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Review on Multifaceted involvement of Perivascular Adipose Tissue in Vascular Pathology

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Highlights

- Perivascular adipose tissue (PVAT) does not only protect the vasculature but also secretes substances which are involved in dictating vascular tones.
- PVAT is classified as white and brown PVAT and they are phenotypically and functionally distinct.
- Under certain conditions, WAT could undergo phenotypic transdifferentiation to obtain a brown-like phenotype called Beige.
- PVAT is a possible target in developing therapies for vascular diseases.

Abstract

Perivascular adipose tissue is a fat tissue deposit that encircles the vasculature. PVAT is traditionally known to protect the vasculature from external stimuli that could cause biological stress. In addition to the protective role of PVAT, it secretes certain biologically active substances known as Adipokines that induce paracrine effects on proximate blood vessels. These Adipokines influence vascular tones.

There are different types of PVAT and they are phenotypically and functionally distinct. These are the White and Brown perivascular adipose tissues. Under certain conditions, White perivascular adipose tissue could undergo phenotypic switch to attain a Brown PVAT- like phenotype. This type of PVAT is referred to as Beige PVAT.

The morphology of Adipose tissue is influenced by species, age and sex. These factors play significant roles in adipose tissue mass, functionality, paracrine activity, and predisposition to vascular diseases. The difficulty that is currently experienced in extrapolating animal models to human physiology could be traceable to these factors.

Up till now, the involvement of PVAT in the development of vascular pathology is still not well understood. Brown and White PVAT contribute differently to vascular pathology. Thus, the PVAT could be a therapeutic target in curbing certain vascular diseases.

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In this review, knowledge would be updated on the multifaceted involvement of PVAT in vascular pathology and also explore its vascular therapeutic potential.

Keywords; PVAT, Adipokines, Brown Adipose Tissue, White Adipose Tissue, Vascular pathology

Abbreviations

PVAT, Perivascular Adipose Tissue; BAT, Brown Adipose Tissue; WAT, White Adipose Tissue; VAT, Visceral Adipose Tissue; UCP-1, Uncoupling Protein-1; PVADRF, PVAT derived Relaxing Factors.

1. Introduction

Perivascular adipose tissue (PVAT) is a special form of Adipose tissue (AT) that shields the blood vessels. Interestingly, all blood vessels are surrounded by AT except the blood vessels located in the brain [1]. The proximity of PVAT to blood vessels allows its participation in various cardiovascular processes [2].

Traditionally, PVAT was thought to be a passive system that protects the vasculature from external injuries. However, current studies have shown that PVAT secretes biologically active substances with paracrine effects on the vasculature. These substances are referred to as Adipokines. They are secreted by adipocytes then infiltrate into the vasculature. The adipokines exert their paracrine effects which then influence the vascular tones [3]. Generally, Adipokines could be anti-inflammatory or pro-inflammatory, thereby possessing the potency to modulate vascular properties [4].

PVAT is of two different types which are structurally and functionally distinct. The PVAT could either be brown adipose tissue (BAT) or white adipose tissue (WAT). Phenotype shown by PVAT is said to be largely dependent on their anatomical locations. For example, the thoracic aorta is surrounded by brown PVAT while the abdominal aorta PVAT shows the WAT-like phenotype [5]. Interestingly, the WAT could undergo phenotypic switch under certain conditions to attain a brown-like phenotype called Beige adipose tissue [6].

White adipose tissue serves as the energy reservoir needed for metabolism. WAT shows distinct features and has different functions from their Brown counterparts. On the other hand, BAT serves as the channel for energy dissipation. That is, channel of energy release. Therefore, vascular homeostasis could be attained by striking a balance between BAT and WAT [7].

Generally, excessive caloric or dietary intakes affect adipose tissue's morphology. AT dysfunction causes architectural alterations which are partly characterized by increased adipocyte size (hypertrophy). This gives more room for ectopic lipid deposition and macrophage infiltration [8][9]. The infiltrated macrophages could inflict paracrine effects on the vasculature, leading to vascular inflammation. It has been previously reported that PVAT inflammation increases the risk of cardiovascular disease onset [10].

Adipokines have been implicated to participate either actively or passively in vascular disease pathology. Notwithstanding, some have been reported to show vascular protective properties. This multifunctional attributes of PVAT in vascular disease have always been a concern. It has led to the inability to characterize PVAT as either a friend or a foe. However, a better understanding of PVAT participation in vascular disease will help scientists in vascular diseases' targeting. Thus in this review, knowledge would be updated on the multifaceted involvement of PVAT in vascular pathology and its possibility of being a potent therapeutics target.

2. The White, Brown and Beige Adipose Tissue

Adipose tissue is a loose connective tissue widely distributed throughout the body. It is involved in energy storage, metabolic homeostasis, and maintenance of equilibrium between energy storage and expenditure [11].

Adipose tissue comprises of the white adipose tissue (WAT) and the brown adipose tissue (BAT) which are morphologically and functionally different. The WAT has the sole responsibility of energy storage in contrast to the thermoregulatory role of BAT [12].

White adipose tissue stores energy with the capability to expand its cells in other to meet metabolic requirements [13][14]. Phenotypically, WAT possesses slightly homogenous-large fat droplets serving as an energy reservoir within its adipocytes [15].

In contrast, BAT dissipates energy. It contains several mitochondria [15] which balances the excess energy storage possibility of WAT to maintain thermoregulation. BAT possesses many mitochondrial cells that use uncoupling protein 1 (UCP-1) to actively participate in the catalysis of ATP synthesis [16]. UCP-1 is a membranous protein specific to BAT. It helps in thermogenesis through protons translocation across BAT mitochondria [17]. It is known that a reduced amount of brown adipose tissue could be a possible mechanism underpinning ectopic fat deposition.

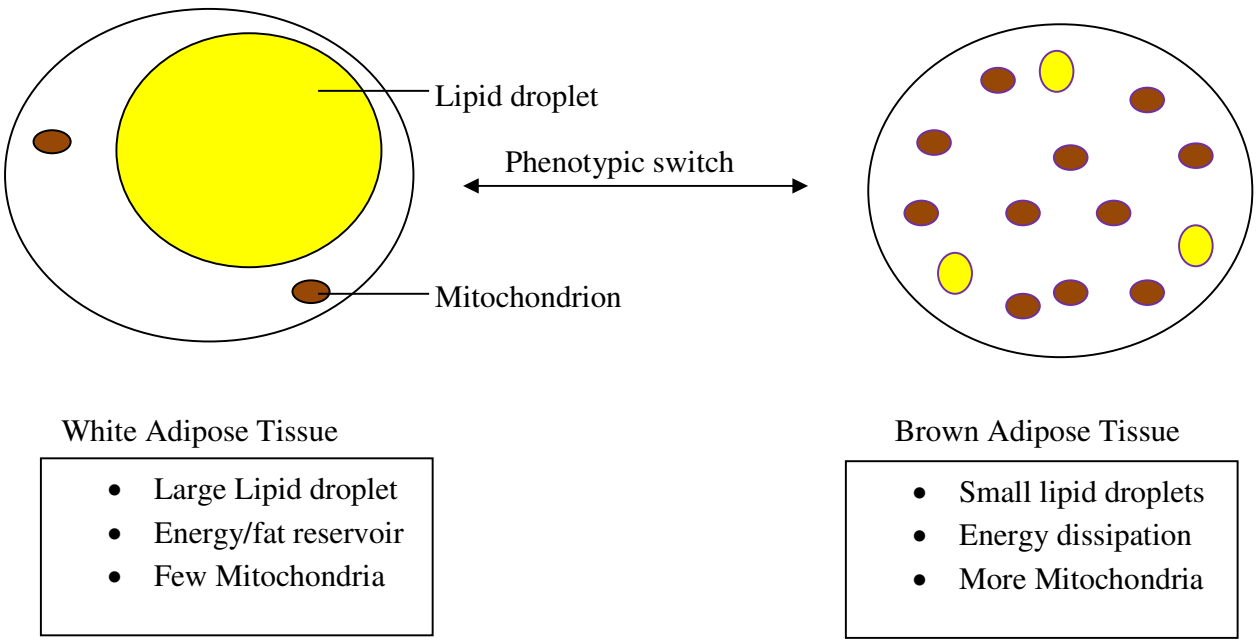

Figure1. Structural and functional differences between WAT and BAT

PVAT generally shows the BAT phenotype [18][19]. Notwithstanding, the phenotype of a PVAT shielding a specific blood vessel is said to be location dependent. *Khanh-Van Tran et al.* observed this when comparing PVATs isolated from Thoracic and abdominal aortas [20].

Under certain conditions, white adipose tissue could undergo phenotypic transdifferentiation to take up a brown-like phenotype called Beige. This phenomenon has been reported to be a mechanism employed in maintaining vascular homeostasis [21].

Adipose tissue phenotypic switch could be initiated by different physiological processes. Exercise has been reported to induce AT phenotypic switch via different mechanisms but primarily by activating thermogenesis in energy-storing WAT. This dissipates the excess energy stored and instigates the browning process in which WAT takes up a brown-like phenotype. Another important mechanism is via exercise-induced Irisin production that activates WAT browning process [22][23]. The phenotypic switch of AT could be a therapeutic strategy in maintaining metabolic balance, especially in obesity.

3. Differential adiposity; Influence of Age, Sex and species

Adipose tissue morphology and functionality is influenced by certain physiological factors such as age, sex, and species, etc. Aging is a critical factor that influences adipose tissue mass, dysfunction, and predisposition to vascular diseases. The middle-aged mice have been reported to show more perivascular adipose tissue hypertrophy and visceral adiposity. This interesting report by *Eva Schutz et al.* shared insight on the effect of age on adipose tissue morphology and functionality. 52 weeks old male rats (middle-ages) were compared with the 16 weeks old counterparts in an experimental setup. The morphometric analysis and Hematoxylin/Eosin staining showed elevated glucose levels, increased perivascular adiposity, and increased vascular injury in the middle-aged group. This study eventually hypothesized that age could influence adipose tissue morphology and its paracrine based vascular activity [24].

Furthermore, *Demerath et al.* published an interesting report on differential visceral adiposity concerning to sex, age, and race. The report published showed that these factors influenced visceral adipose tissue deposition [25]. This agrees with the clinical research conducted by *Jean Pierre et al*. which reported that ethnicity/race and sex play influential roles in visceral adiposity and metabolic profiles [26].

Lipogenesis is differential in humans and rats. This was shown by lesser expression of fatty acid synthase and acetyl-CoA carboxylase 1 mRNA concentrations ($P < 0.05$) in humans than rats. This shows a lesser activity of the lipogenic pathway in humans compared to rats [27].

Adipose tissue deposition is heterogeneous in males and females. Irrespective of the body mass index, females are known to carry about 10 percent more body fats compared to males [28]. These factors (Sex, race, and age) should be considered in investigating predisposition to vascular diseases such as Atherosclerosis. It is necessary for researchers to do more

comprehensive profiling of differential adiposity comparing different factors. This would validate and provide more data on the influence of sex, race, age, and species on the distribution of adipose tissue. Besides, it would aid research translations to clinics.

Most researchers employ rats for researches relating to adipose tissue biology. However, the metabolic differences between humans and rats make it difficult for research translation to application ports. That is, difficulty in extrapolating data from animal models to human physiology and pathophysiology. These differential factors should be put into account at the experimental design phase.

4. PVAT, Vascular contractility and Protection

PVAT secretes bioactive molecules which could act as anti-contractile factors that aid vascular relaxation. However, the function of PVAT goes beyond the production of vasorelaxant molecules. It is also known to attenuate induced stress [29].

An interesting study by *Zaborsker et al*. reported the anti-contractile role of PVAT in the offspring of obese rats. These rats were naturally pre-programmed to develop obesity and cardiovascular risk factors. However in the study, the author observed a significant reduction in vascular reactivity to norepinephrine. Their result showed that the PVAT confers anti-contractile property on vasculature via the release of nitric oxide synthase. The anti-contractile effect was reverted by NOS inhibitor [30].

It is necessary to note that reports are saying the anti-contractile role of PVAT may be location dependent. Such a report was published by *Victorio et al. 2016*. The authors investigated the anti-contractile role of PVAT of the thoracic and abdominal aortas. Surprisingly, the PVAT from Thoracic aorta gave anti-contractile support to the aorta but such was not observed with PVAT of abdominal aorta. Also, abdominal PVAT was found to exhibit reduced endothelial nitric oxide synthase [31]. This could imply that the anti-contractile role of PVAT may not be a general phenomenon as anatomical location may influence the PVAT anti-contractile function. Thus, the differential phenotype of abdominal PVAT could have pro-atherogenic implications.

Vascular Smooth muscle dictates vascular contractility. Smooth muscle dysfunction alters contraction and relaxation capacity of blood vessels which may impair normal blood pressure. However, loss of Smooth muscle function is an underlying mechanism in vascular dysfunction and also, loss of vascular contractility [32]. Simvastatin effect on smooth muscle integrity was examined by *Kang et al*. It was observed that Simvastatin halted aortic smooth muscle function which then translated to vascular apoptosis via calcium ion influx disruption [33]. The Smooth muscle drives the desired response of vasculature to external stress.

5. PVAT, Morphological dysfunction and Vascular inflammation

Generally, PVAT could become dysfunctioned and this may be attributed to excess calories, nutrition, or any other triggers. Adipose tissue dysfunction is a possible reason for the loss of the anti-contractile role of PVAT due to inflammation [34].

Published evidences have suggested a bi-directional biocommunication between the PVAT and the vasculature. It is known that inflammation progresses from inside to outside and vice versa of blood vessels. Pro-inflammatory flow from outside to inside could be traced to dysfunctioned/Atrophied PVAT [5][35].

The adipocytes derived factors are biological agents which could be hormones, chemokines or peptides with paracrine or autocrine actions. Nevertheless, the PVAT phenotypes could influence adipokines production. Increased adiposity is a key factor that influences changes in adipokines production. Healthy PVAT tends to produce adipokines with anti-contractile paracrine effects [3].

Obesity is a metabolic state that impacts adipose tissue phenotypes, adipokines secretion, and vascular functions. It is characterized by increased adipocyte size enabling the secretion of Monocyte chemoattractant Protein (MCP-1). The process then favors the recruitment of pro-inflammatory adipokines [36]; a molecular mechanism underpinning atherosclerosis. This process is more typical of WAT compared to their brown counterparts. It is probably consequential of larger adipocyte size exhibited by WAT that gives room for pro-inflammatory macrophage infiltration [37].

On the other hand, lean animals are mainly composed of brown adipose tissue. This ensures activation of macrophages with possible secretion of anti-inflammatory cytokines. The anti-inflammatory (M2) and pro-inflammatory cytokines (M1) of PVAT origin could exhibit phenotypic transdifferentiation. This phenomenon of phenotypic switch is hugely influenced by change in animals' metabolic profile or state [38].

Dysfunctioned PVAT is characterized by increased oxidative state, decreased production of adipocyte derived vasorelaxing factors and increased production of pro-inflammatory adipokines that infiltrates to proximate vasculature [39].

6. Adipokines transport mechanisms; paracrine effect of Adipokines

Adipokines could infiltrate into an adjacent vasculature. They exert paracrine effects that influence vascular tones. Infiltration of pro or anti-inflammatory adipokines to the proximate vasculature enables the exertion of their paracrine effects on the vasculature. The infiltrated adipokines dictate vascular tones serving as either vasodilator or vasoconstrictor. Therefore, these adipokines could exert anti or pro-atherosclerotic action on adjacent vasculature.

Infiltration of adipokines to adjacent vasculature follows different mechanisms such as diffusion. This involves the translocation of local adipokines to the vascular wall following the concentration gradient. This may translate into vascular wall remodeling in response to infiltrated adipokines [40][41]. Also, adipokines could be transported to adjacent vasculature via direct release into the vasa vasorum which allows downstream transport into the arterial wall via iliac artery [42][43].

The vasa vasorum transport mechanism has been reported to be bidirectional; vasa vasorum depicts the outside to inside and the vasa vasorum retrograde transport mechanisms. Outside to inside transport mechanism aids the translocation of PVAT derived relaxation factors, Macrophages, Adipokines to vascular wall via iliac artery [44]. However, systemic macrophages could also be transported to the intima layer of the vascular wall following the reverse transport mechanism i.e., the vaso vasorum retrograde transport. The vasa vasorum retrograde transport mechanism could be found in the report of *Uchida et al*. The authors observed that systemic low-density Macrophages penetrated the myocardium and the pericoronary adipose tissue following retrograde mode [45].

Furthermore, receptor-mediated transport is another mechanism that ensures adipokines paracrine effects. Certain receptors are expressed in the vasculature through which adipokines induce agonism to trigger biological signaling [46].

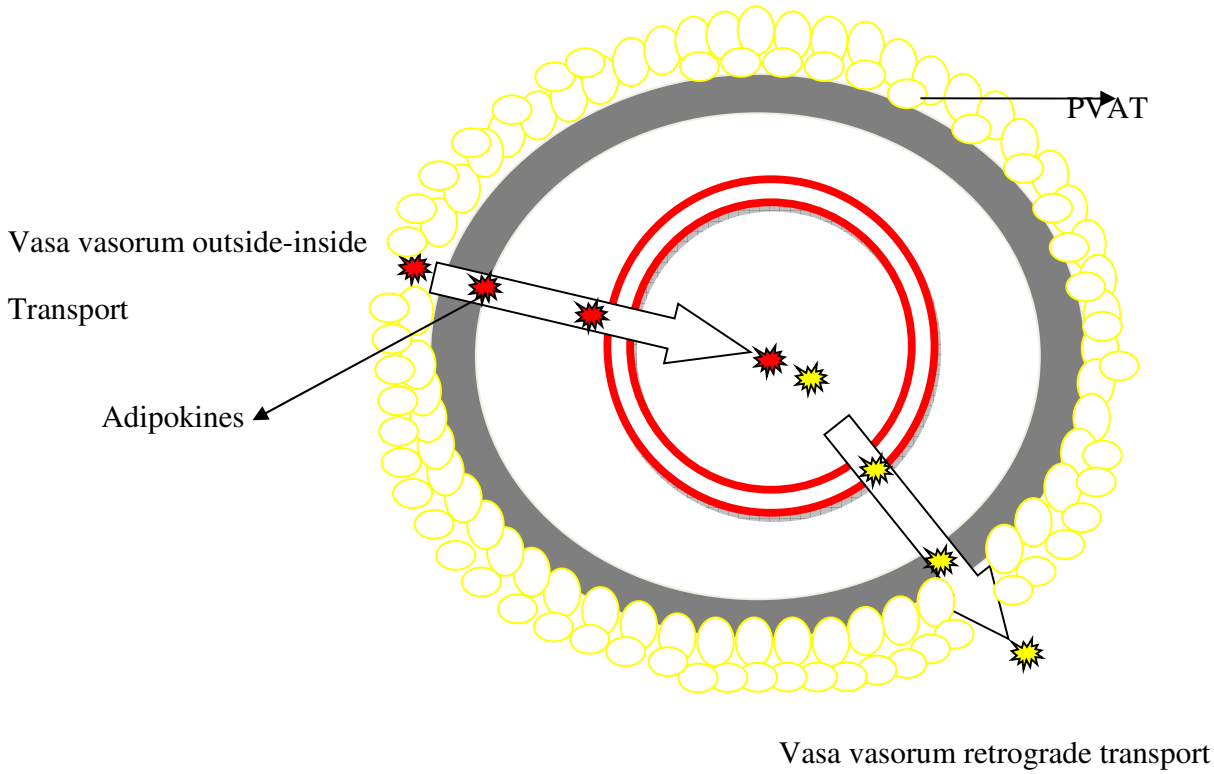

Figure2. Transport mechanisms showing outside to inside infiltration of adipokines in to the vasculature and retrograde movement of systemic macrophages to vascular wall.

Research on adipokines and their involvement in Atherosclerosis development is still on the move. A cross-sectional study on Plasma Leptin correlation with atherosclerosis in type 2 diabetic patients shows a positive relationship. The result from the study showed a significant association between plasma Leptin and the coronary calcification score [47]. Although reports on Leptin has been contradicting.

We have certain reports showing the anti-contractile contribution of PVAT derived Leptin when in synergy with other relaxant factors [48][49]. At this point, it is important to make a clear difference between the physiological and therapeutic Leptin levels regarding vascular tone dictation.

Adiponectin (APN) seems to show a contrary correlation. Different reports attest to the inverse relationship between plasma Adiponectin and atherosclerosis pathology. Based on the contrasting influence of Leptin and Adiponectin in atherosclerosis, Leptin to Adiponectin ratio has been proposed as a model of evaluating vascular endothelial dysfunction [50]. Even though Adiponectin has been reported to attenuate vascular inflammation and Atherosclerosis, the molecular mechanism that underpins APN is still not well known. However, inhibition of NF-ҚB and its transcription factors is a possible anti-vascular dysfunction mechanism deployed by Adiponectin [51].

Another interesting study by *Nishimura et al* researched the possible relationship between plasma Omentin, Adiponectin and Atherosclerosis. The study suggested that Omentin has an inverse relationship with Atherogenesis in type 2 diabetes and may have an anti-atherosclerotic function in concert with circulating Adiponectin [52].

As an opinion, the use of plasma level of adipokines to correlate its involvement in pathology should not be relied on and clinically should not be a major diagnostic tool. The increase in plasma concentration of certain adipokines could be likened to immune response to vascular injury or may be perceived as a marker for vascular injury induction.

Adipokines	**Origin**	**Vasoactivity**	**Mechanism of action**	**Reference(s)**
Chemerin	BAT	Initiates and Promotes aortic atherosclerosis	By promoting NF-kBp65 expression and p38 MAPK phosphorylation	[53] [54]
Adiponectin	WAT and BAT	Amelioration of Atherosclerotic plaque	Down regulation of VCAM-1 and ICAM-1	[55] [56][57]
Omentin	VAT	Protects against high glucose induced endothelial dysfunction	Restoration of endothelial dependent relaxations by inhibiting oxidative stress and increasing Nitric oxide production	[58][59]
Leptin	WAT and BAT	Promotes VSMC phenotypic switch	Increased p38 MAPK phosphorylation	[60][61][62]

Visfatin	WAT	Induction of vascular endothelial dysfunction and tissue inflammation	Via the activation of NLRP3/IL-1β/IL-1 Signaling pathway	[63][64]
Resistin	WAT	Induction of hypertension	Activation of Renin-Angiotensin System (RAS)	[65][66]
Apelin	WAT	Maintenance of vascular structure	Upregulation of endothelial Nitric Oxide	[67][68]
Vaspin	WAT	Modulation of Endoplasmic Reticulum stress	Upregulation of pAKt and pAMPK	[69][70]

Table1. The table showing certain PVAT derived vasoactive compounds, their primary source(s), bioactivity and the molecular mechanism of action.

7. Adipocyte-derived relaxing factors; Potassium channel agonists

PVAT is not only known to exhibit protective roles against external stress. It also produces certain substances that relax the vasculature. Such substances could be gaseous in nature, such as Nitric oxide or could be peptide or hormone-like [29].

Voltage-gated Potassium channel is a key membrane port involved in vascular homeostasis. Its activation results in the efflux of potassium ion (K^+), closure of voltage dependent calcium channel and thus, enhancing vasorelaxation [71].

Potassium channel agonists are said to mimic the effects of PVADRF. Thus, there is a rationale that ADRFs act through voltage gated potassium channel activation [72]. *Lee et al.* investigated the role of a perivascular adipose tissue derived methyl palmitate in vascular function. Interestingly, Methyl Palmitate caused vasorelaxation by opening voltage-gated potassium channels on smooth muscle cells [73].

Nitric oxide synthase (NOS) catalyzes the production of Nitric oxide (NO), a widely reported PVADRF. NO also activates voltage-gated potassium channel [74]. Apart from the above mentioned, different researchers have published involvement of the vasorelaxation factors in voltage-gated potassium channel activation [75][76][77].

Potassium ion channels undergo alteration in vascular pathological conditions. Alteration of the potassium ion channel causes membrane depolarization. This leads to vasoconstriction and abnormality in vascular tones. Modulation of potassium channel is a molecular approach in vascular pharmacology [78]. *Clement-Chomienne et al.* published an interesting result on how Angiotensin II-induced blood vessel constriction and blood vessel apoptosis partly via potassium ion channel inhibition mechanism [79]. At the moment, Implication of the voltage-gated

potassium channel in vascular tone dictation is not yet fully explored. However, pharmacological manipulation of voltage-gated potassium channel is worthy of more explorations in the search for vascular therapies.

8. Perspectives and Pharmacological implication

There is absolutely no doubt about the involvement of PVAT in vascular pathology. Aside from the traditional protective role of PVAT, there are tones of reports on the paracrine effect of PVAT derived biological substances (Adipokines) on vasculature. The role of PVAT in vasculature seems to depend on factors such as anatomical location, age, sex, and PVAT phenotypes.

Considering the widely reported roles of BAT as a channel of energy expenditure, more attention should be given to BAT therapeutic possibilities. For example, Exploring BAT transplantation as a therapeutic mean seems promising [80][81]. Exploring different means of maintaining a balance between WAT and BAT will be a unique strategy for maintaining vascular homeostasis.

Furthermore, the development of small molecules with pharmacological ability of activating voltage-gated potassium channel is also a promising route in vascular therapeutics. These molecules may serve as a potassium ion channel agonists which would trigger vasodilation. Small molecules could also be targeted towards the process of PVAT phenotypic transdifferentiation.

In conclusion, further research is needed to explore the possibility of targeting PVAT as a promising therapeutic means for vascular disease. As an opinion, extensive profiling of different adipokines is needed to ascertain their exact roles in the vasculature. Also, scientists need to give a clear distinction between the physiological and therapeutic involvement of these adipokines in vascular dysfunction.

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