METABOLIC DISORDERS

Browning fat

White adipose tissue (WAT) stores energy, whereas brown adipose tissue (BAT) expends energy to provide heat and is capable of defending against hypothermia and obesity. Therapeutic strategies aimed at exploiting this thermogenic process are therefore receiving considerable attention for the treatment of obesity and related metabolic disorders. Now, writing in *Cell*, Ye and colleagues identify transient receptor potential cation channel vanilloid 4 (TRPV4) as a novel therapeutic target in metabolic disease; its inhibition in mice promotes an energy-burning BAT-like phenotype and reduces inflammation in WAT, protecting mice from diet-induced obesity and insulin resistance.

BAT thermogenesis is dependent on the activation of uncoupling protein 1 (UCP1), which uncouples oxidative phosphorylation in mitochondria to dissipate the electrochemical gradient as heat. Although BAT stores are minimal in adults, it has recently emerged that UCP1-positive BAT-like cells — termed beige or 'brite' fat cells — can develop in white fat depots, a process often described as 'browning'. Given that PPARγ co-activator 1α (PGC1α) is a key transcriptional co-regulator of UCP1, the authors set out to identify compounds capable of increasing PGC1α expression and inducing browning of WAT.


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First, they carried out a quantitative PCR-based screen of 3,000 compounds and identified the non-selective TRPV antagonist AMG-9810 as a positive regulator of PGC1α expression in white adipocytes. Knockdown of individual TRPV channel isoforms using short hairpin RNA (shRNA) revealed that the effect of AMG-9810 on PGC1α was mediated via TRPV4. Moreover, TRPV4 knockdown increased the expression of PGC1α, UCP1 and genes involved in mitochondrial oxidative phosphorylation — a 'browning' gene programme. Interestingly, the expression of pro-inflammatory genes was decreased — WAT inflammation is associated with insulin resistance.

In accordance with these *in vitro* findings, genetic deletion of TRPV4 in mice (*Trpv4*$^{-/-}$ mice) upregulated the expression of UCP1 and PGC1α, and downregulated the expression of pro-inflammatory cytokines in subcutaneous fat (SubQ fat; a WAT depot), when compared to wild-type mice. In addition, the expression of genes known to be enriched in BAT was elevated in SubQ fat of *Trpv4*$^{-/-}$ mice. Consequently, *Trpv4*$^{-/-}$ mice were resistant to obesity and adipose tissue inflammation, and exhibited improved insulin sensitivity. The reduced weight gain of *Trpv4*$^{-/-}$ mice appeared to be due, at least in part, to an increased energy expenditure associated with an elevated thermogenic gene programme in WAT.

Finally, the authors assessed the effects of pharmacological inhibition of TRPV4 by treating diet-induced obese mice with the TRPV4-specific antagonist GSK205 twice daily for 7 days. The agent significantly increased the expression of thermogenic genes and reduced the expression of pro-inflammatory chemokines in WAT, improving glucose tolerance compared to control mice. Importantly, the compound was well tolerated.

In summary, these findings identify TRPV4 as a common regulator in WAT thermogenic and inflammatory pathways, and suggest that TRPV4 antagonists could be beneficial in the treatment of metabolic disorders. However, as the authors note, although TRPV4 is highly expressed in WAT, it is also found in many other tissues and has been implicated in a variety of biological processes, which may limit the therapeutic window of such agents.

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ORIGINAL RESEARCH PAPER Ye, L. *et al.* TRPV4 is a regulator of adipose oxidative metabolism, inflammation, and energy homeostasis. *Cell* **151**, 96–110 (2012)
FURTHER READING Tseng, Y.-H., Cypess, A. M. & Kahn, C. R. Cellular bioenergetics as a target for obesity therapy. *Nature Rev. Drug Discov.* **9**, 465–482 (2010)