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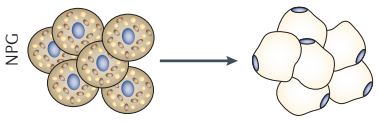
ADIPOSE TISSUE

Direct beige-to-white conversion

New research published in *Cell Metabolism* has uncovered the mechanism underlying the maintenance of beige adipocytes. The findings could lead to new approaches for the treatment of obesity.

"While previous studies have suggested that beige fat disappears once external stimuli such as cold are removed, the underlying mechanism by which beige adipocytes disappear has, until now, remained completely unknown," explains lead investigator Shingo Kajimura of the University of California, San Francisco. "We set out to understand the mechanisms of beige adipocyte maintenance, with a view to developing new approaches for maintaining beige fat for longer."

The researchers treated *Ucp1*$^{Cre/+}$*;Rosa26-GFP* reporter mice with the β3-adrenergic receptor agonist CL316,243 for 7 days and monitored morphological and molecular changes in UCP1-positive beige adipocytes *in vivo*. Whereas treatment resulted in a substantial increase in the number of GFP-positive beige adipocytes (containing multilocular lipids and co-expressing UCP1) in inguinal white adipose tissue (WAT), GFP-positive adipocytes had almost complete loss of multilocular lipids and UCP1 expression 15–20 days after withdrawal of CL316,243. Similar results were observed after mice were acclimated from cold (6 °C) to ambient temperature.



To determine whether the beige adipocytes directly reverted to white adipocytes or whether they de-differentiated via an intermediate state, the team developed a single-cell monitoring system to track morphological changes in individual beige adipocytes *ex vivo* following withdrawal of CL316,243. GFP-positive beige adipocytes reverted to white adipocytes as early as 3 days after CL316,243 withdrawal, with 80% of cells reverting by day 10; no evidence of intermediate precursor cells were found. RNA sequencing analysis confirmed that reversal of beige adipocytes to white adipocytes correlated with attainment of a WAT-enriched gene expression profile. The findings provide the first rigorous morphological and molecular evidence for direct beige-to-white conversion of adipocytes *in vivo*.

Kajimura and his team went on to show that the adipocyte transition was associated with a progressive decline in the expression of genes related to mitochondrial components and function (indicative of loss of mitochondria), increased autophagy and activation of lysosome biogenesis. Importantly, inhibition of autophagy by UCP^{+}-adipocyte-specific genetic deletion of *Atg5* or *Atg12* in mice prevented the loss of beige adipocytes after withdrawal of thermogenic stimuli (CL316,243 or cold), maintained thermogenic potential and protected against high-fat-diet-induced obesity and insulin resistance. "Our findings provide the first evidence that mitophagy in beige fat significantly influences whole-body energy homeostasis and glucose homeostasis," explains Kajimura. "We believe our study will facilitate a new and complementary approach to improve whole-body energy homeostasis and glucose homeostasis, particularly in individuals with obesity."

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ORIGINAL ARTICLE Altshuler-Keylin, S. *et al.* Beige adipocyte maintenance is regulated by autophagy-induced mitochondrial clearance. *Cell Metab.* http://dx.doi.org/10.1016/j.cmet.2016.08.002 (2016)

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