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ATVB IN FOCUS:
Adipose Tissue and Vascular and Immune Cell Cross Talk: Implications for Obesity and Vascular Disease

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Perivascular Adipose Tissue Regulates Vascular Function by Targeting Vascular Smooth Muscle Cells

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ABSTRACT: Adipose tissues are present at multiple locations in the body. Most blood vessels are surrounded with adipose tissue which is referred to as perivascular adipose tissue (PVAT). Similarly to adipose tissues at other locations, PVAT harbors many types of cells which produce and secrete adipokines and other undetermined factors which locally modulate PVAT metabolism and vascular function. Uncoupling protein-1, which is considered as a brown fat marker, is also expressed in PVAT of rodents and humans. Thus, compared with other adipose tissues in the visceral area, PVAT displays brown-like characteristics. PVAT shows a distinct function in the cardiovascular system compared with adipose tissues in other depots which are not adjacent to the vascular tree. Growing and extensive studies have demonstrated that presence of normal PVAT is required to maintain the vasculature in a functional status. However, excessive accumulation of dysfunctional PVAT leads to vascular disorders, partially through alteration of its secretome which, in turn, affects vascular smooth muscle cells and endothelial cells. In this review, we highlight the cross talk between PVAT and VSMC and its roles in vascular remodeling and blood pressure regulation.

Key Words: brown adipose tissue ■ cardiovascular diseases ■ endothelial cells ■ hypertension ■ vascular smooth muscle cells

Adipose tissue develops naturally and is required for normal physiology in mammals. It is regarded as the largest endocrine organ which produces and secretes a large number of adipokines, cytokines, and chemokines into the blood, affecting the functions of other organs from a distance.[1] Adipose tissues at different locations are distinct in morphology and composition. The visceral and omental adipose tissues are pure white adipose tissue (WAT), while the subcutaneous adipose tissue is beige adipose tissue (BeAT) with clusters of adipocytes showing similar characteristics to classical brown adipose tissue (BAT) among the white adipocytes.[2] Perivascular adipose tissue (PVAT) shows characteristics of BeAT in human[3] and BAT-like in mice.[4] However, PVAT is not always BAT in mice and humans. It depends on the anatomic location and environmental/metabolic context.[5,6] Excessive WAT accumulation is associated with cardiovascular diseases (CVD), hypertension, type 2 diabetes mellitus, cancers, and other diseases, while BeAT and BAT might be negatively associated with CVD.[7–10] The association between CVD and obesity was thought to operate through endocrine roles of adipose tissue. However, PVAT is tightly adherent to most blood vessels, including the aorta and arteries such as carotid, coronary, and mesenteric arteries. The paracrine effects of PVAT on blood vessels have not received much attention for a long time until 1991.[11] Growing data from clinical and experimental animal models indicate that PVAT is engaged in paracrine cross-talk with blood vessels and

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Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ACTA2	α-smooth muscle actin
AMPK	AMP-activated protein kinase
Ang II	angiotensin II
ANP	atrial natriuretic peptide
Anxa1	annexin A1
AT1R	type 1 angiotensin II receptor
BAT	brown adipose tissue
BeAT	beige adipose tissue
bFGF	basic fibroblast growth factor
BKCa	large-conductance $Ca2^{+}$-activated K^{+}
BMP	bone morphogenetic proteins
BP	blood pressure
CBS	cystathionine β-synthase
CGRP	calcitonin gene-related peptide
CSE	cystathionine γ-lyase
CTRP9	C1q/TNF-related protein 9
CVD	cardiovascular diseases
EC	endothelial cells
EFS	electrical field stimulation
ERK	extracellular signal-regulated kinase
EV	extracellular vesicles
FGF21	fibroblast growth factor 21
H2S	hydrogen sulfide
HFD	high-fat diet
HGF	hepatocyte growth factor
ILGFBP-3	insulin-like growth factor-binding protein-3
MAO-A/B	monoamine oxidase A/B
MCP-1	monocyte chemotactic protein-1
MMP-2/9	matrix metallopeptidases
MSCs	mesenchymal stem cells
mTOR	mammalian target of rapamycin
Myf5^{+}	myogenic factor 5
NCC	neural crest cells
NMN	nicotinamide mononucleotide
NO	nitric oxide
NOS	nitric oxide synthase
OPN	osteopontin
p38 MAPK	p38 mitogen-activated protein kinases
PDGF-BB	platelet-derived growth factor-BB
PGC1	PPARγ coactivator 1
PGE2	prostaglandin E2
PGI2	prostacyclin
PLGF	placental growth factor
PPARγ	peroxisome proliferator-activated receptor-γ
PRDM16	PR domain containing 16
PVAT	perivascular adipose tissue
PVCF	PVAT-derived contracting factors
PVRF	PVAT-derived relaxing factors
RFP	red fluorescent protein
ROS	reactive oxygen species
SM22α	smooth muscle protein 22-α
SOD	superoxide dismutase
SSAO	semicarbazide-sensitive amine oxidase
Tgfbr2	transforming growth factor β receptor 2
TGFβ	transforming growth factor-β
UCP-1	uncoupling protein-1
VEGF	vascular endothelial growth factor
VEGF-R	VEGF-receptor
VSMC	vascular smooth muscle cells
WAT	white adipose tissue
Wnt1	wingless-type MMTV integration site family, member 1

Highlights

- Perivascular adipose tissue (PVAT) is a unique adipose tissue and is involved in all the aspects of vascular physiology and pathophysiology.
- Existence of PVAT is critical to maintenance of the vasculature in a normal functional status, partially through paracrine factors. Dysfunctional PVAT secretes disease-promoting factors which cause abnormal changes towards various pathologies in the underlying layers of the blood vessels.
- Reversing the white features of PVAT to brown characteristics or maintaining PVAT beige features might be a crucial strategy to maintain a healthy vasculature.
- PVAT secretes both PVCF (PVAT-derived contracting factors) and PVDF (PVAT-derived relaxing factors), which precisely and concurrently control the blood vessel tone together with the systemic neurohumoral fluid system.
- Extensive and deeper research on the paracrine signaling from PVAT and its cross talk with the underlying vascular cells, including endothelial cells, vascular smooth muscle cells, and fibroblasts under physiological and pathological conditions, is urgently needed.

is involved in the physiological homeostasis and pathological changes of the cardiovascular system.[12–15] Other reviews in this series discuss the cross talk between PVAT and other vascular cells, such as endothelial cells (ECs) and immune cells. This review specifically discusses the cross talk between PVAT and vascular smooth muscle cells (VSMCs) and its roles in vascular remodeling and blood pressure (BP) regulation.

DEVELOPMENTAL ORIGINS OF PVAT ADIPOCYTES

UCP-1 and PPARγ Are Key Molecules of PVAT Adipocytes

The precise process and mechanisms of PVAT development remain unclear. The discovery of unique cell markers provided powerful tools to study the development of adipose tissues, including PVAT. Thoracic PVAT harbors have 2 types of adipose progenitor cells: $CD105^+/CD73^+/CD45^-/CD140A^+/CD31^-$ and $CD105^-/CD73^+/CD45^-/CD44^+/CD90^+/CD29^+/CD34^-$, both able to differentiate into UCP-1 (uncoupling protein-1, brown adipocyte marker) positive adipocytes in vitro.[16,17] PPARγ (peroxisome proliferator-activated receptor-γ) is a key transcription factor for differentiation of all types of adipocytes. Disruption of PPARγ expression in adipocyte precursors will block maturation of adipose tissues. Consistently, PPARγ deletion in adipocytes results in lipodystrophy in mice.[18]

Adipocytes Might Originate From Precursors in Neighboring Tissues

Adipocytes from different locations may have distinct precursors. Albeit limited, experimental evidence documented that adipocytes share the same precursors with neighboring organs. For example, brown adipocytes in the interscapular area may share common progenitors with myoblasts which can be differentiated into either brown adipocytes or skeletal muscle fibroblasts.[19] PRDM16 (PR domain containing 16) contributes to adipogenesis as a coregulator of PPARγ. Compared with WAT in other depots, PRDM16 is highly expressed in subcutaneous WAT and BAT. Overexpression of PRDM16 in precursors of myoblasts resulted in a switch of differentiation to brown adipocyte lineage.[19]

PVAT Adipocytes and VSMC Share Common Progenitors

In a similar fashion that brown adipocytes in BAT and myoblasts share common progenitors, adipocytes in PVAT may share common progenitors with VSMC in the artery. Primary VSMC with overexpression of PRDM16 cultured in adipocyte differentiation cocktails had increased accumulation of lipid droplets and expression of thermogenic marker genes, suggesting a trans-differentiation to thermogenic adipocytes.[20] Additionally, SM22α (smooth muscle protein 22 α) is first expressed within the dorsal aorta at embryonic day 9.5 and continues to be expressed in VSMC into adulthood.[21] We generated a smooth muscle-specific Cre mouse by knocking in the Cre into the SM22α promoter and deleted floxed PPARγ in VSMC.[22] We found that PVAT was completely missing throughout the thoracic and abdominal aorta and the mesenteric artery. However, the adipose tissues in other locations were not affected.[4] Together with a recent study that showed that PVAT in mouse starts to develop after birth,[23] this phenotype suggests that PVAT adipocytes potentially share the same $SM22\alpha^+$ precursors with VSMC.

Neural Crest Cells and Mesenchymal Stem Cells Are Other Sources of PVAT Adipocytes

A more precise and recent study identified that adipocytes in PVAT from the aortic arch area belong to distinct populations. Lineage tracing indicated that adipocytes in the anterior PVAT are primarily derived from $SM22\alpha^+$ progenitors, whereas lateral PVAT contains both $SM22\alpha^+$ and $Myf5^+$ (myogenic factor 5) cells.[23] An additional study found that a subset of adipocytes in the PVAT at the aortic arch area originates from neural crest cells (NCC). The NCC-derived stromal vascular fraction can be differentiated into both brown and white adipocytes.[24] These studies demonstrated that PVAT adipocytes originate from $SM22\alpha^+$ progenitors and NCC. On the other side, PVAT harbors multipotent mesenchymal stem cells (MSC). Single-cell RNA sequencing revealed that stromal cells in thoracic PVAT express genes related to vasculature development.[25] Furthermore, MSC in PVAT could differentiate to the VSMC lineage.[26]

In summary, these studies demonstrated that VSMC, perivascular MSCs, and PVAT adipocytes share common precursors. Although the literature discussed above show the contributions of various lineages to PVAT and to VSMC, there are several interesting questions that are still left unaddressed. For example, it is unknown whether PVAT from different lineages behaves any differently from one another; it is unknown whether the plasticity of PVAT lineages is involved in development of CVD such as atherosclerosis, hypertension, aortic aneurysm, etc. It was reported that adipose lineage cells in general, participate in formation of the blood vessels and enhance neovascularization in ischemic muscle in mice.[27] It is likely that the progenitors in PVAT could be differentiated into VSMC which may contribute to vascular remodeling, as described below.

CONTRIBUTIONS OF SIGNALING FROM PVAT TO VSMC AND VASCULAR REMODELING

Neointima formation is one of the major features of vascular remodeling, especially under vascular injury conditions such as atherosclerosis or mechanical damage. As described below, the adipocytes, stem cells, immune cells, and other components in PVAT, such as extracellular vesicles (EV), can produce and secrete PVAT-derived factors such as adipokines, cytokines and growth factors which regulate vascular remodeling.[28]

Perivascular Cells and Vascular Remodeling

The origins of cells in the neointima remains unclear. It was reported that MSC from bone marrow contribute to neointima formation.[29–35] Other literature points to contributions of local VSMC to neointima formation. Injurious stimuli may change VSMC from a contractile to a synthetic phenotype, which results in migration and proliferation.[36–42] Recently, the contribution of resident progenitors from the adventitia or PVAT to neointima formation has also been explored. Those progenitors could migrate to the injury site where they differentiate towards vascular lineages. A study using a vein graft model in the mouse carotid artery demonstrated this possibility. Transplantation of RFP (red fluorescent protein)-labeled progenitors isolated from PVAT into the adventitial side of the vein graft significantly increased neointima formation in the graft. Interestingly, the RFP signal was found in the neointima area, and the RFP-positive cells in the neointima expressed the VSMC marker ACTA2 (α-smooth muscle actin), indicating that progenitors in PVAT contributed to neointima formation.[43]

The characteristics of the progenitors in PVAT change during the aging process. Matrigel implants with embedded periaortic stem cells from young mice placed in the perivascular area of carotid arteries after ligation injury showed that those cells differentiated into EC or myofibroblasts in the neointima. These cells also differentiated into brown-like adipocytes in the perivascular region. Importantly, coculture of VSMC with brown adipocytes differentiated from periaortic stem cells from young mice significantly inhibited VSMC proliferation. In contrast, brown adipocytes differentiated from periaortic stem cells of old mice promoted VSMC proliferation. These results suggest that periaortic stem cells from young mice differentiate into brown-like adipocytes and inhibit neointima formation, while aged stem cells lose this capability and promote neointima hyperplasia in the injured artery.[25]

Additionally, as described above, periaortic PVAT may differentiate from NCC which highly express Wnt1 (wingless-type MMTV integration site family, member 1). Knockout of PPARγ mediated by Wnt1-Cre resulted in delay and dysplasia of PVAT development. Infusion of Ang II (angiotensin II) to these mice did not significantly change the systolic BP when compared with that of wild-type mice. However, Ang II infusion markedly aggravated media thickness and collagen accumulation in common carotid arteries but not the aortic arch.[24]

Thus, in addition to MSC from bone marrow, local VSMC and progenitors from the adventitia, resident progenitors from the PVAT contribute to neointima formation during vascular remodeling. Mechanistically, TGF-β (transforming growth factor-β) signaling promotes differentiation of PVAT resident progenitors into VSMC since they express Tgfbr2 (transforming growth factor β receptor 2) and Anxa1 (annexin A1). Treatment of PVAT-derived progenitors with TGFβ promoted differentiation towards VSMC.[43] The characteristics of those progenitors in PVAT and other signaling pathways which contribute to vascular remodeling remain unexplored. Additionally, the mechanisms underlying the enhanced Ang II-induced vascular remodeling in mice lacking PVAT in the aortic arch region due to deletion of PPARγ in NCC remain unknown. Additionally, the contributions of PVAT to vascular remodeling in disease conditions could be mediated by increased macrophages and T-lymphocytes infiltrating into a proinflammatory PVAT, which is reviewed independently in this series.

EV in PVAT and Vascular Remodeling

Most cell types in the cardiovascular system including EC, VSMC, macrophage, and cardiomyocytes produce and release EV into the extracellular space. EV enclose biological contents derived from the original cells and can be classified into exosomes (ranging from 30 to 100 nm), microvesicles/microparticles (ranging from 200 nm to 1 μm), and apoptotic bodies (ranging from 1 to 4 μm) according to their biogenesis and sizes. Exosomes are formed within the endosomal network and released by fusion with the plasma membrane. Microvesicles/microparticles are directly shed from the plasma membrane. Apoptotic bodies are released as blebs from cells undergoing apoptosis. EV are crucial regulators of vascular homeostasis by transferring biological messages including mRNAs, proteins, and noncoding RNAs to neighboring cells as cargo.[44,45] For example, EC and VSMC can communicate through the release of EV, and laminar shear stress on EC induce production of EV containing miR-143/145, which inhibits proliferation and migration of VSMC.[46–48]

PVAT also secretes EV which may convey paracrine signaling from PVAT to VSMC through microRNAs in EV. Obese mice secrete abundant EV containing microRNAs, which evoke inflammatory responses in PVAT and VSMC phenotypic switch from a contractile to a synthetic phenotype in aorta. VSMC can uptake EV secreted from PVAT and the encapsulated microRNAs, such as miR-221-3p, promote VSMC proliferation and migration.[49] It is unclear which types of cells in PVAT generate EV. Mesenchymal stem cells in adipose tissue generate EV which were found to exert effects on angiogenesis, cell survival and apoptosis, inflammation, tissue regeneration, and reduction of disease pathology.[50] Further studies are needed to examine the origins, characteristics, and function of EV in PVAT and their potential as mediators of cross talk with VSMC and EC.

PVAT-Derived Adipokines and Vascular Remodeling

PVAT-derived mediators such as adipokines, cytokines, reactive oxygen species (ROS), and gaseous compounds

might contribute to vascular remodeling. We focus on PVAT-derived adipokines and their roles in vascular remodeling in this review.

Adiponectin is one of the most abundant adipokines normally produced and released by PVAT under physiological or pathophysiological conditions.[51] Neointima formation upon intravascular injury was markedly enhanced when PVAT was removed. Interestingly, neointima formation was markedly reduced by local perivascular delivery of recombinant adiponectin or transplantation of subcutaneous adipose tissue to the artery injury area.[52] Accordingly, neointima after injury was increased in adiponectin-deficient mice and the conditioned medium from subcutaneous fat attenuated VSMC proliferation in response to PDGF-BB (platelet-derived growth factor-BB).[52]

Leptin is another abundant adipokine in adipose tissues, including PVAT. Recombinant leptin or conditioned medium from visceral adipose tissue stimulated VSMC proliferation in vitro.[53] Hydrosoluble protein growth factor(s) with a molecular mass >100 kDa released from PVAT adipocytes stimulated VSMC proliferation, which is enhanced in leptin receptor-deficient obese Zucker rats.[54] These studies suggested that PVAT-derived leptin influences VSMC and is involved in neointima formation. Indeed, overexpression of leptin in PVAT enhanced cell proliferation and neointima formation in wild-type mice but not in leptin receptor-deficient mice.[53] Neointima formation was also enhanced by transplantation of visceral adipose tissue from obese wild-type mice on a high-fat diet (HFD) to the carotid artery of immune-deficient mice. Interestingly, transplantation of visceral adipose tissue from ob/ob mice could not increase neointima formation, highlighting the importance of PVAT-derived leptin on vascular remodeling.[53]

It has been well established that obesity is positively correlated with vascular dysfunction, partially due to inflammation and oxidative stress in adipose tissues.[55] However, PVAT mass is markedly increased under the obese condition. Incubation of VSMC with conditioned medium from PVAT of obese rats promoted VSMC phenotypic switch,[56] which was defined as any change in the normal function or structure of the differentiated VSMC.[57] PVAT-derived adipokines might contribute to the VSMC phenotypic switch. Obesity is associated with increased leptin expression in visceral adipose tissue as well as in PVAT.[53] Pretreatment with a leptin receptor antagonist inhibited obese PVAT-induced VSMC phenotypic switch.[56] Mechanistically, p38 MAPK (p38 mitogen-activated protein kinases) signaling pathway is involved in VSMC phenotypic switch induced by obese PVAT. Leptin receptor antagonist upregulated p38 MAPK phosphorylation which was associated with inhibition of VSMC phenotypic switch.[56]

The roles of the cAMP/ERK (extracellular signal-regulated kinase)/p38 MAPK signaling pathway on PVAT-mediated VSMC proliferation was further evidenced by studies of visfatin, an adipokine preferentially expressed in PVAT, compared with subcutaneous and visceral adipose tissues. Visfatin could act as a nicotinamide phosphoribosyltransferase and biosynthesize NMN (nicotinamide mononucleotide) which mediated a proliferative response in VSMC via ERK and p38 MAPK signaling pathways.[58]

ERK signaling also contributes to VSMC phenotypic switch mediated by the adipokine CTRP9 (C1q/TNF-related protein 9), which is secreted by adipose tissue. CTRP9 functions as an adipokine that reduces serum glucose levels and is down-regulated in obese mice.[59] Interestingly, CTRP9 enhanced VSMC differentiation mediated by hypoxia.[60] Systemic delivery of an adenoviral vector expressing CTRP9 or CTRP9 recombinant protein significantly reduced neointima formation.[61] CTRP9 could attenuate VSMC proliferation induced by PDGF-BB which was associated with an increase in cAMP levels and a decrease of ERK phosphorylation in VSMCs,[61] suggesting that PVAT-derived CTRP9 might inhibit neointima formation via the cAMP-ERK signaling pathway. However, direct evidence is still needed. CTRP9 also significantly restrained VSMC proliferation through suppression of the TGF-β1/ERK1/2 pathway and promoted apoptosis in response to hypoxia,[62] suggesting that the TGF-β1/ERK pathway in VSMC inhibits proliferative signals from PVAT. Additionally, CTRP9 treatment significantly blocked the migratory potential of VSMC by decreasing the expression of the MMP-2/9 (matrix metallopeptidases). PVAT inflammatory responses significantly increased expression of activated MMP-2 in PVAT which leads to increased TGF-β1 in VSMCs. This, in turn, results in VSMC proliferation.[62]

PVAT-derived resistin might mediate OPN (osteopontin) expression since a resistin-neutralizing antibody could attenuate obese PVAT-induced OPN expression.[63] Alternatively, physiological levels of resistin could induce a shift of VSMC proliferation to apoptosis when VSMC are cocultured with macrophages.[64] Since resistin in PVAT is mostly colocalized with macrophages, questions arise on the cellular source of local resistin in PVAT and the relative contribution of local and systemic resistin to vascular remodeling. Additionally, homocysteine is a known independent risk factor for CVD. Homocysteine can induce VSMC migration through adipocyte-derived resistin,[65] which was associated with increased PKCε-dependent expression of MMP.[66] Intimal hyperplasia and VSMC dysfunction associated with resistin were also related to PKCε- dependent Nox activation and ROS generation.[67] Coculture with PVAT from obese mice significantly increased OPN expression via the AP-1 signaling pathway in VSMC.

There are more adipokines secreted from PVAT than those discussed above.[68] However, their role in VSMC growth and physiology and the underlying mechanisms

remain to be systematically investigated. Adipokines such as leptin and chemerin also mediate formation of blood vessels through stimulating EC proliferation and migration, which is discussed in another review in this series. Furthermore, inflammatory signals from PVAT regulate the functions of cells in the vascular wall including VSMC, which is specifically discussed in another review in this series.

PVAT-Derived Growth Factors and Vascular Remodeling

Growth factors, including thrombospondin-1, serpin-E1, TGF-β, PDGF-BB, VEGF (vascular endothelial growth factor), bFGF (basic fibroblast growth factor), PLGF (placental growth factor), HGF (hepatocyte growth factor), and ILGFBP-3 (insulin-like growth factor-binding protein-3), have well-known effects in stimulation of VSMC proliferation and migration and have been previously reviewed.[69–71] PVAT adipocytes express and secrete high amounts of all those growth factors.[72,73] The significance of PVAT-derived growth factors on vascular remodeling is highlighted by a study on VEGF from PVAT of patients with type 2 diabetes mellitus. Conditioned medium from PVAT adipocytes significantly increased expression of VEGF-R (VEGF-receptor) 1 and 2 and VEGF secretion from VSMC, which further induced VSMC proliferation.[74] Further studies are needed to investigate the effects of growth factors from PVAT on VSMC survival and growth.

In summary, these studies have demonstrated that PVAT-derived factors or multiple types of cells in PVAT are actively involved in adjacent vascular remodeling under disease conditions (Figure 1). This cross talk is critical to normal vascular function as well. However, PVAT produces and secretes a multitude of factors including adipokines, cytokines, growth factors, and other factors yet undetermined. The types and mechanisms of these PVAT-derived factors on vascular remodeling remain to be further investigated. Follow-up extensive studies will be needed to further understand the contribution of PVAT to vascular remodeling and elucidate the underlying mechanisms.

PVAT REGULATES VASCULAR TONE BY TARGETING VSMC

PVAT-derived bioactive factors not only contribute to vascular remodeling but are also involved in vascular homeostasis by modulating vascular tone. Next, we summarize the recent progress regarding PVAT-derived factors on vascular tone regulation.

Using in vitro organ bath or wire myograph techniques, the vasoactivities of blood vessel rings from thoracic aorta, abdominal aorta, mesenteric, carotid or coronary arteries with or without PVAT (or by incubation of vessel rings with a conditioned buffer from an intact piece of PVAT or with PVAT extracts) was studied. The presence of PVAT on the vessel rings markedly attenuated

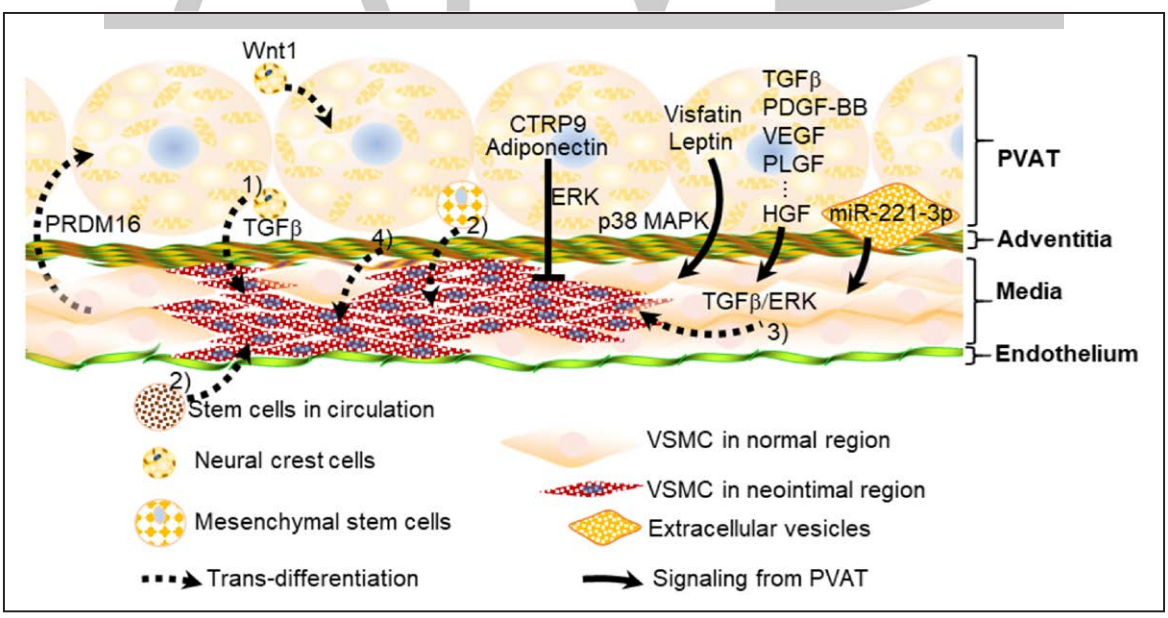

Figure 1. Cross talk between perivascular adipose tissue (PVAT) and vascular smooth muscle cells (VSMC) in vascular remodeling.

Smooth muscle-like cells in the neointimal area of the vascular wall originate from 4 sources: (1) Wnt1 (wingless-type MMTV integration site family, member 1) positive progenitors in PVAT; (2) PVAT-resident or bone marrow-derived mesenchymal stem cells; (3) local VSMC stimulated by signaling from PVAT adipocytes and mediated by adipokines, growth factors, and extracellular vesicles; and (4) adventitia-derived cells. Additionally, Wnt1-positive progenitors in PVAT and VSMC in the vascular wall can be differentiated into brown-like adipocytes in PVAT. CTRP9 indicates C1q/TNF-related protein 9; ERK, extracellular signal-regulated kinase; PLGF, placental growth factor; PRDM16, PR domain containing 16; TGF-β, transforming growth factor β; and VEGF, vascular endothelial growth factor.

the contractile response to norepinephrine (referred to as anticontractile effect).[11] PVAT's anticontractile effects were observed as well in response to stimulation with phenylephrine, 5-HT (serotonin) or Ang II. The anticontractile property of PVAT was further confirmed by incubation of PVAT-free vessel rings with a PVAT-conditioned solution prepared in vitro, which produced a significant relaxation response.[75,76]

Anticontractile effects of PVAT might be mediated by uptake and metabolism of the vasoactive amines such as dopamine, norepinephrine, and serotonin in PVAT itself.[77] PVAT adipocytes have MAO-A/B (monoamine oxidase A/B) and SSAO (semicarbazide-sensitive amine oxidase) which catalyze the metabolism of amines in PVAT.[77] MAO-A/B catalyzes the oxidative deamination of amines,[78] and SSAO is a multifunctional enzyme that promotes the generation of H_2O_2 and NH_3.[79] Indeed, inhibition of MAO and SSAO, or inhibition of NET (norepinephrine transporter) with nisoxetine increased vasocontraction induced by norepinephrine on vessel rings with PVAT.[77] Additionally, the PVAT's anticontractile effects are mediated by PVRF (PVAT-derived relaxing factors). Recent studies also demonstrated that PVAT secretes PVCF (PVAT-derived contracting factors), which induce blood vessel contraction.[4,80–82] PVRF and PVCF influence local vascular tone through endothelium-dependent or endothelium-independent effects.[83,84]

PVRF Regulate Anticontractile Effects Through NO Production by the Endothelium

The anticontractile effect of PVAT was lost in endothelium-denuded rings,[85] suggesting that intact-endothelium is required to induce relaxation of vessel rings. Endothelium-derived NO (nitric oxide), one of the most potent vascular dilators, stimulates guanylate cyclase in VSMCs, resulting in increase of cyclic GMP and activation of signaling cascades to induce blood vessel relaxation. PVAT expresses eNOS and produces NO.[83] The anticontractile effects of PVAT on blood vessels might be mediated by PVAT-derived NO, since NOS (nitric oxide synthase) inhibition with Nω-nitro-L-arginine methyl ester enhanced the phenylephrine-induced contraction in endothelial-denuded rings with PVAT,[83] indicating that NO might be one of the PVRF. Ang-(1–7) and leptin are PVRF which mediate anticontractile effects in an endothelium-dependent manner since this effect was prevented by inhibition of NOS or NO scavenger.[85,86] The details of endothelium-dependent anticontractile effects of PVAT are discussed in another review in this series.

PVRF Regulate Anticontractile Effects Through Modulation of VSMC Function

Inhibition of NOS attenuated the anticontractile effects of PVAT in PVAT-intact vessel rings.[83,84,87,88] Therefore, it is possible that PVRF, such as NO, directly target VSMC to induce vessel relaxation. Indeed, numerous studies documented that PVAT controls vascular tone through potassium channels in VSMC. Blockage of Ca^{2+}-activated potassium channels by tetraethylammonium chloride, or inhibition of ATP-dependent potassium channels by glibenclamide, or Kv7 (KCNQ) voltage-dependent potassium channels by XE991 in VSMC markedly reduced the anticontractile effects of PVAT.[89–92]

H_2S (hydrogen sulfide) gas is a vasodilator.[93,94] Interestingly, expression of cystathionine β-synthase and cystathionine-γ-lyase, the enzymes required for H_2S endogenous production in PVAT[95] suggests that H_2S is a PVRF. Pretreatment with propargylglycine, an inhibitor of H_2S production, significantly increased the noradrenaline-induced contraction of vessel rings with PVAT.[93,96] ATP-sensitive K^+ channels in VSMC might mediate the anticontractile effects of PVAT-derived H_2S.[93,97,98] Ang-(1–7) might act as a hyperpolarizing factor through K (Ca) channels as well to cause relaxation of the blood vessel.[86]

However, these results are based on pharmacological evidence in vitro. The specificity of these drugs in vivo is uncertain. Studies using K^+ channel knockout mice suggest more complicated mechanisms behind the roles of K^+ channels in PVAT's anticontractile effects. $Kcna5^{-/-}$ arteries and wild-type arteries incubated with neomenthyl diphenylphosphine oxide, an inhibitor of the Kv1.5 potassium channel, showed normal vasoconstriction in response to phenylephrine in the presence and absence of PVAT. KV current density and response to inhibition by XE991, a KCNQ channel blocker, were normal in mesenteric artery VSMC isolated from $Kcna5^{-/-}$ mice.[91] Additionally, the anticontractile effects of PVAT in $Kcnq1^{-/-}$ mesenteric arteries were comparable to those in wild-type mice. The anticontractile effects of PVAT were not affected by KV 7.1 channel blockers such as chromanol 293B and HMR1556. VSMCs isolated from $Kcnq1^{-/-}$ mice exhibited normal peak KV currents. The KV 7.2-5 channel opener retigabine caused similar relaxation in $Kcnq1^{-/-}$ and wild-type vessels as well. Therefore, KV 7.1 channels were apparently not involved in the control of arterial tone by PVAT.[99]

It is possible that only part of them mediate PVAT's anticontractile effects. At least 5 classes of K^+ channels including BKCa (large-conductance Ca^{2+}-activated K^+) channels, KCa3.1(intermediate-conductance Ca^{2+}-activated K^+) channels, KV (multiple isoforms of voltage-gated K^+) channels, KATP channels, KIR (inward-rectifier K^+) channels, and K2P (members of the 2-pore K^+) channels are expressed in VSMC.[100] Only inhibition of BKCa channel or knockout BKCa blocked PVAT-induced anticontractile effects.[101] Additionally, PVAT from different locations (ie, thoracic aorta, abdominal aorta, or mesenteric artery) might mediate anticontractile effects via distinct K^+ channels.

Whether other mechanisms contribute to PVAT's anticontractile effects needs to be further investigated. Thus, for instance, it is unclear whether PVAT-derived adipokines mediate PVAT's anticontractile effects through modulation of VSMC function. PVAT-conditioned solution transfer studies documented that PKG (cGMP-dependent protein kinase) was necessary for PVAT's paracrine effects on smooth muscle and endothelium of blood vessels. The anticontractile effect of PVAT was not present in arterial rings isolated from $PKG^{-/-}$ mice or arterial rings isolated from wild-type mice with inhibition of PKG signaling. Activation of PKG by ANP (atrial natriuretic peptide) rescued the loss of PVAT's anticontractile effects on wild-type vessel rings, but not on $PKG^{-/-}$ vessel rings upon hypoxia stimulation. Interestingly, adiponectin expression in PVAT adipocytes was reduced in $PKG^{-/-}$ mice, and ANP could not restore the reduced anticontractile capacity of PVAT from $adiponectin^{-/-}$ mice. These data suggest that PVAT-derived adiponectin modulates vascular tone via PKG signaling in VSMC.[102]

PVCF Induces Contractile Effects

Apart from anticontractile effects, PVAT also induces contractile effects on VSMC. Perivascular nerve activation by EFS (electrical field stimulation) elicited a frequency-dependent contractile response in mesenteric artery rings both in the presence and absence of PVAT, but the amplitude of contraction was higher in arterial rings with PVAT than in those without PVAT,[103] suggesting that PVAT can release vasoconstrictors. Interestingly, Ang II treatment of mesenteric artery rings enhanced EFS-induced contraction, while arterial rings with intact PVAT treated with ACE (angiotensin-converting enzyme) inhibitor or AT1R (type 1 angiotensin II receptor) blockers showed reduced vessel contraction induced by EFS.[104]

PVAT's contractile effects were further evidenced by incubation of PVAT-null vessel rings with extracts or conditioned buffer of PVAT. We found that incubation of vessel rings of aorta, mesenteric, or carotid artery from mice lacking PVAT with extracts of thoracic or mesenteric PVAT, which were obtained by mincing PVAT into small pieces or homogenizing PVAT, markedly constricted the vessel rings.[4] Pretreatment of the blood vessel rings with AT1R blockers significantly attenuated contraction of the vessel rings induced by PVAT extracts,[80] demonstrating that PVAT-derived Ang II contributed to the contractile effects of PVAT. Additionally, the conditioned buffer of coronary PVAT increased the baseline tension of coronary arteries, and this effect was dependent on the amount of PVAT added to the bath.[81] The increase in the basal tone of the coronary artery was markedly augmented by the conditioned buffer from PVAT of obese swine compared with lean swine. Additional proof-of-principle studies demonstrated that PVAT-derived calpastatin constricts arterial rings via the Rho-kinase pathway and an increase in VSMC Ca^{2+} handling via $Ca_v1.2$ channels and H_2O_2-sensitive K^+ channels.[81]

PVAT can release neurotransmitters to constrict blood vessels as well.[82] PVAT surrounding the rat thoracic aorta contains significant amounts of 5-HT. Fenfluramine increased the secretion of 5-HT and norepinephrine from PVAT. Consistently, the contraction of thoracic aortic rings with PVAT in response to fenfluramine was higher than rings without PVAT. This effect was diminished by prazosin (an α-adrenergic receptor antagonist) or nisoxetine (a NET inhibitor).[82] This phenotype was also observed in PVAT from the renal artery. The maximum contraction to the sympathomimetic tyramine was higher in the renal artery with PVAT versus without PVAT, and this effect was also reduced by prazosin and nisoxetine.[105]

In addition to 5-HT, the adipokine chemerin and its receptor ChemR23 colocalize with tyrosine hydroxylase, a sympathetic nerve marker, in mesenteric PVAT. Treatment of the vessel rings with intact PVAT with CCX832, an antagonist of ChemR23, or with prazosin blocked chemerin-9 or EFS-induced vessel ring contraction.[106,107]

These studies demonstrate that calpastatin, Ang II, 5-HT, chemerin, and norepinephrine locally produced in PVAT are potent PVCF which stimulate blood vessel constriction, most likely through their respective receptors on VSMC.

Potential Mechanisms Underlying PVAT-Induced VSMC Contractility

PVAT's contractile effects might be regulated by oxidases including nicotinamide adenine dinucleotide phosphate oxidase, SOD (superoxide dismutase), and catalase. PVAT expresses the p67phox subunit of the nicotinamide adenine dinucleotide phosphate oxidase, Mn-SOD (superoxide dismutase), and CuZn-SOD.[84,103] Stimulation of PVAT with norepinephrine increased Mn-SOD expression, decreased catalase expression, and induced O_2^- generation in PVAT.[108] Thus, it was hypothesized that mitochondria-derived ROS in PVAT modulates vascular reactivity.[108] Uncoupling mitochondria, as well as removal of H_2O_2, increased the contraction in vessel rings with PVAT present in response to norepinephrine.[108] EFS increased O_2^- generation in isolated PVAT, and this effect was attenuated by NAD(P)H oxidase inhibition. Treatment with NAD(P)H oxidase inhibitors (apocynin and DPI) further attenuated the contraction in response to EFS in the vessel rings with PVAT than in those without PVAT, while exogenous O_2^- augmented the contractile response to EFS and to phenylephrine in vessel rings without PVAT.[103] Therefore, PVCF mediated ROS generation in PVAT acts as a pivotal signaling molecule regulating VSMC contraction.

Bioactive Factors in PVAT can act as Either PVRF or PVCF

EFS elicits an anticontractile effect on mesenteric arteries with PVAT in an endothelium-independent manner.[109,110] Furthermore, sympathetic stimulation in PVAT triggers the release of adiponectin via β3-adrenoceptor activation.[110] PVAT also acts as a reservoir for noradrenaline, preventing it from reaching the vessel and causing contraction.[110] Additionally, perivascular sympathetic-sensory interactions have been shown to regulate CGRP (calcitonin gene-related peptide)-mediated vasodilation in rats via the release of methyl palmitate.[109] Therefore, in addition to the data discussed above showing that EFS induces VSMC contraction via ROS, stimulation of perivascular sympathetic nerves results in secretion of both PVCF and PVRF.

Actually, the same factor in PVAT can act as either PVRF or PVCF. PVAT-derived H_2S acted as an anticontractile factor in normotensive Wistar rats. However, in spontaneously hypertensive rat, the H_2S in PVAT acted as a procontractile factor which was associated with the stimulation of perivascular nerves.[96] The procontractile effect of H_2S in the arterial wall could represent a pathological feature. Similar to H_2S, PVAT-derived prostanoids such as PGE2 (prostaglandin E2) and PGI2 (prostacyclin) were responsible for anticontractile effects of the normal PVAT.[84,89,103,111] On the other side, PVAT-secreted thromboxane TXB2, PGE2, and PGF2α were responsible for the impairment of PVAT's anticontractile effects upon HFD feeding.[112] Therefore, H_2S and prostanoids in PVAT have anticontractile effects under normal conditions, while they induce contractile effects under disease conditions, likely reflecting pathological changes in the target cells. Further studies are needed to distinguish the contributions of the cellular targets, VSMC, and EC, on the contractile/anticontractile effects of these PVAT-secreted bioactive factors.

In summary, the experimental data discussed demonstrate that PVAT produces PVRF such as H_2S, Ang (1–7) and methyl palmitate, which could induce vasodilation by opening K^+ channels on VSMC. PVAT also releases PVCF such as calpastatin, Ang II, 5-HT, chemerin and norepinephrine which could induce vasoconstriction by, in some cases, still underdetermined mechanisms, albeit most likely mediated by their receptors on VSMC. Thus, those PVAT-derived bioactive factors collectively and coordinately regulate vascular tone by targeting VSMC (Figure 2).

PVAT MODULATES VASCULAR TONE AND BP IN VIVO

VSMC are the medium layer and an essential structural component of the blood vessels. VSMC play critical physiological functional roles in the regulation of vascular tone. As described above, in vitro experimental data documented that PVAT-derived factors regulate vascular tone in part by targeting VSMC. Therefore, it was hypothesized that PVAT modulates BP under physiological and pathophysiological conditions.

BP exhibits a robust circadian rhythm, which causes a dipping phenotype of BP between light-on and light-off periods in mice. It is unclear regarding the essential and physiological significance of the circadian rhythm and dipping pattern of BP in humans. However, in

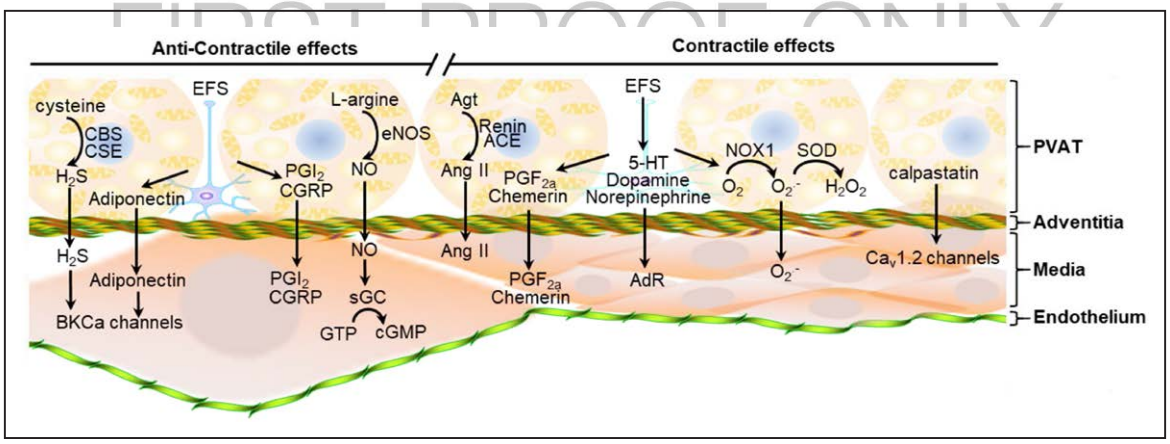

Figure 2. Perivascular adipose tissue (PVAT) regulates vascular smooth muscle cells (VSMC) dilation and contraction. PVAT regulates vascular tone through relaxing factors and contractile factors. PVAT adipocytes express CBS (cystathionine β-synthase), CSE (cystathionine γ-lyase), and eNOS (endothelial nitric oxide synthase). CBS and CSE catalyze generation of H_2S (hydrogen sulfide) from cysteine, which induces VSMC dilation by opening BKCa (calcium activated K^+-channels) on VSMC, and eNOS-dependent nitric oxide (NO) production from L-arginine which induces vasodilation mediated by the cGMP signaling pathway. Additionally, EFS (electrical field stimulation) induces PVAT adipocytes to release adiponectin, PGI2 (prostacyclin) and CGRP (calcitonin gene-related peptide) which induce vasodilation as well. On the other side, EFS induces PVAT release of 5-HT, dopamine and norepinephrine which cause VSMC contraction thorough adrenergic receptors (AdR) on VSMC. EFS also induces VSMC contraction by stimulating secretion of PGF_{2a}, chemerin and O_2^- from PVAT adipocytes. Additionally, PVAT adipocyte-derived calpastatin might induce VSMC contraction mediated by $Ca_v1.2$ channels on VSMC. Ang II indicates angiotensin II; and SOD, superoxide dismutase.

hypertension, sleep apnea, and even shift work, this balanced rhythm is perturbed.[113,114] Changes in the dipping phenotype in particular, which may manifest from dippers to extreme dippers, nondippers, and reverse dippers, have been associated with adverse outcomes.[115–117] Lack of nocturnal BP fall (nondipping) has been shown to be more closely associated with target organ damage and worsened cardiovascular outcome compared with essential hypertension in patients with dipping pattern.[118] Apart from the central circadian clock in the suprachiasmatic nucleus of the hypothalamus, a local biological clock in VSMC of the blood vessels contributes to regulation of BP circadian rhythm.[58,119,120] It was unknown if PVAT-derived factors target VSMC to regulate circadian rhythm and dipping patterns of BP.

We reported that the BP of mice lacking PVAT generated by deletion of PPARγ in VSMC was comparable with that in mice with intact PVAT during the night period (active phase in mice). However, the BP of mice lacking PVAT was markedly lower during day-time when the mice were in the resting phase, which resulted in an extreme-dipper phenotype.[4,22] This phenotype might be caused by a lack of PVAT because the development of adipose tissue in other locations such as subcutaneous, gonadal, para-renal, and interscapular was not affected.[4] Notably, another mouse model, in which PPARγ was deleted in VSMC by a transgenic SM22α Cre mouse tool, showed intact PVAT. This mouse model displayed a hypertensive phenotype.[121] A dominant negative PPARγ mutation (P467L) associated with hypertension in humans[122] showed hypertension as well in a mouse model carrying the same mutation in VSMC.[120] Therefore, the hypotensive phenotype in mice lacking PVAT was most likely caused by a lack of PVAT, rather than by deficiency of PPARγ in VSMC.

PVAT regulation of the BP dipper pattern was further documented by another mouse model with Agt (angiotensinogen) deficiency in brown adipocytes.[80] As described above, Ang II is one of the PVCF. We found that UCP1-Cre-mediated deficiency of Agt in brown adipocytes reduced Ang II levels in thoracic PVAT and decreased BP in the resting phase without affecting BP in the active period, which also caused an extreme-dipper BP.[80] However, the limitation of this mouse model is that Agt was also deleted in brown adipocytes in other locations which may affect the overall secretome from BAT. Currently, we do not have evidence that BAT-derived Ang II systemically affects BP because the plasma levels of Ang II were not reduced in brown adipocyte selective Agt deficient mice.[80] Additionally, we reported that PVAT has a peripheral clock. Knockout of Bmal1 in brown adipocytes of mice also reduced BP during the resting phase and we further documented that Bmal1 transcriptionally regulates Agt expression and Ang II generation in PVAT.[80]

Thus, while there are limitations intrinsic to each model, these results from mouse models demonstrated that paracrine effects of PVAT contribute to circadian BP regulation and may account for the yet not fully understood clinical observations associated with the dipper and nondipper phenotypes in humans. The CVD outcomes associated with the regulation of BP dipping by PVAT and the contributions of cross talk between PVAT and VSMC to this phenotype should be further investigated.

ALTERED PVAT FEATURES FROM BAT-LIKE TO WAT-LIKE CONTRIBUTES TO OBESITY-ASSOCIATED HYPERTENSION

PVAT is not only involved in BP regulation under physiological conditions but also in hypertension. The results from animal studies indicated that HFD feeding significantly increased PVAT mass,[123] which results in white-like characteristics of PVAT. Notably, the anticontractile effects of PVAT were attenuated under the obese condition.[87,124,125] The PVAT with changes in features from BAT-like to WAT-like might be associated with hypertension due to loss of PVAT's anticontractile effects. When the PVAT was removed from vascular rings, the relaxant responses to vasodilators were no different between rings isolated from obese and lean mice, suggesting that obesity did not impair the intrinsic vascular bed reactivity but rather the regulatory PVAT function.[126] Therefore, it is likely that PVAT's dysfunction is related to the development of obesity-associated hypertension. Indeed, mesenteric arterial rings incubated with aortic PVAT from rats on a HFD for 6 months demonstrated lower endothelium-dependent relaxation. This effect was absent in mesenteric arterial rings incubated with aortic PVAT from rats on a standard chow diet.[123] The impaired anticontractile effects of PVAT upon HFD feeding were not only dependent on the endothelium but also consequence of reduced NO bioavailability due to L-arginine deficiency and eNOS uncoupling in white-like PVAT.[88,127–129] Ex vivo L-arginine treatment and arginase inhibition could reverse obesity-induced vascular dysfunction.[128]

Additionally, obesity and aging cause inflammation in white-like PVAT characterized by infiltration of macrophage and dendritic cells with high expression of inflammatory adipokines and cytokines, including resistin, visfatin, leptin, MCP-1 (monocyte chemotactic protein-1), TNF-α, and IL-6,[63,125,130,131] while the mRNA levels of the anti-inflammatory mediator adiponectin are decreased in obese PVAT. Depletion of dendritic cells improved the ability of PVAT to augment acetylcholine-induced vasorelaxation and anticontractile activity.[132] On the other side, HFD reduction of the anticontractile effect of PVAT was associated with reduced adiponectin secretion and AMPK (AMP-activated protein kinase) phosphorylation.[133] Chronic adiponectin treatment normalized NO-dependent vasorelaxation by increasing eNOS phosphorylation in mesenteric arteries

of HFD-fed rats.[134] PVAT from AMPKα1 knockout mice had increased macrophage infiltration and significantly reduced adiponectin secretion.[133] Coculture of VSMCs with PVAT adipocytes from rats on an HFD reduced the AMPK phosphorylation and increased mTOR (mammalian target of rapamycin) phosphorylation.[123] Aortic Rictor is an essential mTORC2 component. HFD feeding reduced Rictor gene expression in PVAT. Increased contraction and impaired dilation were found in thoracic aortic rings with PVAT from adipocyte-specific Rictor deficient mice, and inhibition of iNOS normalized vascular reactivity in aortic rings from Rictor$^{-/-}$ mice.[135] PVAT's anticontractile effect mimicking the obese phenotype was also lost in mice deficient in eosinophils. Eosinophil reconstitution restored PVAT's anticontractile effects accompanied by increased NO bioavailability and adiponectin in PVAT.[136]

Inflammation also stimulated generation of O_2^- and H_2O_2 in PVAT from HFD-fed mice. Vessel rings with intact obese PVAT showed increased contraction to phenylephrine. Inactivation of O_2^-, dismutation of mitochondrial-derived H_2O_2, or uncoupling of oxidative phosphorylation decreased phenylephrine-induced contraction in vessels with PVAT from HFD-fed mice.[124,125] Consistently, SOD [Cu-Zn], peroxiredoxin-1 and adiponectin were reduced in obese humans compared with healthy subjects.[127] Incubation with SOD, catalase or TNF-α attenuated contractility in vessel rings presenting normal PVAT, while incubation of aortic rings containing obese PVAT with anti-TNF-α antibodies or free radical scavengers partially restored the anticontractile effect of PVAT.[87,127] Additional data from genetically modified mice further support the conclusion that inflammation and oxidative stress in PVAT altered the PVAT's anticontractile effects under obese conditions. PVAT from obese mice lacking TNF-α receptors in PVAT prevented H_2O_2 generation and vasocontraction.[124] Conversely, the anticontractile function of PVAT was impaired in mice with PVAT-specific IL-18 deficiency. This was accompanied by decreased Mn-SOD expression in deformed mitochondria in PVAT and increased PVAT whitening.[137]

Thus, brown-like PVAT could prevent inflammation and oxidative stress under physiological conditions, while white-like PVAT was accompanied by increases in inflammation and oxidative stress and decrease of NO bioavailability under obese conditions. The alteration of brown-like PVAT to white-like PVAT might be associated with the development of hypertension under obese conditions.

POTENTIAL FOR PREVENTION OF HYPERTENSION BY RESTORING BROWN-LIKE PVAT

PVAT displays heterogeneity according to species and locations. The PVAT is brown-like at areas of larger size blood vessels and is white-like at areas of the smaller size blood vessels. Compared with the same locations, the PVAT of rodents is more brown-like than that of humans. Nevertheless, there are clusters of brown-like adipocytes

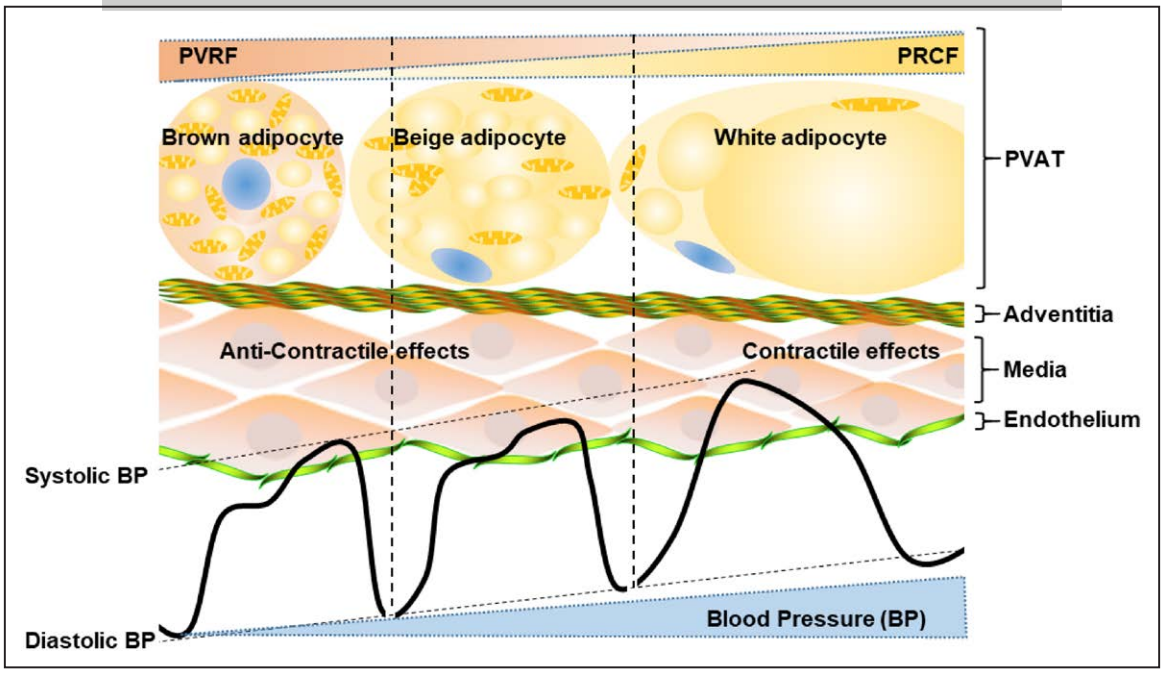

Figure 3. Strategy for hypertension prevention through perivascular adipose tissue (PVAT) browning.
Brown-like adipocytes in PVAT produce more PVAT-derived relaxing factors (PVRF), while white-like adipocytes produce more PVAT-derived contraction factors (PVCF). PVRF mediate anticontractile effects of PVAT and reduce BP (blood pressure), while PVCF account for contractile effects of PVAT and increase blood pressure. Induction or maintenance of PVAT browning by drugs, but not cold stimuli, can be an efficient strategy to prevent hypertension development.

in PVAT, or BeAT, of both rodents and humans.[138] Obesity is one of the risk factors for primary hypertension. As described above, the PVAT gradually changes into white-like characteristics during development of obesity, which is associated with alterations of PVAT paracrine profiles, including those factors involved in VSMC growth, regulation of vascular tone and BP. Conservation of PVAT's brown-like features might be a strategy to prevent development of hypertension by maintaining the homeostasis of blood vessels (Figure 3).

Multiple strategies including cold stimuli or growth factors such as FGF21 (fibroblast growth factor 21),[139] ANP (atrial natriuretic peptide),[140] and BMP (bone morphogenetic proteins)[141] are able to convert white-like WAT into BeAT through a browning process. It is hypothesized that browning is beneficial to prevent obesity and associated CVD. Therefore, restoring the normal beige features of human PVAT might reverse or prevent development of vascular disorders.[142] It is unknown whether the whitening-like process of PVAT under obese conditions results in elevation of BP. However, it is reasonable to hypothesize that restoring PVAT to brown-like characteristics could be a potential strategy for hypertension treatment.

Even though cold acclimation is the strongest stimuli to induce WAT browning process, unfortunately, cold significantly increases BP and heart rate and leads to more cardiac events.[143] Therefore, strategies other than cold stimuli are required to safely induce WAT or PVAT browning. Indeed, mitoNEET is a mitochondrial membrane protein that is regulated by thermogenic genes such as PGC1 (PPARγ coactivator 1). We reported that overexpression of mitoNEET in brown adipocytes, including PVAT adipocytes, significantly prevented arterial stiffness[144] and atherosclerosis.[145] The Crataegus sp. extract WS 1442 is an herbal compound that is beneficial in supporting cardiovascular function in heart failure patients.[146] Treatment of obese mice with WS 1442 normalized vascular function without changing fat mass. The effect was associated with enhanced acetylation and phosphorylation levels of eNOS in PVAT.[147] Further studies are needed to test the effects of these factors on the PVAT browning process and the readouts on BP regulation, especially under hypertension associated with obesity. Further studies are needed to elucidate the underlying mechanisms for these observations and develop targeted therapeutics.

PERSPECTIVES AND CONCLUSIONS

There is no doubt that endocrine roles of adipose tissues, through adipokines, chemo/cytokines, hormones, and other yet unknown factors, contribute systemically to many aspects of the physiology of the cardiovascular system. The dysfunction of adipose tissues, such as obesity, is one of the major risk factors for CVD. In that regard, PVAT is unique because it is adjacent and intimately integrated within the blood vessel wall and the significance of PVAT in development and prevention of CVD should not be ignored. PVAT is involved in all aspects of vascular physiology and pathophysiology. As a component of the vasculature, development, and existence of PVAT is critical to maintenance of the vasculature in a normal functional status, partially through paracrine factors. Dysfunctional PVAT, such as obese PVAT or aging PVAT, secretes disease-promoting factors which cause abnormal changes towards various pathologies in the underlying layers of the blood vessels, the so-called outside-to-inside paradigm of PVAT effects on vascular pathologies. To comprehensively understand the vascular physiology and pathophysiology, in addition to understanding PVAT itself, more extensive and deeper research on the paracrine signaling from PVAT and its cross-talk with the underlying vascular cells, including EC, VSMC, and fibroblasts under physiological and pathological conditions, is urgently needed. Adipocytes in PVAT are beige adipocytes which show mixed features of both brown and white adipocytes. Brown adipocytes are believed to promote energy expenditure and promote beneficial effects on the vascular system. There is evidence showing that PVAT is able to transform towards a fat tissue with increased white features during development of obesity and aging. Thus, reversing the white features of PVAT to brown features or maintaining PVAT beige features might be a crucial strategy to maintain a healthy vasculature. Additionally, PVAT secretes both PVCF and PVRF, especially in response to the same stimuli, suggesting that PVCF and PVRF precisely and concurrently control the blood vessel tone together with the systemic neurohumoral fluid system. The balance of PVCF and PVRF in the regulation of BP dipper pattern should be given more attention to develop novel strategies to maintain the physiological dipper pattern to prevent exacerbated adverse outcomes and CVD development. Finally, even though this review focuses on the cross talk between PVAT and VSMC and its roles in vascular remodeling and BP regulation, the paracrine secretomes of PVAT and their roles in development of CVD should be systematically and extensively studied.

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Disclosures

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