NIH Public Access
Author Manuscript
Circulation. Author manuscript; available in PMC 2013 August 28.

Published in final edited form as:
Circulation. 2012 August 28; 126(9): 1012–1015. doi:10.1161/CIRCULATIONAHA.112.123521.

Fifty Shades of Brown: Perivascular Fat, Thermogenesis, and Atherosclerosis

Florian W. Kiefer, MD, PhD[1,2], **Paul Cohen, MD, PhD**[1,2,3], and **Jorge Plutzky, MD**[1,2]

[1]Harvard Medical School, Boston, MA

[2]Vascular Disease Prevention Program, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA

[3]Dana Farber Cancer Institute, Boston, MA

Keywords

Editorials; muscle, smooth; obesity; PPAR; brown adipose tissue

The Evolving View of Fat

The relationship between increased body mass index and risk for diabetes 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 oxidant species can also exert both local and distant effects that may be integral to the development of diabetes, atherosclerosis, and their complications. To an increasing extent, adipose tissue is now understood as an organ playing important physiologic and pathologic roles. Both the absence of fat, as with certain lipodystrophies, and excess adiposity, are associated with diabetes, with mechanisms that appear to include infiltration of inflammatory cells into adipose tissue and the release of systemic mediators.

To these and the many other adipocyte actions that continue to be uncovered, recent work has added another critical dimension to our evolving view of fat: the specific location of a given adipose depot. Subcutaneous white fat, visceral white fat, brown fat, epicardial fat, and perivascular fat - including fat around the coronaries, the thoracic aorta, and the abdominal aorta - have all been identified as distinct depots that exert unique local and systemic effects (Table 1). Recent work proposes the existence of beige fat as a distinct entity on this spectrum. These issues are of particular interest given studies suggesting that brown adipose tissue (BAT), which drives thermogenesis, is variably present in humans, associated with decreased adiposity, and may be a therapeutic target. In this issue of

Address for Correspondence: Jorge Plutzky, MD, Harvard Medical School, 77 Ave Louis Pasteur, NRB 742, Boston, MA 02115, Tel: 617-525-4360, Fax: 617-264-5145, jplutzky@rics.bwh.harvard.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest Disclosures: None.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Circulation, Chang and colleagues add to this still emerging picture by providing the intriguing observation that a deficiency of peroxisome proliferator-activated receptor γ (PPARγ a master transcriptional regulator of adipogenesis - specifically in vascular smooth muscle cells (VSMC) results in an absence of perivascular fat. As a result, these VSMC PPARγ-deficient mice (SMPG KO mice as referred to in this paper), are left with impaired lipid clearance, endothelial dysfunction, and decreased intravascular temperature in response to cold exposure. These results further highlight the potential importance of different adipose depots and argue for further consideration of how distinct depots of adipose tissue may influence inflammation and atherosclerosis.

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 kidney. 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 [1]. 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 in order to compare 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 [2].

The amount of PVAT correlates with overall adiposity [3]. In the non-obese 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' [4, 5]. While 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 to lean controls, PVAT from obese subjects reportedly has markedly diminished vasodilatory capacity [6]. Numerous epidemiological studies find an association between the amount of PVAT and cardiovascular risk factors as well as atherosclerosis itself [2]. Although this line of investigation has raised core questions about how PVAT might exert effects on the vasculature, experimental data showing a causal relationship between PVAT and vascular disease, or that might help explain this association, 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* [7]. Several groups, including these authors, had previously generated mice with a targeted deletion of the nuclear hormone receptor PPARγ in VSMC, 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 [8]. In this round of studies, Chang et al uncovered an apparently overlooked aspect to the phenotype of mice lacking PPARγ in their VSMC, 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, prior groundbreaking work found a shared

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

relationship between skeletal muscle cells and adipose tissue, although the link was between muscle and BAT. Several prior studies have suggested that PVAT has more characteristics of BAT than WAT. In keeping with notions of depot specificity, thoracic PVAT was more like BAT, while abdominal PVAT retained more WAT-like features. Detailed studies comparing BAT and thoracic PVAT have supported and extended these observations, with transcriptional profiling revealing nearly overlapping gene expression patterns between BAT and PVAT in a rodent model[9]. Chang et al also found a striking similarity between PVAT and BAT on both expression profiling and proteomic analyses.

In contrast to the consistent finding of BAT-like characteristics of PVAT, the responses of BAT and PVAT to high fat diet has varied. Some groups have reported that BAT and/or PVAT, are resistant to the increased inflammatory responses seen in visceral adipose tissue (VAT) in response to increased caloric intake, including adipose tissue inflammatory cell count, while others have not[10,11]. Perhaps this variability in study results indicates the extent to which BAT and its salient features may respond to different factors like age, diet, and genotype, and thus be modifiable. Regardless, the fact that PVAT resembles BAT generates fundamental questions about how brown fat, or adipose tissue that either resembles brown fat or is induced to take on brown fat characteristics, modulates arterial function and atherosclerosis. The work by Chang et al, which takes an important step in addressing these issues, must be put in the context of what is currently known, and rapidly being uncovered, about BAT and adipose depots that have or can take on BAT-like characteristics.

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) [12].

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 physiologic body temperature, which is so essential for survival, a challenge. Recently, active BAT has also been identified in adult humans using ^{18}F-fluorodeoxyglucose PET-CT, a breakthrough observation that has helped drive clinical and therapeutic interest in brown fat [13–15]. 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[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[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, pharmacologic stimulation using the sympathomimetic ephedrine, which activates BAT in preclinical models, had no effect on BAT in humans[18]. These issues highlight the current challenges in harnessing BAT activation as a therapeutic target that would be predicted to 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 WAT, which has recently been achieved in different mouse models. A number of proteins including transcription factors, co-regulators, enzymes and hormones have been identified to regulate the transformation of classical white into BAT-

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

like or beige adipocytes with the common *in vivo* phenotype of increased energy expenditure and protection against obesity[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[20].

Browning the Vasculature?

Animal studies and more recent clinical evidence argue that decreasing adiposity by activating BAT and potently 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[21]. However, more evidence is needed about how fat with increased thermogenic potential effects atherosclerosis, inflammation and diabetes.

Cold studies in apolipoprotein E5-deficient mice, a model of severe hypertriglyceridemia, demonstrated that BAT activation can completely normalize pathologic serum lipid concentrations by enhancing triglyceride uptake and oxidation [22]. In this issue of *Circulation,* Chang et al extend these findings by studying this VSMC-specific PPARγ-deficient mouse model that lacks perivascular fat, including through use of an experimental system that monitored intravascular temperature [7]. Like classical brown fat, PVAT generates heat and is activated by cold, responses, consistent with the similarities between PVAT and BAT seen by these authors and others. To assess the physiological relevance of these thermogenic properties of PVAT, the authors studied the pro-atherosclerotic ApoE-deficient mouse model. When housed at colder ambient temperature, which is shown to activate PVAT, the mice had evidence of reduced atherosclerosis. However, cross-breeding SMPG KO and ApoE-deficient mice generated double-mutant mice with increased atherosclerosis at both standard and colder temperatures. Surprisingly, the protection against atherosclerosis seen in cold-exposed mice held even after surgical removal of interscapular BAT, but was lost in mice lacking perivascular fat. The authors also implicate PVAT in the regulation of endothelial function via prostacyclin, but find that brown-like PVAT had no impact on inflammatory cytokine levels.

This data presented here by Chang et al provides 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 questions are raised by these results while other key issues remain to be resolved. Does deleting PPARγ in VSMCs and the subsequent loss of a specific fat depot reveal a precursor cell or developmental step shared by VSMC and PVAT? Does PPARγ in the VSMC 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 many 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 between white, beige, and brown.

References

1. Iozzo P. Myocardial, perivascular, and epicardial fat. Diabetes Care. 2011; 34(Suppl 2):S371–379. [PubMed: 21525485]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

2. Britton KA, Fox CS. Perivascular adipose tissue and vascular disease. Clin Lipidol. 2011; 6:79–91. [PubMed: 21686058]
3. Lehman SJ, Massaro JM, Schlett CL, O'Donnell CJ, Hoffmann U, Fox CS. Peri-aortic fat cardiovascular disease risk factors, and aortic calcification: the Framingham Heart Study. Atherosclerosis. 2010; 210:656–661. [PubMed: 20152980]
4. Soltis EE, Cassis LA. Influence of perivascular adipose tissue on rat aortic smooth muscle responsiveness. Clin Exp Hypertens A. 1991; 13:277–296. [PubMed: 2065467]
5. Lohn M, Dubrovska G, Lauterbach B, Luft FC, Gollasch M, Sharma AM. Periadventitial fat releases a vascular relaxing factor. FASEB J. 2002; 16:1057–1063. [PubMed: 12087067]
6. Greenstein AS, Khavandi K, Withers SB, Sonoyama K, Clancy O, Jeziorska M, Laing I, Yates AP, Pemberton PW, Malik RA, Heagerty AM. Local inflammation and hypoxia abolish the protective anticontractile properties of perivascular fat in obese patients. Circulation. 2009; 119:1661–1670. [PubMed: 19289637]
7. Chang L, Villacorta L, Li R, Hamblin M, Xu W, Dou C, Zhang J, Wu J, Zeng R, Chen E. Loss of perivascular adipose tissue upon smooth muscle cells PPARγ deletion is associated with impaired intravascular thermoregulation and enhanced atherosclerosis. Circulation. 2012; 126 XXX-XXX.
8. Sigmund CD. Endothelial and vascular muscle PPARgamma in arterial pressure regulation: lessons from genetic interference and deficiency. Hypertension. 55:437–444. [PubMed: 20038751]
9. Fitzgibbons TP, Kogan S, Aouadi M, Hendricks GM, Straubhaar J, Czech MP. Similarity of mouse perivascular and brown adipose tissues and their resistance to diet-induced inflammation. Am J Physiol Heart Circ Physiol. 2011; 301:H1425–H1437. [PubMed: 21765057]
10. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006; 444:860–867. [PubMed: 17167474]
11. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res. 2005; 96:939–949. [PubMed: 15890981]
12. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev. 2004; 84:277–359. [PubMed: 14715917]
13. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, Schrauwen P, Teule GJ. Cold-activated brown adipose tissue in healthy men. N Engl J Med. 2009; 360:1500–1508. [PubMed: 19357405]
14. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, Kolodny GM, Kahn CR. Identification and importance of brown adipose tissue in adult humans. N Engl J Med. 2009; 360:1509–1517. [PubMed: 19357406]
15. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto NJ, Enerback S, Nuutila P. Functional brown adipose tissue in healthy adults. N Engl J Med. 2009; 360:1518–1525. [PubMed: 19357407]
16. Wu J, Bostrom P, Sparks LM, Ye L, Choi JH, Giang AH, Khandekar M, Virtanen KA, Nuutila P, Schaart G, Huang K, Tu H, van Marken Lichtenbelt WD, Hoeks J, Enerback S, Schrauwen P, Spiegelman BM. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell. 2012; 150:366–376. [PubMed: 22796012]
17. Ouellet V, Labbe SM, Blondin DP, Phoenix S, Guerin B, Haman F, Turcotte EE, Richard D, Carpentier AC. Brown adipose tissue oxidative metabolism contributes to energy expenditure during acute cold exposure in humans. J Clin Invest. 2012; 122:545–552. [PubMed: 22269323]
18. Cypess AM, Chen YC, Sze C, Wang K, English J, Chan O, Holman AR, Tal I, Palmer MR, Kolodny GM, Kahn CR. Cold but not sympathomimetics activates human brown adipose tissue in vivo. Proc Natl Acad Sci U S A. 2012; 109:10001–10005. [PubMed: 22665804]
19. Langin D. Recruitment of brown fat and conversion of white into brown adipocytes: strategies to fight the metabolic complications of obesity? Biochim Biophys Acta. 2010; 1801:372–376. [PubMed: 19782764]
20. Kiefer FW, Vernochet C, O'Brien P, Spoerl S, Brown JD, Nallamshetty S, Zeyda M, Stulnig TM, Cohen DE, Kahn CR, Plutzky J. Retinaldehyde dehydrogenase 1 regulates a thermogenic program in white adipose tissue. Nat Med. 2012 May 6. [Epub ahead of print].

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

21. Kortelainen ML. Association between cardiac pathology and fat tissue distribution in an autopsy series of men without premortem evidence of cardiovascular disease. Int J Obes Relat Metab Disord. 1996; 20:245–252. [PubMed: 8653146]

22. Bartelt A, Bruns OT, Reimer R, Hohenberg H, Ittrich H, Peldschus K, Kaul MG, Tromsdorf UI, Weller H, Waurisch C, Eychmuller A, Gordts PL, Rinninger F, Bruegelmann K, Freund B, Nielsen P, Merkel M, Heeren J. Brown adipose tissue activity controls triglyceride clearance. Nat Med. 2011; 17:200–205. [PubMed: 21258337]

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Characteristics of Selected Adipose Depots

	Perivascular Adipose Tissue	Brown Adipose Tissue	Visceral Adipose Tissue
Location	Surrounding blood vessels, direct contact with adventitia	In humans, mainly cervical, supraclavicular, paraspinal paraaortic	Within the peritoneum, between organs
Physiologic function	Mechanical blood vessel support; Control of vascular tone	Body temperature regulation in infants; Contributor to energy balance in adults?	Storage of excess calories (triglycerides); Endocrine function through adipokines
Signature proteins, patterns	Increased BAT vs WAT gene expression depending on location	UCP-1, CIDEA, PGC-1α, PRDM16, COX8b	Adiponectin (low), leptin, omentin, visfatin
Non-shivering thermogenesis	High; mainly intravascular temperature?	High in infants; Contributor in adults?	Very low; Inducible in genetic mouse models
Inflammation with high fat diet, obesity	Data controversial, variable: very little to increased	Limited cytokine production; Few inflammatory cells	Increased cytokine and chemokine release; Increased inflammatory cells (macrophage)
Obesity and diabetes	Positive correlation with fat mass; pathophysiologic role?	Negative correlation with fat mass; Protective in rodents	Positive correlation with fat mass; Pathogenic
Atherosclerosis	Data controversial, variable: Protective through thermogenesis, vasodilation in mice; Pathogenic through inflammation?	Negative correlation with sub-clinical atherosclerosis; Potentially protective: indirectly through weight loss, metabolic effects? Directly?	Positive correlation with fat mass; Pathogenic through inflammation, diabetes

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, 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 pathologic conditions. See text and selected reviews for additional details. Abbreviations: CIDEA, cell death-inducing DFFA-like effector a; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PRDM16, PR domain containing 16; COX8b, cytochrome c oxidase, subunit VIIIb.