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REVIEW ARTICLE

Understanding the Biology of Thermogenic Fat: Is Browning A New Approach to the Treatment of Obesity?

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Obesity is characterized by an excess of white adipose tissue (WAT). Recent evidence has demonstrated that WAT can change its phenotype to a brown-like adipose tissue known as beige/brite adipose tissue. This transition is characterized by an increase in thermogenic capacity mediated by uncoupling protein 1 (UCP1). This browning process is a potential new target for treating obesity. The aim of this review is to integrate the different mechanisms by which beige/brite adipocytes are formed and to describe the physiological, pharmacological and nutritional inducers that can promote browning. An additional aim is to show evidence of how some of these inducers can be used as potential therapeutic agents against obesity and its comorbidities. This review shows the importance of brown and beige/brite adipose tissue and the mechanisms of their formation. Particularly, the two theories of beige/brite adipocyte origin are discussed: *de novo* differentiation and transdifferentiation. The gene markers that identify these types of adipocytes and the involvement of microRNAs in the epigenetic regulation of the browning process is also discussed. Additionally, we describe the transcriptional control of UCP1 expression by some of the inducers of browning. Furthermore, we describe in detail how some bioactive dietary compounds can induce browning and their subsequent beneficial health effects. The evidence suggests that browning is a new potential strategy for the treatment of obesity and obesity-associated metabolic disorders. © 2017 IMSS. Published by Elsevier Inc.

Key Words: Beige/brite adipocytes, Browning, Dietary bioactive compounds, Obesity, Thermogenesis.

Origin of the Study of BAT and Thermogenesis

In the history of the study of brown adipose tissue (BAT) and thermogenesis, hibernation first gained attention because it was intriguing how an organism could slow its metabolic rate, descend body temperature and rewarm (arousal phase) in order to survive the winter. In 1551, Gessner described for the first time the existence of BAT; he mentions that marmots had fat in the back that was ''neither fat nor flesh, it was something in between'' (1). Several years later, BAT became known as the ''hibernation gland'', but its function was unknown until 1963 when Smith and Hock and Smalley and Dryer showed that BAT was the key to producing the heat needed for rewarming during the arousal phase of hibernation (2,3). Nedergaard and Lindberg, in 1979, proposed a mechanistic pathway for the rewarming process that included the stimulation of brown fat cells by the sympathetic nervous system (SNS) in order to start the breakdown of the lipids stored as free fatty acids (FFA) (4). Brown fat cells have a characteristic that distinguishes them from other cell types, which is that the oxidation of FFA is not necessarily coupled to ATP production. This is due to the existence of a protein located in the inner mitochondrial membrane, uncoupling protein 1 (UCP1), which allows protons to leak into the mitochondrial matrix, and the energy generated that would be used to synthesize ATP is dissipated as heat (5,6). This heat production by BAT is a physiological response of mammals for

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resisting cold temperatures (non-shivering thermogenesis) or metabolizing the excess nutrients in high calorie diets (7).

BAT Structure

BAT has a characteristic yellow-brown color due to its high content of mitochondria, and it also has a lobulated surface that is innervated and very well vascularized (8).

Brown adipose tissue is derived from a population of cells located in the dermomyotome of the mesodermal layer, which express myogenic factor five ($MYF5^+$) and paired-box 7 ($PAX7^+$). These precursor cells can further differentiate into muscle cells or BAT cells. The fate of the BAT lineage is driven by specific transcription factors including peroxisome proliferator-activated receptor gamma (PPARγ), PR domain containing 16 (PRDM16), Euchromatic histone lysine methyltransferase 1 (EHMT1), Early B-Cell factor 2 (EBF2), Zinc finger protein 516 (ZFP516), and CCAAT/enhancer-binding protein beta (C/EBPβ) among others (9,10) that will be described below (Figure 1).

Active BAT has been observed in the interscapular region of human infants, whereas in adults, BAT is found in small amounts and was believed to have lost its function. Interestingly, recent studies by Cypess in 2009 and Van Marken Lichtenbelt in 2009 show that BAT activity is not lost; it simply needs to be activated by cold (11,12). The main locations of the BAT in humans are the sternocleidomastoid muscles of the neck, the cervical−supraclavicular region, the armpits, the groin muscles, the adrenal glands, the para-aortic adipose tissue of the thoracic cage between the subscapularis and pectoralis muscles, and around the viscera in the abdominal cage (omentum tissue) (13−16).

Some of the characteristics of BAT at the cellular level are the presence of several small lipid droplets inside the cytoplasm and a high number of large mitochondria compared with other cell types (17,18). These large mitochondria have high thermogenic activity due to an abundance of the UCP1 protein (19).

Thermogenesis

UCP1: Definition, Description and Metabolic Activity

Uncoupling protein 1 is the hallmark protein responsible for inducing thermogenesis. UCP1 is ubiquitously expressed in the mitochondrial inner membrane of brown adipocytes, and it is highly induced in brown-like adipocytes. Its main activity is the dissipation of the proton gradient generated by the respiratory chain, thus increasing the permeability of the mitochondrial matrix and allowing a leakage of protons. Therefore, it reduces the efficiency of cellular respiratory machinery, resulting in an increase of heat dissipation, which provides the thermogenic properties of the tissue (20). It has been described that the other UCP members, UCP2 and UCP3, have the same structure as UCP1 but differ in their localization. UCP2 is expressed ubiquitously, and UCP3 is present mainly in muscle. In addition, there are two members of this family, UCP4 and UCP5, that are mainly located in the central nervous system (CNS) (21). However, this family's role in adaptive thermogenesis relies upon UCP1 (19) since the ablation of the gene induces a phenotype sensitive to cold (22). However, UCP1-KO mice do not exhibit protection against diet-induced obesity when the mice are held at thermoneutral temperatures (20−24°C) (22). Nonetheless, with age, the UCP1-KO mice tend to increase adipose tissue depots due to a low oxidation rate of FFA. The presence of UCP1 in BAT confers the characteristic that makes BAT vital for the regulation of the organism's global energy expenditure, making it a potential therapeutic target for some metabolic diseases such as obesity and diabetes (20).

Unravelling the mechanism of BAT activation is then necessary for the treatment of obesity. Indeed, BAT activity has been shown to be reduced in obese patients (23). BAT is innervated by the SNS and highly vascularized; hence, the activation and thermogenic function of BAT depends on the SNS (24). A well-characterized activator of BAT is a cold environment. Upon cold exposure, the efferent pathways of SNS are activated, releasing catecholamines such as norepinephrine (NE). The binding of NE to the β-adrenergic receptors (β-AR), which are abundantly expressed in brown adipocytes and present in white adipocytes, triggers a signal transduction cascade that leads to an increased expression of thermogenic genes (25).

This signaling pathway requires an increase in the cAMP concentration, which leads to the enhanced activity of protein kinase A (PKA). PKA then promotes the cAMP response element binding protein (CREB) and p38 mitogen-activated protein kinase (p38-MAPK), which later induce the downstream transcription of thermogenic genes such as *Ucp1* (13). Other BAT activators are natriuretic peptides that bind to their receptor natriuretic peptide receptor (NPR) to enhance the cyclic guanosine monophosphate (cGMP) concentration and activate protein kinase G (PKG), which also elicit the transcription of thermogenic genes. PKG works in parallel with the adrenergic PKA pathway to trigger lipolysis. As a result, there is a release of FFA, which is then an available substrate for the respiratory chain to boost UCP1 protein activity (25). In this manner, we observe that BAT activators not only induce the transcription of the *UCP1* gene but also provide a substrate for the electron transport chain.

Transcription of the thermogenic genes occurs when the enzyme RNA polymerase binds to DNA, and its attachment depends on proteins, called transcription factors, that bind to specific locations within the promoter region of the *Ucp1* gene, called response elements, to initiate the