

## Review article

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T.J.GUZI<sup>1,2</sup>, D.MANGALAT<sup>2</sup>, R.KORBUT<sup>1</sup>

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### ADIPOCYTOKINES – NOVEL LINK BETWEEN INFLAMMATION AND VASCULAR FUNCTION?

<sup>1</sup>Chair of Pharmacology and Department of Internal Medicine, Jagiellonian University School of Medicine, Krakow, Poland <sup>2</sup>Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

Obesity and obesity related diseases are a major public health problem. Recent studies have shown that fat tissue is not a simple energy storage organ, but exerts important endocrine and immune functions. These are achieved predominantly through release of adipocytokines, which include several novel and highly active molecules released abundantly by adipocytes like leptin, resistin, adiponectin or visfatin, as well as some more classical cytokines released possibly by inflammatory cells infiltrating fat, like TNF- $\alpha$ , IL-6, MCP-1 (CCL-2), IL-1. All of those molecules may act on immune cells leading to local and generalized inflammation and may also affect vascular (endothelial) function by modulating vascular nitric oxide and superoxide release and mediating obesity related vascular disorders (including hypertension, diabetes, atherosclerosis, and insulin resistance) but also cancer or non-alcoholic fatty liver diseases. Present review, in a concise form, focuses on the effects of major adipocytokines, characteristic for adipose tissue like leptin, adiponectin, resistin and visfatin on the immune system, particularly innate and adaptive immunity as well as on blood vessels. Macrophages and T cells are populating adipose tissue which develops into almost an organized immune organ. Activated T cells further migrate to blood vessels, kidney, brain and other organs surrounded by infiltrated fat leading to their damage, thus providing a link between metabolic syndrome, inflammation and cardiovascular and other associated disorders.

Certain treatments may lead to significant changes in adipocytokine levels. For example include beta-2 adrenoceptor agonists, thiazolidinediones as well as androgens lead to decrease of plasma leptin levels. Moreover future treatments of metabolic system associated disorders should focus on the regulation of adipocytokines and their modes of action.

**Key words:** *inflammation, obesity, leptin, adiponectin, resistin, visfatin, adipose tissue, vascular function, endothelium, nitric oxide*

## INTRODUCTION

Obesity is associated with increased occurrence of numerous diseases including hypertension, dyslipidaemia, insulin resistance and diabetes, atherosclerosis comprising a “metabolic syndrome”(1). Obesity also predisposes to several other independent diseases like asthma, breast cancer or non-alcoholic liver steatosis (fatty liver disease) (2). Although these associations have been unquestionably proven in large clinical trials, their mechanisms and therefore prospects for therapeutic interventions remain unexplained.

Obesity is accompanied by generalized inflammation, characterized by increased plasma CRP levels as well as by dys-regulated cytokine production by monocytes, lymphocytes and other immune cells (3). Pathways leading to those changes have, until recently, remained not defined. Simultaneously, the presence of obesity has long been associated with the presence of endothelial and vascular dysfunction, which provides partial explanation of how does obesity may lead to cardiovascular diseases (4-6). The mechanisms by which obesity leads to vascular dysfunction and vascular disorders like hypertension are unknown. It is possible that alterations of immune function can link obesity to vascular disorders and risk factors for atherosclerosis (7). Indeed, recent data show that adipocytes as well as other cells present within fat tissues, are capable of releasing numerous vasoactive factors leading to cardiovascular morbidity in obese individuals. These adipocyte derived substances exert significant effects on the immune system, thus modifying inflammation. These factors, are termed “adipocytokines” in relation to fat tissue being their source. Present review will focus primarily on discussing the inter-relationships between different adipocytokines and their effects on inflammation and vascular function.

As the prevalence of obesity increases in modern society, there has been a concomitant rise in investigations directed at this organ of “dysfunction”: adipose tissue.

All of the above developments caused a vital change in our understanding of adipose tissue – it is no longer considered just an energy storage organ, but a real endocrine organ, hormones of which have not yet been fully characterized (8). Moreover, the more we understand about the actions and nature of adipocytokines, the more it becomes clear that adipose tissue is also, if not predominantly, an immune organ, and obesity related diseases like hypertension or atherosclerosis are in fact – immune disorders.

*Characteristics of adipocytokines*

Adipocytokines are bioactive mediators released from the adipose tissue including adipocytes and other cells present within fat tissues. These include several novel and highly active molecules released abundantly by adipocytes like leptin, resistin, adiponectin or visfatin, as well as some more classical cytokines released possibly by inflammatory cells infiltrating fat, like TNF- $\alpha$ , IL-6, MCP-

1 (CCL-2), IL-1 (9). The most abundantly expressed within the adipose tissue are leptin and adiponectin. Interestingly some reports indicate that adipocytes may also release the latter, more classical cytokines.

Typical adipocytokines like leptin or adiponectin have been initially recognized through their role in the regulation of energy storage and homeostasis. For example, leptin, acting centrally within the CNS (10) plays an important role as a negative regulator of appetite control (11, 12). Further research has shown that receptors for those proteins, are widely expressed, throughout the cardiovascular and immune system (13-15).

The effects of adipocytokines on vascular function, immune regulation and adipocyte metabolism makes them key players in the pathogenesis of metabolic syndrome, a cluster of clinical symptoms including obesity, insulin resistance, hypertension, and dyslipidemia (1). Metabolic syndrome is one of the major risk factors of cardiovascular morbidity and mortality (16, 17). Release of adipocytokines may explain mechanisms of the relationship of obesity to cardiovascular phenotypes including hypertension, and atherosclerosis mainly through their ability to affect and modify endothelial and vascular function (15) as well through their modulating effects on immune functions (9) which will be described in following paragraphs.

### *Leptin*

Leptin was one of the first adipocytokines identified (18-20), and immediately has drawn substantial research attention. Leptin is a 167 amino-acid protein, encoded by the *ob* gene, belonging to a cytokine family, located within 7q31.3 locus (21). Adipocytes are the primary sites of leptin expression, although it has also been shown to be expressed in gastric wall, vascular cells, placenta, ovary, skeletal muscle and liver (8, 22-24). As discussed above leptin role in appetite control within so called “brain-gut axis” provides a satiety signal through its actions on CNS receptors within the hypothalamus (12, 24, 25). Mice with mutated *ob* gene (*ob/ob* mice) develop severe obesity in relation to the lack of satiety signaling within their brain gut axis (18). Similarly, adults with leptin deficiency (extremely rare genetic disorder) show increased appetite and obesity which can be treated by leptin. The phenotype of these subjects includes also T cell hypo-responsiveness, hyperinsulinemia and insulin resistance, hyperlipidemia, immune dysfunction and neuroendocrine abnormalities (26, 27).

Plasma levels of leptin levels in humans are in a few ng/ml range (28). Leptin levels are closely correlated with the fat mass, and decrease with weight reduction (29). Like majority of neurohormones leptin levels exhibit important circadian rhythms (with peak during night). Several agonists have been shown to increase leptin release from adipocytes. These include TNF- $\alpha$  and other pro-inflammatory cytokines, insulin, glucose, estrogens. Other vasoactive factors like angiotensin II or endothelin may also lead to leptin release (30), although this is still under

investigation, as this phenomenon may occur locally and does not seem to affect plasma levels of leptin during angiotensin II infusion (31).

Leptin receptors (a family of splice variants – OB-R, differing with the size of cytoplasmic C terminus) are expressed in number of different tissues, which brought the attention of researchers to the fact that leptin has a very widespread range of actions (10, 22, 23, 32-37), particularly within the cardiovascular and immune system (13, 14). Different splice variants of the receptors may differ in relation to signaling pathways and sites of expression, with OB-Rb (long isoforms as the major signaling one; *Tab. 1*). It is important to note that receptor splicing differs between mouse and human.

Such ubiquitous expression of the receptors in humans and widespread binding of leptin in various organs, indicates it's role in a constellation of vital processes including growth, metabolic control, immune regulation, insulin sensitivity regulation, reproduction. These aspects of leptin actions have been extensively reviewed elsewhere (8, 9, 38-40).

### *Adiponectin*

Adiponectin appears to be a second well known adipocytokine released by fat cells, but in contrast to leptin it seems to have several beneficial and protective effects. These effects include anti-inflammatory, vasculoprotective, anti-diabetic effects. Adiponectin (also known as 30-kDa adipocyte complement-related protein; Acrp30) is a 247 amino-acid protein monomer which forms trimers which further polymerize into larger polymeric complexes varying in size between 180kDa (hexameres; LMW) or 400-600kDa (16-meres; HMW) (8). Interestingly the highest biological activity appears to be exerted by trimers, however certain functions like NFkappaB activation can be caused only by 8 and higher complexes.

Levels of adiponectin in human blood are between 5-10 mg/ml (relatively high) and are decreased in subjects with insulin resistance and type 2 diabetes and adiponectin-deficient mice exhibit insulin resistance and diabetes (41). Moreover, administration of adiponectin causes glucose-lowering effects and ameliorates

*Table 1.* Major known leptin receptors in humans, their expression and signaling mechanisms

Receptor		Expression	Signaling
OB-Ra	Short isoforms	Ubiquitous; major role in blood brain barrier transport.	JAK IRS-I
OB-Rb	Long isoforms	hypothalamus, monocytes, lymphocytes, enterocytes, endothelial cells, smooth muscle cells, pancreatic beta cells adipocytes	JAK-STAT pathway (STAT 3,5,6) ERK p38
OB-Re	Soluble truncated receptor	Circulating in plasma (can be produced as truncated or cleaved by MMPs)	n/a

insulin resistance (42). This insulin-sensitizing effect of adiponectin seems to be mediated by an increase in fatty-acid oxidation through activation of AMP kinase and PPAR-alpha (43).

Two adiponectin receptors (AdipoR1 and AdipoR2) have been recently identified (44). AdipoR1 is abundantly expressed in skeletal muscle, whereas AdipoR2 is predominantly expressed in the liver (44). These two adiponectin receptors are predicted to contain seven transmembrane domains, but to be structurally and functionally distinct from G-protein-coupled receptors (44).

Although it may seem that adiponectin's primary sites of action are peripheral, it also acts centrally within the brain-gut axis (45)

However, in spite of numerous potential beneficial effects of adiponectin, there are also suggestions of its possible pro-inflammatory effects, which are yet to be determined (46)

### *Resistin*

Resistin has been named for the fact that it conveys the resistance to insulin (47). Resistin is a 114 amino-acid peptide present in humans most likely in the form of a few splice variants. Monomeric peptides may create oligomeric structures. Circulating resistin levels are increased in mouse models of obesity and in obese humans and are decreased by the anti-diabetic drug rosiglitazone, and increased in diet-induced and genetic forms of obesity and administration of anti-resistin antibody has been shown to improve blood sugar and insulin action in mice with diet-induced obesity (47). Similarly resistin has been implicated in the pathogenesis of diabetic complication and diabetes (48). Moreover, treatment of normal mice with recombinant resistin impairs glucose tolerance and insulin action. Insulin-stimulated glucose uptake by adipocytes is enhanced by neutralization of resistin and is reduced by resistin treatment (47).

Source of resistin is under dispute now (48), as it may not come directly from the adipocytes, and may rather originate from inflammatory cells infiltrating fat tissue (49, 50). Release of resistin appears to be stimulated by inflammation, LPS, IL-6, hyperglycemia, growth and gonadal hormones. While released within the fat tissue resistin acts on adipocytes themselves leading to insulin resistance.

Further characterization of resistin is necessary as its exact role and mechanism of action is poorly defined.

### *Visfatin and Apelin*

Visfatin is the most recently identified adipocytokine (known previously as pre-B cell colony enhancing factor; PBEF) which appears to be preferentially produced by visceral adipose tissue (51), and has insulin-mimetic actions. Visfatin expression is increased in animal models of obesity and its plasma concentrations are increased in humans with abdominal obesity or type 2 diabetes mellitus. Visfatin binds to the insulin receptor at a site distinct from insulin and

exerts hypoglycemic effect by reducing glucose release from hepatocytes and stimulating glucose utilization in peripheral tissues (52). The latter property could make this molecule very useful in the potential treatment of diabetes. Interestingly, known as PBEF, visfatin was also identified in inflammatory cells and its levels were increased in various inflammatory conditions (51).

Apelin is another short peptide released from adipocytes upon stimulation by e.g. insulin. In line with this, plasma apelin levels are increased in obesity associated with insulin resistance and hyperinsulinemia (52). Three forms of apelin, consisting of 13, 17, or 36 amino acids, all originating from a common 77-amino-acid precursors (52). In the cardiovascular system, apelin elicits endothelium-dependent, nitric oxide-mediated vasorelaxation and reduces arterial blood pressure (53). In addition, apelin demonstrates potent and long-lasting positive inotropic activity.

Biology and cardio-vascular effects of apelin and visfatin have been recently extensively reviewed elsewhere (52), and will not be discussed in large extent here.

#### *Effects of adipocytokines on immune system*

The fact that excessive amounts of adipose tissue are related to increased systemic inflammation has been proven in both clinical and experimental setting (9). This is related to the ability of adipocytes to produce cytokines as well as the inflammatory infiltration of fat by monocytes, macrophages and possibly other inflammatory cells like lymphocytes. The relative importance of those compartments of fat in obese individuals remains disputed (49).

#### *Classical cytokines*

Several “classical” cytokines such as TNF- $\alpha$ , IL-6, or selected chemokines can be released from adipocytes, and may participate in the regulation of obesity as well as insulin resistance etc. Both TNF- $\alpha$ , and to a larger extent IL-6 are expressed in adipocytes, themselves. In fact nearly 30% of total IL-6 in obese individuals can originate from adipocytes (54). Chemokines produced within adipocytes include MCP-1 and IL-6 and may be responsible for macrophage infiltration of adipose tissue (54). Other chemokines like RANTES (CCL-5) may be released as well, leading to the recruitment of other e.g. T cells which can participate in further production of numerous cytokines (55). Inflammatory cells, infiltrating fat create a milieu which perpetuates inflammation within the adipose tissue and activates adipocytes themselves to produce inflammatory mediators and adipocytokines, closing a vicious circle of inflammation related to obesity (56). One of the very important aspects of classical cytokines derived from inflammatory cells is their importance in the pathogenesis of the metabolic syndrome. For instance TNF- $\alpha$  deficient obese mice (ob/ob, leptin deficient mice) did not develop insulin resistance to the same extent as obese mice which had functional TNF- $\alpha$  pathway (57). It is however not completely clear where does

the TNF- $\alpha$ , important in insulin resistance coming from in this model. Interestingly, inhibition of NF $\kappa$ B pathway (important in the induction of classical cytokines including TNF- $\alpha$ ) has been shown to attenuate insulin resistance, also when NK $\kappa$ B pathway was inhibited genetically only in myeloid cells (58). Importantly, TNF- $\alpha$  is also expressed in adipocytes and along with CRP may be a very important predictor of overall morbidity and mortality in individuals with metabolic syndrome (59).

### *Leptin*

Although leptin is not a classical cytokine several immune cells (including polymorphonuclear leukocytes, monocytes, macrophages and lymphocytes) bear leptin receptors and their activity can be modulated by leptin (60-63). Most of leptin pro-inflammatory activities appear to be mediated by a long OBRb receptor (see *Tab. 1*). Leptin has certain structural similarities to classical cytokines like IL-6, GM-CSF or IL-12 (9). Interesting data regarding the role of leptin in mediating immunity have been obtained in two models giving insight into leptin biology (i.e. *ob/ob* mice lacking leptin and *db/db* mice showing leptin resistance). Mice lacking leptin show numerous pathologies of the immune system. In fact leptin has been postulated to play an important role in linking nutritional status to immune system (64).

The most evident effects seem to occur on the level of adaptive immunity. Leptin-deficient (*ob/ob*) mice have severe thymic atrophy and this finding suggests that this hormone is required for normal thymopoiesis, although the role of leptin may be more complex in the setting of inflammation stimuli such as LPS. Leptin administration induced weight loss and stimulated thymopoiesis in *ob/ob* mice, but did not stimulate thymopoiesis in wild-type C57BL/6 nor BALB/c mice (65). Surprisingly, in endotoxin-stressed mice, leptin prevented LPS-induced thymus weight loss and stimulated TCR $\alpha$  gene rearrangement. Hick et al demonstrate that leptin has a selective thymo-stimulatory role in settings of leptin deficiency and endotoxin administration, and may be useful for protecting the thymus from damage and augmenting T cell reconstitution in these clinical states (65). Interestingly leptin appears to protect also from TNF- $\alpha$  induced toxicity.

Acting on monocytes leptin induces release of other cytokines such as TNF-alpha or IL-6 as well as CCL2 and VEGF (9). Moreover it leads to increased proliferation and differentiation of monocytes. Acting on neutrophils leptin leads to an increase of CD11b expression as well increased neutrophil chemotaxis and oxidative burst (9, 15, 66), all of which are very important in innate immune responses and regulation of pathogen colonization of the skin and mucosa (67).

As mentioned above the major actions of leptin appears to occur on the level of adaptive immune responses, mainly in T cell regulation. Leptin induces cytokine producing capacity switch towards Th1 producing cells (64, 66, 68, 69),

Table 2. Brief summary of major effects of 3 key adipocytokines on the immune system and in the vascular system.

Adipocytokine	Immune system effects	Vascular effects
Leptin	Pro-inflammatory Increase in T cell activation, and cytokine release proliferation Promotes Th1 response Increases NK cell activation Increases macrophage activation and cytokine release (TNF- $\alpha$ /IL-6 etc) Activates neutrophils and increases their chemotaxis and oxidative burst. ?Prevents inflammatory damage in conditions of overt immune system stimulation?	Induces endothelial dysfunction Increases blood pressure Atherosclerosis Increases ICAM, VCAM Plasma levels related to hard clinical endpoints  but acutely releases NO from endothelium
Adiponectin	Anti-inflammatory Decreases T cell activation and proliferation Inhibits NFkB dependent cytokine release and adhesion molecule expression (including TNF- $\alpha$ /IL-6) Increases IL-10 Inhibits phagocytosis and oxidative burst (?)	Vasculo-protective Prevents atherosclerosis Is decreased in hypertension Correlated with HDL and inversely with LDL Plasma levels not related to hard endpoints
Resistin	Pro-inflammatory Activates NFkB dependent cytokine release and adhesion molecule expression (including TNF- $\alpha$ /IL-6)	Pathogenic Impairs bradykinin dependent vasorelaxations (NO and EDHF) No effect on acetylcholine dependent vasorelaxations (NO) VEGF and MMP up regulation

particularly by increasing interferon gamma and TNF- $\alpha$  and IL-2 producing capacity. Moreover, leptin causes generation, maturation, and survival of T cells. In our own experiments T cell activation markers on the surface of CD4<sup>+</sup> T cells

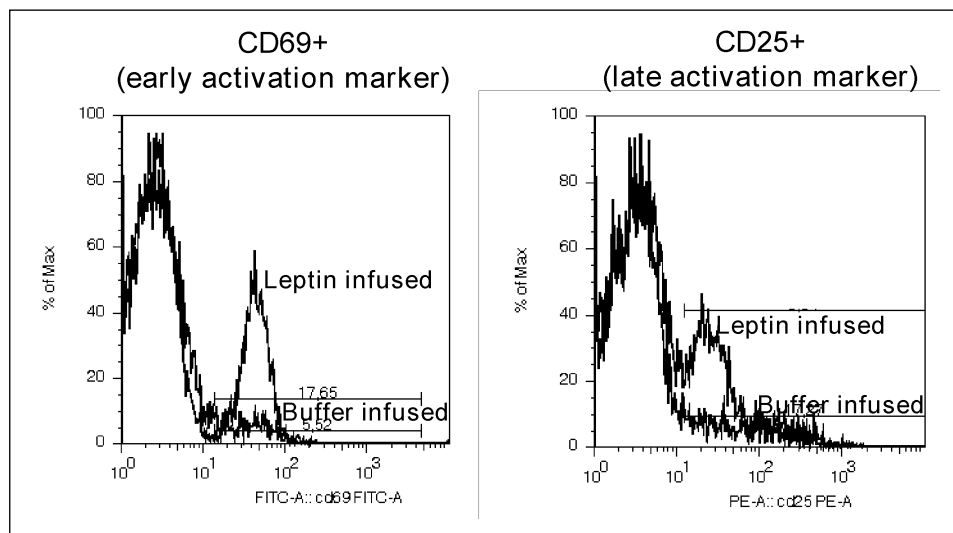


(including IL-2 receptor CD25 molecule) were dramatically increased in response to a 14 day infusion of leptin (*Figure 1*; note increase in CD25+(mid; T act) but not (high; T regs) cells). Mixed lymphocyte cultures have in turn shown that leptin induces proliferation of CD4+CD45RA+ T cells and inhibits proliferation CD4+ CD45RO+ T cells (memory) (69). Administration of leptin to mice reversed the immunosuppressive effects of acute starvation.

It should however be noted that in the models of severe inflammation leptin appears to exert suppressive effects which are contrary to described above – thus leads to decrease of Th1 type cytokines and increase of Th2 cytokines and decrease in T cell proliferation. Thus leptin effects on the immune system appear to depend not only on the leptin concentrations, but also on the status of the immune system.

The complexity of the picture is increased by findings that leptin deficient mice show resistance to certain autoimmune diseases and the susceptibility is recovered by leptin administration (70-72). In fact leptin may lead to enhancement of auto-immune reactions, in part maybe by reducing T regulatory cells. Leptin levels are also increased in patients with autoimmune diseases (66).

Summarizing, the predominant actions of leptin lead to the activation of the immune system, particularly monocytes, T cells and neutrophils. Further studies are however important to further determine potential protective effects of leptin in certain severe inflammatory conditions that have been implicated by some mouse models.



*Fig. 1.* Leptin induced changes of activation markers expression on peripheral CD4+ T cells. Leptin was infused in C57Blk/6 mice for 14 days. Flow cytometry was performed to detect the presence of surface molecules CD69 (early activation marker) and CD25 (late activation marker). Second peak indicates cell population positive for studied marker. (TG; DM; unpublished data)

It is also important to note that in vivo leptin may lead to certain compensatory responses and interplay with other adipocytokines like adiponectin, which could in part explain beneficial actions of leptin in those models.

### *Adiponectin*

Adiponectin, as has been discussed above is considered to be a “beneficial” adipocytokine. Certain inflammatory mediators, such as TNF- $\alpha$  or IL-6 which have been shown to increase leptin expression in adipocytes lead to a decrease of adiponectin expression and release. It is interesting that levels of adiponectin in obese individuals have shown to be decreased even though it comes primarily from adipose tissue. However inflammation associated with obesity could explain these observations by inhibiting adiponectin expression (9). The relationship between adiponectin and TNF- $\alpha$  seems to be reciprocal, as adiponectin knockout mice show high levels of tumor necrosis factor-alpha (TNF-alpha) mRNA in adipose tissue and high plasma TNF- $\alpha$  concentrations (73). The latter effects of adiponectin are likely to be mediated by inhibition of NFkB pathway. As such adiponectin can lead to numerous changes of immune cell functions that are NFkB dependent as well as vascular adhesion molecular expression further reducing inflammation. Acting on adaptive immunity, in contrast to leptin, adiponectin inhibits T cell activation and proliferation, although data regarding adiponectin effects on adaptive immune responses are relatively sparse.

Adiponectin also inhibits B lymphopoiesis, but only when stromal cells were present and only when cultures were initiated with the earliest category of lymphocyte precursors (74).

Adiponectin induces the production of the anti-inflammatory mediators IL-10 and IL-1RA in human monocytes, monocyte-derived macrophages, and dendritic cells (75). In addition, adiponectin significantly impairs the production of the pro-inflammatory cytokine IFN- $\gamma$  (75). Moreover, adiponectin-treated macrophages exhibit reduced phagocytotic capacity (75).

It is important to note that different forms of adiponectin may exhibit differential actions on the immune system. Low molecular weight (LMW)-adiponectin as well as high molecular weight form (HMW) both induce apoptosis in non-differentiated monocytic THP-1 cells, reduce macrophage scavenger receptor (MSR) A mRNA expression, and stimulate phosphorylation of adenosine monophosphate-activated protein kinase (46). However, HMW form induces IL-6 in human monocytes while LMW form reduces LPS-mediated IL-6 release and furthermore, stimulates immunosuppressive IL-10 secretion, most likely by reducing the abundance of inhibitor of nuclear factor (NF)-kappaB kinase  $\beta$ , leading to a diminished nuclear translocation of NF-kappaB p65 (46).

Finally adiponectin is able to inhibit Toll-receptor activation and its consequences. Globular form of adiponectin suppressed TLR-mediated NF-kappaB signaling AdipoR1 receptor. This inhibition of TLR-mediated IkappaB phosphorylation and NF-kappaB activation was eliminated by the pretreatment of cycloheximide or an antibody against AdipoR1 (76).

Adiponectin, acting on NK cells, a key component of innate immune system, suppresses the IL-2-enhanced cytotoxic activity of NK cells without affecting basal NK cell cytotoxicity (77). This effects appears to be also mediated via the AMP-activated protein kinase-mediated inhibition of NF-kappaB activation(77). IFN-gamma enhances NK cell cytotoxicity by causing an increase in the levels of expression of TRAIL and Fas ligand. The production of IFN-gamma, one of the NF-kappaB target genes in NK cells, was also found to be suppressed by adiponectin, accompanied by the subsequent down-regulation of IFN-gamma-inducible TRAIL and Fas ligand expression (77).

The interaction of adiponectin with the immune system is also related to the fact that the elastase derived from macrophages is critical for the generation of active globular form of adiponectin (78).

### *Resistin*

As discussed above the importance of resistin in inflammation may be emphasized by the fact that immune cells appear to be a very important if not the most important source of this adipocytokine. Resistin mRNA has been found in human PBMC and was increased by pre-treatment with certain cytokines such as IL-6 and TNF- $\alpha$ , IL-1, IL-12 or lipopolysacharride (79). Interestingly resistin itself leads to increased release of numerous pro-inflammatory cytokines TNF-alpha and IL-12, from macrophages and monocytes. Importantly the levels of induction of these cytokines by resistin were high, comparable to 5 microg/ml lipopolysaccharide effects (80). Both oligomeric and dimeric forms of resistin were able to activate these cytokines suggesting that the inflammatory action of resistin is independent of its conformation (80). The pro-inflammatory nature of resistin was further evident from the ability of this protein to induce the nuclear translocation of NF-kappaB transcription factor as seen from electrophoretic mobility shift assays (80) and resistin pro-inflammatory effects are reduced in the conditions of NF-kappaB inhibition. Thus pro-inflammatory actions of resistin are related to the activation of NFkappaB pathway (80), which makes resistin's actions on the immune system in a direct opposition to adiponectin's.

Effects of resistin on the immune system are as of current time, relatively poorly defined, particularly little is known in regard to its effects on the adaptive immune system.

Finally an important effect of resistin on inflammation is related to its ability to induce vascular adhesion molecule expression, thus increasing leukocyte infiltration to tissues, including fat.

*Effects of adipocytokines on cardiovascular functions*

In parallel to their effects in the immune system, adipocytokines exhibit extensive effects in the vascular system. While both of these aspects of actions of adipocytokines are likely to be related to each other (as inflammation is critical for virtually all cardiovascular diseases (81)), some actions occur independently, as they can be observed in studies of direct vascular effects of adipocytokines *in vitro* and as adipocytokine receptors have been identified on endothelial cells and vascular smooth muscle cells.

Obesity is a common risk factor for diseases of the vasculature, namely coronary atherosclerosis and hypertension. Elucidating additional potential links and pathways from obesity to these disease processes is vital for understanding the intricate role of adipose tissue on the cardiovascular system (14), which can be very useful in designing future therapeutic approaches.

*Leptin*

Leptin receptors initially described in the hypothalamus (82), have been shown to be present in endothelial cells. For instance human umbilical vein endothelial cells, used widely, (HUVECs) show not only leptin receptor, but also leptin-induced tyrosine phosphorylation and transcription factor Stat3 activation (83), which are important in regulating endothelial responses to leptin. Moreover leptin receptors have been shown to be present in human vasculature as well as in various animal models (84). Chronic infusion of leptin, at levels comparable to obesity, has caused a dose-dependent increase in arterial blood pressure in rats (85). Simultaneously chronic hyperleptinemia leads to significant endothelial dysfunction (84), defined as loss of nitric oxide bioavailability and production by endothelium. Similarly, leptin has been implicated in the pathogenesis of endothelial dysfunction in pre-eclampsia (86). Some actions of leptin can be explained by activation of NADPH oxidase system (87). NADPH oxidases have been shown to be critical in the regulation of oxidative stress in human vasculature in different models (88-90) particularly in relation to risk factors of atherosclerosis, and their activity is directly involved in the pathogenesis of endothelial dysfunction in various cardiovascular disease states (91-93).

Interestingly, leptin has also been shown to have a dose-dependent increase in sympathetic nerve activity, however, with no evident blood pressure or heart rate response (94). It is therefore possible that leptin can simultaneously provide a counteracting effect to actually lower or equilibrate blood pressure by simultaneous actions on vascular tissues, brain and immune system. In sympathectomized rats, leptin infusion was in fact found to cause hypotension. It is interesting that while some studies show that leptin may lead to an impairment of endothelium dependent relaxations, it simultaneously causes direct vascular relaxation, an effect blunted by endothelial denudation (95). These effects are mediated by acute release of nitric oxide production and vasodilatation by leptin

(96-98). However, a contradictory study showed a lack of vasodilator effect between leptin-infused and non-infused arteries (94). Moreover some other studies show that, leptin may exert vasodilator effects via a NO-independent pathways particularly in human coronary arteries (99). Likely each of these mechanisms plays a particular role in altering vascular dilatory functions. Further studies are still needed to clarify the contributions to vascular phenomenon such as blood pressure regulation, local, and systemic vasodilatory effects of leptin. It is also important to note that systemic hyperleptinemia leads to a decrease in obesity, which through numerous mechanisms could actually decrease endothelial function (and even decrease endogenous leptin levels) (96).

Finally, the varying effects of leptin on nitric oxide and superoxide systems might be related to genetic variability in either leptin receptors or even target molecules which could include eNOS polymorphisms (100, 101), as well as polymorphisms within vascular oxidases (102). These issues remain to be elucidated.

#### *Leptin: beneficial or detrimental adipocytokine?*

Data currently available do not sufficiently explain whether leptin serves a beneficial or detrimental role in the cardiovascular system in vivo. Particularly little is known in relation to humans.

Pathogenetic role of leptin in atherosclerosis has been implicated. It has been shown that high fat diet induced neo-intimal proliferation is associated with increased expression of leptin receptor mRNA and protein (103). In contrast to *ob/ob* leptin deficient mice fed the same diet who had no vessel involvement despite diabetes, hyperlipidemia, and worsening obesity. Leptin receptor is expressed within atherosclerotic plaques (103) and leptin infusion in the *ob/ob* mice resulted in luminal stenosis suggesting a direct link between leptin and atherosclerosis (104). This has also been explored in humans, particularly in the WOSCOPS study which prospectively looked at leptin levels before and after a coronary event in Scotland and despite adjustments for age, systolic blood pressure, lipids, BMI, and CRP still retained significance suggesting leptin as an independent risk factor for atherosclerosis (105). There have been several human clinical trials supporting this strong correlation in myocardial infarction (106), coronary artery calcification (107), and stroke (108) suggesting a more definitive relationship between leptin and the development of clinically pertinent coronary lesions.

Leptin has also shown to have pro-thrombotic properties. With the leptin receptor found to be on human platelets promoting platelet aggregation (109), *ob/ob* mice received arterial injury and it was found that there was a prolonged time of vessel patency and time to thrombus formation compared to wild type mice. Platelet aggregation again was supported with leptin infusion in both wild-type and *ob/ob* mice (110). Other studies have specifically investigated this point

with leptin deficient, leptin-receptor deficiency, and leptin-receptor platelet deficiency mice models with similar results of increased time to thrombosis, reversed in the leptin deficient mice with leptin infusion (111). The effects of leptin on thrombin induced and related changes (112) remain to be described.

Leptin effect on cardiac myocytes has also been described. Impairment of ventricular myocyte function has been shown with leptin administration, and appeared to be mediated through the endothelin-1 receptor via the NADPH oxidase pathway (113, 114). This has been supported by other studies evaluating a NO dependent pathways in leptin-induced cardiomyocyte contractile dysfunction (115). These mechanisms can be important in human hearts as well, particularly that it shows high levels of expression of NADPH oxidases (116).

However, leptin has not been shown to be only an injurious cytokine. Recent studies, particularly in animal models, have indicated that acute administration of induced cardiac ischemia in mice subsequently infused with leptin showed reduction in infarct size (117). Leptin deficiency caused left ventricular hypertrophy adjusted for increased BMI in the *ob/ob* mice studied with restoration of myocyte size and wall thickness with leptin infusion (118), however the effects of changes of body weight and fat content should be remembered in this context and have not been sufficiently taken into account by authors of that nice study. Other studies have found contradictory results to previously described leptin-induced myocyte dysfunction and in fact found impairment in cardiomyocyte systolic and diastolic function in leptin-deficient *ob/ob* mice (119).

The effects of leptin on endogenous anti-oxidant capacity in human vasculature (120) should also be taken into account although has not been addressed so far.

Leptin has proven to be a multi-faceted cytokine, particularly in the cardiovascular system. However, there is much conflicting research in regards to detrimental or positive effects of leptin. There is also a time element that plays a role in leptin's actions – perhaps differences in acute administration (e.g. in reperfusion) versus chronic elevation of leptin levels as seen in obesity, may play a vital role in leptin's intensity of action. Also, concentrations of leptin to determine effects may also factor in these discrepancies, lower dosages versus supra-physiologic levels each contributing in varying degrees.

### *Adiponectin*

Adiponectin, in contrast to leptin, has been consistently shown to have protective vascular effects, in line with other beneficial effects described in the above paragraphs as an anti-diabetic and anti-inflammatory agent.

Adiponectin knockout mice show increased neo-intimal proliferation in response to vascular injury (41) which may be mediated by decreased NO bioavailability of vascular ROS production (121, 122) as well as by reduction of

vascular inflammation (see above). These data on the potential role of adiponectin in atherosclerosis are further enhanced by findings that adiponectin can prevent atherosclerosis in ApoE knockout mice (123). Similar results were supported in another study which proposed the mechanism of adiponectin-induced vascular protection via EGF and other endothelial growth factors by attenuating endothelial cell proliferation, terming an intriguing concept of the “adipo-vascular axis”(73). This adipocytokine has shown to decrease human aortic smooth muscle cells growth and migration response to growth factors (73) and decreasing macrophage phagocytic effect and production of TNF- $\alpha$  (124), as discussed above.

A first population-based study looking at the relationship between small-dense LDL particles and adiponectin relationship, found an inverse relationship of low adiponectin levels with smaller LDL densities (125). Another study supported this LDL finding and also found a positive correlation with HDL, independent of age, sex, and BMI (126). However, a recent study, which looked at markers of inflammation such as lipoprotein particles, CRP levels, adiponectin, and insulin levels and did not find adiponectin to be correlated to CHD death, suggesting that simply serum concentration of this hormone may not be associated with hard clinical endpoints (127).

The importance of decreased adiponectin levels in hypertension may be emphasized by findings of decreased adiponectin plasma levels in hypertensive mice, particularly in response to angiotensin II infusion (31).

The potential benefits of adiponectin are the multiple mechanisms, via endothelium-proliferation regulations to the inflammatory effects on the vasculature, targeted therapy utilizing adiponectin may prove beneficial in future studies. Oral hypoglycemic agents, particularly pioglitazone, have been studied with an eye to metabolic parameters, including serum adiponectin levels secondary to its known anti-atherogenic effect. Statistically significant increase in adiponectin was detected (128).

### *Resistin*

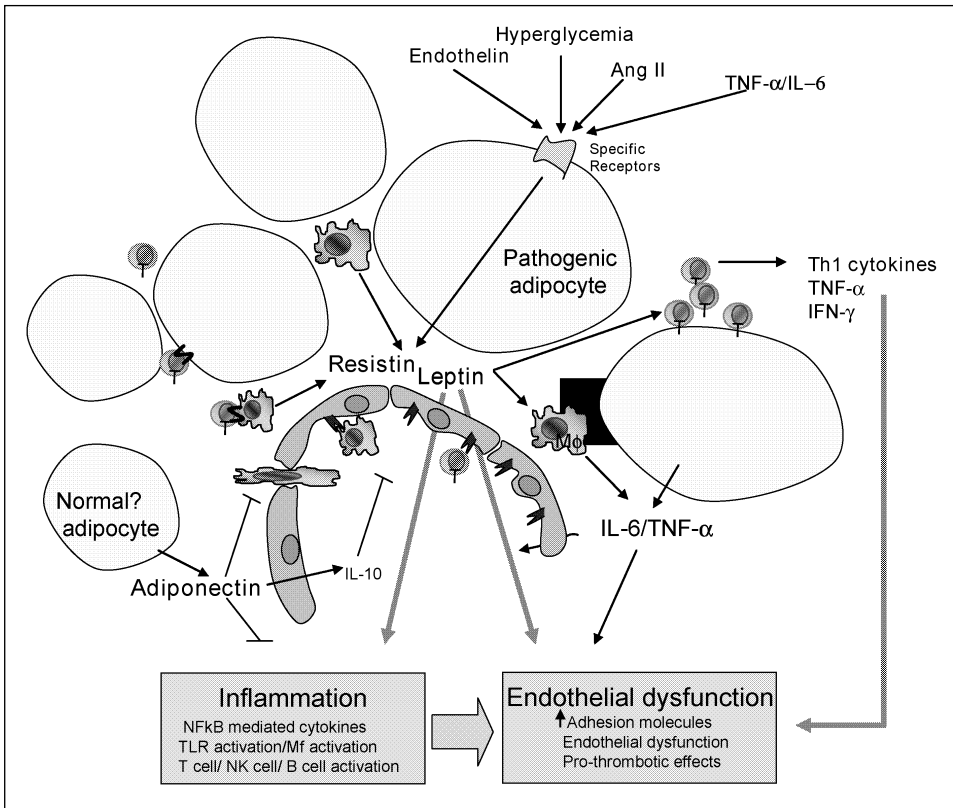
Resistin's role in endothelial function regulation has been relatively poorly defined so far. In an attempt to better clarify resistin's vascular mechanism in coronary vessels, isolated coronary rings and anesthetized dogs were found to have weakened endothelium dependent vasodilation with bradykinin, indicating some effects on endothelial function (129). However no effects were observed on acetylcholine induced vasodilatation (129). This conflict could indicate that resistin impairs predominantly EDHF - rather than NO- dependent vasorelaxations. No effect was reported on coronary blood flow, arterial pressure, or heart rate (129). Several studies have indicated an angiogenic aspect to resistin in endothelial cells (130), particularly targeting this mechanism to VEGF and MMP upregulation (131).

It is important to point out that resistin's effects may be mediated in the vascular tissues by NADPH oxidases in a similar fashion to effects of leptin discussed above (132).

However, it must be pointed out that comparison studies between the mouse and human expression of resistin showed that increased resistin expression occurred with myeloid lines than from adipocytes in a greater extent than in humans (133).

Effects of resistin on cardiovascular biology remain to be elucidated in detail yet.

In summary, adipocytokines, a relatively novel group of peptides and proteins, released by adipocytes and fat associated tissues can clearly modulate both immune functions and vascular function, both of which play critical role in cardiovascular morbidity and mortality. These aspects of adipose tissue properties, discussed in this review have been summarized in the *Figure 2*. While the interplay between the immune system and vascular cells is well documented



*Fig. 2.* Summary of “adipocyte-vascular axis” and role of major adipocyte - derived factors (leptin resistin and ghrelin) in the regulation of vascular and immune functions. Detailed description is provided in individual sections in the text of the paper.



in some vascular diseases like vasculitis or atherosclerosis, in other vascular phenotypes particularly associated with metabolic syndrome (e.g. hypertension) this interplay remains to be elucidated in more detail. Moreover one has to remember about other molecules involved in metabolic syndrome which are important in appetite control and adipocytes metabolism, which do not per se seem to originate from adipose tissue and have not been discussed in the present review. Ghrelin, is a good example of such peptide, linking gastrointestinal tract and satiety regulation to vascular function (134), particularly that it is released in response to certain immune related stimuli (135).

It is important to note that certain treatments, already employed in cardiovascular medicine may lead to significant changes in adipocytokine levels. For example include beta-2 adrenoreceptor agonists, thiazolidinodiones as well as androgens lead to decrease of plasma leptin levels. Moreover future treatments of metabolic system associated disorders should focus on the regulation of adipocytokines and their modes of action.

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Author's address: Prof. Richard Korbut MD PhD, Chair of Pharmacology, Jagiellonian University School of Medicine, 31-531 Krakow, 16 Grzegorzeczka, Poland.  
E-mail: r.korbut@cyf-kr.edu.pl