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EDITORIAL

Editorial: The Yin and Yang of Perivascular Adipose Tissue in Vascular Disease

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Since 1847, after the first publication of research on adipose tissue [1], over 118,000 publications in PubMed now demonstrate that adipose tissues are widely distributed in the body and involved in many aspects of health and diseases. There is no doubt that presence of appropriate amounts of adipose tissue is essential to maintain the healthy status of the body, while excess adipose tissue over time leads to obesity and obesity-associated complications such as diabetes, cardiovascular diseases, cancer, and other chronic illnesses [2]. Almost all of this knowledge is derived from research on white adipose tissue (WAT) because it was long believed that brown adipose tissue (BAT) was not presented in adult humans [3]. Although Y. Tanuma and colleagues published data in 1976 indicating the presence of thermogenic brown adipocytes in perirenal adipose tissue in adults that responded to stimuli by oxidation of stored fat [4], it was not until 2009 that active research on BAT was spurred with the "rediscover" of active BAT in adult humans under cold acclimation [5–7]. After a decade of intensive research, now it is well-accepted that activation of BAT or conversion of WAT to BAT-like, which is referred to as "browning," could be potential targets to overcome the complications caused by excess WAT [8]. The endocrine homeostasis of adipose tissue is critical in maintaining health or causing obesity-related cardiovascular diseases [9]. However, in the vascular system, the paracrine roles of perivascular adipose tissue (PVAT) on vascular biology were overlooked until Soltis and Cassis, in 1991, demonstrated that the PVAT around the aorta affects the contraction ability of vessel rings in response to norepinephrine [10]. Since then, over 700 publications in PubMed indicate that PVAT is not solely a structural supporting material to the aorta, but that it also secretes many, some yet uncharacterized, PVAT-derived factors that profoundly contribute to vascular homeostasis and development of vascular diseases such as hypertension, atherosclerosis and aneurysm through an "outside-to-inside" signaling targeting the underlying layers in the vessel [11–14]. PVAT at different locations is either brown-like or the so-called "beige" adipose tissue and there is strong evidence that PVAT has similar functional characteristics as classical brown or "beige" adipose tissue. However, as PVAT is closely adjacent to the vessel wall, the direct paracrine effects of PVAT on the underlying vessel wall should not be overlooked and have become a field of increasingly active research. The publications on PVAT biology in this Special Section of Cardiovascular Drugs and Therapy further contribute novel findings relative to PVAT's roles in vascular function.

Cheng et al. review the current knowledge regarding PVAT-derived factors of relevance to vascular function, PVAT innervation, and experimental strategies to study the roles of PVAT in vitro and in vivo, including different animal models and modified PVAT content [15]. The presence of different types of adipocytes including brown, beige, and white in PVAT at different sites along the blood vessels underscores the difficulty and complications in studying the specific roles of PVAT on vascular biology and vascular diseases. Available tools for Cre-based knock out in adipocyte-selective mouse models with the expression of the *Cre* recombinase driven by fatty acid binding protein 4 (aP2), adiponectin, or resistin promoters will delete the studied gene in all types of adipocytes. A recently developed uncoupling protein 1 (Ucp1)-Cre mouse approach has been used to delete genes in brown adipocytes in PVAT and BAT in the interscapular and other regions [13]. Thus, although somewhat more specific, it is still difficult to distinguish the biology of PVAT from BAT depots with this model. Similar difficulties and complications are seen in other cell types, such as endothelial and smooth muscle cells, with intrinsic heterogeneity in different vascular trees or organs.

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PVAT acquires a pro-inflammatory phenotype with accumulation of inflammatory cells and production of pro-inflammatory adipocytokines which contribute to migration of vascular smooth muscle cells in obesity. Horimatsu et al. present work indicating that abdominal PVAT transplantation onto the abdominal aorta (one strategy to modify PVAT content) inhibited endothelium-dependent relaxation in the thoracic aorta and increased inflammation. Reduced adiponectin expression in the transplanted PVAT might remotely affect endothelial function and atherosclerosis development in the thoracic aorta, thus suggesting a wider, endocrine role of PVAT. These findings highlight that obesity-induced PVAT inflammation could contribute to endothelial dysfunction and atherosclerosis in a remote manner [16].

Aging leads to adipose tissue dysfunction, especially progressive loss of brown properties (or "whitening") in PVAT, which may contribute to vascular diseases related to aging. Pan et al. present evidence that aging inhibits perivascular adipocyte browning. They show that miR-146b is a novel modulator of perivascular adipocyte browning in response to cold stimulus, while loss of miR-146b-3p in preadipocytes in PVAT contributes to PVAT "whitening" in aging mice. This study links the roles of microRNAs in PVAT dysfunction and aging [17].

Furthermore, obesity is associated with increased arterial stiffness, which is an inevitable consequence of the aging process and is considered an early stage in the development of cardiovascular diseases. Our current knowledge on the relationship between PVAT and arterial stiffness is very limited. Chang et al. demonstrate that diet-induced obesity increased arterial stiffness associated with decreased expression of the mitochondrial protein mitoNEET in PVAT. Furthermore, overexpression of mitoNEET in PVAT (with surgical removal of interscapular BAT to partially rule out BAT contribution) prevents obesity-induced arterial stiffness associated with decreased PVAT inflammation in aging mice [18]. These findings and the study from Pan et al. [17] discussed above suggest that PVAT is a potential target to prevent cardiovascular diseases associated with aging.

Finally, the resident adipose progenitor cells (APCs) in human PVAT might play potential roles in PVAT accumulation during obesity. Boucher et al. characterized APCs from human PVAT negative for CD45 and CD31, while positive for CD73, CD105, and CD140A, which could be differentiated into UCP1-positive adipocytes through the small GTPase Rab27a signaling pathway. Therefore, it is possible that Rab27a in resident APCs in PVAT may regulate PVAT expansion during obesity [19].

The new findings reported in this Special Section further support the current notion that PVAT is a unique adipose tissue depot that contributes to vascular homeostasis while also has the potential to profoundly perturb the vasculature under certain pathological conditions, and suggest that targeting PVAT may be a promising therapeutic strategy for treating and preventing obesity-driven and aging-related vascular diseases.

Several questions on PVAT (patho)physiology still remain unresolved and will need to be systematically addressed in order to further understand the dynamic nature and roles of PVAT in health and disease. First, there is the question of autocrine, paracrine, and endocrine functions of PVAT. For example, the true identity of PVAT-derived relaxing and contracting factors, pro-inflammatory and anti-inflammatory adipokines, and their balance and mechanisms of action still need to be explored or confirmed. Certain factors which were found in other adipose tissue depots such as H_2S, angiotensin II, adiponectin, leptin, resistin, etc. were identified in PVAT as well, although PVAT may present unique nuances regarding those systems. Thus, for instance, although angiotensin II in PVAT plays a role in circadian regulation of blood pressure, PVAT, unlike WAT, does not express significant levels of renin [14]. Additionally, little is known about the contribution of PVAT to endocrine effects in cross talk among organs, for example, liver, heart, skeletal muscle, etc., herein influencing the coordinated regulation of lipids and glucose metabolism [20]. Second, the directionality of PVAT function is an open question and the direction of (patho)physiological communication between PVAT and the rest of the vascular wall needs to be clarified. Does "outside-to-inside" signaling from PVAT towards vascular smooth muscle and endothelial cells maintain vascular homeostasis and/or drives vascular diseases? Conversely, does "inside-to-outside" signaling from the underlying vascular layers maintain PVAT function and/or cause PVAT dysfunction? Is there a dynamic balance instead and, if so, how is it regulated? Third, the real nature of "browning" and "whitening" dynamics is still unsolved. Does it involve changes at the individual adipocyte level or does it reflect selection and expansion of alternative resident progenitors? Or is it a combination of both? Additionally, the cross-talk between PVAT and other adipose tissues in other depots should be studied. This will require development of PVAT-specific genetic animal models and tools which currently pose a difficult challenge. The publications in this issue regarding PVAT include a summary of the current state of the field and its challenges, contribute new aspects towards understanding the roles of PVAT and highlight the significance of PVAT in cardiovascular health and disease. We are grateful to our contributors for sharing their critical and original work.

References

1. Norman G. Aneurism of the abdominal aorta, simulating disease of the kidney: rupture into the lumbar adipose tissue. Prov Med Surg J. 1847;11(22):598–9.
2. Labib M. Acp best practice no 168. The investigation and management of obesity. J Clin Pathol. 2003;56(1):17–25.
3. Himms-Hagen J. Obesity may be due to a malfunctioning of brown fat. Can Med Assoc J. 1979;121(10):1361–4.

4. Tanuma Y, Ohata M, Ito T, Yokochi C. Possible function of human brown adipose tissue as suggested by observation on perirenal brown fats from necropsy cases of variable age groups. Arch Histol Jpn. 1976;39(2):117–45.
5. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, et al. Cold-activated brown adipose tissue in healthy men. N Engl J Med. 2009;360(15):1500–8.
6. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, et al. Functional brown adipose tissue in healthy adults. N Engl J Med. 2009;360(15):1518–25.
7. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med. 2009;360(15):1509–17.
8. Chondronikola M, Sidossis LS. Brown and beige fat: from molecules to physiology. Biochim Biophys Acta. 2018.
9. Nakamura K, Fuster JJ, Walsh K. Adipokines: a link between obesity and cardiovascular disease. J Cardiol. 2014;63(4):250–9.
10. Soltis EE, Cassis LA. Influence of perivascular adipose tissue on rat aortic smooth muscle responsiveness. Clin Exp Hypertens A. 1991;13(2):277–96.
11. Xiong W, Zhao X, Garcia-Barrio MT, Zhang J, Lin J, Chen YE, et al. MitoNEET in perivascular adipose tissue blunts atherosclerosis under mild cold condition in mice. Front Physiol. 2017;8:1032.
12. Brown NK, Zhou Z, Zhang J, Zeng R, Wu J, Eitzman DT, et al. Perivascular adipose tissue in vascular function and disease: a review of current research and animal models. Arterioscler Thromb Vasc Biol. 2014;34(8):1621–30.
13. Xiong W, Zhao X, Villacorta L, Rom O, Garcia-Barrio MT, Guo Y, et al. Brown adipocyte-specific PPARgamma (peroxisome proliferator-activated receptor gamma) deletion impairs perivascular adipose tissue development and enhances atherosclerosis in mice. Arterioscler Thromb Vasc Biol. 2018;38:1738–47.
14. Chang L, Xiong W, Zhao X, Fan Y, Guo Y, Garcia-Barrio M, et al. Bmal1 in perivascular adipose tissue regulates resting-phase blood pressure through transcriptional regulation of angiotensinogen. Circulation. 2018;138(1):67–79.
15. Cheng CK, Bakar HA, Gollasch M, Huang Y. Perivascular adipose tissue: the sixth man of the cardiovascular system. Cardiovasc Drugs Ther 2018.
16. Horimatsu T, Patel AS, Prasad R, Reid LE, Benson TW, Zarzour A, et al. Remote effects of transplanted perivascular adipose tissue on endothelial function and atherosclerosis. Cardiovasc Drugs Ther. 2018.
17. Pan XX, Cao JM, Cai F, Ruan CC, Wu F, Gao PJ. Loss of miR-146b-3p inhibits perivascular adipocyte browning with cold exposure during aging. Cardiovasc Drugs Ther 2018.
18. Chang L, Zhao X, Garcia-Barrio M, Zhang J, Eugene Chen Y. MitoNEET in perivascular adipose tissue prevents arterial stiffness in aging mice. Cardiovasc Drugs Ther. 2018.
19. Boucher JM, Robich M, Scott SS, Yang X, Ryzhova L, Turner JE, Pinz I, Liaw L. Rab27a regulates human perivascular adipose progenitor cell differentiation. Cardiovasc Drugs Ther 2018.
20. Kim JB. Dynamic cross talk between metabolic organs in obesity and metabolic diseases. Exp Mol Med. 2016;48:e214.