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# Molecular crosstalk in perivascular adipose tissue: mechanisms of inflammation, metabolic dysregulation, and therapeutic opportunities in cardiovascular disease

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The escalating recognition of perivascular adipose tissue (PVAT) as a molecular nexus in cardiovascular disease (CVD) pathogenesis necessitates a comprehensive synthesis of its spatiotemporal dynamics and therapeutic potential. This review synthesizes PVAT's roles in vascular inflammation, metabolic dysregulation, and emerging diagnostic strategies, emphasizing molecular cross-talk and spatial heterogeneity. We explore PVAT's molecular interactions in obesity, diabetes, and hypertension, elucidating its contribution to inflammation, oxidative stress, and endothelial dysfunction. Advanced imaging techniques, notably the perivascular fat attenuation index (FAI) and circulating biomarkers, are highlighted for early CVD detection. Novel therapeutic strategies, including lifestyle modifications, pharmacological interventions, and gut microbiota modulation, are discussed. Finally, we emphasize multi-omics approaches and propose a roadmap bridging basic and clinical research to advance PVAT-based CVD management.

#### KEYWORDS

perivascular adipose tissue, biomarkers, vascular inflammation, atherosclerosis, cardiovascular disease

### 1 Introduction

Perivascular adipose tissue (PVAT) is of paramount importance as it closely surrounds blood vessels and releases a variety of active substances through paracrine and autocrine mechanisms (1, 2). PVAT is essential in the complex process of regulating vascular tension, which is vital for the proper functioning of the cardiovascular system. By maintaining the elasticity of blood vessels, PVAT ensures that they can efficiently accommodate the flow of blood, adapting to changes in pressure and volume (3). Furthermore, PVAT is involved in the intricate processes of lipid and energy metabolism, highlighting its importance in the body's overall metabolic functions (4). In addition to these roles, PVAT also plays a significant part in regulating inflammation and immune responses, demonstrating its multifaceted contributions to both vascular health and systemic metabolism (5).

Conversely, under pathological conditions such as obesity and diabetes, PVAT function becomes impaired. The secretion of active substances becomes unbalanced, leading to excessive release of inflammatory factors and disordered immune regulation (6, 7). This dysfunction contributes to impaired vascular endothelial function, accelerated atherosclerosis, and a series of vascular pathologies, thereby becoming a significant driving factor in the onset and progression of cardiovascular diseases (CVDs), which profoundly impacts overall health and disease processes (8-10). The recently discovered role of PVAT as a modulator of circadian rhythms—via Bmal1-dependent secretion of heme-binding protein-links nocturnal blood pressure dipping to adipose redox cycles (11), thereby offering mechanistic insights into cardiovascular events related to morning surges.

Although the significance of PVAT in both cardiovascular physiological and pathological processes has gained increasing recognition; however, current research in this area continues to encounter several limitations. This review challenges three prevailing assumptions: (1) Homogeneity Fallacy: PVAT is not a monolithic entity; rather, it represents a mosaic of adipocyte subtypes and immune niches characterized by distinct spatial metabolic programming. (2) Paracrine-Centric View: Mechanotransduction through the extracellular matrix-integrin signaling of PVAT may be as significant as soluble factors in contributing to vascular stiffening. (3) Therapeutic Neutrality: The PVAT-specific effects of current anti-diabetic drugs remain unquantified, which poses a risk of off-target consequences. By integrating single-cell omics, advanced imaging techniques, and data from interventional trials, we propose a novel framework for PVAT-centric cardiovascular therapeutics—one that emphasizes depot-specific targeting, optimization of circadian rhythms, and modulation of the microbiome-adipose axis.

#### 2 Paracrine effects and bi-directional cross-talk of PVAT in cardiovascular function

### 2.1 Anatomical location and cellular composition

Anatomically, PVAT surrounds most large blood vessels, excluding the pulmonary and brain vasculature and the microcirculation (12, 13). PVAT is specifically designated as adipose tissue that resides within a radial distance equivalent to the vessel's own width, measured from the outer wall of a blood vessel. When dealing with vessels exceeding a diameter of 2 cm, notably the aorta, PVAT can expand up to a maximum of 2 cm away from the vessel wall (1). This tissue is intimately associated with blood vessels, forming a distinct layer encircling the adventitia. Its distribution patterns vary considerably, contingent upon the vessel's location and size. Notably, in larger arteries like the aorta, PVAT can constitute a substantial depot, whereas in smaller vessels, it may manifest as a thinner, more delicate layer. In rodents, the PVAT surrounding the thoracic aorta consists of brown adipose tissue (BAT), whereas the PVAT around the abdominal aorta is made up of a combination of white adipose tissue (WAT) and a portion of BAT (14, 15). In humans, the phenotype of thoracic aortic PVAT is characterized as brown. In the case of neonates and during the early developmental stages, human epicardial adipose tissue (EAT) exhibits both morphological and functional characteristics that closely resemble those of BAT. This similarity is particularly significant in the context of early life. However, under typical physiological conditions, the brown fat-like attributes of EAT diminish considerably as a person ages, transitioning from childhood into adulthood. This decline highlights the dynamic nature of PVAT and its changing roles throughout the life course (16, 17).

Cellularly, PVAT harbors adipocytes, macrophages, neutrophils, dendritic cells, mast cells, eosinophils, T cells, B cells, and various other cell types. These cells interact to maintain the functionality and microenvironmental homeostasis of PVAT (18) (Figure 1A). The adipocytes can be white, brown, or beige, each with unique characteristics and functions, BAT and beige fat function differently than WAT (Table 1). While WAT mainly acts as an energy reservoir, accumulating surplus chemical energy in the form of triacylglycerol (TAG), both BAT

Abbreviations PVAT, perivascular adipose tissue; CVDs, cardiovascular diseases; BAT, brown adipose tissue; WAT, white adipose tissue; EAT, epicardial adipose tissue; TAG, triacylglycerol; snRNA-seq, single-nucleus RNA sequencing; UCP1, uncoupling protein 1; ROS, reactive oxygen species; AMPK, adenosine monophosphate-activated protein kinase; 4-HNE, 4-hydroxynonenal; PPAR, peroxisome proliferator-activated receptor; T2DM, type 2 diabetes mellitus; IL-6, interleukin-6; TNF- $\alpha$ , tumor necrosis factor-alpha; EVs, extracellular vesicles; ESCRT, endosomal sorting complex required for transport; MVBs, multivesicular bodies; Nrg4, neuregulin-4; RAAS, renin-angiotensinaldosterone system; IFN-7, interferon-gamma; IL-17, interleukin-17; CT, computed tomography; FAI, fat attenuation index; CCTA, coronary computed tomography angiography; AI, artificial intelligence; MRI, magnetic resonance imaging; PET, positron emission tomography; VAT, visceral adipose tissue; GLP-1, glucagon-like peptide-1; SGLT2-i, sodium-glucose cotransporter 2 inhibitors; ACS, acute coronary syndrome; MACE, major adverse cardiovascular events; β3-AR, β3-adrenergic receptors.



(A) The cellular composition of perivascular adipose tissue (PVAT) includes adipocytes, macrophages(M2), neutrophils, dendritic cells, mast cells, eosinophils, T cells, B cells, and various other cell types. (B) Balance of anti-inflammatory and pro-inflammatory adipokines. (C) Leptin, resistin, RBP4, TNF- $\alpha$ and IL-6 can activate the JNK, NF- $\kappa$ B, and JAK-STAT pathways, leading to insulin resistance. (D) Pro-inflammatory factors contribute to endothelial cell dysfunction, as well as the migration of vascular smooth muscle cells and monocytes, ultimately leading to atherosclerosis. (E) The reduction of adiponectin, Ometin, and H2S, alongside the increase in TNF- $\alpha$ , IL-6, and resistin, contributes to increased arterial stiffness and vascular tone. This biochemical imbalance promotes the secretion of renin and activates the RAS system, ultimately resulting in hypertension.

and beige fat are noted for their elevated metabolic activity, employing chemical energy for the generation of heat (24). The thermogenic capacity of BAT and beige fat plays an essential role in sustaining body temperature regulation, achieving energy equilibrium, and managing body weight (25). PVAT's role transcends its anatomical proximity to vasculature, functioning as a dynamic signaling interface with depot-specific molecular signatures.

Recent single-nucleus RNA sequencing (snRNA-seq) analyses reveal three distinct adipocyte subpopulations in human thoracic PVAT: uncoupling protein 1(UCP1) thermogenic, ADIPOQ endocrine, and fibro-inflammatory adipocytes-each exhibiting unique vascular crosstalk patterns (24, 26-30). Notably, In models, periaortic PVAT demonstrates higher murine mitochondrial density compared to mesenteric depots, correlating with enhanced fatty acid oxidation and reactive oxygen species (ROS) buffering capacity (31). This spatial metabolic specialization challenges the traditional dichotomy between white and brown adipocytes, suggesting that PVAT exists as a continuum of plastic phenotypes. Furthermore, it contests the conventional viewpoint of the "Homogeneity Fallacy" regarding PVAT.

# 2.2 PVAT in normal vascular physiology: paracrine and endocrine effects

PVAT releases a variety of bioactive molecules, including adipokines (32), cytokines (33), and growth factors (34). Studies conducted in animal models have demonstrated that these molecules can influence vascular function through endocrine or mechanisms. Under paracrine normal physiological circumstances, PVAT has a net effect of vasodilation, antioxidation, and anti-inflammation on the blood vessels. The vasodilatory function is influenced by the secretion of various factors from adipocytes, which are specialized cells in adipose tissue. Among these factors are adiponectin (35), apelin (36), leptin (37), and omentin (38), each playing a significant role in the regulation of vascular tone. These bioactive compounds contribute to vasodilation through two primary mechanisms. Secondly, they may indirectly promote the production of endothelium-derived vasodilators, including nitric oxide (NO) and the endothelium-derived hyperpolarizing factor. This results in enhanced blood circulation and improved vascular performance. Animal experiments have confirmed this effect (39). Interestingly, differences have been observed among various

Comparison items	White adipocytes	Beige adipocytes	Brown adipocytes
Morphological	Contain a large lipid droplet occupying most of	Have some small lipid droplets, more	Have multiple small lipid droplets, abundant
features	the cell volume, with a flattened nucleus in a	mitochondria, and the nucleus is in the center of	and large mitochondria, and a round nucleus in
	"half-moon" shape (19)	the cell (19)	the center of the cell (19)
Distribution location	Widely distributed in subcutaneous tissue and	Mainly in subcutaneous WAT and a small	Mainly in neck, shoulders, clavicle, around
	around internal organs	amount in other parts	spine, between scapulae, adrenal glands, etc.
Main function	Store energy	Have both energy storage and thermogenic	Generate heat by oxidizing fatty acids and other
		functions, and can be activated for	substances to maintain body temperature
		thermogenesis under specific conditions	balance and consume energy
Thermogenic-related	Basically do not express UCP1 (20)	Contain UCP1 but usually with low expression	Highly express UCP1 (21)
proteins		and can be highly expressed under specific	
		stimuli (21)	
Impact on health	Excessive amount can lead to obesity and	Activation can help improve obesity and related	Beneficial to health, can stabilize blood sugar
	related chronic diseases (22)	metabolic disorders	and enhance insulin sensitivity, etc. (23)
Content in human	Most abundant.	Between white adipocytes and brown adipocytes	Less
body			

TABLE 1 Distribution and functionality of white, beige, and brown adipocytes.

ethnic groups (40). This intricate interplay underscores the importance of adipocyte-derived factors in maintaining vascular health and regulating blood pressure. The paracrine functions of adipocytokines released from PVAT exhibit significant antioxidant and anti-inflammatory properties. These effects may be mediated by activating the 5'adenosine monophosphateactivated protein kinase (AMPK) and NO signaling pathways in nearby blood vessels. In mouse experiments, the downregulation of AMPK inhibits the synthesis of NO, which lead to a reduction in the anti-contraction activity PVAT and a decrease in the BAT phenotype (31). This interaction suggests that the release of adipokines from PVAT not only influences the local vascular environment but also plays a crucial role in modulating vascular health. By engaging these signaling mechanisms, adipokines contribute to the maintenance of vascular homeostasis, potentially offering protective benefits against inflammatory processes and oxidative stress in the surrounding tissues (41).

PVAT is crucial in the intricate two-way communication with the vascular wall (Table 2). Through this interaction, PVAT can react to paracrine signals released by the vascular cells, resulting in phenotypic alterations in the adipocytes located within the PVAT. As a result of these alterations, the composition of the secretory products released by PVAT is modified. These secretory products subsequently exert paracrine effects on the vascular wall itself, influencing its function and behavior (18, 60). It plays a crucial role in maintaining vascular health by secreting a variety of vasoactive factors. These factors encompass a diverse range of substances, including (61-63). Through the release of these biologically active molecules, PVAT contributes to the modulation of vascular functions, which can influence processes such as blood flow and vascular tone (18, 64). Under conditions of heightened oxidative stress in the vascular system, substances resulting from lipid peroxidation, such as 4-hydroxynonenal (4-HNE), are emitted by the walls of blood vessels (65). The substances infiltrate the adjacent PVAT, subsequently activating signaling pathways associated with peroxisome proliferatoractivated receptor (PPAR)-y in the perivascular adipocytes. This activation leads to elevated levels of adiponectin expression and release from PVAT, an essential factor for diminishing oxidative stress in blood vessels, acting as a protective mechanism against oxidative damage in the vascular environment (66, 67).

The balance between adipokines may be crucial in determining the overall impact of PVAT on cardiovascular health (Figure 1B). Understanding the complex interactions among these factors could yield new insights into the pathophysiology of obesityrelated CVD and inform the development of novel treatment strategies. Adiponectin, a vasodilatory adipokine primarily secreted by adipocytes, plays an important role in the anticontractile function of PVAT and is significant for regulating insulin sensitivity and glucose metabolism (68). In instances of obesity, the levels of plasma adiponectin decrease, which aids in the progression of hypertension (69), atherosclerosis (70), and diabetes (71). Leptin is another prominent adipokine that plays a crucial role in regulating appetite and body weight (72). In instances of obesity, there is an increase in leptin secretion; nonetheless, it is common for individuals to develop resistance to leptin (73). Leptin is capable of promoting vasodilation via mechanisms that rely on the endothelium as well as those that do not. In contrast, consistently elevated leptin levels may contribute to vasoconstriction (74, 75). Additionally, high levels of leptin have been associated with obesity-related conditions, including myocardial infarction (76, 77) and stroke (78). Apelin expression increases in obesity and interacts with the abnormal function of PVAT during the onset and progression of CVD, such as hypertension (79) and atherosclerosis (80). Visfatin is highly secreted by VAT and PVAT, and it appears to play a role in atherosclerosis while being associated with a vasopressor effect (81). Omentin is an adipokine that possesses both anticontractile and anti-inflammatory characteristics. It enhances the bioavailability of NO, exhibits antioxidant properties, and provides protective effects against ischemic stroke by improving atherosclerosis (82, 83).

In addition to adipokines, PVAT also secretes various other factors, including cytokines, growth factors, and gaseous messengers. These factors can influence vascular function and play a role in the pathophysiology of CVDs. For instance,

Main bioactive components	Specific substances	Function	Physiological role	Pathological association
Adipokines	Adiponectin	Anti—inflammatory, enhance insulin sensitivity, anti—athero (42)	Regulate metabolism, reduce inflammation, maintain vascular health (43)	Linked to obesity, type 2 diabetes mellitus (T2DM), CVD; low in obese (44)
	SFRP5	Anti—inflammatory, regulate fat tissue inflammation	Inhibit inflammation pathways in fat	Related to obesity—related issues, useful in anti—inflammation (45)
	Omentin	Anti—inflammatory, improve insulin sensitivity.	Regulate inflammation, glucose uptake, and metabolism	Changed in obesity/diabetes, a biomarker and target (46)
	Apelin	Regulate cardio, angiogen, water—salt, partly anti—inflammatory	Affect heart, blood vessels, fluid balance	Linked to cardio diseases, obesity, metabolic syndrome (47)
	Leptin	Regulate appetite/energy, anti— inflammatory	Control weight, balance fat/energy, reproductive/immune role	Obese have leptin resistance, related to obesity/eating (48)
	Chemerin	Regulate fat cell, immune cell, inflammation	Guide immune cells, affect fat cells in immunity/metabolism	Linked to obesity, inflammation; levels up in obese (49)
	Visfatin	Insulin—like, regulate blood sugar, inflammation	Promote glucose uptake, regulate inflammation	Related to obesity, insulin resistance, diabetes (50, 51)
	Resistin	Maybe involved in insulin resistance, pro—inflammatory	Affect insulin, blood sugar, and inflammation	Linked to obesity and T2DM risk (52)
	Wnt5a	In fat cell metabolism/differentiation, may regulate inflammation	Affect fat cell features, communication, and signaling	Linked to fat metabolism issues like obesity (53)
	RBP4	Transport retinol, related to insulin resistance, pro—inflammatory	Affect fat/liver metabolism, insulin signaling	Linked to obesity, T2DM, metabolic syndrome; risk factor (54)
Cytokines	IL-6 (adipose)	Pro—inflammatory	Mediate adipose tissue response	Elevated in obesity, related to CVD (55)
	TNF-α (adipose)	Pro-inflammatory	Induce adipose inflammation	Linked to insulin resistance, CVD (56)
Gas Messengers	NO	Relax vessels, regulate tone, immune	Relax PVAT—related vessels	Decrease in PVAT issues leads to problems (57)
	H <sub>2</sub> S	Relax vessels, anti—oxidant, anti— inflammatory (58)	Protect PVAT, regulate tension	Abnormal levels cause PVAT dysfunction (59)

TABLE 2 Main bioactive components in PVAT: biological functions in the vascular bed.

interleukin-6 (IL-6) (84) and tumor necrosis factor-alpha (TNF- $\alpha$ ) (85) are pro-inflammatory cytokines released from PVAT in conditions such as obesity. Vascular inflammation, oxidative stress, and dysfunction of the endothelium can be initiated by these cytokines, which, in turn, play a role in the progression of CVDs (86). Additionally, hydrogen sulfide (H<sub>2</sub>S), a gaseous messenger released from PVAT, exhibits antioxidant and vasodilatory effects under physiological conditions (87). However, in obesity and other pathological states, the production of H<sub>2</sub>S may be altered, resulting in modifications to vascular function (88, 89). NO is a well-recognized vasodilator that plays a significant role in mediating the anti-contractile effect in PVAT (90). Initially, obesity may induce an adaptive increase in NO levels; however, chronic obesity ultimately results in diminished NO bioavailability (91). NO-dependent endothelial dysfunction is a critical initial step in the development of CVDs, particularly in the pathogenesis of atherosclerosis and hypertension (92). Furthermore, NO dysfunction also impacts myocardial remodeling (93). The above conclusions are mainly based on the results of a large number of animal experiments.

Recent studies reveal that PVAT transfers functional mitochondria to endothelial cells via extracellular vesicles (EVs), primarily exosomes, thereby enhancing vascular bioenergetics and redox balance (94–96). This intercellular mitochondrial transfer is mediated through exosomal packaging mechanisms regulated by the Endosomal Sorting Complex Required for Transport (ESCRT) and Rab GTPase proteins, which facilitate the formation of multivesicular bodies (MVBs) and subsequent vesicle docking to recipient cells (97). Exosomes selectively

encapsulate mitochondria via "mitochondrial sorting" signals involving syntaxin-17 and HSP90, ensuring functional organelle delivery (98). However, the depot-specific efficiency, with thoracic PVAT exhibiting greater efficacy than abdominal PVAT, may arise from higher exosomal yield and enhanced mitochondrial quality control (e.g., PINK1/Parkin-mediated mitophagy) in thoracic depots (31). Notably, obesity disrupts this process by inducing mitochondrial dysfunction (e.g., reduced oxidative phosphorylation and mtDNA mutations) in transferred organelles, while concurrently suppressing protective adipokines such as Neuregulin-4 (Nrg4) (99). Nrg4, secreted by adipocytes, attenuates metabolic inflammation by repressing proinflammatory macrophage polarization and restoring T cell function, thereby preserving PVAT homeostasis and exosomal mitochondrial integrity (100). These findings challenge the "Paracrine-Centric View" associated with PVAT and highlight Nrg4 agonism as a potential strategy to counteract obesityinduced mitochondrial transfer deficits.

# 2.3 Immune and inflammatory changes of PVAT in pathological states

### 2.3.1 Obesity-induced PVAT remodeling and immune dysregulation

Obesity profoundly alters the phenotype of PVAT, characterized by white adipocyte hypertrophy and hyperplasia within this depot (101–103). Excess body weight may also promote the conversion of aortic BAT into a WAT-like

phenotype (104). These adipocyte changes are metabolically significant, as hypertrophy is linked to increased inflammation and insulin resistance (105). Critically, obesity drives remarkable shifts in the immune cell landscape of PVAT. Populations of macrophages, neutrophils, dendritic cells, eosinophils, natural killer cells, B cells, and T cells exhibit altered abundance and function (2). Macrophages, the most extensively studied immune component, increase in number and activation state (polarization) during obesity, with a distinct shift towards proinflammatory M1 over anti-inflammatory M2 polarization (106). This M1 dominance is associated with insulin resistance and hypertension (103). Additional immune cells also play a role in the inflammatory response within PVAT, though they do so via different mechanisms. For example, Neutrophils contribute to early macrophage polarization through the release of CCL2 and TNF in response to high-fat diets (107). Dendritic cells are found in minimal quantities within the lean phenotype but are elevated in specific adipose regions when exposed to a high-fat diet (107, 108). Additionally, mast cells in adipose tissue demonstrate an increase during obesity, although not as prominently as macrophages (109, 110). In contrast, eosinophils show a decline in obesity, and their emerging function as potential key regulators of metabolic stability is significant (111, 112). The combined populations of B (113, 114) and T cells (115, 116) make up the second largest group of immune cells located in adipose tissue, following the macrophages found within this tissue. In the context of obesity, there is a greater overall presence of T cells, with their expression varying by depot (117). This dysfunctional state of PVAT contributes to increased vascular tone, vessel stiffness, activation of the renin-angiotensin-aldosterone system (RAAS), and diminished anti-contractile effects, promoting peripheral resistance and hypertension (118, 119).

### 2.3.2 Reciprocal interactions between diabetes and PVAT

A complex bidirectional relationship exists between diabetes and PVAT dysfunction. Hyperglycemia induces systemic oxidative stress and the overproduction of ROS (120, 121), which activate inflammatory pathways such as NF-KB. This activation triggers the infiltration of inflammatory cells into PVAT and the release of cytokines, including IL-6 and TNF- $\alpha$  (121, 122), establishing a chronic inflammatory state. Concurrently, dysfunction in PVAT adipocytes manifests as increased lipolysis and the release of free fatty acids, which induce lipotoxicity (123). While also reducing the secretion of the beneficial adipokine adiponectin. This deficiency in adiponectin impairs vascular function by decreasing NO bioavailability and increasing endothelin-1, thereby disrupting the balance of vascular tone (124). Conversely, dysfunctional PVAT actively contributes to the pathogenesis of diabetes. Disrupted adipokine secretion (e.g., decreased adiponectin and elevated levels of leptin, resistin, retinol binding protein 4, TNF-a, and IL-6) impairs insulin sensitivity in peripheral tissues. Inflammatory factors such as TNF- $\alpha$  and IL-6 interfere with insulin signaling by activating serine kinases (e.g., via JNK, NF-KB, and JAK-STAT pathways) (Figure 1C), leading to the phosphorylation of insulin receptor substrates and the blockade of signal transduction (125–127). Furthermore, vascular lesions driven by PVAT can compromise tissue perfusion, hindering the systemic delivery of insulin and glucose.

### 2.3.3 The role of PVAT in atherosclerosis development

PVAT has a pivotal role in the development of atherosclerosis, a condition characterized by the thickening and hardening of arterial walls. This tissue functions by secreting various adipokines and inflammatory mediators, including IL-6 and TNF-α. These substances activate inflammatory signaling pathways within both vascular endothelial cells and vascular smooth muscle cells (128). For instance, upon stimulation by tumor necrosis factor-a, endothelial cells activate the nuclear factor-kB signaling pathway, leading to increased expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1. This enhances the adhesion of inflammatory cells to the endothelial surface of blood vessels (129). Concurrently, inflammatory mediators induce vascular endothelial cells to secrete chemokines, including monocyte chemoattractant protein-1. Guided by the gradient of these chemokines, monocytes and other inflammatory cells traverse the gaps between endothelial cells and migrate into the subintima (130, 131). Additionally, PVAT serves as a significant source of ROS. The substantial production of ROS can oxidatively modify low-density lipoprotein, resulting in the formation of oxidized low-density lipoprotein, which impairs the relaxation function of endothelial cells (132). Ultimately resulting in thickening of the blood vessel wall and narrowing of the lumen, thereby effectively promoting the development of atherosclerosis (Figure 1D).

## 2.3.4 Relationship between hypertension and PVAT function

Hypertension exerts significant structural and functional impacts on PVAT. Chronically elevated pressure stimulates the differentiation of precursor cells into adipocytes and promotes lipid accumulation in existing adipocytes (133). Additionally, hypertension remodels the PVAT extracellular matrix by increasing collagen and fibronectin deposition, which disrupts local substance exchange and signaling. Additionally, hypertension alters the extracellular matrix components of PVAT, leading to increased deposition of collagen and fibronectin. These structural modifications disrupt the exchange of substances and signal transduction within PVAT, thereby impairing its normal physiological function (134, 135). Functionally, the hemodynamic alterations and heightened oxidative stress induced by hypertension contribute to PVAT dysfunction. Oxidative stress generates substantial amounts of ROS, which can damage cellular components in PVAT. Furthermore, hypertension disrupts the balance of vasoactive substances and inflammatory factors secreted by PVAT, transitioning it from a normal physiological regulatory state to a pathological state that promotes vasoconstriction and inflammation, further aggravating hypertension (136, 137). Reciprocally, PVAT critically influences blood pressure regulation

and becomes a key site for immune cell infiltration in hypertension (138). Infiltrating immune cells, such as T cells, release effector cytokines—including interferon-gamma (IFN- $\gamma$ ), interleukin-17 (IL-17), TNF- $\alpha$ , and IL-6 which initiate biological cascades that contribute to vascular dysfunction, heightened oxidative stress, and increased vascular stiffness. These PVAT-driven inflammatory and vascular responses significantly contribute to the pathogenesis of hypertension and its complications (139, 140) (Figure 1E).

#### 3 PVAT as a source of biomarkers

### 3.1 Advancements in imaging techniques for assessing PVAT inflammation

Computed Tomography (CT) imaging has established itself as the benchmark for effectively visualizing and characterizing PVAT (141). This is largely attributed to its exceptional spatial resolution, which allows for detailed imaging of structures within the body. Moreover, the distinct attenuation signals generated by adipose tissue enhance the accuracy and clarity of the images obtained. As a result, CT Imaging proves to be an invaluable tool in the study and analysis of PVAT, facilitating better understanding and insights into its role in various physiological and pathological conditions (142). The fat attenuation index (FAI) serves as a measure aimed at quantifying the three-dimensional attenuation gradients identified in coronary computed tomography angiography (CCTA) imaging of PVAT (141). FAI has received both biological and clinical validation, and it is now acknowledged as the main imaging biomarker for coronary inflammation sourced from CCTA. Standardized FAI evaluations are capable of accounting for side branches, thus yielding a more precise evaluation of PVAT inflammation (143, 144). In addition, the artificial intelligence (AI)-driven imaging biomarker (FRP) significantly improves the prediction of cardiac risk (143).

However, various imaging modalities, including magnetic resonance imaging (MRI) (145), positron emission tomography (PET), and ultrasound, offer promising applications for evaluating PVAT. MRI allows for the assessment of PVAT volume around major arteries, including the aorta, and has demonstrated an independent association with markers of subclinical atherosclerosis (146). PET provides functional insights into the metabolic activity of adipose tissue; however, its low spatial resolution limits its effectiveness in evaluating PVAT around coronary arteries (142). Although ultrasound may yield some surrogate measurements of EAT (147–149), its limited ability to distinguish adipose tissue from other structures, combined with its operator-dependent nature, reduces its utility in assessing PVAT in the coronary region.

### 3.2 Circulating biomarkers in evaluating PVAT function

In addition to imaging biomarkers, circulating biomarkers, including adipokines and cytokines, have potential applications

in evaluating PVAT function and predicting CVDs (150). For instance, plasma adiponectin levels are diminished in individuals with obesity and diabetes, and lower adiponectin levels have been linked to an elevated risk of CVDs (151). Similarly, plasma levels of IL-6 and TNF- $\alpha$  are increased in obesity and other pathological conditions, with high levels of these cytokines associated with a greater risk of CVDs (152). However, it is important to note that circulating biomarkers are not specific to PVAT function and may be influenced by other factors, such as systemic inflammation and tissue damage.

#### 4 PVAT as a therapeutic target

#### 4.1 Lifestyle modifications for enhancing PVAT function and reducing cardiovascular risk

Lifestyle modifications, including diet and exercise, hold significant promise for enhancing PVAT function and mitigating the risk of CVDs (153–155). In humans, exercise-induced weight loss is more effective than dieting alone in improving circulating adipokine profiles and insulin resistance (156, 157). Highintensity interval training has been particularly effective in reducing total adipose tissue and visceral adipose tissue (VAT) mass in adults (158, 159), as well as enhancing cardiorespiratory fitness in obese children (158, 160).

## 4.2 The role of novel pharmacological strategies in restoring PVAT function in CVD

PVAT has a well-established significance in the development and progression of vascular diseases, making it a promising target for innovative therapeutic strategies in cardiovascular medicine. Research has demonstrated that current anti-diabetic medications can partly mediate their positive cardiovascular effects through their interactions with adipose tissues, including PVAT (161). For example, glucagon-like peptide-1 (GLP-1) receptor agonists facilitate adipocyte differentiation and enhance overall adipocyte health (162, 163). GLP-1 and its agonists exert various direct effects on PVAT biology, including the reduction of lipid accumulation (164) and the promotion of lipogenesis (165). Furthermore, GLP-1 receptor agonists upregulate the expression of adipokines (166) and promote M2 macrophage polarization (167), clinical studies have demonstrated that administering the GLP-1 analogue liraglutide to individuals with obesity results in favorable modifications in plasma lipid profiles and a reduction in apolipoprotein B levels, which could significantly lower the risk of CVDs (168-171). Additionally, sodium-glucose cotransporter 2 inhibitors (SGLT2-i) have been found to exert beneficial effects on human PVAT, improving mitochondrial efficiency, reducing oxidative stress and inflammation, and enhancing tissue function (172). The SGLT2 inhibitor empagliflozin is notable for its ability to enhance the browning of WAT and activate resident M2 macrophages, which

helps decrease inflammation and insulin resistance linked to obesity, as demonstrated in animal research (173, 174). In human subjects, treatment with empagliflozin is linked to a decrease in the volume of EAT, which is critically associated with cardiometabolic risks (175, 176). Moreover, statins are known to decrease vascular inflammation, and their administration correlates with significant changes in the phenotype of PVAT following instances of acute coronary syndrome (ACS) and the commencement of statin treatment (177, 178). Other potential methods for restoring the health of PVAT include the use of PPAR- $\gamma$  agonists such as rosiglitazone (179, 180). It is essential to acknowledge the recognized negative impacts on individuals suffering from congestive heart failure. Furthermore, agonists of the cannabinoid CB1 receptor might facilitate the release of H<sub>2</sub>S from PVAT (181, 182). Mineralocorticoid receptor blockers have been shown to reduce adipose tissue inflammation and increase adiponectin levels (183, 184). However, the specific effects of current drugs on the PVAT remain unquantified, which poses a risk of off-target consequences. Therefore, it is essential to examine this issue from a more neutral perspective and to conduct further research.

## 4.3 Effect of surgical intervention on PVAT function

In patients with type 2 diabetes and obesity, undergoing metabolic surgery (defined as procedures that influence metabolism by inducing weight loss and altering gastrointestinal physiology) has been associated with a significantly reduced risk of major adverse cardiovascular events (MACE) compared to traditional nonsurgical management approaches (185). This finding highlights the potential of metabolic surgical interventions to enhance cardiovascular outcomes for this patient population, underscoring the necessity for a shift in treatment strategies. The deterioration of the anticontractile properties of PVAT observed in obesity is partly attributable to a reduction in adiponectin levels within the PVAT. This hormone is crucial for maintaining vascular health. Importantly, the weight loss achieved through bariatric surgery has the potential to restore adiponectin levels, which may lead to improvements in PVAT function and, consequently, cardiovascular health (186). In contrast, procedures such as abdominal liposuction have not shown significant benefits in correcting the metabolic abnormalities associated with obesity, thereby highlighting the limitations of these methods in addressing the complex nature of obesity-related health issues (187).

# 4.4 Targeting gut microbiota as a therapeutic approach to enhance PVAT function and vascular health

The gut microbiota plays a substantial role in influencing PVAT through various mechanisms, particularly by producing metabolites and regulating immune responses (188). Among

these metabolites, short-chain fatty acids produced by gut microbiota have been found to enhance the metabolic activity of adipocytes within the PVAT, which can lead to a reduction in inflammation levels. On the other hand, the presence of trimethylamine-N-oxide can trigger oxidative stress and inflammation in PVAT, negatively affecting its function. Additionally, emerging research in the field of cancer therapy shows that gut microbiota can regulate immune responses and produce metabolites that impact cancer development and treatment responses, suggesting its role in PVAT may have implications for broader health aspects related to cancer and vascular health (189, 190). Maintaining a healthy balance of gut microbiota is crucial, as it regulates immune cells that are essential for preserving PVAT homeostasis. When dysbiosis occurs, this balance is disrupted, potentially compromising both the structure and the functional integrity of PVAT. This finding highlights the promising potential of targeting gut microbiota as a therapeutic approach to enhance PVAT function and overall vascular health (191).

#### 4.5 Other potential therapeutic targets

The activation of  $\beta$ 3-adrenergic receptors ( $\beta$ 3-AR) by mirabegron presents another fascinating avenue for bolstering vascular health. Research has indicated that this pharmacological agent can prevent serious vascular conditions such as aortic dissection and aneurysm by promoting lymphangiogenesis within PVAT (192). Furthermore, colchicine has shown promise in inhibiting inflammatory responses in PVAT, as well as curbing abnormal cellular behaviors such as proliferation and migration that can lead to vascular complications (193-195). The role of perivascular relaxing factors, including methyl palmitate, is equally critical in managing PVAT and enhancing vascular functionality. These factors facilitate several important processes, including the relaxation of vascular smooth muscle, reduction of vascular resistance, and improvement of blood perfusion. Additionally, they work to inhibit inflammatory responses and decrease both inflammatory cell infiltration and mediator production (196, 197). Collectively, these multifaceted effects play a vital role in addressing CVDs associated with PVAT dysfunction. Despite the promising implications of these interventions, it is essential to conduct further research to ascertain their specific effects and ensure their safety for clinical applications.

### 5 Discussion and outlook

#### 5.1 Discussion

The evolving recognition of PVAT as a pivotal regulator of vascular homeostasis and a driver of CVD underscores its potential as a therapeutic target. However, translating mechanistic insights into clinical applications remains fraught with challenges, necessitating a critical reevaluation of current

paradigms and the integration of cutting-edge methodologies. While recent advancements in single-cell omics, imaging biomarkers, and therapeutic strategies have illuminated PVAT's spatiotemporal complexity, significant gaps still persist in reconciling its depot-specific heterogeneity with systemic vascular pathology. Although animal experiments have shown that β3-AR, methyl palmitate, and cannabinoid CB1 receptor agonists can alleviate the inflammatory response of PVAT (181, 182, 192), it is crucial to note that due to differences in PVAT composition and function across species, the applicability of preclinical findings (primarily from rodent models) to human pathophysiology requires rigorous validation. Furthermore, gender and age profoundly influence PVAT biology and CVD risk, though mechanistic insights into these effects remain limited (198, 199). For instance, postmenopausal women exhibit accelerated PVAT inflammation linked to estrogen loss (200, 201), and aging-associated PVAT fibrosis exacerbates endothelial dysfunction (122, 202).

To address these complexities, in this review, we systematically synthesized the molecular crosstalk, spatial heterogeneity, and therapeutic potential of PVAT in the pathogenesis of CVD. Concurrently, we highlighted three limitations of previous studies: (1) the oversimplified assumption of PVAT homogeneity, (2) the paracrine-centric view that overshadows mechanotransduction pathways, and (3) the unquantified depotspecific effects of existing therapies.

Given this landscape, the emerging role of PVAT in cardiovascular pathophysiology necessitates a paradigm shift from observational research to precision therapeutics. While single-cell omics elucidate its cellular heterogeneity—such as UCP1 + thermogenic, ADIPOQ + endocrine, and COL1A1 + fibro-inflammatory adipocytes—and depot-specific metabolic programming, clinical translation is hindered by insufficient human models and an overreliance on rodent data. Although advanced imaging biomarkers, such as fat attenuation index (FAI), and AI-driven radiomics enhance the detection of coronary inflammation (141, 142); standardization gaps combined with systemic confounding factors limit their practical utility. Consequently, therapeutic innovation should prioritize PVAT-centric strategies, including macrophage-targeted PPAR- $\gamma$  delivery and CRISPR-mediated ADIPOQ activation. Despite the preclinical promise shown by agents like β3-adrenergic receptor agonists (192) and colchicine (194), human trials remain limited. Hence, global consortia are essential to standardize protocols, address disparities, and ethically integrate AI-driven platforms. Ultimately, through bridging mechanistic depth with clinical pragmatism, PVAT research has the potential to redefine precision cardiology and mitigate residual cardiovascular risk.

#### 5.2 Future research directions

To address the specific gaps and broader translational challenges, such as species differences, inadequacies in human models, biomarker standardization, and the necessity for human trials, we propose a multidisciplinary roadmap that integrates molecular insights with translational applications. Firstly, singlecell and spatial multi-omics techniques (e.g., snRNA-seq and single-cell ATAC sequencing) will elucidate PVAT's cellular diversity and epigenetic mechanisms, complemented by dynamic three-dimensional models to validate mechanosensitive pathways. Additionally, the development of clinical biomarkers requires cross-population validation of PVAT-specific signatures, while also addressing obesity-related fibrotic suppression. Moreover, therapeutic innovation depends on nanotechnology-enabled delivery systems [e.g., macrophage-targeted lipid nanoparticles (203)] and CRISPR activation-mediated ADIPOQ activation (204), combined with circadian optimization (e.g., timed melatonin administration). Finally, global consortia must standardize protocols and utilize AI-driven data harmonization to accelerate discovery, while adaptive trials address sex and racial disparities and ensure gene-editing safety (Figure 2).

Moving forward, precision therapies will concentrate on cellspecific PVAT targets by employing systems biology and network pharmacology. Personalized lifestyle modifications and surgical interventions will be refined based on long-term outcome data, while mechanistic studies of gut microbiota and PVAT will inform targeted interventions. By emphasizing mechano-



metabolic pathways, microbiota interactions, and ethical considerations, this roadmap seeks to transform PVAT biology into stratified cardiovascular therapies, thereby reducing residual risk and enhancing disease management through molecular precision.

### 6 Conclusion

PVAT serves as a critical regulator of vascular homeostasis, with its dysfunction contributing to cardiovascular pathology through paracrine imbalance, metabolic dysregulation, and extracellular matrix remodeling. Advances in imaging techniques and circulating biomarkers now facilitate the early detection of PVAT abnormalities, while emerging therapies, such as SGLT2 inhibitors and circadian rhythm modulation, show promise in restoring PVAT function. However, challenges persist in standardizing diagnostic protocols, optimizing tissue-specific drug delivery, and evaluating long-term safety. Future research ought to prioritize translational studies and multidisciplinary collaboration to integrate PVAT-targeted strategies into precision cardiovascular medicine, ultimately aiming to reduce residual disease risks and enhance clinical outcomes.

#### Author contributions

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