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RESEARCH REVIEW

Effects of Adipocyte-Derived Cytokines on Endothelial Functions: Implication of Vascular Disease

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Adipose tissue has recently emerged as an active endocrine organ that secretes a variety of metabolically important substances, collectively called adipocytokines or adipokines. In this review we summarize the effects of the adipokines leptin, adiponectin, and resistin on the vasculature and their potential role for pathogenesis of vascular disease. Leptin is associated with arterial wall thickness, decreased vessel distensibility, and elevated C reactive protein (CRP) levels. Leptin possesses procoagulant and antifibrinolytic properties, and it promotes thrombus and atheroma formation, probably through the leptin receptors by promoting vascular inflammation, proliferation, and calcification, and by increasing oxidative stress. Research for development of pharmacologic antagonism for the leptin receptor is currently under way. Adiponectin inhibits the expression of the adhesion molecules ICAM-1, VCAM-1, and P selectin. Therefore, it interferes with monocyte adherence to endothelial cells and their subsequent migration to the subendothelial space, one of the initial events in the development of atherosclerosis. Adiponectin also inhibits the transformation of macrophages to foam cells *in vitro* and decreases their phagocytic activity. Resistin, discovered in 2001, represents the newest of the adipokines and was named for its ability to promote insulin resistance. Resistin increases the expression of the adhesion molecules VCAM-1 and ICAM-1, up-regulates the monocyte chemoattractant chemokine-1, and promotes endothelial cell activation via ET-1 release. Although many aspects of its function need further clarification, it appears that resistin will add significantly to our knowledge of the pathophysiology of vascular disease and the metabolic syndrome.

Key Words: **adipocyte; adipokine; adipocytokine; leptin; adiponectin; resistin; endothelial function; vascular disease; atherosclerosis.**

INTRODUCTION

Atherosclerosis is a disease process that starts in fetal life [1] and is associated with a significant morbidity and mortality. Leading predisposing factors include hyperlipidemia, cigarette smoking, hypertension, obesity, and diabetes. Type 2 diabetes is closely associated with obesity and is caused by a relative resistance to insulin, which has recently emerged as a significant vascular hormone with important links to the pathophysiology of atherosclerotic vascular disease [2].

Recent studies have transformed our thinking about the adipocyte. It is no longer viewed as a passive energy storage tissue; instead, it has been recognized to produce a number of metabolically and hormonally active substances, collectively called adipokines or adipocytokines [3]. These adipokines consist of polypeptides but also nonprotein factors that are known to affect different functional categories including immunity function (complement factors and haptoglobin), endocrine function (leptin, sex steroids, and various growth factors), metabolic function (fatty acids, adiponectin, and resistin), and cardiovascular function (angiotensinogen and plasminogen activator inhibitor-1). Adiponectin, leptin, and resistin may have syner-

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gistic or competitive activity to insulin. Insulin resistance is an important factor for the development of coronary heart disease, supported by studies in animal models [4] and humans [5]. Therefore, these investigations have the potential to provide useful insight into the pathogenesis of vascular disease.

In this review, we present the current understanding of the complex role of the adipocyte-derived hormones leptin, adiponectin, and resistin on the endothelial cell function and the pathogenesis of atherosclerotic vascular disease. Mechanisms of action and data from animal and human studies, as well as controversies surrounding their function, are discussed.

LEPTIN

Leptin (from the Greek word *leptos* meaning thin) was identified by positional cloning in 1993 [6] as a key molecule in the regulation of body weight and energy balance. Subsequent research has revealed that the effect of leptin is not restricted to appetite and food intake. Leptin is a pleiotropic molecule with a broad variety of different biological actions, including reproductive function, regulation of the hypothalamic–pituitary–adrenal (HPA) axis, glucose and insulin metabolism, lipolysis, sympathetic nerve activity, immune response, hematopoiesis, and angiogenesis. Leptin is a 167 amino acid secreted protein encoded by the *ob* gene. It is predominantly expressed by adipocytes, and its plasma levels correlate well with the body fat mass [7]. The protein is comprised of four α-helices and two short β-strands, containing an intrachain disulfide bond necessary for its biological activity [8].

Adipocyte leptin expression is transcriptionally regulated, with the status of the energy stores in white adipose tissue and the adipocyte size as major determinants. In addition, leptin expression and serum levels increase after food intake. In contrast, leptin expression is rapidly suppressed with food restriction, exceeding the rate at which fat mass and adipocyte size is reduced [7].

Leptin receptor (LR) is encoded by the *db* gene. From the five isoforms of the receptor, the long form is expressed throughout the body and has been located in the hypothalamus, monocytes, natural killer cells, CD4 and CD8 lymphocytes, pancreatic β-cells, enterocytes, and endothelial cells [9].

Leptin and the Vasculature

The effects of leptin on the vasculature vary, and the exact mechanism remains unclear. Direct vasodilatory actions of leptin have been inconsistently reported. Fruhbeck [10] demonstrated that acute administration of leptin increases endothelial nitric oxide release in anesthetized Wistar rats but not in the leptin-receptor-deficient Zucker rat. These results suggest that the vasodilatory effect of leptin was mediated through leptin-receptor-dependent release of endothelial nitric oxide. Interestingly, despite nitric oxide release, decreased blood pressure was only observed in sympathectomized rats, suggesting that leptin-dependent activation of the sympathetic nervous system might offset the vasodilatory and nitric oxide-dependent effect of leptin [10, 11]. Moderate reductions in renal plasma flow and glomerular filtration rate were also observed in these experiments, suggesting that renal vasoconstriction occurs when the effect of leptin on endothelial cells is inhibited. Leptin in high doses has been demonstrated to increase human forearm blood flow [12] and dilate human coronary arteries *in vivo* [13]. However, the vasodilation mechanism appears to be independent of endothelial release of nitric oxide because NG-onomethyl-L-arginine, a nitric oxide synthase inhibitor, did not alter the vasodilatory action of leptin.

In contrast with results showing a vasodilator effect, leptin does not alter mesenteric blood flow in conscious Sprague Dawley rats treated with nitric oxide synthase inhibitors. Also, leptin does not change mesenteric blood flow in the presence of the α-adrenergic blockers prazosin and yoimbine, despite increased sympathetic activity to lumbar nerves [14]. Similarly, leptin does not alter renal, mesenteric, and hindquarters blood flow in conscious Long-Evans rats treated with a nitric oxide synthase inhibitor [15]. Additionally, β2-adrenergic blockade does not change regional blood flow in the presence of leptin. These results together contradict those of Fruhbeck [10] and suggest that leptin does not alter nitric oxide-dependent vascular reactivity of resistance vessels, even when α and β adrenergic peripheral vascular actions are inhibited. Intriguingly, systemic leptin administration does not attenuate renal or hindlimb vasoconstriction caused by sympathetic nerve stimulation. This result suggests that any direct vascular effects of leptin might be insufficient to oppose sympathetically mediated vasoconstriction [16]. So, while high concentrations of leptin may possess vasodilator properties through stimulation of nitric oxide generation, the exact effects of leptin on vascular function *in vivo* are still unclear.

The physiological role of leptin on the vasculature is supported by experimental results showing that leptin replacement in leptin-deficient obese ob^-/ob^- mice reverses endothelial dysfunction. However, whether weight loss could have confounded the interpretation of results is unclear because a pair-fed group of mice was not studied to control for reduced food intake of ob^-/ob^- mice treated with leptin [17].

Insulin may interact with leptin to modulate vascular function. The mechanism by which leptin induces nitric oxide production in some vascular beds is in part related to the activation of the Akt-endothelial nitric

oxide synthase phosphorylation pathway [18]. Insulin enhances leptin-dependent vasodilation by increasing endothelial nitric oxide release and by potentiating Akt and endothelial nitric oxide synthase phosphorylation [19]. Concomitantly, leptin increases insulin sensitivity in rats and may improve vascular responses to insulin in states of insulin resistance [20]. Thus, the cross-talk between leptin and insulin could have important implications in the pathophysiology of vascular dysfunction of metabolic syndrome, particularly in obesity-related hypertension.

Leptin and Atherosclerotic Disease

A number of observations correlate serum leptin with the pathogenesis of atherosclerotic vascular disease. Human plasma leptin concentrations are independently associated with the intima-media thickness of the common carotid artery, an early atherosclerosis marker [9]. Elevations in leptin concentrations in adolescents are associated with decreased arterial distensibility [21]. *Ob*$^{-}$*/ob*$^{-}$ mice are markedly resistant against diet-induced atherosclerosis [7]. Wild-type mice on an atherogenic diet show increased leptin levels and develop enhanced neointimal wall thickening after carotid artery injury. These lesions show a high LR expression. *Ob*$^{-}$*/ob*$^{-}$ mice do not show this diet-induced wall thickening despite the clear presence of atherosclerosis risk factors like diabetes, obesity, and hyperlipidemia. However, wall thickening can be induced in *ob*$^{-}$*/ob*$^{-}$ mice after leptin administration [22]. Leptin receptors are found on the endothelium [23], macrophages, and foam cells [24] and on vascular smooth muscle cells [25]. Interaction with these receptors appears to be the first step in the leptin-induced atheroma formation. Leptin also contributes to arterial thrombosis after vascular injury, and its prothrombotic effects are probably mediated through the platelet LR [26].

Two small case-control studies in Sweden first reported the association of leptin with myocardial infarction [27] and stroke [28]. The prospective West of Scotland Coronary Prevention Study (WOSCOPS) also showed that leptin moderately but independently increases the relative risk of coronary artery disease [29, 30]. Even though dyslipidemia does not appear to be independently related with leptin after correction for adiposity, leptin possesses complex proliferative, oxidative, proinflammatory, and prothrombotic actions that may help explain these epidemiological associations. Leptin administration to culture media to reach physiological and pathophysiologic concentrations dose-dependently increases both migration and proliferation of rat vascular smooth muscle cells [25] through activation of phosphatidylinositol-3-kinase and mitogen-activated protein kinases. In addition to its direct proliferative effect, leptin stimulates osteogenic transformation of cultured vascular cells that are prone to develop calcified lesions [31]. Leptin also appears to be an important factor for the regeneration of the endothelial intimal layer after vascular injury. It has been observed that neointimal formation after experimental endovascular injury in leptin receptor-deficient *db/db* mice is substantially reduced by 90% as compared with leptin-sensitive wild-type mice [32]. Together, these observations suggest that leptin may contribute to vascular remodeling and senescence, and perhaps arterial restenosis after angioplasty. Leptin also increases oxidative stress through multiple mechanisms. In bovine aortic endothelial cells, leptin dose-dependently increases the formation of reactive oxygen species in a process coupled with increased fatty acid oxidation and activation of protein kinase A [33]. In rats, chronic induction of hyperleptinemia decreases paraoxonase-1 activity, an antioxidant enzyme contained in plasma lipoproteins. Leptin-dependent reduction in paraoxonase-1 activity is followed by increased plasma and urinary concentration of isoprostanes reflecting increased oxidative stress [34]. Oxidative stress can cause direct endothelial or vascular smooth muscle damage but may also operate as an indirect factor to increase serum atherogenic factors. By increasing oxidative stress and activating protein kinase C, leptin increases the secretion of atherogenic lipoprotein lipase from macrophages *in vitro* [35].

Stimulation of low-grade vascular inflammation is another mechanism by which leptin could promote endothelial dysfunction and atherogenesis [36]. Leptin deficient *ob*$^{-}$*/ob*$^{-}$ mice and leptin receptor-deficient *db*$^{-}$*/db*$^{-}$ mice are susceptible to infections due to immune system suppression. Leptin replacement ameliorates immune system function in *ob*$^{-}$*/ob*$^{-}$ mice, but not in the *db*$^{-}$*/db*$^{-}$ mouse [37], as would be expected in a receptor-deficient model. Furthermore, *in vitro* administration of leptin to lipopolysaccharide (LPS)-activated macrophages collected from *ob*$^{-}$*/ob*$^{-}$ and *db*$^{-}$*/db*$^{-}$ mice substantially potentiates secretion of tumor necrosis factor and interleukins-2 and -6. These results indicate that leptin is involved in the regulation of immune function and cytokine secretion in *ob/ob* mice. Currently, information regarding the interaction between leptin and inflammatory reactions in humans is limited.

In a cross-sectional study [38] involving young healthy men, leptin was independently associated with C reactive protein, a well-recognized marker of atherosclerotic vascular risk. It is unknown whether this is a causal association. As previously stated, leptin is independently associated with decreased arterial distensibility in healthy adolescents within a wide range of body-mass indices (BMIs) [21]. In line with the evidence from *in vitro* studies, this result could reflect accelerated vascular aging and remodeling in adoles-

cents that might be associated with higher plasma leptin concentrations. In summary, these experimental results strongly suggest that leptin may contribute to the pathophysiology of atherogenesis by promoting vascular inflammation, proliferation, and calcification, and by increasing oxidative stress.

Leptin may be indirectly involved in the pathogenesis of atherosclerosis via effects on blood pressure. A positive correlation is found between mean blood pressure and leptin serum levels in lean subjects with essential hypertension [39]. The effects of leptin on blood pressure can vary between chronic and acute administration. Chronic intravenous injection of leptin in Sprague–Dawley rats increases their arterial pressure [40], while acute intravenous injection of leptin in sympathectomized rats decreases their arterial pressure [11]. Intracerebroventricular leptin administration in rats or in rabbits increases blood pressure through an increased lumbar and renal sympathetic nerve activity [41, 42]. An observation that may help explain this apparent effect of leptin on blood pressure is that *in vitro* treatment of human umbilical vein endothelial cells (HUVECs) with leptin induces endothelin-1, a known potent vasoconstrictor [43].

Strategies to antagonize the leptin activity are being developed. These include the use of the secreted leptin receptor (sLR) [44, 45] or the use of leptin antagonists, such as R128Q or LPA-2 [7]. The main effects of leptin on food intake and energy expenditure occur at the level of the hypothalamus, whereas the effect on the vascular system is mediated by receptors on peripheral target cells. Therefore, developing a selective leptin inhibitor that acts only in the peripheral receptors appears to be a prerequisite of effective leptin antagonism.

Thrombosis and Leptin

Experimental evidence mostly from animals suggests that leptin could be an important procoagulant factor. Thrombi originating from arterial lesions in ob^-/ob^- mice are unstable as compared with littermate controls. Leptin replacement normalizes thrombus formation in ob/ob mice. Furthermore, aggregation of platelets is attenuated in ob^-/ob^- and db^-/db^- mice but leptin normalizes platelet aggregation only in ob^-/ob^- mice [46]. The time for thrombus formation is prolonged in ob^-/ob^- and db^-/db^- mice after carotid lesion formation [26]. Moreover, bone marrow transplanted from db^-/db^- mice to normal mice delays thrombus formation in the transplant recipients, suggesting that platelet leptin receptors are important for normal thrombogenesis. Leptin also increases human platelet aggregation *in vitro* by a receptor-dependent mechanism [47]. In addition, leptin modestly decreases the expression of thrombomodulin, an anticoagulant protein, in cultured HUVECs [47].

Fibrinolysis may also be modulated in part by leptin. One human study, adjusted for differences in adiposity and age, found a significant association between leptin and decreased tissue plasminogen activator activity, and high PAI-1 activity, in men and postmenopausal women [48]. These prothrombotic actions of leptin could potentially contribute to the increased risk of obese subjects in developing acute coronary events, venous thrombosis, and pulmonary thromboembolism.

ADIPONECTIN

Human adiponectin was isolated from the plasma as gelatin binding protein of 28 kDa [49]. It contains 244 amino acid residues and consists of a 20-residue signal sequence, an N-terminal region without homology to any known proteins, a collage-like region, and a C-terminal globular domain. Under normal conditions, adiponectin gene is expressed almost exclusively in the adipose tissue. However, adiponectin mRNA appears in hepatocytes after treatment with carbon tetrachloride or IL-6 [50, 51].

Several mechanisms regulate the expression of adiponectin. Insulin and insulin-like growth factor-1 (IGF-1) both up-regulate adiponectin expression [52], whereas TNF-α as well as activation of the peroxisome proliferators-activated receptor α (PPARα) have the opposite effect [53]. The role of β3 adrenergic receptor activation remains controversial [50, 53]. Finally, there is evidence of adiponectin receptor on human aortic endothelial cells that acts through cAMP protein kinase A activation [54, 55]. However, more studies are needed in this area.

Adiponectin and Vascular Disease

Several studies have indicated that adiponectin possesses anti-inflammatory properties and thus may negatively modulate the process of atherogenesis. One of the initial steps in atherogenesis is adherence of monocytes to endothelial cells and their migration into subendothelial space, where they take up oxidized lipoproteins and transform them into foam cells. Adiponectin dose dependently suppresses TNF-α-stimulated adherence of monocytes to cultured human endothelial cells. This effect results from inhibition of the expression of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intercellular adhesion molecule-1 (ICAM-1). TNF-α increases, whereas adiponectin reduces, the amount of these proteins and their respective mRNAs in endothelial cells [56]. The mechanism of adiponectin action in endothelial cells has been further investigated. TNF-α activates nuclear transcription factor NF-κB in these cells by stimulating protein kinase NIK (NF-κB inducing kinase), which phosphorylates the NF-κB inhibitor, IκB, initiating its degradation and thus leading to

NF-κB activation. NF-κB stimulates the expression of cytokines and adhesion molecules involved in the inflammatory process. Adiponectin inhibits TNF-α dependent phosphorylation and degradation of IκB. The effect of adiponectin is specific for the IκB-NF-κB pathway because no changes in the phosphorylation of other proteins induced by TNF-α have been observed. The inhibition of IκB phosphorylation is most likely mediated by the cAMP-protein kinase A pathway because it is mimicked by the membrane-permeable cAMP analogue, dibutyryl-cAMP, and blocked by inhibitors of either adenylate cyclase or protein kinase A [50, 54].

In addition, adiponectin decreases the cholesterol esters content in macrophages by about 50% and inhibits transformation of macrophages to foam cells *in vitro*. The effect is mediated by decreased expression of scavenger receptors class A Type 1, which are responsible for uptake of modified low-density lipoproteins (LDLs) by macrophages. It has no effect on class B (CD36) scavenger receptor expression. Also, adiponectin inhibits specific binding of oxidized LDLs and their uptake by macrophages [57] and specifically inhibits proliferation of myelomonocytic bone marrow progenitor cells and induces their apoptosis by reducing the expression of antiapoptotic gene Bcl-2 [55].

Adiponectin also inhibits proliferation of human peripheral blood monocytes, reduces their phagocytic activity, and inhibits TNF-α expression stimulated by LPS, but not by IL-1 or IL-6 [55]. Thus, adiponectin can suppress atherogenesis by inhibiting the adherence of monocytes, reducing their phagocytic activity and decreasing the accumulation of modified lipoproteins in the vascular wall. These data suggest that adiponectin deficiency associated with obesity and/or type 2 diabetes may contribute to accelerated atherogenesis in these states. In support of this hypothesis, the circulating adiponectin concentration has been found to be lower in patients with ischemic heart disease than in age- and BMI-matched controls [56]. Similar results have been observed among patients with type 2 diabetes mellitus [58]. However, adiponectin is found in the subendothelial space of carotid arteries which have been injured by a catheter [59] and in atherosclerotic lesions with injured endothelium in human abdominal aorta [57, 60]. Thus, it is also possible that the lower plasma adiponectin in these patients is secondary to accelerated degradation of the protein due to its accumulation in the vessel wall. In a recently published prospective study, Zoccali *et al.* [60] have shown that low levels of adiponectin are related to subsequent cardiovascular events in hemodialyzed patients. This study confirms that hypoadiponectinemia plays a causative role in atherogenesis, at least in patients with end-stage renal disease.

RESISTIN

Resistin is a member of a newly discovered family of cysteine-rich secretory proteins called "resistin-like molecules" (RELM) or "found in the inflammatory zone" (FIZZ). It was initially discovered in a screen to identify potential targets of the thiazolidinedione (TZD) class of insulin sensitizers in 3T3-L1 adipocytes [61]. Resistin is encoded by the *Retn* gene, and is secreted as a disulfide-linked dimer [62]. In mice, the *retn* gene is expressed almost exclusively in white adipose tissue and the protein is detectable in adipocytes and in the blood. This observation suggests that resistin is produced primarily by adipose tissue and may act at sites distant from where it is produced [61]. Unlike murine resistin, human resistin is expressed at low levels in adipocytes but is readily detectable in mononuclear blood cells [63, 64].

Resistin appears to be an important regulator of glucose homeostasis, adipogenesis, and, potentially, inflammation [65, 66]. Obesity induced by a high fat diet, mutation of the leptin gene (ob^-/ob^- mice), or the leptin receptor gene (db^-/db^- mice) is associated with increased circulating resistin concentrations [50]. Resistin induces insulin resistance in mice and regulates the deposition of adipose tissue through a negative feedback mechanism. However, its exact mechanism of action and regulation of expression remain controversial. Animal studies aiming at clarifying the role of PPAR receptor on resistin secretion have been inconclusive, and resistin expression has been found to be both up- and down-regulated after stimulation of this receptor [50, 61, 67]. The effect of insulin is also controversial. Insulin down-regulated resistin expression in 3T3-L1 adipocytes [68], whereas *in vivo* studies in mice and rats have shown a stimulatory effect [67].

Recently, in addressing the function of resistin in insulin resistance, mice lacking resistin were generated by Banerjee *et al.* by replacing the coding exons of the gene (rstn) with the lacZ reporter [30]. These rstn (K/K) mice on a chow diet had normal glucose tolerance. Their fasting glucose levels were 20–30% lower as compared with wild-type mice. However, when fed a high-fat diet, these mice showed significantly better glucose tolerance as compared with wild-type mice. Nevertheless, fasting insulin levels and insulin tolerance were not altered in rstn (K/K) mice on either chow or high fat diets. However, hyperinsulinemic euglycemic glucose clamp studies of rstn (K/K) mice indicated a higher glucose infusion rate with a dramatic reduction in glucose production, but without significant differences in whole body glucose disposal as compared with wild-type mice.

Transgenic mice overexpressing a human IgG constant region (hFc)-resistin fusion protein that blocks inhibition of adipocyte differentiation mediated by resistin has also been generated [69]. The resistin fusion

protein forms homo- or heterooligomers with the endogenous resistin and with other members of the resistin/FIZZ family. It is likely that the hFc domain blocks the resistin interaction with its receptor. Transgenic mice in these studies seemed to demonstrate a more severely affected phenotype with respect to glucose homeostasis and obesity. These mice showed increased adiposity in a transgene dose-dependent manner, secondary to adipocyte differentiation and hypertrophy, with subsequent increased circulating leptin and adiponectin levels. Interestingly, they also demonstrated an enhanced glucose tolerance to chow and high-fat diets compared to wild-type strains. This overall complex phenotype of insulin sensitivity and adipogenesis could stem from a chronic impairment of the inhibitory function of resistin on adipocyte differentiation, and it is likely to arise from the heterooligomerization of the hFc-resistin with other RELM members [70].

Resistin and Vascular Disease

The effect of insulin on endothelial cell function and the overall physiology of the vasculature have been well documented [2]. It was, therefore, legitimate to presume that resistin would affect the vascular endothelium. A few such studies have recently appeared in the literature. Verma *et al.* [71] investigated the effect of resistin on human saphenous vein endothelial cell activation. They have found that resistin promotes endothelial cell activation by promoting ET-1 release. They have also proved that it up-regulates VCAM-1 and the monocyte chemoattractant chemokine-1 (MCP-1), while it down-regulates the expression of TNF- receptor-associated factor-3 (TRAF-3), an inhibitor of CD40 ligand signaling [71]. In a similar manner, Kawanami *et al.* [72] investigated the effects of resistin on human aortic endothelial cells. They have found that resistin induces the expression of the adhesion molecules VCAM-1, ICAM-1, and pentraxin 3, a marker of inflammation, which shares high homology with the C-reactive protein and that this is done via an NF-κB dependent pathway. In their studies, pitavastatin, an HMG CoA inhibitor, inhibited resistin-induced VCAM-1 activation in a dose dependent manner, but it failed to inhibit the expression of ICAM-1. Adiponectin inhibited the resistin induced up-regulation in VCAM-1 and to a lesser extent ICAM-1 expression. Taken together, these data indicate that resistin activates endothelial cells and may promote the initiation or perpetuation of the atherosclerotic state. Further questions, however, remain. For instance, because energy metabolism is different between mice and humans, do the observations made in rodents apply to human physiology? How does resistin interfere with insulin signaling? Are there any receptors in the endothelium or the smooth muscle cells of the vessel wall? If yes, what studies are needed to identify resistin receptors and their distribution among different organs, as well as the signaling pathways that regulate resistin activity on endothelial cells?

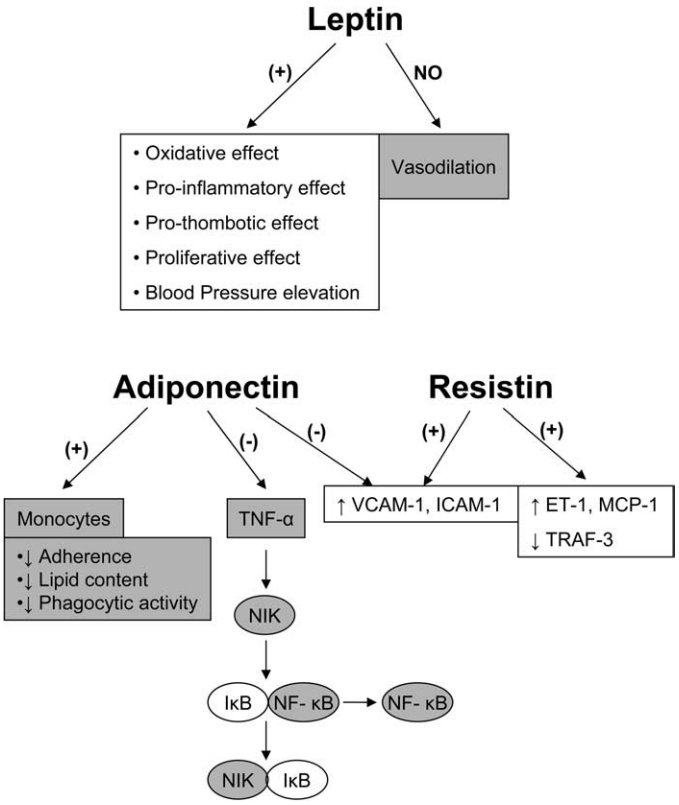

FIG. 1. Adipokines interact in a complex way to regulate endothelial function and ultimately atherosclerosis. Leptin possesses prothrombotic, proinflammatory, oxidative, and proliferative properties. It also elevates systemic blood pressure, despite a NO-dependent induced vasodilation. Adiponectin regulates monocyte functions, inhibits the TNF-α dependent NF-κB up-regulation, and down-regulates the expression of adhesion molecules VCAM-1 and ICAM-1. Resistin has been shown to promote the release of ET-1 and favors the expression of VCAM-1, ICAM-1, MCP-1, TRAF-3, and pentraxin-3 adhesion molecules. NF-κB, nuclear factor kappa B; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemoattractant chemokine-1; ET-1, endothelin-1; TRAF-3, TNF- receptor-associated factor-3.

Resistin is an exciting new molecule, and answers to these questions are expected to improve our understanding of the pathophysiology of vascular disease and the metabolic syndrome in general.

SUMMARY

The identification of adipokines is intriguing from both a theoretical and clinical point of view. There are several lines of evidence to support the notion that at least the three adipokines discussed above are involved in the pathogenesis of atherosclerotic disease (Fig. 1). As further data from human studies are accumulated,

the role of adipokines will continue to evolve. The development of pharmacologic antagonists is a very attractive idea and may have implications for both the treatment of atherosclerotic disease as well as that of diabetes.

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