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A Review Article in:

The role of perivascular adipose tissue in modulating vascular function

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Abstract

Perivascular adipose tissue is defined as adipose tissue surrounding blood vessels. Perivascular adipose tissue is present in mammals, but their size increases with increasing adiposity. The research of perivascular adipose tissue (PVAT) started with a simple and elegant study published in 1991 after the discovery of PVAT in rat's aorta. It represents around 3% of the total body adipose tissue mass. While initially it's thought to provide primarily mechanistic support for the vasculature, in recent years it has become clear that PVAT is critical for the regulation of vascular/endothelial function in both physiology and pathology. Recent evidence from clinical and experimental animal models indicate that PVAT is engaged in paracrine cross-talk with blood vessels and is involved in the physiological homeostasis and pathological changes of the cardiovascular system. It has potential roles in regulation of vascular function. Thus, it may contribute in some vascular disorders. Studies found that the PVAT mainly has protective behavior in regard to vascular abnormalities. However, a lot of its mystery is not resolved. Here we review the recent evidence regarding the role of perivascular adipose tissue in modulating the vascular function.

Introduction

Because of the significant incidence of obesity-related cardiovascular disease around the world, researchers have been focusing more on the link between body weight, cardiovascular risk factors, and clinical cardiovascular disease. When compared to broad measures of adiposity, such as BMI, body fat distribution may be more strongly correlated with obesity-related comorbidities and cardiovascular disease. Ectopic fat, defined as fat deposition in nontraditional places such as the heart, kidneys,

and blood vessels, may play a role in the development of cardiovascular disease by exerting a harmful effect on nearby structures (1).

Perivascular adipose tissue, which is directly adhering to blood arteries, is one such ectopic fat depot. Fat surrounding major arteries, as well as organ-specific fat depots in which adipose tissue surrounds the organ's vasculature, are examples of perivascular adipose tissue. Periaortic fat belongs to the first group, while epicardial, pericardial, and peri-renal fat belong to the second (2).

Animals with low fat content have small size of perivascular adipose tissue, but the size rises as obesity grows (3). The composition of perivascular adipose tissue differs depending on the kind of blood artery. Resistance large vessels have both brown and white adipose tissue, whereas small vessels have mostly white adipose tissue (3). Certain organ-specific fat depots, such as epicardial and perirenal fat, are included in the phrase 'perivascular adipose tissue.' Fat wraps around the coronary and renal blood arteries, respectively, to form these fat depots. Given its placement around muscle resistance arteries in obese rats, intramuscular adipose tissue may be a subtype of perivascular adipose tissue (4).

Figure 1 show the structure of an artery wall with its PVAT to the outside.

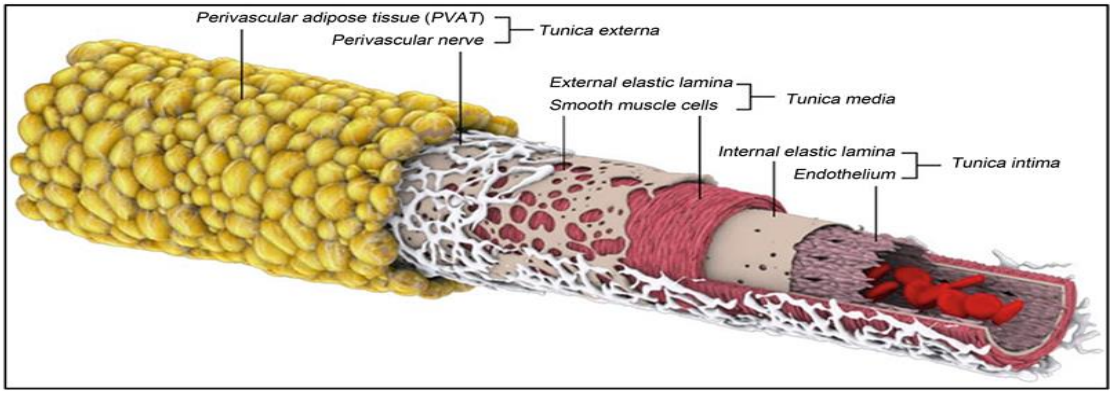

Figure 1. The structure of an artery wall including the Perivascular adipose tissue to the outside. The PVAT is positioned in the external layer of the artery (Tunica externa, also known as Tunica adventitia), where it retains the physical function of protecting the artery in addition to its paracrine properties that influence the arterial tone. (The figure obtained from 37).

It accounts for roughly 3% of total body adipose tissue mass. Initially thought to provide solely mechanistic support for the vasculature. PVATs importance in the control of vascular/endothelial function in both physiology and disease has been obvious in recent years. PVAT produces chemicals that are important for maintaining vasomotor tone and modifying vascular function in normal circumstances (5). This includes the beneficial adipocyte-derived relaxing factor (ADRF), which has been found to regulate essential homeostatic blood vessel activities and impact vasomotor tone. Despite extensive investigation, the nature of this ADRF is unknown, with prominent candidates being adiponectin, hydrogen peroxide, H2S (hydrogen sulfide), prostacyclin, angiotensin 1–7, or EDHF (endothelium derived hyperpolarizing factor) (6).

Anatomy and regional variations

Adipose tissues are empirically color-coded as white (WAT), brown (BAT), and beige/brown-in-white (brite) adipose tissues. The color explicitly reflects the main adipocyte population and the amount of iron-containing mitochondria in each adipocyte. The more mitochondria, the darker the color is. In addition to major depots, there are other location-specific adipose tissues, including mammary “pink” adipose tissue and bone marrow adipose tissue, which is primarily red in young individuals and turns yellow during aging. It would undoubtedly be oversimplified if we classify adipose tissues based solely on the appearing color and neglect their complexity and heterogeneity. Classical inter-scapular BAT has been previously assumed to contain a homogeneous population of brown adipocytes. A recent study has revealed a new brown adipocyte subpopulation with low thermogenic activity coexists with the classical high thermogenic brown adipocytes (32). A PVAT is usually named for the name of the vessel to which it is connected, such as pericoronary adipose tissue, which refers to the fat tissue surrounding the coronary artery. Various non-standard names for the same PVAT have been used over the years, which might be confusing or even deceptive. PVAT encircling the coronary artery or epicardial adipose tissue, for example, was abbreviated as "C-PVAT," "PVAT-CA," or even "epi" for short. It is fairly rare for these terms to be misunderstood, as in the case of pericardial and epicardial fat. These facts support the necessity for PVAT nomenclature to be standardized. To define these topics, some research articles have adopted a hybrid structure (31). Figure 2 show the common regional and anatomical variations.

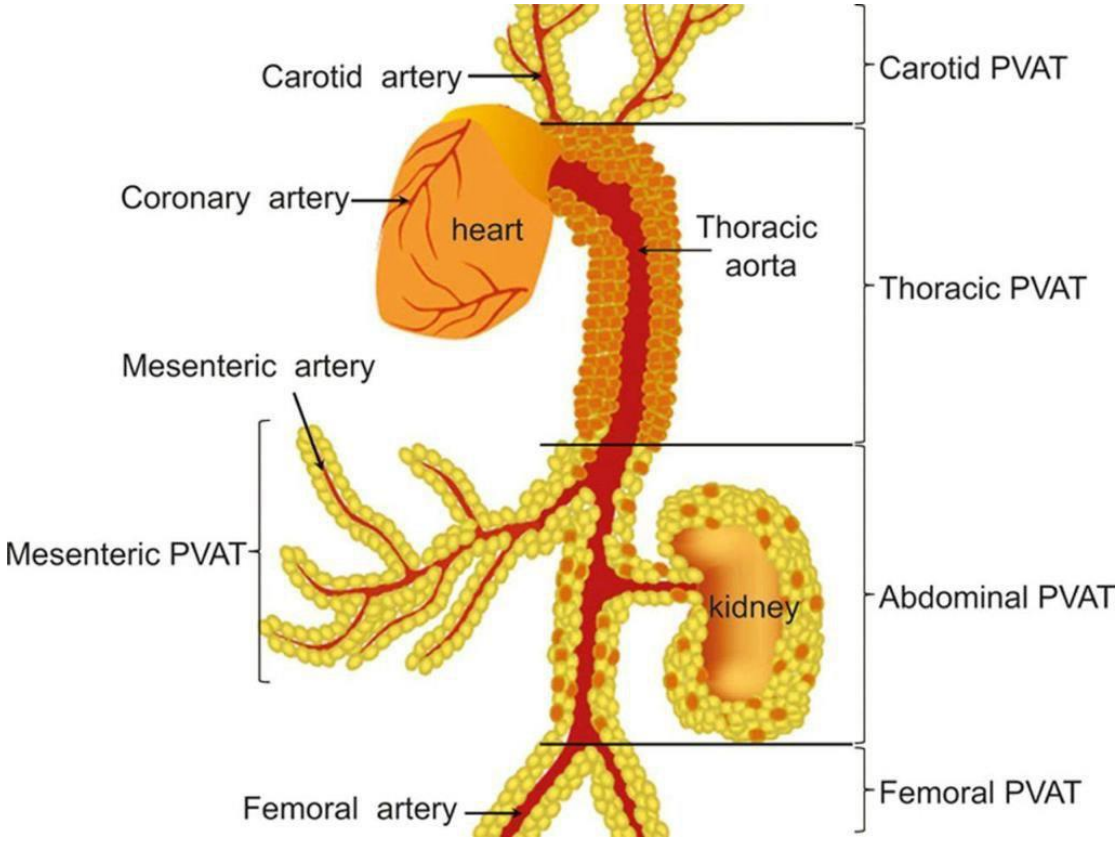

Figure 2. Types of perivascular adipose tissue (PVAT). PVAT can be classified as white, brown, and beige according to different anatomic locations. In rodents, brown PVAT surrounds the thoracic aorta, and white PVAT surrounds small arteries, such as mesenteric, carotid, and femoral arteries, whereas the abdominal aorta is surrounded by beige PVAT. PVAT is absent from the murine coronary artery. (The figure obtained from **36**)

PVAT in health and disease

The field of perivascular adipose tissue (PVAT) research began with a simple and elegant study published by Soltis and Cassis (1991) (25). They observed that rat aortic rings cleaned of its surrounding adipose tissue displayed a decreased sensitivity to norepinephrine, while responses to KCl and phenylephrine or acetylcholine remained unaltered. A decade later Lohn et al. concluded that PVAT released a soluble adventitia derived relaxing factor that causes vasodilation by opening vascular smooth muscle

K+ channels (34). In 2018, we have a lot more knowledge about how this adipose tissue around a blood vessel might change vascular tone (22). The original research was done on an isolated rat thoracic aorta, indicating that removing the PVAT around the aorta moved the contraction to Norepinephrine to the left in a functionally dependent manner. These findings were the first to reveal that the PVAT was more than just a structural support system, and they were followed by a major study in 2002 that showed that PVAT from healthy people contained substances that relax contracted arteries directly (22) . PVAT has been dubbed "anti-contractile" as a result of these and other findings (22).

PVAT's potential to benefit a vessel in good condition is further reinforced by the fact that it generates other relaxant compounds including palmitic acid methyl ester, shelters atheroprotective B cells, and has mitochondrial function that helps to prevent atherosclerosis. The "no-touch" approach improves saphenous vein graft function in humans by preserving PVAT, a finding that recommends maintaining the PVAT layer intact in isolated veins before grafting. PVAT collaborates with the vessels it surrounds; this is a biologically significant interaction, given the relevance of the chemical insulin receptor substrate 2 (IRS2) in modulating insulin-induced changes in vasomotor tone in a PVAT-dependent way (23).

Obesity is an important risk factor for insulin resistance and hypertension, and it is associated with several impairments in the microcirculation, including impaired endothelial function and rarefaction. Recent studies have shown that PVAT relates to endothelium-dependent vasodilatation and inflammation by secreting a variety of substances that affect vascular tone and infiltration of inflammatory cell (33). However, the mechanisms controlling the quantity of PVAT and its secretion of

adipokines remain to be determined. Because PVAT is located within insulin target tissues, controls (micro) vascular function, and is associated with insulin resistance, it may well contribute to the pathogenesis of type 2 diabetes and cardiovascular disease (33).

Chemicals produced by PVAT

Adipose tissue, like endocrine cells, manufacture and secrete a variety of chemicals. Adipose tissue is the largest endocrine organ in this respect, and adipocytes create around 600 hundred different factors, collectively known as adipokines or adipocytokines (30) . PVAT-to-artery paracrine communication, also known as "vasocrine" communication, actively controls vascular inflammation and arterial remodeling. PVAT depots that are anatomically distinct can emit a wide variety of adipokines. This topic has been extensively researched and discussed in previous literatures (30). Table 1 show the chemicals that produced by PVAT

Table 1. PVAT-generated autocrine and paracrine factors.

Type of PVAT	Anti-inflammatory factors	Pro-inflammatory factors
Cardiac PVAT,	Adiponectin Omentin IL-10	MCP-1 (CCL2), IL-8, IL-6, Leptin, MIP-1α (CCL3) TNF-α, IL-1β, IL-13) Visfatin, TNF-α Chemerin, Vispin, Apelin Plasminogen activator inhibitor-1, Resistin
Thoracic		IL-6, TNF-α, RANTES (CCL5 IL-17A, IL12p40, CXCL10,

PVAT	Adiponectin IL-10, IL-4	CX3CL1,Leptin \Resistin ,Visfatin
abdominal peri-aortic PVAT	Adiponectin IL-10	IL-1, IL-6, MIP-1α (CCL3) RANTES, IL-8, MCP-1 Leptin, Platelet-derived gro Resistin and visfatin, Chemerin
White PVAT (mesenteric, femoral, common carotid)	Adiponectin IL-10	IFN-γ, IL-17, MCP-1, TNF-α, IL-6, Plasminogen CCL2, CCL5 and CX3CL1, IL-1β,

CX3CL1, C-X3-C motif chemokine ligand 1; CXCL10, C-X-C motif chemokine ligand 10; CXCL16, C-X-C motif chemokine ligand 16; IFN-c, Interferon-c; IL, interleukin; MCP-1 (CCL2), monocyte chemoattractant protein-1 (C-C motif chemokine ligand 2); MIP-1α (CCL3), macrophage inflammatory protein-1α (C-C motif chemokine ligand 3); RANTES (CCL5), Regulated upon activation, normal T cell expressed and presumably secreted (C-C motif chemokine ligand 5); TNF-α, Tumor necrosis factor-α

The link between CVD and obesity was assumed to be due to adipose tissue's endocrine functions. Most blood vessels, including the aorta and arteries like the carotid, coronary, and mesenteric arteries, are strongly adherent to PVAT. PVAT is involved in physiological homeostasis and pathological changes of the cardiovascular system, according to growing evidence from clinical and experimental animal models. PVAT is involved in paracrine cross-talk with blood vessels and is involved in physiological homeostasis and pathological changes of the cardiovascular system (8).

In the past years, several adipokines have been shown to alter vascular tone and vessel wall inflammation. These effects can be achieved either

directly through interaction with the vascular endothelium or indirectly through increased monocyte infiltration into the arterial wall. Tumor necrosis factor (TNF), IL-6, non-esterified fatty acids, leptin, and adiponectin are adipokines that operate directly on vascular endothelium, whereas MCP-1, IL-8, and resistin promote monocyte adherence to vascular endothelium (9).

TNF was the first cytokine discovered to be released by adipose tissue. TNF expression in adipose tissue is significantly higher in obese people. TNF has been shown to impede insulin-stimulated glucose absorption in skeletal muscle when compared to lean people. Increased plasma levels of TNF are linked to poorer capillary recruitment in humans, therefore this effect could be mediated in part by TNF's effects on microvascular endothelium (10).

In its globular form, adiponectin is a tiny protein with a molecular weight of 30 kDa. Its collagenous N-terminal region allows multimers to form, which bind to the adiponectin receptors ADIPOR1 and ADIPOR2 for intracellular signaling. Adiponectin's functions are mediated by a number of other proteins, including T-cadherin. These benefits are multifaceted, ranging from boosting pancreatic beta cell survival and insulin secretion to insulin sensitivity, renal, and cardiac protection, as well as important local autocrine and systemic anti-inflammatory actions. Adiponectin can influence blood vessel function through a variety of pathways, including vasorelaxation, AMPK-mediated endothelial nitric oxide (NO) synthase (eNOS) activation, protection from endothelial injury, and anti-inflammatory effects (11).

Leptin is another important adipocyte-specific hormone that is mostly released by WAT adipocytes and functions to signal energy status and regulate hunger via hypothalamic leptin-receptor activation. Because its

circulating levels are proportional to adipose tissue mass, hyperleptinemia is a common feature of most obesity types. However, the hyperleptinemia seen in human obesity is linked with peripheral leptin resistance, similar to the hyperinsulinemic and insulin resistant state seen in diabetes, due to multiple reasons. Leptin, like adiponectin, has a variety of systemic functions, including influencing endocrine hypothalamic-pituitary signals to the gonads, thyroid, and adrenal gland, as well as insulin sensitivity, bone metabolism, and immune system function. The effects of leptin are generally those of vasodilation in the cardiovascular system, where the six leptin receptors are also present, generating hypotension upon acute in vivo infusion and exerting direct vasodilatory effects on numerous arterial beds (12-13).

Anti-contractile effect of PVAT

PVAT had an anti-constrictive effect when electrically activating sympathetic nerves and when stimulated with arginine-vasopressin (AVP) and norepinephrine, according to a study. PVAT, on the other hand, had a proconstrictive effect on acetylcholine responses. Evidence suggests that 3-adrenoceptors play a role in sympathetic and noradrenergic PVAT function, and that their activation triggers the release of an anti-contractile substance, possibly adiponectin (14).

PVAT possesses the capacity to act in a paracrine manner, on the blood vessel, the function of which it modulates via complex mechanisms (the observation that the effects of contractile amines was very different when applied via the intimal side or through the adventitial side) (35). New molecules released from PVAT are constantly being added to the already impressive list of adipokines, cytokines, ROS, lipid species, and gaseous molecules that PVAT produces. Changes in PVAT's anticontractile function in obesity, metabolic syndrome, hypertension, or atherosclerosis

are linked to an imbalance in adipokine secretion, as well as inflammation and oxidative stress, all of which lead to vascular dysfunction. The chronology of these events is unclear, but it appears that PVAT infiltration by immune cells, which causes the cascade of diseases, is a significant step in PVAT dysfunction in cardiovascular disease, albeit the trigger for this is unknown. A greater understanding of PVAT physiology could lead to the development of vascular dysfunction therapeutics as well as ways for targeting these therapies to PVAT (6).

Pro-contractile effect of PVAT

PVAT, like adipocytes in other anatomical regions, secretes bioactive chemicals such as adipokines and other cytokines that influence cardiovascular function, according to growing data. PVAT-derived or adipocyte-derived contractor factors are two types of diffusible factors that can cause direct vasocontraction (denoted ADCFs herein). Contractility experiments employing isolated arteries with and without PVAT, as well as isolated PVAT and its conditioned media (a specific media used to culture the tissue in vitro) under physiological settings, provide a lot of evidence. Adipocytes have been shown to have a local renin–angiotensin–aldosterone system (RAAS), which includes angiotensinogen and angiotensin converting enzyme (ACE) for the production of the powerful vasoconstrictor angiotensin II (Ang II). The composition and location of adipose tissues can influence the expression of RAAS components. PVAT is assumed to express all RAAS components, and that PVAT-derived Ang II induces contractions in rat mesenteric arteries via activating AT1 receptors (23).

Ang II has also been shown to play a role in the local inflammation associated with hypertension and obesity, stimulating the infiltration of immune cells, including T-lymphocytes and macrophages, into PVAT and

the production of reactive oxygen species . PVAT's role as a source of Ang II in the modulation of vascular tone and blood pressure, particularly in hypertension and obesity, has yet to be determined. Furthermore, the generation and function of PVAT-derived Ang II are expected to be localized. Because AT1 receptor activation has been demonstrated to diminish browning (the change of white AT to brown AT) of adipose tissue and promote adipocyte hypertrophy, insulin resistance, and weight gain in mice, Ang II may worsen PVAT dysfunction (24).

PVAT and atherosclerosis

There is a scarcity of studies on PVAT in atherosclerosis. The majority of these studies in humans were conducted in epicardial adipose tissue, which has the advantage of allowing researchers to explore phenomena near to the coronaries but cannot be completely compared to pericoronary PVAT. A number of research reviewed elsewhere have linked increased epicardial adipose tissue size to atherosclerotic plaques, the degree of coronary artery stenosis, and cardiovascular events. Adipokine secretion was shown to be imbalanced in this tissue, with molecules that promote inflammation and VSMC proliferation, such as IL-6, plasminogen activator inhibitor 1 (PAI-1), TNF, visfatin, and leptin, being raised while anti-inflammatory adipokines, such as adiponectin, were decreased. The absence of PVAT in the intramyocardial parts of coronary arteries made them less likely to develop atherosclerosis (15-16).

PVAT and hypertension

PVAT reduces agonist-induced vascular constriction via two mechanisms: an endothelium-dependent mechanism triggered by transferable PVRF and a non-transferable endothelium-independent mechanism. The transferable PVRF causes endothelial NO release and

subsequent activation of K + channels, resulting in relaxation, whereas the nontransferable anticontractile mechanism involves PVAT production of H2O2 and subsequent activation of smooth muscle soluble guanylyl cyclase (sGC), resulting in contraction. These findings add to our existing knowledge of the mechanisms through which PVAT influences vascular function (17).

Because sGC inhibition counteracted PVAT's anticontractile impact in PVAT and E intact (PVAT+E+) arteries, and removed the inhibitory effect of exogenously administered H2O2 on phenylephrine-induced contraction in PVAT E arteries, it was assumed that sGC activation was involved. These findings support prior observations that H2O2 works as a non-NO sGC activator in bovine and porcine coronary arteries. Inhibition of sGC caused a small but considerable contraction of the PVAT with removed E (PVAT-E) arteries, but not the PVAT+ E arteries, indicating that sGC was consistently activated in the aortic rings with intact PVAT (18).

During the development of obesity, the PVAT gradually changes into white-like characteristics, which is linked to changes in PVAT paracrine profiles, including those implicated in VSMC growth, vascular tone regulation, and blood pressure. The preservation of PVAT's brown-like characteristics could be an approach for preventing hypertension by preserving blood vessel homeostasis (20).

Multiple techniques, such as cold stimuli or growth hormones like FGF21 (fibroblast growth factor 21), ANP (atrial natriuretic peptide), and BMP (bone morphogenetic proteins), have been shown to transform white adipose tissue to brown adipose tissue. Browning is thought to be useful in the prevention of obesity and CVD. As a result, restoring the natural beige characteristics of human PVAT may be able to reverse or prevent the

development of vascular diseases. It is unknown whether the whitening-like process of PVAT causes an increase in blood pressure in obese people. It is reasonable to speculate, however, that returning PVAT to brown-like properties could be a viable hypertension therapy method (21). As shown in figure 3

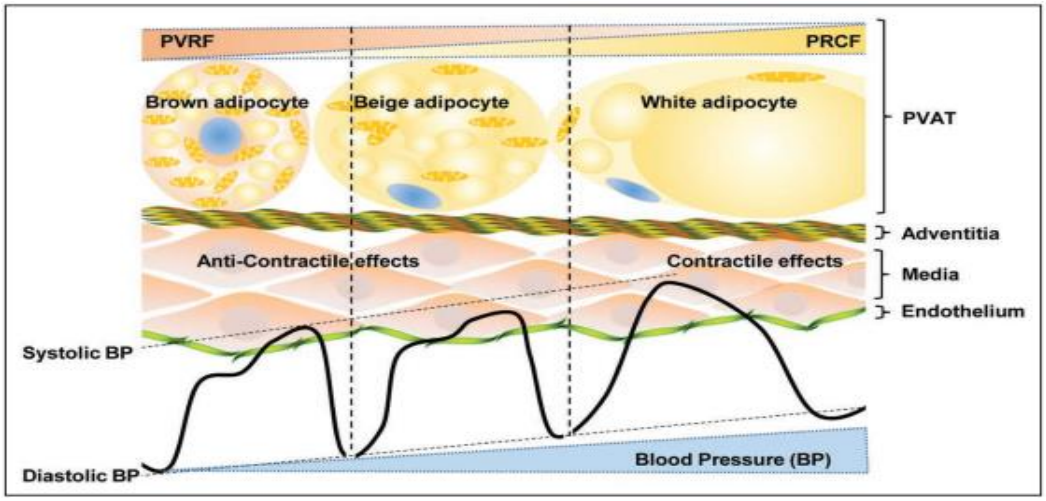

Figure 3. Strategy for hypertension prevention through perivascular adipose tissue (PVAT) browning.

PVAT and inflammation

Adipose tissue causes inflammation in obesity by producing and secreting cytokines and chemokines locally. As fat rises, inflammation spreads throughout the body. The increase of activated macrophages in adipose tissue is a key aspect of inflammation. The main source of pro-inflammatory cytokines in adipose tissue is macrophages, and recent research suggests that macrophage release of proinflammatory cytokines induces obesity-related insulin resistance(19) . The creation of monocyte chemoattractant protein-1 (MCP-1) is triggered by an increase in adipocyte size, which draws macrophages to adipose tissue. Both BMI and adipocyte size were excellent predictors of the percentage of CD68-expressing

macrophages in human subcutaneous adipose tissue, according to immunohistochemistry (19).

PVAT influences VSMC growth and migration

Extensive plasticity is an inherent property exhibited by fully mature VSMCs, which are ordinarily in a non-proliferative, contractile state, but switch to a proliferative, synthetic phenotype during response to injury. In proliferative vascular disorders such atherosclerosis, restenosis, graft vasculopathy, and hypertension, VSMC growth (proliferation and/or hypertrophy) and migration play a key role. The most well-known example of VSMC phenotypic shift to proliferation and migration in atherosclerosis is atherosclerosis. Restenosis at arterial injury sites after angioplasty is caused by intimal hyperplasia, which involves VSMC proliferation and migration from the media to the intima. For phenotypic conversion, the local microenvironment, such as growth factors/inhibitors and mechanical effects, is critical. According to the available direct and indirect evidence, factors released from perivascular fat may act as regulators of VSMC proliferation and migration (26).

Some types of cells are encouraged to proliferate by adipocytes. However, until Yang et al. cultivated VSMCs in conditioned media from 3T3-L1-derived differentiated adipocytes or 3T3-L1 preadipocytes, the effect of adipocytes on VSMC proliferation remained unknown. They discovered that conditioned media from developed adipocytes, rather than that from preadipocytes, can trigger VSMC proliferation. Because this proliferation is inhibited by proteinase K treatment but not by phospholipase B, the growth factor(s) present in the conditioned media from mature adipocytes could be a protein(s) (to hydrolyze lysophosphatidic acid). Furthermore, the protein(s) is/are trypsin resistant (27).

Visfatin is an adipokine that was first identified in 2005. This protein, also known as pre-B cell colony-enhancing factor, is a nicotinamide phosphoribosyltransferase enzyme that converts nicotinamide to nicotinamide mononucleotide (NMN). It is mostly produced and secreted from visceral fat rather than subcutaneous fat as a novel adipokine. Obesity raises the level of circulating visfatin. It could provide insight into the impact on VSMC (28).

Dysregulation of Vascular Function Induced by PVAT Dysfunction

PVAT dysfunction causes vascular dysregulation by increasing peripheral resistance and vascular tone, which is caused by an elevated inflammatory state in obese people. The loss of the PVAT anticontractile action was linked to elevated blood pressure in animal models with diet-induced obesity. The specific cause of vascular dysfunction in obesity is yet unknown; however, some pathways, such as the renin–angiotensin–aldosterone system (RAAS) abnormalities and the dysregulation of PVAT-derived factors, are thought to be implicated. The loss of ADR and PDRF's anticontractile action is caused by pathological changes in their production and secretion. Endothelial dysfunction is a key factor in the pathophysiology of obesity-related microvascular and macrovascular problems (29).

Conclusion

Perivascular adipose tissue has begun to gain interest and attention from the pharmaceutical institute because it's potential possible association with many vascular disorders such as hypertension and atherosclerosis. The recent discovery of it structure and secrete opened the door for researchers to hope about the possible contribution of the PVAT in the treatment of CVD and other inflammatory conditions.

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