Emma De Fabiani

Editorial

Brown-like adipocytes colonizing white fat: A (r)evolutionary way to fight obesity?

In the last decades obesity has become one of the greatest threats to human health due to its prevalence worldwide and the associated risk of developing major chronic diseases such as diabetes, cardiovascular diseases, and cancer.

According to WHO, overweight and obesity are defined as ''abnormal or excessive fat accumulation that presents a risk to health''. Nevertheless, we all know that being fat takes multiple forms, depending on where the fat accumulates preferentially: excessive fat depots around one's waist (abdominal fat) give rise to an ''apple-like'' figure, while a ''pear-shaped'' body results from abnormal build up in the lower parts, thighs and backside, mainly consisting of subcutaneous fat.

Hence, fat is characterized by *different anatomical locations* featuring *different biological functions*. The best known is the functional difference between white and brown adipose tissue: while white adipose tissue (WAT) is mainly implicated in lipid storage and secretion of adipokines, non-shivering thermogenesis is the main characteristic of brown adipose tissue (BAT).

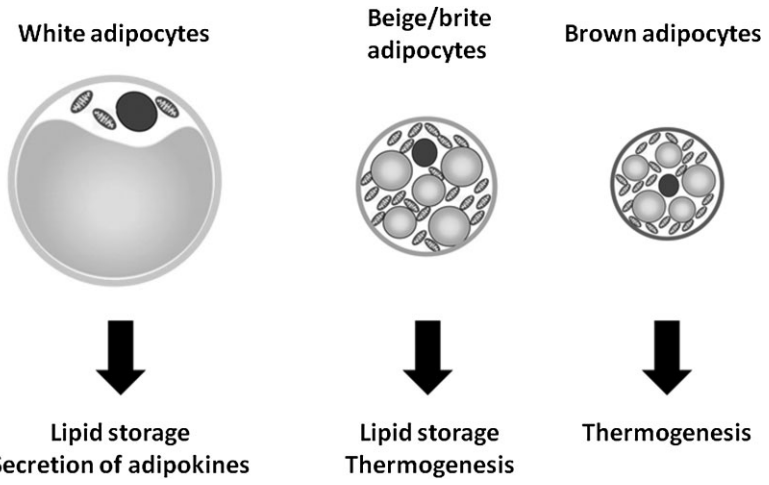
The discovery that BAT is functional also in adult humans and that its dysfunction is associated with aging and metabolic diseases [1–3] have triggered a sort of ''Copernican'' revolution in the way of thinking about its impact on energy balance and metabolic homeostasis.

One of the key questions scientists working in the field have been trying to answer relates to the origin of the main cellular components of WAT and BAT, white and brown adipocytes, respectively. Both adipocyte types derive from pluripotent mesenchimal/mesodermal stem cells residing either in the vascular stroma of adipose tissue or in the bone marrow. However, experimental evidence indicates that commitment of intermediate precursor cells to white or brown pre-adipocytes and complete differentiation to mature phenotype proceeds through independent pathways [4].

In the last 4–5 years we have witnessed remarkable advances in the comprehension of the transcriptional determinants and mechanisms responsible for the development of brown adipocytes. Myocytes and brown adipocytes share common progenitor cells (cells expressing the myogenic transcription factor Myf5). The *zinc finger protein PRDM16* lays at a crucial crossroad in the developmental pathway of these cells, since it has been demonstrated as a master factor specifying the *brown lineage* [5–7]. This protein exerts its function by interacting with other transcription factors and coactivators such as peroxisome proliferator activated receptor (PPAR) α and γ, members of the C/EBP family, and PPAR γ coactivator 1 (PGC-1) proteins. All these factors are well known key determinants of the brown adipose phenotype. Thus, PRDM16 plays a dual role: on the one hand, it triggers a transcriptional program specific of brown adipocytes, and on the other, it represses the expression of typical markers of muscle cells and white adipocytes.

A further level of complexity in the biology of adipose tissues is the observation that some white adipocytes, under certain circumstances, can acquire intermediate metabolic features, which are collectively defined as ''*brite*'' or ''*beige*'' *phenotype*. The ''brite'' (brown-in-white) theory raises from the observation that chronic treatment with PPARγ agonists induces transcriptional and functional changes, increased PGC-1α expression, mitochondrial biogenesis and thermogenic capacity [8], associated with stabilization of PRDM16 protein [9]. Occurrence of intermediate adipocytes characterized by a similar ''beige'' phenotype was reported in the adipose tissue of mice overexpressing COX-2, an enzyme involved in prostaglandins synthesis [10]. In the last couple of years a number of studies have reported ''browning'' or induction of a ''beige'' phenotype of white adipose tissue as a result of multiple signals and regulatory pathways, for example

- the metabolic hormone *fibroblast growth factor (FGF) 21*, which is produced by several tissues including fat, can act in an autocrine/paracrine fashion, by promoting thermogenesis



White adipocytes are the main reservoir of body fat. Their ability to store large amount of triacylglycerols prevents accumulation of fat in lean tissues (lipotoxicity). White adipose tissue also secretes a variety of signaling molecules that contribute to metabolic homeostasis (i.e. regulation of food intake, insulin sensitivity, etc.). Brown adipocytes derive from a distinct set of precursor cells with respect to white adipocytes, they are enriched in mitochondria and express high levels of uncoupling protein 1. All together these features make these cells competent for thermogenesis. ''Browning'' of adipocytes in white fat gives rise to cells with an intermediate phenotype, the ''beige/brite'' phenotype, characterized by increased mitochondrial biogenesis and ability to burn fatty acids producing heat. Induction of ''beige/brite'' adipocytes may represent a key tool to fight obesity and metabolic dysfunction.

as a consequence of ''browning'' (increased expression of uncoupling protein 1) of WAT [11]

- *microRNA miR-196a*, causes brown adipogenesis of white fat progenitor cells by suppressing the expression of a white-fat gene, the transcription factor Hoxc8. Consistently, overexpression of miR-196a in mice is associated to enhanced energy expenditure and resistance to obesity [12]
- *TRPV4*, a member of a family of ion channels, negatively regulates PGC-1α and the thermogenic gene program. Mice lacking this protein exhibit elevated thermogenesis and are protected against diet induced obesity and metabolic derangements [13]
- pharmacological inhibition of *class I histone deacetylases* transcriptionally reprograms WAT toward a phenotype more similar to brown fat (induction of PGC-1α and uncoupling protein 1). This change couples with increased energy expenditure and thermogenesis and amelioration of the metabolic profile in diabetic mice [14]

I believe that the ''brite/beige'' adipocytes represent an important step in the ''Copernican revolution'' of adipose tissues and hold promises for finding new ways to fight obesity and related metabolic diseases, thanks to their ability to ''waste'' stored lipids as heat. The recent discovery that ''beige'' adipocytes are present in humans [15] further strengthens this view.

It took thousands of years to the human species to evolve and survive in harsh environmental conditions, extreme climates, famine, etc. White adipose tissue, the ''savings account'' of metabolic fuel, together with brown adipose tissue, the body's ''heating plant'', have greatly contributed in the metabolic adaptation to environmental stresses. The new challenge mankind has to cope with is the imbalance between energy intake (too high) and expenditure (too low). Brown-like adipocytes colonizing white fat – the ''brite/beige'' adipocytes – appear as an efficient response to handle excessive fuel load.

More investigations are needed to find which and how genetic factors, nutritional components, lifestyle, etc. affect adipose tissues' functions. I hope that authors of the *European*

Journal of Lipid Science and Technology will soon contribute to this topic: we are writing a new exciting chapter in adipose tissues' (r)evolution!

Emma De Fabiani
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References

[1] van Marken Lichtenbelt, W. D., Vanhommerig, J. W., Smulders, N. M., Drossaerts, J. M. et al., Cold-activated brown adipose tissue in healthy men. *N. Engl. J. Med.* 2009, *360*, 1500–1508.

[2] Virtanen, K. A., Lidell, M. E., Orava, J., Heglind, M. et al., Functional brown adipose tissue in healthy adults. *N. Engl. J. Med.* 2009, *360*, 1518–1525.

[3] Cypess, A. M., Lehman, S., Williams, G., Tal, I. et al., Identification and importance of brown adipose tissue in adult humans. *N. Engl. J. Med.* 2009, *360*, 1509–1517.

[4] Park, K. W., Halperin, D. S., Tontonoz, P., Before they were fat: Adipocyte progenitors. *Cell Metab.* 2008, *8*, 454–457.

[5] Seale, P., Kajimura, S., Yang, W., Chin, S. et al., Transcriptional control of brown fat determination by PRDM16. *Cell Metab.* 2007, *6*, 38–54.

[6] Seale, P., Bjork, B., Yang, W., Kajimura, S. et al., PRDM16 controls a brown fat/skeletal muscle switch. *Nature* 2008, *454*, 961–967.

[7] Kajimura, S., Seale, P., Kubota, K., Lunsford, E. et al., Initiation of myoblast to brown fat switch by a PRDM16-C/EBP-beta transcriptional complex. *Nature* 2009, *460*, 1154–1158.

[8] Petrovic, N., Walden, T. B., Shabalina, I. G., Timmons, J. A. et al., Chronic peroxisome proliferator-activated receptor gamma (PPARgamma) activation of epididymally derived white adipocyte cultures reveals a population of thermogenically competent, UCP1-containing adipocytes molecularly distinct from classic brown adipocytes. *J. Biol. Chem.* 2010, *285*, 7153–7164.

[9] Ohno, H., Shinoda, K., Spiegelman, B. M., Kajimura, S., PPARgamma agonists induce a white-to-brown fat conversion through stabilization of PRDM16 protein. *Cell Metab.* 2012, *15*, 395–404.

[10] Vegiopoulos, A., Muller-Decker, K., Strzoda, D., Schmitt, I. et al., Cyclooxygenase-2 controls energy homeostasis in mice by de novo recruitment of brown adipocytes. *Science* 2010, *328*, 1158–1161.

[11] Fisher, F. M., Kleiner, S., Douris, N., Fox, E. C. et al., FGF21 regulates PGC-1alpha and browning of white adipose tissues in adaptive thermogenesis. *Genes Dev.* 2012, *26*, 271–281.

[12] Mori, M., Nakagami, H., Rodriguez-Araujo, G., Nimura, K. et al., Essential role for miR-196a in brown adipogenesis of white fat progenitor cells. *PLoS Biol.* 2012, *10*, e1001314.

[13] Ye, L., Kleiner, S., Wu, J., Sah, R. et al., TRPV4 is a regulator of adipose oxidative metabolism, inflammation, and energy homeostasis. *Cell* 2012, *151*, 96–110.

[14] Galmozzi, A., Mitro, N., Ferrari, A., Gers, E. et al., Inhibition of class I histone deacetylases unveils a mitochondrial signature and enhances oxidative metabolism in skeletal muscle and adipose tissue. *Diabetes*, epub October 15, 2012, DOI: 10.2337/db12-0548.

[15] Wu, J., Bostrom, P., Sparks, L. M., Ye, L. et al., Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell* 2012, *150*, 366–376.

