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METABOLISM

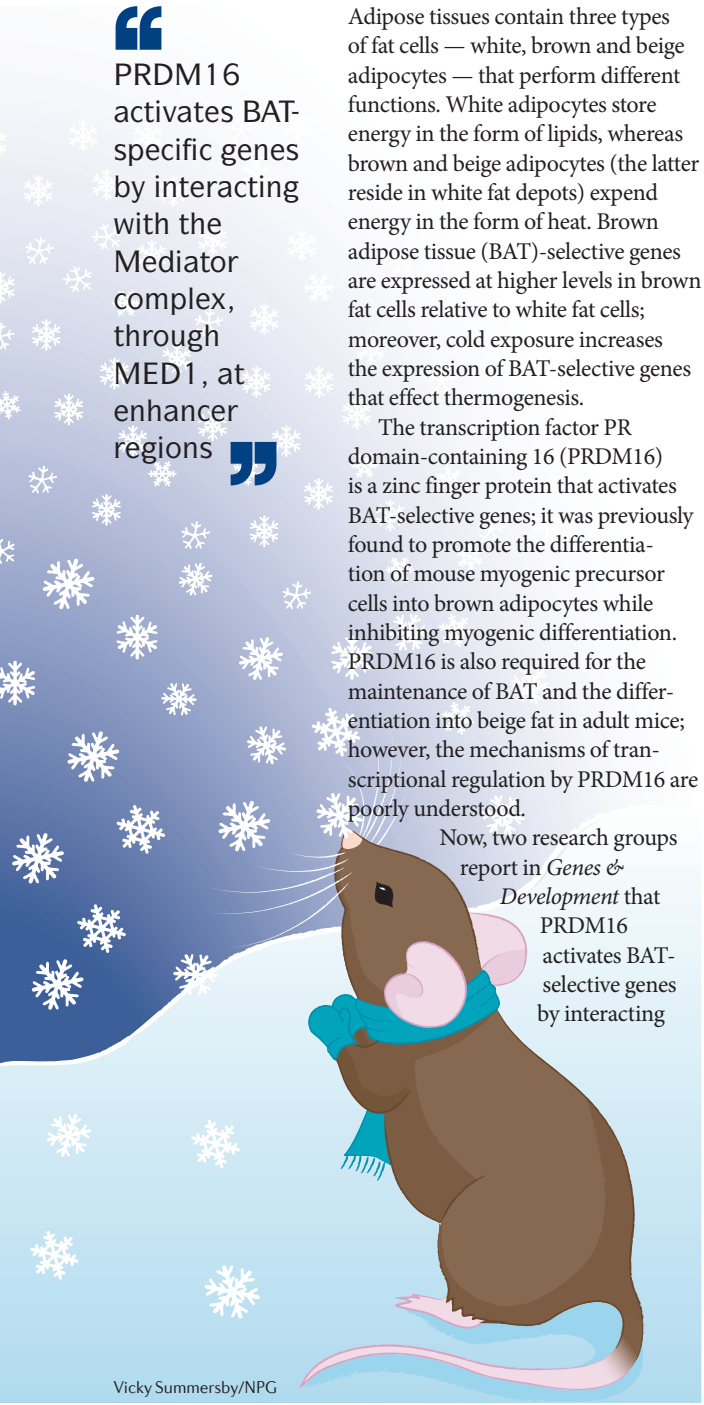
Transcriptionally activating brown fat

> PRDM16 activates BAT-specific genes by interacting with the Mediator complex, through MED1, at enhancer regions

Adipose tissues contain three types of fat cells — white, brown and beige adipocytes — that perform different functions. White adipocytes store energy in the form of lipids, whereas brown and beige adipocytes (the latter reside in white fat depots) expend energy in the form of heat. Brown adipose tissue (BAT)-selective genes are expressed at higher levels in brown fat cells relative to white fat cells; moreover, cold exposure increases the expression of BAT-selective genes that effect thermogenesis.

The transcription factor PR domain-containing 16 (PRDM16) is a zinc finger protein that activates BAT-selective genes; it was previously found to promote the differentiation of mouse myogenic precursor cells into brown adipocytes while inhibiting myogenic differentiation. PRDM16 is also required for the maintenance of BAT and the differentiation into beige fat in adult mice; however, the mechanisms of transcriptional regulation by PRDM16 are poorly understood.

Now, two research groups report in *Genes & Development* that PRDM16 activates BAT-selective genes by interacting directly with the Mediator complex subunit MED1, and that this involves changes in chromatin architecture.



Vicky Summersby/NPG

Using ChIP-seq (chromatin-immunoprecipitation followed by sequencing) in mouse BAT, Harms *et al.* found that PRDM16 binding is highly enriched at a broad set of BAT-selective genes and that the levels of chromatin-bound PRDM16 correlate with levels of RNA polymerase II binding at these genes, suggesting that it activates their transcription. Furthermore, they found that PRDM16 recruits MED1 to these sites. Indeed, DNA binding of MED1 at BAT-selective genes was decreased dramatically in *Prdm16*-knockout brown adipocytes; this led to lower expression of its target genes.

As the Mediator complex regulates transcription in part through bridging distal enhancers and promoters, Harms *et al.* also investigated whether PRDM16 promotes long-range chromatin interactions. Chromatin conformation capture (3C) assays revealed that PRDM16 is required for the interaction between promoters of BAT-selective genes and distal PRDM16 and MED1 binding sites in brown adipocytes. Moreover, they identified >500 super-enhancers in BAT, many of which were bound by MED1 in a PRDM16-dependent manner and are likely to regulate the expression of PRDM16-activated genes.

Iida *et al.* used cell-free systems reconstituted with purified transcription factors to investigate the mechanism by which PRDM16 facilitates activation of the *Ucp1* (uncoupling protein 1) gene, which is the major thermogenic gene in BAT. They show that PRDM16 is recruited to the mouse *Ucp1* enhancer (located 2.5 kb upstream of the transcription start site) through direct interactions with the MED1 subunit of the enhancer-bound Mediator complex, and that this directly enhances thyroid hormone receptor-driven transcription of *Ucp1*. Their biochemical studies further indicate that PRDM16 and MED1 interact directly through the amino-terminal zinc finger domain of PRDM16 and the conserved N terminus of MED1. Their results were substantiated by cell-based studies, which indicated that optimal induction of *Ucp1* in mouse embryonic fibroblasts in response to forskolin (which mimics the β-adrenergic response in beige and brown adipocytes) requires both PRDM16 and MED1.

Together, these studies indicate that PRDM16 activates BAT-specific genes by interacting with the Mediator complex, through MED1, at enhancer regions, and by controlling chromatin architecture.

White adipose tissue expands in obesity, whereas cold-stimulated brown and beige fat activity correlates with reduced adiposity and weight loss. Thus, understanding the molecular mechanisms that regulate brown and beige fat specification and activity may reveal new therapeutic avenues to treat diabetes and related disorders.

Kim Baumann

ORIGINAL RESEARCH PAPERS Harms, M. J. *et al.* PRDM16 binds MED1 and controls chromatin architecture to determine a brown fat transcriptional program. *Genes Dev.* **29**, 298–307 (2015) | Iida, S. *et al.* PRDM16 enhances nuclear receptor-dependent transcription of the brown fat-specific *Ucp1* gene through interactions with Mediator subunit MED1. *Genes Dev.* **29**, 308–321 (2015)

FURTHER READING Allen, B. L. & Taatjes, D. J. The Mediator complex: a central integrator of transcription. *Nature Rev. Mol. Cell Biol.* http://dx.doi.org/10.1038/nrm3951 (2015) | Heinz, S. *et al.* The selection and function of cell type-specific enhancers. *Nature Rev. Mol. Cell Biol.* http://dx.doi.org/10.1038/nrm3949 (2015)