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ADIPOSE TISSUE

Noncanonical beige fat thermogenesis

Uncoupling protein 1 (UCP1) has long been considered the sole mediator of beige thermogenesis and its associated metabolic effects. A new study challenges this dogma by reporting a noncanonical, UCP1-independent thermogenic mechanism in beige fat that controls whole-body energy homeostasis.

Mice with transgenic expression of *Prdm16* (*Prdm16*Tg; which increases beige fat mass) were crossed with *Ucp1*$^{-/-}$ mice. "This model allowed us to determine the extent to which beige fat function depends on UCP1," explains lead investigator Shingo Kajimura.

Following an initial demonstration that UCP1 is dispensable for beige fat thermogenesis, RNA-seq of inguinal white adipose tissue (iWAT) was conducted. Their investigation revealed elevated expression of genes encoding proteins involved in calcium (Ca^{2+}) cycling, sarco/endoplasmic reticulum Ca^{2+}-ATPase 2b (SERCA2b; encoded by *Atp2a2*) and ryanodine receptor 2 (RyR2), in *Prdm16*Tg × *Ucp1*$^{-/-}$ mice compared with controls. Pharmacological SERCA2b inhibition or *Atp2a2* deletion in *Ucp1*$^{-/-}$ adipocytes markedly abrogated noradrenaline-induced cellular respiration, and adipose-specific *Atp2a2* deletion in mice completely blunted noradrenaline-induced beige thermogenesis compared with controls, suggesting that SERCA2b is required for beige thermogenesis.

> "the SERCA2b–RyR2 pathway controls beige fat thermogenesis"

Next, the extent to which Ca^{2+} influx determines UCP1-independent thermogenesis was investigated. Noradrenaline increased intracellular Ca^{2+} levels and cellular respiration in *Ucp1*$^{-/-}$ beige adipocytes, which was blocked by intracellular (but not extracellular) Ca^{2+} depletion. Moreover, pharmacological stabilization or overexpression of RyR2 enhanced Ca^{2+} cycling and stimulated thermogenesis in *Ucp1*$^{-/-}$ beige adipocytes.

Following a high-fat diet, *Prdm16*Tg × *Ucp1*$^{-/-}$ mice gained less bodyweight and had improved glucose tolerance and insulin sensitivity, compared with *Ucp1*$^{-/-}$ mice. Moreover, glycolysis and tricarboxylic acid metabolism was enhanced in iWAT and the SERCA2b–RyR2 pathway was shown to control glucose utilization in *Ucp1*$^{-/-}$ beige adipocytes.

The findings show that the SERCA2b–RyR2 pathway controls beige fat thermogenesis and improves systemic glucose homeostasis independently of UCP1. "This is paradigm-shifting to the field and it was very surprising to us," concludes Kajimura. "We plan to determine the quantitative contribution of canonical thermogenesis by UCP1 and noncanonical thermogenesis by SERCA2b to the regulation of whole-body energy homeostasis."

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ORIGINAL ARTICLE Ikeda, K. *et al.* UCP1-independent signaling involving SERCA2b-mediated calcium cycling regulates beige fat thermogenesis and systemic glucose homeostasis. *Nat. Med.* http://dx.doi.org/10.1038/nm.4429 (2017)