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2

Functions of Adipose Tissue and Adipokines in Health and Disease

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1. Introduction

The notion of white adipose tissue (WAT) as an active contributor to whole-body homeostasis, rather than as a mere fat depot, began to take identity with the discovery of leptin in 1994 [1]. This 16 kDa protein secreted by adipocytes was found to be the product of the gene obese (ob), which is mutated in a murine form of hereditary obesity. From this point on, WAT has been found to produce more than 50 cytokines and other molecules. These "adipokines" participate, through endocrine, paracrine, autocrine or juxtacrine mechanisms of action, in a wide variety of physiological or physiopathological processes, including food intake, insulin sensitivity, vascular sclerotic processes, immunity and inflammation [2,3,4]. They are currently considered to play a crucial role in crosstalk among the adrenal, immune and central and peripheral nervous systems, among others.

Obesity, the condition originally motivating the spate of research on WAT, is now regarded as a pro-inflammatory state, several markers of inflammation having been found to be elevated in obese subjects [5]. It is thought that excess WAT can contribute to the maintenance of this state in three ways: through inflammation-inducing lipotoxicity; by secreting factors that stimulate the synthesis of inflammatory agents in other organs; and by secreting inflammatory agents itself. Adipokines include a variety of pro-inflammatory peptides (including TNFα, secretion of which by adipocytes was observed even before the discovery of leptin [6]). These pro-inflammatory adipokines appear to contribute significantly to the "low-grade inflammatory state" of obese subjects with metabolic syndrome [7], a cluster of metabolic abnormalities including insulin resistance, dyslipidaemia and alteration of coagulation that is associated with increased risk of cancer, type II diabetes, cardiovascular complications and autoimmune inflammatory diseases.

WAT also produces, possibly as an adaptive response, anti-inflammatory factors such as IL1 receptor antagonist (which binds competitively to the interleukin 1 receptor without

triggering activity within the cell) and IL10 (circulating levels of which are also elevated in obese individuals).

2. Cellular and molecular alterations of white adipose tissue in obesity

One of the consequences of the production and local release of cytokines and adipokines by adipocytes is the recruitment of large numbers of immune cells, including monocytes and T-lymphocytes, into adipose tissue. In particular, pro-inflammatory cytokine levels and macrophage density in visceral fat depots are much higher than in subcutaneous adipose tissue. While the mechanisms underlying the recruitment and activation of macrophages in adipose tissue remain poorly understood, there is emerging evidence that adipose tissue-secreted chemokines are largely responsible for the recruitment, retention and activation of macrophage precursors (monocytes) in fat. Monocyte chemoattractant protein-1 (MCP-1) has been implicated as one of the major mediators of the monocyte recruitment that occurs in adipose tissue, while macrophage colony stimulating factor (M-CSF) is believed to mediate the conversion of monocytes to macrophages in adipose tissue. Other candidate adipocyte-derived molecules that have also been implicated in macrophage recruitment/activation in adipose tissue include free fatty acids and lipoprotein lipase.

The primary function of resident macrophages of adipose tissue remains still unclear. It has been proposed that macrophages clear dead (apoptotic and necrotic) cells. Actually, adipocytes undergoing necrosis secondary to hypertrophy may lead to macrophage activation (with the accompanying release of inflammatory mediators) and their subsequent elimination from adipose tissue Another potentially important role of adipose tissue macrophages is modulation of adipocyte function. Cross-talk between adipocytes and macrophages is evidenced by the ability of each cell type to enhance the production of protein mediators by the other. For instance, adipocyte conditioned media can elicit large increases in the production/release of TNFa, IL-6 and NO by macrophages, while TNF-a released from macrophages inhibits the production of adiponectin by adipocytes. Likely consequences of this cross-talk between macrophages and adipocytes include amplification and perpetuation of the inflammatory phenotype that is induced by the expanding mass of body fat.

In humans, macrophage infiltration is correlated with both adipocyte size and BMI and is reduced after surgery-induced weight loss in morbidly obese subjects. There is also a preferential infiltration of macrophages into omental *vs.* subcutaneous fat, a phenomenon exaggerated by central. The majority of macrophages in obese adipose tissue aggregates in "crown-like structures" completely surrounding dead (necrotic-like) adipocytes and scavenging adipocyte debris.

3. Leptin

Leptin is a 16 kDa non-glycosylated peptide hormone encoded by the gene obese (ob), the murine homologue of the human gene LEP [1]. Structurally, it belongs to the class I cytokine superfamily, consisting of a bundle of four α-helices. It is mainly produced by adipocytes, and circulating leptin levels are directly correlated with WAT mass. It decreases food intake and increases energy consumption by acting on hypothalamic cell populations [8,9], inducing anorexigenic factors (CART, POMC) and inhibiting orexigenic neuropeptides

(NPY, AGRP and orexin), and leptin levels are negatively correlated with glucocorticoids [10] and positively with insulin [11]. Its own synthesis is mainly regulated by food intake and eating-related hormones, but also depends on energy status, sex hormones (being inhibited by testosterone and increased by ovarian sex steroids) and a wide range of inflammation mediators [12, 13] (being increased or suppressed by pro-inflammatory cytokines depending on whether their action is acute or chronic). Through the mediation of these latter agents, leptin synthesis is increased by acute infection and sepsis. As a result of the effects of sex hormones, leptin levels are higher in women than in men even when adjusted for BMI, which may be relevant to the influence of sex on the development or frequency of certain diseases [14], such as osteoarthritis [56]. Thus leptin appears to act not only as an adipostatin, the function in relation to which it was discovered, but also as a general signal of energy reserves [2] that is involved in a wide variety of other functions, including glucose metabolism, the synthesis of glucocorticoids, the proliferation of CD4+ T lymphocytes, cytokine secretion, phagocytosis, regulation of the hypothalamic-pituitary-adrenal axis, reproduction, and angiogenesis [15]. It can accordingly be described as a cytokine-like hormone with pleiotropic actions.

Leptin exerts its biological actions by binding to its receptors. These are encoded by the gene diabetes (db) and belong to the class I cytokine receptor superfamily, which includes receptors for IL6, LIF, CNTF, OSM, G-CSF and gp130. Alternative splicings of db give rise to six receptor isoforms: the soluble form Ob-Re, which lacks a cytoplasmic domain; four forms with short cytoplasmic domains (Ob-Ra, Ob-Rc, Ob-Rd and Ob-Rf); and the long form Ob-Rb, which is found in almost all tissues and appears to be the only form capable of transducing the leptin signal.

As in the case of other class I cytokine receptors, the main routes by which Ob-Rb appears to transmit the extracellular signal it receives are JAK-STAT pathways [16], which involve JAK2 phosphorylating tyrosines in the cytoplasmic domain of the receptor. In particular, mutation of the intracellular tyrosine Y1138 of murine Ob-Rb prevents STAT3 activation and results in hyperphagia, obesity and impaired thermoregulation, and replacing Y1138 with a serine residue likewise causes pronounced obesity in knock-in mice. However, since Y1138S knock-in mice do not exhibit other defects of db/db mice, such as infertility, the role of leptin in the processes that are disrupted in these latter conditions must be independent of STAT3 [17]. Indeed, the other two cytoplasmic tyrosines of murine Ob-Rb, Y985 and Y1077, have been shown to bind other intracellular signalling molecules [16, 18]. The early studies of leptin focused on its anorexigenic action. Both in humans and rodents, leptin levels are closely correlated with body mass index, and defects of the genes encoding for leptin and its receptors give rise to severe obesity and diabetes. Treating leptin-deficient mice with leptin induces a reduction in food intake accompanied by an increase in metabolic rate and weight loss. Mutations of these genes in humans appear to be rare, but the cases that are known have occurred in families with a high prevalence of morbid obesity; again, leptin administration has ameliorated all the problems associated with leptin deficiency. As noted in previous sections, leptin participates in the control of food intake by acting on an intricate neuronal circuit involving hypothalamic and brainstem nuclei [19], where it integrates a variety of different orexigenic and anorexigenic signals.

Leptin therapy is not an effective treatment for morbid obesity that is not due to congenital deficiency of leptin or leptin receptors. In these noncongenital types of obesity, leptin

concentrations are already high as a consequence of increased fat mass. The persistence of obesity in spite of high leptin levels suggests that high leptin levels can induce leptin resistance. This may occur due to a leptin-induced increase of SOCS3, which blocks intracellular transmission of the leptin signal [20], but our understanding of leptin resistance is still limited.

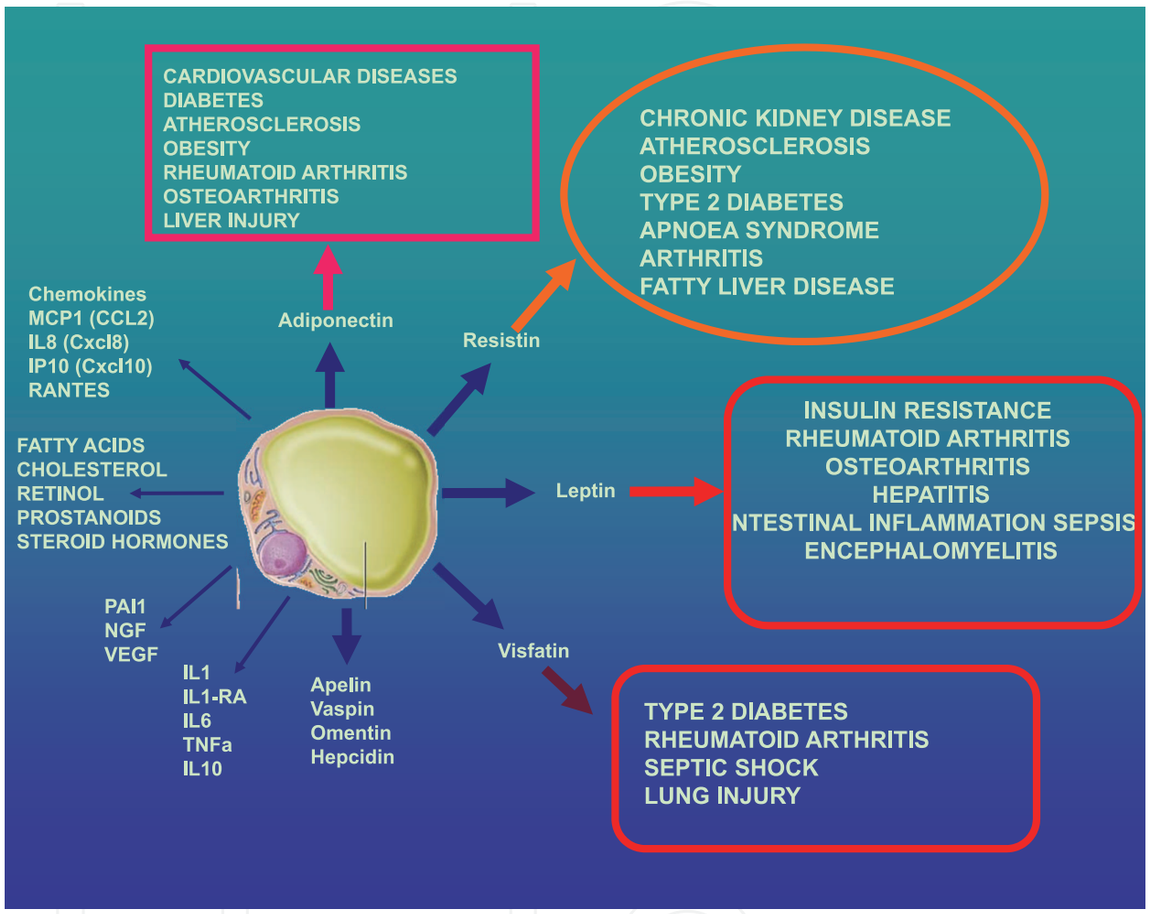

Fig. 1. A schematic representation of white adipose tissue (wat) functions. Besides to be the main energy store of the body and the site of synthesis of steroids and prostanoids, wat is also a source of a plethora of novel factors that modulate the immune/inflammatory response and promote atherosclerosis, vascular dysfunction and insulin resistance.

Db/db mice, which lack leptin receptors, suffer from thymus atrophy [21], and ob/ob mice, which lack leptin, are immunodeficient. Leptin must therefore play a role in immunity. This presumably explains why the murine immune system is depressed by acute starvation and reduced caloric intake, both of which result in low leptin levels [33], and why this depression is reverted by administration of exogenous leptin.

It promotes phagocyte function [24] and induces the synthesis of eicosanoids [25], nitric oxide [26] and several pro-inflammatory cytokines [26] in macrophages and monocytes. It increases IFNγ-induced production of nitric oxide synthase in murine macrophages [26]. It induces chemotaxis and the release of reactive oxygen species by neutrophils [27, 28]. It

influences the proliferation, differentiation, activation and cytotoxicity of natural killer (NK) cells [29].

It may protect dendritic cells from apoptosis and promote their lipopolysaccharide-induced maturation and a cytokine production profile featuring low levels of IL10 and high levels of IL12, TNFα and costimulatory molecules, which favours the proliferation of allogeneic CD4+ T cells (whereas leptin receptor deficiency and sequestration of leptin have the opposite effects and result in depressed proliferation of allogeneic CD4+ T cells) [30]. Finally, it modifies T-cell balance, induces T-cell activation, and alters the pattern of T-cell cytokine production by directing T-cell differentiation towards a T_{H1} response [31, 32].

Leptin also prevents glucocorticoid-induced thymocyte apoptosis, and increases thymic cell counts [33]. The low circulating CD4+ T-cell counts, impaired T-cell proliferation and impaired release of T-cell cytokines exhibited by young human patients with morbid obesity due to congenital leptin deficiency are all ameliorated by administration of recombinant human leptin. The fact that several T-cell antigens are expressed aberrantly in both ob/ob and db/db mice suggests that leptin may influence the growth, differentiation and activation of T cells by interacting with T-cell co-stimulatory antigens such as CTLA4 and dipeptidyl peptidase IV [34]. It is possible, however, that in the thymus T cells are affected by leptin only indirectly, via other signalling molecules: fetal db/db thymi develop normally when transplanted into wild-type hosts; neither the thymus weight and cellularity nor the cellular and humoral immune responses of wild-type mice are affected by transplantation of bone marrow cells from db/db mice more than by transplantation from db/+ mice; and thymus weight and cellularity are decreased when bone marrow cells are transplanted from wild-type mice to db/db mice [47].

A salient aspect of the effects of leptin in the immune system is its action as a pro-inflammatory cytokine: it is produced by inflammatory cells [35], and leptin mRNA expression and circulating leptin levels are increased by a number of inflammatory stimuli, including IL1, IL6 and lipopolysaccharide (LPS) [36]. Leptin-deficient mice are less prone than non-leptin-deficient mice to develop inflammatory diseases, regardless of whether these involve innate or adaptive immunity; reported conditions include experimentally induced colitis, experimental autoimmune encephalomyelitis, type I diabetes and experimentally induced hepatitis [2]. In the innate case, a reported imbalance between pro- and anti-inflammatory cytokines [37] suggests that leptin is able to modify the cytokine secretion pattern of monocytes and macrophages through a STAT3-mediated mechanism [38]. In the adaptive case, resistance may be due to the above-noted influence of leptin deficiency on T_{H1}/T_{H2} balance [39]. When transferred to T-cell-deficient mice, murine CD4+ $CD45RB^{high}$ T cells from db/db mice do not induce colitis as rapidly as do $CD4^{+}$ $CD45RB^{high}$ T cells from non-db/db mice, which feature leptin receptors [40]. Also, in rats with chemically induced intestinal inflammation, circulating leptin levels are elevated, and correlate with the degree of inflammation and the development of anorexia, during the first day following the induction of inflammation [41]. Serum leptin levels are likewise high in human patients with acute ulcerative colitis, in whom inflamed colonic epithelial cells secrete leptin into the intestinal lumen, where it is able to activate NFkB [42]. Thus leptin appears to play a significant role in intestinal inflammation as well as in the development of associated anorexia.

Mice in which experimental autoimmune encephalomyelitis (EAE) has been induced by inoculation of appropriate self-antigens constitute an animal model of human multiple sclerosis, a disease in which leptin levels in serum and cerebrospinal fluid are high and are negatively correlated with CD4+ CD25+ regulatory T cells [43]. Ob/ob mice do not develop EAE in response to EAE-inducing antigens, but this resistance is abolished by administration of leptin, and the abolition of resistance is accompanied by a switch from a T_{H2} to a T_{H1} pattern of cytokine release [44]. Also, the onset of EAE in wild-type mice is preceded by an increase in circulating leptin and is delayed by acute starvation [35]. Of particular interest is the finding that during the active phase of EAE leptin is secreted by both macrophages and T cells that have infiltrated the central nervous system (CNS), and that secretion by activated T cells appears to constitute an autocrine loop sustaining their proliferation [35]. By contrast, however, leptin secretion by T cells seems to have at most a marginal role in experimentally induced colitis and hepatitis, in which conditions no differences have been found between ob/ob and wild-type T cells regarding their ability to induce inflammation [45].

Serum leptin levels increase preceding not only the onset of EAE [35], but also the onset of diabetes in female non-obese diabetic (NOD) mice, in which leptin administration augments inflammatory infiltrates, increases interferon γ production by peripheral T cells, and speeds up the destruction of pancreatic β cells [46]. These latter findings suggest that leptin may promote the development of type 1 diabetes through a T_{H1} response.

Finally, leptin administration increases both inflammatory and platelet responses in humans during caloric deprivation [48], and in WAT-less mice increases T-cell–mediated hepatic inflammation [49]. Together with a number of other neuroendocrine messengers, leptin appears to play a major role in autoimmune diseases such as rheumatoid arthritis. In patients with rheumatoid arthritis, circulating leptin levels are high [51, 52], and leptin production is much higher in osteoarthritic cartilage than in normal cartilage [55].

Of all the connective tissues that compose a skeletal joint, articular cartilage is the most damaged by rheumatic disease. Under pathological conditions, control of the balance between synthesis and degradation of extracellular matrix by chondrocytes is lost, and the production of a host of inflammation mediators by these cells eventually leads to complete loss of cartilage structure [53, 54]. The finding that administration of exogenous leptin increases IGF1 and TGFβ1 production by rat knee joint cartilage has suggested that high circulating leptin levels in obese individuals may protect cartilage from osteoarthritic degeneration [55]. However, most of the evidence points the other way: in rheumatoid arthritis patients a fasting-induced fall in circulating leptin is associated with CD4+ lymphocyte hyporeactivity and increased IL4 secretion [50]; experimental antigen-induced arthritis is less severe in leptin-deficient ob/ob mice than in wild-type mice [39]; and in cultured chondrocytes type 2 nitric oxide synthase (NOS2) is activated by the combination leptin plus IFNγ (though by either without the other) [57], and NOS2 activation by IL1 is increased by leptin [58] (nitric oxide has well-documented pro-inflammatory effects on joint cartilage, triggering the loss of chondrocyte phenotype, chondrocyte apoptosis, and the activation of metalloproteases). Intracellularly, the joint action of IL1 and leptin involves JAK2, PI3K, MEK1 and p38.

A pro-inflammatory effect of leptin on cartilage would be in keeping with the fact that, in comparison with men, women have both higher circulating leptin levels and a greater propensity to develop osteoarthritis [56]. It would also explain association between obesity

and inflammatory conditions, especially those related with alterations of cartilage homeostasis.

4. Adiponectin

Adiponectin, also called gelatin binding protein 28 (GBP28), adipose most abundant gene transcript 1(apM1), and 30 kDa adipocyte complement-related protein (Acrp30, AdipoQ), is a 244-residue protein that, as far as is known, is produced prevalently by WAT. It increases fatty acid oxidation and reduces the synthesis of glucose in the liver [61]. Ablation of the adiponectin gene has no dramatic effect on knock-out mice on a normal diet, but when placed on a high-fat, high-sucrose diet they develop severe insulin resistance and exhibit lipid accumulation in muscles [62]. Circulating adiponectin levels tend to be low in morbidly obese patients and increase with weight loss and with the use of thiazolidinediones, which enhance sensitivity to insulin [67].

Adiponectin acts mainly via two receptors, one (AdipoR1) found mainly in skeletal muscle and the other (AdipoR2) in liver (for a third route, see the next section). Transduction of the adiponectin signal by AdipoR1 and AdipoR2 involves the activation of AMPK, PPAR (α and γ) and presumably other signalling molecules also. Adiponectin exhibits structural homology with collagen VIII and X and complement factor C1q, and circulates in the blood in relatively large amounts in oligomeric forms (mainly trimers and hexamers, but also a 12-18-mer form [59]), constituting about 0.01% of total plasma protein. Whether the various oligomers have different activities, which would make the effect of adiponectin controlable through its oligomerization state, is somewhat controversial and may depend on target cell type: although authors working with myocytes reported that trimers activated AMP-activated protein kinase (AMPK) whereas higher oligomers activated NFκb, it has also been reported that 12-18-mers promote AMPK in hepatocytes [60].

Although adiponectin was discovered nearly at the same time as leptin, its role in protection against obesity and obesity-related disorders only began to be recognized some years later. It is now beginning to be recognized that, in addition, it has a wide range of effects in pathologies with inflammatory components, such as cardiovascular disease, type 2 diabetes, metabolic syndrome and rheumatoid arthritis. One indication of a relationship between adiponectin and inflammation is provided by the finding that its secretion by cultured adipocytes is inhibited by pro-inflammatory cytokines such as IL6 [65] and TNFα [66]. More recently, an explanation of how hypoadiponectinaemia might contribute to the development of inflammation-related diseases has been suggested by the finding that adiponectin promotes the phagocytosis of apoptotic cells (by interacting with calreticulin on the phagocyte surface), since the accumulation of apoptotic débris is known to be able to cause inflammation and immune system dysfunction [67]. In the remainder of this section we look at the relationship of adiponectin to inflammatory processes in several types of pathology.

Adiponectin has been described as a potent anti-atherogenic factor that protects vascular endothelium against atherogenic inflammation through multiple effects on the endothelium itself and other vascular structures [63]. It inhibits the adhesion of monocytes to endothelial cells, reduces the synthesis of adhesion molecules and tumor necrosis factor, and reduces NFκB levels [64]. Subnormal levels of adiponectin have been linked to inflammatory atherosclerosis in humans [69], and in animal models they are associated with increased vascular smooth cell proliferation in response to injury, increased free fatty acid levels, and insulin resistance [70]. The conjunction of pro-diabetic and pro-atherogenic effects of

reduced adiponectin levels, as seen in metabolic syndrome, make adiponectin a link between obesity and inflammation.

In contrast to its protective role against obesity and vascular diseases, it appears that in skeletal joints adiponectin is pro-inflammatory and involved in matrix degradation. Plasma adiponectin levels in rheumatoid arthritis patients are higher than in healthy controls [51] (and adiponectin levels in synovial fluid are higher in rheumatoid arthritis patients than in patients with osteoarthritis [72]). In human synovial fibroblasts adiponectin selectively induces, via the p38 MAPK pathway, two of the main mediators of rheumatoid arthritis, IL6 and matrix metalloproteinase 1 [71]. Chondrocytes also present functional adiponectin receptors, activation of which leads to the induction of type 2 NOS via a signalling pathway that involves PI3 kinase; and adiponectin-treated chondrocytes similarly increase IL6, TNFα and MCP1 synthesis (but not release of prostaglandin E_2 or leukotriene B_4). Taken together, these results suggest that it may be worth considering adiponectin as a potential target of treatment for degenerative joint diseases. On the other hand, the high adiponectin levels of patients with rheumatoid arthritis can also be interpreted as an attempt to overcome the well-known pro-inflammatory effect of leptin, for example by counteracting the pro-inflammatory effects of TNFα and reducing the production of IL6 and CRP in rheumatoid arthritis [73].

In experimental models of liver injury, adiponectin has been reported to have anti-inflammatory effects: in rodents, adiponectin administration improves liver function in both alcoholic and non-alcoholic fatty liver disease as the result of TNF suppression, and in mice it reduces liver enzyme levels, hepatomegaly and steatosis [74], attenuates liver fibrosis [75], and protects against LPS-induced liver injury [76].

Finally, there is also evidence that adiponectin may influence the development of certain neoplasias and the course of wound healing [77, 78].

5. Resistin

Resistin is a dimeric protein that received its name from its apparent induction of insulin resistance in mice. It belongs to the FIZZ (found in inflammatory zones) family (now also known as RELMs, i.e. resistin-like molecules). The first member this family to be discovered, FIZZ1 (also known as RELMα), is a protein that is found in above-normal levels in the bronchoalveolar fluid of mice with experimentally induced asthma [79]. FIZZ2 (RELMβ) was discovered in the proliferating epithelium of intestinal crypt [80]. Resistin (FIZZ3) has been found in adipocytes, macrophages and other cell types. In rodents, a fourth FIZZ protein, RELMγ, has been identified in WAT and haematopoietic tissues [81].

As noted above, it has been postulated that resistin mediates insulin resistance, but this role may be limited to rodents. Initial enthusiasm for this theory, which provides a direct link between adiposity and insulin resistance [83], was quickly quenched by contradictory findings in both mice and humans. It nonetheless appears safe to assert that resistin levels depend upon both nutritional state and hormonal environment; that they are low during fasting and restored by refeeding; and that growth hormone, catecholamines and endothelin 1 are all able to increase resistin secretion [82].

5.1 Resistin and inflammation

That resistin is involved in inflammatory conditions in humans is suggested by its secretion in appreciable quantities by mononuclear cells. Also, resistin levels are correlated with those

of cell adhesion molecules such as ICAM1 in patients with obstructive sleep apnoea [87], and in atherosclerotic patients are positively associated with other markers of inflammation, such as soluble TNF-R type II and lipoprotein-associated phospholipase A2 [88]. Furthermore, LPS has been reported to induce resistin gene expression in primary human and murine macrophages via a cascade involving the secretion of pro-inflammatory cytokines [86]; and in human peripheral blood mononuclear cells resistin appears both to induce [85] and be induced by [84] IL6 and TNFa (induction of these cytokines by resistin occurring via the NFκB pathway [85]). However, both TNFα and IL6 downregulate resistin or have no effect in adipocytes [84].

A pro-inflammatory role of resistin in atherosclerosis is suggested by reports that in vascular endothelial cells it induces the inflammation marker long pentraxin 3 [90] and promotes the release of endothelin 1 and production of VCAM1, ICAM1 and monocyte chemotactic protein 1 (MCP1) [89]. In murine models of atherosclerosis, resistin is present in sclerotic lesions at levels that are proportional to the severity of the lesion [92]. In humans resistin is associated with coronary artery calcification, a quantitative marker of atherosclerosis [91].

There are indications that resistin may also be involved in the pathogenesis of rheumatoid arthritis: resistin has been found in the plasma and the synovial fluid of rheumatoid arthritis patients [92], and injection of resistin into mice joints induces an arthritis-like condition, with leukocyte infiltration of synovial tissues, hypertrophy of the synovial layer and pannus formation [85]. However, plasma resistin levels in rheumatoid arthritis patients appear to be no different from those found in healthy controls [51,85]; and although in some studies of rheumatoid arthritis patients resistin levels were higher in synovial fluid than in serum (which shows that circulating levels of adipokines do not necessarily reflect the situation in the joint), the discrepancy may be due simply to the increased permeability of inflamed synovial membrane [93].

6. Other adipokines

6.1 Visfatin

Visfatin is an insulin-mimetic adipokine that was originally discovered in liver, skeletal muscle and bone marrow as a growth factor for B lymphocyte precursors (whence its alternative name, pre-B-colony enhancing factor, or PBEF). It is up-modulated in models of acute lung injury and sepsis. It was re-discovered by Fukuhara et al. [94] using a differential display technique to identify genes that are relatively specifically expressed in abdominal fat. Circulating visfatin levels are closely correlated with WAT accumulation, visfatin mRNA levels increase in the course of adipocyte differentiation, and visfatin synthesis is regulated by several factors, including glucocorticoids, TNFα, IL6 and growth hormone. In an experimental model of obesity-associated insulin resistance, circulating visfatin levels increased during the development of obesity, apparently due solely to secretion by abdominal WAT (since visfatin mRNA increased only in this tissue, not in subcutaneous WAT or liver). However, visfatin is not only produced by WAT, but also by endotoxin-challenged neutrophils, in which it prevents apoptosis through a mechanism mediated by caspases 3 and 8 [95]. Also, patients with inflammatory bowel diseases have increased circulating visfatin levels and increased levels of visfatin mRNA in their intestinal epithelium; and visfatin has been shown to induce chemotaxis and the production of IL1β, TNFα, IL6 and costimulatory molecules by CD14+ monocytes, and to increase their ability

to induce alloproliferative responses in lymphocytes, effects which are mediated intracellularly by p38 and MEK1 [96]. Visfatin is therefore certainly pro-inflammatory in some circumstances. In addition, circulating visfatin is higher in patients with rheumatoid arthritis than in healthy controls [51]. Even though it is currently unclear what is visfatin physiological role or relevance in the context of rheumatoid arthritis, it may reflect modulation of the inflammatory or immune response by visfatin; or it may forms part of a compensatory mechanism that facilitates the accumulation of intra-abdominal fat so as to prevent rheumatoid cachexia; or it may simply be an epiphenomenon.

6.2 Apelin

Apelin is a bioactive peptide that was originally identified in bovine stomach extracts as the endogenous ligand of the orphan G protein-coupled receptor APJ [97]. It is derived from a 77-amino-acid prepropeptide that is cleaved into a 55-amino-acid fragment and then into shorter forms. The physiologically active form is thought to be apelin 36, although the pyroglutamylated form of apelin 13, which is also produced endogenously, is more potent. Boucher et al. [98] recently found that apelin is produced and secreted by mature human and murine adipocytes, and that the apelin mRNA levels found in these cells are similar to those found in the stroma-vascular fraction (which contains other cell types present in adipose tissue) and in organs such as kidney and heart [98]. In obese humans plasma apelin levels are significantly higher than in lean controls [98,100], and that this may be due to production by WAT is suggested by the finding that in several murine models of obesity above-normal plasma apelin levels are accompanied by above-normal apelin mRNA levels in adipocytes [98]. TNFα increases both apelin production in adipose tissue and blood plasma apelin levels when administered to mice by intraperitoneal injection [99]. Intriguingly, in mice with diet-induced obesity, macrophage counts and the levels of pro-inflammatory agents such as TNFα seem to rise progressively in adipose tissue before a rise in circulating insulin levels indicates the onset of insulin resistance [101]. So, it could be conceivable that in adipocytes there is a substantial regulation of apelin synthesis exerted by TNFα, leading to sustained apelin secretion in obesity.

Thus, one may envisage that over-production of apelin in the obese may be an adaptive response that attempts to forestall the onset of obesity-related disorders such as mild chronic inflammation, hypertension and cardiovascular dysfunctions. Accordingly, further elucidation of the role of apelin is of major interest.

6.3 Vaspin

Vaspin (visceral-adipose-tissue-derived serpin) was discovered by Hida et al. [102] as a serpin (serine protease inhibitor) that was produced in the visceral adipose tissue of Otsuka Long–Evans Tokushima Fatty rats at the age when obesity and plasma insulin concentrations reach a peak; thereafter, vaspin production decreased as diabetes worsened and body weight fell in untreated mice, but serum vaspin levels were maintained by treatment with insulin or pioglitazone. Administration of vaspin to obese mice improved glucose tolerance and insulin sensitivity, and reversed altered expression of genes that may promote insulin resistance.

Kloting et al. [103] reported that human vaspin mRNA is not detectable in the adipose tissue of normal, lean, glucose-tolerant individuals, but can be induced by increased fat mass, decreased insulin sensitivity, and impaired glucose tolerance. The regulation of vaspin gene expression seems to be fat depot-specific. The induction of vaspin by adipose tissue may

constitute a compensatory mechanism in response to obesity, severe insulin resistance and type 2 diabetes.

7. Conclusions

It is now clear that adipokines play multiple important roles in the body, and the increasing research effort in this area is gradually revealing the intricate adipokine-mediated interplay among white adipose tissue, metabolic diseases and inflammatory (auto)immune illnesses. Although many issues remain foggy, in this section we outline several possible avenues for therapeutic action that this work has already opened.

There is now a huge amount of data on the promotion of inflammation by high circulating leptin levels. It might perhaps be possible to control the amount of bioavailable circulating leptin, and hence to prevent leptin-induced inflammation, by means of a soluble, high-affinity leptin-binding molecule analogous to the soluble TNFα receptors used to treat rheumatoid arthritis. Alternatively, it might be possible to block the leptin receptor with monoclonal humanized antibodies or mutant leptins that are able to bind to the receptor without activating it. An obvious proviso here is that receptors mediating the influence of leptin on food intake should not be blocked, lest the patient develop hyperphagia and obesity; but the fact that this influence is exerted in the brain, on the other side of the blood-brain barrier, would seem to make such discrimination possible. At present, little is known in this area because current anti-leptin agents were developed to control the adipostatic effects of leptin, and hence to cross the blood brain barrier.

The anti-atherosclerotic and vasoprotective effects of adiponectin are another source of inspiration for possible pharmacological approaches to inflammatory diseases. In particular, one strategy against diabetes and relevant cardiovascular and metabolic diseases might be to tackle the hypoadiponectinaemia associated with these conditions. Given the high levels of adiponectin in the blood, exogenous administration of the adipokine itself would probably have little effect; but drugs that specifically enhance endogenous adiponectin production, such as thiazolidinediones, might well prove to be effective. It should not be forgotten, of course, that the primary causes of obesity are generally nutritional and lifestyle factors such as overeating and physical inactivity, and that front line treatment of obesity-related hypoadiponectinemia and obesity-related hyperproduction of detrimental adipokines therefore essentially involves the correction of these factors.

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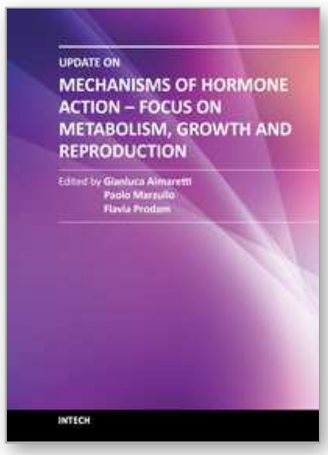

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The purpose of the present volume is to focus on more recent aspects of the complex regulation of hormonal action, in particular in 3 different hot fields: metabolism, growth and reproduction. Modern approaches to the physiology and pathology of endocrine glands are based on cellular and molecular investigation of genes, peptide, hormones, protein cascade at different levels. In all of the chapters in the book all, or at least some, of these aspects are described in order to increase the endocrine knowledge.

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