METABOLISM

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A cold, brite start

“the whitening of former brite adipocytes ... involves the conversion to a functionally different cell type

Brown adipose tissue, which maintains body temperature in newborn humans through non-shivering thermogenesis, is replaced by white adipose tissue for energy storage during the first few years of life. Adult humans can induce brown-like adipocytes in white adipose tissue — known as brown-in-white (brite) adipocytes — as a functional response to prolonged cold. Wolfrum and colleagues use a lineage-tracing approach *in vivo* to show that this ‘briter’ response occurs through direct transdifferentiation of white to brown adipocytes.

Similarly to humans, C57BL/6 mice can induce brite adipocytes, which are located in the inguinal region. After 1 week of cold stimulation (8°C), expression of the brown adipocyte marker *Ucp1* (uncoupling protein 1) was increased in the inguinal fat, and *Ucp1* expression levels were reduced to baseline approximately 5 weeks after the mice were returned to a normal temperature (23°C). Increased expression of *Ucp1* correlated with an increase in the number of fat cells with a multilocular phenotype (containing many small lipid droplets), which is associated with brown fat. The inguinal adipose tissue reverted to the unilocular morphology (one large lipid droplet) of white fat after 5 weeks at 23°C (known as ‘whitening’). So, cold stimulation leads to reversible briter of inguinal adipose tissue.

Whitening could result from the apoptosis of brite adipocytes, dedifferentiation of brite adipocytes or conversion of brite adipocytes to white adipocytes. To trace the origin and fate of brite adipocytes, the authors generated two transgenic mouse strains for transient or permanent labelling of *Ucp1*-expressing cells. In *Ucp1*-GFP mice, brite (and brown) adipocytes reversibly express GFP under the control of the *Ucp1* promoter. In *Ucp1*-CreER × ROSA-tdRFP mice, brite (and brown) adipocytes that express *Ucp1* during tamoxifen treatment are permanently labelled with red fluorescent protein (RFP).

The percentage of RFP⁺ cells in inguinal fat (that is, brite adipocytes) in cold-stimulated *Ucp1*-CreER × ROSA-tdRFP mice fed a tamoxifen diet was unchanged when the mice were returned to 23°C on a tamoxifen-free diet, which rules out apoptosis of brite adipocytes during warm adaptation. Furthermore, the heat-induced decrease in expression of brown adipocyte markers was much greater for inguinal RFP⁺ brite cells than for RFP⁺ classic brown adipocytes from interscapular fat, which shows that whitened adipocytes are not destimulated brown adipocytes. The expression of transcripts associated with white adipocytes (such as those encoding leptin and resistin) was increased in former brite adipocytes but not in classic brown adipocytes during whitening. Together, the results indicate that the whitening of former brite adipocytes involves the conversion to a functionally different cell type with the characteristics of white adipocytes.

Ucp1-tracer mice — generated by crossing the two transgenic mouse strains to label present and past *Ucp1* expression — were used to show the bidirectional nature of this conversion. When the tracer mice were subjected to a ‘cold-warm-cold’ adaptation schedule, with tamoxifen-dependent induction of RFP expression during the first but not the second cold exposure, most of the RFP⁺ cells in inguinal fat that were labelled as a result of briter during the first cold adaptation became GFP⁺ and had a brown adipocyte phenotype during the second cold stimulation. So, a subset of inguinal adipocytes can cycle between white and brite phenotypes in adult mice as a physiological adaptation to temperature change. The authors suggest that this ability could be manipulated in obese humans to induce adipocyte briter and hence increased energy expenditure.

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