 GENE EXPRESSION

Methyltransferases 'talk' at histone H3

NPG

G9a mediates the recruitment of PRC2 to a subset of target genes to promote silencing

Lys9 of histone 3 (H3K9) is methylated by G9a and G9a-like protein (GLP), and H3K27 is methylated by Polycomb repressive complex 2 (PRC2); these modifications silence gene expression. Although 'crosstalk' between these methylation marks had been suggested, the underlying mechanisms were unclear. Now Mozzetta *et al.* show that G9a and GLP interact with PRC2, and that G9a mediates the recruitment of PRC2 to a subset of target genes to promote silencing.

PRC2 comprises of SUZ12 (suppressor of zeste 12 homologue), EED (embryonic ectoderm development), RbAp46 (Rb-associated protein 46; also known as RBBP7), RbAp48 and EZH2 (enhancer of zeste homologue 2; which is the Lys27 methyltransferase in PRC2). The authors observed that SUZ12, EED and EZH2 interact with G9a and GLP in HeLa cells and mouse embryonic stem (ES) cells. Analysis of direct binding *in vitro* indicated that G9a and GLP are likely to interact with PRC2 through EZH2.

As these Lys9 and Lys27 methyltransferases interact, the authors sought to determine whether they regulate common genes. They generated the mRNA expression profile of *G9a*^{-/-}, *Glp*^{-/-} and *G9a*^{-/-} *Glp*^{-/-} ES cells and considered the results in the context of published data for *Ezh2*^{-/-} and *Eed*^{-/-} ES cells. In the absence of G9a and/or GLP, as well as in the absence of EZH2 or EED, 487 genes were upregulated; these genes encode proteins with roles in differentiation and development. Furthermore, analysis using chromatin immunoprecipitation followed by sequencing in ES cells revealed that 958 genes were bound by both G9a and PRC2, 207 of which were upregulated in the absence of G9a and/or GLP. Thus, G9a, GLP and PRC2 seem to bind to, and repress, a subset of common genes.

The authors also found that the recruitment of EZH2 to many of its targets was impaired in the absence of G9a and/or GLP and that this was accompanied by a decrease in H3K27 trimethylation (H3K27me3). Moreover, wild-type G9a (but not a catalytically inactive mutant) facilitated the recruitment of EZH2 to an artificial promoter and also re-established EZH2 occupancy and H3K27me3 at PRC2 target genes in *G9a*^{-/-} cells. Hence, catalytically active G9a recruits PRC2 to specific targets to enable H3K27me3.

This study reveals that the crosstalk between H3K9 and H3K27 methylation is mediated, at least in part, by the G9a-mediated recruitment of PRC2 to a subset of genes. Interestingly, the authors found that this mechanism is likely to be prevalent in the maintenance of neuronal gene silencing.

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