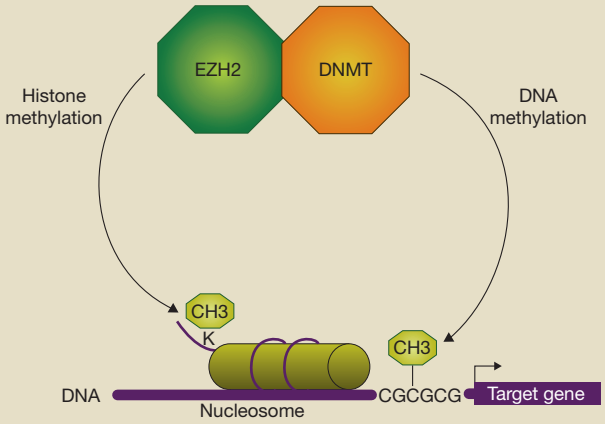
Pathways to silencing unite

Although cells contain the full complement of genes, only a subset of these are actively transcribed at different stages of development. These differential patterns of gene expression are established, in part, by epigenetic mechanisms (such as histone and DNA methylation) that transmit these patterns to daughter cells during cell division. Two silencing pathways have been shown to be involved in heritable gene repression: modification of histones by the Polycomb group (PcG) proteins and the addition of methyl groups to cytosine nucleotides in the regulatory regions of target genes by DNA methyltransferases (DNMTs). DNMT1 methylates newly replicated DNA that is passed to the progeny of dividing cells, but how PcG induced silencing is inherited is not known. An interaction between DNMTs and PcG proteins may explain how these epigenetic modifications are inherited. A recent study by Viré *et al.* (*Nature* **439,** 871; 2006) now shows that these pathways are mechanistically linked.

The group began by investigating whether specific components of these two pathways interact. They found that DNMTs interacted *in vitro* and *in vivo* with the PcG protein EZH2, demonstrating a physical link between components of two separate silencing mechanisms.

A gene known to be regulated by EZH2, *MYT1*, was examined to determine the functional relationship between these two pathways. *MYT1* is a zinc finger transcription factor whose expression was previously shown to be repressed by EZH2-mediated histone methylation. Intriguingly, inhibition of DNA methylation resulted in increased levels of *MYT1* transcripts, indicating that this EZH2-target gene is also regulated by DNA methylation. Depletion of EZH2, DNMT1, DNMT3a or DNMT3b by RNA interference resulted in increased levels of *MYT1* RNA, elegantly demonstrating that silencing of the expression of this gene requires both pathways.

But do DNMTs directly bind to *MYT1*? Chromatin immunoprecipitation showed that EZH2, DNMT1, DNMT3A and DNMT3B all bound to the promoter region of *MYT1*. Vivé *et al.* then examined whether EZH2 was required for DNMT to bind to the *MYT1* promoter.



The Polycomb group protein EZH2 adds methyl groups to the tails of histone proteins, primarily to Lys 27 of histone H3. Viré *et al.* show that EZH2 physically recruits DNMTs to certain target genes. The recruited DNMTs then catalyse CpG methylation in the region of the methylated histones.

When EZH2 protein levels were depleted, less DNMTs bound to the *MYT1* promoter; similar results were observed for other EZH2 target genes. Overexpression of EZH2 resulted in increased DNA methylation at the promoters of the genes examined, whereas depletion resulted in less DNA methylation. Together, this clearly demonstrates that the PcG protein EZH2 is necessary for DNA methylation through direct association with DNMTs.

This study is the first demonstration of a physical interaction between two proteins from two key epigenetic silencing pathways. Moreover, the coupling of histone methylation and DNA methylation, through EZH2-dependent DNA methylation, may preserve the PcG protein epigenetic mark and provide a potential mechanism for transmitting it to daughter cells.

Although there are examples of where repression induced by EZH2 histone methylation is not coupled to DNA methylation, the link between the two pathways opens new avenues to explore how specific gene expression patterns are maintained from generation to generation.

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