OBESITY

PPARγ2 piles on the pounds

Weakness for snacks. Unused gym membership. Taking the lift, not the stairs. All could be blamed for a few extra inches on our waistlines. Now, as two papers in *Genes & Development* reveal, a key culprit — albeit at the molecular level — is the γ2 isoform of the peroxisome proliferator-activated receptor (PPARγ2).

PPARγ, a nuclear hormone receptor that regulates gene expression, has received much attention in recent years, in part owing to its emerging link with fat-cell development, or adipogenesis. PPARγ and another transcription factor, C/EBPα, are both known to be crucial in adipogenesis, but their exact role has been hard to establish, as they positively regulate each other's expression. Although previous studies have shown that addition of PPARγ can induce adipogenesis in the absence of C/EBPα, it was not known whether the converse was true. As described in the first of the two papers, researchers in Bruce Spiegelman's lab have clarified this issue by generating a cell line lacking PPARγ. They used this cell line to show that C/EBPα has no ability to promote adipogenesis in the absence of PPARγ, thus indicating that PPARγ is the key regulator in a single adipogenic pathway, rather than PPARγ and C/EBPα each being able to act independently to promote adipogenesis.

However, PPARγ has two main isoforms, PPARγ1 and PPARγ2. Although their expression patterns differ — PPARγ1 is expressed in various cells including fat cells, whereas PPARγ2 expression is fat-cell specific — the two isoforms are expressed at comparable levels in fat cells, so their relative importance to adipogenesis was not clear. This question was addressed by Heidi Camp and colleagues in the second paper. Using transcriptional repressors engineered to bind specifically to the *PPARγ* gene via novel zinc fingers, they created cells lacking PPARγ, which, as in previous work, were unable to develop into fat cells. Then, by selectively restoring the expression of either PPARγ1 or PPARγ2 using retroviruses, they showed that only PPARγ2 could reactivate adipogenesis.

These advances in our understanding of adipogenesis further the hope that rational manipulation of this process could be a therapeutic strategy for combating obesity. However, in animal models, direct and powerful inhibition of adipogenesis leads to lipodystrophy, indicating that a more measured approach — for example, pharmacological reduction of PPARγ in a controlled manner — is likely to be a necessity.

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References and links

ORIGINAL RESEARCH PAPERS Rosen, E. D. *et al*. C/EBPα induces adipogenesis through PPARγ: a unified pathway. *Genes Dev.* **16**, 22–26 (2002) | Ren, D. *et al*. PPARγ knockdown by engineered transcription factors: exogenous PPARγ2 but not PPARγ1 reactivates adipogenesis.*Genes Dev.* **16**, 27–32 (2002)

FURTHER READING Rosen, E. D. *et al*. PPARγ is required for the differentiation of adipose tissue *in vivo* and *in vitro*. *Mol. Cell* **4**, 611–617 (1999)