CRISPR-Engineered Human Brown-Like Adipocytes Prevent Diet-Induced Obesity and Ameliorate Metabolic Syndrome in Mice

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Abstract

Brown and brown-like beige/brite adipocytes dissipate energy, and have been proposed as therapeutic targets to combat metabolic disorders. However, therapeutic effects of cell-based therapy in humans remain unclear. Here, we created human brown-like (HUMBLE) cells that acquired key features of human brown fat by engineering human white preadipocytes using the CRISPR/Cas9-SAM-gRNA to activate endogenous uncoupling protein 1 expression. Obese mice that received HUMBLE cell transplants showed a sustained improvement in glucose tolerance and insulin sensitivity, as well as increased energy expenditure. Mechanistically, increased arginine/nitric oxide (NO) metabolism in HUMBLE adipocytes promoted the production of NO, which was carried by S-nitrosothiols and nitrite in red blood cells to activate endogenous brown fat and improve glucose homeostasis in recipient animals. Taken together, these data demonstrate the utility of using CRISPR/Cas9 technology to engineer human white adipocytes to display brown-like phenotypes, and open up an exciting cell-based therapeutic opportunity to combat obesity and diabetes.