Brown Adipose Tissue, Not Just a Heater
Lin Chang, Minerva T. Garcia-Barrio, Y. Eugene Chen

Adipose tissues are distributed in multiple depots in the body of animals including human beings and rodents. In the past decades, the biology of adipose tissues has been intensely studied. Currently, it is well accepted that the existence of adipose tissues is essential to maintain normal physiological activities and health. However, excessive accumulation of adipose tissues in their original depots and ectopic accumulation of lipids especially in the liver and skeletal muscles lead to obesity and insulin resistance, which will further cause lethal cardiovascular complications. Mechanistically, it has been established that macrophage infiltration and oxidative stress in adipose tissues cause malfunction of the adipose tissue, resulting in the secretion of numerous inflammatory factors and adipocyte-derived hormones that negatively regulate functions of the target organs such as heart and blood vessels and eventually lead to cardiac and vascular diseases. Notably, adipose tissue may be originally differentiated from cells in the vasculature or share the same precursors with vasculature cells. Also, adipogenesis always is accompanied by angiogenesis of blood vessels. Thus, the relationship between adipose tissue and blood vessels is drawing much attention on aspects relating to both physiology and shared origin.

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One of the primary functions of adipose tissue is to store extra triglycerides in the form of lipid droplets. However, the sizes and distributions of lipid droplets are considerably different in different adipose tissue depots. Most adipose tissues in the human body comprise adipocytes containing a single large lipid droplet with fewer mitochondria, which is called white adipose tissue (WAT) and is distributed in visceral and subcutaneous regions. It is well accepted that visceral WAT is positively associated with development of cardiovascular diseases (CVDs) and related complications, whereas subcutaneous WAT may be inversely associated with CVDs. Indeed, recent studies have shown that subcutaneous WAT harbors a few particular adipocytes containing multiple smaller size lipid droplets and more mitochondria. Immunohistological, gene, and protein profile studies demonstrated that these cells are classical brown adipocytes. Therefore, subcutaneous WAT actually is a mixture of white and brown adipose tissue (BAT), which was recognized as beige adipose tissue (BeAT). Importantly, many compounds such as rosiglitazone, a peroxisome proliferator–activated receptor γ ligand, growth factors such as fibroblast growth factor 21 and hormones such as irisin or the stimulation with cold or β3-adrenergic receptor agonists significantly increased the numbers of characteristically brown adipocytes in WAT, which is called the browning process.

Studies focusing on browning WAT are extremely relevant and critical because these particular adipocytes express UCP-1 (uncoupling protein-1), which promotes heat production over ATP production in the mitochondria. This process leads to more energy expenditure, which underlies the apparent opposite aspects of WAT function in alternative depots or physiological contexts. Therefore, it is hypothesized that accumulation of BeAT may be positively associated with cardiovascular protection. Unfortunately, the investigation of BAT has been largely ignored because of the long-held belief that BAT was not present in adult human beings. Interestingly, the adult humans do have BAT in specific body regions, even though the amount of such BAT is small (~32–85 g) when compared with the body weight of adult human beings. Its capability for energy expenditure in the whole body and herein its effects in preventing obesity and CVDs remain largely unknown. We think that BAT is not only a heater but also an endocrine organ like WAT, which secretes numerous factors and interacts with neighboring organs.

Regarding the relationship between adipose tissue and CVDs, the perivascular adipose tissue (PVAT), the adipose tissue specifically surrounding blood vessels, was extensively studied in recent years. All the adipose tissues surrounding the blood vessel tree in the cardiovascular system should be classified as PVAT (Figure). Particularly, mesenteric PVAT was traditionally recognized as visceral WAT, which is believed to be positively associated with CVDs. It is well known that obesity is one of the risk factors for hypertension. Interestingly, in lean individuals, PVAT has anticontractile properties, and consistently, PVAT from obese individuals loses its anticontractile properties. To date, multiple substances secreted by PVAT contribute to the PVAT anticontractile role. H₂O₂ is one of the anticontractile factors in both aortic and mesenteric PVAT. Previous studies documented that aortic PVAT has a BAT phenotype, whereas mesenteric PVAT has a WAT phenotype in rodents. Friederich-Persson et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology investigated the adipose phenotype in different depots in mice by analyzing mRNA levels of markers for WAT, BAT, and BeAT. The results indicated that mesenteric PVAT displayed expression of both WAT- and BeAT-specific markers, hence establishing that mesenteric PVAT is not pure WAT, but a BeAT-like adipose tissue. As discussed above, BeAT shares partial characteristics of

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classic BAT. Friederich-Persson et al demonstrated that similar to mesenteric and aortic PVAT, interscapular BAT releases \( \text{H}_2\text{O}_2 \) and exerts an anticontractile effect as well, which does not directly influence endothelium-dependent and -independent vascular relaxation. Because Nox4 is predominately expressed in BAT and produces \( \text{O}_2^- \), BAT in the context of Nox4 deficiency fails to exert the anticontractile effect. Even though \( \text{H}_2\text{O}_2 \) in BAT is partially the result of dismutation of \( \text{O}_2^- \), BAT from animals deficient for the \( \text{O}_2^- \)-producing enzymes Nox1 and 2 still exerts anticontractile effects on blood vessels. The mechanisms underlying the anticontractile properties of PVAT are largely unknown. Vascular smooth muscle cells (VSMCs) are the targets for factors released from PVAT to regulate vascular tone. Friederich-Persson et al documented that only PKG-1 (cyclic GMP-dependent kinase G-1) in VSMCs is a contractility-relevant target of \( \text{H}_2\text{O}_2 \), even though \( \text{H}_2\text{O}_2 \) also activates PKA (protein kinase A). Yet, PKA in VSMCs does not seem to be involved in the anticontractile effect of \( \text{H}_2\text{O}_2 \) released from

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**Figure.** The perivascular adipose tissue (PVAT) phenotype and vascular homeostasis. **A**, PVAT shows stronger brown adipose tissue (BAT)-like phenotype in smaller animals, such as rodents, whereas it shows relatively increasing white adipose tissue (WAT)-like phenotype in larger animals such as rabbits, pigs, or humans. **B**, PVAT is beige adipose tissue (BeAT) in nature and surrounds most blood vessels with varying phenotypes in different vascular beds. **C**, PVAT could be turned into BAT- or WAT-like phenotype in response to bioactive factors, temperature, nutrition status, and obesity. **D**, In healthy conditions, BAT-like PVAT effectively regulates homeostatic vascular tone by secreting adipocyte-derived hormones. On the other end of the continuum, WAT-like PVAT shows exacerbated oxidative stress and inflammatory phenotype and promotes cardiovascular diseases (CVDs). The continuum afforded by the different degrees of BeAT-like phenotypes during browning of WAT and, conversely, the transition to a WAT-like phenotype from BAT during disease progression can operate as an adaptive response that can be brought about by mild oxidative stress, initial adaptive inflammatory response, pharmacological treatment, or weight loss interventions. This phenomenon could also underlie the obesity paradox associated with the relative protection against CVDs observed in overweight conditions.
BAT. Indeed, incubation of vascular tissue with BAT results in reduced phosphorylation of vascular MYPT1 and MLC20, both downstream targets of active PKG-1 in VSMCs and induce smooth muscle contraction. Unlike pure BAT, BeAT-like mesenteric PVAT exerts anticontractile effects through different mechanisms, which are yet unclear. Significantly, further browning of resident BeAT-like mesenteric PVAT increased anticontractility through a mechanism similar to interscapular pure BAT, suggesting perhaps a continuum of changing adaptive (and, eventually, maladaptive) responses depending on the degree of browning of the PVAT.

These findings raise extremely interesting issues with regard to the study itself, its insights into understanding the physiology and pathophysiology of BeAT-like or BeAT-potential of PVAT in humans, and its implications for targeted therapy of CVDs. Because PVAT tightly surrounds most blood vessels, PVAT-derived factors, including H₂O₂, will locally affect immediate neighboring cells in the vessel walls, leading to either physiological benefit or pathophysiological harm for the vessel walls. Currently, it is unclear whether PVAT is associated with CVDs, especially hypertension, atherosclerosis, and aneurysms. Phenotypic changes in PVAT ultimately may affect the development of CVDs. Apart from the specific roles of endothelial cells and VSMCs in CVDs, there is no doubt that further understanding of CVDs in humans will require extensive research to understand the various phenotypes of resident PVAT, as underscored in this article. Browning of human PVAT is not just a means to improve a heater function, but, as a paracrine organ, it can be a powerful therapeutic target for CVDs.

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Disclosures

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