Brown adipose tissue (BAT) induction emerges as a promising strategy to ameliorate metabolic diseases such as obesity, insulin resistance, and type 2 diabetes mellitus by promoting energy expenditure and insulin sensitivity. A recent study by Rahman et al (1) in this issue of Endocrinology provides intriguing evidence that inducible BAT (iBAT), also known as beige/brite fat, is also anabolic to the bone. In light of the skeletal fragility in diabetic patients and the bone loss side effects of current diabetic drugs, BAT induction holds an exciting potential as a strategy to simultaneously improve metabolic and skeletal fitness.

iBAT suppresses many metabolic symptoms associated with obesity and diabetes (reviewed in Refs. 2 and 3). Clinical studies have reported that increased BAT activity in humans correlates with not only reduced metabolic disorders but also elevated bone mineral density and skeletal mass. Consistent with the epidemiological evidence, mouse genetic models with BAT ablation or uncoupling protein 1 (UCP1) deficiency exhibit increased propensity to develop diet-induced obesity and diabetes, whereas mouse genetic models with BAT induction confer resistance to obesity and insulin resistance. Nonetheless, whether and how BAT modulates skeletal homeostasis is an important yet underexplored question. This study by Rahman et al (1) begins to fill this void by reporting that BAT induction is accompanied by bone gain in mice. Using a previously described iBAT mouse model in which the transcription factor Forkhead box C2 (FoxC2) is overexpressed in the adipocytes (*FoxC2AD^+/Tg*), this study shows that browning of the adipose tissue leads to an increase in bone mass and bone turnover via novel paracrine and endocrine mechanisms.

Lineage tracing and molecular characterization has classified BAT into 2 distinct populations (4, 5): the developmentally programmed classical BAT that originates from Myf5 progenitors and closely relates to muscle and the iBAT or beige/brite fat that originates from Myf5 progenitors that emerges from white adipose tissue (WAT) upon stimuli such as cold exposure. Bone marrow adipose tissue (BMAT) represents another type of fat, the lineage and function of which is less understood (6). BMAT has been reported to increase under various physiological, pathological, and pharmacological conditions. For example, BMAT increases during puberty as well as aging; in disorders such as estrogen deficiency, diabetes, and anorexia nervosa; and by drugs such as the insulin sensitizer rosiglitazone. The nature of BMAT under these various situations is unclear, but both WAT- and BAT-like characteristics have been attributed to BMAT and may be dynamically regulated.

Marrow fat gain is often accompanied by bone loss, largely due to the differentiation competition between marrow adipocyte and osteoblast from mesenchymal stem cells. Several hormones and transcription factors that promote marrow adipogenesis also inhibit osteoblastogenesis, such as the nuclear receptor peroxisome proliferator-activated receptor γ (7, 8), fibroblast growth factor 21 (9) and the circadian deadenylase nocturnin (10). In contrast, hormones and transcription factors that promote osteoblastogenesis suppress adipogenesis, such as β-catenin, semaphorin-3A, retinoblastoma 1, and type 1 cannabinoid receptor (CB1) (reviewed in Refs. 6 and 11).

The current study provides evidence that browning of WAT and BMAT in *FoxC2AD^+/Tg* mice leads to an increase in bone formation and bone turnover, thus turning fat from foe to friend of the skeleton. The anabolic effects on bone are accomplished by the cell-cell interaction between iBAT and bone cells including osteoblast and osteocytes (Figure 1). One mechanism involves the iBAT secretion of systemic and osseous factors, including IGF-binding protein 2 and Wnt10b, to increase osteoblastogenesis and enhance the levels of phosphor-Akt and β-catenin. Another mechanism involves the iBAT regulation of osteocyte function to suppress its expres-
Inducible brown adipose tissue, or beige fat, is anabolic for the skeleton. Endocrinology. 2013;154:2687–2701.


