British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2011.01370.x
www.brjpharmacol.org

Themed Section: Fat and Vascular Responsiveness

REVIEW

Epicardial perivascular adipose tissue as a therapeutic target in obesity-related coronary artery disease

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Keywords
perivascular adipose tissue; epicardial adipose tissue; endothelial dysfunction; leptin; adiponectin; adipokines; coronary artery disease; coronary circulation; inflammation; obesity

Received
29 December 2010
Revised
20 February 2011
Accepted
27 February 2011

Adipose tissue is an active endocrine and paracrine organ that may influence the development of atherosclerosis and vascular disease. In the setting of obesity, adipose tissue produces a variety of inflammatory cytokines (or adipokines) that are known to modulate key mechanisms of atherogenesis. In particular, adipose tissue located on the surface of the heart surrounding large coronary arteries (i.e. epicardial perivascular adipose tissue) has been implicated in the pathogenesis of coronary artery disease. The present review outlines our current understanding of the cellular and molecular links between perivascular adipose tissue and atherosclerosis with a focus on potential mechanisms by which epicardial perivascular adipose tissue contributes to obesity-related coronary disease. The pathophysiology of perivascular adipose tissue in obesity and its influence on oxidative stress, inflammation, endothelial dysfunction and vascular reactivity is addressed. In addition, the contribution of specific epicardial perivascular adipose-derived adipokines (e.g. leptin, adiponectin) to the initiation and expansion of coronary disease is also highlighted. Finally, future investigative goals are discussed with an emphasis on indentifying novel therapeutic targets and disease markers within perivascular adipose tissue.

LINKED ARTICLES
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Abbreviations
ADRF, adipose-derived relaxing factor; AMPK, adenosine monophosphate-activated protein kinase; eNOS, endothelial nitric oxide synthase; ICAM-1, intercellular adhesion molecule 1; MetS, metabolic syndrome; NO, nitric oxide; PKC, protein kinase C; PVAT, perivascular adipose tissue; VSMC, vascular smooth muscle cell

Introduction

Adipose tissue is widely accepted to be an active endocrine and paracrine organ that produces a variety of cytokines (or adipokines) that influence key pathogenic mechanisms of atherogenesis (Lau *et al.*, 2005). Many of these adipokines have been shown to influence a wide spectrum of haemodynamic, metabolic and immunologic factors, including insulin sensitivity (adiponectin and resistin), inflammation (IL-8, monocyte chemotactic protein 1, leptin, chemerin), vascular reactivity (leptin, resistin, tumour necrosis factor-alpha, adiponectin, visfatin, omentin) and coagulation (plasminogen activator inhibitor-1) (Juge-Aubry *et al.*, 2005; Knudson *et al.*, 2005; Trayhurn and Wood, 2005; Dick *et al.*, 2006; Goralski *et al.*, 2007; Gruen *et al.*, 2007; Beltowski *et al.*, 2008; Yamawaki *et al.*, 2009; 2010; Zhang *et al.*, 2009). Studies demonstrating that expression of specific adipokines is substantially altered with weight gain (Monzillo *et al.*, 2003; Silha *et al.*, 2003; Gnacinska *et al.*, 2010) have prompted the recent hypothesis that adipose-derived cytokines are critical factors

that link obesity with vascular dysfunction and disease (Lau *et al.*, 2005). However, the detailed cellular and molecular mechanisms by which adipokines influence obesity-related vascular disease remain poorly understood.

Recent evidence indicates that adipose tissue, which surrounds virtually all large arteries throughout the body [i.e. perivascular adipose tissue (PVAT)],' is capable of affecting vascular homeostasis through the production of local 'vasocrine' adipokines (Xu *et al.*, 2010). The purpose of the present review is to outline the current understanding of the cellular and molecular links between PVAT and vascular disease with a focus on potential mechanisms by which epicardial PVAT may contribute to obesity-related coronary artery disease. The pathophysiology of PVAT in obesity and its influence on oxidative stress, inflammation, endothelial dysfunction and vascular remodelling is addressed. In addition, the contribution of specific epicardial perivascular adipose-derived adipokines to the initiation and expansion of coronary disease is also highlighted. Finally, future investigative goals are discussed with an emphasis on indentifying novel therapeutic targets and disease markers within PVAT. The reader is also directed to other recent reviews on the effects of PVAT by Vela *et al.* (2007), Iacobellis and Sharma (2007), Sacks and Fain (2007), Rajsheker *et al.* (2010), Ouwens *et al.* (2010) and Verhagen and Visseren (2011).

Versatility of perivascular adipose tissue

While abdominal adiposity has received considerable attention, there is a developing hypothesis that local visceral adipose tissue may contribute to unfavourable cardiometabolic complications (Mazurek *et al.*, 2003; Iacobellis and Sharma, 2007; Rosito *et al.*, 2008; Clement *et al.*, 2009; Ding *et al.*, 2009; Greif *et al.*, 2009; Mahabadi *et al.*, 2009). Although PVAT has been proposed to provide structural support and insulation to blood vessels in its native setting (Sacks *et al.*, 2009), it is clear that the full spectrum of PVAT function remains to be delineated. PVAT has no fascia separating surrounding adipocytes from the vascular wall (Ouwens *et al.*, 2010), and adipocytes have been demonstrated to invade the outer region of the adventitia in the setting of obesity (Sacks and Fain, 2007; Chatterjee *et al.*, 2009). Hence, these local perivascular adipocytes possess a dynamic capacity to mobilize near vessels with the potential for unimpeded cellular communication.

Human PVAT has a diverse phenotypic expression pattern consistent with both brown and white adipocytes (Police *et al.*, 2009; Sacks *et al.*, 2009). While brown adipocytes have been identified within PVAT surrounding the thoracic aorta of obese mice (Police *et al.*, 2009), results from Sacks *et al.* (2009) demonstrated that human epicardial PVAT has augmented expression of the brown adipocyte markers uncoupling protein-1, PR-domain-missing 16 and peroxisome proliferator-activated receptor gamma coactivator-1 alpha. Interestingly, a positive association was observed between epicardial uncoupling protein-1 and body mass index despite an inverse relationship between brown adipose and body mass index. Given this heterogeneous nature, it is not difficult to appreciate that PVAT-derived factors influence a variety of (patho)physiological functions. In addition to adipose-derived relaxing factor (ADRF) production (Soltis and Cassis, 1991; Lohn *et al.*, 2002; Dubrovska *et al.*, 2004; Verlohren *et al.*, 2004; Gao *et al.*, 2005; Galvez *et al.*, 2006; Malinowski *et al.*, 2008), visceral and PVAT have been associated with angiogenesis (Rhoads *et al.*, 2009), mesenchymal stem cell recruitment (Crisan *et al.*, 2008), vascular smooth muscle cell (VSMC) growth (Wang *et al.*, 2009), cardiomyocyte electrical activity (Kourliouros *et al.*, 2010) and vascular endothelial function (Gao *et al.*, 2007; Payne *et al.*, 2008; 2009). Interestingly, adipose tissue surrounding the heart has been clinically associated with coronary artery disease (Ishikawa *et al.*, 1997; Mazurek *et al.*, 2003; Cheng *et al.*, 2008; Gorter *et al.*, 2008; Greif *et al.*, 2009; Verhagen and Visseren, 2011). These clinical associations are important because they suggest an alternative, local pathway for the development of obesity-associated vascular disease. Hence, 'local obesity' (i.e. epicardial PVAT) may be an important regulator of vascular function and disease progression.

Epicardial perivascular adipose tissue and coronary artery disease

Epicardial adipose tissue is a visceral thoracic fat depot located along the large coronary arteries (i.e. perivascular) and on the surface of the ventricles (Figure 1). Importantly, this naturally occurring adipose depot expands with obesity (Sarin *et al.* 2008; Ding *et al.*, 2009), and atherosclerotic plaques have been shown to occur predominantly in epicardial coronary arteries that are encased in PVAT (Montani

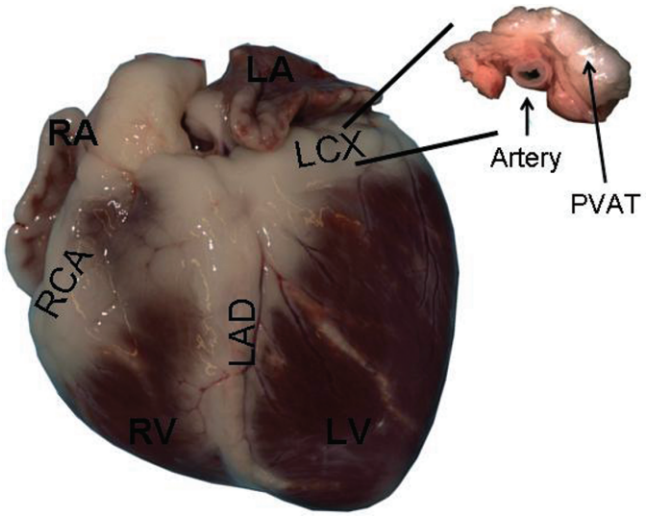

Figure 1

Representative picture showing naturally occurring PVAT on the heart. PVAT is closely associated with the underlying coronary vasculature and is increased with obesity. RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; PVAT, perivascular adipose tissue.

et al., 2004; Sacks and Fain, 2007; Sarin *et al*. 2008; Greif *et al*., 2009). The severity of these lesions also directly correlates with the volume of epicardial PVAT (Greif *et al*., 2009). Interestingly, patients with a myocardial muscle bridge have limited atherosclerosis within the portion of the vessel surrounded by muscle, as opposed to vessels surrounded by PVAT (Ishii *et al*., 1998). Importantly, the Framingham Heart Study (Schlett *et al*., 2009; Lehman *et al*. 2010) and Multi-Ethnic Study of Atherosclerosis (Ding *et al*., 2009) identified epicardial and pericardial adipose volume as independent risk markers for cardiovascular and coronary heart disease. In comparison with the Framingham risk score (which accounted for age, systolic blood pressure, total cholesterol and smoking status), epicardial PVAT volume was by far the strongest predictor of coronary atherosclerosis (odds ratios of 2.8 vs. 4.1) (Greif *et al*., 2009). Surprisingly, in many of these clinical studies no association between body mass index and coronary atherosclerosis was detected.

These observations have prompted many to speculate that local adipokine production and inflammation directly links epicardial PVAT with coronary vascular dysfunction. Results from Baker *et al*. (2006) and Cheng *et al*. (2008) documented pathogenic adipokine profiles from human epicardial PVAT. Specifically, Baker *et al*. reported increased macrophage infiltration (and potentially increased inflammation) within epicardial adipose compared to abdominal adipose tissue. Subsequent studies confirmed this findings and further demonstrated augmented expression of numerous epicardial PVAT adipokines, including leptin, resistin, tumour necrosis factor-alpha, interleukin-6, interleukin-16, visfatin and chemerin. Table 1 summarizes the relationship between epicardial PVAT expression, coronary artery disease and obesity/metabolic syndrome. It is also important to acknowledge that other studies have observed a distinct correlation between diminished adiponectin expression and the degree of coronary disease (Greif *et al*., 2009; Karastergiou *et al*., 2010). These observations are critical as plasma biomarkers likely fail to adequately reflect local tissue levels of these various factors, and traditional cardiovascular therapies do not directly target local signals from PVAT (Mazurek *et al*., 2003; Iacobellis and Sharma, 2007).

In spite of current evidence, there is still considerable uncertainty regarding the proposed pathologic role of epicardial PVAT. Particularly, determining how factors produced within the adventitia are able to traverse the arterial wall remains a critical question. While this issue is not the primary focus of this review, it is nonetheless important to emphasize that the coronary vasa vasorum is a potential conduit that could traffic harmful adipokines between PVAT and the vascular wall (Herrmann *et al*. 2001; Moreno *et al*., 2006; Gossl *et al*., 2007). Results from Herrmann *et al*. demonstrated that increased coronary vasa vasorum neovascularization preceded overt coronary endothelial dysfunction and atherosclerotic disease in domestic swine fed a high cholesterol diet. These experimental findings have subsequently been confirmed in at risk patient populations (Staub *et al*., 2010). Together, current investigations call attention to the temporal relationship of PVAT inflammation, vasa vasorum neovascularization, endothelial dysfunction and atherosclerosis.

Interestingly, previous studies indicate that endovascular injury induces rapid up-regulation of pro-inflammatory adipokines within PVAT (Takaoka *et al*., 2010), including epicardial PVAT (Okamoto *et al*., 2001). Hence, while the surrounding PVAT may signal from the outside in, the vasculature in theory has a similar capacity to directly communicate with the adventitia and PVAT. These findings support the hypothesis that endothelial and VSMCs have the potential to crosstalk with surrounding PVAT. The remainder of this review will discuss current experimental evidence and cellular mechanisms that tie PVAT derived adipokines with known mechanisms of atherogenesis.

Epicardial perivascular-derived adipokines and endothelial dysfunction

The 'response-to-injury' hypothesis linking endothelial injury with the development of atherosclerosis was first proposed by Ross in the early 1970s (Ross and Glomset, 1973; Ross, 1993a,b). Specifically, endothelial dysfunction is hypothesized to be the critical initiating step in the development of atherogenesis. If not quelled, circulating leukocytes will ultimately migrate beneath the endothelial layer and subsequently stimulate VSMCs to proliferate. In an effort to link obesity with cardiovascular disease, several adipokines have been experimentally shown to significantly impair endothelial function. In particular, leptin, resistin and tumour necrosis factor-alpha have all been shown to diminish endothelial-dependent vasodilation (i.e. induce endothelial dysfunction) when administered exogenously at pathophysiologically relevant concentrations (Beltowski *et al*., 2004; Kougias *et al*. 2005; Knudson *et al*. 2005; Dick *et al*., 2006; Picchi *et al*., 2006; Galili *et al*., 2007; Zhang *et al*., 2009).

In contrast, adiponectin has been associated with endothelial improvement and vascular protection (Beltowski *et al*., 2008). Specifically, adiponectin stimulates nitric oxide (NO) production in vascular endothelial cells (Chen *et al*., 2003) and has been found to directly improve endothelial function through endothelial NO synthase (eNOS)-dependent pathways (Li *et al*., 2007; Deng *et al*. 2010). Adiponectin also reduces oxidative stress, further protecting the endothelium in the inflammatory setting of obesity (Li *et al*. 2007; Tao *et al*., 2007). Importantly, while the PVAT expression of leptin, resistin and tumour necrosis factor-alpha is increased with obesity (Table 1), adiponectin expression is significantly diminished (Cheng *et al*., 2008; Greif *et al*. 2009). In spite of these investigations, questions still remain about the 'pathophysiological' link between PVAT-derived adipokines and endothelial dysfunction.

To date, few studies have examined the effects of epicardial PVAT on endothelial function. Data from our laboratory were among the first to demonstrate that epicardial PVAT selectively impairs coronary endothelial-dependent dilation both *in vitro* and *in vivo* in normal, healthy dogs (Payne *et al*., 2008). The mechanism of this impairment is primarily related to the attenuation of coronary endothelial NO production via a PKC-β dependent, site-specific phosphorylation of eNOS at the Thr^{495} inhibitory site (Payne *et al*., 2009). In contrast to studies in canines, epicardial PVAT appears to have little/no

Table 1

Relationship between epicardial PVAT expression, coronary artery disease and obesity/metabolic syndrome

Adipokine	Species	Condition	Expression	References
Leptin	Swine	MetS + CAD	↑↑ protein	Payne *et al.* (2010)
	Human	CAD	↑ mRNA, ↑↑ protein secretion	Cheng *et al.* (2008)
				Langheim *et al.* (2010)
				Shibasaki *et al.* (2010)
Resistin	Human	CAD	↑↑ mRNA, ↑↑ protein secretion	Langheim *et al.* (2010)
Adiponectin	Human	Obese	↓protein secretion	Karastergiou *et al.* (2010)
		CAD	↓ mRNA, ↓↓ protein secretion	Langheim *et al.* (2010)
				Cheng *et al.* (2008)
				Karastergiou *et al.* (2010)
				Iacobellis *et al.* (2005)
				Eiras *et al.* (2008)
			↓protein	Spiroglou *et al.* (2010)
		Obese + CAD	↓protein secretion	Karastergiou *et al.* (2010)
TNF-α	Human	CAD	↔ mRNA, ↑↑ protein secretion	Cheng *et al.* (2008)
				Langheim *et al.* (2010)
		Obese + CAD	↑↑mRNA, ↑↑ protein secretion	Mazurek *et al.* (2003)
IL-6	Human	CAD	↑↑ mRNA, ↑↑ protein secretion	Cheng *et al.* (2008)
				Eiras *et al.* (2008)
				Shibasaki *et al.* (2010)
				Langheim *et al.* (2010)
		Obese + CAD	↑↑ mRNA, ↑↑ protein secretion	Mazurek *et al.* (2003)
IL-1β	Human	CAD	↑ mRNA	Shibasaki *et al.* (2010)
		Obese + CAD	↑↑ mRNA, ↑↑ protein secretion	Mazurek *et al.* (2003)
MCP-1	Human	CAD	↑↑ mRNA	Shibasaki *et al.* (2010)
				Langheim *et al.* (2010)
		Obese + CAD	↑↑ mRNA, ↑↑ protein secretion	Mazurek *et al.* (2003)
NPR-C	Human	CAD	↑ mRNA	Shibasaki *et al.* (2010)
Adrenomedullin	Human	CAD	↑ mRNA	Shibasaki *et al.* (2010)
			↓ mRNA, ↓ protein	Iacobellis *et al.* (2009)
Visfatin	Human	CAD	↑↑ protein secretion	Cheng *et al.* (2008)
			↑ protein	Spiroglou *et al.* (2010)
PAI-1	Human	CAD	↑↑ mRNA	Langheim *et al.* (2010)
MIF	Human	CAD	↓ mRNA	Langheim *et al.* (2010)
IL-1Rα	Human	Obese + CAD	↑ protein secretion	Karastergiou *et al.* (2010)
sICAM-1	Human	CAD	↑ protein secretion	Karastergiou *et al.* (2010)
		Obese + CAD	↑ protein secretion	
IL-16	Human	CAD	↑ protein secretion	Karastergiou *et al.* (2010)
		Obese + CAD	↑ protein secretion	
IL-13	Human	Obese	↑ protein secretion	Karastergiou *et al.* (2010)
		CAD	↑ protein secretion	
RANTES	Human	Obese	↑ protein secretion	Karastergiou *et al.* (2010)
		CAD	↑ protein secretion	
		Obese + CAD	↑ protein secretion	
Chemerin	Human	CAD	↑ protein	Spiroglou *et al.* (2010)
UCP-1	Human	MetS	↔ mRNA	Sacks *et al.* (2009)
		Diabetes	↔ mRNA	

Table 1

Continued

Adipokine	Species	Condition	Expression	References
PRDM16	Human	MetS	↔ mRNA	Sacks *et al.* (2009)
		Diabetes	↔ mRNA	
PGC-1α	Human	MetS	↑ mRNA	Sacks *et al.* (2009)
		Diabetes	↑ mRNA	
$sPLA_2$	Human	CAD	↑ mRNA	Dutour *et al.* (2010)
PPAR-γ	Human	CAD	↔ mRNA	Shibasaki *et al.* (2010)
NPR-A	Human	CAD	↔ mRNA	Shibasaki *et al.* (2010)

↔ no change; ↑ < 50% increase; ↑↑ > 50% increase; ↓ < 50% decrease; MetS, metabolic syndrome; CAD, coronary artery disease; TNF-α, tumour necrosis factor-alpha; IL-6, interleukin-6; IL-1β, interleukin-1 beta; MCP-1, monocyte chemotactic protein-1; NPR-C, natriuretic peptide receptor-C; PAI-1, plasminogen activator inhibitor-1; MIF, macrophage migration inhibitory factor; IL-1Rα, interleukin-1R alpha; sICAM-1, soluble intercellular adhesion molecule-1; IL-16, interleukin-16; IL-13, interleukin-13; RANTES, regulated upon activation, normal T-cell expressed and secreted; UCP-1, uncoupling protein-1; PRDM-16, PR domain containing 16; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator 1-alpha; $sPLA_2$, secretory phospholipase A_2; PPAR-γ, peroxisome proliferator-activated receptor-gamma; NPR-A, natriuretic peptide receptor-A.

effect on coronary endothelial-dependent dilation in normal lean swine (Reifenberger *et al.*, 2007; Bunker and Laughlin, 2010; Payne *et al.* 2010) or in swine with familial hypercholesterolaemia (Bunker and Laughlin, 2010). We propose that these disparate findings are related to species differences in epicardial PVAT adipokine expression between canines and swine (Company JM *et al.*, 2010; Payne *et al.*, 2009; 2010). However, further studies are needed to more directly address this issue. Although these investigations were conducted in healthy animal models, they suggest a potential constitutive regulatory role for epicardial PVAT-derived adipokines in the 'healthy' coronary circulation. This hypothesis is supported by recent experimental results documenting the relationship between epicardial adipose thickness and coronary microvascular function. In particular, Sade and colleagues found epicardial adipose thickness to be an independent predictor of diminished coronary flow reserve in women with angiographically normal coronary arteries (Sade *et al.*, 2009).

Recent findings from our laboratory also indicate that the detrimental effect of epicardial PVAT on coronary endothelial function is markedly exacerbated in obese Ossabaw swine with the metabolic syndrome (MetS) (Payne *et al.*, 2010). We found that MetS epicardial PVAT significantly augmented underlying endothelial dysfunction of isolated coronary arteries from MetS swine, and that this effect was mediated primarily via a protein kinase C (PKC)-beta-dependent pathway. Other studies have also documented similar effects of PVAT from obese rodents on endothelial function in aortic (Ma *et al.*, 2010) and mesenteric arteries (Marchesi *et al.*, 2009; Ketonen *et al.* 2010). These findings are consistent with the marked changes in phenotypic expression in obese PVAT, as outlined in Table 1, and underscore the need to consider a causative role for the local production and paracrine release of harmful adipokines from PVAT in MetS-induced coronary disease.

Little research has focused on delineation of the specific adipokines and underlying mechanisms by which PVAT influences the initiation of coronary disease in obesity/MetS. One adipokine that has received recent attention is leptin. Although early studies found that leptin mediates endothelial-dependent vasodilation (Kimura *et al.*, 2000; Lembo *et al.* 2000), our laboratory demonstrated that this response occurs only at pharmacologic concentrations (>160 $ng \cdot mL^{-1}$) of leptin (Knudson *et al.*, 2005; 2008). In contrast, leptin at relevant obese concentrations (<90 $ng \cdot mL^{-1}$) significantly attenuates endothelial function both *in vivo* and *in vitro* (Knudson *et al.*, 2005; Korda *et al.* 2008; Payne *et al.*, 2010). More detailed discussion of this issue can be found in the recent reviews by Knudson *et al.* (2008) and Tune and Considine (2007).

Consistent with the earlier study of Cheng *et al.* (2008) in patients with coronary artery disease , we recently found leptin expression was significantly elevated in epicardial PVAT from MetS relative to lean swine (Table 1; Payne *et al.*, 2010). Importantly, coronary endothelium was observed to express functional leptin receptors, and the exacerbation of endothelial dysfunction produced by MetS PVAT was almost entirely reversed by inhibition of leptin signaling. Additional data also support that leptin-induced endothelial dysfunction (Knudson *et al.*, 2005; Galili *et al.*, 2007; Payne *et al.*, 2010) is mediated largely through a PKC-beta-dependent signalling pathway (Payne *et al.*, 2010), which is known to be activated by obesity/MetS (Bohlen, 2004; Casellini *et al.*, 2007; Tinsley *et al.*, 2008; Mehta *et al.* 2009; Payne *et al.*, 2009; 2010). Identification of leptin as a key epicardial PVAT-derived adipokine is noteworthy, as previous studies examining the role of leptin in vascular disease suggest this adipokine is also involved with many other key aspects of atherogenesis, including (i) potent chemoattraction for circulating monocytes (Gruen *et al.*, 2007); (ii) accumulation of cholesterol esters in foam cells (O'Rourke *et al.*, 2001); (iii) lower levels of plasma high density lipoprotein cholesterol and apolipoprotein AI concentration (Rainwater *et al.* 1997; Hergenc *et al.*, 1999); (iv) activation of acute phase reactants

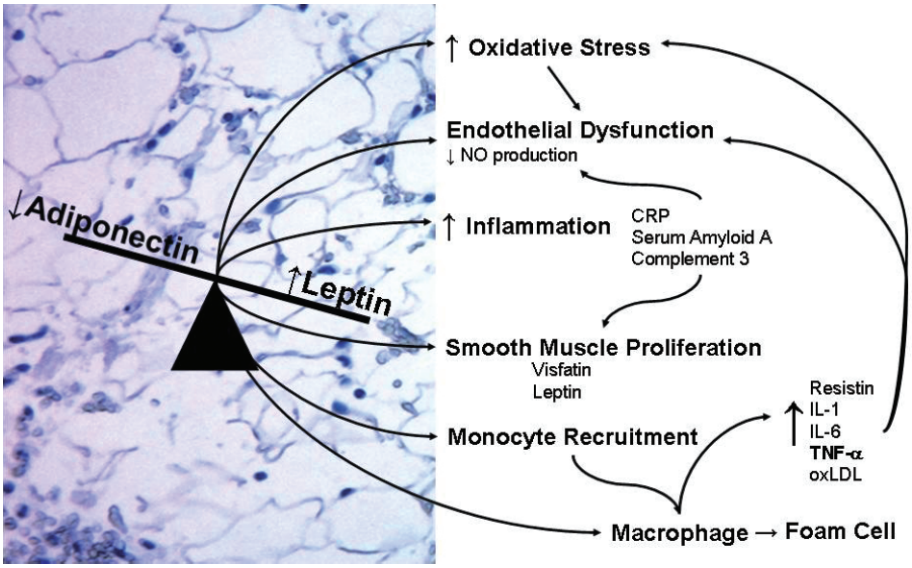

Figure 2

Schematic diagram outlining the regulatory balance between adiponectin and leptin on mediators of atherogenesis. Diminished expression of adiponectin with increased expression of leptin in epicardial PVAT is associated with the activation of key atherogenic pathways in the setting of the metabolic syndrome. CRP, C-reactive protein; IL, interleukin-1 and 6; TNF, tumour necrosis factor-alpha; oxLDL, oxidized low density lipoprotein.

such as C-reactive protein and serum amyloid A (Kazumi *et al.*, 2003; Shamsuzzaman *et al.*, 2004); (v) increases in oxidative stress and modification of plasma lipoproteins (Porreca *et al.*, 2004); as well as (vi) increases in DNA-binding activity of proinflammatory transcription factors AP-1, NFκB and MCP-1 (Bouloumie *et al.*, 1999).

Decreased adiponectin expression in obese, epicardial PVAT also provides a permissive environment for coronary inflammation and endothelial dysfunction (Table 1). As previously stated, adiponectin administration has been shown to improve endothelial function in the setting of obesity via adenosine monophosphate-activated protein kinase (AMPK)-mediated phosphorylation of eNOS at Thr^{176} (Deng *et al.*, 2010). Greenstein *et al.* (2009) also documented that adiponectin secretion from PVAT increased NO bioavailability and caused endothelial-dependent vasodilation in healthy patients, but this effect was lost in obese patients with MetS. This apparent obesity-related 'loss of function' of PVAT-derived adiponectin is supported by recent evidence demonstrating that recombinant adiponectin administration successfully reverses the harmful effects of epicardial adipose-derived factors (Karastergiou *et al.*, 2010). Specifically, epicardial adipose conditioned media from patients with coronary artery disease induced marked atherogenic changes in endothelial cells; including increased adhesion of monocytic cells and increased expression of intercellular adhesion molecule 1 (ICAM-1). This pro-inflammatory and pro-atherogenic phenotype was reversed by administration of adiponectin. These findings implicate the up-regulation of epicardial PVAT-derived leptin and the down-regulation of PVAT adiponectin expression, as critical upstream regulators of a number of complex atherogenic pathways associated with obesity-induced coronary artery disease that should be further explored (see schematic diagram in Figure 2).

Perivascular adipose tissue and potentiated vasoconstriction

A limited amount of evidence has developed suggesting PVAT potentiates vasoconstriction of isolated arteries. This is important because various vasoconstrictor pathways have been shown to be augmented in the setting of the MetS; for example, neurohumoral mediators play a significant role in obesity-related coronary vascular dysfunction (Knudson *et al.*, 2007). Data from the Gao laboratory supports that PVAT enhances mesenteric arterial contraction to electrical field stimulation of perivascular nerves via angiotensin II and NADPH oxidase-mediated increases in superoxide production (Gao *et al.*, 2006; Lu *et al.*, 2008; Huang *et al.*, 2010). PVAT also potentiates contractions to potassium chloride in control but not in hypertensive rats (Lee *et al.*, 2009). It should be pointed out that the 'potentiated vasoconstriction' may actually represent attenuation of vasodilator influences by superoxide (Marchesi *et al.*, 2009). This is important, as previous studies have demonstrated that PVAT exerts anti-contractile effects via potassium channel activation in VSMCs (Gollasch and Dubrovska, 2004; Verlohren *et al.*, 2004). Furthermore, alternative studies in the coronary circulation have found no (Payne *et al.*, 2010) or modest anti-contractile effects (Reifenberger *et al.*, 2007; Bunker and Laughlin, 2010) of epicardial PVAT on coronary artery contractions. These discrepant findings point to the need for further studies in this area.

Perivascular adipose tissue and vascular remodelling

Further support for a paracrine role for PVAT in the pathogenesis of cardiovascular disease can be found in studies

implicating local PVAT-derived factors in VSMC hypertrophy, proliferation and vascular remodelling (Thalmann and Meier, 2007; Rajsheker *et al*., 2010). Marchesi *et al*. (2009) demonstrated that PVAT inflammation was associated with hypertrophic vascular remodelling in resistance arteries of obese mice with MetS, while Ruan *et al*. (2010) documented that PVAT-derived complement 3 stimulated adventitial fibroblast migration and differentiation through a c-Jun N-terminal kinase pathway in hypertensive rats. These observations appear to be a highly dependent on location, as the morphological changes of adventitial thickening and myofibroblast clustering were tightly associated with the presence of local PVAT. These findings are consistent with correlative studies in humans which showed that classic cardiovascular risk factors are positively associated with adventitial thickness (including PVAT) and structural alterations of the carotid media (Skilton *et al*., 2009).

Results from Barandier *et al*. (2005) illustrate that PVAT directly alters VSMC activity as conditioned medium of cultured perivascular adipocytes from high fat fed rats was found to significantly stimulate VSMC proliferation. Interestingly, they also found that this proliferative effect of PVAT was absent in leptin receptor deficient rats. More recent data suggest that PVAT-derived visfatin triggers VSMC proliferation through the production of the novel signaling molecule nicotinamide mononucleotide (Wang *et al*., 2009). Evidence for an *in vivo* connection between PVAT and vascular remodelling is supported by the findings of Okamoto *et al*. (2001) who found a marked increase in epicardial PVAT inflammation following standard balloon angioplasty in swine. Additionally, Takaoka *et al*. (2010) conducted 'proof-of-principle' experiments in which tumour necrosis factor-alpha was delivered locally to the surrounding periadventitia of tumour necrosis factor-alpha-deficient mice. Following endovascular balloon injury, neointimal hyperplasia was observed to be significantly enhanced by supplemental administration of tumour necrosis factor-alpha to PVAT. In a similar study, this group further demonstrated that adiponectin-deficient mice showed markedly enhanced lesion formation that was reversed by local delivery of recombinant adiponectin to PVAT (Takaoka *et al*., 2009). These results provide evidence of a physiologic link between PVAT and VSMC hypertrophy and remodelling that should be further explored.

Conclusions and therapeutic potential of targeting perivascular adipose tissue

Epicardial PVAT is a naturally occurring adipose depot that has been shown to increase with obesity and to directly correlate with the extent and severity of coronary artery disease (Sarin *et al*., 2008; Ding *et al*., 2009; Greif *et al*., 2009). The investigations discussed within this review highlight the experimental evidence that is mounting in support of the hypothesis that PVAT influences key pathways of atherogenesis including oxidative stress, inflammation, endothelial dysfunction and vascular remodelling (Figure 2). While the exact cellular and molecular mechanisms remain to be delineated, many recent studies have begun to uncover key phenotypic changes in epicardial PVAT that occur in the setting of obesity/MetS and coronary artery disease (Table 1). These alterations provide a preliminary list of potential adipokines, each of which represent novel therapeutic targets for the treatment of obesity-related cardiovascular disease. We hypothesize that an imbalance in epicardial PVAT expression between pro-atherogenic leptin and anti-atherogenic adiponectin represents a critical upstream mechanism that contributes to the initiation and expansion of coronary disease in MetS. While targeting of leptin and/or adiponectin may serve as an advantageous starting point, the most appropriate theoretical approach remains unclear. Specifically, it remains uncertain whether future therapies should aim to enhance anti-atherogenic adipokines or inhibit pro-atherogenic adipokines. While this review focused on pathogenic mechanisms, PVAT may serve an equally important role to protect vascular function (Greenstein *et al*., 2009; Zhang and Zhang, 2009; Deng *et al*., 2010). Finally, additional epidemiological and experimental research is needed to mechanistically link epicardial PVAT with coronary artery disease. Future experimental studies should focus on providing evidence of a causal relationship between PVAT and atherosclerosis; while epidemiological studies should try to link epicardial PVAT with coronary events. While current investigations are promising, many questions remain regarding the exact pathways and mechanisms by which PVAT-derived adipokines influence vascular homeostasis in health and disease.

Acknowledgements

This work was supported by NIH grants R01 HL092245 (JDT) and F31 HL095362 (GAP).

Conflicts of interest

None.

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