The Evolving View of Fat
The relationship between increased body mass index and risk for diabetes mellitus or cardiovascular disease is well established. Such observations have driven considerable interest into the nature of adipose tissue and what mechanisms might help explain how adipose tissue and specific aspects of adipocyte biology influence cardiometabolic disorders. For example, adipocytes are now recognized as a source of mediators released into the circulation, like the adipokines resistin and adiponectin, which can modulate inflammation, insulin sensitivity, and atherosclerosis. Other molecules released from adipocytes like free fatty acids and reactive oxygen species can also exert both local and distant effects that may be integral to the development of diabetes mellitus, atherosclerosis, and their complications. To an increasing extent, adipose tissue is now understood as an organ playing important physiological and pathological roles. Both the absence of fat, as with certain lipodystrophies, and excess adiposity are associated with diabetes mellitus, with mechanisms that appear to include infiltration of inflammatory cells into adipose tissue and the release of systemic mediators.

Perivascular Adipose Tissue
Perivascular adipose tissue (PVAT) refers in general to the fat surrounding arteries as well as the fat that surrounds the vasculature of organs such as the heart and kidneys. The distinctions in the anatomic locations of fat in relation to the heart reflects the complexity of these issues: intramyocardial fat, which is within the myocardium itself; epicardial fat, which resides between the myocardium and visceral pericardium and is in direct contact with the coronary arteries; and pericardial fat, which is present between the visceral and parietal pericardium or adherent to the parietal pericardium. Studies have reported relationships between each of these different adipose depots and clinically relevant issues, highlighting the need for considering how investigators defined the adipose tissue in their work when comparing study results. The focus in the discussion here is more on PVAT, which is the fat in direct continuity with the adventitia of blood vessels. Not unlike the evolution of perspectives on the endothelium, initial views of the PVAT as primarily a supportive, structural element have been replaced by PVAT now being understood as a dynamic endocrine organ modulating responses of the nearby vasculature by releasing adipokines and bioactive molecules, regulation of immune cell movement into the vessel wall, and influence over insulin signaling.

The amount of PVAT correlates with overall adiposity. In the nonobese state, the most well characterized role of PVAT is in regulating vascular responsiveness. In vitro studies of arterial preparations indicate that vasoconstriction is blunted in the presence of PVAT, suggesting the existence of a still unidentified adipocyte derived relaxing factor. Although PVAT may have beneficial properties in the lean state, in the setting of increased adiposity, and its associated constellation of metabolic abnormalities, this specific adipose depot surrounding the vasculature appears to promote vascular dysfunction and atherosclerosis. As compared with lean controls, PVAT from obese subjects reportedly has markedly diminished vasodilatory capacity. Numerous epidemiological studies find an association between the amount of PVAT and cardiovascular risk factors as well as atherosclerosis itself. Although this line of investigation has raised core questions about how PVAT might exert effects on the vasculature,
experimental data explaining or even showing a causal relationship between PVAT and vascular disease have been limited.

The proposed link between PVAT and atherosclerosis is now strengthened by the studies from Chang et al. in this issue of Circulation. Several groups, including these authors, had previously generated mice with a targeted deletion of the nuclear hormone receptor PPARγ in VSMCs, which resulted in higher blood pressure, abnormal vasomotor function, more atherosclerosis, and more frequent aneurysm formation in response to various stimuli, including high-fat diet. In this round of studies, Chang et al uncovered an apparently overlooked aspect to the phenotype of mice lacking PPARγ in their VSMCs, namely a lack of PVAT but not other adipose depots. This unexpected finding suggests that the developmental origins of PVAT and VSMCs are somehow linked, perhaps through some proximal shared precursor cells. Interestingly, previous groundbreaking work found a shared relationship between skeletal muscle cells and adipose tissue, although the link was between muscle and BAT. Several previous studies have suggested that PVAT has more characteristics of BAT than white adipose tissue. In keeping with notions of depot specificity, divergent functions and responses also occur between species, especially under pathological conditions. See text and selected reviews for additional details. CIDEA indicates cell death–inducing DFFA-like effector a; PGC-1 and the potential pathophysiologic relevance of each depot to diabetes mellitus, obesity, and atherosclerosis is becoming increasingly apparent. Of note, although physiological function Mechanical blood vessel support; Location Surrounding blood vessels, direct contact with adventitia

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Key characteristics of perivascular, brown, and visceral adipose tissue are summarized, including data from mice and humans. The depot-specific biology of fat and the potential pathophysiologic relevance of each depot to diabetes mellitus, obesity, and atherosclerosis is becoming increasingly apparent. Of note, although many depot characteristics overlap in human and rodents, divergent functions and responses also occur between species, especially under pathological conditions. In humans, mainly cervical, supra-clavicular, paraspinal, paraaortic body temperature regulation in infants; Contributor to energy balance in adults? Storage of excess calories (triglycerides); Endocrine function through adipokines. 

Brown Adipose Tissue

Unlike white fat, which stores energy in the form of triglycerides, brown fat, which contains a large number of mitochondria, dissipates energy by uncoupling electron transport from the generation of adenosine triphosphate (ATP). This process of uncoupled respiration is mediated by uncoupling protein-1 (UCP-1) and results in increased fatty acid oxidation, decreased fat stores, and heat production (thermogenesis).

In keeping with its need to radiate heat via the circulation, BAT is highly vascularized. BAT had been thought to be present in humans, mainly in infants, where the relatively large surface to volume ratio makes maintaining physiological body temperature, which is essential for survival, a challenge. Recently, active BAT has also been identified in adult humans using 18F-fluorodeoxyglucose positron emission tomography, a breakthrough observation that has helped drive clinical and therapeutic interest in brown fat. Importantly, most recent evidence suggests that the deposits of brown fat in adult humans have the gene expression pattern and immunohistochemical characteristics of beige fat, a
newly described cell type with properties intermediate between white and classic brown fat.\(^\text{16}\) Nevertheless, human BAT depots are metabolically active, particularly in response to cold. Cold stimulation in humans leads to enhanced energy expenditure and weight loss, with increased glucose and fatty acid uptake in BAT, but not in other metabolically-active tissues like skeletal muscle or white fat.\(^\text{17}\) Exercise also increases brown fat, suggesting that perhaps BAT action may underlie some of exercise’s health benefits. In contrast to cold exposure and exercise, pharmacological stimulation using the sympathomimetic ephedrine, which activates BAT in preclinical models, had no effect on BAT in humans.\(^\text{18}\) These issues highlight the current challenges in harnessing BAT activation as a therapeutic target that might limit obesity and perhaps its associated metabolic and cardiovascular problems.

An alternative approach to dissipating energy through increased thermogenic activity is by browning or beiging of white adipose tissue, which has recently been achieved in different mouse models. A number of proteins including transcription factors, coregulators, enzymes, and hormones have been identified as regulating the transformation of classic white into BAT-like or beige adipocytes with the common in vivo phenotype of increased energy expenditure and protection against obesity.\(^\text{19}\) Among white fat stores, particularly the subcutaneous depots are susceptible for browning, but recent work by our own group has identified that visceral fat may also be manipulated into acquiring brown fat characteristics, with concomitant protection against diet-induced weight gain and glucose intolerance.\(^\text{20}\)

**Browning the Vasculature?**

Animal studies and more recent clinical evidence argue that decreasing adiposity by activating BAT and potentially oxidizing fatty acids would, in most settings, indirectly benefit the vasculature. In fact, in humans, cervical BAT size is negatively correlated with body mass index and the degree of coronary atherosclerosis.\(^\text{21}\) However, more evidence is needed about how fat with increased thermogenic potential effects atherosclerosis, inflammation, and diabetes mellitus.

Cold studies in apolipoprotein E–deficient mice, a model of severe hypertriglyceridemia, demonstrated that BAT activation can completely normalize pathological serum lipid concentrations by enhancing triglyceride uptake and oxidation.\(^\text{22}\) In this issue of Circulation, Chang et al\(^\text{7}\) extend these findings by studying this VSMC-specific PPAR\(\gamma\)-deficient mouse model that lacks perivascular fat, including through their use of an experimental system that monitored intravascular thermoregulation and enhances atherosclerosis.\(^\text{119}\) This data presented here by Chang et al\(^\text{7}\) provide another valuable example of the specific nature and function of different adipose depots while also placing PVAT in the growing literature regarding brown fat and its potential beneficial effects, including ones on the vasculature. Additional intriguing and important questions are raised by these results. Does deleting PPAR\(\gamma\) in VSMCs and the subsequent loss of a specific fat depot reveal a precursor cell or developmental step shared by VSMCs and PVAT? Does PPAR\(\gamma\) in the VSMCs help define the characteristics of adjacent perivascular fat? Although the histology and mRNA/protein profile of perivascular is reminiscent of classic BAT, is perivascular fat a true brown or rather a beige adipose depot? Ultimately, the most important questions will be the relative contribution of different brown and brown-like fat depots to lipid metabolism, diabetes, and atherosclerosis in humans, and whether or not thermogenesis can be targeted for therapeutic purposes. Although undoubtedly the answers to these questions will involve many studies and extensive data from various models, it also seems clear that understanding the spectrum of cardiometabolic disorders will involve a deeper perspective on the vivid contrasts and nuances of shade that exist in fat between white, beige, and brown.

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None.

**References**


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