

The therapeutic potential of brown adipose tissue

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The increased prevalence of obesity and type 2 diabetes are increasing dramatically in the United States and worldwide, resulting in health organizations and researchers to consider diabetes as an epidemic (1). The increasing rates of obesity and type 2 diabetes have increased the importance of elucidating the molecular basis for obesity, as well as potential therapeutic treatments for this condition.

Brown adipose tissue (BAT) can increase energy expenditure and protect against obesity. BAT is a thermogenic tissue that contains large amounts of mitochondria to dissipate chemical energy as heat (2). Upon stimulation (i.e., cold exposure, feeding), BAT uses stored lipid as its initial substrate. BAT stimulation activates the release of free fatty acids from triglycerides droplets, and BAT uses uncoupling protein 1 (UCP1) to uncouple the respiratory chain and results in heat production (3-6). BAT also plays a major role in glucose disposal, and an increase in BAT, either by mass or activation, can improve metabolism (6-8). Glucose that is not immediately utilized accumulates as glycogen (9), and eventually converted to lipids to replace the triglyceride droplets.

The high capacity of BAT for both glucose and lipid oxidation makes this tissue a potential target for decreasing plasma glucose, lipids, and lowering the risks of type 2 diabetes and obesity (10). This has led to recent studies focused on increasing the number of BAT-precursors and BAT-like cells in other tissues, and on increasing the amount of BAT using models such as transplantation. BAT-progenitors have been identified in skeletal muscle and white adipose tissue (WAT) (11,12), indicating that it could be possible to increase the oxidative capacities of these tissues by targeting these progenitor cells. Studies investigating secreted factors such as BMP-7 (12), FGF21 (13,14), BDNF (15), or irisin (16) have indicated that these proteins can control the commitment and differentiation of BAT progenitors and

therefore have significant potential as treatments for obesity and metabolic disease. Additional studies have examined the effects of increasing regulators of brown adipogenesis such as PRDM16 (17,18). PRDM16 is a transcriptional co-regulator that regulates the development of brown adipocytes (17). This study demonstrated that transgenic expression of PRDM16 in WAT resulted in an increase in BAT-like adipocytes in subcutaneous WAT. This increase in BAT-like adipocytes increased energy expenditure, protected against weight gain, and improved glucose tolerance in response to a high-fat diet (18). Thus, the increase in BAT-like adipocytes in WAT improved overall metabolic health.

Recent work using rodent models has examined the therapeutic potential of increasing the amount of BAT to improve glucose homeostasis. Transplantation of embryonic BAT corrected type 1 diabetes (T1D) in streptozotocin-treated (STZ) mice (19). The increase in BAT restored euglycemia and normalized glucose tolerance in recipient mice. The normalization of glucose metabolism was independent of increases in insulin concentration, but correlated to the recovery of WAT in the recipient mice. This was likely a result of the embryonic BAT stimulating the regeneration of the endogenous WAT, resulting in increased circulating adiponectin, leptin, and IGF-1 concentrations. Increases in leptin and adiponectin correlate with restoration of glucose homeostasis (20-22). Studies in our laboratory demonstrated that increasing BAT mass by transplantation in adult male mice on a chow-diet significantly improved glucose homeostasis (8). This transplantation also resulted in a complete reversal of high-fat diet-induced insulin resistance. The increase in BAT amplified insulin-stimulated glucose uptake into endogenous BAT, WAT, and heart, acting in an endocrine manner to improve whole-body glucose metabolism. These increases in glucose metabolism were attributed to increases in circulating IL-6,

as the transplantation of BAT from IL-6 knockout mice (*Il-6^{-/-}* BAT) did not alter glucose tolerance in recipient mice. Transplantation of *Il-6^{-/-}* BAT also did not increase circulating FGF21, or result in the same improvements in body weight or % fat mass observed in mice receiving wild-type BAT. These data demonstrate that the increase in BAT-derived circulating IL-6 is linked to an improvement in glucose metabolism, and further supports the idea that BAT is a potential target for treatment of obesity-related disease.

As the rates of obesity and type 2 diabetes reach epidemic levels, the development of new therapies and treatments to combat obesity become increasingly critical. BAT is clearly a unique tissue with the potential to improve whole-body metabolism. Therapies based on activation of BAT, whether it be by increasing BAT-like cells, or increasing BAT mass by transplantation, are avenues with great potential that could be used to improve metabolic health.

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References

- International Association for the Study of Obesity. International Obesity Taskforce. Available online: <http://www.iaof.org/>, accessed October 30, 2012.
- Lowell BB, Spiegelman BM. Towards a molecular understanding of adaptive thermogenesis. *Nature* 2000;404:652-60.
- Rothwell NJ, Stock MJ. Effects of age on diet-induced thermogenesis and brown adipose tissue metabolism in the rat. *Int J Obes* 1983;7:583-9.
- Gesta S, Tseng YH, Kahn CR. Developmental origin of fat: tracking obesity to its source. *Cell* 2007;131:242-56.
- van Marken Lichtenbelt WD, Vanhommel JW, Smulders NM, et al. Cold-activated brown adipose tissue in healthy men. *N Engl J Med* 2009;360:1500-8.
- Bartelt A, Bruns OT, Reimer R, et al. Brown adipose tissue activity controls triglyceride clearance. *Nat Med* 2011;17:200-5.
- Cawthorne MA. Does brown adipose tissue have a role to play in glucose homeostasis? *Proc Nutr Soc* 1989;48:207-14.
- Stanford KI, Middelbeek RJ, Townsend KL, et al. Brown adipose tissue regulates glucose homeostasis and insulin sensitivity. *J Clin Invest* 2013;123:215-23.
- Glick Z, Teague RJ, Bray GA, et al. Compositional and metabolic changes in brown adipose tissue following a single test meal. *Metabolism* 1983;32:1146-50.
- Nedergaard J, Bengtsson T, Cannon B. New powers of brown fat: fighting the metabolic syndrome. *Cell Metab* 2011;13:238-40.
- Crisan M, Casteilla L, Lehr L, et al. A reservoir of brown adipocyte progenitors in human skeletal muscle. *Stem Cells* 2008;26:2425-33.
- Tobin JF, Celeste AJ. Bone morphogenetic proteins and growth differentiation factors as drug targets in cardiovascular and metabolic disease. *Drug Discov Today* 2006;11:405-11.
- Kharitonov A, Shiyanova TL, Koester A, et al. FGF-21 as a novel metabolic regulator. *J Clin Invest* 2005;115:1627-35.
- Hondares E, Iglesias R, Giralt A, et al. Thermogenic activation induces FGF21 expression and release in brown adipose tissue. *J Biol Chem* 2011;286:12983-90.
- Cao L, Choi EY, Liu X, et al. White to brown fat phenotypic switch induced by genetic and environmental activation of a hypothalamic-adipocyte axis. *Cell Metab* 2011;14:324-38.
- Boström P, Wu J, Jedrychowski MP, et al. A PGC1- α -dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature* 2012;481:463-8.
- Seale P, Kajimura S, Yang W, et al. Transcriptional control of brown fat determination by PRDM16. *Cell Metab* 2007;6:38-54.
- Seale P, Conroe HM, Estall J, et al. Prdm16 determines the thermogenic program of subcutaneous white adipose tissue in mice. *J Clin Invest* 2011;121:96-105.
- Gunawardana SC, Piston DW. Reversal of type 1 diabetes in mice by brown adipose tissue transplant. *Diabetes* 2012;61:674-82.
- Fukushima M, Hattori Y, Tsukada H, et al. Adiponectin gene therapy of streptozotocin-induced diabetic mice using hydrodynamic injection. *J Gene Med* 2007;9:976-85.
- Yu X, Park BH, Wang MY, et al. Making insulin-deficient type 1 diabetic rodents thrive without insulin. *Proc Natl Acad Sci U S A* 2008;105:14070-5.
- Wang MY, Chen L, Clark GO, et al. Leptin therapy in insulin-deficient type I diabetes. *Proc Natl Acad Sci U S A* 2010;107:4813-9.

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