Nature Reviews Molecular Cell Biology | Published online 14 Sep 2016; doi:10.1038/nrm.2016.125

Vicky Summersby/NPG

METABOLISM

Mitophagy turns beige adipocytes white

> “inhibiting mitophagy to maintain beige adipocytes may have therapeutic potential”

Beige adipocytes are thermogenic fat cells that emerge from white adipose tissue (WAT) following exposure to cold stimuli or β-adrenergic receptor (β-AR) agonists. However, after withdrawal of the promoting signal, beige adipocytes revert to a white-adipocyte phenotype by unclear mechanisms. Altshuler-Keylin *et al.* now reveal that beige-to-white adipocyte transition requires mitophagy (mitochondria-specific autophagy), the inhibition of which leads to the maintenance of beige adipocytes.

Beige adipocytes express high levels of uncoupling protein 1 (UCP1), a transcription factor that switches on their thermogenic programme. The authors generated mice expressing GFP–UCP1 and observed that treatment with a β3-AR agonist induced an increase in the numbers of GFP–UCP1-positive beige adipocytes in inguinal WAT. However, 15–20 days after agonist withdrawal, these adipocytes expressed low levels of UCP1 and displayed characteristics that are typical of white adipocytes. These phenotypic changes were coupled with an increase and decrease in the expression of white and beige adipocyte genes, respectively. Thus, on withdrawal of the β3-AR agonist, beige adipocytes take on the characteristic of white adipocytes; this does not seem to depend on an intermediate cell precursor.

The authors observed that the expression of genes, the products of which are implicated in mitochondrial function and biogenesis, was unchanged on exposure to the β3-AR agonist, but it decreased upon agonist withdrawal and the concomitant beige-to-white adipocyte transition, suggesting that this transition is coupled to a decline in mitochondria number and function. Furthermore, in mice subjected to the β3-AR agonist and withdrawal, genes encoding key autophagy and lysosomal proteins were upregulated, as was autophagosome formation. This indicates that, upon transition to a WAT-like phenotype, beige adipocytes activate autophagy, and that mitophagy could eliminate mitochondria in these cells. Indeed, in inguinal WAT, deletion of autophagy-related protein 12 (ATG12) or ATG5, or the chemical inhibition of autophagy, increased UCP1 and mitochondrial gene expression following β3-AR treatment and its subsequent withdrawal (or following cold exposure and rewarming). Thus, mitophagy seems to be required for the beige-to-white transition of adipocytes.

Looking for the mechanism that regulates mitophagy in this situation, the authors found that the expression of microphthalmia-associated transcription factor (MITF), which promotes the expression of proteins involved in autophagosome formation and lysosome biogenesis, was increased on initiation of the beige-to-white transition. Protein kinase A (PKA) is known to negatively regulate autophagy and to promote the development of beige adipocytes in response to β-AR stimulation. Further experiments revealed that the β3-AR agonist activated the cAMP–PKA pathway to repress MITF; this coincided with a decrease in the expression of genes that encode components of the autophagy machinery.

Finally, the authors asked whether blocking mitophagy to inhibit the beige-to-white adipocyte transition influenced thermogenesis, and whether it could decrease the risk of obesity and insulin resistance — protective roles that are associated with the presence of beige adipocytes. Indeed, ATG12-knockout mice gained less weight than control mice, following chronic treatment with a β3-AR agonist and withdrawal, when fed on a high-fat diet. These mice also showed improved systemic glucose homeostasis.

In short, mitophagy eliminates mitochondria during the beige-to-white adipocyte transition, thereby limiting the thermogenic capability of these cells; inhibiting mitophagy to maintain beige adipocytes may have therapeutic potential.

Katharine H. Wrighton

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)

FURTHER READING Inagaki, T., Sakai, J. & Kajimura, S. Transcriptional and epigenetic control of brown and beige adipose cell fate and function. *Nat. Rev. Mol. Cell Biol.* **17**, 480–495 (2016)