Commentary

MOLECULAR METABOLISM

Visualizing browning in vivo*

Marcelo O. Dietrich [1,2,*]

Brown adipose tissue (BAT) is the main site of non-shivering thermogenesis in mammals. In humans, BAT was first described in infants [1], and for several decades it was thought to be absent in adults. Recently, the presence of functional BAT was found in healthy adults [2–4]. These findings opened new avenues for the investigation of BAT function in the regulation of energy metabolism. More strikingly, it was found that the white adipose tissue (WAT) can convert to BAT [5] in physiological conditions. Tools to investigate the regulation of BAT activity and conversion of WAT to BAT in vivo were lacking. In this issue of *Molecular Metabolism*, Quarta and colleagues [6] demonstrate the use of hybrid CT/PET imaging to identify the conversion of WAT to BAT in vivo in adult mice. These findings will lead to new opportunities for the prospective study of BAT function in mammals.

BAT is a form of adipose tissue that contains a high density of specialized mitochondria, which dissipate the production of energy in the form of ATP to generate heat. The critical molecular player in brown adipocytes to allow thermogenesis is UCP1, a mitochondrial uncoupling protein that deviates the proton flux from ATPase to produce heat. UCP1 expression is highly specific to brown and beige adipocytes and absent in white adipocytes. Therefore, the expression of UCP1 has been used as a molecular marker of conversion of WAT in BAT, a process known as "browning". The role of BAT and UCP1 in energy metabolism and on physiology in general has been emphasized by a recent study showing that mutations in UCP1 might account for the exceptional longevity in the naked mole rat [7]. Activation of BAT occurs during cold exposure, in a process that relies on sympathetic nervous system (SNS). In the study by Quarta et al. [6], the authors demonstrate the use of a PET tracer, 11C-*meta*-hydroxyephedrine, a NE analog, as an indirect tool to label BAT and the conversion of WAT to BAT. Because BAT is highly innervated by the SNS, and because the SNS is a critical determinant of BAT function, this tracer showed robust characteristics to label SNS-depended BAT activity in vivo. The authors showed functional applications of the tracer, for example, the utilization of PET/CT imaging to identify diet-induced changes in SNS-mediated BAT thermogenesis. In a rodent model of obesity, it has presented further in vivo evidences for impaired thermogenesis by BAT, a factor in the development of obesity and its associated disorders, in obese animals compared to lean controls. Utilizing similar approaches, it is possible to visualize the use of this tool to investigate the effects of distinct manipulations in the physiology of SNS-induced BAT activity. For example, such PET tracers could be used to identify mediators of diet/temperature/exercise-induced thermogenesis. Because physiological interventions can change BAT activity and impact metabolism in general, it is important to dissect the pathways that regulate such changes. The use of an in vivo approach that allows the follow-up of animals is ideal and will certainly shed new light on SNS-mediated BAT activity regulation. Obviously, one caveat of such an approach is the infrastructure necessary to perform such studies, which is still limited to a few centers around the world.

In the paper by Quarta et al. [6], the authors were able to visualize WAT to BAT conversion in mice, showing further evidences for the occurrence of browning in vivo. This set of findings have a large impact on the study of WAT to BAT conversion, as it will allow investigators to test in vivo the mechanisms involved in physiological (and perhaps, pathological) browning. However, it is important to mention that the tracer used in this study largely labels tissues in the abdominal cavity other than WAT. The non-adipose tissue labeling precludes the analysis of browning in fat depots located in the abdominal cavity. The only fat depot that could be visualized by Quarta and collaborators was the inguinal subcutaneous WAT [6]. Therefore, the use of this tracer to study browning in vivo is limited to this WAT compartment, and new studies will be necessary to develop tools to enhance the contrast between browning sites in the abdominal cavity and other organs. It is relevant to note that this tracer is already available to use in humans, and it will be important to see whether browning can be detected in humans as well. It is also possible that the larger body size and increased spatial resolution related to body size in humans compared to mice may show browning in other WAT compartments, not only subcutaneous fat. WAT has been considered a heterogeneous tissue [8], with several different types of WAT responding differently to physiological and pharmacological stimulations. Thus, it will be critical to develop tools that can help to elucidate how different WATs convert to BAT in vivo. The first step has been taken by Quarta et al. [6], and it opens space for greater exploration.

BAT activity relies greatly on glucose and fat acid oxidation. Lipid droplets inside brown and beige adipocytes serve as substrates for oxidative utilization in mitochondria, and generation of heat by UCP1. Importantly, fatty acid themselves act as activators of uncoupling activity in the mitochondria, thus enhancing heat production, dissipating proton gradient and, consequently, increasing oxidative phosphorylation in the respiratory chain. Despite the important role of fatty acids as energy substrates in the BAT, glucose is also utilized as a fuel source to sustain high rates of oxidative phosphorylation, as indicated by fluoro-deoxy-gluose (FDG) PET imaging [6]. In the future, it will be important to combine different tracers to allow the investigation of BAT activity and fuel partitioning in vivo during physiological manipulations.

This commentary refers to "^{11}C-meta-hydroxyephedrine PET/CT imaging allows *in vivo* study of adaptive thermogenesis and white-to-brown fat conversion, by C. Quarta et al." (10.1016/j.molmet.2013.04.002).

[1]Section of Comparative Medicine, Yale University, New Haven, CT 06520, USA [2]Department of Biochemistry, UFRGS, Porto Alegre, RS 90035, Brazil

*Correspondence address: Section of Comparative Medicine, Yale University, New Haven, CT 06520, USA. Email: marcelo.dietrich@yale.edu, dietrich.mo@gmail.com

Received July 4, 2013 • Accepted July 4, 2013 • Available Online 17 July 2013

http://dx.doi.org/10.1016/j.molmet.2013.07.004

With the advance of imaging, several new tracers are been synthesized and the use of PET scan is expanding to allow physiological studies in vivo. The use of SNS analogs to label the activity of the SNS and, indirectly, browning will certainly lead to the discovery of new tracers with enhanced contrast and more diffuse and specific labeling of BAT and WAT–BAT conversion. The involvement of BAT activity in the development of obesity and related disorders also contributes to the importance of developing tracers that can be used to study BAT function and WAT–BAT conversion in vivo. The new tool presented by Quarta and colleagues starts to bridge such a gap and will help the scientific community to test BAT function and browning.

CONFLICT OF INTEREST

None declared.

REFERENCES

[1] Dawkins, M.J., and Scopes, J.W., 1965. Non-shivering thermogenesis and brown adipose tissue in the human new-born infant. Nature 206:201–202.

[2] Cypess, A.M., et al., 2009. Identification and importance of brown adipose tissue in adult humans. The New England Journal of Medicine 360:1509–1517.

[3] van Marken Lichtenbelt, W.D., et al., 2009. Cold-activated brown adipose tissue in healthy men. The New England Journal of Medicine 360:1500–1508.

[4] Virtanen, K.A., et al., 2009. Functional brown adipose tissue in healthy adults. The New England Journal of Medicine 360:1518–1525.

[5] Seale, P., et al., 2007. Transcriptional control of brown fat determination by PRDM16. Cell Metabolism 6:38–54.

[6] Quarta, C.L., Lodi, F., Mazza, R., Giannone, F., Boschi, L., Nanni, C., Nisoli, E., Boshi, S., Pasquali, R., Fanti, S., Iozzo, P., and Pagotto, U., 2013. 11C-*meta*-Hydroxyephedrine PET/CT imaging allows in vivo study of adaptive thermogenesis and white-to-brown fat conversion. Molecular Metabolism 2:153–160.

[7] Kim, E.B., et al., 2011. Genome sequencing reveals insights into physiology and longevity of the naked mole rat. Nature 479:223–227.

[8] Tchkonia, T., et al., 2013. Mechanisms and metabolic implications of regional differences among fat depots. Cell Metabolism 17:644–656.

