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ADIPOSE TISSUE

Bile acid–TGR5 axis promotes beiging

> TGR5 is required for beiging under environmental cues

Although activation of the bile acid-responsive G protein-coupled receptor TGR5 is known to increase energy expenditure and reduce fat mass by increasing basal metabolic rate, it is unknown whether this phenotype is in part mediated by subcutaneous white adipose tissue (scWAT) beiging. A new study now identifies the bile acid–TGR5 axis as a novel pathway that elicits beige remodelling in scWAT and modulates mitochondrial function in mice.

Initial experiments demonstrated that cold exposure promoted scWAT beiging in $Tgr5^{+/+}$ mice, but not in $Tgr5^{-/-}$ mice, and that $Tgr5^{+/+}$ mice fed a high-fat diet supplemented with a bile acid mimetic (INT-777) exhibited increased beige remodelling in scWAT, suggesting that TGR5 is required for beiging under environmental cues. "As TGR5 is ubiquitously expressed, we decided to repeat the same set of experiments in a transgenic mouse model with adipose tissue-specific TGR5 deletion ($Tgr5^{Adipoq-/-}$)," explains lead investigator Kristina Schoonjans. Compared with $Tgr5^{Adipoq+/+}$ littermates, $Tgr5^{Adipoq-/-}$ mice showed impaired cold-induced thermoregulation and scWAT beiging, confirming the indispensibility of TGR5.

To determine whether the sympathetic nervous system was involved in TGR5-dependent beiging, $Tgr5^{+/+}$ or $Tgr5^{-/-}$ mice were housed at thermoneutrality. Compared with vehicle, daily administration of INT-777 increased mitochondrial content and induced expression of beige adipocyte markers such as uncoupling protein 1 (UCP1) exclusively in $Tgr5^{+/+}$ mice, illustrating that TGR5 can promote beiging independently of environmental cues.

A novel mechanism underlying TGR5-dependent beiging was also uncovered. In adipocytes isolated and differentiated from $Tgr5^{+/+}$ mice, INT-777-dependent activation of TGR5 increased mitochondrial biogenesis, improved mitochondrial function and promoted mitochondrial β-oxidation by increasing lipolysis and substrate availability. In addition to prototypical PKA signalling, TGR5 signalling was mechanistically shown to modulate the mitochondrial network by promoting mitochondrial fission via the extracellular signal-regulated kinase (ERK)–dynamin-1-like protein (DRP1) pathway.

Taken together, the findings identify TGR5 as a druggable therapeutic target that primes the metabolic, transcriptional and mitochondrial reprogramming necessary for beige remodelling. "We anticipate that our study will open new perspectives in the field of obesity and obesity-related metabolic disorders," concludes Schoonjans.

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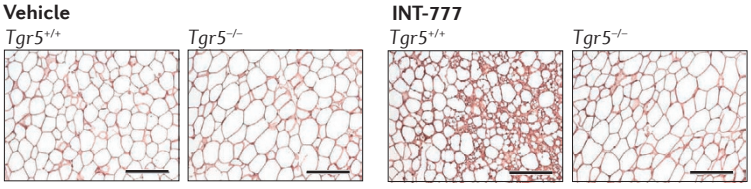

UCP1 immunostaining in scWAT from $Tgr5^{+/+}$ and $Tgr5^{-/-}$ mice at thermoneutrality, treated with INT-777 or vehicle. Scale bars, 50 μm. Permission obtained from Velazquez-Villegas, L. A. *et al. Nat. Commun.* **9**, 245 (2018), CC BY 4.0.

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