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Perivascular adipose tissue inflammation in vascular disease.

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Abstract

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 vaso-protective adipocyte derived relaxing factors (ADRFs) and increased production of paracrine factors such as resistin, leptin, cytokines (IL-6, TNF-α) and chemokines (RANTES, MCP-1). These adipocyte-derived factors initiate and orchestrate inflammatory cell infiltration including primarily T cells, macrophages, dendritic cells (DCs), B cells as well as NK cells. Protective factors such as adiponectin can reduce NADPH oxidase superoxide production and increase nitric oxide 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 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 molecular and cellular responses are uniquely different from classical visceral or subcutaneous adipose tissue or from adventitia, emphasizing unique structural and functional features of this adipose tissue compartment. Therefore, it is essential to develop techniques for monitoring PVAT characteristics and assessing its inflammation. This will lead to better understanding of the early stages of vascular pathologies and development of new therapeutic strategies focusing on perivascular adipose tissue.

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 & Haring, 2016). While initially considered to provide primarily mechanistic support for the vasculature, in the recent years it became 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 (Galvez et al., 2006; Gao, 2007; Gollasch & Dubrovska, 2004). 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 (Brown et al., 2014; Szasz, Bomfim & Webb, 2013). 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 nitric oxide (NO) and its role in the regulation of vascular function was at the central stage of vascular biology, thus this report was not sufficiently appreciated, until further studies showing the release of classical vascular relaxing factor from the PVAT (Lohn, Dubrovska, Lauterbach, Luft, Gollasch & Sharma, 2002). Several interesting investigations such as those of Gollasch (Fesus et al., 2007; Galvez et al., 2006; Gollasch & Dubrovska, 2004; Lohn, Dubrovska, Lauterbach, Luft, Gollasch & Sharma, 2002) and Gao (Gao, 2007; Gao, Lu, Su, Sharma & Lee, 2007; Gao et al., 2006), 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 receptors (Takemori et al., 2007). Moreover, the deletion of peroxisome proliferator-activated receptor gamma (PPAR-γ) 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 number of metabolic factors including AMPK (5' adenosine monophosphate-activated protein kinase) (Almabrouk, Ewart, Salt & Kennedy, 2014; Almabrouk, Ugusman, Katwan, Salt & Kennedy, 2016). In pathologies associated with

vascular dysfunction, release of ADRF is diminished while PVAT releases number of paracrine factors such as adipokines (resistin, leptin, visfatin), cytokines (IL-6, TNF-α), chemokines (regulated upon activation normal T cell expressed and secreted (RANTES, CCL5), monocyte chemoattractant protein 1(MCP-1, CCL2)) - all of which can directly affect vascular smooth muscle and endothelial cells and which initiate and orchestrate vascular inflammation. This imbalance between production and release of protective factors and pro-inflammatory molecules has been termed in similarity to endothelial dysfunction − the PVAT dysfunction (Guzik, Mangalat & Korbut, 2006; Guzik, Marvar, Czesnikiewicz-Guzik & Korbut, 2007). Such dysfunctional PVAT has been reported in a range of vascular pathologies including atherosclerosis, hypertension, diabetes and obesity (Guzik, Mangalat & Korbut, 2006; Ignacak, Kasztelnik, Sliwa, Korbut, Rajda & Guzik, 2012). While specific mechanisms and characteristics of PVAT dysfunction may differ, its inflammatory characteristics constitutes 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 is unique and different to mechanisms observed in typical visceral fat in obesity (Mikolajczyk et al., 2016). This difference results not only from its direct location next to vascular wall but also most likely from 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 in relation to atherosclerotic plaque development and vascular calcifications (Lehman, Massaro, Schlett, O'Donnell, Hoffmann & Fox, 2010), hypertension or aortic abdominal aneurysm (AAA). While presence of PVAT inflammation is a common feature of vascular disease state its characteristic varies between different pathologies (Fig 1).

Perivascular adipose tissue –brown or white?

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. Brown adipose tissue is associated with thermogenesis, while WAT serves for lipid storage. WAT is less vascular and less metabolically active in comparison to BAT. Both BAT and WAT are under control of sympathetic nervous system, but nerve supply is denser in BAT than in WAT (Harms & Seale, 2013). These differences are reviewed elsewhere (Harms & Seale, 2013), and have been summarized in Table 1.

Differences in both histologic and metabolic profile are also linked to differential immuno-inflammatory properties of these different types of adipose tissues (Galvez-Prieto et al., 2008). PVAT is different from other fat depots in the body through possible dynamic interplay between white and brown adipocytes, which result in differential functional properties (Table 1). In rodents, PVAT surrounding thoracic aorta is mainly brown although narrow strip immediately adjacent to 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(Brown et al., 2014; Wang, Xu, Guan, Su, Fan & Miao, 2009). In humans, PVAT has been attributed more histologic properties of WAT. However, its comparison to 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 much less differentiated phenotype than in typical WAT (Chang et al., 2012; Chatterjee et al., 2009; Galvez-Prieto et al., 2008), as indicated by less efficiency in 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 to WAT (Chang et al., 2012). PVAT is characterized by a less differentiated phenotype than classical visceral fat, closer to pre-adipocytes with particular propensity for release of pro-inflammatory factors and growth factors. PVAT, to greater extent than other adipose tissue compartments, is a conglomerate of various cell types, including adipocytes, preadipocytes, and mesenchymal stem cells. Pathological conditions such as angiotensin II (Ang II) or pro-atherosclerotic factors increase de-differentiation in PVAT adipocytes (Iwai et al., 2009; Tomono, Iwai, Inaba, Mogi & Horiuchi, 2008). This coincides with NF-κB dependent increases of pro-inflammatory cytokines such as IL-6, IL-8 or chemokines such as MCP-1 or RANTES (Mikolajczyk et al., 2016; Skurk, Herder, Kraft, Muller-Scholze, Hauner & Kolb, 2005; Skurk, van Harmelen & Hauner, 2004).

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 PPAR-γ is essential for 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. 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, Chatterjee, Tang, Hui & Weintraub, 2014).

PVAT inflammation in vascular pathologies

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

Atherosclerosis: Role of immunity and inflammation in atherosclerosis has been known for several decades now (Hansson & Hermansson, 2011). Studies of immune mechanisms of atherosclerosis have initially focused on neo-intima and atherosclerotic plaque. Recent evidence suggests a key role of perivascular inflammation at various stages of atherosclerosis (Skiba et al., 2016). Importantly, perivascular inflammation precedes atherosclerotic plaque and even development of endothelial dysfunction and oxidative stress in Apolipoprotein E-/- (Apoe-/-) mice (Skiba et al., 2016). While 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 KO mice) are characterized by increased production of proinflammatory cytokines such as IL-6 and IL-1 in perivascular adipose tissue (Lohmann et al., 2009). Furthermore, perivascular inflammation is associated with marked increase of chemokines such as MCP-1 (CCL2) (Manka et al., 2014), MIP-1α (macrophage inflammatory protein 1-alpha, CCL3) (Moos et al., 2005) and RANTES (Sakamoto, Tsuruda, Hatakeyama, Imamura, Asada & Kitamura, 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 adventita and adipose tissue (Galkina, Kadl, Sanders, Varughese, Sarembock & Ley, 2006; Moos et al., 2005) and correlated with age and lesion size (Moos et al., 2005). Increased number of T cells and macrophages in adventitial layer of abdominal aorta of Apoe-/- has been reported (Sakamoto, Tsuruda, Hatakeyama, Imamura, Asada & Kitamura, 2014). Adventitial T and B cells are present at early stages of atherosclerosis as loose aggregates (Galkina, Kadl, Sanders, Varughese, Sarembock & Ley, 2006; Moos et al., 2005), while in late stages they can form adventitial tertiary lymphoid organs (ALTOs) (Akhavanpoor, Wangler, Gleissner, Korosoglou, Katus & Erbel, 2014; Hu et al., 2015). Recently, Galkina group have shown that smooth muscle cell-derived IL-17C plays proatherogenic role by supporting perivascular recruitment Th17 cells. IL-17c-/-Apoe-/- displayed reduction of aortic leukocytes accumulation (Butcher, Waseem & Galkina, 2016). Pro-inflammatory IL-17A-producing T cells are present in the adventitia and blockade of IL-17A lead to reduction of macrophage accumulation 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 perivascular adipose tissue essential for this process. Indeed transplantation of PVAT on the carotid artery increased vascular remodelling upon wire injury through adventitial inflammation and angiogenesis in LDL receptor knockout animals (Manka et al., 2014). Endovascular injury significantly upregulates pro-inflammatory MCP-1, TNF-α, IL-6, plasminogen activator inhibitor-1 and downregulates 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 on cholesterol diet (Lohmann et al., 2009). There are more macrophages (CD68+ cells) in the PVAT and adventita in the LDLr-/- animals than in media and intima, in both atherosclerotic and non-atherosclerotic areas of the vessels (Ding, Mizeracki, Hu & Mehta, 2013). Consistently, Yamashita at al., (2008) showed that macrophages in the media and adventitia, not in the intima, are most important in expansive atherosclerotic remodelling via matrix degradation and smooth muscle cell reduction. In human atherosclerosis, perivascular macrophages near atherosclerotic lesion are polarized towards 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. STAT4 deficiency reduces development of atherosclerosis and PVAT inflammation in Apoe-/- mouse (Dobrian et al., 2015) and in insulin resistant obese Zucker rats (Pei, Gu, Thimmalapura, Mison & Nadler, 2006). Apoe-/- animals show higher numbers of CD45+ cells in PVAT, but not in visceral fat, compared to Apoe-/- STAT4-/- mouse. In particular, the number of CD8+ T cells is dramatically increased in PVAT of Apoe-/-mice. Reduction of PVAT inflammation was also associated with diminished expression of CCL5, CXCL10, CX3CL1 and TNF-α in STAT4-deficient Apolipoprotein E-deficient mice. Furthermore, STAT4 deficiency induces a bias toward 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 vascular adventitia via endothelial cell signalling (Schmidt et al., 2010). These studies are further supported by findings that vasoprptective compounds such as Mas receptor agonists prevent atherosclerosis through reduction of chemokines expression and accumulation on immune cells in PVAT (Skiba et al., 2016).

While macrophages and T cells regulate PVAT inflammation in atherosclerosis, important role for perivascular mast cells have recently been identified (Kennedy, Wu, Wadsworth, Lawrence & Maffia, 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 cells activation promotes monocyte adhesion in CXCR2- and vascular cell adhesion molecule 1 (VCAM1)-dependent manner (Bot et al., 2007).

Hypertension: Hypertension is associated with the activation of renin-angiotensin-aldosteron system (RAS) and increased vascular oxidative stress. Both, Ang II and ROS play crucial role in the initiation and maintenance of vascular inflammation. Primary site of 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 & Touyz, 2011), which may play a key role in modulating perivascular inflammation in hypertension. Additionally, PVAT expresses a complex ROS machinery containing nicotinamide adenine dinucleotide phosphate oxidase (NADPH), eNOS (endothelial nitric oxide synthase) and antioxidative enzymes (Guzik et al., 2005; Szasz, Bomfim & Webb, 2013). PVAT-derived ROS can promote endothelial dysfunction, which could be achieved either by endothelial NO-scavenging by PVAT derived ROS or through modulation of perivascular inflammation that then affects endothelial function (Even, Dulak-Lis, Touyz & Dinh Cat, 2014; Ketonen, Shi, Martonen & Mervaala, 2010). During progression of hypertension, immune cells accumulate mainly in perivascular fat tissue surrounding both large and resistance vessels such as 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., 2007; Mikolajczyk et al., 2016).

Mice lacking T cells or monocytes exhibit blunted inflammation in response to various hypertensive stimuli (Guzik et al., 2007; 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 with further promote chemotaxis toward adipose tissue (Guzik et al., 2007; Hoch et al., 2009; Mikolajczyk et al., 2016). 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 was associated with elevation of 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 coexist with atherosclerosis. Numerous inflammatory cells are involved in AAA formation such as neutrophils, macrophages, T and B cells as well as 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, Thatcher, Charnigo, Daugherty & Cassis, 2009). Deficiency of 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 promoting degradation of aortic wall cells (Folkesson et al., 2016).

In summary, PVAT inflammation is a characteristic feature of vascular pathologies. While there is number of similarities between perivascular inflammation in hypertension and atherosclerosis, there are also key differences (Fig 1). While in atherosclerosis perivascular immune infiltrates, relatively quickly form organized structures, forming eventually ATLOs (adventitial tertiary lymphoid organs), 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 may either be related to specific aneurysm pathology or may be lined 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 (PGI2) and increased production of vascular damaging and pathologically activating molecules such as ROS, endothelin, thromboxanes (Channon & 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,

CXCL10 (Ide, Hirase, Nishimoto-Hazuku, Ikeda & Node, 2008; Mateo et al., 2006), which can induce leukocyte migration or activation.

Increased ICAM1 (intracellular adhesion molecule) and VCAM1 expression, on vascular endothelium, is one of the hallmarks of endothelial dysfunction, linking it to inflammation. When such dysfunction occurs in microvessels and vasa vasorum of PVAT – it will lead to the development of perivascular infiltration, emphasizing a bi-directional relationship between vascular endothelium and PVAT.

Oxidative stress, characterized by overproduction of superoxide anion and hydrogen peroxide is a key feature of endothelial dysfunction. It results in rapid scavenging of NO in 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 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, Wanchu & Bhatnagar, 2011).

Vascular smooth muscle cells are a considerable source of chemokines and cytokines, such as CCL2, CCL7, CCL20, CXCL1, CX3CL1, CXCL5 and IL-6, IL-23a, IL-1β (Butcher, Waseem & Galkina, 2016). All of these can be essential for an induction of perivascular inflammation. Increased expression of key chemokines in the vascular wall is observed at early stages of atherosclerosis or hypertension. Chemokines receptors, such as CCR2, CCR5 and CXCR4 are also upregulated by oxygen radicals (Chan et al., 2012; Zhang, Chen, Song, Chen & Rovin, 2005). 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

Role of chemokines in initiating and orchestrating inflammation and specific immune responses is widely recognised (Henrichot et al., 2005). These small molecular weight molecules (7-12 kDa) can be divided into 4 subclasses, C, CC, CXC and CX3C chemokines based on the position of N-termal cysteine (van der Vorst, Doring & Weber, 2015). Chemokines and their receptors are widely expressed on vascular cells and on leukocytes and play a key role in the recruitment immune cells to the sites of inflammation or injury in response to chemokine gradient in many cardiovascular diseases. Conditioned media from PVAT induces a chemotaxis of monocytes and T cells (Chatterjee et al., 2013; Miao & Li, 2012;

Mikolajczyk et al., 2016). Role of CCL2, CCL5 and CX3CL1 in the recruitment of circulating monocytes and T cells in atherosclerosis is well established (Charo & Taubman, 2004; van der Vorst, Doring & Weber, 2015). CCL2 produced by adipocytes has been identified as a potential factor contributing to macrophage infiltration into adipose tissue (Chan et al., 2012; Kanda et al., 2006). RANTES chemokine, in turn, can be produced by T cells, macrophages, VSMC, endothelial cells as well as PVAT adipocytes (Krensky & Ahn, 2007; Mateo et al., 2006; Surmi & Hasty, 2010) and is key in recruitment of leukocytes into inflammatory or infection sites (Marques, Guabiraba, Russo & Teixeira, 2013). RANTES chemokine is increased in PVAT in hypertension (Guzik et al., 2007) and is characteristic for early stages of atherosclerosis (Podolec et al., 2016; Veillard et al., 2004). RANTES chemokine receptors (CCR1, CCR3 and CCR5) are elevated in vascular diseases in clear relation to PVAT inflammation (de Jager et al., 2012; Guzik et al., 2007; Marques, Guabiraba, Russo & Teixeira, 2013; Mikolajczyk et al., 2016). Recently, we have demonstrated that RANTES-/- reduces angiotensin II-induced accumulation of T cells, macrophages and DCs in the PVAT (Mikolajczyk et al., 2016). Genetic deletion or blockade of chemokine RANTES, using the peptide antagonist Met-RANTES, inhibits leukocyte infiltration to the site of inflammation (Marques, Guabiraba, Russo & Teixeira, 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 a IFN-γ inducible protein produced by T cells, NK and NKT cells, monocytes, DCs but also by fibroblasts and endothelial cells (Bondar, Araya, Guzman, Rua, Chopita & Chirdo, 2014). It is particularly important in chronic inflammation, including atherosclerosis and hypertension (Ide, Hirase, Nishimoto-Hazuku, Ikeda & Node, 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 via binding to CXCR3. The CXCL10/CXCR3 axis is important in regulating T cell responses in atherosclerosis. Deficiency of CXCR3 or using CXCR3 antagonist reduces lesion formation in Apoe-/- animals, reduce T cell migration and upregulates anti-inflammatory molecules (van Wanrooij et al., 2008; Veillard et al., 2005). Expression of CXCL10 is reduced in the PVAT of STAT4-/-Apoe-/- mice which, are protected from PVAT inflammation (Dobrian et al., 2015). Expression of CXCL10 correlates with STAT1 phosphorylation in vascular cells in plaques from human carotid arteries (Chmielewski et al., 2014) and STAT1 and NF-κB both regulate CXCL10 (Veillard et al., 2005). CXCL10 has direct effects on vascular wall cells as it induces migration and proliferation of endothelial cells and VSMC. Ide et al. demonstrated

that IP-10 increases the expression of RAS components in endothelial cells (Ide, Hirase, Nishimoto-Hazuku, Ikeda & Node, 2008), making it almost a prototypical "bi-directional" cytokine in vascular biology, through which 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 AT inflammation in obesity.

In diseases such as hypertension, hypercholesterolemia or diabetes PVAT inflammation may occur in the absence of obesity or metabolic syndrome. This may be related to vicinity of blood vessel wall, which affects development of vascular inflammation and in relation 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 to well described inflammation within classical visceral adipose tissue depots. This is manifested by 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 hypercholesterolemia. This is in contrast to typical visceral fat where macrophage dependent inflammation predominates from the earliest stages of disease (Wu et al., 2007). Perivascular T cells represent 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., 2007; 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+ lymphocytes infiltrated PVAT may also functionally differ depending on their content of granzyme B/perforin or IFN-γ/TNF-α (Broere, Apasov, Sitkovsky & van Eden, 2011). Ang II and hypertension increase the percentage of circulating T cells with effector phenotype which next accumulate in PVAT trigger inflammation and promote vascular dysfunction (Guzik et al., 2007; 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,CCR3) (Vinh et al., 2010). and adhesion molecules (CD44) which

are key to their recruitment to PVAT (Guzik et al., 2007; Mikolajczyk et al., 2016). Substantial proportion of PVAT CD4+ and CD8+ T cells expressed CD25 activation marker and produce IFN-γ and TNF-α. Ang II induce a shift of T cells toward TH1 producing IFN-γ, which is dependent on T cell AT1 receptor (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 and presence of the forkhead transcription factor (FOXP3) and through release of suppressive anti-inflammatory cytokines (IL-10, TGF-β) has critical roles in immune homeostasis and preventing excessive immune responses (Sakaguchi, Miyara, Costantino & Hafler, 2010). Interestingly, adoptive transfer of T$_{regs}$ ameliorates vascular dysfunction, reduces blood pressure and infiltration of immune cells in blood vessels and perivascular tissue in Ang II-treated mice (Matrougui et al., 2011). T$_{reg}$ also prevent 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 that were also found in the PVAT, may mediate cell death through perforin/granzyme-dependent pathways (Grossman, Verbsky, Barchet, Colonna, Atkinson & Ley, 2004), controlling immune responses but also affecting apoptosis and function of adjacent vascular cells. While other subpopulations of T cells such as invariant NK T cells etc 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 & Mallat, 2014). Little is known about B cell characteristics and 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, Spizzo, Diep, Drummond, Widdop & Vinh, 2014), but are also scattered independently of other immune cells. Chan et al found that Ang II-induced hypertension was associated with increase of activated of B cells in the PVAT. Moreover, this was associated with 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 better understanding of the links between pro- and anti-inflammatory B cells in PVAT is needed. The links between 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, Chawla & Pollard, 2013). Macrophage infiltration in adipose tissue has been 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 adventitia during hypercholesterolemia and hypertension, also in the absence of obesity (Chan et al., 2012; Moore et al., 2015) and release free radicals via NOX2 NADPH oxidase (Kotsias, Hoffmann, Amigorena & Savina, 2013). Infiltrating macrophages produce cytokines such as IL-6, IFN-γ, TNF-α, that change vascular and PVAT cell biology. While M1 macrophages, were classically defined in obesity and atherosclerosis, recent studies point to significant M2 macrophage infiltration 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, Chawla & Pollard, 2013), while M2 produce IL-10 and participate in TH2 type and pro-fibrotic responses (Murray & Wynn, 2011). PVAT macrophages are also important in the regulation of T cells activation through antigen presentation, expression costimulatory ligands and release of mediators that modulate their function and/or chemotaxis (Shirai, Hilhorst, Harrison, Goronzy & Weyand, 2015). T cell dependent responses may reciprocally regulate PVAT macrophage infiltration. For example, loss of *Lnk* gene, which increased 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 (Mikolajczyk et al., 2016; Wei, Spizzo, Diep, Drummond, Widdop & Vinh, 2014). This has been identified in hypertension and is enhanced by chronic oxidative stress leading to formation of immunogenic isoketal-protein adducts, which can accumulate in DCs and promote T cells activation (Kirabo et al., 2014; Wu et al., 2016). Dendritic cells release mediators such as IL-1β, IL-6 and IL-23 which 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., 2007; Marko et al., 2012) (Fig 2). Moreover, blocking of CD28/CD80/CD86 co-stimulation axis between DC and T cells prevent PVAT inflammation (Vinh et al., 2010). However, the role of DCs either in PVAT or 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) (Fig 2).

NK cells: Natural Killer 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 (ATLOs): Antigen presenting cell (APC)- T cell interactions occur primarily in secondary lymphoid organs such as lymph nodes and the spleen (Junt, Scandella & Ludewig, 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 hypertension (Fig 1). Such interactions could trigger development of and be sustained by tertiary lymphoid organs (TLOs) (Hansson & 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, pulmonary hypertension, and in patients with chronic obstructive pulmonary disease (Neyt, Perros, GeurtsvanKessel, Hammad & Lambrecht, 2012; Perros et al., 2012; Yadava, Bollyky & Lawson, 2016). Interestingly, TLO formation is reversible when inflammation is resolved or after therapeutic intervention (Drayton, Liao, Mounzer & Ruddle, 2006).

Development of TLOs is orchestrated by various chemokines and cytokines such as CXCL12, CXCL13, CCL19, CCL20, CCL21, lymphotoxin-α and lymphotoxin-β (Akhavanpoor, Wangler, Gleissner, Korosoglou, Katus & Erbel, 2014; Rangel-Moreno et al., 2011). Interestingly, also IL-17 contributes to the formation of TLOs (Rangel-Moreno et al., 2011). Immune cells can be organized in follicle-like structures called ALTOs. They can be found in murine models of atherosclerosis and AAA (Hu et al., 2015; Spear et al., 2015). Recently, Hu et al. in very elegant study showed that aging immune system employs ALTOs to control atherosclerosis related T cell immunity. VSMC- lymphotoxin β receptors (LTβRs) maintain ALTO 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 substantial number of immune cells during perivascular inflammation are recruited by chemotaxis (Henrichot et al., 2005), some immune cells in the vascular wall are chronically resident within the vessel wall. This includes primarily resident macrophages (Ensan et al., 2016; Robbins et al., 2013), which can proliferate in atherosclerotic plaque and potentially in PVAT, as well as resident memory T cells (Schenkel, Fraser, Beura, Pauken, Vezys & Masopust, 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 such recruitment based on peripheral blood subpopulations of either monocytes or T cells remains disputable (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). Survival of resident arterial macrophages depends on chemokines, in particular on fractalkine (CX3CL1) axis, expression of which is critical in human atherosclerosis and vascular disease (Lucas, Bursill, Guzik, Sadowski, Channon & Greaves, 2003).

Similarly to myelo-monocytic 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 (Clark, 2015; Mackay et al., 2013). T_{RM} cells express low level of receptors such as CCR7 (Bromley, Thomas & Luster, 2005; Clark, 2015) and sphingosine-1-phosphate receptor 1 (Resop, Douaisi, Craft, Jachimowski, Blom & Uittenbogaart, 2016) which promote exit cells from the tissues. T_{RM} cells express high levels of CD44 and low levels of CD62L and release number of effector cytokines such as IFN-γ or TNF-α (Slifka & Whitton, 2000). Subset of T_{RM} cells mediate the protective immunity, however, dysregulation of T_{RM} can contribute to autoimmune and inflammatory diseases. While potential role of T_{RM} in vascular pathologies is of great interest, other lymphocytes, including classical effector T cells, natural killer T cells, NK cells and T_{reg} cells have been described in PVAT. Most of these are likely acutely recruited into PVAT.

T cell recruitment to PVAT may be controlled by sympathetic nervous system nerve endings in PVAT and adventitia (Guzik & Mikolajczyk, 2014; Itani et al., 2016; Marvar et al., 2010). Recent evidence suggests 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, induces VSMC proliferation and endothelial dysfunction (Chatterjee et al., 2013; Miao & Li, 2012; Mikolajczyk et al., 2016). This is in part mediated by adipokines, which has been reviewed elsewhere (Mattu & Randeva, 2013; Tilg & Moschen, 2006), but may also be dependent on cytokines released by activated inflammatory cells in the PVAT. Most evidence, point to the key role of IFN-γ, IL-17, IL-6 and TNF-α in regulating this process (Matusik, Guzik, Weber & Guzik, 2012) (Fig 2).

Pro-inflammatory cytokines and endothelial function: IFNγ is one of the key cytokines produced by T cells, NK cells as well as some vascular cells. IFN-γ classical function is in the activation of monocytes/macrophages along with polarisation of immune cells into pro-inflammatory phenotype (Knorr, Munzel & Wenzel, 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, 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).

Interleukin-6 which is produced by macrophages, T cells, DC as well as PVAT adipocytes can directly affect endothelial cells (Pietrowski, Bender, Huppert, White, Luhmann & Kuhlmann, 2011). It mediates increase of superoxide production and endothelial dysfunction by affecting NO-cGMP signalling pathway (Orshal & Khalil, 2004; Schramm, Matusik, Osmenda & Guzik, 2012). IL-6 deficiency prevents vascular dysfunction in spite of various damaging stimuli (Schrader, Kinzenbaw, Johnson, Faraci & Didion, 2007). Treatment of C57BL/6J animals *in vivo* or *ex vivo* incubation blood vessels with IL-6 impairs endothelium-dependent relaxation (Wassmann et al., 2004). IL-6 is also necessary for TH17 cells differentiation (Bettelli et al., 2006), another T cell subpopulation with strong pro-inflammatory impact on endothelial and vascular smooth muscle cells. IL-17 is a potent activator of the endothelial cells promoting expression of adhesion molecules (Roussel et al., 2010). IL-17A activates RhoA/Rho-kinase and increases inhibitory eNOS Thr495 phosphorylation in endothelial cells leading to decreased NO production (Nguyen, Chiasson, Chatterjee, Kopriva, Young & Mitchell, 2013). IL-17A, IFN-γ as well as IL-6 synergize their effects with TNF-α to modulate inflammatory responses (Ruddy et al., 2004). TNF-α is produced by a wide range of cells types including immune cells, vascular cells and adipocytes (Mendizabal, Llorens & Nava, 2013). Stimulation

of endothelial cells with this pro-inflammatory cytokine decrease eNOS expression (Hot, Lenief & Miossec, 2012) by destabilization of eNOS mRNA (Neumann, Gertzberg & Johnson, 2004). TNF-α, through NF-κB, 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., 2007). Moreover, TNF-α increases expression of endothelial adhesion molecules and production of pro-inflammatory chemokines such as CCL5, CCL7, CCL8 or CXCL9 (Hot, Lenief & Miossec, 2012). Combined treatment with TNF-α and IL-17 promotes synergistic activation of endothelial cells to express adhesion molecules and chemokines that enhance immune cells migration (Griffin et al., 2012). Contrary action is performed by IL-10, produced by T regulatory cells, selected macrophages and DCs (Krause et al., 2015; Saraiva & O'Garra, 2010). This anti-inflammatory cytokine reduces NADPH-dependent oxidative stress and increases production of NO by enhancing phosphorylation and activation of eNOS (Kassan, Galan, Partyka, Trebak & Matrougui, 2011). IL-10 inhibits activation of p38 MAPK (mitogen-activated protein kinase), which contributes to stimulation of pro-inflammatory cytokines but can also regulate NADPH oxidases (Konior, Schramm, Czesnikiewicz-Guzik & Guzik, 2014; Kontoyiannis et al., 2001).

Effects of cytokines produced by immune cells on VSMCs: Inflammatory cytokines released in PVAT modulate smooth muscle cell constriction, proliferation and migration (McMaster, Kirabo, Madhur & Harrison, 2015). Similarly 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 vascular AT1 receptors and mediates medial hypertrophy (Schrader, Kinzenbaw, Johnson, Faraci & Didion, 2007). It also enhances constriction of the blood vessels (Orshal & Khalil, 2004). Further, 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 & Dong, 2013). IL-17A induces expression of mRNA for collagens I, III and V in a p38MAP kinase dependent fashion leading to collagen deposition 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, hydrogen peroxide and therefore can regulate redox sensitive pro-inflammatory cytokines (IL-6, MCP-1, granulocyte-colony stimulating factor, granulocyte-macrophage colony-stimulating factor) (Pietrowski, Bender, Huppert, White, Luhmann & Kuhlmann, 2011). Synergistically with TNF-α, IL-17A increases the expression of CCL8,

CSF3 (colony stimulating factor 3), CXCL2 and CCL7 in human aortic smooth muscle cells (Madhur et al., 2010).

Interferon-γ can also act directly on VSMC 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 ICAM1 mRNA expression in smooth muscle cells (Chung et al., 2002). IFN-γ has also strong impact on superoxide production by upregulation expression and activity of NOXs in human aortic smooth muscle cells (Manea, Todirita, Raicu & Manea, 2014).

Effects of cytokines produced by immune cells on perivascular adipocytes: As discussed above, part of the effects, through which inflammation mediates vascular function is dependent on regulation of classical adipokine expression and release. Adiponectin has a wide range of anti-inflammatory effects whereas leptin has a pro-inflammatory effects (Tilg & Moschen, 2006). Both are also critical in regulating vascular function making them prototypical bi-directional adipokines in vascular biology (Antonopoulos et al., 2015; 2016; Woodward, Akoumianakis & Antoniades, 2016) including potent NO-releasing vasorelaxant properties (Cheng et al., 2007). Production of adiponectin can be inhibited by pro-inflammatory cytokines such as TNF-α, IL-6 and IL-17A (Fasshauer et al., 2003; Maeda et al., 2002; Noh, 2012). Leptin is produced mainly by adipocytes and has structural similarity to IL-6, IL-12, IL-15. IL-17A and TNF-α increase leptin production (La Cava & Matarese, 2004; Noh, 2012). Leptin apart from direct effects on endothelial NO production and VSMCs can affect leukocyte chemotaxis, release of oxygen radicals, VSMC proliferation and expression of adhesion molecules on endothelial and vascular smooth muscle cells (La Cava & Matarese, 2004). While adiponectin and leptin have been well investigated, PVAT shows particularly high expression of resistin, which also exerts pro-inflammatory effects. Resistin upregulates the expression of VCAM1 and ICAM and/or induction of CCL2 as well as endothelin-1 from endothelial cells (Bokarewa, Nagaev, Dahlberg, Smith & Tarkowski, 2005) and can induce endothelial dysfunction. Gene expression of resistin is induced by pro-inflammatory cytokines including IL-1, IL-6 and TNF-α (Kaser, Kaser, Sandhofer, Ebenbichler, Tilg & Patsch, 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

Dual role of PVAT in the regulation of vascular function is closely linked with PVAT as a site of development of vascular inflammation. 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 lipoathrophic mice. This led to conclusion that "fat is not always bad". Soon however, in parallel to endothelial dysfunction, a concept of dysfunctional PVAT has been developed, characterized by loss of PVAT protective properties. This has been linked initially to changes in 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 (Fig 3). This occurs in number of pathologies including hypertension, early atherosclerosis, hypercholesterolemia or diabetes. Importantly loss of perilipin, which directly induces such change in PVAT phenotype results in 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 will be – PVAT inflammation appears to be a tightly regulated process, early in the vascular disease pathogenesis, that can constitute a valuable target for future therapies.

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Tables of Links

TARGETS	
Other protein targets[a]	CD44
TNF-α	CD69
CD3	CXCR3
GPCRs[b]	**Enzymes**[e]
Angiotensin 1-7	APMK
CCR2	eNOS
CCR3	**Nuclear hormone receptors**[c]
CCR4	PPARγ

LIGANDS	CXCL3
Adiponectin	CXCL5
Ang II	IFN-γ
CCL12	IL-10
CCL2	IL-17A
CCL20	IL-17C
CCL5	IL-1β
CCL7	IL-23
CCL8	IL-6
CXCL1	Leptin
CXCL10	PGI$_2$

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,e]Alexander et al., 2015a,b,c,d,e).

Abbreviations

AAA - aortic abdominal aneurysm

ADRF - adipocyte derived relaxing factor

Ang II - angiotensin II

Apoe - Apolipoprotein E

ATLO - adventitial tertiary lymphoid organ

BAT - brown adipose tissue

CCL - chemokine (C-C motif) ligand

CD - cluster of differentiation

CX3CL - chemokine (C-X3-C motif) ligand

CXCL - chemokine (C-X-C motif) ligand

CXCR - CXC chemokine receptor

EDRF – endothelium-derived relaxing factor

eNOS - endothelial nitric oxide synthase

MCP-1 - monocyte chemoattractant protein 1, CCL2

NADPH - nicotinamide adenine dinucleotide phosphate-oxidase

PVAT - perivascular adipose tissue

RANTES - regulated upon activation, normal T cell expressed and secreted, CCL5

STAT - Signal transducer and activator transcription

TH17 - IL-17 producing T cells

T$_{reg}$ - T regulatory lymphocytes

T$_{RM}$ - tissue-resident memory T cell

VCAM1 - vascular cell adhesion molecule 1

VSMCs - vascular smooth muscle cells

WAT - white adipose tissue

TLO - tertiary lymphoid organs
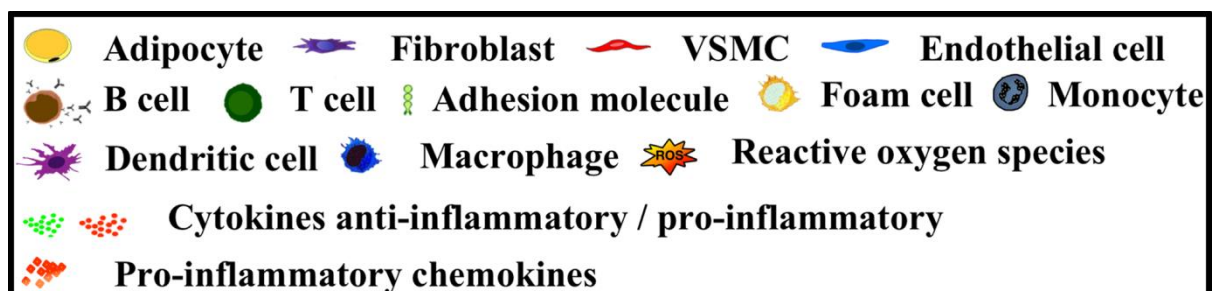
Author Contributions

R.N. Drafting the manuscript and preparation of figures.

T.J.G. Drafting the manuscript and final approval of the version to be published.

Competing Interests' Statement – none

Figure Legends:

Figure 1. **Central role of perivascular adipose tissue inflammation in the regulation of vascular disease**. Differential role of PVAT and vascular compartments in physiological state and in the development of vascular pathology in hypertension and atherosclerosis.

Figure 1.

	Physiological state	Hypertension	Atherosclerosis

PVAT
Adventitia
Media
Endothelium
Lumen

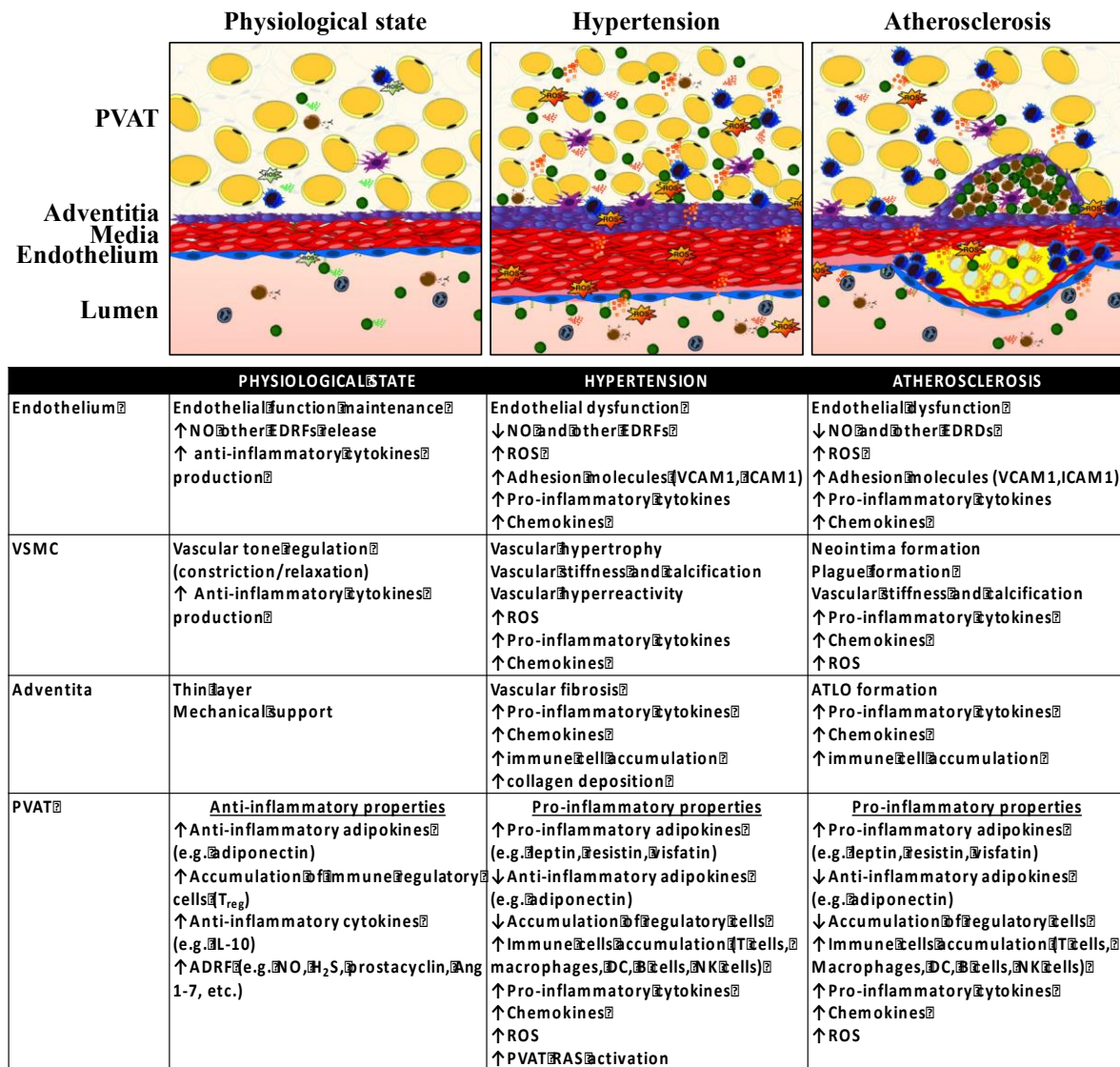|	PHYSIOLOGICAL STATE	HYPERTENSION	ATHEROSCLEROSIS
Endothelium	Endothelial function maintenance ↑NO other EDRFs release ↑ anti-inflammatory cytokines production	Endothelial dysfunction ↓NO and other EDRFs ↑ROS ↑Adhesion molecules (VCAM1, ICAM1) ↑Pro-inflammatory cytokines ↑Chemokines	Endothelial dysfunction ↓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
Adventita	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 (e.g. adiponectin) ↑Accumulation of immune regulatory cells (T_{reg}) ↑Anti-inflammatory cytokines (e.g. IL-10) ↑ADRF (e.g. NO, H_2S, prostacyclin, Ang 1-7, etc.)	__Pro-inflammatory properties__ ↑Pro-inflammatory adipokines (e.g. leptin, resistin, visfatin) ↓Anti-inflammatory adipokines (e.g. 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 (e.g. leptin, resistin, visfatin) ↓Anti-inflammatory adipokines (e.g. adiponectin) ↓Accumulation of regulatory cells ↑Immune cells accumulation (T cells, Macrophages, DC, B cells, NK cells) ↑Pro-inflammatory cytokines ↑Chemokines ↑ROS

Figure 2. **Cellular and humoral components of PVAT inflammation and their interactions in the regulation of vascular homeostasis and vascular dysfunction**. Detailed description is provided within the text.
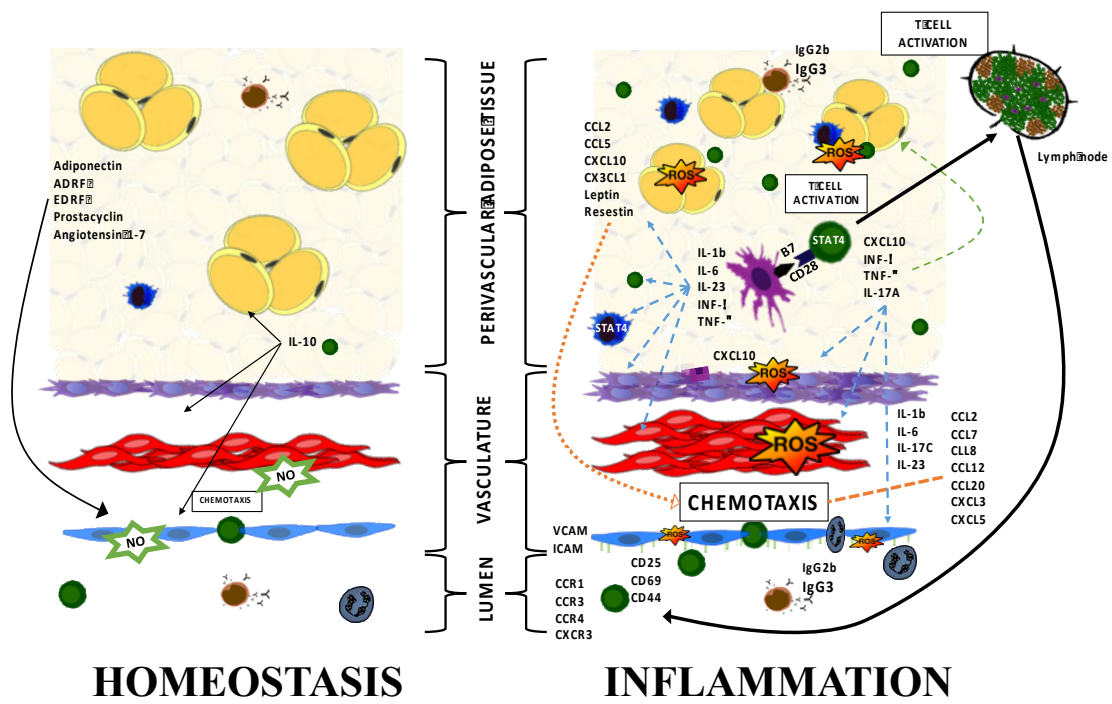
Figure 2.

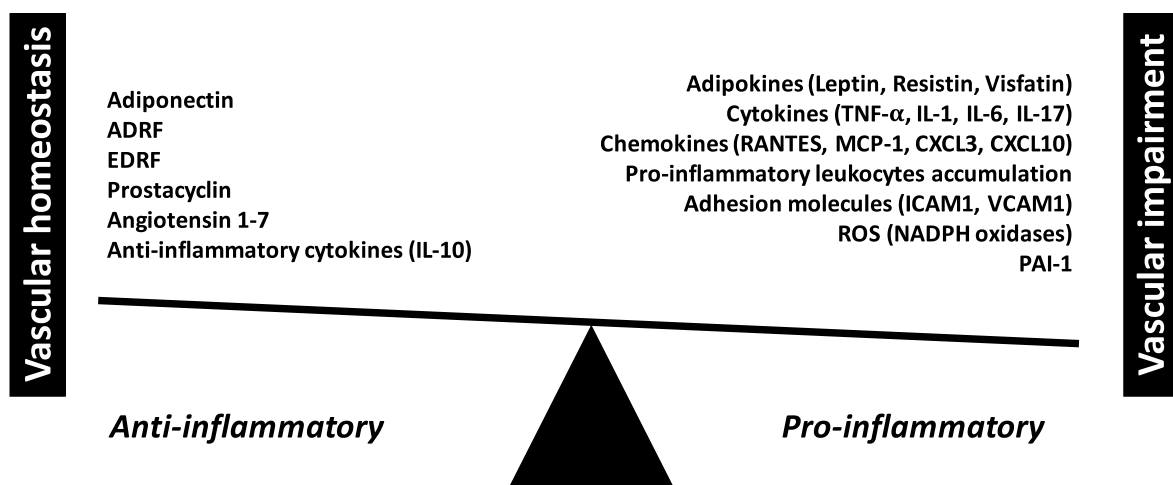Figure 3. **Balancing anti- vs. pro-inflammatory properties and functions of perivascular adipose tissue.**

Figure 3.

Table 1. Key differences between white, brown and perivascular adipose tissue

	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 & Seale, 2013)
Mitochondria/UCP1	+/+ (nearly undetectable)	+++/+++	++(+)/++(+)	Cedikova et al. (2016)
Adipocyte specific genes	PPARγ, 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, Kogan, Aouadi, Hendricks, Straubhaar and Czech (2011); Harms and Seale (2013)