Nature Reviews Molecular Cell Biology | AOP, published online 12 December 2012; doi:10.1038/nrm3497

MACMILLAN MEXICO/Mark Ruffle (The Organisation)

DEVELOPMENT

G9A covers all bases

Like all cell differentiation processes, adipogenesis is tightly regulated through epigenetic modifications, which control whether a given gene is expressed or repressed. Previous work had revealed epigenetic mechanisms that promote the expression of peroxisome proliferator activated receptor-γ (PPARγ), the master regulator of adipogenesis. Here, Ge and colleagues reveal that the histone methyltransferase G9A (also known as EHMT2) blocks PPARγ expression through the addition of an epigenetic mark and also promotes the expression of WNT10A, a negative regulator of adipogenesis.

G9A is primarily responsible for histone H3 dimethylation at Lys9 (H3K9me2), which is thought to promote gene silencing. The authors observed that H3K9me2 levels were high specifically on the *Pparg* locus but were low on genes encoding other regulators of adipogenesis. Moreover, H3K9me2 levels on *Pparg* markedly decreased during adipocyte differentiation. Consistent with this, G9A was enriched throughout the promoter and gene body regions of both PPARγ isoforms (*Pparg1* and *Pparg2*). Moreover, G9A deletion significantly increased *Pparg2* expression by promoting the binding of the transcription factor C/EBPβ (CCAAT/enhancer-binding protein-β) to the *Pparg2* promoter, ultimately enhancing adipogenesis. Together, these findings suggest that G9A inhibits adipogenesis by adding a repressive H3K9me2 mark on the *Pparg* promoter.

Interestingly, the authors observed that depletion of G9A also decreased the expression of WNT10A and attenuated canonical WNT signalling, which is thought to inhibit adipogenesis. This effect could be rescued through the addition of G9A or of G9A lacking enzymatic activity. Similarly, administration of the G9A inhibitor BIX01294 — which specifically interferes with the methyltransferase activity and decreases H3K9me2 levels — increased *Pparg* expression but had no effect on WNT10A expression. Thus, G9A seems to promote WNT10A expression independently of its enzymatic activity.

Finally, the authors confirmed their findings *ex vivo*. They observed that white preadipocytes isolated from G9A-knockout mice showed enhanced adipogenesis and increased expression of *Pparg* and of other adipogenic markers.

So, G9A seems to repress adipogenesis by targeting two fronts: inhibiting *Pparg* expression and promoting *Wnt10a* expression. Further work is now needed to determine how G9A itself is targeted to the *Pparg* locus.

Rachel David

ORIGINAL RESEARCH PAPER Wang, L. *et al.* Histone H3K9 methyltransferase G9a represses *PPARγ* expression and adipogenesis. *EMBO J.* 23 Nov 2012 (doi:10.1038/emboj.2012.306)
FURTHER READING Cristancho, A. G. & Lazar, M. A. Forming functional fat: a growing understanding of adipocyte differentiation. *Nature Rev. Mol. Cell Biol.* **12**, 722–734 (2011)