Pro-contractile effects of perivascular fat in health and disease

Ramirez JG, O'Malley EJ, Ho WSV.

Vascular Biology Research Centre, St George's University of London, Cranmer Terrace, London SW17 0RE, UK

Abstract

Perivascular adipose tissue (PVAT) is now recognised as an active player in vascular homeostasis. Expansion of PVAT in obesity and the possible role of PVAT in vascular dysfunction has attracted much interest. In terms of the regulation of vascular tone and blood pressure, PVAT has been shown to release vasoactive mediators, for instance angiotensin peptides, reactive oxygen species, chemokines and cytokines. The secretory profile of PVAT is altered by obesity, hypertension and other cardiovascular diseases, leading to imbalance between its pro-contractile and anti-contractile effects. PVAT adipocytes represent an important source of the mediators, but infiltrating immune cells may become more important under conditions of hypoxia and inflammation. This review describes recent advances on the effects of PVAT on vascular tone regulation, highlighting the evidence for a pro-contractile action in health and disease. The role of the endothelium, vascular smooth muscle, immune cells and probably perivascular nerves in PVAT function is also discussed.

TARGETS	
GPCRs[a]	**Enzymes**[d]
adrenoceptor	ACE
AT_1	Akt
ChemR23	AMPK
ET_A	COX
Ion channels[b]	eNOS
BK_{Ca}	ERK
K_v7	mTOR
Nuclear hormone receptors[c]	PKC
PPARγ	Rho kinase

LIGANDS	
Adiponectin	IL-10
Ang 1-7	Insulin
Ang II	Leptin
Adrenaline	MCP-1
Chemerin	NO
cGMP	Noradrenaline
ET-1	PGE_2
Hydrogen peroxide	RANTES
Hydrogen sulphide	TNFα
IL-6	TXA_2
IL-8	

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bph.13767

These Tables of Links list key protein targets and ligands in this article that are hyperlinked* to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al*., 2016), and are permanently archived in The Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c,d]Alexander *et al*., 2015a,b,c,d).

Abbreviations

ACE, angiotensin-converting enzyme; ADCF, adipocyte-derived contractile factor; ADRF, adipocyte-derived relaxing factor; ADV, adventitia; Ang, angiotensin, COX, cyclooxygenase; DOCA, deoxycorticosterone acetate; EC, endothelium; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; ET1, endothelin-1; ET_A, endothelin ET_A receptor; H_2S, hydrogen sulphide; MCP-1, monocyte-chemoattractant protein-1; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NO, nitric oxide; PGE_2, prostaglandin E_2; PKC, protein kinase C; PVAT, perivascular adipose tissue; RANTES, regulated on activation, normal T Cell expressed and secreted; ROS, reactive oxygen species; SHRSP, stroke-prone spontaneously hypertensive rat; SM, smooth muscle; thromboxane A_2, TXA_2; TNFα, tumour necrosis factor-α; mTOR, mechanistic target of rapamycin

Introduction

Perivascular adipose tissues (PVAT) were originally thought to only provide structural support and thus routinely removed in vessel contractility studies. However, the growing prevalence of obesity, characterised by excessive adipose tissues, and the realisation that adipose tissues act as a complex paracrine and endocrine organ (Gustafson *et al.*, 2007; Ahima & Flier, 2000) has drawn attention to a functional role of PVAT, which might also provide a mechanistic link between obesity and vascular dysfunction. PVAT is now recognised as a specialised fat depot around most blood vessels, releasing diffusible factors that modulate local vascular reactivity and inflammatory status and, as a result, may contribute to pathophysiological changes seen in cardiovascular diseases, diabetes and obesity (reviewed in, Szasz *et al*., 2013; Yudkin *et al.*, 2015; Gil-Ortega *et al*., 2015; Fernandez Alfonso *et al*., 2017). Indeed, the Framingham Heart Study shows that a higher volume of PVAT around thoracic aorta is associated with metabolic risk factors and higher prevalence of cardiovascular disease in volunteers (Lehman *et al.*, 2010; Britton *et al.*, 2012). Numerous mechanisms have been suggested to underlie the cross talk between PVAT and vascular cells, but the regulation of PVAT function, particularly the balance between its beneficial and deleterious effects remains poorly defined. In 1991, Soltis and Cassis reported that, in rat aorta, PVAT potentiated contractions to a sympathomimetic but reduces that to noradrenaline due to reuptake by adrenergic nerves in PVAT. Subsequently, PVAT was also found to reduce responses to other vasoconstrictors, leading to the proposal of PVAT-derived (PVRFs) or adipocyte-derived relaxing factors (ADRFs). Much of the research has since focused on identifying these relaxing factors and establishing their vascular actions (see Gollasch, 2012 and Withers *et al.*, 2014 for reviews). However, there is also evidence for the production of contractile factors from PVAT, which were initially termed perivascular adipocyte-derived contractor factors (PVCFs; Gao, 2007) and later adipocyte-derived contractile factors (ADCFs;

Meyer *et al*., 2013). This adds to a complex scenario of anti-contractile vs pro-contractile properties of PVAT. In this review, we intend to provide an update on the balance between relaxant and contractile effects of PVAT, highlighting a potential shift from an anti-contractile action of PVAT in health to a pro-contractile action in obesity and related cardiovascular diseases.

Composition of PVAT

Adipose tissue surrounding blood vessels is not physically separated from the vascular wall by a fascial layer, providing access for its paracrine effects. In general, brown adipocytes are larger in size, with smaller oil droplets and larger numbers of mitochondria than white adipocytes, which store triglycerides. Morphological and gene expression analysis indicate that whilst perivascular adipocytes often resemble white adipocytes, they are distinct from visceral and subcutaneous fat and display characteristics of both white and brown adipocytes; sometimes referred to as beige adipocytes. For instance, perivascular adipocytes of human coronary arteries are smaller and irregularly shaped, with fewer differentiation markers but higher expression of some brown adipocyte-related genes, when compared to subcutaneous adipocytes (Chatterjee *et al.*, 2009). The precise phenotype appears to depend on the vascular region and species (Szasz *et al*., 2013; Gil-Ortega *et al*., 2015). Adipocytes around thoracic aorta are more similar to brown adipocytes, at least in rodents (Gálvez-Prieto *et al.*, 2008a; Padilla *et al.*, 2013*)*. However, adipocytes from abdominal aorta and mesenteric arteries are closer to white adipocytes in both rodents and humans (Henrichot *et al.*, 2005; Police *et al.*, 2009; Padilla *et al.*, 2013).

Importantly, adipose tissues are dynamically regulated, showing cellular and metabolic plasticity. Sustained obesity is associated with increases in size and/or number of PVAT white adipocytes (Marchesi *et al.*, 2009; Ketonen *et al.*, 2010; Ma *et al.*, 2010; Greenstein *et al*., 2009). These are accompanied by functional changes, including altered secretion pattern of PVAT (Greenstein *et al*., 2009; Chatterjee *et al*., 2009; Ketonen et al., 2010). On the other hand, increased proportion of brown to white adipocytes (browning of adipose tissues) promotes thermogenesis and might represent a protective mechanism against metabolic diseases (Pellegrinelli *et al*., 2016), and perhaps improve vascular function in obesity and atherosclerosis (Fitzgibbons *et al*., 2011; Chang *et al*., 2012).

In addition to adipocytes, PVAT contains other important cell types such as macrophages, T-lymphocytes and fibroblasts, which may also contribute to PVAT function. Indeed, infiltration of immune cells in PVAT is characteristic of disease states associated with vascular inflammation (Omar *et al.*, 2014; Pellegrinelli *et al*., 2016). Expansion of PVAT also likely involves generation of pre-adipocytes from resident mesenchymal stem cells and maturation of pre-adipocytes (Pellegrinelli *et al*., 2016). Moreover, PVAT is also innervated by sympathetic nerves (Bulloch and Daly, 2014; Darios *et al.*, 2016), which could stimulate the browning of PVAT. Nonetheless, the interactions among perivascular adipocytes, immune cells and nerves in vascular regulation remain poorly defined. Adipocytes, which are the main cellular component of PVAT, are known to release vasoactive substances (e.g. ADRF and ADCF), but immune cells and sympathetic nerves might serve as additional sources (e.g. Gao *et al*., 2006; Lumeng *et al*., 2007; Dashwood and Loesche, 2011; Nguyen

et al., 2011). Where possible, we will highlight the likely cellular source(s) of vasoactive substances within PVAT.

Evidence for contractile factors from PVAT

Similar to adipocytes in other anatomical locations, increasing evidence suggests that PVAT secretes bioactive molecules, including adipokines and other cytokines that regulate cardiovascular function. A number of these diffusible factors can induce direct vasocontraction, and maybe referred to as PVAT-derived or adipocyte-derived contractor factors (denoted ADCFs herein), which are highlighted in **Table 1**. Much of the evidence comes from contractility studies using isolated arteries with and without PVAT, combined with isolated PVAT and its conditioned media under physiological conditions.

Adipocytes are known to express a local renin-angiotensin-aldosterone system (RAAS), including angiotensinogen and angiotensin converting enzyme for synthesis of the potent vasoconstrictor, angiotensin II (Ang II; Cassis *et al.*, 2008; Karlsson *et al.*, 1998). The expression of RAAS components can vary depending on the composition and location of adipose tissues (Cassis *et al*., 1988; Engeli *et al.*, 1999; Galvez-Prieto *et al.*, 2008a; Riedel *et al*., 2016). PVAT is thought to express all components of RAAS and that PVAT-derived Ang II promotes contractions through AT_1 receptor activation in rat mesenteric arteries (Lu *et al*., 2010). Gao and co-workers proposed that Ang II acts indirectly by stimulating superoxide radical production from NADPH oxidase in PVAT adipocytes or the vascular wall itself (Gao *et al.*, 2006; Lu *et al.*, 2008). Ang II has also been shown to play a role in local inflammation associated with hypertension and obesity, stimulating infiltration of immune cells including T-lymphocytes and macrophages in PVAT and production of reactive oxygen species (Police *et al.*, 2009; Guzik *et al.*, 2007; Mikolajczyk *et al.*, 2016). However, the importance of PVAT as a source of Ang II in the control of vascular tone and blood pressure, particular in hypertension and obesity, remains to be established. Moreover, it is likely that the production and function of PVAT-derived Ang II show regional heterogeneity (Galvez-Prieto *et al.*, 2008a). Ang II can also further exacerbate PVAT dysfunction, since AT_1 receptor activation has been shown to reduce browning of adipose tissue, and promote adipocyte hypertrophy, insulin resistance and weight gain in high fat-induced obesity in mice (Graus-Nunes *et al*., 2017).

In the initial study by Soltis and Cassis (1991), PVAT greatly enhanced contractions to electrical field stimulation or the indirect sympathomimetic tyramine in rat aorta, suggesting a role for sympathetic nerve activity in PVAT. Sympathetic nerves have been reported in PVAT of human saphenous veins (Dashwood and Loesche, 2011). The role for sympathetic innervation in the regulation of vascular tone and blood pressure is well established. Elevated sympathetic activity is also associated with hypertension, including obesity-associated hypertension (Thalmann and Meier, 2007), however the interaction between PVAT and local sympathetic activity in healthy and disease conditions has not been scrutinised. Sympathetic activity and subsequent release of catecholamines are known to regulate lipolysis, and proliferation and differentiation of adipocytes activation through α- and β-adrenoceptors. Recent evidence has also suggested that adipocytes and alternatively activated macrophages in adipose tissues may synthesize and release noradrenaline and adrenaline (Vargovic *et al.*, 2011; Nguyen *et al*., 2011). In thoracic aorta and superior mesenteric arteries, where PVAT enhances contraction via α_1-adrenoceptors, noradrenaline and its synthetic

enzymes are detected in PVAT adipoctyes (Ayala-Lopez *et al.*, 2014). PVAT-dependent contractions to the sympathomimetic tyramine have also been reported in the same large arteries (Soltis and Cassis, 1991; Ayala-Lopez *et al.*, 2014). Tyramine is traditionally used to release catecholamines from sympathetic nerve endings, but the possibility of an action on adipocytes or immune cells in PVAT cannot be excluded.

Another factor that may contribute to the contractile effects of PVAT is the adipokine, chemerin (**Table 1**). Chemerin, in particular chemerin-9, evokes direct vasocontraction and enhances agonist-induced contractions via its G-protein-coupled receptor, ChemR23 in rat and human arteries. Moreover, these effects are exaggerated in thoracic aorta and mesenteric arteries with reduced endothelium-dependent relaxation, a phenomenon often found in hypertension and obesity (Watts *et al.*, 2013). A follow-up study by the same group (Darios *et al.*, 2016) has also shown that PVAT-derived chemerin potentiates sympathetic contraction through ChemR23, which is co-localised with tyrosine hydrolase in sympathetic nerves of rat superior mesenteric artery. Direct application of chemerin to isolated aorta or mesenteric artery also augments agonist-induced contraction in a manner dependent on endothelin ET_A receptor and ERK activation (Lobato *et al*., 2012), and increases systolic blood pressure in mice (Kunimoto *et al*., 2015). Thus, chemerin might play a particularly important role in some forms of hypertension and obesity.

In addition to chemerin, cytokines derived from PVAT might also increase vascular tone. For instance, tumour necrosis factor-α (TNFα) and interleukin-6 (IL-6) are known to enhance contractions, probably via upregulation of endothelin signalling or reduced nitric oxide (NO) production and endothelium-dependent relaxation, especially in obese patients (Greenberg *et al*., 1985; Orshal and Khalil, 2004; Virdis *et al*., 2015). High-fat diet has also been shown to promote IL-6 expression in human coronary PVAT (Chatterjee *et al*., 2009).

Aortic and small mesenteric PVAT also release contractile cyclooxygenase (COX) products, including thromboxane A_2 (TXA_2) and PGE_2 (Meyer *et al.*, 2013; Mendizabal *et al.*, 2013). In the same vascular regions, contraction to prostanoids and their receptor expression are enhanced in obese mice (Traupe *et al.*, 2002) or diabetic rats (Ishida *et al*., 2012). Interestingly, however, a significant amount of PVAT-derived TXA_2 and PGE_2 are also detected in healthy controls suggesting a possible physiological role (Meyer *et al.*, 2013). Prostanoids might also mediate PVAT-induced endothelial dysfunction in both normotensive and hypertensive rats (Mendizabal *et al.*, 2013), contributing to a pro-contractile effect of PVAT. It remains to be clarified how the secretory pattern of various prostanoids is altered in pathophysiological conditions.

Taken together, PVAT is capable of releasing multiple contractile factors, which elicit direct vasocontraction, or enhance nerve- or agonist-mediated contractions by acting on the vascular smooth muscle. These factors appear, at least partly, active in healthy conditions especially in larger arteries. Previous studies have reported elevated systemic levels of angiotensin II, superoxide, catecholamines, contractile prostanoids, TNFα, chemerin and leptin in hypertension, diabetes or obesity (Brunner *et al*., 2005; Gu *et al*., 2015), but PVAT is yet to be established as a major source of these mediators. There is however evidence pointing to increased responsiveness to chemerin, TNFα and prostanoids in aorta and resistance arteries (Watts *et al.*, 2013; Meyer *et al.*, 2013; Traupe *et al.*, 2002; Ishida *et al*., 2012; Virdis *et al*., 2015). In addition to acute vasocontraction, sustained elevation of some of the ADCF, such as superoxide, Ang II and TNFα, might stimulate vascular smooth muscle growth and arterial stiffness (Fleenor *et al.*, 2014; Almabrouk *et al*., 2014; Kunimoto

et al., 2015; Noblet *et al*., 2016; also reviewed by Miao & Li, 2012, Aroor *et al.*, 2013 and Villacorta & Chang, 2015), commonly found in atherosclerosis, hypertension and ageing. In line with this, PVAT expression of chemerin is positively correlated with atherosclerosis in human aorta and coronary artery (Spiroglou *et al.*, 2010). The vascular remodelling effect of PVAT is also associated with endothelial dysfunction, a hallmark of cardiovascular diseases. For vascular tone regulation, a reduction in endothelium-dependent relaxation would exaggerate the pro-contractile effects of PVAT and will be further explored in the following section.

Evidence for PVAT-induced endothelial dysfunction

The vascular endothelium is critical for maintaining cardiovascular homeostasis, and its dysfunction is considered an early sign or predictor of cardiovascular diseases, including those associated with obesity and diabetes (Brunner *et al.*, 2005). Endothelial dysfunction can manifest, for example, as reduced endothelium-dependent relaxation, endothelium-dependent contraction, leukocyte adhesion and reduced anti-coagulation properties. In **Table 2**, we highlight some of the studies demonstrating the inhibitory effect of PVAT on responses to endothelium-dependent relaxants, which could enhance vasocontraction and might be particularly relevant to hypertension linked to obesity and diabetes. Where possible, the specific PVAT-derived mediators and disease conditions involved are also indicated in **Table 2**.

A primary mechanism of action for PVAT is reduced NO production or bioavailability, although NO-independent signalling pathways may also be compromised. Given the physical distance between PVAT and the endothelium particularly in conduit arteries, it is thought that mediators released by PVAT are involved. They include NADPH oxidase-derived reactive oxygen species (superoxide, hydrogen peroxide) and pro-inflammatory cytokines (leptin, TNFα, IL-6, resistin, visfatin) (Payne *et al*., 2010; Ketonen *et al.*, 2010; Marchesi *et al.*, 2009; Greenstein *et al*., 2009; Vallejo *et al*., 2011; Aghamohammadzadeh *et al*., 2016). Importantly, targeting dysregulation of these PVAT factors, which accompanies adipocyte hypertrophy in obesity and metabolic syndrome can improve endothelial function (Marchesi *et al*., 2009; Aghamohammadzadeh *et al*., 2016). Circulating visfatin levels may also predict the extent of endothelium-dependent, flow-mediated dilation in patients with atherosclerosis and diabetes (Romacho *et al.*, 2013). These findings support the clinical relevance of PVAT dysfunction in vascular health. Indeed, oxidative stress and increased production of pro-inflammatory cytokines, as well as endothelial dysfunction, have been closely linked to the pathophysiology of obesity, hypertension, atherosclerosis, and insulin resistance.

On the other hand, PVAT can also reduce endothelium-independent relaxation. In many studies, the presence of PVAT has no significant effect on relaxation to NO donors (Payne *et al.*, 2008; Ma *et al.*, 2010; Vallejo *et al*., 2011; Lee *et al.*, 2014). However, Tune and co-workers (Owen *et al.*, 2013; Noblet *et al.*, 2015) have shown that PVAT inhibits distinct subtypes of K^+ channels in coronary smooth muscle of lean versus diet-induced obese pigs. Another adipokine, nesfatin-1 has also been shown to reduce smooth muscle cGMP production in mesenteric arteries, and increase arterial blood pressure in rats (Yamawaki *et al*., 2012).

Evidence for relaxant factors from PVAT

In contrast to the aforementioned (pro)contractile actions, numerous PVAT-derived mediators are vasorelaxants and therefore exert anti-contractile effects, which have been the focus of a number of excellent reviews (e.g. Gollasch, 2012 and Withers *et al.*, 2014). PVAT relaxants include adiponectin, omentin, leptin, angiotensin 1-7 (Ang 1-7), NO, hydrogen peroxide and hydrogen sulphide (H_2S) (Dubrovska *et al.*, 2004; Gao *et al.*, 2007; Lee *et al.*, 2009; Payne *et al.*, 2010; Gil-Ortega *et al.*, 2010; Schleifenbaum *et al.*, 2010). Again, isolated tension recording and bioassay experiments have been instrumental in establishing an anti-contractile action of PVAT in arteries from rodents and humans. Of note, the presence of PVAT reduces contraction to some, but not all, vasoconstrictors (Soltis and Cassis, 1991; Lohn *et al.*, 2002; Verlohren *et al.* 2004; Gao *et al.*, 2005b; Malinowski *et al.*, 2008; Greenstein *et al.*, 2009). Under physiological conditions, adipocytes are thought to be the main cellular source of these factors, which are sometimes referred to as ADRFs (Soltis and Cassis, 1991; Lohn *et al.*, 2002; Verlohren *et al.*, 2004).

Diverse signalling mechanisms have been proposed, including endothelial NO release, cGMP generation, reactive oxygen species, and opening of various K^+ channel subtypes, but independent of COX products or sympathetic nerves (Gollasch, 2012 and Withers *et al.*, 2014). Accumulating evidence suggests that the anti-contractile effect of PVAT relies on smooth muscle K^+ channels. Specifically, activation of voltage-gated K^+ channels (K_V7) and Ca^{2+}-activated K^+ channels (BK_{Ca}) through endothelium-independent and -dependent pathways respectively. Interestingly, in healthy rat coronary septal arteries, increases in PVAT mass also reduces Rho kinese-dependent Ca^{2+} sensitivity in vascular smooth muscle (Aalbaek *et al*., 2015). This contrasts the observation that PVAT from pig coronary artery enhances vasocontraction via Rho kinase (Owen *et al.*, 2013).

As for a pathological role, a loss or reduced relaxant effect of PVAT is often reported in disease states. In spontaneously hypertensive rats, there is a loss of anti-contractile effect in mesenteric arteries possibly due to downregulation of K_V7 channels in vascular smooth muscle or reduced PVAT production of Ang 1-7, one of the ADRF candidates (Galvez *et al.*, 2006; Galvez-Prieto *et al.*, 2008b; Li *et al.*, 2013). In experimental models of obesity and metabolic syndrome, increases in PVAT-derived leptin (Gill-Ortega *et al.*, 2009), superoxide, hydrogen peroxide (Gao *et al.*, 2005a; Rebolledo *et al.*, 2010; Ketonen *et al.*, 2010; Aghamohammadzadeh *et al.*, 2016) or free fatty acid level (Sun *et al.*, 2013) also play a role in aorta, mesenteric or subcutaneous arteries. Although PVAT produce the vasorelaxants adiponectin and NO, obesity is associated with reduced PVAT adiponectin and reduced endothelial NO release and bioavailability, partly due to oxidative stress (c.f. **Figure 2**). For example, in rodent mesenteric arteries, this can be rescued by superoxide dismutase and catalase, which remove superoxide and hydrogen peroxide respectively, or anti-oxidants (Marchesi *et al.*, 2009; Aghamohammadzadeh *et al.*, 2016). Despite an upregulation of leptin, there is an impairment of leptin-induced NO release from the endothelium in hypertension and obesity models (Beltowski *et al.*, 2003; Rahmouni *et al.*, 2005; Galvez-Prieto *et al.*, 2012). This implicates PVAT in vascular leptin-resistance, which exacerbates the cardiovascular complications associated with obesity.

Other data suggest that, in obesity and diabetes, downregulation of PVAT-derived adiponectin might lead to upregulation of superoxide and TNFα, and reduced endothelial NO production and relaxation (c.f. **Table 2**; Virdis *et al*., 2015; Hou *et al*., 2016; Nacci *et al*., 2016). It is often unclear why PVAT-derived relaxants are downregulated in disease states, but hypoxia in PVAT might be a contributing factor (Withers *et al*., 2011). A local reduction of PVAT adiponectin (Virdis *et al*., 2015; Aghamohammadzadeh *et al*., 2016) without concomitant changes in its circulatory levels is also evident in human obesity (Dreier et al., 2016). Of particular relevance to insulin resistance and diabetes, adiponectin is known to activate AMP-activated protein kinase (AMPK), a key intracellular energy sensor that improves insulin sensitivity and modulate adipocyte metabolism and inflammation (see Almabrouk *et al*., 2014 for reivew). AMPK in endothelium and vascular smooth muscle also regulates vascular tone and remodelling (Ma et al., 2010; Meijer *et al.,* 2013; Almabrouk *et al*., 2014), and probably contribute to the cardiovascular benefits of the anti-diabetic drugs, glitazones which are Peroxisome Proliferator-Activated Receptor gamma (PPARγ) agonists and AMPK activators. Interestingly, a recent study suggests that AMPK in PVAT is required for the secretion of adiponectin in mouse aorta (Almabrouk *et al*., 2016), providing a molecular mechanism for cross-talks with hypoxia and other PVAT-derived vasoactive substances that activate or inhibit AMPK (Almabrouk *et al*., 2014; Virdis *et al*., 2015).

Anti-contractile versus pro-contractile effects of PVAT

The co-existence of pro-contractile and anti-contractile actions of PVAT may seem contradictory but such dual effects have also been demonstrated in the same arteries and within the same studies (Soltis and Cassis, 1991; Lohn *et al.*, 2002; Ketonen *et al.*, 2010; Li *et al.*, 2013; Aalbaek *et al.*, 2015). Indeed, some of the PVAT-derived factors such as leptin, TNFα, IL-6 and hydrogen peroxide are known to have both contractile and relaxant properties (Brian and Faraci, 1998; Orshal and Khaliil, 2004; Thakali *et al.*, 2006; Virdis *et al*., 2015). Upregulation or downregulation of these factors can also compromise endothelial function (c.f. **Table 2**). It is therefore not surprising that the balance between pro-contractile and anti-contractile function, and how it is altered in disease conditions is under increasingly intense investigations.

Both relaxant and contractile actions of PVAT effects are detectable in healthy conditions, at least in thoracic aorta, mesenteric and coronary artery (Soltis and Cassis, 1991; Dubrovska *et al.*, 2004; Verlohren *et al.* 2004; Payne *et al.*, 2010). Many studies have proposed a predominantly anti-contractile action in health, although it is possible that the net effect on vascular tone depends on the anatomical location and experimental conditions used. As discussed in the previous section, systemic arteries (including mesenteric artery, thoracic and abdominal aorta) and coronary arteries often show a reduced production or responsiveness to PVAT-derived relaxants or other vasorelaxants in hypertension, obesity and diabetes. This, together with an underlying contraction induced by PVAT, which can also be enhanced in some forms of hypertension and obesity (c.f. **Table 1**), would promote a net contractile action of PVAT (**Figure 1**). This may result in sustained vasoconstriction. Indeed, PVAT dysfunction is correlated with raised arterial blood pressure in obese rats (Aghamohammadzadeh *et al.*, 2016). Genetic deletion of PPARγ in mouse perivascular adipocytes during development results in the absence of PVAT and hypotension, pointing to a key role for PVAT in blood pressure regulation (Chang *et al.*, 2012). However, we are yet to fully understand how PVAT function transitions from health to disease, and how best to reverse the

adverse effects of PVAT. In the case of obesity, weight loss through bariatric surgery or caloric restriction might reduce PVAT inflammation and improve NO bioavailability, resulting in normalised blood pressure (Aghamohammadzadeh *et al*., 2013; Bussey *et al*., 2016).

Interactions between adipocytes and immune cells in PVAT

Aside from vascular reactivity, many of the PVAT-derived mediators are also critical players in vascular inflammation. Evidence suggests that a pro-inflammatory phenotype of PVAT is a common feature of hypertension, obesity, insulin resistance and atherosclerosis (Chatterjee *et al.*, 2009; Omar *et al.*, 2014; Almabrouk *et al.*, 2014; Mikolajczyk *et al.*, 2016). Adipocytes are the main component in PVAT, but immune cells such as macrophages and T-lymphocytes also play an important role in regulating PVAT function, and provide an alternative source of vasoactive mediators. As part of the pathological remodelling of adipose tissues, obese rodents and humans have a higher PVAT mass and adipocyte hypertrophy (Marchesi *et al.*, 2009; Ma *et al.*, 2010; Greenstein *et al*., 2009). The hypertrophied PVAT likely exceeds the diffusion limit of oxygen and suffers from hypoperfusion, leading to local hypoxia (Hosogai *et al*.., 2007; Greenstein *et al*., 2009). The hypoxic state is linked to increased expression of the chemokine MCP-1 in PVAT, which in turn promotes recruitment and infiltration of macrophages, which act as a major source of TNFα (see Gustafson *et al.*, 2007 for review; Ketonen *et al.*, 2010). Through upregulation of the other chemokines IL-8 and RANTES in PVAT and superoxide in PVAT and vascular cells (**Table 2**), PVAT also stimulates recruitment of monocytes and lymphocytes in arteries from models of obesity, hypertension or metabolic syndrome (Henrichot *et al*., 2005; Marchesi *et al*., 2009; Mikolajczyk et al., 2016). **Figure 2** illustrates how dysregulation of PVAT-derived factors might occur in these disease states.

At the same time, there is an upregulation of pro-inflammatory mediators (e.g. TNFα and IL-6) and a downregulation of anti-inflammatory mediators (e.g. adiponectin and IL-10), from adipocytes and macrophages (Greenstein *et al.*, 2009; Chatterjee *et al.*, 2009; Lumeng *et al.*, 2007). The resultant pro-inflammatory phenotype has been linked to the loss of PVAT-induced relaxation and this deficit may be partially reversed by TNFα antagonists or IL-6 antibodies (Greenstein *et al.*, 2009; Ozen *et al.*, 2015; Aghamohammadzadeh *et al.*, 2016). Endothelium-dependent relaxation is also likely compromised by PVAT-derived TNFα and reactive oxygen species (Virdis *et al.*, 2015). In macrophage-deficient mice, the ability of hypoxia to inhibit PVAT relaxation is greatly reduced, supporting a key role for PVAT macrophages (Withers *et al.*, 2011). In addition, there is an accumulation of leukocytes in PVAT, so much so that deficiency in P-selectin glycoprotein ligand-1 (Psgl-1), a ligand essential for leukocyte attachment and rolling at the endothelium, prevents endothelial dysfunction and inflammation induced by PVAT in obese mice (Wang *et al.*, 2012).

In contrast to the case for obesity, the size of PVAT adipocytes and PVAT mass are often reduced in experimental models of hypertension, including spontaneously hypertensive and DOCA-salt hypertensive rats (Galvez *et al.*, 2006; Ruan *et al.*, 2010). Despite this, a recent study has demonstrated that Ang II-induced hypertension increases PVAT expression of RANTES, resulting in increased T-lymphocyte infiltration and impaired endothelium-dependent relaxation (Mikolajczyk *et al.*, 2016; **Figure 2**). It should be noted that whilst adipokines such as chemerin, adiponectin and leptin are released from PVAT adipocytes, many of the PVAT-derived chemokines, cytokines and

reactive oxygen species might be produced by multiple cell types within PVAT, including adipocytes and immune cells (see also Szasz *et al*., 2013 and Pellegrinelli *et al*., 2016 for reviews). Furthermore, vascular cells produce some of the same pro- or anti-inflammatory mediators from PVAT, and also express receptors for these mediators. Therefore, the interplay among adipocytes, infiltrated immune cells and vascular cells would need to be further explored.

PVAT dysfunction in humans

The past ten years have seen growing interests in PVAT dysfunction. Whilst the current data on human PVAT remain limited, they broadly agree with those obtained in animal models. For instance, anti-contractile effects of PVAT is compromised in small arteries of patients with metabolic syndrome or obesity (Greenstein *et al.*, 2009; Aghamohammadzadeh *et al.*, 2013), and that human PVAT shows distinctive expression pattern of pro-inflammatory mediators, including IL-6, MCP-1 and leptin, compared to subcutaneous adipose tissue (Rittig *et al.*, 2012; Mauro *et al.*, 2013). However, the functional significance of various ADCFs and ADRFs may differ. For example, adiponectin appears to play a more important role in PVAT relaxation in humans than in rodents (Fesus *et al*., 2007; Greenstein *et al.*, 2009; Meijer *et al.*, 2013). In patients undergoing coronary bypass surgery, initial experiments suggest that saphenous vein graft with intact adventitia and PVAT, as opposed to a conventional free graft, reduces vasospasm and potentially improves its patency (Dashwood *et al.*, 2009). Thus, it might be concluded that PVAT exerts a predominantly anti-contractile effects in humans. In contrast, individuals with more PVAT in brachial artery has diminished hyperaemic blood flow (Rittig *et al.*, 2008), suggesting a basal contractile influence of PVAT. Further characterisation of PVAT-derived factors from different vascular regions are needed. Thus far, mechanistic studies have been performed on the more accessible vessels from volunteers, namely the internal thoracic artery (Gao *et al.*, 2005a; Malinowski *et al.*, 2008), small arteries in gluteal fat (Greenstein *et al.*, 2009; Aghamohammadzadeh *et al.*, 2013) and saphenous veins (Dashwood *et al.*, 2009).

The Framingham Heart Study reported a correlation between periaortic fat mass and hypertension or diabetes irrespective of the body mass index, but a causal relationship is yet to be established (Lehman *et al.*, 2010; Britton *et al.*, 2012). In addition to reduced body weight, bariatric surgery in severely obese patients has been shown to restore PVAT-induced relaxation, improve inflammatory cytokines profile and NO bioavailability, and reduce macrophage infiltration and systolic blood pressure (Aghamohammadzadeh *et al.*, 2013). More recently, in diet-induced obese rats, calorie restriction and sustained weight loss has similarly been found to reverse PVAT-mediated vascular damage (Bussey *et al.*, 2016). These data support the contribution of PVAT dysfunction to the pathogenesis of obesity and metabolic syndrome. Elevated circulatory level of chemerin also correlates with impaired endothelial function and increased arterial stiffness in hypertensive patients (Gu *et al*., 2015). The specific role played by PVAT relative to other fat depots merits further investigations, particularly in view of the differential responses to high fat diet in white and brown adipocytes (Fitzgibbons *et al*., 2011).

When assessing data from animal and human experimental studies, it is also important to consider the effect of ageing, an independent risk factor for cardiovascular diseases. Ageing exacerbates aorta PVAT dysfunction, with increases in oxidative stress and macrophage infiltration, and a pro-inflammatory secretion pattern of cytokines and chemokines (Bailey-Downs *et al.*, 2013; Mauro *et al.*, 2013; Fleenor *et al.*, 2014). This effect is at least partly mimicked by medium conditioned with aged aorta PVAT, and is accompanied by endothelial dysfunction in aorta, especially in diet-induced obese mice (Bailey-Downs *et al.*, 2013). Thus, PVAT may also contribute to the endothelial dysfunction and vascular remodelling seen in ageing. On the other hand, PVAT relaxation is inhibited in ageing mice (Agabiti-Rosei et al., 2017), hinting at an overall pro-contractile action of PVAT during ageing. Further investigations will need to clarify the PVAT function in healthy versus pathological ageing. It is also worth noting that the age of rodent models of obesity vary (Lutz and Woods, 2012) and are generally younger than subjects of clinical studies.

Conclusion

In this review, we have focused on the effects of PVAT on vascular tone regulation. It is apparent that PVAT exerts both contractile and relaxant actions through the release of autocrine/paracrine factors from adipocytes and infiltrating inflammatory cells in PVAT (**Figure 1**). PVAT is therefore an integral part of vascular function, including cross-talk with the endothelium, smooth muscle, immune cells and perivascular nerves. The balance between pro-contractile and anti-contractile effects maybe tissue-specific but modulation by obesity and hypertension induces a shift towards a pro-contractile, pro-inflammatory and pro-oxidative phenotype (**Figure 2**). This PVAT dysfunction may also occur in other obesity-related disorders, including metabolic syndrome, diabetes and atherosclerosis. However, despite a much better knowledge on the structure and function of PVAT, there are still many unanswered questions. The molecular mechanisms that regulate PVAT quantity and composition, and secretion of vasoactive factors in health and disease, which likely exist in a continuum, remain elusive. Although there is experimental evidence for PVAT dysfunction in the pathogenesis of hypercontractility in disease states, it is also possible that it has a protective and adaptive role in vascular homeostasis. Moreover, the function of PVAT relative to the systemic influence of visceral and subcutaneous fat remains to be clarified. Given the heterogeneity in PVAT function in different anatomical regions and species, more studies using human tissues are required.

Conflict of interest

The authors declare no conflicts of interest.

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Table 1. PVAT-derived contractile factors. Studies that demonstrate PVAT production of mediators, which either induce direct contraction or potentiate contractions to other vasoconstrictors, are highlighted.

↑, increase; →, lead to; ACE, angiotensin-converting enzyme; Ang II, angiotensin II; COX, cyclooxygenase; DOCA, deoxycorticosterone acetate; eNOS, endotheliual nitric oxide synthase; ERK, extracellular signal-regulated kinase; ET1, endothelin-1; ET_A, endothelin ET_A receptor; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NO, nitric oxide; PGE_2, prostaglandin E_2; PVAT, perivascular adipose tissue; SHRSP, stroke-prone spontaneously hypertensive rat; thromboxane A_2, TXA_2; TNF α, tumour necrosis factor-α

Contractile factor	**PVAT expression**	**Effect**	**Vascular bed**	**Reference**
Ang II	Ang II protein; angiotensinogen and ACE mRNA in PVAT adipocytes	↑ Sympathetic contraction	Rat superior mesenteric artery	Lu *et al.*, 2010
	Ang II protein, angiotensinogen, ACE and chymase mRNA		Rat thoracic aorta Rat (resistance) mesenteric artery	Galvez-Prieto *et al.*, 2008a
Superoxide	Superoxide; NADPH oxidase protein in PVAT adipocytes	↑ Sympathetic contraction (via tyrosine kinase and ERK, but independent of NO)	Rat superior mesenteric artery	Gao *et al.*, 2006
Catecholamines	Noradrenaline and adrenaline in PVAT adipocytes	Contraction	Rat thoracic aorta Rat superior mesenteric artery	Ayala-Lopez *et al.*, 2014
	Noradrenaline from sympathetic nerve endings	Contraction	Rat thoracic aorta	Soltis and Cassis, 1991
Prostanoids	TXA_2 in PVAT-conditioned buffer; COX-1 and COX-2 mRNA	↑ Agonist-induced contraction (independent of NOS or ET_A).	Mouse thoracic aorta (only in monogenic obesity and diet-induced obesity)	Meyer *et al.*, 2013
	PGE_2 in PVAT (or PVAT-conditioned buffer)	Contraction	Rat mesenteric artery	Mendizabal *et al.*, 2013;
TNFα	TNFα protein in PVAT adipocytes	↑ Contraction to eNOS inhibition ↑ ET-1 and NADPH oxidase-derived superoxide in	Human small arteries from visceral fat (enhanced in obese patients)	Virdis *et al.*, 2015

		vascular cells		
IL-6	IL-6 in PVAT adipocytes		Human coronary artery (enhanced with high fat diet)	Chatterjee *et al*., 2009
Chemerin	Chemerin protein in PVAT adipocytes	Contraction ↑ agonist-induced contraction (enhanced by endothelial removal or NOS inhibition)	Rat thoracic aorta Rat superior mesenteric artery (enhanced responses in DOCA-salt hypertensive but not diet-induced obese or SHRSP rats)	Watts *et al.*, 2013
	Chemerin protein in PVAT adipocytes	Contraction ↑ agonist-induced contraction	Human resistance mesenteric artery	Watts *et al.*, 2013
	Chemerin protein in PVAT adipocytes	↑ Sympathetic contraction	Rat superior mesenteric artery	Darios *et al*., 2016
Leptin	(PVAT-conditioned buffer)	↑ Agonist- and depolarisation-induced contraction (via increased voltage-gated Ca^{2+} entry) ↑ Smooth muscle proliferation	Pig coronary artery (enhanced in diet-induced obesity)	Owen *et al.*, 2013; Noblet *et al*., 2016

Table 2. Inhibitory effect of PVAT on endothelium-dependent relaxation. This is often demonstrated by studying the effects of PVAT on responses to endothelium-dependent relaxants that are applied to isolated arteries or isolated vascular cells. Upregulation or downregulation of PVAT-derived factors are thought to exaggerate the reduction in endothelium-dependent relaxation in disease states. However, in some studies the diffusible factors responsible for the inhibitory effects of PVAT on endothelial function are not identified.

↑, increase; ↓, decrease; →, lead to; AMPK, adenosine monophosphate-activated protein kinase; AT_1, angiotensin II receptor type 1; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; IRS-1, insulin receptor substrate-1; MCP-1, monocyte chemoattractant protein-1; mTOR, mechanistic target of rapamycin; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NO, nitric oxide; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C, PVAT, perivascular adipose tissue; TNFα, tumour necrosis factor-α; RANTES, regulated on activation, normal T cell expressed and secreted

PVAT-derived factor	**Proposed mechanism of inhibition**	**Endothelium-dependent relaxant affected**	**Vascular bed**	**Reference**
Resistin	↓ IRS-1 and PI3K activity in endothelium → ↓ eNOS activity	Insulin	Mouse aorta Mouse mesenteric artery	Gentile *et al*., 2008
	↑ Endothelial superoxide → ↓ eNOS expression	Bradykinin	Pig coronary artery	Kougias *et al*., 2005
Adiponectin	↓ Adiponectin in PVAT → ↓ AMPK and Akt phosphorylation	Insulin	Mouse resistance artery from skeletal muscle (only in genetic model of obesity and Type 2 diabetes)	Meijer *et al.,* 2013
Unknown	↓ AMPK phosphorylation → ↑mTOR phosphorylation → ↓ eNOS expression	Acetylcholine	Rat thoracic aorta and mesenteric artery (only in diet-induced obesity)	Ma *et al.*, 2010
Leptin	↑ Leptin in PVAT and ↑ leptin receptor expression → ↑ PKCβ activity in vascular cells	Bradykinin	Pig coronary artery (only in obesity with metabolic syndrome)	Payne *et al.*, 2010
Unknown	↑ PKCβ-mediated eNOS phosphorylation → ↓ endothelial NO	Bradykinin	Dog coronary artery	Payne *et al.*, 2008; Payne *et al.*, 2009
Unknown	↓ Endothelial Ca^{2+} signal	Acetylcholine Methacholine	Rat coronary septal artery	Aalbaek *et al.*, 2015

Unknown (but independent of superoxide, prostanoids, ET-1 and AT_1)	↑ Endothelial caveolin-1 → ↓ NO production	Acetylcholine	Rat thoracic aorta	Lee *et al.*, 2014
Superoxide Hydrogen peroxide Leptin MCP-1	↑ Superoxide, hydrogen peroxide, leptin and MCP-1 in PVAT	Acetylcholine	Mouse abdominal aorta (only in diet-induced obesity)	Ketonen *et al.*, 2010
Visfatin	↑ NADPH oxidase activity in vascular cells → ↓ endothelial NO	Bradykinin or acetylcholine	Rat and human resistance mesenteric arteries	Vallejo *et al*., 2011
TNFα Adiponectin	↑ TNFα and ↓ adiponectin in PVAT → NADPH oxidase activation → ↓ eNOS expression → ↓ basal endothelial NO ↑ superoxide and ET-1 in vascular cells		Human small arteries from visceral fat (enhanced effects in obesity)	Virdis *et al*., 2015
RANTES	↑ RANTES → ↑ T-lymphocytes in PVAT but not visceral fat ↑ Ang II-induced superoxide production in vascular cells	Acetylcholine	Mouse thoracic and abdominal aorta (enhanced in Ang II-induced hypertension)	Mikolajczyk *et al.*, 2016

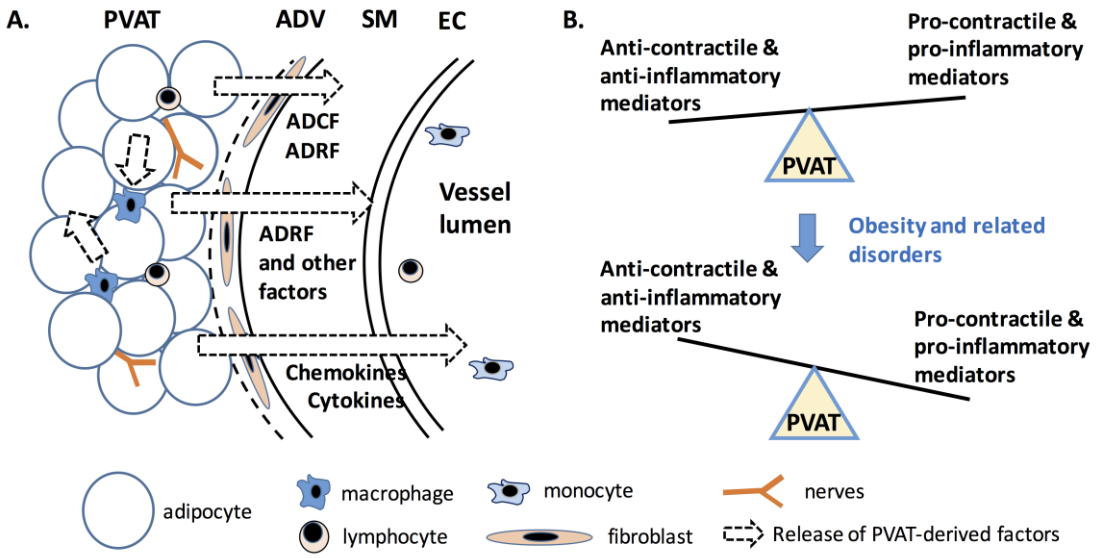

Figure 1

Figure 1. Regulation of vascular tone by PVAT in health and disease. (A) PVAT releases a diverse group of bioactive and diffusible substances, including leptin, adiponectin, angiotensin II, angiotensin 1-7, catecholamines, reactive oxygen species, nitric oxide, hydrogen sulphide, cytokines such as tumour necrosis factor-α and interleukin-6, and chemokines such as MCP-1 and RANTES. These mediators modulate vascular tone through a paracrine action on the endothelium, vascular smooth muscle and immune cells. The chemokines and cytokines regulate migration of immune cells into PVAT, and activated macrophages and lymphocytes within PVAT can also release additional cytokines. (B) In healthy conditions, PVAT tends to exert a net anti-contractile effect. Pathophysiological stimuli for example in obesity, hypertension and diabetes alter the secretary pattern of PVAT, leading to increased pro-contractile and decreased anti-contractile actions. This imbalance is characteristic of PVAT dysfunction in disease states. Other changes in PVAT composition and function include adipocyte hypertrophy, infiltration of macrophages and lymphocytes, and inflammation within PVAT and vascular cells.

ADCF, adipocyte-derived contractile factor; ADRF, adipocyte-derived relaxing factor; ADV, adventitia; EC, endothelium; PVAT, perivascular adipose tissue; SM, smooth muscle

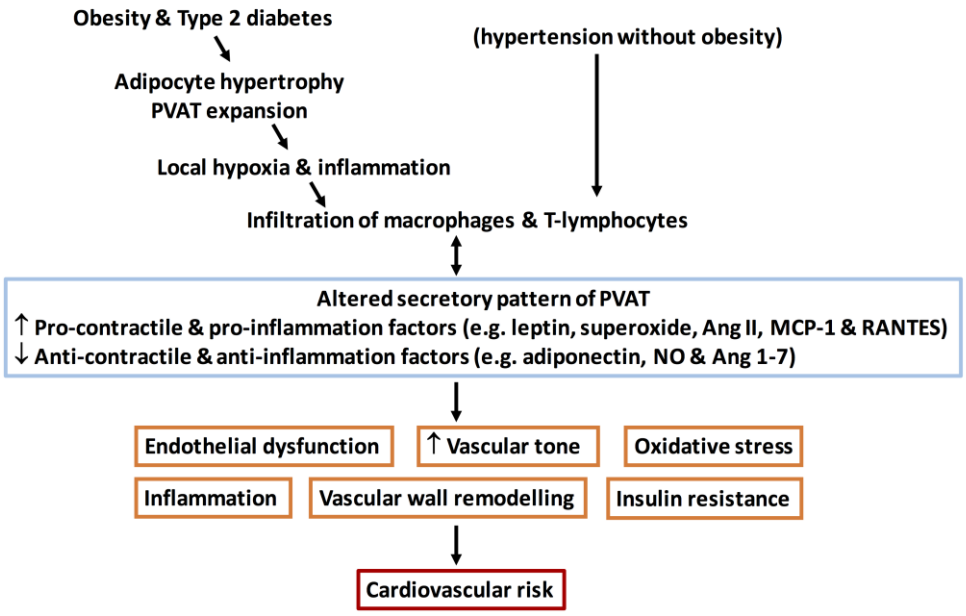

Figure 2

Figure 2. Proposed mechanisms of PVAT dysfunction in obesity, diabetes and hypertension. PVAT dysfunction is characterised by changes in its secretory pattern and increased occurrence of activated macrophages and lymphocytes in PVAT. In addition to adipocytes, activated immune cells within PVAT also release additional cytokines. In obesity and Type 2 diabetes, PVAT dysfunction is likely triggered by adipocyte hypertrophy and increases in PVAT mass. PVAT expansion is not a prerequisite for PVAT dysfunction since the size of adipocytes and overall PVAT mass maybe reduced in some forms of hypertension in the absence of obesity.

Ang 1-7, angiotensin 1-7; Ang II, angiotensin II; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; RANTES, regulated on activation, normal T cell expressed and secreted;