

Changing white into brite adipocytes. Focus on “BMP4 and BMP7 induce the white-to-brown transition of primary human adipose stem cells”

Editorial

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Obesity is a metabolic disease that is assuming epidemic proportions. Obesity is caused by an imbalance between energy intake and energy expenditure, resulting in an excess of body fat. Obesity-associated diseases include diabetes, insulin resistance, dyslipidemia, liver steatosis, hypertension, heart diseases, and increased incidence of certain cancers. Few pharmacological approaches are available for the treatment of obesity, apart from dieting and changes in lifestyle, and new drugs and strategies are required. Two types of adipose tissue are present in mammals, white and brown (WAT and BAT, respectively), which have distinct phenotypes and functions. White adipocytes are unilocular, with a large lipid droplet, whereas brown adipocytes are multilocular and have many lipid droplets. The function of WAT is to store energy. In contrast, BAT dissipates energy, producing heat at the expenses of lipid combustion, a process that is accomplished by uncoupling protein 1 (UCP1), which is a BAT-specific mitochondrial protein that by uncoupling oxidative phosphorylation produces heat instead of ATP. The main activators of UCP1 are cold exposure and adrenergic stimulation, but many other hormones, including thyroid hormones, increase UCP1 activity. Analysis of the lineage of brown and white adipocytes has revealed that each has a different embryonic origin. Surprisingly, brown adipocytes have a myogenic origin and express *Myf5*, which is also found in myoblasts. The differentiation of brown and white adipocytes can be characterized using a panel of markers. In WAT, it is possible to find clusters of adipocytes that have been called brite (brown-white) or beige adipocytes. They are multilocular and express UCP1, as well as *Cidea* and other markers of brown adipocytes. They are present in discrete amounts and are more frequent in certain anatomical locations, such as the inguinal fat in rodents. Brite adipocytes are distinct from brown adipocytes with regard to their embryonic origin and gene expression signature. The presence, abundance, and activity of brite adipocytes are regulated in a different way than brown adipocytes. Many experimental models, especially mouse models with deletion of a single gene, have shown that mice were leaner when BAT was more active or when brite adipocytes were induced, whereas a loss of function of BAT led to increases in the percentage of body fat or to insulin resistance. Mice are resistant to weight gain when brown fat activity is increased. This means that by increasing the activity of BAT a reduction in metabolic disease can be achieved. Many groups have attempted to identify the processes that induce WAT to brite adipocyte transition, to determine if BAT and brite adipocytes are the same or different cells, and to establish the mechanisms of reactivation or induction of BAT activity. In this issue of the *American Journal of Physiology-Cell Physiology*, Elsen et al. characterize the induction of UCP1 in response to BMP7 and BMP4 in human white adipocytes. They also show that BMP4, described to be involved in white adipocyte commitment, induces UCP1 in human white adipocytes as well as other markers of browning [peroxisome proliferator-activated receptor- (PPAR) and PPAR coactivator 1 (PGC1)], and decreases markers of white adipocytes (TCF21). The transition to brite adipocytes can be followed using CD137 as a marker of browning of human adipocytes. In 2009, three different groups reported the presence of BAT in adult humans and its modulation by high body mass index, sex, and age. Previously, several groups reported the presence of BAT in humans, but from 2009 onwards it became clear that BAT could be a strategy to fight against obesity. Both BAT and brite adipocytes have been found in humans. However, it still remains to be proven that active BAT in humans is able to fight obesity.

Many questions remain to be answered: Which are the regulators of the transition of white into brown or beige adipocytes? Which are the best anatomical locations to undergo such transformation? Are the mechanisms and processes similar in mice and humans? Are brite/beige adipocytes a cellular entity that is distinctly different from brown and white adipocytes, as indicated by some reports? In addition, moreover, how much might the activation of BAT and increased production of brite adipocytes contribute to increased energy expenditure? The work of Elsen et al. advances our understanding of adipose cell physiology, which may hold the key to effective obesity prevention and treatment.