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GENE EXPRESSION

An ncRNA relocation package

> ncRNAs … promote the relocalization of target genes between nuclear subcompartments and thereby regulate gene expression

The localization of a gene within the nucleus is important for controlling its expression, and it must be coordinated with subnuclear architecture. Here, Yang *et al.* have defined a new mechanism by which the dynamic methylation of a chromatin-binding protein, Polycomb 2 (PC2), can switch its association with distinct non-coding RNAs (ncRNAs) to promote the relocalization of target genes between nuclear subcompartments and thereby regulate gene expression during growth signalling.

Yang *et al.* initially set out to test the significance of a known interaction between the histone methyltransferase SUV39H1 and PC2. Using mass spectrometry and mutational analysis, they found that PC2 is dimethylated at Lys191 and that this modification is added specifically by SUV39H1 and removed by Lys-specific demethylase 4C (KDM4C). They next asked whether PC2 methylation might be relevant for cell cycle and growth control. Chromatin immunoprecipitation followed by sequencing (ChIP–seq) analysis showed that dimethylated PC2 was enriched at E2F1 target gene promoters and that serum stimulation, which triggers the activation of E2F1 target genes, increased the levels of demethylated PC2 and the recruitment of KDM4C here. Moreover, depletion of KDM4C prevented the expression of E2F1 target genes in response to serum, highlighting a requirement for PC2 demethylation. Indeed, overexpression of a mutant form of PC2 that mimics the demethylated form increased cell proliferation in HeLa cells and primary fibroblasts, whereas PC2 depletion impaired cell proliferation in response to serum.

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The nucleus is organized into regions that are potentially repressive or activating for gene expression, so the authors asked whether PC2 might contribute to the relocation of genes upon the induction of growth signalling. Consistent with this, closer inspection revealed that, whereas methylated PC2 associates with markers for repressive Pc group (PcG) bodies, unmethylated PC2 localizes to the more 'activating' environment of interchromatin granules (ICGs). This was paralleled by a similar relocalization of PC2-associated E2F1 target genes to ICGs upon serum stimulation, and both required the demethylation of PC2.

Because ncRNAs have been implicated in promoting the formation of nuclear bodies, the authors examined whether they may interact with PC2 and regulate its localization. Indeed, methylated PC2 was found to interact with *TUG1* ncRNA (which they show localizes to PcG bodies), whereas unmethylated PC2 interacted with *NEAT2*, an ncRNA that associates with ICGs. Association with these ncRNAs altered the binding specificity of PC2 for distinct histone modifications: PC2 binding to *TUG1* promoted association with repressive histone methylation marks and PC2 binding to *NEAT2* switched this preference to activating acetylated histone marks. Furthermore, these ncRNAs were relocated to anchor growth control genes within particular nuclear bodies. Depletion of *TUG1* resulted in mislocalization of growth control gene promoters outside PcG bodies even in the absence of serum, and conversely, depletion of *NEAT2* prevented the relocalization of a target gene to ICGs after serum stimulation and disrupted serum-induced gene expression.

How might unmethylated PC2 promote gene activation in response to serum? Yang *et al.* found that PC2 directly promotes the sumoylation of E2F1 at Lys266, probably both *in vitro* and *in vivo*, in response to serum and that this is required for normal serum-induced gene expression. Moreover, this function of PC2 appears to be sensitive to the presence of particular ncRNAs.

This study provides numerous insights into how gene expression is orchestrated in concert with subnuclear architectural structures. It shows that specific ncRNAs, through interaction with a modified chromatin-binding protein, have the ability to nucleate molecular platforms in different regions of the nucleus. Furthermore, it seems that ncRNA binding with such factors can modulate their preference for different histone modifications and thereby mediate dynamic changes in gene expression.

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ORIGINAL RESEARCH PAPER Yang, L. *et al.* ncRNA- and Pc2 methylation-dependent gene relocation between nuclear structures mediates gene activation programs. *Cell* **147**, 773–788 (2011)