Adipokines: The missing link between insulin resistance and obesity

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Abstract

White adipose tissue was believed to be just an energy-storage organ, but it is now recognized to be an active participant in energy homoeostasis and physiological functions such as immunity and inflammation. Macrophages are components of adipose tissue and actively participate in its activities. Adipose tissue is known to express and secrete a variety of products known as ‘adipokines’, including leptin, adiponectin, resistin and visfatin, as well as cytokines and chemokines such as tumor necrosis factor-alpha, interleukin-6 and monocyte chemoattractant protein-1. The release of adipokines by either adipocytes or adipose tissue-infiltrated macrophages leads to a chronic subinflammatory state that could play a central role in the development of insulin resistance and type 2 diabetes, and the increased risk of cardiovascular disease associated with obesity.

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1. Introduction

In spite of the considerable progress in their diagnosis, prevention and treatment, cardiovascular diseases remain the number one cause of death worldwide. This is partially due to the rapidly growing incidence of obesity, which is a well-known independent risk factor for insulin resistance, diabetes, dyslipidaemia, high blood pressure and thrombosis. The increasing incidence of obesity, leading to metabolic complications or ‘metabolic syndrome’, is now recognized as a major public health problem.

Adipose tissue is an active metabolic tissue that secretes multiple metabolically important proteins known as ‘adipokines’ [1,2]. Some adipokines play a major role in insulin resistance and cardiovascular complications associated with obesity, especially central or visceral obesity. There are several differences between visceral and subcutaneous tissue, including the expression of different genes involved in insulin resistance and inflammation.
Adipokines are proteins produced and secreted by adipocytes [1]. Several studies have shown that the production of some adipokines is affected in obesity, in type 2 diabetes and in the metabolic syndrome. (Fig. 1)

2.1. Leptin

One major breakthrough in the understanding of energy-balance regulation and adipose tissue biology was the description of leptin, a product of the ob gene [4]. Leptin is almost exclusively expressed and produced by white adipose tissue—specifically, by differentiated adipocytes [5]. Subcutaneous fat is responsible of 80% of total leptin production. This was shown in cultures ex vivo where the production of leptin was higher in subcutaneous adipocytes than in those of deeper origin. Leptin plasma concentration [6] and mRNA expression in adipose tissue [7] are directly related to obesity severity, as an increase of fat mass is associated with an increase of leptin, which makes leptin an indicator of total fat mass.

Although the principal biological effect of leptin in the central nervous system is the control of food intake and energy expenditure, there is a significant relationship between leptinemia and the chronic subinflammatory state in obesity, which suggests other possible, peripheral biological effects associated with its cytokine-like structure [5]. Indeed, an increased proinflammatory response has been observed in hyperleptinemia [8,9]. Although the mechanisms by which this association could be explained are not yet clearly identified, leptin is capable of controlling tumour necrosis factor (TNF-α) production and macrophage activation [8]. Moreover, it appears that TNF-α and interleukin (IL)-6 are capable of stimulating adipocyte leptin production [10,11]. Leptin could trigger endothelin-1 and nitric oxide (NO)-synthase synthesis, as well as oxygen-derivative molecular species production [12,13], monocyte chemotactic protein (MCP)-1 expression [14], and endothelial cell proliferation and migration [12,13]. In addition, leptin promotes platelet aggregation [12,13], and cholesterol accumulation in macrophages in hyperglycaemia [15] and in angiogenesis [16].

Taken all together, these observations suggest a potentially deleterious action of leptin on the arterial walls. On the other hand, leptin improves insulin sensitivity through activation of AMP protein kinase (AMPK), which controls cellular concentrations of malonyl-CoA, thereby inhibiting acetyl-CoA carboxylase (the enzyme involved in malonyl-CoA transformation) [17]. As a result, there is a decrease of intracellular malonyl-CoA and a decline of lipogenesis associated with increased fatty-acid beta-
oxidation. In fact, in generalized lipodystrophy, where adipose tissue is nearly absent, leptin administration improves insulin sensitivity [18]. This highlights the influence of this adipocyte hormone on whole-body glucose homoeostasis. However, in common human obesity, there are high circulating leptin levels, suggesting leptin resistance, and leptin administration has little or no effect on insulin resistance. In fact, the leptin-signaling pathway activates suppressor of cytokine signalling (SOCS)-3, which might inhibit insulin signaling [19]. Therefore, while leptin deficiency very likely contributes to insulin resistance when adipose tissue is lacking, leptin resistance is a main feature of human obesity. So far, the precise role of leptin in insulin resistance remains unclear.

2.2. TNF-α

TNF-α is a proinflammatory cytokine produced by numerous cells, but mainly macrophages and lymphocytes. Adipocytes also produce TNF-α in rodents, and in low quantities in humans. In rodents, TNF-α is involved in the pathophysiology of insulin resistance [20]. One of the possible mechanisms by which this cytokine interferes with insulin sensitivity is through abnormal phosphorylation of insulin receptor substrate (IRS)-1. However, as already mentioned, TNF-α is poorly expressed in human adipose tissue, with no differences in fat depots. Moreover, its expression is slightly modified in human obesity [21], and the absence of its production in subcutaneous adipose tissue in obese and lean men has been demonstrated by direct arteriovenous balance measures [22]. This indicates that adipose tissue is poorly or indirectly involved in the increased circulating concentrations of TNF-α seen in obesity. Nevertheless, it is necessary to bear in mind that TNF-α in experiments can accelerate atherosclerosis, mainly through induction of adhesion molecule expression [vascular cell adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1, MCP-1 and selectin-E] in endothelial and vascular smooth muscle cells, resulting in altered endothelium-dependent vasodilatation [23,24], and promotion of endothelial cell apoptosis [25,26].

2.3. Interleukin-6

Interleukin (IL)-6 is a cytokine produced by several cells (fibroblasts, endothelial cells, monocytes) and by adipose tissue, which is increased in obesity [1,2]. In the absence of an acute inflammatory process, approximately 15–30% of circulating IL-6 is from adipose tissue [22]. The ability to secrete IL-6 is higher in visceral than in subcutaneous adipose tissue [27,28]. However, adipose tissue is composed of numerous cells other than adipocytes, and most of the IL-6 comes from the stromal vascular fraction, composed of endothelial cells and monocytes/macrophages [27,28].

IL-6 is a multifunctional cytokine that targets several tissues and cell types. One of its major actions is control of the hepatic production of inflammatory proteins such as C-reactive protein (CRP). There is a positive relationship between IL-6 levels in adipose tissue and circulating CRP levels [29], which is an important cardiovascular risk factor [30]. Visceral adipose tissue produces three times more IL-6 than subcutaneous adipose tissue does [27]. This may explain, in part, the deleterious role of central obesity in cardiovascular diseases. Indeed, IL-6 visceral adipose tissue production could have a direct effect on hepatic metabolism as its venous drainage goes directly to the liver through the portal vein. Thus, IL-6 produced by intra-abdominal adipose tissue could directly contribute to visceral obesity-related hypertriglyceridaemia by stimulating hepatic secretion of triglycerides [very low-density lipoprotein (VLDL)] [31].

Recent studies suggest that IL-6 could be implicated in insulin resistance and its complications [32–34]. The IL-6 receptor belongs to the class I family of cytokine receptors, which uses Janus kinases (JAKs) as intracellular signaling pathways [35]. Studies have demonstrated an interaction between cytokines and insulin signaling pathways leading to decreased insulin signaling in the presence of cytokines. The mechanisms involved are not clear, but there is evidence to suggest the participation of protein kinases and tyrosine phosphatase activation [36] or SOCS interaction with the insulin receptor [37–39]. Chronic elevation of IL-6 plasma levels and the increased cardiovascular risk related to an inflammatory state could be causes of insulin resistance. In contrast, several studies performed in animal models and in humans showed that an acute IL-6 infusion increased skeletal muscle insulin sensitivity [40]. One of the potential mechanisms that may be involved in the stimulation of glucose transport activity by IL-6 is the activation of AMPK [41,42]. However, the highest IL-6 concentration obtained in muscle after exercise is less than 1% of the IL-6 concentration used in experiments in vitro [41], so the effect of IL-6 on glucose transport could be a pharmacological, rather than physiological, effect. It is also possible that the chronic elevation of IL-6 circulating levels, more than acute IL-6 secretion, has a weak or no effect in muscle in vivo, while it could contribute to whole-body insulin resistance, particularly in liver and adipose tissue.

2.4. Adiponectin

Adiponectin is a protein highly expressed in adipose tissue. Its plasma levels are between 5–30 mg/L in lean subjects and represent 0.01% of plasma proteins. It is present in the bloodstream in three main forms: trimer; hexamer; and high molecular weight. Adiponectin mRNA expression varies according to tissue site, being lower in visceral than in subcutaneous tissue [43].

In contrast to other adipokines, adiponectin is underexpressed in obese patients with insulin resistance or type 2 diabetes, and in patients with coronary heart disease. Like leptin, adiponectin enhances insulin sensitivity through activation of AMPK [44]. Adiponectin also affects hepatic glucose production by decreasing the mRNA expression of two essential gluconeogenesis enzymes: phosphoenolpyruvate carboxykinase; and glucose-6-phosphatase [45]. It appears that high-molecular-weight adiponectin may be the most insulin-sensitizing.

In addition to its effects on insulin sensitivity, adiponectin has a vascular-protective effect early in the atherogenesis process by interfering with the regulation of adhesion molecule expres-
sion on vascular endothelial cells [46] and the transformation of macrophages into foam cells [47], and by modulating smooth muscle cell proliferation [48]. Also, adiponectin could reduce the inflammatory response induced by TNF-α, as shown by studies in vitro where macrophage activity and TNF-α production were diminished in macrophages treated with adiponectin [49]. It appears that many adiponectin anti-inflammatory properties come from its anti-TNF-α effects, which could partially explain its protective role in atherosclerosis. On the other hand, adiponectin expression in human adipocytes is reduced by TNF-α and IL-6 [50].

The adiponectin receptors AdipoR1 and AdipoR2 have been cloned [51]. They are located in chromosomes 1q32 and 12p13, respectively. AdipoR1 has an ubiquitous expression with a higher proportion in muscle, whereas AdipoR2 is predominantly expressed in liver. Recently, AdipoR1 and AdipoR2 overexpression, or knockout, animal models have indicated that both proteins serve as the predominant receptors for adiponectin in vivo, and play important roles in the regulation of lipid and glucose metabolism, inflammation and oxidative stress [52,53]. While it is clear that AdipoR1, through AMPK activation, promotes insulin sensitivity, there are conflicting results in terms of the exact influence of AdipoR2 on the regulation of fatty-acid and carbohydrate metabolism.

2.5. Resistin

While searching for new thiazolidinedione targets in adipocytes, Steppan et al. [54] brought to light a gene encoding for resistin. The authors showed that resistin expression was increased in obese animals, and decreased in the presence of thiazolidinediones. In particular, administration of recombinant resistin to normal animals produced insulin resistance, whereas resistin immune neutralization improved insulin sensitivity in obese animals with insulin resistance. In adipocyte cultures, resistin decreased glucose transport in response to insulin, while an anti-resistin antibody produced the opposite effect. Moreover, resistin inhibits adipocyte differentiation [55]. This work was the first to illustrate resistin as a link between obesity and insulin resistance, and quickly led to contradictory publications. In contrast to the Steppan et al. [54] findings, various groups have observed a fall in resistin gene expression in obese and insulin resistance animal models. However, recombinant resistin caused severe hepatic insulin resistance in rodents [56].

A recent study observed a decrease in fasting glucose, improved glucose tolerance and enhanced insulin sensitivity in resistin-gene knockout mice [57]. The absence of resistin could allow activation of AMPK and reduce gene expression encoding for hepatic gluconeogenesis enzymes. In this case, resistin activity differed from that of leptin and adiponectin, both known to activate AMPK. Finally, resistin-deficient animals with high-fat-diet-induced obesity and insulin resistance had reduced fasting glucose compared with matched-weight controls, suggesting that resistin interferes in hyperglycaemia and obesity-related insulin resistance.

Resistin can directly injure endothelium not only by inducing synthesis and secretion of endothelin-1 by endothelial cells, but also by altering adhesion molecule VCAM-1 and MCP-1 expression [58]. In addition, resistin directly stimulates smooth muscle cell proliferation in the human aorta [59].

In humans, resistin studies have produced contradictory findings. First, there is debate over which tissues and cells are responsible for its secretion. Several groups have described the gene or protein expression in human adipose tissue, while others have observed the absence of, or poor, mRNA expression in this tissue. Other cell types in adipose tissue that could be responsible for the production of resistin are monocytes/macrophages [60].

Other points of discussion are resistin circulating levels, its expression in adipose tissue, and its relationship to insulin resistance, diabetes and obesity. Once again, it is difficult, given the current information, to come to any agreement. Although some studies reported an increase of resistin in obesity and type 2 diabetes, most did not show a correlation between resistin circulating levels and body mass index or insulin resistance.

2.6. Serum amyloid A (SAA)

SAA is an inflammatory acute-phase protein associated with systemic inflammation and atherosclerosis, and is used as a predictive marker in coronary accidents or cardiovascular events [61]. Circulating levels of SAA are significantly correlated with insulin resistance in obesity and type 2 diabetes [62]. SAA is expressed in adipose tissue, and this expression is largely increased in obesity and diabetes [63,64]. Also, SAA could participate in lipoprotein metabolic alterations, promoting the linking of HDL-cholesterol to macrophages, thus reducing their cardiovascular-protective effect.

2.7. Plasminogen activator inhibitor (PAI)-1

Fibrinolysis is a physiological antithrombotic process that allows fibrin clot breakdown when they are no longer needed for haemostasis. A decreased fibrinolytic capacity, as a result of increased circulating levels of PAI-1, is considered a cardiovascular risk factor [65]. Three sources of PAI-1 have been described in humans: hepatocytes, endothelial cells and adipose tissue, where adipocyte participation in PAI-1 production is not insignificant [66]. Several clinical surveys have shown that increased circulating levels of PAI-1 were frequently found in patients with central obesity [65,67]. However, the results of PAI-1 expression analysis in adipose tissue are more controversial. Whereas some studies showed an increased PAI-1 mRNA expression and secretion in visceral adipose tissue [68,69], others, using isolated adipocytes from subcutaneous adipose tissue, showed an increase in PAI-1 mRNA expression and secretion with respect to visceral origin cells [70]. Recently, a study in obese patients showed that visceral adipose tissue explants secreted more PAI-1 than those from subcutaneous adipose tissue, and the same tendency has been observed in isolated adipocytes from different sites [66]. In general, it appears that visceral adipose tissue expresses more PAI-1 than does subcutaneous tissue, but this difference could be due to non-adipocyte cell production, as discussed earlier for IL-6. PAI-1 knockout mice
are protected against developing obesity and insulin resistance [71], and numerous studies in humans have reported an association between PAI-1, and cardiovascular and metabolic disorders [65,67,72].

2.8. Angiotensinogen

Angiotensinogen is the precursor of angiotensin-I which, after conversion to angiotensin-II, plays a major role in blood-pressure regulation. Angiotensinogen mRNA expression is increased in visceral fat [73,74], which partially explains the relationship between systemic hypertension and obesity in the metabolic syndrome.

Angiotensinogen knockout mice with selective overexpression of angiotensinogen in adipose tissue develop obesity with a high-fat diet and especially hypertension, which is compatible with involvement of adipose-tissue angiotensinogen secretion in the genesis of this phenotype [75].

2.9. Visfatin

Shimomura et al. recently identified a new adipokine that is mainly synthesized and secreted in visceral fat [76] — hence, the name ‘visfatin’. This factor is present in both human and murine plasma, and is the result of adipocyte differentiation.

Plasma visfatin levels were strongly correlated with fat mass, as measured by tomography scans, while a weak relationship was observed with subcutaneous fat mass [76]. Nevertheless, these results remain controversial [77–82]. In both genetic and nutritional obesity models, visfatin expression is induced only in visceral adipose tissue.

Intravenous infusion of visfatin in normal mice leads to an acute fall of glucose, independent of insulin secretion [76]. This hypoglycaemic effect has been seen in insulin-resistant (KKAy) or insulinopenic (streptozotocine) models. Furthermore, mice chronically infected with an adenovirus encoding for visfatin have duplicate plasma levels of this hormone, and significantly reduced glucose and insulin levels.

Visfatin-deficient animals (−/−) are not compatible with life. Heterozygous animals (visfatin +/-) have two-thirds lower visfatin blood levels than wild-type mice. On the other hand, growth rate, total body weight, food intake, and brown fat levels in omental adipose tissue were higher in visfatin (+/−) mice.

Similarly to insulin, visfatin in vitro enhanced glucose uptake by myocytes and adipocytes, and inhibited hepatocyte glucose release [76]. In addition, visfatin amplifies adipocyte differentiation. Its insulin-like effects are also observed in the insulin-transduction pathway, as this hormone induces tyrosine phosphorylation of insulin receptors IRS-1 and -2, and activation of phosphatidylinositol-3-kinase, protein kinase B and MAP kinase. Surprisingly, visfatin and insulin have the same affinity for the insulin receptor, with visfatin physically interacting with the receptor, but at a different site.

Despite these similarities between visfatin and insulin, there are also important differences [76]. For instance, visfatin levels do not significantly change in fed or fasting states. Plasma levels of visfatin are lower, 10% of insulin levels in a fasting state and 3% in a fed state. These differences in plasma concentrations could account for the mild effect of visfatin in glycaemia. Although it is too early to consider this adipokine in the development of hypoglycaemic drugs, recent research has shown that serum visfatin increases with progressive beta-cell deterioration in type 2 diabetic patients [83].

It could also be that the main functions of visfatin do not involve metabolism. Indeed, in adipose tissue, visfatin is preferentially expressed by macrophages rather than mature adipocytes [84]. In fact, visfatin was originally identified as a pre-B-cell colony-enhancing factor (PBEF) that acts as a growth factor for early-state B cells [85]. PBEF is also expressed in neutrophils from critically ill patients with sepsis in whom rates of apoptosis are profoundly delayed [86]. Recombinant PBEF exerts anti-apoptotic effects through inhibition of caspases-3 and -8. PBEF is, thus, an inflammatory cytokine that plays an essential role in delayed neutrophil apoptosis in clinical and experimental sepsis [86,87]. It could also represent a useful biomarker in acute lung injury [88], and is also highly expressed in carotid plaques from symptomatic individuals within lipid-rich macrophages [89]. There is also a relationship between visfatin and unstable lesions in patients with coronary heart disease, and visfatin can increase matrix metalloproteinase-9 activity in monocytes, and TNF-α and IL-8 in peripheral blood mononuclear cells [89]. All these studies strongly suggest that visfatin could be primarily regarded as an inflammatory mediator involved in several pathological processes.

2.10. Vaspin

Vaspin is an adipokine recently identified as a member of the serine protease-inhibitor family [90]. It is strongly expressed in visceral adipose tissue and is stimulated in mouse [90] and human [91] obesity. Its tissue expression and plasma levels are normalized in the presence of insulin or an insulin-sensitizing drug (pioglitazone) [84]. Moreover, vaspin injected into mice with high-fat-diet-induced obesity improves insulin resistance and carbohydrate tolerance [90].

2.11. Omentin

Omentin cDNA has been identified from wide-scale screening of the human omental-fat cDNA library [92,93]. Omentin transcripts are strongly expressed in visceral adipose tissue, but poorly in subcutaneous fat. Omentin is present in the stromal vascular cells of omental adipose tissue, but not in mature fat cells. Human omentin is a peptide of 313 amino acids, and contains a secretory signal sequence and a fibrinogen-related domain. It is secreted in the culture medium of omental, but not subcutaneous, fat explants. Interestingly, it increases insulin-stimulated glucose uptake in both omental and subcutaneous adipocytes, and promotes Akt phosphorylation [92].

Lean subjects have higher plasma omentin levels than do obese and overweight patients [94]. Plasma omentin levels were inversely correlated with body mass index, waist circumference,
leptin levels and insulin resistance as measured by HOMA-R, and positively correlated with adiponectin and HDL-cholesterol levels. Accordingly, omentin gene expression is decreased with obesity.

2.12. Retinol binding protein (RBP)-4

Adipose-GLUT4 (−/−) knockout mice develop liver and skeletal muscle insulin resistance, while plasma levels of adipokines known to influence insulin sensitivity remain normal. This observation suggests the existence of another factor secreted by adipocytes that interferes with insulin sensitivity. Thereafter, elevated protein RBP-4 plasma levels, synthesized and secreted by adipose tissue, were observed, which suggests an association with insulin resistance in this mouse model [95]. RBP-4 serum levels are elevated in insulin-resistant rodents, and in obese or type 2 diabetic humans. In fact, there is a positive correlation between RBP-4 plasma levels and insulin-resistance severity in obese, glucose-intolerant, type 2 diabetics and in nonobese subjects with a strong family background [96]. Physical exercise reduces RBP-4 levels with improvement of insulin sensitivity [96]. The use of rosiglitazone, an insulin-sensitizing drug, normalized elevated RBP-4 plasma levels. Injection of recombinant RBP-4 into a wild-type mouse caused insulin resistance, whereas gene invalidation provoked improvement of insulin sensitivity. Treatment with fenretinide, a synthetic retinoid that normalizes RBP-4 by increasing its urinary excretion, improved insulin sensitivity in obese rodents. Thus, RBP-4 protein could participate in type 2 diabetes pathophysiology, and might be a new therapy target for the condition.

To summarize the main data currently available for adipokines, it is clear that there is a link between obesity and insulin resistance, and that adipokines very likely contribute to lipid and carbohydrate metabolism. Apparently, increased TNF-α and IL-6 expression and secretion from adipose tissue are involved in both whole-body and local insulin resistance at different tissue sites. On the other hand, adiponectin induces insulin sensitivity, and is the only adipokine known to decrease obesity-related insulin resistance. Besides its metabolic effects, this hormone may also exert antiatherogenic effects. Other adipokines participate in cardiovascular complications such as PAI-1, which has been extensively studied in both animal models and humans (see references [65] and [67] for reviews). Although angiotensinogen from adipose tissue may play a role in hypertension in rodent models, this has not been demonstrated in humans. As for the other recently described adipokines such as resistin, SAA, visfatin, vaspin, omentin and RBP-4, further information is required to interpret their precise metabolic roles.

3. Macrophage infiltration of adipose tissue in obesity

Macrophage infiltration of white adipose tissue is an important feature of the low-grade inflammation of obesity, and is the principal source of IL-6 and TNF-α, which induce insulin resistance in adipocytes. Moreover, body mass index (BMI) is well correlated with the number of macrophages in adipose tissue. However, the cellular and molecular mechanisms involved in such infiltration are poorly understood. It seems that the C-C chemokine receptor 2 (CCR2) and its ligand CCL2 or MCP-1 are necessary for accumulation of inflammatory macrophages [97–101]. MCP-1 and CCR2 knockout mice have fewer macrophages in adipose tissue and low inflammatory gene expression [102].

Like other tissues, adipose tissue has resident macrophages, the function of which is not clear, but they appear to have an anti-inflammatory profile or are ‘alternatively activated’ (M2 phenotype, producing anti-inflammatory cytokines such as IL-10), and may be involved in the remodeling and homeostasis of tissue. Lumeng and co-workers have recently described in diet-induced obese mice that obesity development can provoke a switch from the M2 phenotype to the M1, ‘classically activated’, phenotype, enhancing proinflammatory cytokine production and generating reactive oxygen species. This increase of MCP-1 and CCR2 production leads to recruitment of monocytes/macrophages and production of proinflammatory cytokines [103].

Interestingly, weight loss, even of just a few pounds, not only leads to an improvement of the inflammation in obesity and its comorbidities, but also to a decrease in inflammatory gene expression [99]. Three months after gastric bypass surgery, a reduction of macrophages in the adipose tissue of obese patients was observed, with a decrease in immune-response gene expression, especially those involved in macrophage aggregation [100]. Also, thiazolidinediones are likely to reduce inflammatory gene expression in adipose tissue [104].

At present, it appears that the overwhelming production of proinflammatory cytokines by the adipose tissue of obese animals or individuals, along with a failing production of anti-inflammatory cytokines, may be involved in the pathophysiology of insulin resistance.

4. Inflammation and insulin-resistance signaling pathways

Several researchers have attempted to explain the molecular mechanisms associated with the insulin-resistance-related inflammatory process. Receptors involved in the immune response trigger the transduction pathways that activate the phosphorylation process and transcriptional factors. Proinflammatory cytokines, via activation of their transduction pathways, are able to alter insulin signaling by inactivating IRS through serine/threonine phosphorylation.

Many serine/threonine kinases are involved in the inhibition of phosphorylation of insulin signaling: IKKβ (I-kappa-β kinase), JNK (c-Jun NH2-terminal kinase) and protein kinase C-δ (PKC-δ). IKK and JNK are associated with transcriptional factors nuclear factor (NF)-κB and activating protein (AP)-1, respectively. Both factor pathways are activated in obesity, not only in response to adipokines, but also by increased free fatty-acid concentrations and oxidative stress.

Heterozygous deletion of IKKβ (+/−) can protect against the development of insulin resistance in high-fat-diet-induced and genetically obese ob/ob mice [105]. On the other hand, specific activation of IKKβ in adipose tissue or liver, but not in skeletal muscle, leads to a switch from the M2 to the M1 phenotype, producing anti-inflammatory cytokines such as IL-10.
muscle, can provoke systemic insulin resistance. Correspondingly, selective inhibition of NF-κB in adipose tissue and liver, but not in skeletal muscle, can protect against the development of insulin resistance in nutritional and genetic models of obesity [106].

JNK activity, especially of the JNK1 isoform, is increased in obese mice. JNK1 knockout mice presented partial resistance against obesity, hyperglycaemia and hyperinsulinaemia even in high-fat-diet-induced or genetic obesity [107]. In addition, the liver JNK suppression pathway reduced insulin resistance in diabetic models [108]. As well as its link with insulin resistance, JNK activity regulates insulin production, while selective inhibition of JNK improves insulin production in the pancreatic islets of obese mice in response to glucose.

Involvement of these inflammation pathways in insulin resistance is also suggested by the protective effect of certain anti-inflammatory agents. Indeed, aspirin is not only capable of suppressing IKK and JNK pathways [109,110], but it can also inhibit other serine/threonine kinase activity involved in TNF-α-induced insulin resistance. Furthermore, thanks to its antioxidant properties, aspirin also reduces NF-κB and AP-1 activation by oxidative stress. Aspirin is capable of reducing severe insulin resistance in obese rodent models. In humans, elevated doses of aspirin improved insulin sensitivity in type 2 diabetes [111]. However, the precise mechanism of action of acetylsalicylic acid in carbohydrate metabolism and insulin sensitivity needs further research [112]. Other drugs like thiazolidinediones and statins also have anti-inflammatory properties that could help their metabolic effects.

5. Endoplasmic reticulum stress and insulin resistance

What are the mechanisms that give rise to an inflammatory response in obesity? In other words, how do adipocytes integrate the signal of disrupted metabolic homeostasis into activation of the IKK and JNK pathways, and a chronic inflammation process? Recent research shows that endoplasmic reticulum (ER) is the cellular structure that detects and transmits the signal, and activates pathways such as IKK and JNK.

ER is a cellular organelle involved in the synthesis and processing of secretory and membrane proteins. Certain conditions such as nutritional deficiency, viral infections, hypoxia or excess secretory proteins can lead to impairment of ER function, where proteins are unable to fold properly and, instead, accumulate in the ER lumen. To cope with ER stress, cells trigger a series of pathways known as the ‘unfolded protein response’ (UPR). The UPR activates the inflammatory signal-transduction system, JNK–AP-1 and IKK–NF-κB. Given the adipocyte capacity for protein and ‘lipid’ synthesis and secretion, ER of a differentiated adipocyte is challenged and may be enhanced to meet the increased demand. In the case of obesity, this demand may be even more dramatic as there is an excessive lipid accumulation and changes in adipose tissue structural organization [113]. Furthermore, in nutritional or genetic obesity animal models, there are several biochemical and molecular markers of ER stress [113,114]. During the course of obesity, ER could thus represent a key sensor of cellular lipid flux. In the case of insulin resistance, in vitro experiments have shown that induction of ER stress with pharmacological agents (tunicamycin or thapsigargin) leads to increased IRS-1 serine residues phosphorylation and alter insulin signaling. Depletion of cellular X-box-binding protein (XBP)-1 had the same effect. XBP-1 is the key transcriptional factor that regulates gene expression of several factors involved in ER stress. Insulin resistance, whether pharmacologically induced or related to XBP-1 depletion, uses the JNK pathway. Clearly, overexpression of active XBP-1 protects against ER stress-induced insulin resistance [113].

Approaches in vivo also support a causal relationship between ER stress and insulin resistance. Indeed, in response to a high-fat diet, XBP-1 /− mice are more susceptible than XBP-1 /+ mice to the development of ER stress, insulin resistance and hyperglycaemia. Furthermore, XBP-1 /− mice have altered insulin signaling in liver and adipose tissues.

Other animal models have demonstrated the role of ER stress in insulin resistance and type 2 diabetes. Oxygen-regulated protein (ORP) 150 is a molecular chaperone of the ER regulated by hypoxia, and is also known to protect against ER stress. ORP150 overexpression in diabetic models improved insulin sensitivity, whereas its low expression induced insulin resistance [114,115].

Furthermore, chemical chaperones such as 4-phenyl butyric acid and certain bile acids known to enhance ER protein maturation can normalize hyperglycaemia and restore systemic insulin sensitivity in rodent models of obesity [116]. Moreover, these agents improved insulin signaling in liver, skeletal muscle and adipose tissues.

These observations can have several consequences. First, ER could be a favoured site for cellular metabolic stress to be translated into an inflammatory response through JNK activation. This could serve as a way to better understand the obesity components that lead to ER stress and its pathological consequences. Finally, exploring ER function and proteins may offer new possibilities for therapeutic applications.

6. Conclusion

Research in adipose tissue, and particularly adipokines, has strongly changed our understanding of the pathophysiological relationships between increased adipose tissue in obesity, inflammation, insulin resistance and their complications, mainly cardiovascular. The discovery of macrophage infiltration in adipose tissue in obesity was a major step towards new research perspectives both for a better understanding of the pathophysiology of obesity and for the development of new therapeutic approaches. Adipokines, which are directly produced by adipocytes or adipose tissue macrophages, induce a low-grade chronic inflammatory state that could play a central role in obesity-related cardiovascular complications and insulin resistance. This provides potential new therapeutic targets. However, further studies focused on analyses of subcellular structures and the intracellular signaling pathways involved in the inflammation process are needed. In the same way, it is necessary to determine the mechanisms responsible for the macrophage infiltration of adipose tissue in obesity, and the role of such cellular infiltration in the increased fat mass and pathophysiology of obesity.
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