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Inflammation and metabolic dysfunction: links to cardiovascular diseases

Annika Taube,* Raphaela Schlich,* Henrike Sell, Kristin Eckardt, and Juergen Eckel
Paul Langerhans Group, German Diabetes Center, Duesseldorf, Germany

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Taube A, Schlich R, Sell H, Eckardt K, Eckel J. Inflammation and metabolic dysfunction: links to cardiovascular diseases. *Am J Physiol Heart Circ Physiol* 302: H2148–H2165, 2012. First published March 23, 2012; doi:10.1152/ajpheart.00907.2011.— Abdominal obesity is a major risk factor for cardiovascular disease, and recent studies highlight a key role of adipose tissue dysfunction, inflammation, and aberrant adipokine release in this process. An increased demand for lipid storage results in both hyperplasia and hypertrophy, finally leading to chronic inflammation, hypoxia, and a phenotypic change of the cellular components of adipose tissue, collectively leading to a substantially altered secretory output of adipose tissue. In this review we have assessed the adipo-vascular axis, and an overview of adipokines associated with cardiovascular disease is provided. This resulted in a first list of more than 30 adipokines. A deeper analysis only considered adipokines that have been reported to impact on inflammation and NF-κB activation in the vasculature. Out of these, the most prominent link to cardiovascular disease was found for leptin, TNF-α, adipocyte fatty acid-binding protein, interleukins, and several novel adipokines such as lipocalin-2 and pigment epithelium-derived factor. Future work will need to address the potential role of these molecules as biomarkers and/or drug targets.

adipokines; adipose tissue

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Introduction

Obesity is a metabolic disorder of pandemic proportions and is associated with a variety of metabolic dysfunctions like hypertension, dyslipidemia, insulin resistance, and hyperglycemia (199). Thus it is considered a major risk factor for the development of chronic diseases such as type 2 diabetes (145) and cardiovascular diseases (109, 219). Adipose tissue enlargement ensues as a consequence of a persistent positive energy balance resulting from a sedentary lifestyle, conditioned by environmental and genetic factors. Formerly, the function of adipose tissue was thought to be restricted to insulate and cushion the body, store triglycerides during periods of excess energy and provide the body with energy in the form of free fatty acids in states of energy shortage (89). However, it has become increasingly evident that adipose tissue is also a secretory organ able to release various lipid mediators as well as a multitude of bioactive proteins and peptides, collectively referred to as adipokines (275).

Today, it is commonly accepted that adipokines have essential roles in energy homeostasis, glucose and lipid metabolism, cell viability, control of feeding, thermogenesis, neuroendocrine function, reproduction, immunity, and, importantly, cardiovascular function (88). Accordingly, numerous studies in recent years have demonstrated the pivotal role of adipokines as molecular messengers in the cross talk of adipose tissue with other organs and tissues as well as their contribution to the development of obesity-associated disorders. However, this picture has gained complexity since modern approaches applying highly sensitive analytical techniques have revealed that the adipose tissue output is comprised of hundreds of different factors (4, 130, 226, 334), with additional novel adipokines still being identified (143). Furthermore, it has been described that the adipokine profile may vary between different adipose tissue depots and is altered in pathological conditions such as obesity. In this context, it has been shown that plasma levels of several proinflammatory cytokines as well as acute phase proteins such as C-reactive protein (CRP) are increased in obesity, contributing to a chronic state of low-grade inflammation (67, 326, 327). This systemic inflammatory state has been suggested to be a causative link between obesity and related secondary complications such as cardiovascular diseases (306), by inducing inflammatory processes in the vessel wall. Such processes are considered to be critical determinants of pathological alterations of the vasculature such as thickening of vessel wall, fatty streak formation, or promotion of atherosclerotic plaques.

Previous studies have demonstrated local production of proinflammatory mediators by immune cells of atherosclerotic plaques [for reviews, see Lippy et al. (154) and Zakynthinos and Pappa (329)]; however, in this review we will elucidate the role of adipose tissue-derived factors in the induction of inflammatory processes in the vasculature and focus especially on selected adipokines able to activate nuclear transcription factor-κB (NF-κB) signaling. Furthermore, we will discuss the special role of perivascular fat as a local adipose tissue depot

* A. Taube and R. Schlich contributed equally to this work

Address for reprint requests and other correspondence: J. Eckel, German Diabetes Ctr., Auf'm Hennekamp 65, D-40225 Duesseldorf, Germany (e-mail: eckel@uni-duesseldorf.de).

and its contribution to the development of cardiovascular diseases. In this context, we propose a list of candidates, including well-known as well as novel adipokines, involved in the induction of inflammatory processes and possibly leading to atherosclerotic lesions as well as cardiovascular complications. With this, we provide new insights into the role of adipokines in the complex interorgan cross talk between adipose tissue and the vasculature. Understanding the molecular mechanisms linking inflammation, metabolic syndrome, and cardiovascular diseases is essential to identify possible biomarkers and potential drug targets. These are important steps to improve diagnosis and treatment of cardiovascular diseases.

Obesity-Associated Alterations of Adipose Tissue

Enlargement of adipose tissue ensues as a result of an imbalance between energy intake and expenditure. As a consequence, adipocytes undergo hyperplasia and hypertrophy to meet the increased demand for storage capacities (75, 102). However, a persistent state of energy excess represents an increased burden for the lipid storage and processing capacities of the expanding adipose tissue, resulting in various dysfunctions within the tissue like low-grade chronic inflammation and hypoxia (123, 306). These obesity-associated dysfunctions may lead to changes in the cellular composition of the tissue, including alterations in the number, phenotype, and localization of immune, vascular, and structural cells (199), resulting in an altered adipose tissue secretory output. Increased expression of chemoattractant proteins like monocyte chemoattractant protein-1 (MCP-1) induces recruitment and infiltration of additional macrophages. These contribute to the increased expression of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) (104), thereby further exacerbating the obesity-associated inflamed status of the adipose tissue (301, 306, 313). Additionally, obesity-associated adipocyte hypertrophy has also been associated with a shift of the adipocyte secretome to a more proinflammatory composition (253). In this context, a positive correlation has been described between adipocyte size and secretion of various proinflammatory factors such as TNF-α, IL-6, IL-8, MCP-1, leptin, and granulocyte colony-stimulating factor (253). Whereas the majority of adipokines have been found to be increased in obesity, the expression of adiponectin is decreased (107). Unlike many other adipokines, adiponectin has been correlated to insulin-sensitizing, anti-inflammatory, and anti-proliferative properties (8, 152, 203). Therefore, adiponectin has been attributed a cardioprotective role.

These observations demonstrate that the adipose tissue output dramatically changes in pathological conditions such as obesity. However, the adipokinome may already vary depending on the site of the adipose tissue depots (199). Adipose tissue in the visceral and the subcutaneous compartment are the two most abundant depots, and it has been shown that they produce unique profiles of adipokines (199, 287). In this context, visceral adipose tissue has received special attention since various studies have found a positive correlation between the amount of visceral adipose tissue and cardiovascular diseases (23, 216). Recent studies have even proposed that visceral adiposity, measured as waist circumference, is a more precise risk indicator for type 2 diabetes and cardiovascular diseases than whole body obesity (113, 160, 229, 239). On the one hand this may be attributed to its location, as it drains directly into the portal vein (9). Special depots of visceral adipose tissue, perivascular and epicardial tissue, might also be located around blood vessels and the heart, respectively, where they specifically affect local tissues, as further discussed below. On the other hand, the visceral adipokinome contains many proinflammatory cardiovascular risk factors, such as IL-6 and plasmin activator inhibitor-1 (PAI-1) (10, 288), which contribute to the close association of visceral adipose tissue and cardiovascular disease.

The Adipo-Vascular Axis

Obesity is often associated with and represents a major risk factor for the development of cardiovascular diseases. Cardiovascular diseases are responsible for one of the highest mortality rates worldwide, accounting for 16.7 million deaths each year (49, 159), mostly because of the life-threatening complications of coronary artery and cerebrovascular disease (92). While cardiovascular diseases may be characterized by alterations like coronary artery calcification, thickening of vessel wall, formation of fatty streak and atherosclerotic plaques, vessel stiffness, and/or hypertension, atherosclerosis may be considered the principal contributor (2, 24, 228). Originally, atherosclerosis was believed to be a merely passive accumulation of cholesterol in the vessel wall; however, since novel data indicate underlying inflammatory processes to play a major contributing role (203, 221), this review aims to elucidate the role of proinflammatory adipokines in the pathogenesis of atherosclerosis.

To comprehend the influence of adipokines on the development of atherosclerosis, understanding the complex course of events taking place in the pathogenesis of atherosclerosis is important. It has been demonstrated that in the early stages of atherosclerosis, endothelial cells may be activated by various inflammatory stimuli, including a diet rich in saturated fat, hypercholesterolemia, obesity, hyperglycemia, insulin resistance, hypertension, and smoking, triggering the expression of adhesion molecules like vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intracellular adhesion molecule-1 (ICAM-1) (110, 203, 228). This increases the adherence of monocytes, which infiltrate the subendothelial space and accumulate within the intima (196, 198). In response to overexpression of macrophage colony-stimulating factor in the inflamed intima, which is induced by modified low-density lipoprotein, monocytes are converted to activated macrophages (203). These may then convert to foam cells by receptor-mediated incorporation and accumulation of lipoprotein particles (61, 203). The formation of foam cells and their continued accumulation in the intima, accompanied by proliferation and migration of smooth muscle cells (SMCs) from the media, leads to the first stage of the atherosclerotic lesion, the fatty streak (110). Continued exposure to atherosclerotic factors promotes the progression to more complex atherosclerotic plaques, until destabilizing factors like thinning of the fibrous cap and high foam cell content elicit rupture of a plaque, triggering thrombus formation (110). This in turn may either obstruct the lumen immediately or detach to form an embolus blocking blood flow distal to its origin. Consequently, such atherothrombosis may result in myocardial or brain infarction.

As mentioned above, a major risk factor for the development of atherosclerosis is obesity and the associated adipokines. To elucidate the molecular basis of this adipo-vascular axis, numerous studies have attempted to assess the impact of various adipokines on the cells of the vessel wall. In this context it has been described that various processes may be affected by adipokines. As abnormal proliferation and migration of SMCs located in the arterial intima has been suggested to be a central event in atherosclerosis (227, 241), adipokines able to induce proliferation or migration have to be considered as potential players in this process. Similarly, the activation of inflammatory signaling by adipokines like TNF-α, leptin, and PAI-1 has been suggested to contribute to the development of cardiovascular diseases (196, 245) by stimulating the generation of endothelial adhesion molecules, proteases, and other mediators, which may enter the circulation in soluble form (203). In this context the transcriptional regulator NF-κB plays a central role, as it mediates the expression of a multitude of genes. Among many others, the expression of adhesion molecules ICAM-1, VCAM-1, and E-selectin has been described to be mediated via NF-κB activation (197, 198). Thus adipokine-induced activation of NF-κB may promote adherence, diapedesis, and accumulation of immune cells such as monocytes or lymphocytes in the vessel wall, which play a central role in atherosclerotic plaque formation (203). Additionally, NF-κB activation is involved in SMC proliferation (144) and mediates the expression of a variety of proinflammatory molecules by macrophages and SMCs (14).

In recent years a number of studies have investigated the impact of selected adipokines on the different steps in the pathogenesis of atherosclerosis mentioned above. However, intensive research on the adipokinome in recent years has *1*) demonstrated the very complex nature of the secretory output of adipocytes, *2*) suggested novel roles for well-known adipokines, and *3*) identified a number of novel adipokines associated with a vasoactive potential. As this multitude of studies conducted in various species and different models makes it difficult to identify promising candidates for drug target or biomarker validation, this review provides a novel summary of available data and evaluation of the vasoactive potential of currently known adipokines based on the evidence found in literature. As a general overview, Table 1 provides a list of adipokines currently described to be associated with cardiovascular disease, including their impact on proliferation, inflammation, and NF-κB activation. However, this list is likely to soon require updating as an increasing number of adipokines are rapidly identified and associated with a vasoactive potential.

The fact that this multitude of adipokines has been found to modulate vascular homeostasis underlines the pivotal role of the adipokinome in the adipose tissue/vessel cross talk. Because of these findings, we propose that obesity-induced inflammatory processes within the adipose tissue and the paracrine action of the associated proinflammatory adipokinome trigger endothelial dysfunction and vascular inflammation, which may ultimately lead to atherosclerosis, heart attack, or stroke (Fig. 1).

Adipokines with a Tight Link to Cardiovascular Disease

To analyze in more detail the adipokines presented in Table 1, we selected those adipokines with reported effects on NF-κB activation. Since NF-κB is one of the major transcription factors that has been linked to both cardiovascular health and diseases, it is not suprising that NF-κB has been shown to influence numerous cardiovascular diseases including atherosclerosis (283). The function of NF-κB is largely dictated by the genes that it targets for transcription and varies according to stimulus and cell type (283). We are certainly aware that several adipokines induce cardiovascular diseases independent of NF-κB; however, this is not part of this review.

Here we have distinguished two groups of adipokines. The first group represents adipokines with a tight link to cardiovascular diseases based on evidences from in vitro and clinical studies (Table 2) as well as from animal models (Table 3). The second group includes adipokines with less strong evidence for the development of cardiovascular diseases, since data from animal models are not available either because the animal model has not been generated up till now or the specific knockout is lethal, as for VEGF.

Adiponectin and leptin: classical adipokines. Adiponectin, almost entirely produced by adipocytes, is one of the most comprehensively studied adipokines, and in human obese subjects its levels are diminished (176). It has been shown to positively influence energy consumption and fatty acid oxidation in muscle and liver, thereby reducing the triglyceride content (264). Transgenic mice overexpressing adiponectin exert an improved lipid profile (15, 194). Adiponectin has been suggested to be an important factor modulating the cardiovascular system because of its anti-atherogenic and anti-inflammatory effects. In macrophages and endothelial cells, it acts via suppression of TNF-α (196) and proinflammatory cytokines such as IL-6 (308) and directly ameliorates endothelial dysfunction by increasing nitric oxide (NO) production (52, 96). In addition, adiponectin reduces vascular SMC proliferation and migration (207). The role of adiponectin as an cardioprotective adipokine is further supported by results from clinical studies. While increased adiponectin levels are associated with a decreased risk of myocardial infarction (210), hypoadiponectinemia is observed in patients with coronary atherosclerosis and acute coronary syndrome (ACS) (139, 187). In a recent study, it has been shown that serum adiponectin is associated with biomarkers of insulin resistance, inflammation, and endothelial dysfunction, which are independent risk factors for cardiovascular diseases (65). In addition, results from animal studies have revealed that adiponectin exerts beneficial effects at mostly all stages of the atherosclerotic process (200).

Leptin, which directly influences food intake, was the first adipokine identified (90) and is primarily synthesized by white adipose tissue (164). The results of clinical studies investigating the contributions of leptin to the pathophysiology of cardiovascular complications are controversial, leaving the precise role of leptin unclear (266). Some studies have reported elevated leptin levels in patients with ACS (19, 246) and described an association between circulating leptin levels and risk of coronary artery disease (CAD) (289, 305). However, the findings of other studies have indicated no clinically relevant association with risk of CAD (26, 122, 302). The effects of leptin on endothelial cells and vascular SMCs are better investigated and comprise increased NO production via activation of endothelial NO synthase (eNOS) (285) and increased expression and activity of inducible NO synthase (iNOS), respectively (222). However, leptin also increases the expression of

Table 1. *Overview of adipokines associated with cardiovascular disease*

Adipokine	Proliferation	Inflammation	NF-κB Activation	Depot
Adiponectin	↓ (8, 144, 180)	↓ (197)	↓ (197)	↑ v(192, 258); ↑ sc(68, 155)
Adipsin	–	↑ (53, 276)	–	↑ v(10)
A-FABP	↑ (58)	↑ (152)	↑ (152)	↑ v(89)
Angiotensin II	↑ (47, 180)	↑ (236, 314)	↑ (279)	–
ANGPTL2	–	↑ (193, 199)	–	↑ sc(78)
Apelin	–	↑ (53)	–	–
Chemerin	↑ (125)	↑ (93) ↓ (318)	↑ (242)	↔(84)
CXCL5	–	↑ (199)	–	–
DPP-4	↑ (143)	–	–	↑ v(143)
G-CSF	↑ (40)	↑ (262)	–	–
IL-1β	↑ (180, 276)	↑ (53, 276)	↑ (307, 314)	↔(233)
IL-4	↑ (274) ↓ (282)	↑ (53)	↔(307)	–
IL-6	↑ (180, 276)	↑ (53, 195, 199)	–	↑ v(62, 73)
IL-8	↑ (180)	↑ (53)	↑ (172)	↔(233); ↑ v(28)
Il-10	↓ (180)	↓ (337)	↓ (178, 337)	(–)
IL-18	↑ (37)	↑ (53, 199)	↑ (37)	(–)
Leptin	↑ (108, 180, 304)	↑ (195, 199, 276)	↑ (108)	↑ sc(10, 182)
Lipocalin 2	–	↑ (199) ↓ (330)	↓ (60)	–
MCP-1	↑ (180, 276)	↑ (53, 199)	–	↑ v(29)
MIF	↑ (180) ↔(240)	↑ (53, 240)	↑ (232)	↑ v(5); ↔(254)
MIP-1a	↑ (162, 276)	↑ (98)	–	–
Nesfatin-1	–	↑ (318)	–	↑ sc(213)
Omentin	–	↓ (318, 319)	–	↑ v(321)
PAI-1	↑ (41, 54, 180); ↓ (137)	↑ (203) ↓ (212)	–	↑ v(62, 245); ↑ sc(59); ↔(3)
PDGF	↑ (333)	–	–	–
PEDF	↑ (64)	↑ (64)	↑ (64)	↑ v(291)
RANTES	↔(244)	↑ (177)	–	↑ sc(163)
RBP4	–	↑ (111, 199)	–	↑ v(60); ↑ sc(233)
Resistin	↑ (180)	↑ (22, 141, 199)	↑ (22, 247)	↔(179)
Sfrp5	–	↓ (195, 199)	–	–
TGFβ	↑ (277)	↑ (276)	–	↔(3)
TNFα	↑ (180, 276)	↑ (195, 199)	↑ (198, 307)	↔(10, 89)
TSP1	↑ (260) ↓ (265)	↓ (260)	↓ (271)	↑ v(214)
Vaspin	–	↓ (208, 318)	↓ (208)	↑ v(272)
VEGF	↑ (32, 66, 125)	↑ (129)	↑ (175)	↑ v(62)
Visfatin	↑ (180)	↑ (199, 225)	↑ (225)	↔(17)

A-FABP, adipocyte fatty acid-binding protein; ANGPTL2, angiopoietin-like 2; CXCL5, C-X-C motif chemokine 5; DPP-4, dipeptidyl peptidase-4; G-CSF, granulocyte colony-stimulating factor; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MIF, macrophage migration inhibitory factor; MIP-1α, macrophage inflammatory protein-1α; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; PEDF, pigment epithelium-derived factor; RANTES, regulated upon activation, normal T-cell expressed, and secreted; RBP4, retinol binding protein 4; Sfrp5, secreted frizzled-related protein 5; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; TSP1, thrombospondin 1; VEGF, vascular endothelial growth factor; ↑, parameter activated; ↓, parameter decreased; ↔, parameter unchanged; ↑ v, adipokine predominantly expressed in visceral adipose tissue; ↑ sc, adipokine predominantly expressed in subcutaneous adipose tissue.

PAI-1 (250) and CRP (249) in human vascular endothelial cells.

Furthermore, leptin-deficient mice, which are extremely obese, are protected from atherosclerosis despite other metabolic risk factors, indicating that this adipokine contributes directly to cardiovascular diseases (95).

TNF-α and macrophage migration inhibitory factor: macrophage-associated cytokines. TNF-α is one of the most extensively examined proinflammatory cytokines that plays an important role in atherosclerosis as well as in other inflammatory and metabolic disorders, which are known risk factors for cardiovascular diseases. Upregulation of TNF-α in the vascular wall of carotid and coronary arteries promotes endothelial apoptosis thus leading to impairment of endothelial function (45, 46). Moreover, TNF-α induces phenotypic changes in vascular SMCs (263) as well as their migration (82, 83, 118, 263), proliferation (215), and apoptosis (300), which are all critical for the initiation and progression of vascular lesions. In TNF-α/apolipoprotein E (ApoE) double knockout mice most proatherosclerotic factors such as IL-1β, MCP-1, and NF-κB are downregulated (309). Furthermore, TNF-α plasma concentrations are positively correlated with carotid intima-media thickness (IMT) (252) and increased in patients with premature CAD (118), thus further emphasizing the important role of TNF-α for the development of cardiovascular diseases.

Macrophage migration inhibitory factor (MIF) is expressed in various tissues such as adipose tissue and regulates acute inflammatory as well as adaptive immune reactions (70). MIF expression is induced by proatherogenic stimuli, such as oxidized low-density-lipoprotein (31), and it has been shown to become upregulated in macrophages, endothelial cells, and SMCs during the development of atherosclerotic lesions (18, 31). Its expression correlates with increased IMT and lipid deposition in the aorta of mice and in advanced human carotid artery plaques (136, 238). A recent study suggested high MIF levels as an independent risk factor for future coronary events in CAD patients with impaired glucose tolerance/type 2 diabetes mellitus (166). MIF influences the proliferation and migration of macrophages and vascular cells (205, 240), and MIF-deficient SMCs display impaired proliferation. MIF defi-

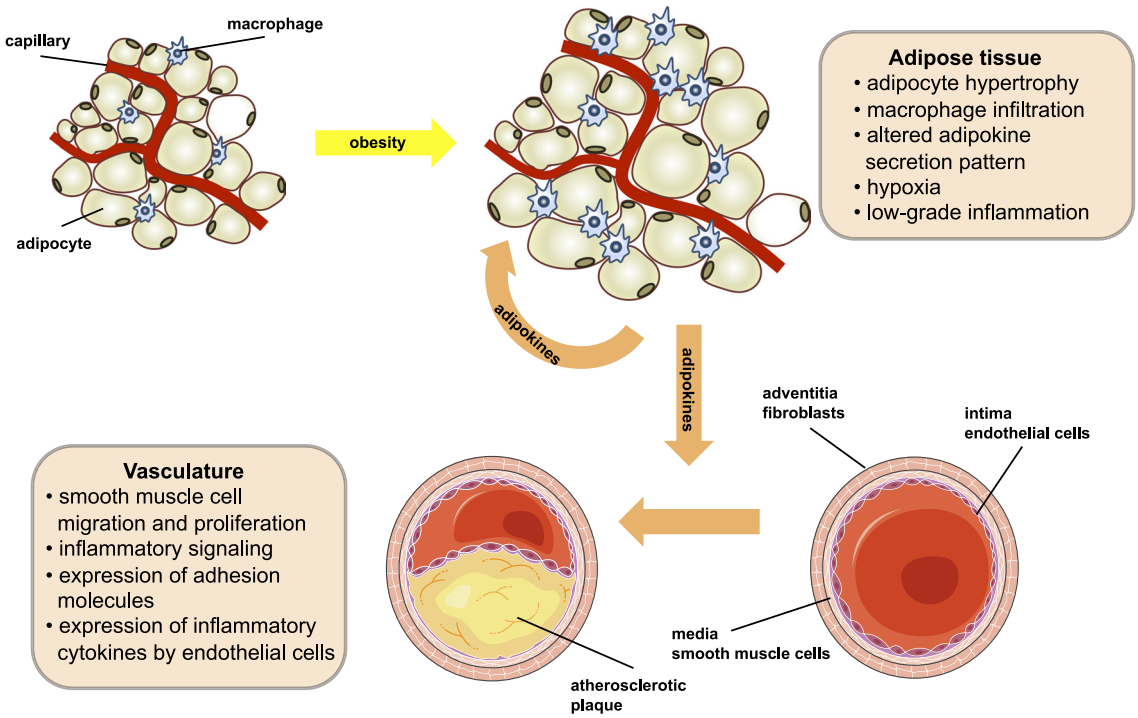

Fig. 1. Obesity-induced adipose tissue inflammation triggers endothelial dysfunction and vascular inflammation.

ciency in LDL receptor-knockout mice prevented diet-induced atherogenesis, as shown by decreased IMT and lipid deposition in the aorta (205). Taken together, these results suggest that MIF could be an important player in the pathogenesis of atherosclerosis and may represent a potential drug target for the treatment of inflammatory and cardiovascular diseases (184).

Adipocyte fatty acid-binding protein and lipocalin-2: small lipid-binding proteins. Adipocyte fatty acid-binding protein (A-FABP) is one of the most abundant intracellular lipid transport proteins in adipocytes (167, 312), regulating lipid metabolism by promoting diffusion, sequestration, and transport of long-chain fatty acids (71). In addition, A-FABP is secreted and it has been shown that high levels are associated with a worse cardiometabolic risk profile (311). Furthermore, A-FABP serum levels are positively associated with the metabolic syndrome (106), CAD (220), and carotid IMT (324), whereas they are inversely associated with endothelial function (7). In human endothelial cells, the expression of A-FABP can be induced by VEGF-A, bFGF (58), and lipids, leading to reduced activity of eNOS and NO production (146). In addition, knockdown of A-FABP reduced endothelial cell proliferation (58).

The expression of lipocalin-2 in adipocytes was first described by Lin and colleagues (157), and is markedly induced during differentiation of preadipocytes to adipocytes (16). Clinical as well as experimental studies indicate an important role of lipocalin-2 as an inflammatory adipokine in obesity and related complications (34, 60, 297). In patients with CAD lipocalin-2 levels are increased and independently associated with systolic arterial blood pressure, insulin resistance, and decreased HDL cholesterol levels (43). In addition, a high expression of lipocalin-2 has been shown in atheromatous human plaques that were associated with increased matrix metalloproteinase-9 activity (273). Serum lipocalin-2 levels are also elevated in various obese rodent models and human obesity (297, 320, 330) and positively correlated with adiposity, hypertriglyceridemia, hyperglycemia, insulin resistance, and high-sensitive CRP (297). In vascular SMCs, mRNA and protein expression of lipocalin-2 is increased upon IL-1β treatment in a NF-κB-dependent manner (30). Furthermore, lipocalin-2 knockout mice are protected against diet-induced endothelial dysfunction (158). However, lipocalin-2 may also have anti-inflammatory effects since it suppresses LPS-induced cytokine production in macrophages and antagonizes effects of TNF-α on adipocytes and macrophages (330).

A-FABP as well as lipocalin-2 are adipokines linking obesity with vascular diseases and are involved in the pathogenesis of atherosclerotic plaque. Interestingly, serum levels of A-FABP are positively associated with those of lipocalin-2 (63, 181, 278, 311). The increased release of these two adipokines in conditions of obesity may contribute to the pathogenesis of endothelial dysfunction and atherosclerosis.

Interleukins: family of immune system's messengers. Proinflammatory cytokines of the interleukin family are considered to be key players in the chronic vascular inflammation that is typical for atherosclerosis and cardiovascular diseases (171). IL-1β is a prototypic proinflammatory cytokine with different biological functions, inducing the production of different cytokines and chemokines. In vitro studies demonstrated that IL-1β increases the expression of cell adhesion molecules (295), MCP-1 (156), and lipocalin-2 (30) in vascular SMCs. In addition, it stimulates the migration (299) and proliferation of these cells (128, 234). In the ApoE/IL-1β double knockout mouse model, IL-1β deficiency decreases the severity of atherosclerosis (121, 134), further supporting the important role of IL-1β in vascular disorders.

IL-4 is a proinflammatory cytokine and plays a critical role in the progression of atherosclerosis. In endothelial cells, IL-4

Table 2. *Overview of adipokines with a tight link to cardiovascular diseases based on data obtained in in vitro and in vivo studies*

Adipokine	In Vitro Studies	Clinical Studies
Adiponectin	- Suppression of inflammatory cytokines (196, 308) - EC: ↑ NO production (97), ↓ NO inactivation (52), ↓ apoptosis (131, 310, 332) - VSMC: ↓ proliferation (8, 144, 207), ↓ migration (8, 165)	- Inversely asssociated with markers of insulin secretion, endothelial function, and inflammation (65) - Hypoadiponectinemia in patients with coronary atherosclerosis (139) and ACS (187) - Increased levels associated with a decreased risk of myocardial infarction in healthy men (210)
A-FABP	- EC: expression induced by VEGF-A, bFGF (58), and lipids (146), associated with ↓ phosphorylated eNOS and ↓ NO production (146), ↑ proliferation (58)	- High levels associated with worse cardiometabolic risk profile (311) - Serum levels positively associated with the Metabolic Syndrome (106), CAD (220), carotid IMT (324) - Circulating levels inversely associated with endothelial function (7)
IL-1β	- EC: ↑ VCAM-1 ectodomain release (251) and ↑ expression of MCP-1 (174) - VSMC: ↑ expression of cell adhesion molecules (296), MCP-1 (156), and lipocalin-2 (30) - VSMC: ↑ migration (299); ↑ proliferation (128, 234)	- High levels of IL-1β in patients with unstable angina (202) - ↑ Levels of IL-1β mRNA in coronary arteries of patients with ischemic heart disease (76)
IL-4	- EC: ↑ expression of inflammatory mediators (39, 224), ↑ ROS generation (149), ↑ apoptosis (148) - VSMC: ↑ proliferation and 12-lipoxygenase expression (190), ↑ migration (294)	- Circulating levels higher in patients with CAD (115) - IL-4 mRNA rarely (74) or not observed in atherosclerotic plaques (280)
IL-8	- Modulator of monocyte-endothelial interaction under flow conditions (81) - EC: expression induced by TNFα (322) and homocysteine (79), ↑ proliferation (204), ↑ migration (267, 338) - VSMC: ↑ proliferation and 12-lipoxygenase expression (190), ↑ migration (298, 328), regulation of VCAM-1 (94, 331)	- Concentrations significantly higher in CAD patients (100) - Levels predicts cardiovascular events (112) - Higher levels in patients with early coronary atherosclerosis (85) - Expression increased in coronary atherectomy tissue (248) and atherosclerotic plaques (124)
IL-10	- Macrophages: inhibition of inflammatory molecules, ↓ apoptosis (91) - EC: inhibition of TNFα-, IL-1β- or LPS-induced expression of IL-6 and IL-8 (39), ↑ eNOS expression, ↑ NO production (35) - VSMC: inhibition of TNFα- and bFGF-stimulated proliferation and migration (178, 243)	- Elevated plasma levels predict long-term adverse outcomes in ACS (36) - Some studies report higher levels in patients with ACS (133, 183), while other studies report lower levels in patients with CAD (115) and unstable angina (256)
IL-18	- EC: secretion induced by CRP (317), ↑ apoptosis (37, 335) - VSMC: ↑ proliferation (37, 217), ↑ migration (37), ↑ expression of IL-6, IL-8 and MCP-1 (230)	- Expressed in human carotid atherosclerotic plaques (169) - Serum levels as a strong independent predictor of death from cardiovascular causes in patients with CAD (20) - Serum levels associated with carotid IMT (315)
Leptin	- EC: ↑ PAI-1 (250) and CRP expression (249), ↑ eNOS activation and NO production (285), - VSMC: ↑ NOS expression and activity leading to ↑ NO production (222)	- Elevated plasma levels in patients with ACS (19, 246) - Some studies report an association with risk of CAD (289, 305), while other studies found no association with risk of CAD (26, 122, 302)
Lipocalin-2	- VSMC: ↑ expression after IL-1β treatment via NF-κB (30) - Macrophages: supression of LPS-induced cytokine production (330)	- Levels positively associated with e.g., adiposity, hypertriglyceridemia, high sensitivity CRP (297), and CAD (43) - High expression in atheromatous human plaques, associated with increased MMP-9 activity (273)
MIF	- EC and macrophages: induction by oxLDL (31) - VSMC: ↑ migration after short-term exposure (240) - MIF-deficient smooth muscle cells: impaired proliferation and lower proteolytic capacity (205)	- Upregulated during progression of atherosclerosis toward inflammatory stages (31) - High levels as independent risk factor for future coronary events in CAD patients with IGT/T2DM (166)
PEDF	- EC: inhibition of VEGF-induced proliferation and migration (56) -VSMC: ↑ proliferation, activation of inflammatory signaling pathways (64) -VSMC: inhibition of PDGF-BB-induced proliferation and migration (186, 293)	- Higher levels in T2DM patients (114) - Levels strongly associated with the Metabolic Syndrome (316), vascular inflammation, and carotid IMT (268)
TNF-α	- EC: ↑ apoptosis (46) - VSMC: induction of phenotypic changes (263), ↑ migration (83, 118), ↑ proliferation (215), ↑ apoptosis (300)	- Increased plasma concentrations in patients with premature coronary artery disease (117) - Levels positively correlated with carotid IMT (252)
TSP-1	- EC: ↑ expression of cell adhesion molecules (189) - VSMC: stimulation of chemotaxis (147, 191) - ↑ Aggregation and stability of platelet aggregates (188)	No data available

ACS, acute coronary syndrome; bFGF, basic fibroblast growth factor; CAD, coronary artery disease; CRP, C-reactive protein; EC, vascular endothelial cells; eNOS, endothelial nitric oxide (NO) synthase; IGT, impaired glucose tolerance; IMT, intima-media thickness; iNOS, inducible NO synthase; MMP, matrix metalloproteinase; oxLDL, oxidized low-density lipoprotein; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus; VSMC, vascular smooth muscle cells.

Table 3. *Overview of adipokines with a tight link to cardiovascular diseases based on data obtained in animal models*

	Animal Studies
Adiponectin	
KO model	- ↑ Leukocyte-endothelial cell interactions; ↑ E-selectin and VCAM-1 expression; ↓ endothelial NO production (200)
Overexpression	- ↓ Adiposity, altered expression of lipogenic enzymes; ↑ expression of uncoupling proteins (15) - ↓ Fat storage, morbidity and mortality, oxidative DNA damage upon high-fat diet (194)
A-FABP	
KO model	- ↑ Obesity, but no insulin resistance or diabetes, no TNF-α expression in adipose tissue (105) - Improved peripheral insulin resistance, beneficial effect on pancreatic β-cell function and lipid metabolism (281)
IL-1β	
KO model	- ↓ Aortic sinus lesions and lesion area (121, 134) - ↓ VCAM-1 and MCP-1 expression (134)
IL-4	
KO model	- ↓ Plaque area (50) - In contrast, no protection from early atherosclerosis; no differences in the presence and activity of 12/15-lipoxygenase in macrophages (80)
IL-8	
KO model	- ↓ Atherosclerotic lesions (21)
Il-10	
KO model	- ↑ Lesions (209); ↑ susceptibility to atherosclerosis, lipid accumulation, and T-cell infiltration ↓ collagen content (168)
Overexpression	- ↓ Lesions (209)
IL-18	
KO model	- ↓ Lesion size with a more stable phenotype; ↑ serum cholesterol (57)
Leptin	
KO model	- ↑ Plasma cholesterol and triglyceride levels; extensive atherosclerotic lesions throughout the aorta (95)
Lipocalin2-	
KO model	- ↓ Endothelial dysfunction; ↑ basal and insulin-stimulated Akt/eNOS phosphorylation in the aorta (158)
MIF	
KO model	- ↓ Abdominal aorta lipid deposition and IMT, marked retardation of atherosclerosis, ↓ cell proliferation (205)
PEDF	
KO model	- ↑ Microvascular density, excessive angiogenesis, epithelial cell hyperplasie (55)
TNF-α	
KO model	- ↓ Fatty-streak lesions; ↓ expression of proatherosclerotic factors (309)
TSP-1	
KO model	- ↑ Postinfarction inflammatory response, infiltration of neighboring noninfarcted area with macrophages and myofibroblasts; ↑ left ventricular remodeling (72)

KO, knockout.

increases the expression of inflammatory mediators (39, 224), the generation of reactive oxygen species (149), as well as apoptosis (148), whereas it induces proliferation (190) and migration (294) in vascular SMCs. A recent study described higher circulating IL-4 levels in patients with CAD (116), whereas IL-4 mRNA is rarely (74) or not observed in atherosclerotic plaques (280). Data obtained in animal models are controversial. Whereas Davenport and Tipping (50) showed that IL-4 deficiency reduced plaque area and atherosclerotic lesions, George et al. (80) observed no protection from early atherosclerosis.

IL-8 is another cytokine that plays a role in the context of cardiovascular diseases (6). It has been described as a modulator of monocyte-endothelial interaction (81), and its expression is induced by TNF-α (322) and homocysteine (79). In addition, IL-8 promotes endothelial cell proliferation (204) and migration (267, 338), the latter via activation of phosphatidylinositol 3-kinase-Rac1/RhoA pathway (142). In vascular SMCs, IL-8 has been shown to influence VCAM-1 expression (94, 331), proliferation (190), and migration (298, 328).

Moreover, IL-18 act as a proatherogenic factor, as supported by data from IL-18-deficient mice that display reduced atherosclerosis (57). A recent study demonstrated that IL-18 induced proliferation of human SMCs and matrix metalloproteinase induction (217).

In contrast, IL-10 is an anti-inflammatory cytokine, which is thought have an anti-atherogenic potential. IL-10 inhibits TNF-α-, IL-1β-, or LPS-induced expression of IL-6 and IL-8 in endothelial cell (39) and increases eNOS expression and NO production (35). In vascular SMCs, IL-10 prevents migration and proliferation, partially mediated by NF-κB inactivation (178, 243). Furthermore, IL-10 transgenic mice showed reduced atherosclerosis, whereas IL-10-deficient mice exhibited increased early atherosclerotic lesion formation (193), illustrating the anti-atherogenic potential of IL-10. However, results from clinical studies are not consistent as some report higher IL-10 levels in patients with ACS (133, 183), whereas other report lower levels in patients with CAD (115) and unstable angina (256).

Thrombospondin-1 and PEDF: proteins associated with angiogenesis. Thrombospondin-1 (TSP-1) is a member of a protein family that mediates cell-matrix and cell-cell interactions. Experimental data have shown that TSP-1 stimulates the aggregation and stability of platelet aggregates (188), induces the expression of cell adhesion molecules (189) in endothelial cells, and stimulates chemotaxis in vascular SMCs (147, 191). In TSP-1 knockout mice, more extensive postinfarction remodeling has been observed compared with wild-type mice (72). Until now, no clinical data are available for TSP-1.

PEDF, first identified in retinal pigment epithelial cells, is a multifunctional, pleiotropic protein and is expressed in various tissues such as adipose tissue. The role of PEDF in cardiovascular diseases is not completely understood. PEDF has been shown to possess antiangiogenic effects (51) and to inhibit

VEGF-induced endothelial cell migration and proliferation (56) as well as PDGF-BB-induced proliferation and migration of vascular SMCs (186). However, our group recently reported an increased proliferation of vascular SMCs upon PEDF treatment as well as the activation of inflammatory signaling pathways (64). In clinical studies higher PEDF levels in type 2 diabetic patients (114, 316) have been found, and it was shown that PEDF levels are strongly associated with the Metabolic Syndrome (316), vascular inflammation, and carotid IMT (268).

In Fig. 2 we provide an additional schematic overview of the above-described adipokines summarizing their impact on central features of cardiovascular diseases such as proliferation, migration, NO production, and induction of inflammatory cytokines.

Adipokines with Less Strong Evidence for Involvement in Cardiovascular Disease

The following adipokines are also important factors for the development of cardiovascular disease, but these adipokines have diminished evidence linking NF-κB inflammation and cardiovascular diseases, since KO or transgenic studies have not been reported.

Chemerin, resistin, visfatin, and vaspin: novel adipokines. Chemerin is a newly described adipokine that is highly expressed in adipose tissue and liver and effects adipocyte metabolism (223). In humans, its plasma levels have been shown to be associated with inflammation and various components of the Metabolic Syndrome such as BMI, triglycerides, and hypertension (151, 259), whereas no differences were observed between subjects who are nondiabetic and those who have type 2 diabetes (25). Studies in rodents that investigated the role of chemerin with regard to obesity and diabetes have revealed controversial data. In obese *db/db* mice, the expression in adipose tissue and serum levels of chemerin are reduced compared with lean controls (269), whereas its expression is higher adipose tissue of obese diabetic *Psammomys obesus* compared with lean normoglycemic *P. obesus* (25). Experimental data have shown that chemerin promotes proliferation and migration of endothelial cells (125). However, until till now the effects of chemerin on vascular SMCs have not been investigated, and future studies have to determine the impact of chemerin on cells of the vessel wall in relation to cardiovascular diseases.

Resistin was identified as adipokine in 2001 and shown to be increased in diet-induced and genetic forms of obesity in rodents (261) as well as in morbidly obese subjects compared with lean controls (235). In humans, resistin is expressed in and secreted by monocytes and macrophages in addition to adipocytes (140, 170). It promotes vascular SMC migration (120) and proliferation (33), induces monocyte-endothelial cell adhesion, and increases the expression of VCAM-1, ICAM-1, and MCP-1 in endothelial cells (286). Clinical studies have revealed that plasma resistin levels correlate with markers of inflammation and are predictive of coronary atherosclerosis in humans (218). Resistin may therefore represent a potential link between obesity and cardiovascular diseases.

Visfatin is an adipokine that was suggested to act as a proinflammatory since it induces cytokine production (185). In clinical studies it has been shown that visfatin expression was increased in plaques from patients with unstable carotid and coronary atherosclerosis (48). In addition, adipose tissue levels of visfatin were significantly higher in CAD patients relative to control subjects (42). Visfatin induces endothelial cell proliferation and migration, induces eNOS and iNOS, and has antiapoptotic effects in both vascular cell types (1, 161, 225, 284). These data indicate that visfatin may be implicated in the

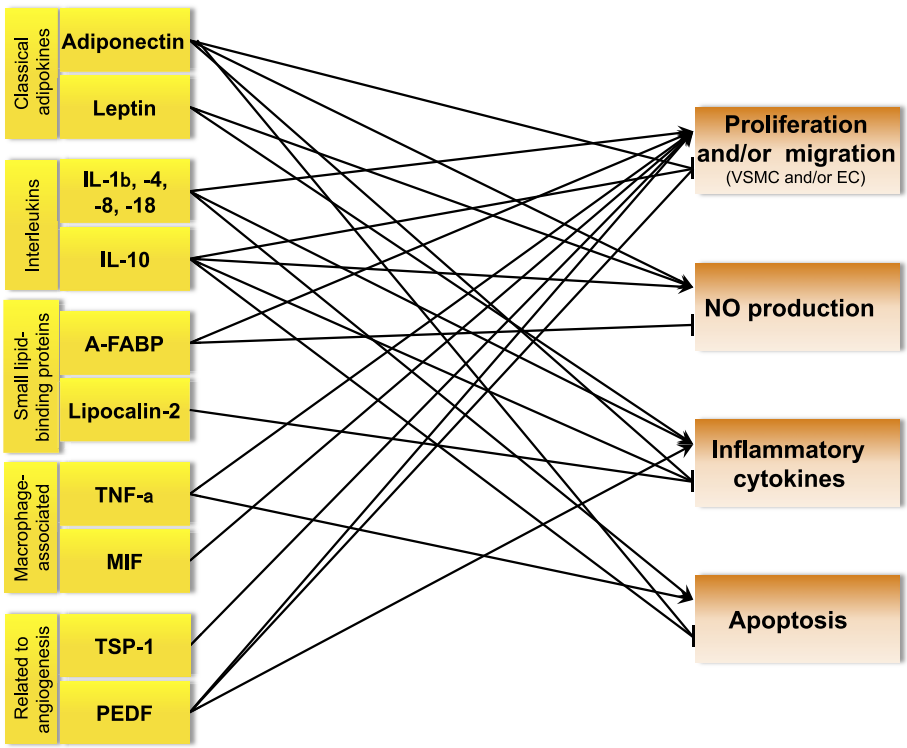

Fig. 2. Effects of selected adipokines. Arrow indicates stimulation. Line indicates inhibition of the respective process. A-FABP, adipocyte fatty acid-binding protein; MIF, macrophage migration inhibitory factor; TSP-1, thrombospondin-1; PEDF, pigment epithelium-derived factor; VSMC, vascular smooth muscle cells; EC, endothelial cells; NO, nitric oxide.

pathogenesis of atherosclerosis and cardiovascular disease (77). Further studies will be needed to clearly define the impact of visfatin in this context.

Vaspin, a serine protease inhibitor, was originally identified as an adipokine predominantly secreted from visceral adipose tissue in Otsuka Long-Evans Tokushima fatty, an animal model of obesity and type 2 diabetes (101). In humans, vaspin mRNA expression in adipose tissue is regulated in a fat depot-specific manner and is associated with parameters of obesity, insulin resistance, and glucose metabolism (135). Plasma levels of vaspin are associated with age, sex, BMI, and insulin resistance (44, 321, 325). Studies investigating an association between circulating vaspin and cardiovascular diseases reported controversial results. One study have reported an association between plasma level and artherosclerosis in women (44), whereas another study have found no association between vaspin concentration and parameters of atherosclerosis severity (11). However, the expression of vaspin has been described in vascular SMCs and foam cells in atherosclerotic lesions (257). In addition, antiapopotic effects of vaspin in endothelial cells have been reported (119). In vascular SMCs, vaspin have been shown to inhibit TNF-α-induced reactive oxygen species generation, NF-κB activation, and expression of ICAM-1, pointing toward a protective role of vaspin (208). Clearly, further investigations have to be conducted to clarify the impact of vaspin for cardiovascular disease.

Angiotensin II and VEGF: proliferative proteins. Angiotensin II, the major effector of the renin angiotensin system, has many functions including vasoconstriction, cell growth, generation of oxidative stress, and inflammation. Angiotensin II has proinflammatory effects in the vascular wall by inducing gene expression of inflammatory cytokines and cell adhesion molecules (173). In vitro studies have revealed that angiotensin II induces proliferation and migration in human vascular SMCs (323) and endothelial cells (336). These experimental findings point to the important cardiovascular actions of angiotensin II. However, the precise mechanisms of angiotensin II in the context of cardiovascular diseases need further investigations.

VEGF is a well-characterized growth factor, which is involved in the regulation and differentiation of the vascular system. However, the results of studies investigating the role of VEGF in the context of cardiovascular diseases are controversial until now. On the one hand, studies predict a beneficial role VEGF for cardiovascular health by enhancing protective vascular functions (255). But on the other hand data obtained in some studies in mouse models of atherosclerosis seem to promote a proatherogenic role of angiogenesis (127, 255). Although VEGF has an important role in various physiological processes, the very same qualities cause it to play a part in the origin and maintenance of various pathological processes, including atherosclerosis (103). To date, our understanding of the mechanisms and the precise role of VEGF in the context of cardiovascular disease in humans remains unclear and is an important question to be addressed in future studies.

Perivascular Adipose Tissue and Cardiovascular Diseases

Perivascular adipose tissue (PVAT) is defined as adipose tissue around blood vessels that occurs in a way that no fascial layer separates this fat depot from the vascular wall. In addition to this barrier-free connection between PVAT, an infiltration of adipocytes into the outer region of the adventitia has been observed (38). In obesity, PVAT is increased in humans and rodents (126, 150). The amount of PVAT was highly associated with visceral obesity and moderately correlated with subcutaneous adipose tissue and body mass index (237). Adipocytes in PVAT have been compared with subcutaneous and visceral adipocytes in humans and rodents in various studies, and there is still controversy as for the classification of PVAT as a depot of white adipose tissue or brown adipose tissue. It appears that PVAT surrounding abdominal and thoracic aortas might be multifaceted as for its adipocyte phenotype (38, 211).

In the obese state, adipose tissue is characterized by infiltration of various immune cells including macrophages and T lymphocytes (301) and low-grade chronic inflammation. Adipocytes of patients who are obese are characterized by increased release of various proinflammatory adipokines such as IL-6 and MCP-1. Most of the studies analyzing differences in adipokine expression and release of adipocytes in the obese state work with subcutaneous or visceral adipocytes. In contrast, little is known on adipokine expression and release in PVAT compared with other fat depots and in pathological states. In vitro differentiated human PVAT adipocytes are characterized by lower adiponectin release and higher secretion of MCP-1 (38). In rodents, PVAT expression of adiponectin and FABP4 (A-FABP) was lower and expression of leptin and MCP-1 was higher in high-fat diet-fed mice compared with those of controls (38, 211). Data on the presence of immune cells in PVAT are controversial. A very recent publication analyzed macrophage content in thoracic PVAT compared with white and brown adipose tissue and found PVAT to be resistant to high-fat diet-induced immune cell infiltration similar to brown adipose tissue (303). In contrast, adipose tissue inflammation in PVAT and macrophage infiltration could be described to be responsible for a loss of anticontractile function of this fat depot in the mesenteric bed (69). Furthermore, adipokines released from PVAT strongly induced the chemotaxis of peripheral blood leukocytes to the interface between PVAT and the adventitia in human atherosclerotic arteries (99). These chemotactic effects have been ascribed to IL-8, and MCP-1 and have been proposed to underlie the accumulation of macrophages and T cells in atherosclerosis.

Vascular relaxation factors, proatherogenic and proinflammatory adipokines, and growth factors secreted from PVAT were found to directly regulate vascular function through paracrine and endocrine effects on the vascular wall. Adipokines that are increased in the obese state such as leptin have been described to affect vascular function on the level of endothelial dysfunction (206). Endothelial dysfunction preceding atherosclerosis is characterized by deregulation of vasoreactivity, increased inflammatory and oxidative stress, and impaired barrier function (12). Oxidative stress has been shown to be increased in PVAT in obesity (231). Vasorelaxing effects of PVAT are lost in human obesity, which is associated with expansion of PVAT (86). The addition of TNF-α and inhibition of adiponectin inhibit the vasodilator activity of PVAT around healthy blood vessels, whereas the blocking of TNF-α by specific antibodies could reverse the obesity-induced defects in vasodilatation. In addition to TNF-α and adiponectin, leptin and resistin could be described to be mediators of endothelial dysfunction (27).

Migration of vascular SMCs from the media to the intima and their proliferation in the synthetic state are crucial steps in arterial wall thickening in atherosclerosis. In vitro, PVAT explants induce proliferation of vascular SMCs (13, 144). Secretory products of PVAT from diet-induced obese rats significantly induced human SMC proliferation compared with that from lean controls (13). Increased neointima formation diet-induced obese mice was accompanied by a decreased expression of adiponectin and induction of inflammatory markers such as MCP-1, TNF-α, IL-6, and PAI-1 in PVAT (270). Importantly, adiponectin-deficient mice display increased neointima formation when compared with wild-type mice, and this effect could be reversed by a local administration of adiponectin to the periadventitial area (138). In line with this, adiponectin has been found to abrogate adipokine-induced SMC proliferation (144). It is currently unknown which factors secreted from PVAT contribute to vascular SMC migration and proliferation. Potential candidates include leptin, resistin, and visfatin, which have been found to directly affect SMCs (33, 153, 292).

For the comprehensiveness of this review, a short paragraph should be devoted to epicardial adipose tissue that is a major fat depot associated with obesity and cardiovascular diseases. As epicardial adipose tissue is directly lying on the surface of the myocardium and also in direct contact with coronary vessels, this depot can also be seen as a special PVAT. While an association between epicardial adipose tissue thickness and the prevalence of cardiovascular diseases and the metabolic syndrome is widely accepted [recently reviewed in Ouwens et al. (201)], few studies analyze a cross talk between epicardial adipose tissue and cardiomyocytes. Secretory products from epicardial adipose tissue induces insulin resistance and defects in contractility and calcium influx in cardiomyocytes with the responsible adipokines still to be identified (87). Cardioprotective effects have been assigned to adiponectin (290), whereas resistin has been characterized as cardiodepressant (132).

Conclusion

Enlarged adipose tissue releases a host of adipokines that play a key role in the interorgan cross talk between adipose tissue and the vasculature. Here we present a novel strategy to narrow down the huge number of potential biomarkers and drug targets by analyzing molecules that activate NF-κB proinflammatory signaling pathways. Comprehensive literature analysis resulted in a final list of known and novel adipokines that we suggest as a major candidates for future work. This should address the role of these molecules in linking obesity, chronic inflammation, and cardiovascular disease and their use as potential targets for diagnosis and treatment.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

A.T., R.S., K.E., and J.E. analyzed data; A.T. and K.E. prepared figures; A.T., R.S., H.S., and J.E. drafted manuscript; A.T., R.S., H.S., K.E., and J.E. edited and revised manuscript; K.E. and J.E. conception and design of research; K.E. and J.E. approved final version of manuscript.

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