Most promising, fenretinide, a synthetic retinoid that is currently in trials as an antineoplastic agent, enhanced the urinary excretion of RBP4, lowered serum RBP4 in mice on a high-fat diet and markedly improved insulin sensitivity [77]. The expression of GLUT4 is greatly reduced in adipocytes but not in muscle cells of obese and insulin resistant mice and humans [79]. The recent study by Yang et al. suggests that adipose tissue might act as a glucose sensor: adipocytes detect the

absence of glucose by GLUT4 and respond by secreting RBP4. The latter inhibits insulin signaling by decreasing PI-3 kinase activity and insulin receptor substrate-1 (IRS-1) phosphorylation in muscle, while expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK) is upregulated in the liver [77]. Consequently, this might cause an increase in circulating blood glucose. Intensive research on the regulation of RBP4 secretion is necessary to support this interesting but still hypothetical model.

In human subjects retinol levels are elevated in patients with T2D [80,81]. A current genetic study has identified an SNP in the RBP4 gene that is associated with T2D in Mongolians [82]. RBP4 levels correlated with the magnitude of insulin resistance among humans with obesity, impaired glucose tolerance, or T2D and among nonobese nondiabetic subjects with a strong family history of T2D [83]. A confirmatory report showed that plasma RBP4 concentrations were higher in impaired glucose tolerance (IGT) and T2D [84], and elevated serum RBP4 was associated with components of the metabolic syndrome, including increased BMI, waist-to-hip ratio, serum triglyceride levels, systolic blood pressure and decreased high-density lipoprotein (HDL) cholesterol [83]. An association of exercise training with reduction of serum RBP4 was only observed in subjects with improved insulin resistance [83].

The observations concerning BMI are, however, controversial since two other groups found no correlation of serum RBP4 with BMI [85] or percentage of body fat [84]. Moreover, Janke et al. did not see a relationship between adipose tissue mRNA expression and serum RBP4, which led them to suggest that an increase in systemic RBP4 in insulin-resistant subjects could not be explained by increased RBP4 production in adipose tissue [85]. The same study found a reduced expression of GLUT4 in overweight or obese subjects, but a robust positive correlation between adipose GLUT4 and RBP4 expression that was completely independent of any other confounding variable, including BMI [85].

Despite all controversy, RBP4 represents a curious new adipokine in mice and humans. Further studies will help understanding its role in the pathogenesis of obesity-related disorders and show whether RBP4 might serve as a potential therapeutic target for the treatment of T2D.

### Visfatin

Searching for genes which are specifically expressed in visceral adipose tissue by differential display, Fukuhara et al. [86] reported that pre-B cell colony enhancing factor (PBEF) is highly expressed in human visceral fat. PBEF was originally cloned and characterized as a 52 kDa protein primarily expressed in bone marrow, liver, and muscle [87]. For years, it was considered a secreted cytokine whose levels increase during infection [88]. Rongvaux et al. proposed that the protein is a nicotinamide phosphoribosyltransferase [89], which was confirmed recently after determining its crystal structure [90].

PBEF was further referred to as "visfatin" [86], because protein levels were increased in visceral adipose tissue of a mouse model for obese T2D, and correlated with visceral fat area (but not subcutaneous fat area) in human subjects. Visfatin was upregulated during adipogenic differentiation, and plasma levels increased during the development of obesity. Visfatin exerts insulin-mimetic effects in cultured cells, i.e., stimulation of glucose uptake and triglyceride incorporation, and intravenous injection of recombinant visfatin to mice lowered plasma glucose within

30 minutes. This effect was accompanied by an increased expression of genes involved in adipogenesis, increased phosphorylation of IRS-1 and IRS-2 in liver, and activation of insulin signaling. Mice heterozygous for a targeted mutation in the visfatin gene had modestly higher levels of plasma glucose in comparison to wild-type littermates. The most intriguing finding was that visfatin binds to and activates the insulin receptor. Further investigations revealed that visfatin binds to the insulin receptor at a site distinct from insulin and with an affinity similar to insulin [86]. The insulin sensitizing effect of visfatin seems to be additive to the effect of insulin suggesting that visfatin may activate insulin-regulated pathways via a novel mechanism.

The original paper stimulated many groups to study the biology of visfatin, and several factors regulating visfatin synthesis have been identified. In 3T3-L1 adipocytes, TNF- $\alpha$ , IL-6, growth hormone, and  $\beta$ -adrenergic receptor agonists inhibited visfatin synthesis, while glucocorticoids had an opposite effect [91,92]. Studies in transgenic mice and humans have shown that cortisol might be locally synthesized from inactive cortisone by 11 $\beta$ -hydroxysteroiddehydrogenase type 1 (11 $\beta$ -HSD1) in visceral adipose tissue [93,94]. Thus, glucocorticoids might contribute to the upregulation of visfatin found in visceral obesity *in vivo* [86]. In 3T3-L1 cells, the PPAR $\gamma$  agonist troglitazone suppressed visfatin gene expression [92]. In contrast, treatment with rosiglitazone in healthy human subjects and incubation of isolated human adipocytes with rosiglitazone increased plasma visfatin expression and its secretion into the medium, respectively [95]. It has been shown that circulating visfatin concentrations are increased by hyperglycemia in healthy subjects and that this effect was blocked by exogenous hyperinsulinemia or somatostatin infusion [96].

The work of Fukuhara et al. also stimulated many groups to evaluate visfatin in their well characterized group of patients. In line with the original paper, some groups found elevated visfatin levels in patients with T2D [97, 98, 99]. Controversial results were found regarding a correlation of visfatin with the degree of obesity [97, 98, 99, 100, 101, 102]. Haider et al. detected elevated visfatin concentrations in patients with T1D, which were lowered by exercise [103]. Weight loss after gastric banding lowered increased plasma visfatin concentrations in morbidly obese patients [102]. Genetic studies have revealed that variations in the visfatin gene might have a minor effect on its mRNA regulation, but do not play a major role in the development of T2D [104].

Several open questions remain unanswered. It is not clear whether visfatin is regulated by thiazolidindiones. In 3T3-L1 cells, troglitazone lowered visfatin mRNA expression [92], while it was upregulated in isolated human adipocytes [95]. In patients with T2D, a 4-week treatment with rosiglitazone did not change plasma visfatin concentration [99]. It is controversial whether visfatin is differentially regulated in subcutaneous and visceral adipose tissue [100, 101]. An interesting twist suggested recently that visfatin is an inflammatory protein, and is predominantly secreted by macrophages [105].

In conclusion, visfatin has recently been identified as a new adipokine. Its role in the modulation of whole body insulin sensitivity and its contribution to the pathogenesis of insulin resistance still needs to be addressed carefully.

### Angiotensinogen (ANG)/Angiotensin II (ANG II)

Adipose tissue is an important site of angiotensinogen or angiotensin II production. Higher levels of angiotensinogen mRNA

levels are detectable in adipose tissue of obese subjects in comparison to lean subjects [106]. In addition, a positive association of BMI and circulating concentrations of angiotensinogen has been found in a clinical study [107]. Angiotensin II is a very potent vasoconstrictor and the risk for hypertension increases with BMI. Thus, it has been assumed that an increased synthesis of angiotensin II by adipose tissue might contribute to obesity-associated hypertension. In fact, overexpression of AGT in adipose tissue in mice resulted in elevated plasma AGT and hypertension [108]. In addition, ANG II seems to exert different pro-inflammatory effects locally in adipose tissue. ANG II stimulates production and secretion of PAI-1, leptin, IL-6 and IL8 in cultivated human adipocytes which can be abolished by blocking of angiotensin-receptor subtype 1 [AT(1)] [109, 110, 111]. In addition, ANG II increases oxidative stress and activates NF $\kappa$ B as well as NAD(P)H oxidase [112, 113].

The clinical relevance of all these findings is still not completely understood. However, in summary all these effects might help understand why lowering ANG II production by angiotensin-converting enzyme inhibitors (ACEIs) and AT(1) receptor blockade leads to improvement of chronic inflammation in practice [112, 113, 114].

### Proinflammatory cytokines

Adipose tissue produces a plethora of other factors which have their origin from either mature adipocytes or other cell types. Pro-inflammatory cytokines are coming to the fore, since obesity has been recognized as a state of low-grade inflammation, and adipose tissue has been accepted as a pathogenic site of obesity-related disorders [115].

In 1993, Hotamisligil et al. [18] showed an increased expression of TNF- $\alpha$  in adipose tissue of genetically obese rats. The idea that a factor produced from white adipose tissue is involved in the development of insulin resistance was revolutionary at that time. Since then, many other factors were described to be secreted from adipose tissue, including transforming growth factor- $\beta$  (TGF- $\beta$ ), interferon- $\gamma$  (IFN- $\gamma$ ), interleukins (IL), such as IL-1, IL-6, IL-10, and IL-8, monocyte chemoattractant protein-1 (MCP-1), and factors of the complement cascade (complement factor 3, metallothionein, angiopoietin-related proteins, plasminogen activator inhibitor-1, fibrinogen) [116, 117, 118, 119, 120].

The circulating levels of these pro-inflammatory factors increase with the enlargement of fat mass. Many of these pro-inflammatory factors are produced by adipocytes and also by activated macrophages. The relative amount of each remains unknown so far. The increase of cytokines together with the finding that obesity is associated with macrophage infiltration in adipose tissue suggests that obesity should be considered as a state of low-grade inflammation.

Indeed, it has been shown that increasing adiposity activates two typical pro-inflammatory pathways, c-jun NH<sub>2</sub>-terminal kinase (JNK) and I $\kappa$ B kinase- $\beta$  (IKK- $\beta$ ) [121, 122, 123, 124]. Concordantly, chemical or genetic inhibition of JNK or IKK- $\beta$ /NF $\kappa$ B (nuclear factor-kappa  $\beta$ ) improves insulin resistance. Several mechanisms have been hypothesized to explain how obesity activates these receptor pathways [TNF receptor, IL-1 receptor, TLR, receptor for advanced glycation end products (RAGE)] and receptor-independent pathways (for example reactive oxygen species, endoplasmic reticulum stress) [125].

Obesity induced IKK- $\beta$  activation results in NF $\kappa$ B translocation to the nucleus and to increased expression of potential mediators that could cause insulin resistance. Obesity-induced JNK activa-

tion, on the other hand, promotes phosphorylation of IRS-2, which in turn prevents normal insulin signal transduction.

The initial events of how obesity might activate inflammation in adipose tissue are not completely understood. One potential mechanism involves the initiation of a state of cellular stress by dietary excess and excess lipid accumulation in adipose tissue.

### Wnt signaling

The Wnt family of secreted signaling molecules has profound effects on diverse developmental processes, including the fate of mesenchymal progenitors. Activation of Wnt signaling inhibits adipogenesis [126]. Thus, transgenic mice in which Wnt10b is expressed from the FABP4 promoter show impaired development of adipose tissue and a decline of total body fat [127, 128]. Consistently, a non-functioning *WNT10B* allele was detected in a family affected by obesity [129].

Recently, Gustafson et al. have shown that IL-6 and TNF- $\alpha$  augmented Wnt signaling in 3T3-L1 preadipocytes thereby preventing adipogenic differentiation and lipid accumulation [130]. Both cytokines increased the expression of inflammatory genes in 3T3-L1 adipocytes [130]. The authors concluded that these findings might help understand the development of local and systemic inflammation as well as ectopic lipid accumulation in obesity.

### Concluding remarks

▼ Endocrinology of adipose tissue remains an exciting research area in which epoch-making findings are still expected. The recently discovered new functions of adipose tissue have elucidated its important role in a complex cross-talk between organs regulating the body's energy homeostasis, insulin sensitivity, lipid metabolism, and the immune system. Thus, adipose tissue and its secretion products have also become a target for drug development. Improved knowledge on the endocrinology of adipose tissue will have implications for the treatment of obesity, diabetes, and cardiovascular diseases.

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