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Review

Adipokines: A link between obesity and cardiovascular disease

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ABSTRACT

Obesity is a risk factor for various cardiovascular diseases including hypertension, atherosclerosis, and myocardial infarction. Recent studies aimed at understanding the microenvironment of adipose tissue and its impact on systemic metabolism have shed light on the pathogenesis of obesity-linked cardiovascular diseases. Adipose tissue functions as an endocrine organ by secreting multiple immune-modulatory proteins known as adipokines. Obesity leads to increased expression of pro-inflammatory adipokines and diminished expression of anti-inflammatory adipokines, resulting in the development of a chronic, low-grade inflammatory state. This adipokine imbalance is thought to be a key event in promoting both systemic metabolic dysfunction and cardiovascular disease. This review will focus on the adipose tissue microenvironment and the role of adipokines in modulating systemic inflammatory responses that contribute to cardiovascular disease.

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Contents

Introduction 250
Obesity-induced changes in adipose tissue microenvironment 250
The adipokine concept 252
Pro-inflammatory adipokine TNFα 252
Role of leptin in metabolic and cardiovascular disease 253
The anti-inflammatory adipokine adiponectin 254
Sfrp5 255
Conclusions 255
Funding sources 255
Disclosures 255
References 255

Introduction

Obesity and associated metabolic disorders are becoming major health care concerns around the world. It is estimated that over 60% of adults and 30% of children are overweight in the USA, and if trends continue more than 50% of the world's adult population will be overweight in a few decades [1–3]. Obesity and its comorbidities have a devastating effect on vascular function and create conditions that favor cardiovascular disease. Obesity promotes cardiovascular disease via many mechanisms including ectopic lipid deposition, hyperglycemia, and the development of a procoagulant state, to name a few. This review will focus on how obesity influences the production in the adipose tissue of pro- and anti-inflammatory cytokines, referred to as adipokines, which contribute to the development of metabolic and cardiovascular diseases.

Obesity-induced changes in adipose tissue microenvironment

To understand how obesity has an impact on cardiovascular function, it is important to first focus on obesity-induced changes in the microenvironment of adipose tissue (Fig. 1). The excess of caloric intake leads to an expansion of the adipose tissue that is initially driven by an increase in the number of adipocytes (adipocyte hyperplasia) mediated by the recruitment and proliferation of adipogenic progenitors [4–7]. This hyperplastic response is severely blunted with age [8], so the sustained exposure to excessive energy intake ultimately leads to an increase in adipocyte size (adipocyte hypertrophy) that compromises the functionality of the

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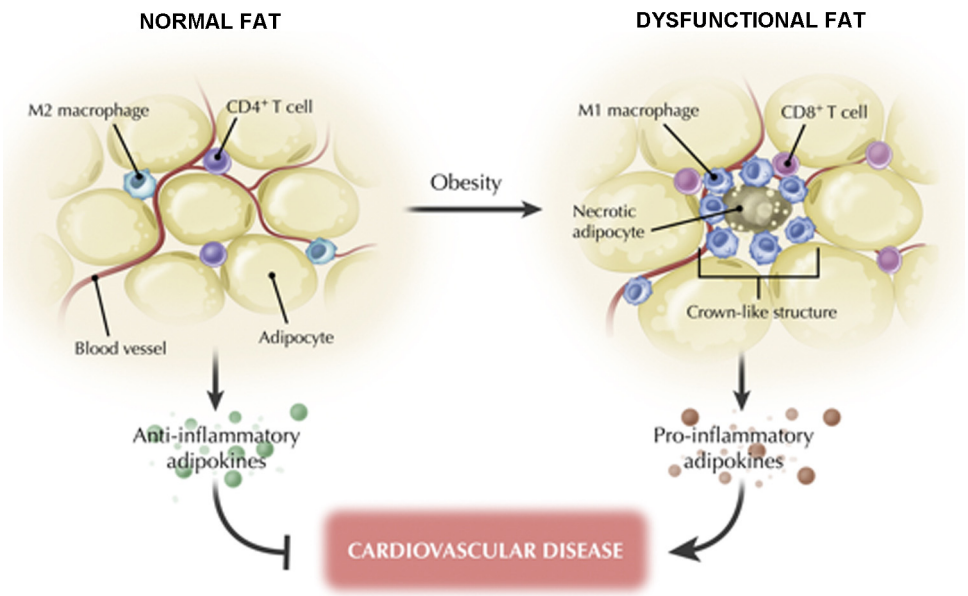

Fig. 1. Obesity-linked changes in adipose tissue composition. Obesity can promote changes in adipose tissue and promote the transition to a metabolically dysfunctional phenotype. As the body develops obesity, adipocytes undergo hypertrophy due to the increased storage of triglycerides. Macrophages in lean fat express markers of a M2 or "alternatively activated" state, whereas obesity leads to recruitment and accumulation of a M1 or "classically activated" state with macrophages and $CD8^+$ T cells in adipose tissue. Metabolically dysfunctional adipose tissue is indicated by the presence of crown-like histological structures that represent activated M1-like macrophages surrounding a necrotic adipocyte and $CD4^+$ T cells. Anti-inflammatory adipokines, such as adiponectin are preferentially produced by lean adipose tissue, whereas high levels of pro-inflammatory factors are produced in obese states.

adipose tissue [6,9]. In advanced obesity, lipid-laden hypertrophied adipocytes undergo necrotic and/or apoptotic cell death, contributing to the recruitment of inflammatory cells and to adipose tissue dysfunction [10–12].

Whereas adipose tissue is mainly composed of adipocytes, other cell types, including lymphocytes, macrophages, fibroblasts, and vascular cells, also appear to have important roles in controlling the functional status of this tissue. Obesity leads to major changes in the cellular composition of adipose tissue and also modulates the phenotype of individual cells within this tissue. For example, adipose tissue from obese organisms is infiltrated by a large number of macrophages, leading to increases in both absolute macrophage number and the relative level of macrophage-to-adipocyte ratio. Macrophage recruitment to adipose tissue is associated with systemic inflammation and insulin resistance [13,14]. In addition to this quantitative change, the macrophage phenotype is also altered by the obese state. The M1/M2 concept is a convenient means for classifying the inflammatory status of the macrophage. Macrophages that accumulate in adipose tissue of obese organisms tend to express genes associated with a M1-like or "classically activated" phenotype. In contrast, adipose tissue macrophages from lean organisms tend to express genes associated with a M2-like or "alternatively activated" phenotype [15]. Stimulation with T helper 1 (T_H1)-type cytokines, including interferon-γ, or bacterial products will promote the M1-like phenotype in macrophages. M1 macrophages produce pro-inflammatory cytokines, such as tumor necrosis factor (TNF)α, express inducible nitric oxide synthase (iNOS), and produce high levels of reactive oxygen and nitrogen intermediates [16]. This class of macrophages is typically associated with inflammation and tissue destruction. On the other hand, M2-like macrophages preferentially express anti-inflammatory cytokines, such as interleukin (IL)-10, and the enzyme arginase-1, which inhibits iNOS activity. These types of macrophages tend to be associated with wound healing, angiogenesis, and the resolution of inflammation [16]. It is believed that M1-like macrophages promote insulin resistance, whereas M2-like macrophages protect against obesity-induced insulin resistance [17]. Supporting this notion, ablation of CD11c-positive, M1-like macrophages normalizes insulin sensitivity in obese mice [18].

Another distinctive feature of adipose tissue from obese organisms is the presence of "crown-like" structures in histological sections. These features represent macrophages that surround dead or dying adipocytes [10,11]. Obese subjects lacking crown-like structures exhibit better metabolic control, diminished inflammatory gene expression, and reduced cardiovascular risk than body mass-matched individuals who display this histological feature [19]. On the other hand, the number of crown-like structures in adipose tissue is correlated with inflammation and insulin resistance in metabolic syndrome patients [10,19]. Typically macrophages function to rapidly remove dead cell debris prior to the disruption of their membranes. Thus, it is tempting to speculate that the presence of crown-like structures signifies a breakdown in the phagocytic process in adipose tissue, thereby exacerbating the pro-inflammatory state.

Obesity also influences the subsets of T cells that are present in adipose tissue, where they appear to function in the regulation of macrophage phenotype. $CD4^+$ regulatory T cells and T_H2-polarized cells are found in higher abundance in the adipose tissue of lean mice, and these cells contribute to the maintenance of adipose tissue function and insulin sensitivity, in part through promoting an anti-inflammatory alternative activation of macrophages [20,21]. On the other hand, under conditions of obesity, the accumulation of $CD8^+$ effector T cells and $CD4^+$ T_H1 cells in the adipose tissue will generate T_H1 signals and initiate the recruitment and activation of macrophages, perpetuating the pro-inflammatory cascade that is associated with insulin resistance [21,22]. Thus, obesity-induced alterations in the balance of T_H1- and T_H2-type signals are likely to influence macrophage recruitment and phenotype in adipose tissue, thereby generating either a pathogenic or a protective environment. B cells also appear to have a pivotal role in obesity-induced adipose tissue inflammation, promoting T cell and macrophage activation and contributing to insulin resistance

[23]. Similarly, mast cells have been reported to accumulate in obese adipose tissue before the appearance of macrophages, and studies in mast-cell deficient mice suggest a role for this cell-type in obesity-associated metabolic dysfunction [24]. Neutrophil infiltration and activation also contributes to adipose tissue dysfunction through the action of neutrophil elastase [25,26]. Finally, it has been reported that eosinophils in adipose tissue promote alternative activation of macrophages and glucose tolerance through the production of the T_H2 cytokine IL-4 [27]. Therefore, the status of immune cells in adipose tissue is an area of intense investigation, and a better understanding of the interplay between inflammation and metabolism is warranted.

Of particular relevance to the subject of this review, a number of provocative studies have made the case that obesity is also associated with changes in vascular structure and function within adipose tissue. Several studies in patients and animal models have shown that obesity causes capillary rarefaction in adipose tissue, and this leads to localized hypoxia [28–31]. In contrast with these studies, a recent report showed that obese human subjects display increased rather than decreased oxygen tension in adipose tissue, despite reduced adipose tissue blood flow [32]. However, it must be noted that, while suggesting an overall hyperoxic state, this latter study does not rule out the possibility of localized hypoxic areas within adipose tissue, and therefore further studies are required in this field. Regardless, the various studies coincide in their findings of decreased adipose tissue capillarization, which may limit nutrient delivery and contribute to insulin resistance. Alternatively, this vascular dysfunction could contribute to adipose tissue inflammation by promoting ischemia-induced adipocyte necrosis, followed by macrophage recruitment and activation. Recent studies with genetically engineered mice have provided conclusive evidence of the role of adipose tissue vascularization in obesity-associated metabolic dysfunction. Experiments with mice overexpressing vascular endothelial growth factor A (VEGF-A) in adipocytes show that increased VEGF-mediated angiogenesis in white adipose tissue can attenuate some of the metabolic effects of diet-induced obesity, such as insulin resistance and hepatic steatosis [33–35]. Conversely, adipocyte-restricted deletion of VEGF-A results in scarce adipose tissue vascularization, which leads to increased adipose tissue inflammation and systemic insulin resistance and glucose intolerance, as well as hepatic steatosis [35]. Furthermore, it has been reported that hypoxia-inducible factor 1α (HIF1α) – a master regulator of VEGF expression – is upregulated during obesity-associated adipose tissue expansion [36]. Interestingly, various experiments in genetically engineered mice suggest that HIF1α does not influence adipose tissue capillarization, but promotes adipose tissue expansion, inflammation, and fibrosis, leading to systemic metabolic dysfunction [37–40].

The phenotypic changes in adipose tissue that result from obesity are also thought to induce vascular endothelial cell activation. Because activated endothelial cells express adhesion molecules and chemotactic factors that contribute to the recruitment of inflammatory cells, it is reasonable to speculate that obesity promotes a vicious cycle of endothelial activation and tissue inflammation that contributes to adipose tissue dysfunction. Supporting this notion, it has been shown that endothelial cells within the adipose tissue of obese mice express higher levels of adhesion molecules such as P-selectin, E-selectin, and intercellular adhesion molecule 1 (ICAM-1). Moreover, administration of anti-ICAM-1 antibody to obese mice prevents leukocyte-endothelium interactions and macrophage infiltration into adipose tissue [41]. In addition, adipose tissue inflammation may also promote a state of systemic endothelial cell activation through the endocrine actions of inflammatory adipokines such as TNFα (see below), which could contribute to obesity-associated cardiovascular disease.

The adipokine concept

Accumulating evidence from animal models indicates that the pathogenesis of obesity-related metabolic dysfunction involves the development of a systemic, low-grade inflammatory state [42,43]. Epidemiological studies have also demonstrated a connection between metabolic disease and a low-grade inflammation. For example, increasing adipose mass in obese women is associated with increased serum levels of the pro-inflammatory marker C-reactive protein (CRP) [44]. Furthermore, high levels of CRP and IL-6, are predictive of the development of type 2 diabetes [44,45]. In contrast, weight loss leads to reductions in circulating levels of CRP and IL-6 [46]. These findings strongly suggest that obesity is highly associated with chronic low-grade inflammation, and it is believed that this obesity-linked inflammatory state is due to changes in the expression of cytokines by adipose tissue. Over the past two decades, it has become apparent that adipose tissue is a source of secreted immunomodulatory proteins, and that these adipokines act as modulators of metabolic and cardiovascular processes.

While adipose tissue is mainly found in visceral and subcutaneous depots, it is also widely dispersed throughout the body. Other depot sites that may be particularly relevant in influencing cardiovascular disease include epicardial, perivascular, and pulmonary adipose tissue. Whilst adipose tissue depots differ from one another based upon their relative levels of adipokine production, obesity will generally favor the production of pro-inflammatory adipokines regardless of depot site location [47–49]. Interestingly, studies in mice suggest that aging in the absence of diet-induced obesity also induces the expression of proinflammatory adipokines, such as TNFα and IL-6 in visceral adipose tissue [50,51].

Most adipokines identified to date are pro-inflammatory and they are upregulated in the obese state. Under conditions of obesity, these adipokines function to promote metabolic and cardiovascular diseases. Pro-inflammatory adipokines include TNFα leptin, IL-6, resistin, RBP4, lipocalin 2, IL-18, ANGPTL2, and others. Here, as examples, we will only discuss TNFα and leptin, but a partial list of other pro-inflammatory adipokines and their cardiovascular actions can be found in Table 1 and Ref. [52]. In addition to the numerous pro-inflammatory adipokines, adipose tissue also secretes a smaller number of anti-inflammatory factors. These factors include adiponectin, that has been the subject of intense investigation [53,54], and SFRP5, that has been recently identified as an adipokine with anti-inflammatory activities [55].

In this regard, it is difficult to discern whether the increase in cardiovascular disease associated with an adipokine imbalance is due to a paracrine mechanism, i.e. the local release of pro-inflammatory factors from epicardial or perivascular adipose tissue, or an endocrine mechanism that is reflected by an increase in serum adipokine levels. One study that shed light on this question performed experiments involving perivascular adipose tissue transplantation between lean and obese mice [56]. This study provided evidence that the perivascular location of adipose tissue is critical in its ability to promote pathological vascular remodeling and that these effects could be attributed to alterations in the levels of adiponectin, an adipokine that will be discussed later.

Pro-inflammatory adipokine TNFα

TNFα is a pro-inflammatory cytokine that is predominantly produced by monocytes/macrophages and is involved in many inflammatory diseases. In 1993, TNFα was found to be induced in adipose tissue in models of diabetes and obesity, providing the initial evidence for a link between inflammation and obesity [57]. TNFα expression is upregulated in the adipose tissue and the serum of patients with obesity, whereas weight loss in obese individuals

Table 1
Adipokines and cardiovascular function.

Adipokine	Inflammation	Cardiovascular function(s)	Reference
Leptin	Pro-inflammatory	See text	
Resistin	Pro-inflammatory	Pro-atherogenic, subclinical marker of atherosclerosis, marker of heart failure, predictive of MI and stroke risk	[168–176]
RBP4	Pro-inflammatory	subclinical marker of atherosclerosis	[177–181]
Lipocalin2	Pro-inflammatory	Unknown	[182,183]
ANGPTL2	Pro-inflammatory	Unknown	[184]
TNF	Pro-inflammatory	See text	
IL-6	Pro-inflammatory	Pro-atherogenic, predictive of MI risk	[185–187]
Adiponectin	Anti-inflammatory	See text	
SFRP5	Anti-inflammatory	See text	
adipolin	Anti-inflammatory	Unknown	[188]
Omentin	Anti-inflammatory	Pro-angiogenic, inhibition of vascular inflammation, subclinical marker of atherosclerosis	[189,190]

RBP4, retinol-binding protein4; ANGPT2, angiopoietin-like protein2; TNF, tumor necrosis factor; IL, interleukin; MI, myocardial infarction.

is associated with a decrease in TNFα levels [58,59]. TNFα levels also correlate with insulin resistance [60]. Mechanistically, TNFα contributes to insulin resistance by inhibiting the activating phosphorylation of the insulin receptor and insulin receptor substrate 1 (IRS1) in muscle and adipose tissues [61]. In animal models of obesity, the inhibition of TNFα leads to an enhancement of insulin signaling in muscle and adipose tissue [57,61,62].

TNFα has numerous pathophysiological roles in the cardiovascular system. TNFα levels are increased by acute and chronic ischemic injuries and under conditions of heart failure in humans as well as animals [63]. As with obesity, aging is associated with a chronic low-grade increase in TNFα levels [50,64]. TNFα acts on monocytes/macrophages, vascular endothelial cells, and smooth muscle cells to induce the expression of many pro-inflammatory, pro-coagulant, and proliferative genes, contributing to atherosclerosis development in animal models [63,65–69]. In vascular smooth muscle cells, TNFα induces migration, proliferation, and apoptosis [70–72], which are cellular processes of major relevance in vascular pathologies. TNFα also induces the rapid expression of adhesion molecules such as E-selectin, vascular cell adhesion molecule-1, and ICAM-1 in endothelial cells [63,73].

TNFα can have deleterious or beneficial effects on the heart in models of ischemia-reperfusion injury and heart failure depending on the amount of TNFα and the duration of exposure [63,74]. Studies aimed at investigating the effects of TNFα neutralization for the treatment of cardiac disease have led to inconsistent results in experimental models and clinical trials. Some, but not all, animal studies have demonstrated that TNFα neutralization or blockade of TNFα receptor (TNFR) can attenuate myocardial damage in animal models of ischemia/reperfusion and heart failure [63]. In contrast, most clinical studies have failed to document the efficacy of TNFα antagonists [63]. The potential reasons for these discrepant findings are manifold. Contributing to this complexity, TNFα exerts its effects via two different receptors, TNFR1 and TNFR2, which exhibit different patterns of expression and induce distinct signaling pathways and cellular processes. TNFR1 is constitutively expressed in most cell types except erythrocytes, whereas expression of TNFR2 is highly regulated and is typically higher in immune cells [75,76]. Both the pro-inflammatory and the proapoptotic actions of TNFα are largely mediated through TNFR1. In contrast, TNFR2 mediates the activation of the protective JAK/STAT3 pathway and is believed to promote tissue repair and angiogenesis [63,76].

Role of leptin in metabolic and cardiovascular disease

The adipokine leptin is the product of the obese gene (ob), that was identified in ob/ob mice through positional cloning [77]. Leptin regulates feeding behavior, and mice that lack leptin show hyperphagia, obesity, and insulin resistance. The delivery of leptin to ob/ob mice reverses these phenotypes [78]. Notably, leptin has been shown to be effective at improving metabolic dysfunction in patients with lipodystrophy or congenital leptin deficiency [79,80]. However, circulating leptin levels typically correlate with adipose tissue mass, and obese humans and rodents have elevated levels of leptin without the expected anorexic responses [78], suggesting that leptin resistance is common in obesity. A number of mechanisms may contribute to leptin resistance. The anorexic effects of leptin result from its actions in the hypothalamus, which are mediated by its binding to the leptin receptor b (LRb) and the activation of JAK2/STAT3 signaling. In obesity, this signaling pathway is blocked through different mechanisms, leading to leptin resistance. One of the major cellular mechanisms contributing to this phenomenon is the STAT3-mediated induction of the inhibitory suppressor of cytokine signaling 3 (SOCS3) protein, which binds the phosphorylated Tyr985 residue in LRb, impairing leptin-induced signaling [81,82]. Conclusive evidence from animal studies supports a primary role for SOCS3 in leptin resistance [83,84]. Additional mechanisms may include LRb binding to the tyrosine phosphatase SHP-2, and activation of the tyrosine phosphatase PTP1B, which dephosphorylates Jak2 and thus diminishes LRb signaling (reviewed in [85]). In addition, it has been suggested that obesity-induced endoplasmic reticulum stress in the hypothalamus also plays a central role in leptin resistance [86].

Leptin is structurally similar to the helical cytokine family that includes IL-2. Inflammatory stimuli increase leptin levels in adipose tissue and in serum [87] and leptin acts on multiple types of immune cells, such as monocytes/macrophages, neutrophils, and T cells, to promote the release of inflammatory cytokines [88–91]. In T cells, leptin specifically increases the production of T_H1-type cytokines, and suppresses production of the T_H2-type cytokine IL-4 [88], thereby polarizing T cells toward a T_H1 cell phenotype. Consistent with these observations, leptin deficiency protects against liver damage in models of T cell-mediated hepatitis and autoimmune encephalomyelitis [88,92,93]. Thus, it is generally accepted that leptin acts as a pro-inflammatory adipokine.

Numerous studies have indicated that leptin plays an important role in cardiovascular diseases. In humans, circulating leptin levels are increased after myocardial infarction [94]. Similarly, leptin levels are also increased in heart failure patients independent of body mass [95], and mechanical unloading reverses this increase [96]. Leptin-deficient mice display greater cardiac hypertrophy [97], increased mortality in a model of viral myocarditis [98], and greater cardiac remodeling in response to chronic ischemic injury [99]. Leptin receptor deficiency also leads to a reduction in ischemia-induced revascularization that is associated with the impaired induction of angiogenesis-regulatory factors in the ischemic tissue [100]. In many of these cases, it has been shown that leptin repletion can reverse the deleterious effects of leptin deficiency. However, it is difficult to ascertain whether leptin depletion or repletion has a direct impact on these changes in cardiovascular function because these manipulations also affect feeding behavior, adipose tissue mass, and numerous systemic metabolic properties. Whereas

leptin can activate protective JAK-STAT and AMPK signaling pathways in cardiovascular tissues, the interpretation of experimental studies on leptin that employ ob/ob mice or diet-induced obese mice are difficult to interpret due to secondary metabolic defects that result from hyperphagia (e.g. hyperglycemia, hyperinsulinemia, insulin resistance) or the development of leptin resistance, respectively. Therefore, studies of cardiovascular disease in mice where the leptin receptor is conditionally ablated in specific cardiac, vascular, or immune cell types may be required to definitely address these issues.

The anti-inflammatory adipokine adiponectin

Adiponectin (also known as ACRP30, AdipoQ, and apM1) was identified as an adipocyte-specific adipokine approximately 15 years ago [101–103]. Adiponectin typically circulates at high levels (3–30 μg/ml) in the blood [104], and is markedly downregulated in obese human subjects. Furthermore, plasma adiponectin level is a good predictor of the risk of type 2 diabetes [105,106]. Adiponectin is synthesized at highest levels by functional adipocytes found in lean organisms but its expression is downregulated in the dysfunctional adipocytes that are associated with obesity. Consistent with this notion, adiponectin expression by adipocytes is inhibited by pro-inflammatory cytokines, hypoxia, and oxidative stress [53,105,106], conditions associated with the adipose tissue milieu of obese organisms.

Evidence from experimental models indicates that adiponectin protects against obesity-linked metabolic disease. The acute administration of adiponectin leads to an improvement in metabolic parameters in a mouse model of obesity [107]. Conversely, adiponectin-deficient mice develop greater insulin resistance when placed on a high calorie diet [108,109], whereas the transgenic overexpression of adiponectin in ob/ob mice improves metabolic parameters independently of weight loss [110]. The beneficial effects of adiponectin on insulin sensitivity appear to be mediated in part by its ability to activate AMPK signaling axis in metabolically important tissues [111,112]. AMPK activation by adiponectin is thought to involve its interaction with the cell surface receptors adiponectin receptor 1 and adiponectin receptor 2 (AdipoR1 and AdipoR2, respectively) [113–115]. In addition, studies suggest that the actions of adiponectin may also be mediated through additional receptors including PAQR3 (renamed AdipoR3) [116], AdipoRX [117], and T-cadherin [118].

Many lines of evidence show that adiponectin has anti-inflammatory functions. Plasma adiponectin levels are negatively correlated with patient CRP levels [104], and adiponectin-deficient mice have higher levels of TNFα in adipose tissue and blood [108]. Despite morbid obesity, transgenic overexpression of adiponectin in ob/ob mice leads to marked improvement in glucose metabolism, which is accompanied by reductions in macrophage infiltration and TNFα expression in adipose tissue [110]. Adiponectin-mediated modulation of macrophage phenotype contributes to its role in controlling inflammation. Macrophages isolated from adiponectin-deficient mice show increased expression of pro-inflammatory M1 markers and decreased expression of anti-inflammatory M2 markers [119]. Conversely, the overexpression of adiponectin in mice stimulates macrophage M2 marker expression. Adiponectin inhibits the transformation of macrophages into foam cells by reducing intracellular cholesteryl ester content [120]. Adiponectin also inhibits Toll-like receptor-mediated nuclear factor-κB activation and stimulates production of the anti-inflammatory cytokine IL-10 by macrophages [121,122]. Given the importance of TNFα expression and macrophage infiltration in adipose tissue dysfunction [13,14,57], the ability of adiponectin to suppress these pro-inflammatory events may be an important feature in its ability to prevent obesity-associated metabolic dysfunction.

Adiponectin is structurally similar to the collectin family of proteins that include complement factor C1q and surfactant proteins A and D. Similar to these abundantly expressed collectin proteins, adiponectin can form high molecular mass oligomers through its ability to multimerize via interactions through its collagen-like domain [53,105]. A property shared by many collectin proteins is their ability to bind to apoptotic cells and facilitate their uptake by macrophages, a feature that is also exhibited by adiponectin [123]. Macrophages in adiponectin-deficient mice display a reduced ability to clear apoptotic debris when challenged by an overload of dead cells. Because phagocytosis of early apoptotic cells will promote an M2-like phenotype in macrophages [124], these data suggest adiponectin's collectin-like function contributes to its anti-inflammatory actions. Finally, it should be noted that adiponectin levels are elevated in autoimmune and chronic inflammatory diseases [125]. While the molecular basis for adiponectin upregulation under these conditions is unknown, it may represent a compensatory response because adiponectin has been shown to ameliorate auto-immunity in a mouse model of lupus [126,127].

*Cardiovascular effects of adiponectin***.** Low serum levels of adiponectin have been associated with coronary artery disease [128], hypertension [129], left ventricular hypertrophy [130], and a greater risk of myocardial infarction [131]. Numerous experimental studies have shown that adiponectin exerts protective actions on cardiovascular cell types including vascular endothelial cells, smooth muscle cells, and cardiac myocytes, and adiponectin-deficient mice display worse outcomes in various models of cardiovascular disease. Importantly, mouse models of adiponectin-deficiency display normal body and fat mass and normal metabolic parameters when fed a normal chow diet. Thus, the cardiovascular actions of adiponectin can be studied independently of its metabolic regulatory effects.

Adiponectin has been shown to exert many vasculoprotective and angiogenic properties. Studies with adiponectin-deficient mice have demonstrated that adiponectin promotes revascularization of ischemic limbs [132,133], and protects against cerebral ischemia-reperfusion [134]. Furthermore, adiponectin inhibits experimental injury-induced neointimal hyperplasia [135]. Adiponectin-deficient mice also develop enhanced salt-induced hypertension due in part to a reduction of endothelial nitric oxide synthase (eNOS) activity [136], and display impaired endothelial cell-dependent vasodilatory responses when fed an atherogenic diet [137]. Finally, some studies, but not all, have shown that adiponectin overexpression inhibits atherosclerotic lesion formation, whereas adiponectin-deficiency leads to augmented atherosclerosis [138–141]. Mechanistically, many of these protective actions of adiponectin are linked to its beneficial effects on endothelial cell function, which are mediated to a great extent by its ability to stimulate NO production through AMPK-dependent activation of eNOS [142–144]. In addition, adiponectin induces the expression of PGI_2–an autacoid that promotes vascular function [145]–and prevents TNFα-induced endothelial cell activation [146,147]. Furthermore, adiponectin has been shown to inhibit proliferation and migration of vascular smooth muscle cells through direct inhibition of PDGF-BB [148], and to promote the differentiation of vascular smooth muscle cells via repression of mammalian target of rapamycin complex 1 (mTORC1) and FoxO4 [149].

Various studies have evaluated adiponectin's actions on the heart. Adiponectin inhibits pressure overload or angiotensin II-induced cardiac hypertrophy, at least in part, through its ability to activate AMPK signaling in myocytes [132,150]. Adiponectin protects the heart from ischemic reperfusion injury [151,152], and it has been shown to be protective in models of systolic and diastolic heart failure [153,154].

While AdipoR1 and AdipoR2 are widely accepted as the main receptors accountable for the metabolic actions of adiponectin [113,114], few studies have investigated adiponectin receptors in cardiovascular tissues. In this regard, T-cadherin, a GPI-anchored adiponectin-binding protein [118], was recently shown to be essential for the cardioprotective and pro-revascularization actions of adiponectin [155,156]. T-cadherin is highly expressed in the plasma membrane of heart, skeletal muscle, and vascular tissue [157], where it co-localizes with adiponectin [155,156]. Of note, T-cadherin-deficient mice phenocopy adiponectin-deficient mice in experimental models of chronic and acute cardiac injury [155] and chronic limb ischemia [156], strongly supporting the role of T-cadherin in mediating the effects of adiponectin in the cardiovascular system. While T-cadherin lacks an intracellular domain and thus is unlikely to have a direct effect on intracellular signaling, it has been proposed to be essential for the recruitment of adiponectin to cardiovascular tissues. Supporting this notion, adiponectin is absent from the heart, vascular endothelium, and skeletal muscle in T-cadherin-deficient mice [155,156,158]. In addition, T-cadherin-deficient mice exhibit significantly elevated serum levels of adiponectin, further supporting the impaired recruitment of adiponectin to cardiovascular tissues in these mice. Conversely, adiponectin-deficient mice have reduced tissue expression of T-cadherin suggesting a regulatory axis between these proteins [155,156,158].

Sfrp5

A recent study has identified Sfrp5, a soluble modulator of Wnt proteins, as an adipokine with anti-inflammatory properties that protects against metabolic dysfunction [55]. Sfrp5 is expressed at highest levels in white adipose tissue of mice. Its expression in adipose tissue is down-regulated in various models of rodent obesity and in the visceral adipose tissue of metabolically dysfunctional obese patients that display crown-like structures. Sfrp5 functions to antagonize noncanonical Wnt5a signaling. Wnt5a is upregulated in fat depots of obese rodents and, as discussed below, it functions to promote inflammatory responses involving macrophages.

Sfrp5-deficient mice are metabolically normal when maintained on a regular diet, but display impaired glucose metabolism and increased fatty liver disease when fed a high caloric diet [55]. The enhanced metabolic dysfunction caused by Sfrp5-deficiency is associated with an increased adipose tissue accumulation of macrophages and increased production of pro-inflammatory cytokines. Mechanistically, Sfrp5 functions to suppress Wnt5a-mediated activation of JUN N-terminal kinase 1 (JNK1) in adipose tissue, and deletion of JNK1 in Sfrp5-deficient mice reverses the metabolic and inflammatory phenotypes. Thus, the increases in obesity-induced adipose tissue inflammation and metabolic dysfunction caused by overactivation of JNK1 signaling in Sfrp5-deficient mice, consistent with the well-described role for JNK1 in regulating insulin resistance and fat inflammation [159–162].

The role of the Sfrp5/Wnt5a regulatory system in cardiovascular disease is relatively unexplored, but a number of recent studies suggest that this may be an interesting area of investigation. It has been shown that Wnt5a functions as a macrophage effector molecule that promotes inflammation in response to microbial infection via the activation of noncanonical Wnt signaling [163,164]. With regard to cardiovascular actions, Wnt5a promotes inflammation in endothelial cells [165], and noncanonical Wnt5a signaling has been shown to suppress angiogenesis through the upregulation of Flt1, an endogenous VEGF inhibitor produced by myeloid cells [166]. Finally, Wnt5a expression has been detected in mouse and human atherosclerotic lesions [165,167]. Thus, it is tempting to speculate that Sfrp5 deficiency, as occurs in obesity, leads to runaway Wnt5a signaling favoring a chronic inflammatory state that promotes cardiovascular disease. Further studies are required to definitively address the role of Sfrp5/Wnt5a signaling in regulation of obesity-linked inflammatory cardiovascular disorders.

Conclusions

Adipose tissues produce various adipokines that function to regulate the microenvironment of adipose tissue and communicate with the brain, heart, vasculature, liver, and muscle. These adipokines have either pro-inflammatory or anti-inflammatory activities, and their balance is critical in maintaining systemic homeostasis. Obesity-induced adipose tissue dysfunction leads to dysregulated adipokine production that has both local and systemic effects on inflammatory cells. This adipokine imbalance leads to the development of a low-grade, chronic inflammatory state that contributes to the development of metabolic and cardiovascular diseases.

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