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EDITORIAL

Brown adipose tissue and browning: More than just a heating device

Tejido adiposo marrón y proceso de marronización: más allá de la generación de calor

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In contrast to the energy-storing white adipose tissue (WAT), brown adipose tissue (BAT) acts as the main site of non-shivering thermogenesis in mammals as a means of enduring cold environments. This is possible due to the presence of uncoupling protein-1 (UCP1) exclusively in mitochondria of brown adipocytes, which uncouples mitochondrial oxidative processes and generates a subsequent production of heat.[1] In doing so, in rodents it has been demonstrated that BAT plays a major role in protection against obesity and associated metabolic alterations due to the energy dissipation performed in this process.[2,3]

It is currently well established that most white and brown adipocytes arise from distinct cell lineages. Classical brown adipocytes, present in anatomically-programmed depots (e.g., the interscapular region), originate from myogenic factor 5 (*Myf5*)-expressing precursor cells, which are also the source of skeletal myocytes. In contrast, the majority of white adipocytes derive from *Myf5*-negative precursors.[4–6] In addition, it is now known that sustained thermogenic activation leads to the so-called 'browning' of WAT, whereby brown adipocyte-like, UCP1-positive cells appear in WAT depots.[7,8] In spite of being thermogenic adipocytes, these cells – usually termed ''beige'' or ''brite'' adipocytes – arise from a *Myf5*-negative cell lineage different from that leading to classical brown adipocytes.[7] The appearance of beige adipocytes has been demonstrated to occur under exercise, cold exposure and in response to β-adrenergic agonists such as CL 316,243.[9] Incidentally, an increase in the activation of beige cells in mice was associated with reduced weight gain and improved glucose tolerance.[10] However, since the discovery of these new type of thermogenic adipocytes, their relevance has been a matter of controversy due to the fact that UCP1 mRNA and protein levels are at least an order of magnitude lower in these cells than in classical BAT in the basal state but, on the other hand, both beige and classical brown adipocyes exhibit similar amounts of UCP1 upon thermogenic requirement.[8,11]

Due to the established assumption that BAT involutes soon after birth and to a lack of techniques to appropriately measure its activity, our understanding of the relevance of this tissue in adult human individuals had been limited until recently. Although the presence of brown adipocytes in adults had been previously described in some conditions such as in outdoor workers in cold climates,[12] and in some diseases (e.g., pheochromocytoma and hibernoma),[13,14] the existence of adult human BAT remained largely ignored until 2009. At that time, the use of positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated

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with computed tomography (18F-FDG PET-CT) confirmed that functional brown adipose tissue is prevalent in adult humans, and, coherently, its occurrence inversely correlates with body mass index.[15–18] Taking these facts into consideration and given the presence of beige fat cells in normal adult humans,[8] the identification of novel molecules capable of inducing browning to produce beige adipocytes could hold promise as a new approach for the treatment of obesity and type 2 diabetes.

Moreover, it is currently in the spotlight not only how powerful BAT is as a heating device, but also whether it could double as an endocrine organ capable of secreting molecules of whole-body metabolic relevance. To offer further insight into this debate, we want to point out a similar discussion that came up on the table many years ago, when some scientists claimed an endocrine role for the WAT existed. This organ was historically considered an inert energy storage depot with few interesting attributes, but the dramatic rise in obesity and its metabolic consequences increased the scientific interest in WAT during the past two decades.[19] Several studies revealed that white adipocytes were highly active endocrine cells that secreted several endocrine factors (e.g., leptin, adiponectin, visfatin and omentin), which have since been collectively termed adipokines. These discoveries permitted the establishisment of a new hormonal network linking WAT with other tissues and organs including skeletal muscle, the adrenal cortex, various regions of the brain and the sympathetic nervous system, modulating many processes including glucose and lipid metabolism.[20,21] Likewise, brown adipocytes were considered until a few years ago merely a site of metabolic energy consumption to produce heat. However, reports that genetic ablation of BAT showed much more profound impact on metabolism than just thermogenic inhibition[22] got back to the field this important question: is BAT just a heating device or is it an endocrine organ as well? The latter seems to be, in fact, the case, as in the last few years, impressive data about BAT transplant have strongly suggested that besides molecules with autocrine/paracrine function, the BAT might also be a source of endocrine factors involved in systemic metabolic changes. Analogously to adipokines, these bioactive molecules released by the BAT have collectively been termed brown adipokines or ''batokines''.[23] Likewise, brown adipokines such as thyroid hormone T_3, fibroblast growth factor 21, bone morphogenetic protein 8B, interleukin 6 or neuregulin 4, enable communication of the brown and beige adipocytes with distant organs in order to coordinate a systemic response to cold, exercise and other metabolic requirements.[23]

Despite the great potential of BAT to treat obesity and related diseases, it is important to point out the possible limitations for using BAT and browning activators as therapeutic agents. An abnormal increase in basal metabolic rate can lead to a hypermetabolic response. In this situation, an increase in the release of free fatty acids and glycerol from fat can take place, leading to excessive glucose production from the liver and excess amino acid release from muscles. Thus, going forward to consider the potential for deleterious side effects and/or unintended metabolic consequences inherent in some browning regimes are likely to be important,[9] and different approaches should be considered. Since individuals suffering from obesity and type 2 diabetes show less amount and activation of BAT, the question would be not only how can we activate brown and beige cells, but also how can we avoid the inhibition of this thermogenic and endocrine tissue in these patients. In this regard, the authors recently published an article demonstrating that a cytokine termed oncostatin M could inhibit BAT and browning process in vitro and in vivo.[24] In the same field, adipocyte-derived lipopolysaccharide-binding protein has been identified as well as another negative regulator of the browning process.[25] A possible therapeutical strategy focused on blocking these ''anti-BAT/browning'' molecules could improve the current scenario in order to find a treatment against obesity and related metabolic disease. Nevertheless, it is important to point out that complete deletion of this kind of molecules could lead to deleterious metabolic effects due to an alteration of inflammatory pathways necessary for a healthy systemic metabolic profile, regardless of body weight regulation.[26]

In conclusion, we are hereby claiming that BAT and browning seem to be more than a heating device, but complex and active regulatory tissues which participate in systemic metabolism through the secretion of endocrine molecules. Scientific goals for the coming years shall be focused on a better understanding of brown and beige adipocyte biology and on the use of novel approaches to increase their activity and/or to avoid their inhibition. Further research on these areas shall provide potential innovative and relevant targets and tools for the treatment of obesity and related metabolic comorbidities.

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