Published in final edited form as:

Trends Endocrinol Metab. 2016 May ; 27(5): 244–246. doi:10.1016/j.tem.2016.03.008.

Human Beige Adipocytes – Epiphenomenon or Drivers of Metabolic Improvements?

Qiong A. Wang¹ and Philipp E. Scherer^{1,*}

¹Touchstone Diabetes Center, Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, Texas 75390, USA

Abstract

Direct evidence that human brown or beige adipocytes improve whole body energy homeostasis, lacks. In a recent report, Min *et al.* implanted proliferated human adipocyte progenitors from a 3D culture system in mice. Implants responded to adipogenic stimuli, and had a beige-like phenotype upon induction that significantly improved systemic metabolic parameters.

Prolonged cold exposure or β -adrenergic stimulation triggers the appearance of clusters of beige adipocytes in subcutaneous adipose tissue in rodent models [1]. Beige adipocytes resemble morphologically classical brown adipocytes, and express UCP-1 and other genes required for thermogenesis. Upon activation, both brown and beige adipocytes can rapidly take up and oxidize large amounts of fatty acids and glucose to produce heat by uncoupling of the mitochondrial respiratory chain. Recently, evidence emerged that beige and brown fat depots are far more prevalent in humans than previously appreciated, and these fat depots may be functionally important for metabolic homeostasis as well [2]. It is assumed that recruitment of large numbers of brown or beige adipocytes or an enhancement of their activity could treat obesity and correct its harmful metabolic consequences.

Earlier studies have demonstrated that adipocyte progenitors are located in the walls of blood vessels within adipose tissue [3]. In a recent report, Min *et al.* successfully proliferated human adipocyte progenitors from explants from human subcutaneous adipose tissue, under a pro-angiogenic condition in a 3D culture system based on Matrigel (Figure 1) [4]. As previously observed *in vivo*, these progenitors are found in tight association with the expanding capillary networks *in vitro*. The study provides the first evidence that human adipocyte progenitors can proliferate well solely upon proangiogenic stimulation. This observation indicates that adipocyte progenitors are not only physically associated with the capillary structures, their proliferation is also achieved simultaneously with the growth of capillaries.

*Correspondence should be addressed to: Philipp E. Scherer, Touchstone Diabetes Center, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX, 75390-8549. Philipp.Scherer@utsouthwestern.edu, Tel: 214-648-8715, Fax: 214-648-8720.

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.

Notably, these newly generated human adipocyte progenitors can be placed into Matrigel and respond very well to a classic adipogenic cocktail, undergoing adipocyte differentiation in association with the newly grown capillaries or in a cell-autonomous manner. Previous *in vitro* adipocyte differentiation protocols using cell lines and primary SVFs can only make multilocular adipocytes in 2D culture systems. Notably, some of the differentiated human adipocytes in the 3D culture system showed unilocular lipid droplets, a morphology closely resembling the appearance of classical white adipocytes *in vivo*.

VEGF-induced stimulation of angiogenesis causes massive beiging of white adipose tissue [5]. What happens to these human adipogenic precursors post VEGF exposure and upon differentiation? Notably, these newly proliferated adipocyte progenitors from human subcutaneous adipose tissue also contained beige progenitors. While a classic adipogenic cocktail prompts the appearance of adipocytes mostly displaying white adipocyte features, adenylate cyclase activation triggers the differentiated human adipocytes to gain features reminiscent of rodent beige adipocytes. There are two possibilities: the first one is that the proliferated progenitors contain beige progenitors, but they differentiate into white-like adipocytes upon stimulation with the classic adipogenic cocktail. It is unlikely, since adipose depots derived from human panniculectomies do not show up in FDG labeling experiments, indicating they do not undergo browning like the rodents. The second possibility is that these white adipocytes can gain some beige phenotype upon stimuli like cold, β -adrenergic stimulation or adenylate cyclase activation, demonstrated previously [6]. Remarkably, when subcutaneously implanting these *in vitro* cultured human beige like adipocytes into immune-deficient NSG mice, the resulting fat pads displayed well-vascularized adipose tissues structure and remained alive for 3 months. Interestingly, these human adipocytes retained high UCP1 expression levels, even after 7 weeks of implantation.

Brown adipose tissue mass in humans is inversely correlated with BMI and adiposity [7], and a cold-induced activation of human brown adipose depots may increase energy expenditure and trigger an improvement in whole body insulin sensitivity [8]. However, direct evidence for the human beige adipocyte to play a metabolically beneficial role is still lacking. Min and colleagues present direct evidence that human beige adipocytes can positively regulate systemic metabolic homeostasis. Immune-deficient NSG mice with implants show lower fasting glucose levels and higher glucose disposal rates during a glucose tolerance test, even when fed with a regular chow diet. After either short-term or long-term high fat diet feeding, mice with human beige adipose tissue implants showed improved glucose tolerance at thermoneutrality. This observation further corroborates the hypothesis that there are metabolic benefits of beige adipose tissue independent of thermogenesis and increased energy expenditure. The implants of human beige adipocytes have higher glucose turnover rates than implants of noninduced human white adipocytes, indicating that they may act as a metabolic sinks for glucose and other metabolites, such as triglycerides. With no difference in whole body glucose turnover, these observations suggest that implants with human beige adipocytes may lead to reduced glucose uptake in other tissues, which may be the major reason for improved hepatic steatosis. It is not clear which implant-derived factors drive this process. The authors performed transcriptional analysis of these cells and highlight the proprotein-convertase subtilisin/kexin type-1 (*PCSK1*), its substrate proenkephalin (*PENK*) and interleukin-33 (*IL33*) as possible mediators, though

additional studies will be required to determine whether these secreted factors directly play a beneficial role.

White, brown and beige adipocytes are relatively well classified in rodent models with their specific morphology and protein markers. Ever since the discovery of brown adipose depots in adult humans, it remains unclear whether adipocytes in these depots resemble beige, brown or both types in rodents. Recent studies showed that brown adipose depots in adult humans are generally heterogeneous with regard to the composition of different adipocyte subclasses. UCP1-positive adipocytes usually colocalize with UCP1 negative cells. Using rodent adipocyte classification scheme as a standard, the UCP1-positive adipocytes in some human depots resemble mostly beige adipocytes in some depots, and in others have a more classical brown adipocyte-like phenotype [9]. Additional studies have shown that human brown adipose depots are composed primarily of beige-like adipocytes, and cold exposure can further increase the ratio of beige to brown adipocytes [10]. Here, the Corvera group used explants from classical human subcutaneous adipose tissue. Although progenitors from these explants can differentiate into adipocytes and can be further induced to obtain a beigelike phenotype, with increased beige adipocyte markers like UCP1, CIDEA and DIO2. However, these beige-like adipocytes remain still different from classical beige/brown adipocytes raised from their distinct progenitors within human brown adipose depots. These newly discovered brown adipose depots are distinct from classical subcutaneous white adipose tissue in humans. Future studies using human brown adipose depots will provide interesting comparisons.

This study opens up new possibilities for studying a variety of adipocyte progenitors in different human adipose depots *in vitro*, not only from healthy individuals but also from individuals with metabolic disease. Illustrating the specific features in each subgroup of adipocyte progenitor cells in a 3D-culture system, and testing these cultures by implanting them into mice, will offer us more insights into the nature of human adipose tissue development, function and regulation. What the study does not answer (and in fact the study was not designed to answer this question) is whether the phenomenon of beiging of adipose tissue presents an opportunity for either weight loss or improvements in insulin sensitivity or both of these processes in the context of human metabolism. However, at least in the context of a rodent model, these cells are capable of conveying metabolic improvements.

Acknowledgments

The authors are supported by US National Institutes of Health grants R01-DK55758, R01-DK099110 and P01DK088761 (to P.E.S.) and K01-DK107788 (Q.A.W.) as well as by Cancer Prevention Research Institute of Texas grant RP140412 (P.E.S.). Figure was illustrated by Richard Howdy, certified medical illustrator, at Visually Medical (VisuallyMedical.com).

References

1. Rosen ED, Spiegelman BM. What We Talk About When We Talk About Fat. *Cell*. 2014; 156:20–44. [PubMed: 24439368]
2. Kajimura S, et al. Brown and Beige Fat: Physiological Roles beyond Heat Generation. *Cell Metabolism*. 2015; 22:546–559. [PubMed: 26445512]

3. Vishvanath L, et al. Pdgfr β + Mural Preadipocytes Contribute to Adipocyte Hyperplasia Induced by High-Fat-Diet Feeding and Prolonged Cold Exposure in Adult Mice. *Cell Metabolism*. 2016; 23:350–359. [PubMed: 26626462]
4. Min SY, et al. Human 'brite/beige' adipocytes develop from capillary networks, and their implantation improves metabolic homeostasis in mice. *Nature Medicine*. 2016; 22:312–318.
5. Sun K, et al. Dichotomous effects of VEGF-A on adipose tissue dysfunction. *Proceedings of the National Academy of Sciences*. 2012; 109:5874–5879.
6. Ye L, et al. Fat cells directly sense temperature to activate thermogenesis. *Proceedings of the National Academy of Sciences*. 2013; 110:12480–12485.
7. van Marken Lichtenbelt WD, et al. Cold-activated brown adipose tissue in healthy men. *New England Journal of Medicine*. 2009; 360:1500–1508. [PubMed: 19357405]
8. Lee P. Temperature-acclimated brown adipose tissue modulates insulin sensitivity in humans. *Diabetes*. 2014; 63:3686–3698. [PubMed: 24954193]
9. Cypess AM, et al. Anatomical localization, gene expression profiling and functional characterization of adult human neck brown fat. *Nature Medicine*. 2013; 19:635–639.
10. Yoneshiro T, et al. Recruited brown adipose tissue as an antiobesity agent in humans. *The Journal of Clinical Investigation*. 2013; 123:3404–3408. [PubMed: 23867622]

Figure 1. Human adipocyte implants improve systemic metabolism in mice

Subcutaneous adipose tissue obtained from elective vascular surgeries is embedded in a Matrigel based 3D culture system. Upon a pro-angiogenic stimulation, comprised of a combination of VEGF, hFGF-B and hEGF, the embedded adipose tissue undergoes capillary sprouting and proliferation of adipocyte progenitors in close contact with the capillary network. Upon adding an adipogenic cocktail, these newly generated adipocyte progenitors differentiate into adipocytes, and can then be induced to gain a beige-like phenotype once treated with forskolin. These beige-like human adipocytes, when mixed with Matrigel and implanted into immune-deficient NSG mice, can be successfully vascularized and preserve beige-specific markers, even weeks after the implantation. NSG mice with the human adipocyte implants have significantly improved metabolic profiles upon a high fat diet-induced metabolic challenge, such as reduced whole body glucose intolerance and reduced liver steatosis.