BMP4-mediated brown fat-like changes in white adipose tissue alter glucose and energy homeostasis

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AUTHOR SUMMARY

Two types of fat storage cells, known as “adipocytes,” coordinately regulate energy balance in humans and other mammals. White adipocytes are specialized to store energy, whereas brown adipocytes produce heat. Promotion of brown adipocyte activity in white adipose tissue helps prevent obesity and its metabolic complications. Bone morphogenetic protein 4 (BMP4) is a member of the bone morphogenetic protein family, which is part of the TGF-β superfamily. BMP4 is essential for embryonic formation and is involved in the development of tissues such as bone and muscle, teeth, and neurons. In the present study, we found that the level of BMP4 in human white adipose tissue is inversely associated with body mass index (BMI). The BMP4 protein also was shown to induce brown adipose tissue-type changes in white adipose tissue, and to increase glucose and energy expenditure in mice models.

White adipose tissue stores energy in the form of triglycerides. However, the increases in cell division or cell size (i.e., hyperplasia and hypertrophy, respectively) of adipocytes that accompany the excessive accumulation of body fat are associated with insulin resistance, type 2 diabetes, and an inflammatory response (1). In contrast, brown adipose tissue activity prevents genetic obesity in rodents (2). Recent studies have identified metabolically active fat cells, known as “brite” (brown-in-white) or “beige” adipocytes, in white fat deposits in both mice and humans (3). The number of active brown adipose tissue cells is inversely correlated with BMI in humans (4). Therefore, the identification of factors that induce brown-like fat cells in white adipose tissue could suggest an approach to preventing and/or treating obesity and its metabolic complications. We previously found that BMP4 induces multipotent C3H10T1/2 stem cells to become preadipocytes (5). Our present findings reveal that the level of BMP4 in human white adipose tissue is inversely associated with BMI, and we explore whether BMP4 regulates the terminal differentiation and metabolic function of adipocytes.

Two mouse models were used in the present study: the BMP4 transgenic mouse in which BMP4 was specifically overexpressed and a knockout mouse in which BMP4 was specifically knocked out in adipose tissue. We assessed the phenotype of adipose tissue and the systematical metabolic alteration in these mice. Our findings revealed that the forced expression of BMP4 in white adipose tissue promotes the acquisition of brown fat-like characteristics, including decreased adipocyte size and lipid droplets, increased mitochondrial biogenesis, and the increased expression of fatty acid-oxidizing genes. Changes in adipose tissue resulted in a systematical increase in basal respiratory rate, increased insulin sensitivity, and decreased blood fat. Similarly, cell culture experiments revealed that treatment with BMP4 during 3T3-L1 adipocyte differentiation leads to a gene-expression profile similar to that of brown fat cells. More importantly, overexpression of BMP4 in white adipose tissue improves insulin sensitivity and protects against diet-induced obesity and diabetes. Conversely, BMP4-deficient mice exhibit enlarged white adipocyte morphology, increased blood fat, and impaired insulin sensitivity. These results reveal an interesting role for BMP4 in the regulation of adipogenesis and metabolism.

We then explored the molecular mechanism of BMP4-induced brown adipose-like changes in white adipose tissue and found that peroxisome proliferator-activated receptor γ coactivator α (PGC1α) was the key regulator during the program. We further demonstrated that activation of the p38/MAPK/activating transcription factor 2 (ATF2) pathway and PGC1α expression by BMP4 play an important role in the induction of white adipose tissue into brown adipose-like tissue.

In the present study, we found that the level of BMP4 in human white adipose tissue is inversely associated with fat mass.


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Mice with overexpressed or absent BMP4 in white adipose tissue revealed that BMP4 induces brown fat-like changes in white adipose tissue in addition to altering metabolism and insulin sensitivity. Therefore, we showed that BMP4-mediated expression of PGC1α proceeds through the p38/MAPK/ATF2 pathway (Fig. P1). These findings indicate that manipulation of BMP4 expression in white adipose tissue may serve as a therapeutic target for the prevention and/or treatment of obesity and its metabolic complications.