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ADIPOSE TISSUE

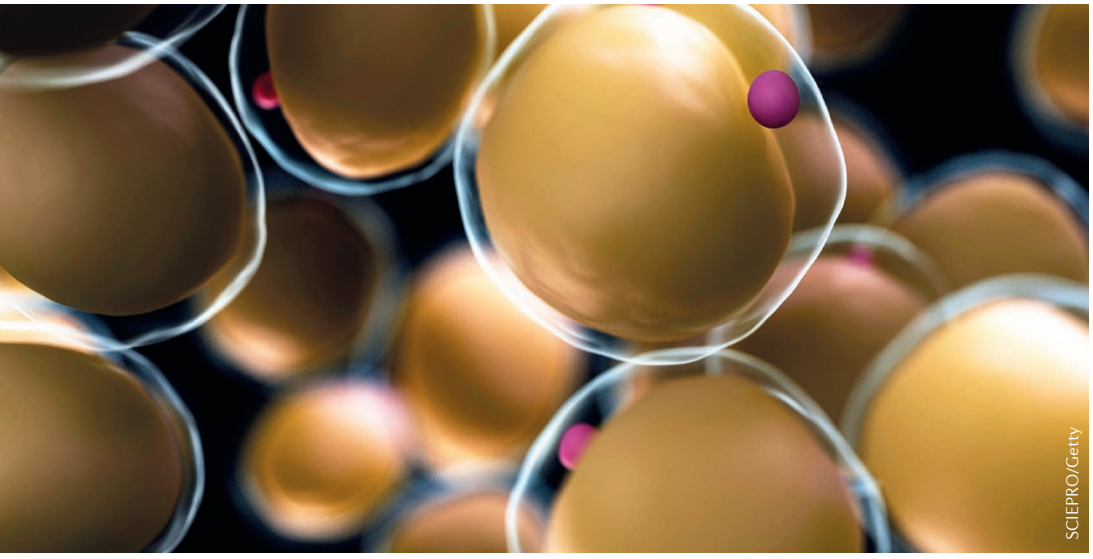
A new generation of PPARγ agonists?

> … roscovitine is a potent activator of brown-like adipocytes…

The peroxisome proliferator-activated receptor-γ (PPARγ) agonist rosiglitazone is an antidiabetic agent that can induce 'browning' of white adipose tissue (WAT), but serious adverse effects have limited its use. However, new research, published in *Cell Metabolism*, shows that roscovitine, a cyclin dependent kinase inhibitor that also activates PPARγ, browns WAT but has a better metabolic profile than rosiglitazone.

In mice, browning can be induced by cold exposure, which can be mimicked with a β-adrenergic receptor agonist, or by activating PPARγ. The two types of brown adipocytes that result from these methods are known as beige and brite adipocytes, respectively. Roscovitine prevents the inhibitory phosphorylation of Ser273 in PPARγ, an amino acid close to two lysines that lead to the browning of WAT when they are deacetylated. Steve Farmer, at Boston University, Massachusetts, USA, and his team reasoned that altering the post-translational modification of Ser273 might have the same effect as deacetylation and induce brite adipocytes.

The team first showed that treatment of white adipocytes with roscovitine activates expression of *Ucp1*, which is a hallmark of brown adipocyte activation. Treating mice with roscovitine daily for 6 weeks induced the browning of WAT to a similar extent as rosiglitazone and a β-adrenergic receptor agonist. Importantly, this treatment led to reduced fat mass, improved glucose tolerance, increased energy expenditure and protection from diet-induced obesity compared with control mice.



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"We demonstrated that roscovitine is a potent activator of brown-like adipocytes in white depots of mice," clarifies Farmer "Unlike the widely prescribed diabetic drug rosiglitazone, which also works through PPARγ, roscovitine enhances energy expenditure and prevents deposition of fat in the liver."

The team also developed a fluoresence-activated cell sorting (FACS)-based method to isolate adipocytes on the basis of their expression of *Ucp1*. This method enabled them to identify specific important transcriptional differences between white, classic brown, beige and brite adipocytes. "We identified novel sets of markers for each population that will be useful for future classification of human brown fat," says Farmer. The findings highlight that brown adipocytes can be recruited from different precursors, which might have important implications for future anti-obesity therapies.

"Knowing the origin of the cells and the mechanisms controlling their recruitment will lead to other strategies for drug discovery," concludes Farmer. "We are investigating other potential activators of browning of white fat; we will then apply our novel FACS isolation method along with molecular profiling to determine their identity."

Tim Geach

ORIGINAL ARTICLE Wang, H. *et al.* Browning of white adipose tissue with roscovitine induces a distinct population of UCP1$^+$ adipocytes. *Cell Metab.* **24**, 835–847 (2016)
FURTHER READING Gross, B. *et al.* PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. *Nat. Rev. Endocrinol.* **13**, 36–49 (2016)