Proinflammatory phenotype of perivascular adipocytes

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Abstract

Perivascular adipose tissue (PVAT) directly abuts the lamina adventitia of conduit arteries and actively communicates with the vessel wall to regulate vascular function and inflammation. Mounting evidence suggests that the biological activities of PVAT are governed by perivascular (PV) adipocytes, a unique class of adipocyte with distinct molecular and phenotypic characteristics. Perivascular adipocytes surrounding human coronary arteries (pericoronary PV adipocytes) exhibit a reduced state of adipogenic differentiation and a heightened pro-inflammatory state, secreting up to 50-fold higher levels of the pro-inflammatory cytokine MCP-1 as compared with adipocytes from other regional depots. Thus, PV adipocytes may contribute to upregulated inflammation of PVAT observed in atherosclerotic human blood vessels. On the other hand, PV adipocytes also secrete anti-inflammatory molecules such as adiponectin, and elimination of PVAT in rodent models has been shown to augment vascular disease, suggesting that some amount of PVAT is required to maintain vascular homeostasis. Evidence in animal models and in humans suggests that inflammation of PVAT may be modulated by environmental factors, such as high fat diet and tobacco smoke, which are relevant to atherosclerosis. These findings suggest that the inflammatory phenotype of PVAT is diverse depending on species, anatomic location, and environmental factors, and that these differences are fundamentally important in determining a pathogenic versus protective role of PVAT in vascular disease. Further research into the mechanisms that regulate the inflammatory balance of PV adipocytes may yield new insight into, and treatment strategies for, cardiovascular disease.

Introduction

The traditional model of the pathogenesis of atherosclerosis has focused on intimal disease, following the paradigm of endothelial injury leading to inflammation, monocyte recruitment and foam cell formation.[1] This view focuses on the luminal aspect of the vessels with the inflammation initiating inside the vessel wall and radiating outward ("inside-out" model), with adventitia and PVAT occupying a relatively passive role. However, this paradigm has come under intense scrutiny as the extent of adventitial inflammation in atherosclerosis has been better appreciated. Indeed, in apolipoprotein E deficient mice, accumulation of T cells and B cells in the lamina adventitia far exceeds that in the intima (up to 80-fold higher),[2] and intense clustering of macrophages and lymphocytes was demonstrated at the border

between the lamina adventitia and PVAT in atherosclerotic human aorta,[3] suggesting that PVAT could play an active role in promoting vascular inflammation. This view is further supported by observations that balloon or wire injury rapidly induces inflammation and perturbs adipokine gene expression profiles in PVAT in pigs and mice.[4, 5] These and other studies have led to a gradual shift towards an "outside-in" model of inflammation in vascular disease and placed PVAT prominently in the spotlight of vascular biology.

The purpose of this review is to discuss current concepts regarding the inflammatory state of PV adipocytes with the recognition that the majority of current knowledge regarding adipocyte origin and function stem from studies of visceral and/or subcutaneous adipose tissues, with limited data on the PV depot. Emerging evidence suggests that PVAT is a unique adipose depot containing a distinct class of adipocytes reflecting the precursor cells (preadipocytes) from which they are derived. A more fundamental understanding of PV adipocytes is required to elucidate the mechanisms whereby PVAT interacts with metabolic factors, chemokines, inflammatory cells and the blood vessel wall to mediate and/or modulate cardiovascular disease.

Adipocytes and inflammation

Adipocytes are traditionally viewed as energy-storage cells that play a key role in energy balance, thermogenesis and glucose homeostasis. However, adipocytes also produce a number of soluble factors ("adipocytokines") that regulate inflammation, and they possess machinery including toll-like receptors that facilitate inflammatory interactions. Adipokines such as resistin[6] and leptin[7] exert predominantly pro-inflammatory effects, while adiponectin is classically anti-inflammatory.[8] Thus, adipocytes can also be viewed as integral components of the immune system.[9, 10] Evolutionarily, adipose tissue was derived from the primitive fat body of insects, which simultaneously serves both the animal's metabolic and immune functions[11]. While higher animals have evolved separate systems to serve these functions (i.e., liver and adipose tissues for metabolism and hematopoietic system for immunity), adipose tissue has retained its basic immune functions.[12] The contribution of adipocytes to inflammation of adipose tissues in the pathogenesis of obesity-related disease is well established.[13, 14] Adipose inflammation, in turn, serves as a major driver of systemic inflammation that links obesity to cardiovascular disease. Although pro-inflammatory adipocytokines are expressed by PVAT, the notion that PVAT may locally contribute to cardiovascular disease is a more recent and less well-founded hypothesis.

Features of PVAT

PVAT is a conglomerate of various cell types including adipocytes, preadipocytes, and mesenchymal stem cells, embedded in a matrix that is invested with microvessels[15, 16] and which may contain a similar system of sympathetic innervation seen in richly innervated brown adipose tissue (BAT) and white adipose tissue (WAT),[16] although evidence regarding PVAT innervation is scarce. In humans, PVAT directly abuts the adventitia of most large conduit arteries in the body, with the notable exception of the cerebral vasculature, and some microvascular beds such as the mesentary. The absence of a separating fascia layer promotes paracrine communications between PVAT and the associated vasculature (Figure 1). As

such, adipocytes from PVAT can infiltrate into the adventitia[3, 17] to facilitate their effects on local inflammation and vascular tone. Indeed, PVAT has been shown to modulate vascular contractility via paracrine release of various factors including adiponectin.[18–22] Furthermore, PVAT is anatomically co-localized with atherosclerotic lesions in humans, correlating with plaque burden and vascular calcifications.[23, 24] Similar to visceral and subcutaneous adipose tissues, PVAT expands during obesity,[25–27] with hypertrophy of both brown and white periaortic adipocytes noted in rodent models of high fat feeding.[28, 29]

Mounting evidence suggests that the phenotype and function of PVAT varies depending on species and anatomic location, displaying features of traditional WAT versus energy-combusting BAT, or an intermediate between the two.[17, 28–32] Most of the published data pertaining to brown adipose phenotype of PVAT were derived from rodent studies; the extent to which this reflects the phenotype of human PVAT is less clear. Human PV adipocytes surrounding coronary arteries exhibit a histological appearance and gene expression pattern more consistent with white rather than brown adipocytes[17, 30] (Figure 1). However, as compared to subcutaneous and perirenal adipocytes derived from the same subjects, these PV adipocytes are smaller in size, less efficient at storing lipid, and express lower levels of adipocyte-specific genes, suggesting a reduced state of adipogenic differentiation.[17] Global gene expression analyses indicate that these features of PV adipocytes map to early developmental differences, consistent with their origination from a distinct precursor cell,[30] as has been proposed for adipose-derived stem cells surrounding perivascular regions of subcutaneous and visceral adipose tissues of mice[33]. In contrast, *in vitro* differentiated PV adipocytes derived from human radial arteries are larger in size and exhibit a high capacity to form lipid droplets, suggesting that the origin and/or differentiation state of human PV adipocytes is variable depending on the vascular bed.[34]

Developmental origins of adipocytes

The majority of research in the origin of adipocytes comes from work on subcutaneous and visceral adipocytes isolated from the stromal vascular fraction (SVF) of homogenized adipose tissues. The emerging consensus is that a majority of the mature adipocytes within each adipose tissue depot derive from precursor cells with distinct embryologic lineages.[35] Indeed, *in vitro* differentiation of preadipocytes typically yields mature adipocytes that recapitulate the phenotype of their *in vivo* counterparts, thus accounting for the basic differences between individual adipocyte depots. However, heterogeneous, multipotent subpopulations of adipose- stromal cells reside within individual fat depots and can give rise to adipocytes with different phenotypes. Lineage analysis studies suggest that the source of adipose progenitor cells in visceral WAT depots is heterogeneous with the lateral plate mesoderm serving as a major contributor, and Wilms' tumour gene 1 (Wt1)-positive progenitors giving rise predominately to epididymal as opposed to retroperitoneal fat. In contrast, Wt1 is not expressed in subcutaneous adipose tissue or BAT; BAT appears to originate mainly in the paraxial mesoderm.[36, 37] Adipose stromal cells isolated from subcutaneous adipose tissues of mice also were suggested to be heterogeneous, with a subpopulation shown to have a neural crest origin, termed neural crest derived adipose stromal cells.[38] These cells were demonstrated to have high adipogenic differentiation potential but markedly attenuated osteogenic and chondrogenic potentials compared to their

non-neural crest adipose stromal cell counterparts.[38] Studies involving PV adipocytes are relatively scarce, and, to the best of our knowledge, point toward an origin distinct from other adipocytes. Inferential evidence suggests that these cells may arise from vascular smooth muscle cell (VSMC) progenitors.[39, 40] Moreover, in a murine model with VSMC-specific PPAR-γ deletion, the animals had normal WAT and BAT depots, but lacked PVAT.[41] Although far from definitive proof, the above data suggest a common embryological origin for PV adipocytes and VSMC.

Nature vs. nurture: adipocyte plasticity

Multiple studies support the idea that the surrounding micro-environment is a critical factor in cell lineage determination of adipose stromal cells.[30, 35] In addition, mature adipocytes have been suggested to possess the ability to de-differentiate into lipid-free fibroblast-like cells, which under proper induction culture *in vivo* or *in vitro*, demonstrated adipogenic, osteogenic, and chondrogenic potentials similar to adipose stromal cells isolated from SVF.[42] Thus, the micro-environment may also regulate the differentiation state and phenotype of mature adipocytes. The function of brown adipocytes is generally linked to thermogenesis and temperature homeostasis, whereas white adipocytes are viewed to be important in energy storage and systemic endocrine functioning. However, this dichotomy has recently been challenged with the discovery of brite (brown-in-white) adipocytes detected in white adipose depots, which may contribute to temperature homeostasis and whole-body metabolism in humans.[43–45] A bidirectional inter-conversion between brite adipocytes and white adipocytes was demonstrated in inguinal fat depots in mice.[32] Cold exposure has been shown to stimulate brown adipocyte hyperplasia and increase metabolic activity in rodent models. In humans, short term cold exposure similarly increased 2-[^{18}F]fluoro-2-deoxyglucose (FDG) uptake in BAT; positron emission tomography images raise the possibility of FDG uptake into fat surrounding the heart and great vessels.[46, 47] Whether cold exposure directly or indirectly affects the function or phenotype of PV adipocytes remains to be determined.

Other dietary cues may also regulate the function of PV adipocytes. Chatterjee et al showed that feeding mice a high fat diet for just two weeks produced marked reduction in the expression of adipocyte-related genes (including the anti-inflammatory adipokine adiponectin) in thoracic PVAT, suggesting a reduction in the state of adipogenic differentiation.[17] Moreover, expression of the pro-inflammatory cytokine MIP-1α was markedly upregulated in the PVAT, whereas expression in subcutaneous and visceral depots was minimally affected. These changes occurred prior to significant recruitment of inflammatory cells to the PVAT depot, suggesting that the PV adipocytes themselves responded adversely to the high fat diet. Likewise, high fat diet disrupted the balance between oxidant production and anti-oxidant defense mechanisms in murine PVAT;[48] the oxidant stress resulting from this imbalance could contribute to amplification of inflammation in the PVAT depot.[49] Consistent with this notion, mice deficient in adipose triglyceride lipase, a key lipolytic enzyme that regulates lipid accumulation in adipose tissues, exhibited marked expansion of the thoracic aorta PVAT depot along with amplification of oxidative stress and inflammation[50]. Interestingly, PV adipocytes (perimesenteric) from smokers, who also exhibit increased oxidative stress, expressed higher

levels of MCP-1 mRNA, and enhanced activity of the $P2X_7R$-inflammasome complex, as compared with adipocytes isolated from non-smokers.[51] Taken together, these data suggest that adipocytes exhibit considerable plasticity in response to environmental cues, and responsiveness of PV adipocytes to noxious stimuli contained in high fat diet and/or tobacco smoke may promote a pro-inflammatory state conducive to the development of atherosclerosis.

Regulation of inflammation by perivascular adipocytes

The inflammatory state of human PVAT has been the subject of intense research in the last decade. Many studies have shown a heightened state of inflammation in PVAT surrounding atherosclerotic blood vessels, both in terms of inflammatory cell infiltration[3, 52, 53] and pro-inflammatory gene expression.[3, 53] However, PVAT is comprised of many cell types, so the specific contribution of PV adipocytes to the global inflammatory state of the tissue is impossible to infer from these studies. Only a few publications have investigated the inflammatory potential of PV adipocytes, either freshly isolated or *in vitro* differentiated. Therefore, the information presented here contains the most current knowledge regarding this topic and is inherently limited in scope. Nevertheless, these data suggest that human PV adipocytes surrounding conduit arteries possess intrinsic pro-inflammatory characteristics. Our laboratory demonstrated that human pericoronary PV adipocytes expressed high levels of MCP-1, IL-8, and IL-6[17] which play a critical role in inflammatory cell recruitment to adipose tissues[3] and are also important in the pathobiology of vascular disease.[54] In particular, release of MCP-1 protein from *in vitro* differentiated PV adipocytes was nearly 50-fold greater than that from adipocytes derived from other regional depots of the same subjects.[17] Human periradial adipocytes likewise expressed higher levels of pro-inflammatory MCP-1 and pro-angiogenic mediators as compared with visceral or subcutaneous adipocytes.[34] In a wire-induced injury model in mice, Jabs et al showed sequential expression of MCP-1 and other cytokines/cytokine receptors in PV tissue starting on the adventitial aspect of the vessel and progressing toward the intima.[55] MCP-1 gene deletion in animal models led to substantial reductions in arterial wall macrophage infiltration and lipid deposition.[56, 57] Conditioned media from PV adipocytes elicited chemotaxis of granulocytes, monocytes, and activated T cells, and stimulated VSMC proliferation, which supports a pathological role for cytokines and growth factors produced by PV adipocytes.[3, 30, 58]

Conversely, pericoronary PV adipocytes secreted markedly less adiponectin (an anti-inflammatory adipokine) as compared with their subcutaneous and perirenal counterparts, which is further consistent with a pro-inflammatory phenotype. It is important to point out that the PVAT was obtained from previously healthy organ donors without a pre-existing history of heart disease, suggesting that the pro-inflammatory phenotype was a fundamental property of the cells and not the product of an atherosclerotic milieu.[17] Extending these studies, we performed genome-wide analyses comparing human subcutaneous and PV adipocytes and showed that PV adipocytes had a strikingly higher expression of genes involved in pro-inflammatory pathways including cell adhesion molecules and complement system factors such as complement 7, complement H, SERPINE2, SERPINE1, and cytosolic PLA_2.[30] In the latter study, the most differentially upregulated gene expressed by PV

adipocytes was tumor necrosis factor receptor superfamily member 11b (osteoprotegerin). Osteoprotegerin is a secreted protein that is best known as a decoy ligand for RANK that regulates osteogenesis, but it also exerts both pro-inflammatory and anti-inflammatory effects, and its levels are elevated in humans with atherosclerosis and in mice fed a high fat diet.[59] As compared with subcutaneous adipocytes, PV adipocytes secreted markedly higher levels of osteoprotegerin protein, raising the possibility that PVAT contributes importantly to systemic osteoprotegerin levels in obesity and atherosclerosis. The functional importance of pro-inflammatory mediator secretion by PV adipocytes was demonstrated using a transendothelial monocyte migration assay. As compared to conditioned medium from subcutaneous adipocytes, medium from PV adipocytes induced a two-fold increase in monocytic cell migration across an endothelial monolayer, supporting a pro-inflammatory phenotype of human pericoronary PV adipocytes.[30]

On the other hand, our microarray data also showed increased expression of certain anti-inflammatory genes by the PV adipocytes, including tumor necrosis factor α-induced protein 6 (TAIP6 or TSG6) and suppressor of cytokine signaling 2 (SOCS2), which suggests that PV adipocytes can also exert anti-inflammatory effects.[30] A protective effect of PVAT is likewise inferred by the observation that removal of PVAT from the femoral artery enhanced neointima formation after wire injury in high fat fed mice, suggesting that the presence of some amount of PVAT is protective and needed to maintain vascular homeostasis.[60] Interestingly, in the latter study, replacement of PVAT with subcutaneous fat from mice fed a chow diet reduced neointima formation, whereas transplanted subcutaneous fat from high fat fed mice was without effect, which further suggests a link between high fat diet and regulation of vascular disease by PVAT. In contrast to these findings, transplanting visceral fat to the murine carotid artery (which is normally devoid of PVAT) enhanced atherosclerosis, mediated in part via P-selectin glycoprotein ligand-1.[61] It must be pointed out that none of the aforementioned studies transplanted authentic PVAT, which differs phenotypically from subcutaneous and other visceral fat depots, so the results of these studies may not be directly applicable to endogenous PVAT. With regard to the effects of dietary fat on PVAT, mice fed a longer-term high fat diet demonstrated reduced macrophage infiltration into regions of brown PVAT,[29] and atherosclerosis was enhanced in mice devoid of PVAT that were housed under conditions of low temperature, most likely due to loss of the systemic metabolic effects of brown PVAT during adaptive thermogenesis.[41] These studies suggest that the inflammatory phenotype of PVAT is diverse depending on species, anatomic location, and environmental conditions, and that these differences are fundamentally important in determining a pathogenic versus protective role of PVAT in vascular disease.

Perspective: balancing pro- versus anti-inflammatory effects of PVAT

The available data, when interpreted in total, suggest that PVAT is capable of both positively and negatively regulating vascular inflammation to modulate vascular disease (Figure 2). Data in human PV adipocytes suggest that MCP-1 is likely to be an important pro-inflammatory mediator that is expressed at high levels and may contribute to vascular disease. PV adipocytes also secrete pro-inflammatory adipokines and express complement system factors and cell adhesion/matrix proteins that may facilitate inflammation. A number

of anti-inflammatory molecules likely counterbalance the pro-inflammatory state of human PV adipocytes. Data in rodent models clearly indicate that PVAT secretes anti-inflammatory factors that can favorably influence vascular pathophysiology. A number of questions remain unanswered, such as how PV adipocytes interact with inflammatory cells, and what role the nervous system might play in regulating PVAT inflammation. Further research into the mechanisms that regulate the inflammatory balance of PV adipocytes may yield new insight into, and treatment strategies for, cardiovascular disease.

Acknowledgments

Abbreviations

BAT	brown adipose tissue
FDG	2-[^{18}F]fluoro-2-deoxyglucose
PV	perivascular
PVAT	perivascular adipose tissue
SOCS2	suppressor of cytokine signaling 2
SVF	stromal vascular fraction
VSMC	vascular smooth muscle cell
WAT	white adipose tissue
Wlt1	Wilms' tumour gene 1

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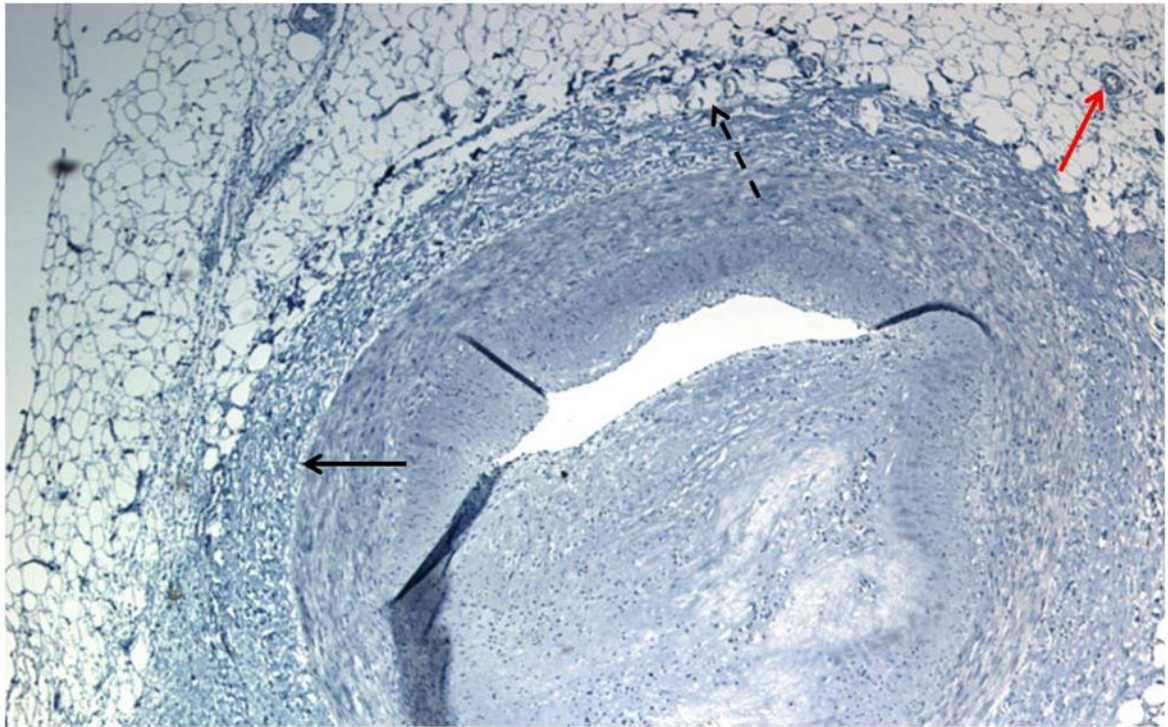
Figure 1.
Histological appearance of human perivascular adipocytes surrounding an atherosclerotic coronary artery. Artery was fixed in formalin, sectioned, and counterstained with hematoxylin. Red arrow points to a blood vessel, solid black arrow denotes location of external elastic lamina, and dashed arrow points to PV adipocytes invading the lamina adventitia lacking a separating fascia. Note that these perivascular adipocytes exhibit an appearance more consistent with unilocular white adipocytes rather than multilocular brown adipocytes.
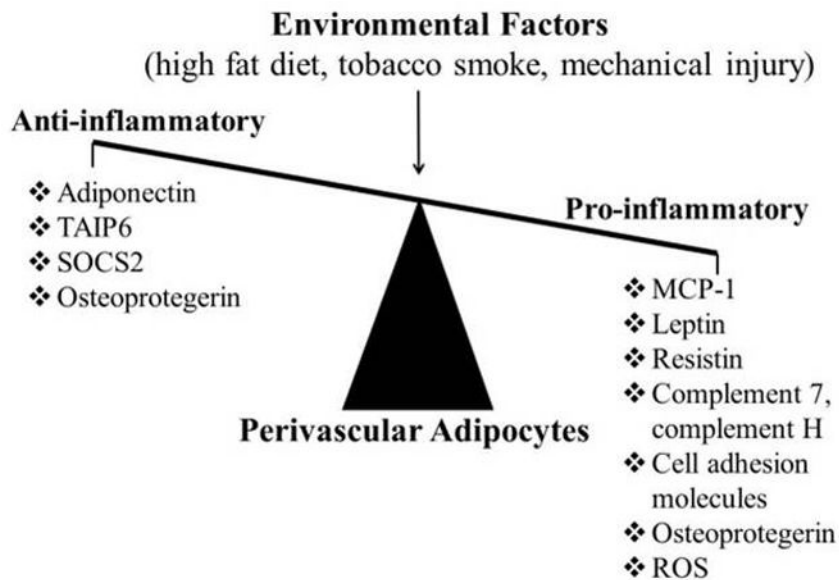
Figure 2.
Balancing pro- versus anti-inflammatory effects of PV adipocytes.
Abbreviations: TAIP6, tumor necrosis factor α-induced protein 6; SOCS2, suppressor of cytokine signaling 2; MCP-1, monocyte chemoattractive peptide-1; ROS, reactive oxygen species.