Going to BAT

By Joanne Kotz, Senior Editor

Two teams are reporting new targets for inducing the conversion of white fat to a brown-like phenotype, or boosting the activity of existing brown fat, that could help treat obesity and related metabolic diseases. A **Brigham and Women's Hospital** team has identified an enzyme that regulates white adipose plasticity,¹ whereas a **University of Cambridge** team has identified a secreted protein that activates brown fat.²

White adipose tissue (WAT) stores energy as triglycerides, and brown adipose tissue (BAT) metabolizes fatty acids to generate heat. The mobilization of triglycerides by brown fat keeps in check the storage of fat by white fat, which helps control weight and overall metabolic status.

BAT was long known to exist in rodents and human infants, primarily as a defense against cold temperatures. In 2009, a trio of papers in *The New England Journal of Medicine* identified BAT in human adults and found that BAT activity was inversely correlated with BMI.³⁻⁵

At least one company is focused on targeting brown fat in obesity and other metabolic diseases. **Ember Therapeutics Inc.** has disclosed programs targeting bone morphogenetic protein 7 (BMP7; OP-1) and irisin, a secreted form of fibronectin type III domain containing 5 (FNDC5). Both proteins play a role in regulating brown fat development.

Gut wrenching

Other groups have been looking for alternative pathways and targets to regulate brown fat formation and activation.

Results from a team led by Jorge Plutzky, director of the Vascular Disease Prevention Program at Brigham and Women's Hospital, suggest the enzyme aldehyde dehydrogenase 1 family member A1 (ALDH1A1) may be a target for inducing the formation of brown-like fat specifically in visceral white fat.

"Considerable attention is now being directed to new insights into different kinds

of fat including subcutaneous versus visceral white fat, the latter being considered the more pathogenic for cardiovascular disease and diabetes," said Plutzky.

Previous work from a Plutzky-led team showed knocking out *Aldh1a1* protected mice from high-fat diet-induced obesity.⁶

His team thus set out to determine whether ALDH1A1 also regulates body weight in humans.

In healthy people of normal weight, ALDH1A1 mRNA and protein levels were higher in visceral white fat than in subcutaneous white fat. In 40 people ranging from normal weight to morbidly obese, ALDH1A1 levels in visceral white fat correlated with BMI.

Next the team looked for the mechanism behind the connection.

Aldh1a1-deficient mice had higher expression of brown fat genes and greater mitochondrial activity in visceral white fat than wild-type mice. In contrast, expression of brown fat genes in subcutaneous white fat and existing brown fat was relatively unchanged in the deficient mice.

Finally, the group tested the effects of antagonizing *Aldh1a1*. In obese mice, an antisense oligonucleotide against *Aldh1a1* decreased weight gain and visceral white fat mass and increased glucose and insulin tolerance compared with a control antisense oligonucleotide.

Pump up your brown fat

Meanwhile, a team co-led by Andrew Whittle and Antonio Vidal-Puig identified a bone morphogenetic protein (BMP) family member, BMP8B, that ramps up thermogenesis in brown fat.

Vidal-Puig is a professor in the metabolic research laboratories at the University of Cambridge. Whittle is a postdoctoral research scientist in Vidal-Puig's laboratory.

Some BMPs are known to play a role in adipogenesis. For example, BMP2 and BMP4 drive white adipocyte formation, whereas BMP7 promotes brown adipocyte formation.

To determine whether BMP8B played a role in regulating fat, the Cambridge team studied mice and found that *Bmp8b* is predominantly expressed in the brain and in mature brown adipocytes.

The researchers next looked to see what role *Bmp8b* played in brown adipose tissue.

Mice exposed to cold had a 140-fold increase in *Bmp8b* expression in brown fat, whereas mice fed a high-fat diet had a fourfold increase. Both conditions activate brown fat.

Also, *Bmp8b*-deficient mice had lower body temperature and greater weight gain—despite reduced food intake—than wild-type mice. The researchers next treated brown adipocyte cultures with BMP8B, which increased stimulation-induced lipolysis compared with that seen in untreated controls.

Collectively, the findings suggested *Bmp8b* could play a role in mediating the activation of brown fat. The team went a step further and hypothesized that *Bmp8b* might be a central regulator of thermogenesis.

Indeed, intracerebroventricular injection of BMP8B led to greater neuronal innervation into BAT, higher core body temperature, lower body weight and better metabolic homeostasis than injection of vehicle.

Therapeutics needed

The challenge for both targets will be developing safe therapeutic leads.

"Although early, we believe there is therapeutic potential of targeting both the ALDH1A1 and BMP8B pathways," said Lou Tartaglia, president and interim CEO of Ember.

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—Jorge Plutzky,
Brigham and Women's Hospital

ALDH1A1 is a member of a large family of aldehyde and retinaldehyde dehydrogenase enzymes, many of which perform essential functions. Thus, “the most significant challenge with ALDH1A1 is developing potent inhibitors that are specific enough and safe enough to treat metabolic disease,” said Tartaglia.

“We are digging more into mechanisms while also exploring how to modulate the target,” said Plutzky. “We have shown at least a proof of concept for antisense approaches, but small molecules may also be possible.” He declined to disclose further details of therapeutic strategies the team will pursue.

“The challenge with BMP8B is that BMP family members are known to be involved in bone formation. The concern would be whether you have a therapeutic window where this could be used without inducing ectopic bone formation,” said Bruce Spiegelman, professor in the Department of Cell Biology at the **Dana-Farber Cancer Institute** and a cofounder of Ember.

Whittle is not pursuing the development of a therapeutic BMP8B variant. Instead, his team is developing an assay that could be used to detect BMP8B in human serum and is working to identify the relevant receptor.

Plutzky declined to disclose the patent or licensing status of the work reported in *Nature Medicine*.

The results reported in *Cell* are unpatented, said Whittle.

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