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Themed Section: Molecular Mechanisms Regulating Perivascular Adipose Tissue – Potential Pharmacological Targets?

REVIEW ARTICLE

Perivascular adipose tissue inflammation in vascular disease

Correspondence Tomasz J. Guzik, BHF Centre for Excellence, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK. E-mail: tomasz.guzik@glasgow.ac.uk

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Ryszard Nosalski[1,2] and Tomasz J Guzik[1,2]

[1]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Scotland, UK, and [2]Department of Internal and Agricultural Medicine, Jagiellonian University, Collegium Medicum, Krakow, Poland

Perivascular adipose tissue (PVAT) plays a critical role in the pathogenesis of cardiovascular disease. In vascular pathologies, perivascular adipose tissue increases in volume and becomes dysfunctional, with altered cellular composition and molecular characteristics. PVAT dysfunction is characterized by its inflammatory character, oxidative stress, diminished production of vasoprotective adipocyte-derived relaxing factors and increased production of paracrine factors such as resistin, leptin, cytokines (IL-6 and TNF-α) and chemokines [RANTES (CCL5) and MCP-1 (CCL2)]. These adipocyte-derived factors initiate and orchestrate inflammatory cell infiltration including primarily T cells, macrophages, dendritic cells, B cells and NK cells. Protective factors such as adiponectin can reduce NADPH oxidase superoxide production and increase NO bioavailability in the vessel wall, while inflammation (e.g. IFN-γ or IL-17) induces vascular oxidases and eNOS dysfunction in the endothelium, vascular smooth muscle cells and adventitial fibroblasts. All of these events link the dysfunctional perivascular fat to vascular dysfunction. These mechanisms are important in the context of a number of cardiovascular disorders including atherosclerosis, hypertension, diabetes and obesity. Inflammatory changes in PVAT's molecular and cellular responses are uniquely different from classical visceral or subcutaneous adipose tissue or from adventitia, emphasizing the unique structural and functional features of this adipose tissue compartment. Therefore, it is essential to develop techniques for monitoring the characteristics of PVAT and assessing its inflammation. This will lead to a better understanding of the early stages of vascular pathologies and the development of new therapeutic strategies focusing on perivascular adipose tissue.

LINKED ARTICLES

This article is part of a themed section on Molecular Mechanisms Regulating Perivascular Adipose Tissue – Potential Pharmacological Targets? To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v174.20/issuetoc

Abbreviations

AAA, aortic abdominal aneurysm; ADRF, adipocyte-derived relaxing factor; Apoe, apolipoprotein E; ATLO, adventitial tertiary lymphoid organ; BAT, brown adipose tissue; CD, cluster of differentiation; EDRFs, endothelium-derived relaxing factors; PVAT, perivascular adipose tissue; STAT, signal transducer and activator transcription; TH17, IL-17-producing T cells; TLO, tertiary lymphoid organs; T_{reg}, T regulatory lymphocytes; T_{RM}, tissue-resident memory T cell; VSMCs, vascular smooth muscle cells; WAT, white adipose tissue

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Tables of Links

TARGETS	
Other protein targets[a]	**Nuclear hormone receptors**[c]
TNF-α	PPAR-γ
CD3	**Catalytic receptors**[d]
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AT_1 receptor	APMK
CCR2	eNOS
CCR3	
CCR4	
CXCR3	
IL-17 receptor	
$S1P_1$ receptor	

LIGANDS	
Adiponectin	GM-CSF
Ang II	ICAM-1
CCL12	IFN-γ
CCL2 (MCP-1)	IL-10
CCL20	IL-17A
CCL5 (RANTES)	IL-17C
CCL7	IL-1β
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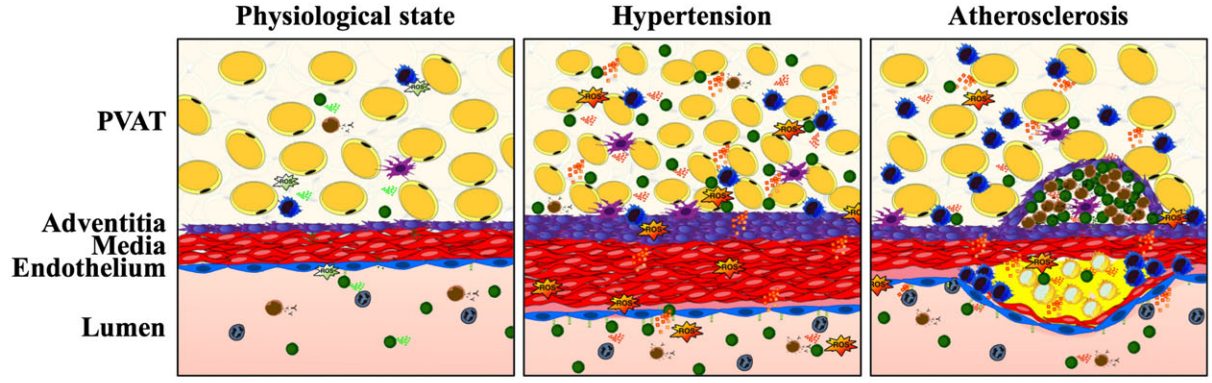
CXCL3	NO
CXCL5	PGI_2
G-CSF	

These Tables list key protein targets and ligands in this article which 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,e]Alexander *et al.*, 2015a,b,c,d,e).

Introduction

Most blood vessels, apart from the vasculature in the brain, are surrounded or embedded in perivascular adipose tissue (PVAT) (Gao, 2007). It represents around 3% of the total body adipose tissue mass (Siegel-Axel and Haring, 2016). While initially considered to provide primarily mechanistic support for the vasculature, in recent years it has become clear that PVAT is critical for the regulation of vascular/endothelial function in both physiology and pathology. In normal conditions, PVAT releases substances key for maintaining vasomotor tone and modulating vessel function (Gollasch and Dubrovska, 2004; Galvez *et al.*, 2006; Gao, 2007). This includes beneficial adipocyte-derived relaxing factor (ADRF), which has been shown to affect vasomotor tone and regulate important homeostatic blood vessel functions. In spite of vast research, the nature of this ADRF remains unidentified with adiponectin, hydrogen peroxide, H_2S (hydrogen sulfide), prostacyclin, angiotensin 1–7 or EDHF (endothelium-derived hyperpolarizing factor) being primary candidates (Szasz *et al.*, 2013; Brown *et al.*, 2014). Studies leading to the discovery of this novel vasorelaxant molecule have been initiated by a finding of Soltis and Cassis (1991) that the presence of PVAT may decrease contractile responses to vasoconstrictive agents. At that time, however, endothelial NO and its role in the regulation of vascular function were at the centre stage of vascular biology; thus, this report was not sufficiently appreciated, until further studies showed the release of classical vascular relaxing factor from the PVAT (Lohn *et al.*, 2002). Several interesting investigations such as those of Gollasch (Lohn *et al.*, 2002; Gollasch and Dubrovska, 2004; Galvez *et al.*, 2006; Fesus *et al.*, 2007) and Gao (Gao *et al.*, 2006, 2007; Gao, 2007) provided further insights into the pharmacology and physiology of these mediators in the PVAT.

The physiological importance of PVAT is emphasized further by studies showing that loss of adipose tissue in lipoatrophic mice (A-ZIP/F1) enhances the contractile responses of blood vessels, resulting ultimately in hypertension partially linked to an up-regulation of vascular angiotensin II type 1 (AT_1) receptors (Takemori *et al.*, 2007). Moreover, the deletion of PPARγ in vascular smooth muscle cells (VSMCs) causes the loss of PVAT in the aorta (Chang *et al.*, 2012). The interactions between PVAT and vascular function are tightly regulated by a number of metabolic factors including AMPK (5′ AMP-activated protein kinase) (Almabrouk *et al.*, 2014, 2017). In pathologies associated with vascular dysfunction, release of ADRF is diminished, while PVAT releases a number of paracrine factors such as adipokines (resistin, leptin and visfatin), cytokines (IL-6 and TNF-α), chemokines [regulated upon activation, normal T cell expressed and secreted (RANTES, CCL5) and monocyte chemoattractant protein 1 (MCP-1, CCL2)] – all of which can directly affect VSMCs and endothelial cells and which initiate and orchestrate vascular inflammation. This imbalance between the production and release of protective factors and pro-inflammatory molecules has been termed, similarly to endothelial dysfunction, the PVAT dysfunction (Guzik *et al.*, 2006, 2007b). Such dysfunctional PVAT has been reported in a range of vascular pathologies including atherosclerosis, hypertension, diabetes and obesity (Guzik *et al.*, 2006; Ignacak *et al.*, 2012). While specific mechanisms and characteristics of PVAT dysfunction may differ, its inflammatory characteristics constitute an important common denominator in a number of vascular pathologies (Figure 1), which will be the primary focus of the current review. Characteristics of inflammation in the PVAT are unique and different to mechanisms observed in typical visceral fat in obesity (Mikolajczyk *et al.*, 2016). This



	PHYSIOLOGICAL STATE	HYPERTENSION	ATHEROSCLEROSIS
Endothelium	Endothelial function maintenance ↑NO other EDRFs release ↑ anti-inflammatory cytokines production	Endothelial dysfunction ↓NO and other EDRFs ↑ROS ↑Adhesion molecules (VCAM1, ICAM1) ↑Pro-inflammatory cytokines ↑Chemokines	Endothelial dysfunction ↓NO and other EDRDs ↑ROS ↑Adhesion molecules (VCAM1,ICAM1) ↑Pro-inflammatory cytokines ↑Chemokines
VSMC	Vascular tone regulation (constriction/relaxation) ↑ Anti-inflammatory cytokines production	Vascular hypertrophy Vascular stiffness and calcification Vascular hyperreactivity ↑ROS ↑Pro-inflammatory cytokines ↑Chemokines	Neointima formation Plague formation Vascular stiffness and calcification ↑Pro-inflammatory cytokines ↑Chemokines ↑ROS
Adventitia	Thin layer Mechanical support	Vascular fibrosis ↑Pro-inflammatory cytokines ↑Chemokines ↑immune cell accumulation ↑collagen deposition	ATLO formation ↑Pro-inflammatory cytokines ↑Chemokines ↑immune cell accumulation
PVAT	Anti-inflammatory properties ↑Anti-inflammatory adipokines (adiponectin) ↑Accumulation of immune regulatory cells (T_{reg}) ↑Anti-inflammatory cytokines (IL-10) ↑ADRF (NO, H_2S, prostacyclin, Ang 1-7, etc.)	Pro-inflammatory properties ↑Pro-inflammatory adipokines (leptin, resistin, visfatin) ↓Anti-inflammatory adipokines (adiponectin) ↓Accumulation of regulatory cells ↑Immune cells accumulation (T cells, macrophages, DC, B cells, NK cells) ↑Pro-inflammatory cytokines ↑Chemokines ↑ROS ↑PVAT RAS activation	Pro-inflammatory properties ↑Pro-inflammatory adipokines (leptin, resistin, visfatin) ↓Anti-inflammatory adipokines (adiponectin) ↓Accumulation of regulatory cells ↑Immune cells accumulation (T cells, Macrophages, DC, B cells, NK cells) ↑Pro-inflammatory cytokines ↑Chemokines ↑ROS

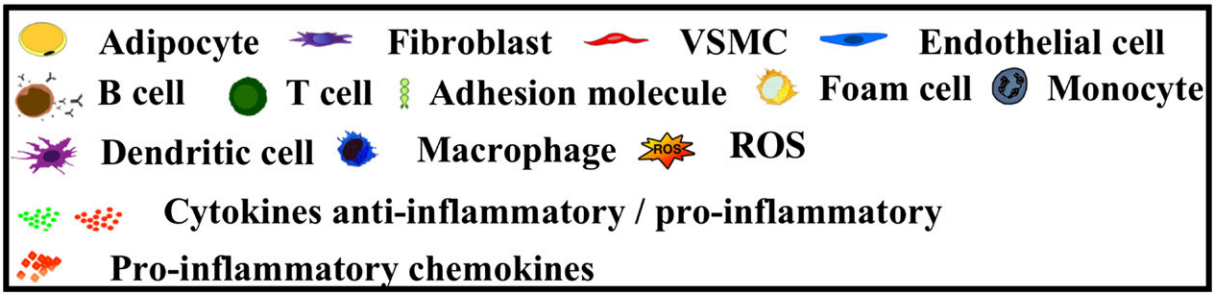


Figure 1

Central role of PVAT inflammation in the regulation of vascular disease. Differential role of PVAT and vascular compartments in the normal physiological state and in the development of vascular pathology in hypertension and atherosclerosis.

difference results not only from its direct location next to vascular wall but also most likely from the differential release of adipokines and chemokines/cytokines.

PVAT expands in a number of pathologies in humans. This can be systemic, for example, in obesity (Greif *et al.*, 2009; Mahabadi *et al.*, 2010). Local expansion of PVAT has been reported to be associated with atherosclerotic plaque development and vascular calcifications (Lehman *et al.*, 2010), hypertension or aortic abdominal aneurysm (AAA). While the presence of PVAT inflammation is a common feature of

vascular disease states, its characteristic varies between different pathologies (Figure 1).

PVAT – brown adipose tissue or white adipose tissue?

Adipose tissue is typically classified as white (WAT), brown (BAT) or beige according to the characteristic colour, but mostly in relation to mitochondrial properties and uncoupling protein 1 (UCP-1) content. BAT is associated with thermogenesis, while WAT serves as a lipid storage. WAT is less vascular and less metabolically active in comparison with BAT. Both BAT and WAT are under the control of the sympathetic nervous system, but the nerve supply is denser in BAT than in WAT (Harms and Seale, 2013). These differences are reviewed elsewhere (Harms and Seale, 2013) and have been summarized in Table 1.

Differences in both their histological and metabolic profile are also linked to differential immuno-inflammatory properties of these different types of adipose tissue (Galvez-Prieto *et al.*, 2008).

PVAT is different from other fat depots in the body through its possible dynamic interplay between white and brown adipocytes, which results in differential functional properties (Table 1). In rodents, PVAT surrounding the thoracic aorta is mainly brown, although a narrow strip immediately adjacent to the vascular adventitia is WAT. The abdominal aorta is surrounded by adipose tissue that is a mixture of brown and white adipocytes, whereas mesenteric arteries are surrounded by mesenteric fat composed mainly of white adipocytes in which these vessels are embedded (Wang *et al.*, 2009; Brown *et al.*, 2014). In humans, PVAT has been attributed to more histological properties of WAT. However, its comparison with typical subcutaneous WAT shows clear differences. In larger vessels, which are of interest in relation to their propensity for atherosclerosis, PVAT commonly displays distinct morphology with adipocytes of a smaller size and of a much less differentiated phenotype than in typical WAT (Galvez-Prieto *et al.*, 2008; Chatterjee *et al.*, 2009; Chang *et al.*, 2012), as indicated by a less efficient lipid storing capacity, and lower expression levels of WAT adipocyte-specific genes, with some clear similarities with those in BAT. Thus, PVAT gene and protein profile is clearly different from that of WAT (Chang *et al.*, 2012). PVAT is characterized by a less differentiated phenotype than classical visceral fat, closer to pre-adipocytes with a particular propensity for the release of pro-inflammatory factors and growth factors. PVAT, to a greater extent than other adipose tissue compartments, is a conglomerate of various cell types, including adipocytes, pre-adipocytes and mesenchymal stem cells. Pathological conditions such as Ang II or pro-atherosclerotic factors increase de-differentiation in PVAT adipocytes (Tomono *et al.*, 2008; Iwai *et al.*, 2009). This coincides with NFκB-mediated increases in pro-inflammatory cytokines such as IL-6, IL-8 or chemokines such as MCP-1 or RANTES (Skurk *et al.*, 2004, 2005; Mikolajczyk *et al.*, 2016).

While clear evidence of the origin of perivascular adipocytes is still lacking, their origin is most likely distinct from other adipocytes. The fact that VSMC PPARγ is essential for the generation of PVAT indicates that plasticity of VSMCs is essential. This is particularly important in the light of the fact that vascular macrophages in atherosclerosis may be largely derived from VSMCs or common precursors. A common embryological origin for perivascular adipocytes and VSMC is therefore very likely and would explain the difference between BAT, WAT and PVAT (Chang *et al.*, 2012; Omar *et al.*, 2014).

Table 1

Key differences between WAT, BAT and PVAT

	WAT	BAT	PVAT	References
Location	Subcutaneous and visceral	Suprarenal, interscapular, neck region in human infants	Surrounds blood vessels	Brown *et al.* (2014)
Morphology	Large adipocytes	Small adipocytes	Small adipocytes	Cedikova *et al.* (2016); Chatterjee *et al.* (2009)
Lipid droplet	Single, large	Multiple, small	Multiple, small	Brown *et al.* (2014); Cedikova *et al.* (2016); Chang *et al.* (2012)
Origin/development	Pdgfr-α progenitors	Myf5+ progenitors	SM22α + progenitors	Brown *et al.* (2014); Harms and Seale (2013)
Major function	Energy storage	Heat production	Vascular regulation, heat production	Chang *et al.* (2012); Harms and Seale (2013)
Mitochondria/UCP1	+/+ (nearly undetectable)	+++/+++	++(+)/++(+)	Cedikova *et al.* (2016)
Adipocyte-specific genes	PPAR-γ, PLIN1, HOXC8, TCF21, TLE3, C/EBPα, Rb, RIP140, APOL7C, DAPL1, NANT, SNCG, STAP1, GRAP2, MEST	ZIC1, LHX8, EVA1, PDK4, EPSTI1, PRDM16, CIDEA, ELOVL3, SCL27A2, COX7A1, CPT1B, KNG2m ACOT11, DIO2, BMP7	Similar to BAT	Cedikova *et al.* (2016); Fitzgibbons *et al.* (2011); Harms and Seale (2013)

PVAT inflammation in vascular pathologies

Morphological, structural and functional alterations of PVAT have been observed in the major vascular pathologies and in association with cardiovascular risk factors including atherosclerosis, hypertension, AAA and diabetic vasculopathies (Figure 1).

Atherosclerosis

A role for the immune system and inflammation in atherosclerosis has been known for several decades now (Hansson and Hermansson, 2011). Studies of immune mechanisms of atherosclerosis have initially focused on neo-intima and atherosclerotic plaques. Recent evidence suggests a key role for perivascular inflammation at various stages of atherosclerosis (Skiba *et al.*, 2016). Importantly, perivascular inflammation precedes atherosclerotic plaque formation and even the development of endothelial dysfunction and oxidative stress in apolipoprotein E−/− (Apoe−/−) mice (Skiba *et al.*, 2016). While the majority of data in atherosclerosis are focused on adventitial inflammation, clear links to PVAT are evident from these studies. Atherosclerotic mice (Apoe−/− or LDL receptor knockout mice) are characterized by increased production of pro-inflammatory cytokines such as IL-6 and IL-1 in PVAT (Lohmann *et al.*, 2009). Furthermore, perivascular inflammation is associated with a marked increase in chemokines such as MCP-1 (CCL2) (Manka *et al.*, 2014), MIP-1α (macrophage inflammatory protein 1-α, CCL3) (Moos *et al.*, 2005) and RANTES (Sakamoto *et al.*, 2014), which attract immune cells into injury sites.

During the progression of atherosclerosis in Apoe−/− mice, macrophages, T cells and DCs are recruited into perivascular adventitia and adipose tissue (Moos *et al.*, 2005; Galkina *et al.*, 2006) and are correlated with age and lesion size (Moos *et al.*, 2005). An increased number of T cells and macrophages in adventitial layer of abdominal aorta of Apoe−/− has been reported (Sakamoto *et al.*, 2014). Adventitial T and beta cells are present at early stages of atherosclerosis as loose aggregates (Moos *et al.*, 2005; Galkina *et al.*, 2006), while in later stages, they can form adventitial tertiary lymphoid organs (ATLOs) (Akhavanpoor *et al.*, 2014; Hu *et al.*, 2015). Recently, the Galkina group has shown that smooth muscle cell-derived IL-17C plays a pro-atherogenic role by supporting the perivascular recruitment of TH17 cells. IL-17c−/−Apoe−/− displayed a reduced accumulation of aortic leukocytes (Butcher *et al.*, 2016). Pro-inflammatory IL-17A-producing T cells are present in the adventitia, and blockade of IL-17A leads to reduction in the accumulation of macrophages and atherosclerosis (Smith *et al.*, 2010).

While many of the above studies focus on adventitial inflammation, which is best characterized in animal models of atherosclerosis, a close interrelationship and lack of clear anatomical border with PVAT makes PVAT essential for this process. Indeed, transplantation of PVAT on the carotid artery increased vascular remodelling after a wire-induced injury in LDL receptor knockout animals, through adventitial inflammation and angiogenesis (Manka *et al.*, 2014). Endovascular injury significantly up-regulates pro-inflammatory MCP-1, TNF-α, IL-6 and plasminogen activator inhibitor-1 and down-regulates anti-inflammatory adipokines, such as adiponectin, within PVAT (Takaoka *et al.*, 2010). Immunohistochemical analyses of periadventitial fat revealed increased macrophages and T cells in Apoe−/− animals compared with WT mice fed a cholesterol diet (Lohmann *et al.*, 2009). There are more macrophages (CD68+ cells) in the PVAT and adventitia in the LDL receptor−/− animals than in the media and intima, in both atherosclerotic and non-atherosclerotic areas of the vessels (Ding *et al.*, 2013). Consistently, Yamashita *et al.* (2008) showed that macrophages in the media and adventitia, but not in the intima, are critically involved in expansive atherosclerotic remodelling via matrix degradation and smooth muscle cell reduction. In human atherosclerosis, perivascular macrophages near atherosclerotic lesions are polarized towards the M2 phenotype (Stoger *et al.*, 2012), but their role in atherosclerosis is still controversial.

Molecular mechanisms of PVAT inflammation in atherosclerosis indicate several key targets. Signal transducer and activator transcription 4 (STAT4) is expressed in adipocytes and immune cells and may participate in PVAT inflammation. A deficiency in STAT4 reduces the development of atherosclerosis and PVAT inflammation in Apoe−/− mouse (Dobrian *et al.*, 2015) and in insulin-resistant obese Zucker rats (Pei *et al.*, 2006). Apoe−/− animals show higher numbers of CD45+ cells in PVAT, but not in visceral fat, compared with Apoe−/−STAT4−/− mouse. In particular, the number of CD8+ T cells is dramatically increased in PVAT of Apoe−/−mice. A reduction of PVAT inflammation was also associated with a diminished expression of CCL5, CXCL10, CX3CL1 and TNF-α in STAT4-and Apoe-deficient mice. Furthermore, a deficiency in STAT4 induces a bias towards anti-inflammatory macrophages producing IL-10 and IL-4 in PVAT of Apoe−/− mouse without affecting their total number (Dobrian *et al.*, 2015). Also, tetrahydrobiopterin treatment markedly reduces leukocyte infiltration into atherosclerotic lesions and the vascular adventitia via endothelial cell signalling (Schmidt *et al.*, 2010). These studies are further supported by findings that vasoprotective compounds such as Mas receptor agonists prevent atherosclerosis through a reduction of chemokine expression and accumulation on immune cells in PVAT (Skiba *et al.*, 2016).

While macrophages and T cells regulate PVAT inflammation in atherosclerosis, an important role for perivascular mast cells has recently been identified (Kennedy *et al.*, 2013). During plaque progression, activated mast cells accumulate in the arterial adventitia and promote macrophage apoptosis and microvascular leakage (Wu *et al.*, 2015). Furthermore, perivascular mast cell activation promotes monocyte adhesion in a CXCR2- and vascular cell adhesion molecule 1 (VCAM1)-dependent manner (Bot *et al.*, 2007).

Hypertension

Hypertension is associated with the activation of the renin–angiotensin–aldosterone system (RAS) and increased vascular oxidative stress. Both Ang II and ROS play a crucial role in the initiation and maintenance of vascular inflammation. The primary site of the initial inflammation in hypertension is within the PVAT and PVAT/adventitial border (Harrison *et al.*, 2011; Kirabo *et al.*, 2014; Mikolajczyk *et al.*, 2016). Almost all components of the RAS, except renin, are

expressed in the PVAT (Galvez-Prieto *et al.*, 2008; Nguyen Dinh Cat and Touyz, 2011), which may play a key role in modulating perivascular inflammation in hypertension. Additionally, PVAT expresses a complex ROS machinery-containing NADPH, endothelial NOS (eNOS) and antioxidative enzymes (Guzik *et al.*, 2005; Szasz *et al.*, 2013). PVAT-derived ROS can promote endothelial dysfunction, which could be induced either by endothelial NO scavenging by PVAT-derived ROS or through the modulation of perivascular inflammation that then affects endothelial function (Ketonen *et al.*, 2010; Even *et al.*, 2014). During the progression of hypertension, immune cells accumulate mainly in perivascular fat tissue surrounding both large and resistance vessels such as the aorta and mesenteric arteries. It is interesting to note that while inflammation is particularly pronounced in PVAT, non-perivascular visceral fat immune cell infiltration is much less pronounced in non-obesity-induced hypertension (Guzik *et al.*, 2007a; Mikolajczyk *et al.*, 2016).

Mice lacking T cells or monocytes exhibit a reduced inflammatory reaction in response to various hypertensive stimuli (Guzik *et al.*, 2007a; Wenzel *et al.*, 2011), whereas loss of lymphocyte adaptor protein (*Lnk)* gene, encoding a negative regulator of T cell activation, markedly enhances perivascular inflammation (Saleh *et al.*, 2015). Moreover, pro-hypertensive stimuli increase tissue-homing markers on leukocytes as well as pro-inflammatory chemokines, both of which further promote chemotaxis toward adipose tissue (Guzik *et al.*, 2007a; Hoch *et al.*, 2009; Mikolajczyk *et al.*, 2016). The accumulation of leukocytes is markedly reduced in IL-17−/− and IL-6−/− Ang II-infused animals (Madhur *et al.*, 2011). Chronic oxidative stress promotes vascular inflammation in hypertension. Mice lacking NADPH oxidase components such as $p47^{phox}$, NOX1 and NOX4 are protected against hypertension (Landmesser *et al.*, 2002; Matsuno *et al.*, 2005), while mice with smooth muscle-targeted overexpression of $p22^{phox}$ (NADPH catalytic subunit) exhibit increased vascular superoxide production, which is associated with an elevation in the total number of leukocytes in PVAT (Wu *et al.*, 2016) and increased susceptibility to vascular dysfunction.

Aneurysms

Abdominal aortic aneurysm is an inflammatory disease associated with marked changes in the cellular composition of the aortic wall and PVAT. Aneurysm formation often coexists with atherosclerosis. Numerous inflammatory cells are involved in AAA formation such as neutrophils, macrophages, T and B cells and mast cells (Sagan *et al.*, 2012; Spear *et al.*, 2015). These immune cells are observed both within PVAT and within luminal thrombi and are partially linked to advanced atherosclerotic plaques (Clement *et al.*, 2015), but they clearly increase susceptibility to AAA formation (Police *et al.*, 2009). A deficiency in TLR4 or myeloid differentiation factor 88 (MyD88) reduced perivascular inflammation and AAA formation (Owens *et al.*, 2011). Apart from contributing to general inflammation, leukocytes in the PVAT may produce proteases such as cathepsins that promote the degradation of aortic wall cells (Folkesson *et al.*, 2016).

In summary, PVAT inflammation is a characteristic feature of vascular pathologies. While there is a number of similarities between perivascular inflammation in hypertension and atherosclerosis, there are also key differences (Figure 1). While in atherosclerosis, perivascular immune infiltrates relatively quickly form organized structures, forming eventually adventitial tertiary organs (ATLOs), in hypertension T cell and B cell infiltration is more scattered. Macrophage infiltration of PVAT is more prominent in atherosclerosis than in hypertension. Aneurysms are so far the only pathology in humans, in which clear PVAT/adventitial ATLO structures have been identified. This either may be related to specific aneurysm pathology or may be aligned to advanced atherosclerosis, which typically accompanies AAA.

How is PVAT inflammation initiated?

Endothelial dysfunction is a key early mechanism of vascular disease. It is characterized by the loss of NO bioavailability accompanied by reduced production of vasoprotective substances, such as prostacyclin (PGI_2) and increased production of vascular damaging and pathologically activating molecules such as ROS, endothelin and thromboxane (Channon and Guzik, 2002). Importantly, the vasoprotective substances such as NO have potent anti-inflammatory properties, which are conveyed through inhibitory effects on adhesion molecule and chemokine expression. Thus, dysfunctional endothelial cells release chemokines such as RANTES, CCL2 and CXCL10 (Mateo *et al.*, 2006; Ide *et al.*, 2008), which can induce leukocyte migration or activation.

Increased ICAM-1 (intracellular adhesion molecule) and VCAM-1 expression, on the vascular endothelium, is one of the hallmarks of endothelial dysfunction, linking it to inflammation. When this dysfunction occurs in microvessels and vasa vasorum of PVAT, it will lead to the development of perivascular infiltration, indicating a bidirectional relationship between the vascular endothelium and PVAT.

Oxidative stress, characterized by the overproduction of superoxide anion and hydrogen peroxide, is a key feature of endothelial dysfunction. It results in rapid scavenging of NO in the blood vessel wall – a key mechanism of endothelial dysfunction in a number of vascular pathologies, but it also leads to activation of redox-sensitive genes within the endothelium, VSMCs and adventitia. Numerous pro-inflammatory genes including cytokines and chemokines as well as adhesion molecules are redox sensitive, linking vascular oxidative stress to inflammatory processes (Shah *et al.*, 2011).

VSMCs are a significant source of chemokines and cytokines, such as CCL2, CCL7, CCL20, CXCL1, CX3CL1, CXCL5 and IL-6, IL-23a and IL-1β (Butcher *et al.*, 2016). All of these can be essential for the induction of perivascular inflammation. Increased expression of key chemokines in the vascular wall is observed at the early stages of atherosclerosis or hypertension. Chemokine receptors, such as CCR2, CCR5 and CXCR4, are also up-regulated by oxygen radicals (Zhang *et al.*, 2005; Chan *et al.*, 2012). Thus, endothelial dysfunction and vascular oxidative stress may initiate and exacerbate PVAT inflammation evoked by key risk factors for atherosclerosis, and chemokines are key mediators of this process.

Chemokines in PVAT inflammation

The role of chemokines in initiating and orchestrating inflammation and specific immune responses is widely recognized (Henrichot *et al.*, 2005). These small molecular weight molecules (7–12 kDa) can be divided into four subclasses, C, CC, CXC and CX3C chemokines, based on the position of the N-terminal cysteine (van der Vorst *et al.*, 2015). Chemokines and their receptors are widely expressed on vascular cells and on leukocytes and play a key role in the recruitment of immune cells to the sites of inflammation or injury in response to a chemokine gradient in many cardiovascular diseases. Conditioned media from PVAT induces a chemotaxis of monocytes and T cells (Miao and Li, 2012; Chatterjee *et al.*, 2013; Mikolajczyk *et al.*, 2016). The role of CCL2, CCL5 and CX3CL1 in the recruitment of circulating monocytes and T cells in atherosclerosis is well established (Charo and Taubman, 2004; van der Vorst *et al.*, 2015). CCL2 produced by adipocytes has been identified as a potential factor contributing to macrophage infiltration into adipose tissue (Kanda *et al.*, 2006; Chan *et al.*, 2012). RANTES (chemokine also known as CCL5), in turn, can be produced by T cells, macrophages, VSMCs and endothelial cells as well as PVAT adipocytes (Mateo *et al.*, 2006; Krensky and Ahn, 2007; Surmi and Hasty, 2010) and is a key factor in the recruitment of leukocytes into inflammatory or infection sites (Marques *et al.*, 2013). RANTES is increased in PVAT in hypertension (Guzik *et al.*, 2007a) and is a characteristic of early stages of atherosclerosis (Veillard *et al.*, 2004; Podolec *et al.*, 2016). RANTES receptors (CCR1, CCR3 and CCR5) are elevated in vascular diseases and are clearly associated with PVAT inflammation (Guzik *et al.*, 2007a; de Jager *et al.*, 2012; Marques *et al.*, 2013; Mikolajczyk *et al.*, 2016). Recently, we demonstrated that RANTES−/− reduces Ang II-induced accumulation of T cells, macrophages and DCs in the PVAT (Mikolajczyk *et al.*, 2016). Genetic deletion or blockade of RANTES, using the peptide antagonist Met-RANTES, inhibits leukocyte infiltration to the site of inflammation (Marques *et al.*, 2013) and is effective in modulating perivascular and plaque inflammation in hypertension (Mikolajczyk *et al.*, 2016) and atherosclerosis (Veillard *et al.*, 2004).

CXCL10 (IP-10) is an IFN-γ-inducible protein produced by T cells, NK and NKT cells, monocytes and DCs but also by fibroblasts and endothelial cells (Bondar *et al.*, 2014). It is particularly important in chronic inflammation, including atherosclerosis and hypertension (Ide *et al.*, 2008). Circulating levels of CXCL10 are increased in hypertension (Antonelli *et al.*, 2008) and coronary heart disease (Safa *et al.*, 2016). CXCL10 exerts its biological effects mainly by binding to CXCR3. The CXCL10/CXCR3 axis is important in regulating T cell responses in atherosclerosis. A deficiency of CXCR3 or using CXCR3 antagonist reduces lesion formation in Apoe−/− animals, reduces T cell migration and up-regulates the expression of anti-inflammatory molecules (Veillard *et al.*, 2005; van Wanrooij *et al.*, 2008). The expression of CXCL10 is reduced in the PVAT of STAT4−/−Apoe−/− mice, which are protected from PVAT inflammation (Dobrian *et al.*, 2015). The expression of CXCL10 correlates with STAT1 phosphorylation in vascular cells in plaques from human carotid arteries (Chmielewski *et al.*, 2014), and STAT1 and NFκB both regulate CXCL10 (Veillard *et al.*, 2005). CXCL10 has direct effects on vascular wall cells as it induces the migration and proliferation of endothelial cells and VSMCs. Ide *et al.* demonstrated that CXCL10 (IP-10) increases the expression of RAS components in endothelial cells (Ide *et al.*, 2008), making it almost a prototypical 'bidirectional' cytokine in vascular biology, through which the vessel wall can regulate inflammation and inflammatory cells that can produce CXCL10 affect vascular wall biology.

Immune cells in PVAT inflammation

PVAT inflammation in vascular pathologies appears to differ from typical visceral adipose tissue inflammation in obesity.

In diseases such as hypertension, hypercholesterolaemia and diabetes, PVAT inflammation may occur in the absence of obesity or metabolic syndrome. This may be related to the vicinity of the blood vessel wall, which affects the development of vascular inflammation, and to the presence of vasa vasorum, enabling greater metabolic activity and a clear route for immune cells to migrate into PVAT. There are numerous differences in cellular and humoral characteristics of PVAT inflammation when compared with well-described inflammation within classical visceral adipose tissue depots. This is manifested by a unique cellular composition and inflammatory cytokine signature (Skiba *et al.*, 2016).

T cells

PVAT T cell infiltration may precede and exceed macrophage infiltration in animal models and in humans with hypertension and hypercholesterolaemia. This is in contrast to typical visceral fat where macrophage-dependent inflammation predominates from the earliest stages of the disease (Wu *et al.*, 2007). Perivascular T cells represent a morphologically and functionally heterogeneous cellular compartment. Both T helper cells (CD4+) and CD8+ cytotoxic cells are present in the PVAT with a high proportion of CD3+CD4-CD8- T cells, which are predominantly γδ T cells (Guzik *et al.*, 2007a; Mikolajczyk *et al.*, 2016). Recent studies of PVAT T cells indicate their effector and memory functions (Itani *et al.*, 2016). These include primarily TH1 and TH17 cells (producing IFN-γ and TNF-α or IL-17, respectively) or in some stages of pathology TH2 cells. CD8+ lymphocyte-infiltrated PVAT may also functionally differ depending on their content of granzyme B/perforin or IFN-γ/TNF-α (Broere *et al.*, 2011). Ang II and hypertension increase the percentage of circulating T cells with an effector phenotype, which next accumulate in PVAT to trigger inflammation and promote vascular dysfunction (Guzik *et al.*, 2007a; Mikolajczyk *et al.*, 2016). PVAT T cells express CD69, CD25 and CD44 markers, which may confer activation as well as tissue phenotype, and they commonly express high levels of receptors for inflammatory chemokines (CCR1, CCR5 and CCR3) (Vinh *et al.*, 2010) and adhesion molecules (CD44), which are key to their recruitment to PVAT (Guzik *et al.*, 2007a; Mikolajczyk *et al.*, 2016). A substantial proportion of PVAT CD4+ and CD8+ T cells express the activation marker CD25 and produce IFN-γ and TNF-α. Ang II induces a shift of T cells towards TH1 that produces IFN-γ, which is dependent on T cell AT_1 receptors (Shao *et al.*, 2003). T regulatory cells (T_{reg}) represent a small but

functionally significant population of T cells in the PVAT. They are characterized by high CD25 levels and the presence of the forkhead transcription factor (FOXP3) and through the release of suppressive anti-inflammatory cytokines (IL-10 and TGF-β) play a critical role in immune homeostasis and prevent excessive immune responses (Sakaguchi *et al.*, 2010). Interestingly, adoptive transfer of T_{regs} ameliorates vascular dysfunction, reduces blood pressure and the infiltration of immune cells in blood vessels and perivascular tissue in Ang II-treated mice (Matrougui *et al.*, 2011). T_{reg} also prevents monocyte/macrophage and T lymphocyte PVAT infiltration associated with various vascular insults such as wire injury, atherosclerosis and Ang II or aldosterone (Kasal *et al.*, 2012). Finally, a subset of CD8+ regulatory cells, which are also found in the PVAT, may mediate cell death through perforin/granzyme-dependent pathways (Grossman *et al.*, 2004), controlling immune responses but also affecting apoptosis and the function of adjacent vascular cells. While other subpopulations of T cells such as invariant NK T cells have been reported in PVAT, their functional importance is not clear.

B cells

In atherosclerosis B cells are primarily localized within the plaque and ATLOs (Sage and Mallat, 2014). Little is known about the characteristics of B cells and their function in the PVAT. This is interesting because recent studies show that B cells constitute up to 20% of PVAT leukocytes where they interact with T cells (Parker, 1993; Wei *et al.*, 2014) but are also scattered independently of other immune cells. Chan *et al.* found that Ang II-induced hypertension was associated with an increased activation of B cells in the PVAT. Moreover, this was associated with an elevation of serum and aortic antibody deposition of IgG2b and IgG3. Depletion of B cells protected against hypertension (Chan *et al.*, 2015). B regulatory cells have also been described in atherogenesis (Strom *et al.*, 2015); thus, a better understanding of the links between pro- and anti-inflammatory B cells in PVAT is needed. The links between a well-characterized role of adventitial and ATLO B cells in atherosclerosis to their PVAT infiltration need to be better understood.

Macrophages

Macrophages typically represent about 10–15% of stromal-vascular fraction, while their number increases to 45–50% during obesity (Wynn *et al.*, 2013). Macrophage infiltration in adipose tissue was first described in a form of crown structures in obesity; it has been linked to the expression of chemokines and adhesion molecules in the fat (Cancello *et al.*, 2005; Kolak *et al.*, 2007). Macrophages accumulate in PVAT and the adventitia during hypercholesterolaemia and hypertension, and also in the absence of obesity (Chan *et al.*, 2012; Moore *et al.*, 2015), and release free radicals via NOX2 NADPH oxidase (Kotsias *et al.*, 2013). Infiltrating macrophages produce cytokines such as IL-6, IFN-γ and TNF-α that change the vascular and PVAT cell biology. While M1 macrophages were classically defined to be associated with obesity and atherosclerosis, recent studies point to a significant infiltration of M2 macrophages in PVAT, which may regulate PVAT adipokine release, as well as perivascular fibrosis. Classically, M1 macrophages produce IL-12 and IL-23 and promote TH1 and TH17 cells (Wynn *et al.*, 2013), while M2 produce IL-10 and participate in TH2-type and pro-fibrotic responses (Murray and Wynn, 2011). PVAT macrophages are also important in the regulation of T cell activation through antigen presentation, the expression of co-stimulatory ligands and release of mediators that modulate their function and/or chemotaxis (Shirai *et al.*, 2015). T cell-dependent responses may reciprocally regulate PVAT macrophage infiltration. For example, loss of the *Lnk* gene, which increases T cell activation, enhances macrophage (F4/80+ cells) infiltration into PVAT, and Ang II infusion enhances this effect (Saleh *et al.*, 2015).

Dendritic cells

DCs are key in regulating adaptive immune responses in cardiovascular diseases. They are located primarily on the adventitia–PVAT border but have been reported in PVAT (Wei *et al.*, 2014; Mikolajczyk *et al.*, 2016). This has been identified in hypertension and is enhanced by chronic oxidative stress leading to the formation of immunogenic isoketal–protein adducts, which can accumulate in DCs and promote T cell activation (Kirabo *et al.*, 2014; Wu *et al.*, 2016). Dendritic cells release mediators such as IL-1β, IL-6 and IL-23 that polarize T cells to produce IL-17A as well as TNF-α and IFN-γ, which has been implicated in hypertension and PVAT inflammation (Guzik *et al.*, 2007a; Marko *et al.*, 2012) (Figure 2). Moreover, blocking the CD28/CD80/CD86 co-stimulation axis between DC and T cells prevents PVAT inflammation (Vinh *et al.*, 2010). However, the role of DCs either in PVAT or the adventitia still raises more questions and answers especially in relation to their migratory capacity into secondary lymphoid organs and in relation to understanding the possible antigens/neo-antigens they would be presenting to activate T cells (Kirabo *et al.*, 2014) (Figure 2).

Natural killer cells

NK cells have been identified in PVAT although their role is much less clearly defined than in visceral adipose tissue, where they link obesity-induced adipose stress to inflammation and insulin resistance in part through IFN-γ release (Wensveen *et al.*, 2015).

Adventitial tertiary lymphoid organs

Antigen-presenting cell–T cell interactions occur primarily in secondary lymphoid organs such as lymph nodes and the spleen (Junt *et al.*, 2008). Such interactions have however been demonstrated in vascular adventitia (Koltsova *et al.*, 2012) and possibly PVAT (A. Vinh, personal communication) in the context of chronic vascular inflammation, in atherosclerosis or in hypertension (Figure 1). Such interactions could trigger the development of and be sustained by tertiary lymphoid organs (TLOs) (Hansson and Hermansson, 2011). TLOs are organized aggregates of immune cells formed in post-embryonic life (GeurtsvanKessel *et al.*, 2009). They can be found around blood vessels in chronic allograft rejection, atherosclerosis and pulmonary hypertension and in patients with chronic obstructive pulmonary disease (Neyt *et al.*, 2012; Perros *et al.*, 2012; Yadava *et al.*, 2016). Interestingly, TLO formation is reversible when inflammation is resolved or after therapeutic intervention (Drayton *et al.*, 2006).

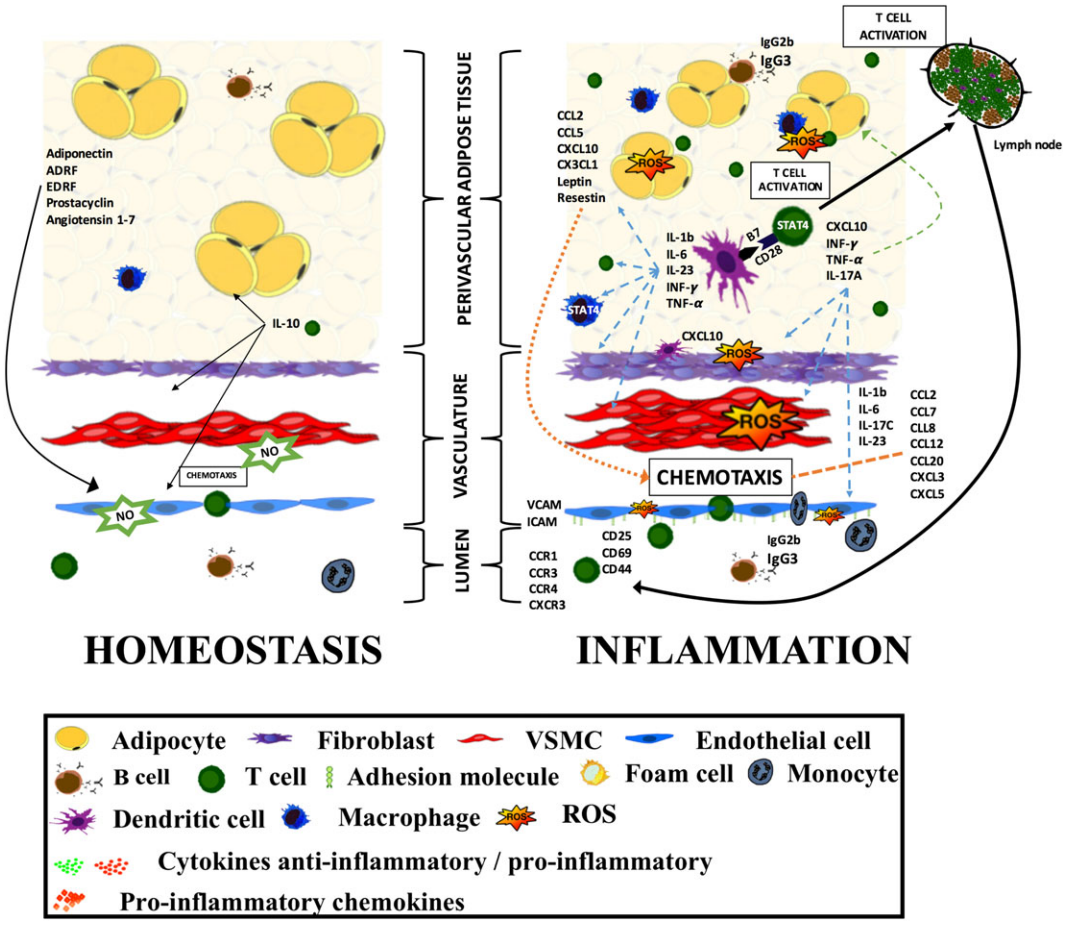


Figure 2

Cellular and humoral components of PVAT inflammation and their interactions in the regulation of vascular homeostasis and vascular dysfunction. A detailed description is provided within the text.

The development of TLOs is orchestrated by various chemokines and cytokines such as CXCL12, CXCL13, CCL19, CCL20, CCL21, lymphotoxin-α and lymphotoxin-β (Rangel-Moreno *et al.*, 2011; Akhavanpoor *et al.*, 2014). Interestingly, IL-17 also contributes to the formation of TLOs (Rangel-Moreno *et al.*, 2011). Immune cells can be organized in follicle-like structures called ATLOs. They can be found in murine models of atherosclerosis and AAA (Hu *et al.*, 2015; Spear *et al.*, 2015). Recently, Hu *et al.* in a very elegant study showed that an aging immune system employs ATLOs to control atherosclerosis-related T cell immunity. VSMC-lymphotoxin β receptors (LTβRs) maintain the ATLO structure and attenuate atherosclerosis (Hu *et al.*, 2015). These structures are evident in human aorta in the context of aortic abdominal aneurysms (Clement *et al.*, 2015).

Origins of PVAT immune cells

While a substantial number of immune cells are recruited by chemotaxis during perivascular inflammation (Henrichot *et al.*, 2005), some immune cells in the vascular wall are chronically resident within the vessel wall. This includes primarily resident macrophages (Robbins *et al.*, 2013; Ensan *et al.*, 2016), which can proliferate in atherosclerotic plaques and potentially in PVAT, as well as resident memory T cells (Schenkel *et al.*, 2014). Resident macrophages are important as they drive the influx of subsequent inflammatory leukocytes, such as monocytes, neutrophils and T cells (Asano *et al.*, 2015). The propensity for this recruitment, based on peripheral blood subpopulations of either monocytes or T cells, remains controversial (Weber *et al.*, 2016). Using multiple fate mapping approaches, it has recently been shown that arterial macrophages arise embryonically from CX3CR1(+) precursors and postnatally from bone marrow-derived monocytes that colonize the tissue immediately after birth (Ensan *et al.*, 2016). The survival of resident arterial macrophages depends on chemokines, in particular on the fractalkine (CX3CL1) axis, the expression of which is critical in human atherosclerosis and vascular disease (Lucas *et al.*, 2003).

Similar to the myelomonocytic cell lineage, PVAT T cells are either acutely recruited during the development of pathology or may have tissue-resident memory T cell (T_{RM} cells) characteristics, identified on the basis of phenotypic markers CD69 and CD103 (Mackay *et al.*, 2013; Clark, 2015). T_{RM} cells express low level of receptors such as CCR7 (Bromley *et al.*, 2005; Clark, 2015) and sphingosine-1-phosphate receptor 1

($S1P_1$ receptor; Resop *et al.*, 2016), which promote exit cells from the tissues. T_{RM} cells express high levels of CD44 and low levels of CD62L and release a number of effector cytokines such as IFN-γ or TNF-α (Slifka and Whitton, 2000). A subset of T_{RM} cells mediates the protective immunity; however, dysregulation of T_{RM} can contribute to autoimmune and inflammatory diseases. While the potential role of T_{RM} in vascular pathologies is of great interest, other lymphocytes, including classical effector T cells, NK T cells, NK cells and T_{reg} cells, have been described in PVAT. Most of these are likely to be acutely recruited into PVAT.

T cell recruitment to PVAT may be controlled by the sympathetic nervous system in PVAT and the adventitia (Marvar *et al.*, 2010; Guzik and Mikolajczyk, 2014; Itani *et al.*, 2016). Recent evidence suggests a central role for T cells of splenic origin in the initiation of inflammation in hypertension (Carnevale *et al.*, 2014, 2016). These studies from Lembo and Carnevale's group show elegantly that hypertensive challenges activate splenic sympathetic nerve discharge to prime immune response and stimulate immune cell egression from the spleen into target organs, including PVAT (Carnevale *et al.*, 2014, 2016).

The characteristics of PVAT dendritic cells may be divergent. This is particularly important in the light of recent discoveries that plasmacytoid DCs play a key role in atherosclerosis and infiltrate atherosclerotic plaques (Sage *et al.*, 2014). Their role in the PVAT remains unclear.

Mechanisms linking PVAT inflammation to vascular dysfunction

Conditioned media from dysfunctional PVAT in models of vascular disease induce VSMC proliferation and endothelial dysfunction (Miao and Li, 2012; Chatterjee *et al.*, 2013; Mikolajczyk *et al.*, 2016). This is in part mediated by adipokines, which has been reviewed elsewhere (Tilg and Moschen, 2006; Mattu and Randeva, 2013), but may also be dependent on cytokines released by activated inflammatory cells in the PVAT. Most evidence points to the key role of IFN-γ, IL-17, IL-6 and TNF-α in regulating this process (Matusik *et al.*, 2012) (Figure 2).

Pro-inflammatory cytokines and endothelial function

IFN-γ is one of the key cytokines produced by T cells, NK cells as well as some vascular cells. The classical function of IFN-γ is in the activation of monocytes/macrophages along with polarization of immune cells into a pro-inflammatory phenotype (Knorr *et al.*, 2014). Importantly, acting on endothelial cells, IFN-γ impairs endothelium-dependent relaxation, as demonstrated in *ex vivo* studies (Mikolajczyk *et al.*, 2016) as well as *in vivo* using IFN-γ knockout mice (Kossmann *et al.*, 2013). Furthermore, a reduced recruitment of IFN-γ-producing cells into PVAT in RANTES−/− hypertensive animals protects them from impaired endothelium-dependent relaxation, while having no effect on endothelium-independent relaxation (Mikolajczyk *et al.*, 2016).

IL-6, which is produced by macrophages, T cells, DCs and PVAT adipocytes, can directly affect endothelial cells (Pietrowski *et al.*, 2011). It mediates the increase in superoxide production and endothelial dysfunction by affecting the NO-cGMP signalling pathway (Orshal and Khalil, 2004; Schramm *et al.*, 2012). IL-6 deficiency prevents vascular dysfunction in spite of various damaging stimuli (Schrader *et al.*, 2007). Treatment of C57BL/6J animals *in vivo*, or *ex vivo* by incubating with blood vessels, with IL-6 impairs endothelium-dependent relaxation (Wassmann *et al.*, 2004). IL-6 is also necessary for TH17 cell differentiation (Bettelli *et al.*, 2006), another T cell subpopulation with a strong pro-inflammatory effect on endothelial cells and VSMCs. IL-17 is a potent activator of endothelial cells promoting the expression of adhesion molecules (Roussel *et al.*, 2010). IL-17A activates RhoA/Rho-kinase and increases inhibitory eNOS Thr^{495} phosphorylation in endothelial cells leading to decreased NO production (Nguyen *et al.*, 2013). IL-17A, IFN-γ and IL-6 have a synergistic effect with TNF-α to modulate inflammatory responses (Ruddy *et al.*, 2004). TNF-α is produced by a wide range of cell types including immune cells, vascular cells and adipocytes (Mendizabal *et al.*, 2013). Stimulation of endothelial cells with this pro-inflammatory cytokine decreases eNOS expression (Hot *et al.*, 2012) by destabilization of eNOS mRNA (Neumann *et al.*, 2004). TNF-α, through NFκB, enhances ROS production by endothelial NADPH oxidases. In hypertension, Ang II infusion stimulates T cells to produce TNF-α and etanercept (TNF-α antagonist) blunts vascular superoxide production (Guzik *et al.*, 2007a). Moreover, TNF-α increases the expression of endothelial adhesion molecules and production of pro-inflammatory chemokines such as CCL5, CCL7, CCL8 or CXCL9 (Hot *et al.*, 2012). Combined treatment with TNF-α and IL-17 promotes the synergistic activation of endothelial cells to express adhesion molecules and chemokines that enhance immune cell migration (Griffin *et al.*, 2012). An opposing action is performed by IL-10, produced by T regulatory cells, selected macrophages and DCs (Saraiva and O'Garra, 2010; Krause *et al.*, 2015). This anti-inflammatory cytokine reduces NADPH-dependent oxidative stress and increases the production of NO by enhancing the phosphorylation and activation of eNOS (Kassan *et al.*, 2011). IL-10 inhibits the activation of p38 MAPK, which contributes to the stimulation of pro-inflammatory cytokines but can also regulate NADPH oxidases (Kontoyiannis *et al.*, 2001; Konior *et al.*, 2014).

Effects of cytokines produced by immune cells on VSMCs

Inflammatory cytokines released in PVAT modulate smooth muscle cell constriction, proliferation and migration (McMaster *et al.*, 2015). Similar to its effects in endothelial cells, IL-6 significantly increases Ang II-mediated ROS production in VSMCs (Wassmann *et al.*, 2004). *In vivo* treatment of C57BL6 animals with IL-6 increases the expression of vascular AT_1 receptors and mediates medial hypertrophy (Schrader *et al.*, 2007). It also enhances the constriction of the blood vessels (Orshal and Khalil, 2004). Furthermore, IL-6 has been reported to play role in VSMC migration and proliferation (Chava *et al.*, 2009). IL-17 receptors are also present on VSMCs (Jin and Dong, 2013). IL-17A induces the expression of mRNA for collagens I, III and V in a p38 MAPK-dependent fashion leading to collagen deposition

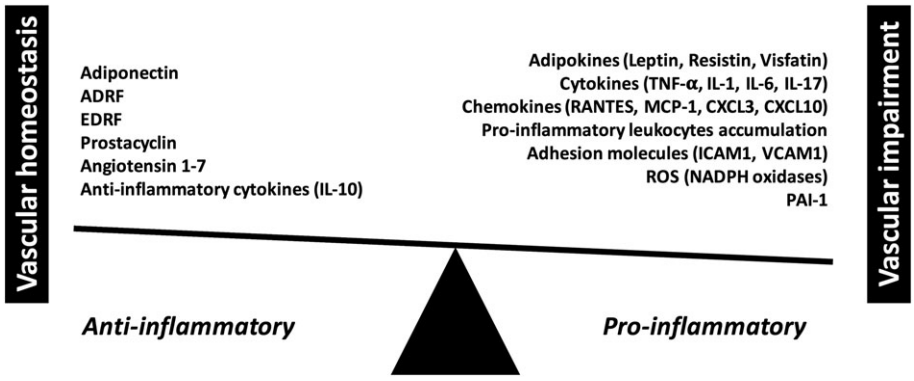


Figure 3
Balancing anti- versus pro-inflammatory properties and functions of perivascular adipose tissue (PVAT).

and loss of aortic compliance (Wu *et al.*, 2014). Blood vessels from Ang II-treated IL-17A−/− mice are protected from vascular dysfunction with dramatically blunted superoxide production and fibrosis (Madhur *et al.*, 2010). This is because IL-17A induces NADPH oxidases to produce superoxide anion and hydrogen peroxide and therefore can regulate redox-sensitive pro-inflammatory cytokines [IL-6, MCP-1, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF)] (Pietrowski *et al.*, 2011). Synergistically with TNF-α, IL-17A increases the expression of CCL8, CSF3, CXCL2 and CCL7 in human aortic smooth muscle cells (Madhur *et al.*, 2010).

IFN-γ can also act directly on VSMCs to induce proliferation (Wang *et al.*, 2007) or apoptosis (Rosner *et al.*, 2006). Neutralization of IFN-γ prevents outward vascular remodelling of human coronary arteries induced by allogenic T cells in SCID/beige mice (Wang *et al.*, 2004). IFN-γ induces ICAM-1 mRNA expression in smooth muscle cells (Chung *et al.*, 2002). IFN-γ also has a strong impact on superoxide production by up-regulation of the expression and activity of NOXs in human aortic smooth muscle cells (Manea *et al.*, 2014).

Effects of cytokines produced by immune cells on perivascular adipocytes

As discussed above, part of the effects, through which inflammation mediates vascular function, are dependent on the regulation of classical adipokine expression and release. Adiponectin has a wide range of anti-inflammatory effects, whereas leptin has pro-inflammatory effects (Tilg and Moschen, 2006). Both are also critical in regulating vascular function making them prototypical bidirectional adipokines in vascular biology (Antonopoulos *et al.*, 2015, 2016; Woodward *et al.*, 2016) abd also have potent NO-releasing vasorelaxant properties (Cheng *et al.*, 2007). The production of adiponectin can be inhibited by pro-inflammatory cytokines such as TNF-α, IL-6 and IL-17A (Maeda *et al.*, 2002; Fasshauer *et al.*, 2003; Noh, 2012). Leptin is produced mainly by adipocytes and is structurally similar to IL-6, IL-12 and IL-15. IL-17A and TNF-α increase leptin production (La Cava and Matarese, 2004; Noh, 2012). Leptin apart from direct effects on endothelial NO production and VSMCs can affect leukocyte chemotaxis, the release of oxygen radicals, VSMC proliferation and expression of adhesion molecules on endothelial cells and VSMCs (La Cava and Matarese, 2004). While adiponectin and leptin have been well investigated, PVAT shows particularly high expression of resistin, which also exerts pro-inflammatory effects. Resistin up-regulates the expression of VCAM-1 and ICAM and/or the induction of CCL2 as well as endothelin-1 from endothelial cells (Bokarewa *et al.*, 2005) and can induce endothelial dysfunction. The gene expression of resistin is induced by pro-inflammatory cytokines including IL-1, IL-6 and TNF-α (Kaser *et al.*, 2003). Finally, dysfunctional adipocytes in PVAT can produce high levels of classical chemokines MCP-1, IL-8 and IL-6, further contributing to PVAT inflammation.

Conclusions

A dual role of PVAT in the regulation of vascular function is closely linked with PVAT as a site of the development of vascular inflammation. A protective role of PVAT in physiological conditions linked to ADRF release has been demonstrated by numerous studies including seminal studies showing increased vascular dysfunction and hypertension in lipoatrophic mice. This led to the conclusion that 'fat is not always bad'. Before long, however, in parallel with endothelial dysfunction, the concept of a dysfunctional PVAT was developed, characterized by the loss of PVAT's protective properties. This was initially linked to changes in the adipokine profile, but it soon became apparent that PVAT dysfunction is orchestrated by inflammatory responses. In such conditions, perivascular adipocytes de-differentiate and are no longer primarily lipid-storing cells but become a metabolically active synthetic tissue that produces pro-inflammatory cytokines and chemokines and precipitates the key role of inflammation in cardiovascular disease (Figure 3). This occurs in a number of pathologies including hypertension, early atherosclerosis, hypercholesterolaemia and diabetes. Importantly, the loss of perilipin, which directly induces this change in PVAT phenotype, results in the development of spontaneous hypertension and vascular dysfunction with striking PVAT adipocyte de-differentiation and inflammatory cell infiltration (Zou *et al.*, 2016). These

studies show that PVAT plays a mechanistic role in the development of vascular dysfunction, closing a vicious circle of vascular disease pathogenesis. It still remains unclear how dysfunctional, inflamed PVAT affects vascular dysfunction, remodelling and disease. Is it just an entry point for adventitial inflammation, or is it itself a source of cytokines and chemokines which affect intimal and medial layers of the vessel as well? Whatever the exact mechanism – PVAT inflammation appears to be a tightly regulated process, which occurs early on in the pathogenesis vascular disease, and can constitute a valuable target for future therapies.

Author contributions

R.N. drafted the manuscript and prepared the figures; T.J.G. drafted the manuscript and approved the final version to be published.

Conflict of interest

The authors declare no conflicts of interest.

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