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Mechanisms linking adipose tissue inflammation to cardiac hypertrophy and fibrosis

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Abstract

Adipose tissue is classically recognized as the primary site of lipid storage, but in recent years has garnered appreciation for its broad role as an endocrine organ comprising multiple cell types whose collective secretome, termed as adipokines, is highly interdependent on metabolic homeostasis and inflammatory state. Anatomical location (e.g. visceral, subcutaneous, epicardial etc) and cellular composition of adipose tissue (e.g. white, beige, and brown adipocytes, macrophages etc.) also plays a critical role in determining its response to metabolic state, the resulting secretome, and its potential impact on remote tissues. Compared with other tissues, the heart has an extremely high and constant demand for energy generation, of which most is derived from oxidation of fatty acids. Availability of this fatty acid fuel source is dependent on adipose tissue, but evidence is mounting that adipose tissue plays a much broader role in cardiovascular physiology. In this review, we discuss the impact of the brown, subcutaneous, and visceral white, perivascular (PVAT), and epicardial adipose tissue (EAT) secretome on the development and progression of cardiovascular disease (CVD), with a particular focus on cardiac hypertrophy and fibrosis.

Introduction

Adipose tissue biology is intricately linked to cardiovascular health, and the growing obesity epidemic increases the prevalence of cardiovascular disease (CVD) risk factors for hypertension, atherosclerosis, and myocardial infarction (MI). The heart has a constantly high demand for ATP generation, and the majority of this energy in healthy myocardium comes from oxidation of fatty acids, with adipose tissue providing a key source of free fatty acids (FFAs) [1]. Furthermore, it is well established that the metabolic fuel source and energy demands of the heart are altered in cardiac pathology, establishing a critical metabolic and physiological link between the heart as a primary source of FFA catabolism and adipose tissue as the primary source of FFA storage [1,2] Obesity comorbidities,

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Author Contribution

S.R.A, A.R.G, A.G., R.N.H., A.P.O.III, and M.T. performed literature searches and drafted the manuscript. A.R.G. created the tables. A.P.O.III made the figure. S.R.A edited and integrated the final manuscript. All authors approved the final version of this manuscript.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

including type 2 diabetes, have been linked to inflammation of the white adipose tissue (WAT) depots in both mice and men [3]. Adipose tissue is becoming increasingly recognized as an important source of paracrine signaling, through means such as adipocyte-derived exosomes and adipokines that influence CVD initiation and progression. In the setting of obesity, hypertrophic adipocytes are known to secrete numerous pro- and anti-inflammatory adipokines that have been shown to play a role in CVD. In addition to adipocytes, other cell types within adipose tissue, including smooth muscle, endothelial cells, fibroblasts, and macrophages, may also contribute to the paracrine signaling properties of adipose tissue [4,5]. Adipose tissue expansion in obesity is accompanied by an increase in total infiltrating immune cells and a shift in macrophage polarization toward a classical 'M1'-like pro-inflammatory activation state [6,7] The relationship between obesity and CVD is indeed an interesting one and the 'obesity paradox', which postulates that while obesity may increase risk factors for CVD, mortality is actually reduced in the presence of obesity, continues to loom large in the field, and is yet to be satisfactorily explained on the mechanistic level [8–10]. The focus of this review is how adipose tissue-derived signaling, specifically associated with The pro-inflammatory milieu of obesity, impacts the development and progression of cardiac hypertrophy and fibrosis.

Heart failure (HF) is a leading cause of mortality in the United States with projections of affecting 8 million adults by 2030 [11]. HF is often preceded by pathological remodeling of cardiac structure and compliance in the forms of left ventricular (LV) hypertrophy (LVH) and fibrosis in response to injury (e.g. ischemia), increased peripheral resistance (e.g. chronic hypertension or obesity), or obstruction (e.g. valvular disease) [12–14]. The initial development of cardiac LVH is a beneficial and compensatory response to maintain cardiac output in the face of hemodynamic stress. Common etiologies for LVH can be physiological (e.g. normal cardiac muscle enlargement associated with athletes or pregnancy), pathological (e.g. in response to chronic hypertension, valvular disease, or MI, or congenital. The underlying physiology and differential molecular mechanism driving pathological and physiological LVH have been reviewed elsewhere [13], but our focus here is on the impact of adipose tissue on pathological cardiac remodeling.

A central theme of LVH that is distinctly specific to pathological hypertrophy is the activation of fibroblasts to myofibroblasts and subsequent accumulation of fibrosis within the myocardium. Fibroblasts in a healthy heart are quiescent, non-dividing cells responsible for homeostatic collagen turnover and continuous restructuring of the extracellular matrix (ECM) to optimize the contractile function of cardiomyocytes [14,15]. Myofibroblasts, on the other hand, have minimal contractile properties, acquire the ability to proliferate and migrate, and are marked by an excess deposition of ECM proteins [14,16]. Both compensated and decompensated hypertrophy and fibrosis are known clinically to be significant contributors and predictors of diastolic and systolic HF [17].

The potential for adipose tissue to impact cardiovascular physiology may seem quite obvious, but many of the mechanisms of how this tissue cross-talk occurs remain as the elusive topic of ongoing work. As this relatively new field grows and expands, so does the understanding that the varying adipose tissue depots have disparate impacts on CVD. First, adipose tissue itself can be broadly defined as either WAT or brown adipose tissue (BAT).

WAT serves primarily as a fat (triglyceride; TG) droplet-rich energy store and can make up to 25% of body weight, whereas BAT is mitochondrial dense and metabolically active, accounting for as much as 20% of all energy expenditure [18]. More recently, beige adipocytes, or BAT-like cells within WAT depots, have been identified and shown to share many similarities with BAT, including expression of BAT marker genes, increased mitochondrial density, and heat induction in response to exercise, cold, or adrenergic stimulation [19,20]. However, due to the complexities of their inducible nature and interspersed location within larger WAT depots, the specific effects of beige adipocytes within the disease setting has been difficult to assess and their contribution remains unclear.

In addition to adipocyte composition (white, brown, beige), it has been known for decades that the specific anatomical location of adipose tissue has been shown to play a key role in cardiac influence [21,22]. For example, growing clinical evidence shows that excess visceral WAT is more strongly associated with CVD and associated comorbidities, potentially due to it being correlated with a more pro-inflammatory state compared with subcutaneous WAT [4,23,24]. Similarly, BAT is thought to be less inflammatory than WAT and have several cardioprotective properties [25]. Here, we will review the current state of the field with regard to the attributed role of visceral and subcutaneous white, brown, perivascular (PVAT), and epicardial adipose tissue (EAT) to cardiac hypertrophy and fibrosis.

Visceral and subcutaneous WAT

WAT acts as a major energy reservoir of the body. WAT also serves as an endocrine organ, where it can secrete hormones, lipids, and cytokines that regulate systemic energy homeostasis [26]. WAT is unique in that it is unilocular, possesses few mitochondria, and tends to be negative for uncoupling protein 1 (UCP1), which is vastly different than BAT [27]. The major anatomical WAT depots include intra-abdominal, upper-body subcutaneous, and lower body subcutaneous [28,29]. Further, intra-abdominal fat depots are made up of omental and mesenteric depots, otherwise termed as visceral fat. Lower body subcutaneous includes gluteal fat, subcutaneous leg fat, and intramuscular fat [29]. Subcutaneous fat is thought to be more heterogeneous, histologically, where it contains more mature unilocular adipocytes intercalated with small multilocular adipocytes. Visceral fat, however, consists of more large unilocular adipocytes and appears to be more uniform in nature [30–32].

In mice, subcutaneous WAT depots express higher levels of browning genes compared with visceral WAT [33]. This is consistent with the notion that the subcutaneous fat depot can undergo extensive browning after cold exposure and the appearance of multilocular beige adipocytes are mainly found in subcutaneous, but not visceral, fat depots [34]. On the contrary, human visceral WAT depots express higher levels of browning genes, suggesting a potential species-specific difference in the beiging of WAT [33]. Aside from these anatomical and genetic differences, it is well established that significant deposition of visceral fat is associated with metabolic syndrome, CVD, and several cancers [35,36]. On the contrary, subcutaneous fat depots are generally recognized to be protective in the context of cardiometabolic disease [35,37,38]. Therefore, the ratio of visceral fat to subcutaneous fat remains a predictor of metabolic syndrome and CVD [39].

Previous studies have reported that obese subjects have increased LV mass, LV wall thickness, and LV internal dimension compared with non-obese subjects [40–42]. Moreover, LV mass is significantly associated with waist-to-hip ratio and with waist-to-height ratio after adjusting for body mass index, suggesting that central obesity is an important risk factor for LV mass in older adults [43]. WAT, along with infiltrating immune cells such as monocytes and macrophages within the stromal vascular fraction (SVF), is known to express pro-inflammatory cytokines such as TNF-α and interleukin-6 (IL-6) in an obesity-dependent manner, though these cytokines are by no means specific to adipose tissue [44]. Here, we discuss the effects of WAT-selective adipokines on CVD, also highlighted in Table 1.

Central obesity and visceral adipose tissue accumulation are both inversely correlated with serum adiponectin [45], an anti-inflammatory adipokine that is traditionally viewed as an adipocyte-specific molecule but has also been found to be expressed locally in adult cardiomyocytes [46]. Adiponectin has been shown to play a protective role in acute ischemic injury [47], perhaps through an autophagy-dependent mechanism [48], and also plays a direct role in post-ischemic cardiac remodeling [49]. It has been demonstrated that mice lacking adiponectin display increased LV wall thickness with an accompanying ~74% decrease in cardiac output after transverse aortic constriction, compared with control animals [50]. Similarly, adiponectin-deficient mice exhibit severe angiotensin II (AngII)-induced cardiac fibrosis which was reversed with adiponectin supplementation [51]. In humans, however, the association between serum adiponectin and cardiac hypertrophy, and CVD risk in general, remains controversial [4]. A study in Japanese men demonstrated that serum adiponectin levels were inversely and independently associated with LV hypertrophy [52]. On the contrary, adiponectin secretion from WAT is dependent on systemic inflammation and stimulated by brain natriuretic peptide [53,54], which is increased in cardiac hypertrophy and HF, suggesting adiponectin to be predictive of adverse cardiac outcomes. Additionally, excessive visceral adiposity is associated with impaired diastolic parameters when assessing LV diastolic function, independently of decreased circulating adiponectin levels [55]. Nonetheless, it is evident that adiponectin is important in the underlying etiology of cardiac hypertrophy and fibrosis, but more work is needed to elucidate the precise mechanism(s) involved.

Leptin, another well-studied adipokine, increases with obesity and has been clinically shown to be associated with increased cardiovascular risk [56–60]. Like adiponectin, leptin is predominately expressed by WAT; however, leptin can also be produced by epicardial and perivascular adipose tissue, as well as directly by cardiac myocytes, and is generally elevated in obese individuals [61]. Studies examining the role of leptin on acute ischemia/hypoxia have suggested that it reduces myocyte apoptosis [62–65] which gives it a cardioprotective effect of reducing myocardial infarct size [66,67]. However, the majority of studies examining the role of leptin in the setting of cardiac hypertrophy have determined it to have a detrimental role of promoting hypertrophic progression, potentially through a p38 MAPK-dependent signaling pathway [68–75]. Leptin has also been shown to modulate collagen synthesis and potentially mediate changes in ECM remodeling enzymes [69,76–78].

Adiponectin and leptin are possibly the most common, but certainly not the only WAT-derived adipokines with the potential to influence cardiac hypertrophy and fibrosis. Fatty

acid binding protein 4 (FABP4) strongly correlates with adiposity and is released from adipocytes where it acts as an adipokine in several organs, including the heart [79–81]. Serum FABP4 concentrations have recently been identified to associate with LV mass in overweight and obese women [82], which is consistent with data in non-obese patients who were hospitalized for acute decompensated HF [83]. Interestingly though, FABP4 was once thought to be expressed primarily in adipocytes [84,85], but has since been shown to also be expressed in monocyte and macrophage lineages [86,87]. Resistin, which is similarly expressed by both mature adipocytes and monocytes/macrophages within the stromal–vascular fraction [88], has been shown to mediate cardiac dysfunction and LV hypertrophy [89,90] while also showing a strong clinical correlation with coronary artery disease (CAD) [91–93] and HF in human patients [94]. Additional adipokines have been suggested to play a cardioprotective role. Recent work demonstrated that specific inhibition of adipose tissue-derived autotaxin protected against HFD-induced LV hypertrophy and dysfunction [95]. Visfatin, secreted primarily by the SVF of WAT [96], has been suggested to reduce myocyte apoptosis [97,98], but has also been shown to play a pro-inflammatory role and mediate atherogenic plaque destabilization [96,99]. Omentin, also expressed primarily by the SVF of WAT [100], has also been suggested to be cardioprotective in the setting of acute ischemic injury, potentially through a reduction in apoptosis [101,102], as well as pathological hypertrophy [103,104]. Circulating omentin levels are also negatively correlated with CAD [105–108].

The specific cell signaling link between subcutaneous adiposity and its influence on cardiac hypertrophy and fibrosis remains poorly defined. In 2013, Ichikawa and colleagues [109] noted that the ratio of visceral adipose tissue to subcutaneous adipose tissue was an independent determinant of LV mass. Recent findings from the Dallas Heart Study demonstrate that lower body subcutaneous fat was associated with higher LV end-diastolic volume, reduced concentricity and wall thickness, and greater cardiac output. Visceral fat, however, remained associated with lower cardiac output and higher vascular resistance [110]. In accordance with mouse data, this information suggests that visceral adipose tissue remains positively correlated with CVD risk including increased LV mass and dysfunction, while subcutaneous adiposity remains protective in this context. Further work is needed to identify the underlying mechanisms, and potential adipose-specific adipokines, that may contribute to the etiology of LV hypertrophy and cardiac dysfunction.

BAT

The existence of functional BAT in adult humans was controversial until 2009 when it was demonstrated that adults indeed possess multiple depots of metabolically active BAT (see Figure 1 for anatomical distribution of BAT in humans) [111,112]. Importantly, it was shown that energy expenditure in BAT could be enhanced through cold or adrenergic stimulation similar to BAT in rodents [111–115]. The thermogenic uncoupling of mitochondrial ATP synthesis, which can account for up to 20% of total energy expenditure [18], is primarily achieved by uncoupling proteins, with UCP1 being expressed specifically in brown and beige adipocytes and the most well-studied mediator of thermogenesis [116].

BAT has an important role in modulating various aspects of cardiovascular health. As other types of adipose tissue have shown to yield a negative cardiovascular effect, BAT has been shown to be cardioprotective in models of myocardial injury, myocardial fibrosis, and LV hypertrophy [117]. As such, transplantation of activated BAT has piqued interest as a novel therapeutic treatment of cardiac injury. Formerly, increasing the presence of adult BAT has served as a therapeutic target for obesity and associated diseases, such as type II diabetes, due to its thermogenic properties [118,119]. Activation of BAT as a therapeutic strategy for weight loss was suggested as early as the 1930s and has continued with agents such as glucocorticoids, capsinoids, and β3-adrenergic receptor (β3-AR) agonists, but all have been unsuccessful in achieving weight reduction without unwanted cardiovascular side effects [114,120–122]. Interestingly, normal cardiac function has been shown to be necessary for BAT-mediated thermogenesis [123]. Conversely, the molecular contributors to BAT development and function, such as norepinephrine, catecholamine, and natriuretic peptide release occurring along with sympathetic nervous system activation, also have clear cardiovascular functions and are correlated with cardiac injury and LV remodeling [117,124,125].

Utilizing a model of catecholamine-induced cardiomyopathy, Thoonen and colleagues [117] demonstrated that *Ucp1*$^{-/-}$ mice had observed increases in cardiomyocyte injury and fibrosis versus proficient controls, suggesting BAT has protective effects in the setting of myocardial injury and cardiac remodeling. They observed exacerbated hypertrophic remodeling of the LV in *Ucp1*$^{-/-}$ mice, accompanied by a decrease in LV systolic function in males, and an increase in hypertrophy in females [117]. The gender differences expressed in this model are consistent with the differences exhibited in models of humans [117,126] and other rodents [127,128]. *Ucp1*$^{-/-}$ mice subjected to isoproterenol treatment also displayed decreased survival and decreased phosphorylation of AKT compared with wild-type controls [117]. The AKT pathway is suggested to be cardioprotective in ischemia and reperfusion injury, and a decrease in phosphorylation is damaging to cardiomyocyte longevity [129–131]. However, upon transplantation of functional BAT to *Ucp1*$^{-/-}$ mice, improvements in myocardial injury and increased survival was observed, suggesting a cardioprotective function of BAT [117].

The complete endocrinological profile of BAT is largely unknown but is suggested to play a cardioprotective role. Compiling evidence suggests BAT yields autocrine and paracrine action through the release of ‘BATokines’, which often act to improve general metabolic function. Functional BAT may improve cardiovascular health just by virtue of an improved metabolic profile, including benefits on glucose metabolism, adipogenesis of BAT, increased energy expenditure, and insulin sensitivity, but is also suggested to mediate cardiac risk through the release of systemic cardioprotective factors [132]. A comprehensive list of BATokines and their roles in cardiometabolic disease can be found in Table 2.

The first BATokine to be identified was the thyroid hormone Triiodothyronine (T3) which has an extensive network of action within the human body, affecting areas such as growth, metabolism, and heart rate [133]. The enzyme type II thyroxine 5′-deiodinase (DIO2) mediates the conversion of T3 from T4 and is shown to be highly up-regulated in brown fat upon activation [133]. Thus, increased levels of plasma T3 are also seen after BAT activation

[25,133,134]. Thyroid hormones have shown cardioprotective effects in humans, however as T3 is not specifically secreted by BAT, the role of specific BAT-mediated production is still unclear [25].

Another BATokine, Fibroblast Growth Factor 21 (FGF21), is secreted by thermogenically stimulated BAT and acts to collectively improve metabolic and cardiac function [135,136]. Importantly, FGF21 also regulates the expression of UCP1 and is critical in the beiging of WAT [137]. FGF21 acts on WAT and the liver and is shown to yield beneficial effects on lipid and glucose metabolism [25,135], as well as having protective effects on type II diabetes [138]. Additionally, FGF21 has been shown to have antihypertrophic and cardioprotective effects in animal models of hypertrophy and ischemia [25,139,140].

Nrg4, another factor secreted by cold-induced BAT, is cardioprotective in mouse models of myocardial ischemia [25,141]. However, Nrg4 is also secreted by other organs such as the liver, so identification of Nrg4 as a product of BAT response to cardiac injury is uncertain.

IL-6, a pro-inflammatory cytokine released by BAT and other tissues, has been suggested to yield a variety of metabolic and cardiac effects. IL-6 has been shown to mediate glucose metabolism and energy expenditure [25]. When IL-6 production is inhibited, mice become highly susceptible to diet-induced obesity and glucose intolerance. However, when chronically activated, mice showed an increase in energy expenditure and the promotion of WAT beiging [142,143]. In studies of BAT transplantation, the metabolic improvements regarding glucose homeostasis and insulin sensitivity were eliminated when BAT from IL-6-null mice was used for transplant, indicating a necessary role for IL-6 in BAT-mediated metabolic function [144]. IL-6 plays a clear, but broad and diverse, role in cardiovascular physiology, making it an important paracrine signaling BATokine, but it is also produced by multiple tissue types, making it not specific to BAT [145].

Nerve Growth Factor (NGF) is a protein secreted by BAT and other tissues, which typically functions to promote sympathetic axon growth and the proliferation of neurons [146]. NGF has also been shown to promote cell survival in models of ischemic injury, as well as improving the general function of perfused diabetic hearts [147–149]. Paradoxically, however, NGF expression in mice is down-regulated upon BAT activation by either cold or adrenergic stimulation, leaving its role as a cardioprotective agent in question [150].

Certainly, there are many more BATokines and pathways of BAT-mediated cross-talk to the heart that are yet to be identified. In fact, while we have recently shown that activity of the RNA binding protein human antigen R (HuR) directly within cardiomyocytes mediates cardiac hypertrophy and fibrosis [151,152], new unpublished data from our lab show that deletion of HuR specifically in adipose tissue elicits the development of cardiac hypertrophy and fibrosis, which is potentially linked to the disruption of BAT-mediated thermogenic function. Interestingly, HuR has been shown to target IL-6 as well as many other inflammatory cytokines [153,154], but the underlying mechanism for the cardiac phenotype of adipocyte HuR-deletion remains unknown. In general, the pro-inflammatory profile of BAT is significantly lower than WAT, producing a phenotypically attenuated inflammatory

tissue [132]. Overall, the endocrinological ability of BAT shows therapeutic avenues for cardiovascular health and CVD risk factors.

Epicardial, pericardial, and perivascular adipose tissue

The nomenclature and classification of epicardial (EAT), pericardial (PAT) and perivascular (PVAT) adipose tissue throughout the literature can be confusing [155–157]. EAT is the adipose depot that lies beneath the surface of the epicardium and shares the same microcirculation vasculature with the myocardium [155,158]. PAT, meanwhile, is contained on the outer surface of the parietal pericardium [159], and may also be referred to as intrathoracic, mediastinal, or paracardial adipose tissue [160]. PVAT is found almost ubiquitously on vasculature throughout the body, with the notable exception of the cerebral vasculature and, because it also comprises the adipose tissue on the coronary arteries, can be difficult to distinguish from EAT [161]. Coupled with the fact that mice have minimal EAT, this makes the nomenclature even more confusing [158].

EAT varies due to multiple different factors such as age, waist circumference, and heart weight which all suggest that aging, abdominal obesity, and myocardial hypertrophy are the main predictors of EAT volume [162–164]. EAT has been shown in adult humans to possess molecular features and a gene profile of beige adipocytes and may play a thermogenic role [165,166]. Evidence has shown that EAT is metabolically active, a source of several adipokines, and is an active endocrine organ [167,168].

Very little is known about the functional roles that epicardial fat play in cardiac hypertrophy or fibrosis. Given the proximity of EAT within the myocardium, it is not surprising that numerous studies have associated both EAT volume and thickness with risk of coronary events and HF (see Ansaldo and colleagues (2019) [164] for a thorough summary of clinical observations linking EAT to CVD). Echocardiography can be used to distinguish EAT from pericardial fat in humans and has been used to demonstrate a clinical correlation between EAT thickness and LV mass [169–171]. However, contrasting studies suggested a decrease in EAT volume in patients with HF [172–174]. Studies conducted on both obese and non-obese men show that men with CAD have more epicardial fat accumulation than those without CAD independent of obesity [162,175]. In fact, surgical removal of EAT has been shown to ameliorate atherogenesis in a porcine model suggesting a causal role for EAT in CAD [176,177].

EAT has been shown to express multiple adipokines, including adiponectin, in a secretome that changes with metabolic and inflammatory states, but the mechanisms by which EAT may contribute to CVD remain unclear [163,164,178–180]. Omentin, which we have previously mentioned as having potential cardioprotective effects [101,102], is increased in EAT in the setting of CAD [181] and may serve as a clinical predictor of adverse cardiovascular outcome [182,183]. Perhaps most interesting is that EAT has been shown to secrete direct mediators of fibrotic remodeling, such as activin A, connective tissue growth factor (cTGF), TGF-β1, and metalloproteinases [184–188]. Secreted factors from human EAT are sufficient to induce fibrosis in an organo-culture model of rat atria [184]. This pro-

fibrotic effect of EAT may be enhanced by a pro-inflammatory state and play a strong predictive and mechanistic role in atrial fibrillation [185,186,189–192].

While these clinical observations are supportive of EAT playing a role in the development of CVD, mechanistic studies in animal models are scarce [163,164,180]. This is in part due to the fact that small animal models such as mice and rats often express little to no epicardial adipose, making them difficult laboratory models for the study of EAT [158]. Surgical resection of EAT in a rat model of MI suppressed inflammatory signaling and improved LV remodeling [193], though its mechanisms of action or direct role on the myocardium remain elusive. The secretome of EAT from guinea pig hearts has been shown to negatively influence myocyte contractility [194], and orosomucoid isolated from the human EAT secretome reduced hypoxia-induced apoptosis in H9c2 cells [195].

Because of the aforementioned nomenclature confusion, delineating the role of PAT can be difficult. Human PAT biopsies reveal elevated levels of the BAT-specific genes UCP1 and PPARγ as compared with subcutaneous adipose tissue, suggesting PAT may function similar to BAT, in a generally cardioprotective manner [196]. However, multiple clinical studies have found positive correlations between PAT volume and LV mass [197–200], systolic dysfunction [198], ejection fraction [199], and cardiac output [201]. Although PAT volume is not a better predictor of CVD than other measures of adiposity [197,200], it nonetheless appears to be associated with the development of cardiac hypertrophy and heart failure.

PVAT, depending on anatomical location, may closely resemble either WAT or BAT [161]. However, adipocytes composing PVAT arise from a different cell lineage than either classical WAT or BAT, sharing lineage markers with vascular smooth muscle cell precursors [202,203].

PVAT undoubtedly plays a critical role in cardiovascular health, with a classic role in mediating vascular tone being identified as early as 1991 when it was shown that intact PVAT blunted the *ex vivo* contractile effects of adrenaline [204]. It was subsequently shown that the same regulatory role for PVAT was also demonstrated for AngII and phenylephrine-mediated contractility in aortic rings [205]. However, obesity induces a shift to more pro-inflammatory state in PVAT that renders it as a vasoconstrictive mediator [206]. Thus, it is not surprising that inflammatory cell infiltration and resulting pro-inflammatory cytokine expression profile within PVAT has been noted to increase under conditions of obesity and high fat feeding [207,208]. The precise mechanisms of this inflammatory switch remain unknown, but are potentially downstream of hypoxia-induced HIF-1α signaling, which has been shown to mediate the up-regulation of pro-inflammatory cytokine gene expression concomitant with reduced expression of anti-inflammatory adiponectin [209–211]. Accordingly, HIF-1α has been shown to increase in obesity, and exposure of PVAT to hypoxia induces inflammatory gene expression and abrogates its vasorelaxive properties [212,213].

Given that PVAT has been shown to mediate both vasodilatory and vasoconstrictive roles, the precise role for PVAT in regulating vascular tone remains somewhat uncertain [25,214]. Since the presence of a direct-acting PVAT-derived relaxing factor (PVDF) was first

hypothesized in 2002, numerous mediators of PVAT-mediated vasorelaxation, such as leptin, adiponectin, and inflammatory cytokines, have been identified [209]. Similarly, PVAT has also been shown to play antithetical roles with regard to atherosclerosis. However, it appears that the role of PVAT leans more protective in metabolically healthy subjects and injurious under conditions of obesity and diabetes, similar to what one might expect from an adipose depot that most closely resembles activatable beige adipocytes [203,215,216].

Conclusion

Collectively, adipose-derived signaling molecules have been established as important contributors to CVD, further strengthening the link between central obesity and CVD risk. It is clear that the secretome from adipose tissue, collectively termed as adipokines, have the potential to have a profound effect on cardiac physiology. Additionally, the secretome profile of adipokines changes with the metabolic state (e.g. lean vs. obese), anatomical location (visceral, subcutaneous, EAT etc.), and cell identity (BAT vs. WAT) of the adipose depot (summarized in Figure 1). The use of animal models has facilitated the experimental investigation of mechanistic and causal relationships between adipose tissue and CVD (see Table 3 for a summary of animal models discussed herein). Thus, while there is tremendous untapped potential in harnessing the effects of adipose tissue on cardiac hypertrophy and fibrosis for the clinical application of diagnostic biomarkers and therapeutic interventions, much work remains to be done to fill the gaps in understanding of how the dynamic changes in adipokines in response to obesity/inflammation effect cardiovascular health.

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Abbreviations

AngII	angiotensin II
BAT	brown adipose tissue
CAD	coronary artery disease
CVD	cardiovascular disease
EAT	epicardial adipose tissue
ECM	extracellular matrix
FABP4	fatty acid binding protein 4
FFA	free fatty acid
FGF21	fibroblast growth factor 21

HF	heart failure
HFD	high fat diet
HIF-1α	hypoxia inducible factor 1 alpha
HuR	human antigen R
IL-6	interleukin-6
LV	left ventricular
LVH	LV hypertrophy
MI	myocardial infarction
NGF	nerve growth factor
Nrg1	neuregulin 1
PAT	pericardial adipose tissue
PVAT	perivascular adipose tissue
SVF	stromal vascular fraction
T3	triiodothyronine
UCP1	uncoupling protein 1
WAT	white adipose tissue

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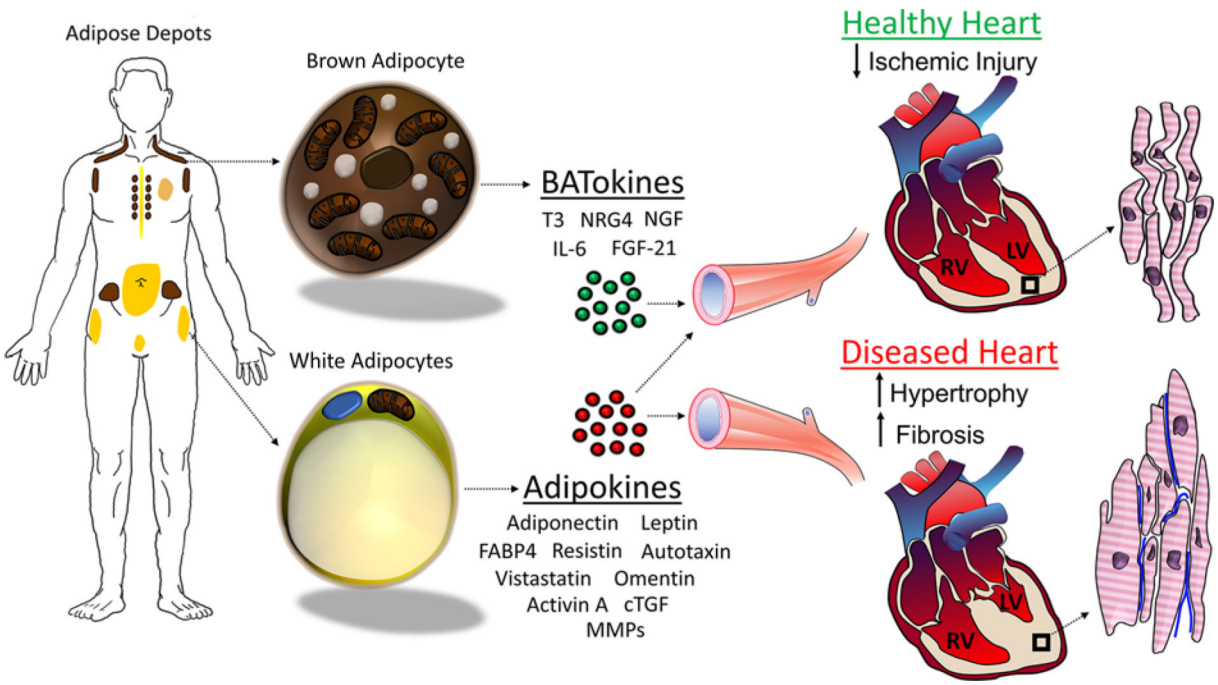

Figure 1. Adipose-mediated paracrine signaling effects on the heart

WAT (yellow color), comprising PVAT, EAT, visceral, subcutaneous, and gonadal, is composed of droplet-rich and mitochondrial poor white adipocytes. BAT (brown color), comprising cervical, supraclavicular, auxillary, paravertebral, and suprarenal, is composed of multilocular and mitochondrial rich brown adipocytes. WAT releases several adipokines, which can result in cardioprotection, but is often associated with increased CVD, including hypertrophied cardiomyocytes and collagen deposition (blue). BAT releases BATokines that are most often associated with promoting healthy myocardium and cardioprotection from ischemic injury.

Table 1

WAT-selective adipokines

Adipokine	Tissue source	Cardiac function in animal models	Clinical correlation with CVD
Adiponectin	WAT, PVAT	Protective in acute I/R [47–49]; reduced ROS [48]; reduced Hypertrophy [50]; reduced fibrosis [51]	Uncertain/contradictory
Leptin	WAT, PVAT, EAT	Protective in acute I/R [62–67]; increased hypertrophy [68–75]; ECM remodeling [69,76–78]	Increased risk, specifically MI [56–60]
FABP4	WAT, SVF	Unknown	Increased LV mass [82,83]
Resistin	WAT, EAT, SVF	Increased LV hypertrophy [89,90]	Increased CAD [91–93]; Increased HF [94]
Autotaxin		Increased hypertrophy and fibrosis [95]	Unknown
Visfatin	SVF	Reduced apoptosis [97,98]; atherogenic plaque	Unknown
		Destabilization [96,99]	
Omentin	WAT, SVF, EAT	Protective in acute I/R [101,102]; reduced hypertrophy [103,104]	Decreased CAD [105–108]
Activin A, cTGF, MMPs	EAT	Increased fibrosis/ECM remodeling [184–188]	Increased atrial fibrillation [185,186,189–192]

Table 2

BATokines

BATokine	Metabolic function	Cardiac function
Thriiodothyronine (T3)	Up-regulated in BAT post activation, effects areas such as growth, metabolism, and homeostasis [25,133,134]	Unclear, but thyroid hormones have shown cardioprotective effects in humans [25]
FGF-21	Beneficial effects on lipid and glucose metabolism [135,138], acts on white adipose tissue and the liver [25,135]	Cardioprotective and antihypertrophic effects in animal models of ischemia and hypertrophy [25,139,140]
NRG4	Adipogenesis and cold induced activation of BAT [25,141]	Cardioprotective effects in mice models of myocardial ischemia [25,141]
IL-6	Mediates glucose metabolism and energy expenditure, promotes browning of WAT [25,142,143,144]	Diverse; cardioprotective effects in HF, contributing factor in cardiac remodeling [145]
NGF	Produced by BAT, but down-regulated upon BAT activation by cold or adrenergic stimulation [146–150]	Promotes cell survival and preserves function in ischemic and diabetic hearts [147–149]

Table 3

Animal models demonstrating direct adipokine/batokine-mediated cardiac effects

Species	Animal Model	Adipokine/BATokine	Observed effect
Mouse	TAC	Adiponectin Omentin	Decreased hypertrophy in wild-type and diabetic (db/db) mice [50] Decreased hypertrohy and fibrosis [104]
	AngII infusion	Adiponectin	Decreased ROS [48]; decreased fibrosis [51]
	Permanent coronary ligation	Adiponectin Leptin	Improved LV function [49] Decreased apoptosis [64]; improved LV function and compensated hypertrophy [75]
	Coronary ischemia/reperfusion	Adiponectin Leptin Visfatin Omentin	Reduced infarct size [47] Reduced infarct size [66]Reduced infarct size [98] Reduced infarct size [101]
	Diet-induced obesity	Autotaxin	Secretion in obesity increased hypertrophy and fibrosis [95]
	Isoproterenol infusion; BAT transplant	BAT (general)	Functional BAT reduced hypertrophy and fibrosis [117]
Rat	Langendorff isolated heart	Leptin	Reduced infarct size [67]
	Permanent coronary ligation	Leptin	Increased hypertrophy and fibrosis [76]
	AAV overexpression	Resistin	Increased hypertrophy, fibrosis, and apoptosis with reduced LV function [90]
	Surgical excision of EAT	EAT (general)	Removal of EAT reduced infarct size and preserved cardiac function [193]
Pig	Surgical excision of EAT	EAT (general)	Removal of EAT reduced CAD [176,177]

Abbreviations: AAV, adeno-associated virus; ROS, reactive oxygen species; TAC, transverse aortic constriction.