



Review

Promotion of Cardiovascular Homeostasis by the Perivascular Adipose Tissue Secretome

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Abstract

Perivascular adipose tissue (PVAT) is a unique fat depot that is distributed around blood vessels, contiguous with the vascular adventitia. Due to this proximity, it serves as a local source of adipokines and vasoregulatory factors. Similar to other adipose depots, PVAT is responsive to changes in metabolic state and, at least in mice, can transition to a thermogenic adipocyte phenotype depending on metabolic health. Cardiovascular disease risk is highly correlated with metabolic health and increases substantially in individuals with obesity or metabolic syndrome. Cardiovascular diseases, including atherosclerosis/coronary artery disease, aortic aneurysm, hypertension, arterial stiffening, and heart failure, have been associated with PVAT dysregulation. Understanding the cardiovascular protective effects of healthy PVAT can provide ways to modify disease progression to re-establish functional homeostasis. This review focuses on experimental studies that specifically define a signaling axis between PVAT and the cardiovascular system that provide cardioprotection. Our focus is primarily on the secreted contents of extracellular vesicles that initiate this adipose signaling axis and regulation of extracellular vesicle release by the trafficking molecule, RAB27a. We review the current literature on human and mouse studies and major categories of PVAT-derived signaling components including microRNAs, lipids, and proteins that contribute to cardiovascular homeostasis.

Keywords: cardiovascular; extracellular vesicles; secretome; signaling; cardiometabolic



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1. Introduction

Cardiovascular disease (CVD) is a heterogeneous group of pathologies involving the heart and vascular system, that collectively represent the leading cause of death in the United States and increasing globally. Conditions ranked by level of mortality include coronary artery disease (~40%), stroke (~18%), other CVD (~17%), hypertensive disease (~14%), heart failure (~9%), and diseases of arteries (~3%). Behaviors and medical conditions such as smoking, poor diet, inactivity, excessive alcohol consumption, high blood pressure, high cholesterol, and obesity all increase the risk for CVD [1]. Communication from the vascular microenvironment to the cardiovascular system is a key mediator of tissue homeostasis. Perivascular adipose tissue (PVAT) has been identified as a source of paracrine signaling factors that either protect the cardiovascular system or participate in pathologic cellular dysregulation, increasing the risk for CVD. PVAT surrounds blood vessels and is an important regulator of vascular tone by secreting cytokines which interact with the blood vessel wall [2]. In conditions of cardiometabolic dysfunction and obesity, PVAT secretes pro-inflammatory cytokines, such as leptin, MCP-1, and TNF-alpha, that

lead to proatherogenic states, concepts which have been previously reviewed [3,4]. While there is extensive literature associating disease-related adipose tissue phenotypes, this review will focus on PVAT-derived factors that are considered cardioprotective, which we define as having effects that suppress cellular changes associated with pathology. We highlight PVAT-derived factors where evidence suggests they may be secreted through signaling microvesicles released extracellularly.

The secretome of a cell or tissue is the combined array of bioactive factors released extracellularly to induce autocrine or paracrine signaling [5]. The cellular secretome is regulated by metabolic state and is fundamental in the body's ability to maintain homeostasis by facilitating communication between major organ systems and tissues. These mediators of communication can be proteins, peptides, RNA species such as mRNAs, microRNAs and lncRNAs, lipids, hormones, and metabolites. The secretome can be further categorized into free circulating factors or those packaged within extracellular vesicles. These vesicles are characterized by size and biogenesis: exosomes (ranging from 30 nm to 100 nm) are formed within the endosomal network and are released through the plasma membrane [6]; micro vesicles/microparticles (ranging from 200 nm to 1 μ m) are directly shed from the plasma membrane; and lastly, apoptotic bodies (ranging from 1 μ m to 4 μ m) are released as membrane blebs.

There are multiple proteins and processes involved in the formation and secretion of exosomes from cells. Intracellular vesicles form larger multivesicular bodies that fuse with the plasma membrane and result in the release of intraluminal vesicles as exosomes. Sorting of cargo within these vesicles is complex and not well characterized; known plasma membrane microdomain proteins, lipids, and structures involved include caveolae, clathrin, ceramide, lipid rafts, dynamin, neutral sphingomyelinase, small GTPases (including RAB family members), and many other proteins related to the cytoskeleton and plasma membrane [7]. Formation of intraluminal vesicles within the multivesicular bodies occurs via at least two pathways—endosomal sorting complex required for transport (ESCRT)-dependent or -independent. The ESCRT pathway contributes to the transport of multivesicular bodies and sorting of exosomal cargo [8]. Interestingly, ceramide contributes to the ESCRT pathway and ESCRT-independent intraluminal vesicle budding [9], which also involve another RAB family member, RAB31 [10].

Exosomes and extracellular vesicles have been reviewed for their roles in cardiovascular diseases as biomarkers and potential therapeutic targets [11–13]. Likewise, adipose tissue-derived exosomes and their target tissues and organs have been widely defined and reviewed in the recent literature [14–17]. We recently identified a novel connection between a member of the Rab GTPase family, RAB27A, and cardiac and vascular dysfunction in vivo [18]. Despite the primary role of RAB27A in exosome biogenesis and secretion and its requirement for metabolic homeostasis, very little is known about RAB27A function in adipose tissue and its signaling functions. However, RAB27A is an interesting target as a mediator of adipose–cardiovascular signaling, as described below.

2. RAB27A Function in Exosome Regulation and Cardiovascular Health

The release of exosomes through membrane docking and fusion relies on protein signal cascades. Rab GTPases, particularly RAB27A and RAB27B, play essential roles in protein trafficking, mediating multivesicular endosome fusion with the plasma membrane, and exosome release into the extracellular space [19–21]. In melanoma cells, loss of RAB27a also changes the protein content of secreted extracellular vesicles or promotes the secretion of a molecularly distinct sub-class of exosomes [22]. Human missense mutations in RAB27A cause Griscelli syndrome type 2 [23–26], and affected individuals have variable levels and onset [27] of impaired melanocyte trafficking, leading to albinism, silver/gray hair coloring,

and impaired immune cell degranulation, often leading to neurological damage [26]. Lifespan for individuals with Griscelli syndrome type 2 is short, with improved prognosis after hematopoietic stem cell transplantation. Because many patients do not survive childhood, age-associated conditions such as heart or vascular disease have not been associated with this population. However, using human genetic data from the Common Metabolic Diseases Knowledge Portal, genetic variants of human *RAB27A* were found to be associated with body mass index, hypertension, and myocardial infarction [18]. These data suggest that in humans, RAB27A function contributes to cardiometabolic homeostasis [28].

RAB27A is produced in human and mouse PVAT [18], and we found that suppression of RAB27A by siRNA in human preadipocytes inhibited adipocyte differentiation [29]. While *Rab27a* generally has a wide expression pattern throughout the body, in the mouse it is not expressed in the heart, while in blood vessels, it is expressed in PVAT, vascular smooth muscle cells, and endothelial cells [18]. The importance of RAB27A in exosome release has been established in loss of several *Rab27a* mouse strains. In one *Rab27a*-null mutant mouse strain, bone marrow-derived endothelial progenitor cells lacking RAB27A had decreased viability, proliferation, and reduced exosome release [30,31]. The cells lacking RAB27A did not induce therapeutic improvement when transplanted after myocardial infarction, unlike bone marrow-derived cells from wild type mice [20].

In a different, independently targeted *Rab27a*-null strain, global loss of RAB27A was associated with age-related cardiovascular defects [18]. At eight weeks of age, *Rab27a*-null male mice had increased vasoconstriction and reduced vasodilation. By 20 weeks of age, the males exhibited a cardiomyopathy phenotype. These loss-of-function data show that RAB27A has cardio- and vasculo-protective effects. RAB27A loss in male mice was associated with delayed glucose clearance in a glucose tolerance test, suggesting changes in insulin regulation or signaling [32,33]. It is possible that the absence of RAB27A may alter the secretome, leading to downstream changes in the phenotype of targeted cells. The loss-of-function phenotypes could be a primary effect of production within the heart and blood vessels themselves or metabolic changes in other tissues that then regulate cardiovascular function. As PVAT-derived molecules have been associated with protection against CVD, we hypothesize that RAB27A plays a role in the release of these cardioprotective factors.

While RAB27a is a candidate regulator of extracellular vesicle signaling in the PVAT-to-heart/vascular axis, it is important to note that this hypothesis needs further in vivo testing. The components of the secretome or extracellular vesicles that are described below have functional activity, and some have been validated as exosomal cargo. However, exact mechanisms and regulation of these RNA, lipid, and proteins specifically by RAB27a-mediated cellular release mechanisms in PVAT are currently under investigation. While we developed a conditional, floxed RAB27a mouse strain [18], currently, there are no PVAT-specific Cre strains that can distinguish RAB27a function in PVAT from other adipose tissues. Ongoing studies are focused on the approach of ex vivo characterization of the secretome of human PVAT.

3. Cardioprotective RNAs Secreted from PVAT

RNAs released in extracellular vesicles, including microRNAs (miR), long non-coding RNAs, mitochondrial RNAs, and mRNAs, play key roles in communication between PVAT and target cells. This communication impacts physiological and pathological vascular development as well as homeostasis.

While PVAT-derived RNA species associated with the progression of cardiovascular pathologies have been identified, new studies have begun to identify RNA contents attenuating and protecting against disease (Table 1). A study by Sun et al. [34] aimed to identify how miRNAs from adipose endothelial cells regulate gene expression and modulate the

development and progression of cardiometabolic phenotypes. miRNA-181b expression in endothelial cells in adipose tissue of obese mice was significantly reduced after 12 weeks on a high-fat diet, and obese mice treated with miRNA-181b showed improved glucose tolerance and insulin sensitivity. Further, the administration of miRNA-181b attenuated endothelial dysfunction, enhanced the production of eNOS, and exerted anti-inflammatory effects [34]. Another study by Liu et al. analyzed the effects of PVAT-derived extracellular vesicles on vascular homeostasis and showed that miR-382-5p was expressed at lower levels in PVAT-derived vesicles from patients with coronary atherosclerotic heart disease than in healthy subjects. miR-382-5p reduced macrophage foam cell formation and increased the expression of cholesterol efflux transporters ABCA1 and ABCG1 downstream of PPAR γ , consistent with a protective effect of this microRNA [35].

Administration of microRNAs through neutrophil membrane-engineered extracellular vesicles (NVEVs) provide therapeutic benefits. Wei et al. engineered NVEVs through the fusion of PVAT-derived extracellular vesicles with neutrophil membrane nanovesicles, resulting in superior targeting to regions of inflamed vasculature. miR-206-3p in NVEVs promoted regression of atherosclerotic plaques through ABCA1 cholesterol efflux and favorable vascular remodeling. Furthermore, administration of the NVEVs in rat models of atherosclerosis significantly attenuated inflammation, stabilized vascular architecture, and reduced macrophage infiltration [36]. The identification and study of protective PVAT-derived microRNAs provide potential therapeutic targets to re-establish cardiovascular homeostasis.

Long non-coding RNAs are another emerging area of interest, although few studies exist on non-coding RNAs specifically in the relationship between PVAT and the cardiovascular system. A study by Xie et al. identified promising findings on the expression of LINC01180, an immune-related lncRNA, as a potential protective factor against the development of atherosclerosis in patients [37]. In this study, LINC01180 was among eight other long non-coding RNA with immune-related functions that were elevated in PVAT from individuals with coronary heart disease. Expression of LINC01180 was found to be associated with the instability of atherosclerotic plaques, suggesting that this is a promising target. Despite the minimal research presently available, long non-coding RNAs are another promising avenue for future RNA studies that may provide important insights into the development and protection against disease.

Table 1. PVAT-derived cardioprotective RNA species.

RNA	Effects	Reference
miRNA-181b	Exerts anti-inflammatory effects; enhances production of endothelial NO synthase (eNOS); attenuates endothelial dysfunction	[33]
miR-382-5p	Reduces macrophage foam cell formation by mediating upregulation of cholesterol efflux transporters, ABCA1, and ABCG1	[34]
miR-206-3p	Enhances cholesterol efflux via miR-206-3p-ABCA1-dependent signaling and upregulation of cholesterol efflux transporters, ABCA1, and ABCG1	[35]
LINC01180	Protective factor against the progression of atherosclerosis	[37]

4. Cardioprotective Lipids Derived from PVAT

The field of lipidomics is fairly young, and there were only limited reports characterizing the lipid content of extracellular vesicles in healthy and diseased states at the time this review was written (Table 2). Studies to date have focused on the links between lipidomic profiles and the development of diseases such as cancer, specifically prostate and ovarian malignancies, and cardiometabolic diseases [38]. Membrane lipids are an integral component of exosomal vesicles generated intracellularly by the budding and fission of multivesicular endosomes [39]. Extracellular vesicles are enclosed by a lipid bilayer with a specific lipid composition of cholesterol, sphingolipids, and phospholipids; however, the extent of this specific enrichment can vary by cell type and metabolic state [39]. Extracellular vesicles thus contribute to carrying lipid cargo between cells, tissues, and organs.

Table 2. Lipid species with evidence for cardiovascular protective activities and/or exosome localization of the major lipid class [40,41].

Lipid Class	Example Species	Cardioprotective Action	References
Triacylglycerides (TAGs) containing polyunsaturated fatty acids	TAG(18:1/18:1/22:6),	Anti-inflammatory PUFA supply; improve endothelial NO signaling	[42]
Prostaglandins containing polyunsaturated fatty acids	Prostaglandin E2-EP4	Protection from ischemic events	[43]
Phosphatidylcholines (PC) and phosphatidylethanolamines (PE) with n3-PUFA chains	PC(22:6-n3) PE(22:6-n3)	Anti-oxidant capacity and protection from ischemic events, linked with better vascular/metabolic outcomes	[44]
Plasmalogens (ether-linked Pls)	PlsPE(16:0/22:6), PlsPC(18:0/20:5)	Anti-oxidant; protect endothelial NO	[42]
Sphingosine-1-phosphate (S1P)	S1P(d18:1)	Enhances NO production, endothelial barrier, and survival signaling	[45,46]
Hexosylceramides (HexCer)	HexCer(d18:1/16:0), HexCer(d18:1/24:0)	Inverse association with CVD risk in some cohorts	[47]
Unsaturated lysophosphatidylcholines (Lyso-PCs)	Lyso-PC(18:2), Lyso-PC(20:4)	Some species linked with better vascular function	[48]
Sphingomyelins (SM, long-chain unsaturated)	SM(d18:1/24:1)	Some species inversely associated with atherosclerosis	[49,50]

4.1. Sphingolipids

Similar to their cells of origin, exosome membranes are asymmetrical, with the outer leaflet enriched in sphingomyelin and the inner leaflet higher in phosphatidylserine species; however, changes in cell membrane lipid organization can influence the distribution of these lipids in the exosomes they secrete [51]. Exosomes are particularly enriched in sphingolipids due to the necessity of forming a membrane with tight curvature, which requires small, conic-shaped lipids. Sphingolipids also function as lipid rafts, essential platforms that support the function of membrane-bound proteins and provide a sorting mechanism for vesicle flow from the Golgi apparatus to the plasma membrane for release [52,53]. One well-designed study by Mahmoud et al. [54] compared extracellular vesicles from healthy, lean individuals to obese individuals and found that those from healthy individuals were characterized by higher levels of sphingomyelin and phospholipids and lower levels of ceramide and free fatty acids. Previous work has already suggested that sphingomyelin and ceramides are markers of cardiovascular disease, and studies have shown a link between circulating ceramides and tissue damage in cardiometabolic dis-

eases [55–57]. Circulating subclasses of sphingolipids, including sphingomyelin, ceramides, and sphingosine-1-phosphate, have been directly linked to the concurrence of diabetic cardiomyopathy, dilated cardiomyopathy, myocardial ischemic heart disease, hypertension, and atherogenesis [49,58].

While most available literature focuses on the link between circulating lipids and the progression of disease, new evidence has emerged on their role in maintaining cardiovascular homeostasis. Sphingosine-1-phosphate can protect the heart against ischemia and reperfusion injury when released together with adenosine [59–61]. Evidence suggests that vesicular sphingolipids and their metabolic enzymes, such as sphingomyelinases and ceramidases, contribute to extracellular vesicle signaling and action by influencing recipient cell sphingolipid levels, potentially contributing to the development of these diseases. The finding that extracellular vesicles contain enzymes that metabolize lipids into molecules with different biological activity [62] expands their metabolic significance. In addition to sphingomyelinases and ceramidases, exosomes contain phospholipase enzymes and cyclooxygenases, allowing cells to compartmentalize the production of bioactive fatty acids [63].

Exosomes are also enriched in glycosylated sphingolipids such as hexosylceramides, which can be associated with pathology [64–66]. In the heart, hexosylceramides are protective against the deleterious effects of ceramide accumulation [67] and they change the biophysical properties of membranes by increasing fluidity.

4.2. Palmitic Acid Methyl Ester

A study by Lee et al. identified the role of PVAT-derived palmitic acid methyl ester (PAME) on vascular tone, an important mediator for the progression of vascular disease [68]. Their study found that PAME, a PVAT-derived relaxing factor, induced vessel vasorelaxation via the opening of K⁺ channels in vascular smooth muscle cells. In addition, they discovered that a reduction in the release of PAME alongside an increase in angiotensin II in PVAT was associated with hypertension, suggesting PAME as a cardiovascular protective lipid [68].

4.3. Phospholipids

The cardioprotective effects of phospholipids containing polyunsaturated fatty acids vs. monounsaturated or saturated fatty acids have been well established. Recent reviews of this topic provide an in-depth review of the cardioprotective effects of these lipids, including the anti-inflammatory properties of specific omega-3 and omega-6 polyunsaturated fatty acids [69,70]. However, more work is needed to clarify the role of polyunsaturated and monounsaturated fatty acid-containing lipids in exosomes and how exosomes may contribute to the distribution of cardioprotective lipids.

4.4. Plasmalogens

Several reports have shown that exosomes contain plasmalogens [71–73], which are ether lipids important for membrane fusion [74] and have strong anti-oxidant and anti-inflammatory functions [75,76]. The content of plasmalogens in exosomes of various origins is estimated to be up to 50% of all lipids. The plasmalogen content of exosomes released from PVAT is unknown and requires further study. However, considering the important biological roles of plasmalogens, we anticipate that they will prove to be an important aspect of cardioprotection in the PVAT–cardiovascular axis.

5. Protective PVAT-Derived Protein Secretome

Several secreted proteins are released from PVAT-derived cells; these are summarized in Table 3.

Table 3. PVAT-derived cardioprotective secreted proteins.

Protein	Effects	Species	References
Adiponectin	An anti-inflammatory adipokine.	Human	[77]
	Protects against vascular neointima lesion formation.	Mice	[78]
	Decreased adiponectin induced inflammatory pathophysiological conditions.	Mice	[79]
	Reversed molecular interactions associated with CAD, such as the adhesion of THP-1 cells to endothelial cells and reduced expression of intercellular adhesion molecules.	Human	[80]
	Reduced expression in obese PVAT; absence contributes to NO inhibition in obesity.	Human	[81]
	An anti-inflammatory adipokine; potentially elicits beneficial effects in the pathogenesis of CAD	Human	[82]
	Contributes to myocyte hyperpolarization; releases NO to induce vasorelaxation	Mice	[83]
	Reduced pro-inflammatory cytokines like TNF- α and IL-6; acts as an anti-inflammatory, and anti-atherogenic.	Mice	[84]
Endothelial Nitric Oxide Synthase (eNOS)	Produces NO that is anti-atherogenic, by controlling vascular smooth muscle proliferation, inhibiting platelet aggregation, leucocyte adhesion, and vascular inflammation.	Mice and Humans	[85,86]
	Produces NO; Uncoupling of eNOS increases ROS production, leading to oxidative stress and inflammation; Obese/metabolic syndrome mice had higher eNOS uncoupling.	Mice	[79]
	Uncoupling contributes to generation of superoxide and impairs tonic NO release; Obese tissue has decreased NO.	Human	[81]
	Uncoupling of eNOS diminishes superoxide production; Uncoupling is a function of arginase induction and L-arginine deficiency; Diet-induced obesity leads to L-arginine and NO deficiency, and eNOS uncoupling.	Mice	[87]
Omentin-1	Recovers anti-contractile action; Improves pro-inflammatory and pro-oxidant PVAT phenotype; Restores NO and inhibits oxidative stress.	Rat	[88]

Table 3. Cont.

Protein	Effects	Species	References
Indoleamine 2,3-dioxygenase metabolite (IDO)	Downregulated in atrial fibrillation; Inhibit TGF-beta1-induced cardiac fibroblast activation; Antifibrotic adipocytokine.	Human	[89]
	Decreased in patients with coronary artery disease; Decreased in fat next to coronary stenotic segments.	Human	[90]
	Increased expression in epicardial adipose in patients with coronary artery disease; plays cardioprotective role.	Human	[91]
	Increased expression in response to cold (brown fat). Mild cold-induced PVAT activation attenuates age-dependent and obesity-induced endothelial dysfunction.	Mice	[92,93]
	Caused a relaxation response in vessels.	Mice	[94]
	Enzymes primarily in brown fat surrounding the thoracic aorta; Depresses aortic contractility.	Rats	[95]

5.1. Adiponectin

Adiponectin is highly secreted from adipose tissue. It can be secreted in exosomes and also regulates exosome secretion. PVAT-derived adiponectin is an important mediator in the promotion of vascular health and the maintenance of homeostatic conditions in the cardiovascular system [96,97]. PVAT adiponectin acts as an anti-atherogenic factor by reducing vascular O₂⁻, a free radical that can cause vascular damage, and increasing PI3/Akt-mediated eNOS phosphorylation, which increases the production of vasorelaxing factors [80]. It also attenuates the secretion of inflammatory factors through AMP-activated protein kinase inhibition of the NF-κB signaling pathway, leading to decreased cardiac inflammation and atherosclerosis. In an aging model of cardiovascular deletion of the endonuclease ERCC1, vasodilation was decreased due to decreased NO production and loss of endothelium-derived hyperpolarization. PVAT under these conditions was shown to partially compensate for decreased vasorelaxation through its secretion of adiponectin [96]. In lean human models, PVAT secretes adiponectin as a mean of protecting against the development of hypertension and diabetes by reducing peripheral vascular resistance and improving nutrient uptake into tissues [98,99]. PVAT adiponectin plays many cardiovascular protective roles by maintaining homeostasis, decreasing cardiac inflammation, inhibiting cardiomyocyte hypertrophy, regulating fibrosis, and suppressing the development of atherosclerosis [100].

The release of adiponectin is mediated by fatty acid-binding protein 4 (FABP4), a nuclear ligand importer, and its targeted receptor, peroxisome proliferator-activated factor (PPAR-γ) [101,102]. Activation of the PPAR-γ signaling cascade in PVAT has been shown to upregulate the adiponectin gene in response to vascular oxidative stress to protect against injury and inflammation [103]. Interestingly, the literature describing the expression of PPAR-γ and FABP4 in PVAT from mice fed high-fat or high-cholesterol diets reports some discrepancies. In a study by Chatterjee et al., mice fed a high-fat diet for two weeks expressed lower levels of adiponectin, PPAR-γ, and FABP4 as compared to chow-fed mice [77]. However, Irie et al. found that mice fed a high-cholesterol diet had upregulated PPAR-γ and FABP4 expression in PVAT at the end of 12 weeks when compared to chow-fed mice [84]. It is possible that two weeks of a high-fat diet was not long enough to induce

adipocyte differentiation, as FABP4 and PPAR- γ are important regulators of differentiation and adipocyte phenotype determination.

The expression of adiponectin has been reported to change based on metabolic status. Multiple studies have found an association between obesity and metabolic syndromes, and reduced levels of PVAT-derived adiponectin in comparison to non-obese individuals. Greif et al. investigated the relationship between pericardial fat volumes and CVD risk factors such as serum adiponectin, inflammatory biomarkers, and the morphology and quantity of coronary atherosclerosis. Elevated pericardial adipose tissue volumes, such as in obesity, were associated with low adiponectin levels, low high-density lipoprotein, elevated TNF- α levels, and increased atherosclerotic lesions [104]. Decreased levels of periadventitial adipose tissue has been associated with disease progression. High-fat, high-sucrose feeding in mice was associated with inflammatory changes and decreased adiponectin expression in periadventitial adipose tissue. These inflammatory changes and decreased adiponectin levels were associated with enhanced neointima formation after endovascular injury. Adiponectin-deficient mice showed increased neointima formation in injured blood vessels [105].

5.2. Endothelial Nitric Oxide Synthase

Endothelial nitric oxide synthase (eNOS) in PVAT regulates the production of nitric oxide (NO), a key vasoprotective element. Uncoupled eNOS can no longer produce NO, but instead creates superoxide, a reactive oxygen species (ROS) that causes tissue damage and inflammation. Reduced bioavailability of NO can lead to endothelial dysfunction associated with atherogenesis. This pathological mechanism has been shown in obesity, where uncoupled eNOS in PVAT results in excess ROS by NAD(P)H oxidase activation, leading to a decrease in NO production [85,87]. A study by Gil-Ortega et al. measured the expression of eNOS and NO bioavailability in mesenteric PVAT of mice fed with a high-fat diet and found undetectable expression. Conversely, superoxide levels were increased in the PVAT of obese mice, and mesenteric endothelial-dependent relaxation was significantly impaired in the high-fat diet group compared to the control [106]. Thus, PVAT eNOS plays a critical role in maintaining cardiovascular health by protecting against harmful ROS. However, the mechanism of how eNOS expression in PVAT is regulated is not fully understood and requires additional research.

5.3. Omentin-1

Omentin-1 is encoded by the gene *intelectin-1* (*ITLN1*), and its expression in PVAT protects against cardiovascular disease by targeting the immune system to reduce pro-inflammatory mediators [107]. Omentin-1 is an antifibrotic adipocytokine that inhibits transforming growth factor (TGF)- β , a key pro-inflammatory activator of cardiac fibroblasts in epicardial adipose tissue [89]. It decreases the levels of pro-inflammatory and pro-oxidant C-reactive protein and nitrotyrosine in PVAT and exerts endothelial beneficial effects by restoring NO levels and inhibiting oxidative stress in animal models of type 2 diabetes [88]. The cardiovascular protective effects of omentin-1 have further been modeled by its administration in disease states. Hiramatsu et al. demonstrated a reduction in lipid droplets, macrophage accumulation, atherosclerotic lesion formation, and mRNA expression of pro-inflammatory mediators, tumor necrosis factor- α , IL-6, and monocyte chemoattractant protein-1, after omentin-1 administration in mice [107]. Furthermore, omentin-1 restored the anti-contractile action of PVAT that was lost in diabetic mice [88].

Consistent with its cardioprotective effects, some studies have found decreased omentin-1 levels in cardiovascular disease. Chen et al. observed that in patients with atrial fibrillation, omentin-1 was downregulated in epicardial adipose tissue and the right

atrial appendages, while TGF- β 1 was upregulated [89]. In patients with coronary artery disease, omentin-1 levels in circulation and epicardial adipose tissue were decreased and was exaggerated in fat tissue directly next to coronary stenotic segments [90]. Thus, local levels of omentin-1 are not always inversely correlated with disease state. Another example of this is the report that omentin-1 expression was increased in the epicardial adipose tissue of non-obese patients with coronary artery disease [91]. It is likely that the overall metabolic health of individuals, as well as local tissue pathology, contributes to omentin-1 production at different sites within the cardiovascular system.

5.4. Fibroblast Growth Factor-21

Fibroblast growth factor-21 (FGF-21), an anti-inflammatory adipokine, is secreted in large amounts by the liver and adipose tissue, but is expressed in lower amounts in the aorta and PVAT [92]. There is limited information on the role of FGF21 from PVAT on vascular homeostasis. A study by Mestres-Arenas et al. aimed to characterize whether expression of bioactive factors known to be produced in brown adipose tissue were secreted in PVAT surrounding the thoracic or abdominal aorta. In the mouse, PVAT surrounding the thoracic aorta resembles brown adipose tissue, whereas PVAT close to the abdominal aorta has a mixture of white adipose tissue and fewer brown-like adipocytes. Cytokines typically produced in brown adipose tissue were higher in the thoracic region and lower in the abdominal region [92], corresponding to their cellular morphology.

Circulating FGF21 has anti-atherosclerotic effects; it reduces lipid and cholesterol profiles, inhibits macrophage migration, inhibits foam cell formation, alleviates oxidative stress by ROS, and reduces the expression of inflammatory cytokines [108–110]. Furthermore, FGF21 promotes the secretion of adiponectin, which results in the reduction in endothelial dysfunction and inhibition of smooth muscle cell proliferation and foam cell formation. As a whole, these effects come together to contribute to FGF21 resistance to the progression of CVD [111,112]. FGF21 is a potential target that, when released from PVAT, could contribute to PVAT's cardioprotective effects.

6. Discussion, Limitations, and Future Directions

PVAT is now understood to mediate a variety of effects on cardiovascular health and disease. There are several outstanding issues related to leveraging this knowledge to promote vascular health in human populations. Firstly, most of the work studying the molecular features in PVAT has occurred in rodent models, which are tractable for the study of metabolic disease, cardiovascular disease and injury, and aging. It is not always straightforward to translate genetic and signaling pathways from rodent models to human disease, so validation is warranted. Molecular analysis of human adipose tissues and comparisons to mouse adipose tissues have been driven through single-cell transcriptomics studies, in particular, for white [113] and beige/brown adipose tissues [114]. More recently, we have analyzed available data from human PVAT from unique cohorts of patients with cardiovascular disease, in comparison to mouse PVAT [115,116]. While there are certainly conserved phenotypes, especially in functionally mature adipocytes, we noted species diversity, especially in adipose progenitor populations. At the morphological level, human PVAT appear similar to subcutaneous white adipose tissue, although adipocyte size has been reported to be smaller. Human PVAT also expresses thermogenic markers such as FGF21, UCP-1, and PGC-1 α in vivo [117], with a similar profile maintained when progenitor cells from human PVAT were derived and differentiated in vitro, compared to progenitor cells from human subcutaneous white adipose tissue [118].

The overall landscape of secreted paracrine factors from PVAT, especially from human tissue, remains an area of active study. Distinct from soluble paracrine factors, the packaging of diverse molecular cargo in extracellular vesicles is expected to provide a longer half-life and potentially allow cargo to be targeted to different organs [119]. There are many categories and types of secreted microvesicles [120], and often it is unclear whether specific molecules are packaged as vesicular cargo or have an association with vesicles. The ExoCarta small extracellular vesicle protein, RNA, and lipid database [41] provides a curated list of molecules experimentally associated with extracellular particles. Using this resource, we have summarized the PVAT-derived cardioprotective factors discussed as evidence of their localization in secreted extracellular vesicles (Figure 1). Of note, there is experimental evidence that some components of extracellular vesicles are conserved between rodents and humans. Adiponectin is an example of this, as it has been characterized in extracellular vesicles from adipocytes in rats [121] and from human bone marrow mesenchymal cells [122]. However, other components of extracellular vesicles have only been studied in one cell type or species and may not be broadly generalizable. There is also expected to be some cell-type specificity in cargo release within vesicles.

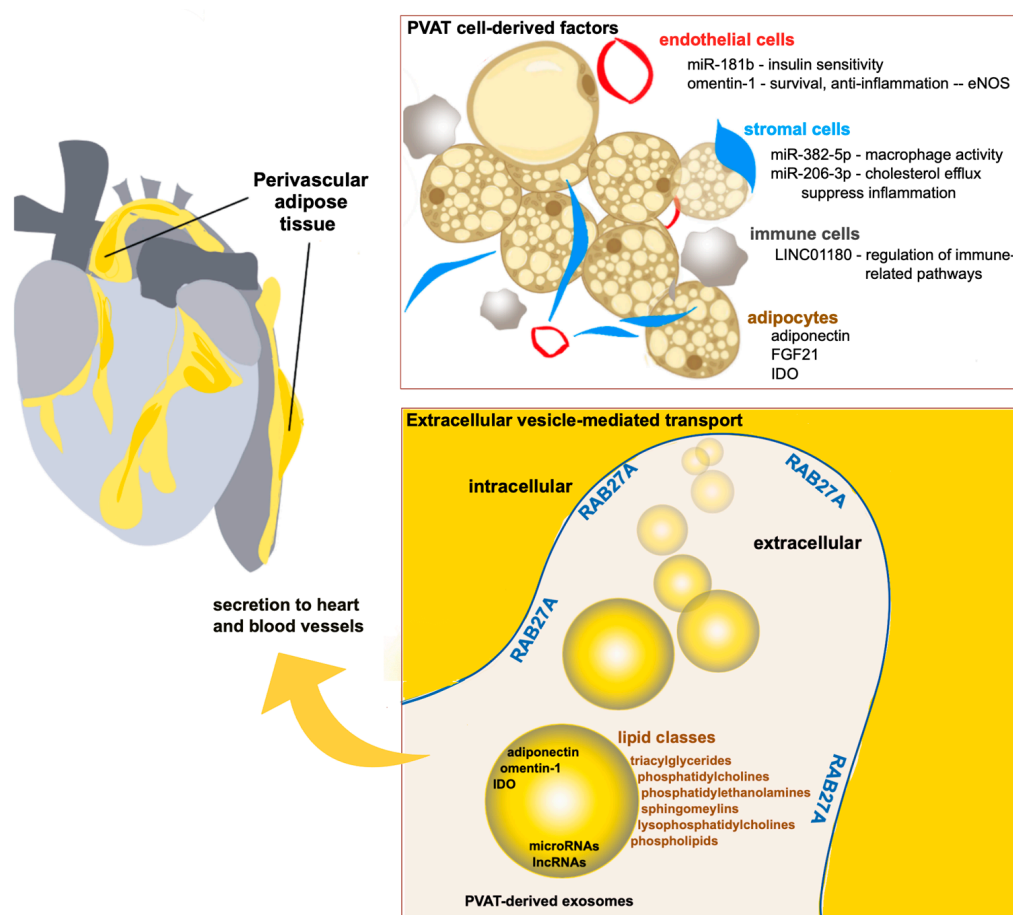


Figure 1. Model of PVAT-derived extracellular vesicle cardioprotective factors. PVAT is contiguous with the vascular adventitia, providing an anatomically linked mechanism for paracrine regulation of vascular smooth muscle cells of blood vessels and the heart. Multiple cell types contribute to the secretome of PVAT. For those molecules that are associated with extracellular vesicles, RAB27a is a critical regulator of multivesicular body fusion with the cellular plasma membrane, allowing for vesicular release. Several lipid classes implicated in cardioprotection have been reported to be associated with extracellular vesicles, as have adiponectin, omentin-1, and IDO.

We propose that RAB27a production in the cardiovascular microenvironment, including in PVAT, is one molecular mechanism by which paracrine signaling occurs from adipose tissue to the heart and blood vessels via extracellular vesicle trafficking [94,95]. Many factors, whether within exosomes or secreted in soluble form, may comprise this adipose–cardiovascular signaling.

Limitations of our current knowledge include the fact that most PVAT studies have been performed in rodent models. Genetic targeting with exosome labeling is being characterized in mouse models [123–126], although it remains a challenge to target PVAT selectively and distinguish it from other adipose depots. Several key studies using human PVAT and PVAT-derived cells have been described, and continuing research in these areas are required to discover whether PVAT-derived molecules identified in model organisms are generalizable to human PVAT signaling capacity.

The role of PVAT-secreted cardioprotective molecules is a novel area of study that provides a potential future target for the treatment of CVD. While PVAT proteins have been heavily researched, there is a gap in knowledge of PVAT-derived RNAs and lipids. Further investigation into RNA and lipid exosomal contents may allow the development of a therapeutic platform for the use of endothelial cells to deliver these anti-inflammatory mediators [35]. Currently, there are emerging therapies, such as canakinumab and colchicine, that target cardiovascular inflammatory pathways and have shown promise in preclinical and clinical trials. However, these treatments are not target-specific, leading to systemic immunosuppression. This drawback can be eliminated using extracellular vesicle technology, which recent studies have begun to demonstrate successfully [35].

Like all adipose depots, PVAT alters its molecular and cellular phenotype with metabolic imbalance, which is reversible. The predicted thermogenic capacity of human PVAT, based on levels of thermogenic markers, decreases with progressive weight gain [117]. Thus, it is feasible that a variety of health interventions intended to promote healthy inflammatory and metabolic profiles will impact the PVAT secretome. One example includes the positive impact of exercise [127,128]. Indeed, one of the PVAT-derived targets of interest, FGF21, may be regulated by aerobic and endurance exercise [129,130]. It is also interesting to consider that protective effects of exercise could also be mediated by changes in the cardiovascular system that sensitize heart or vasculature to PVAT-derived signaling factors [131].

Lastly, future research is necessary to determine how intracellular exosome release proteins modify the type of content released into extracellular space, especially in human cells and tissues. RAB27a is a promising target, since it has already been identified to protect against disease in mice and is associated with human disease-causing mutations. However, it is unknown how the expression of RAB27a modifies the contents of cellular secretions under conditions of metabolic stress. More detailed molecular study of human PVAT in broader clinical populations will allow for the continued development of strategies to promote cardiovascular health and decrease the risk of cardiovascular diseases.

7. Methods

7.1. Eligibility Criteria

The inclusion criteria utilized for the article search are as follows: I. Subjects: mice and human models; II. Exposure: proteins, RNA, or lipids derived from PVAT (mice and human models); III. Outcome: protection against disease progression or upregulation in healthy physiologic states; IV. Study type: case–control; V. Study question: what are the PVAT-derived proteins, RNAs, or lipids that serve as a protective mediator against the progression of cardiovascular disease?

The exclusion criteria are as follows: I. Molecules not derived from any type of PVAT; II. PVAT-derived molecules identified with the progression of CVD or were upregulated during CVD states.

7.2. Search Strategy

The search strategy is summarized in Figure 2. A articles were gathered through searches within Pubmed, Scopus, and Google Scholar. An advanced search strategy was utilized for PubMed, utilizing MeSH terms. Separate searches were conducted for the three molecule types.

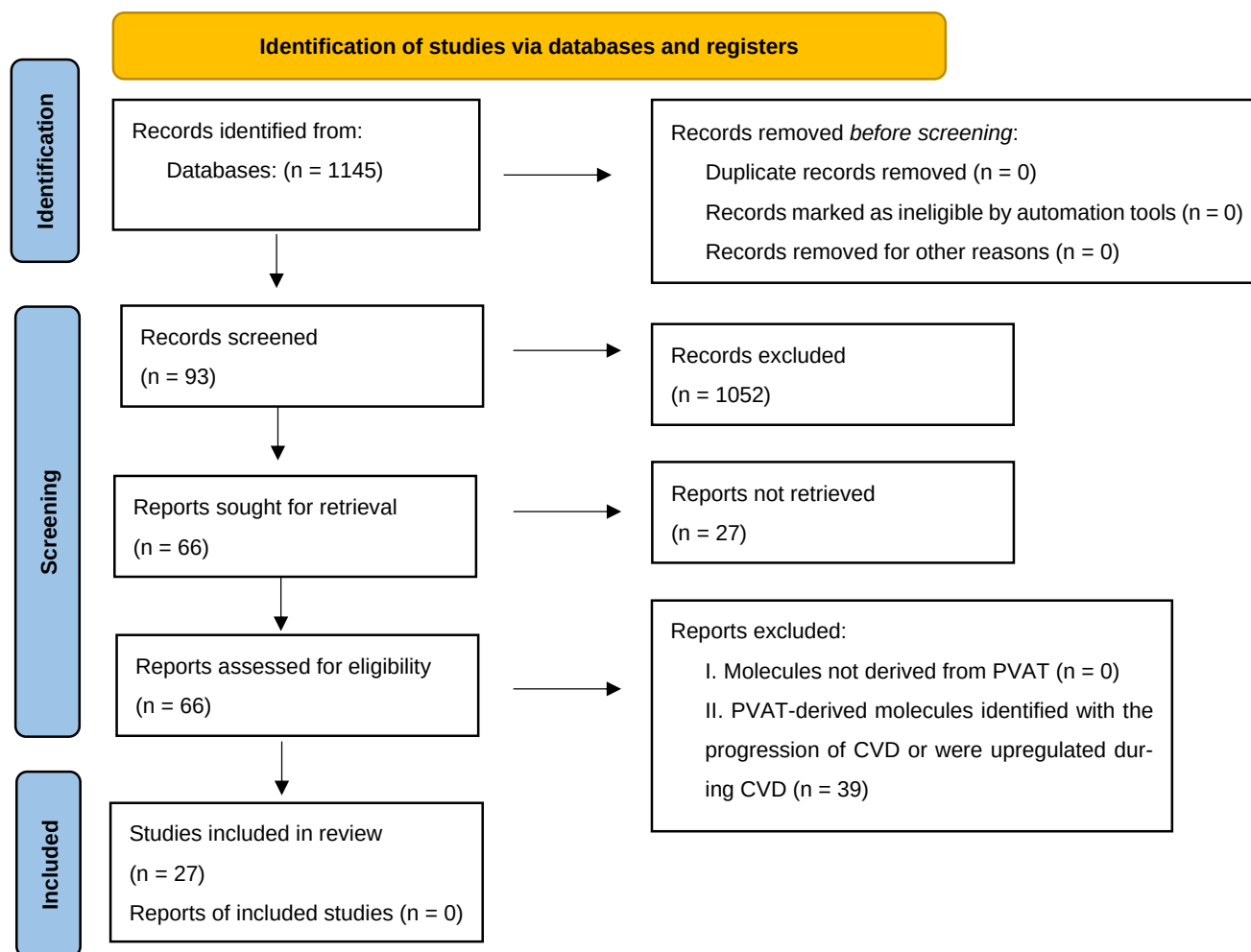


Figure 2. PRISMA flow diagram.

For the search of PVAT-derived proteins in PubMed, the search terms were as follows: ((PVAT) OR ((perivascular) AND (adipose) AND (tissue))) AND ((protein) OR (proteins) OR (extracellular)) AND ((cardiovascular) OR (CVD) OR (atherosclerosis) OR (cardiometabolic)).

For the search of PVAT-derived RNA, the search terms were as follows: ((PVAT) OR ((perivascular) AND (adipose) AND (tissue))) AND ((RNA) OR (mRNA) OR (miRNA) OR (EV)).

For PVAT-derived lipids, the search terms were as follows: ((PVAT) OR ((perivascular) AND (adipose))) AND ((lipids) OR (sphingolipids) OR (phospholipids) OR (lipid)) AND ((secretion) OR (circulating) OR (blood) OR (plasma) OR (extracellular) OR (exosome) OR (exosomal)).

Searches in Scopus and Google Scholar yielded a much broader range of results compared to the PubMed search. The same search parameters for PubMed were utilized in both Scopus and Google Scholar search engines to identify relevant articles that were not included in the PubMed results. Searches were conducted up to July 2025, and references from relevant studies and review articles were included to ensure all relevant information was included.

7.3. Selecting Studies and Data Extraction

Article search results matching the eligibility criteria were pooled into a master Microsoft Excel spreadsheet, which highlighted the publication year, author, title, summary of key findings, background information, methods, biomarkers, and DOI. Multiple tabs were created to sort articles into their identified biomarker: proteins, RNAs, and lipid secretions. Additional articles providing background information on relevant study results were also included to help support and expand upon the importance of study conclusions.

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Abbreviations

The following abbreviations are used in this manuscript:

CVD	cardiovascular disease
eNOS	endothelial nitric oxide synthase
ESCRT	endosomal sorting complex required for transport
FABP4	fatty acid-binding protein 4
FGF21	fibroblast growth factor 21
ITLN1	intelectin-1
NVEV	neutrophil membrane-engineered extracellular vesicles
PAME	palmitic acid methyl ester
PPAR- γ	peroxisome proliferator-activated factor
PVAT	perivascular adipose tissue
TGF	transforming growth factor

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