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GENE SILENCING

Shhh! RNAi-dependent and -independent pathways at work

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The packaging of DNA into heterochromatin domains is crucial for gene silencing and cellular processes, and occurs at centromeres, telomeres and the mating-type locus in *Schizosaccharomyces pombe*. At centromeres, but not at telomeres or the mating-type locus, the formation of heterochromatin domains is dependent on RNA interference (RNAi). Bühler and colleagues now show that an RNAi-independent pathway that involves polyadenylation — and possibly exosome-mediated degradation — is also central to the silencing of centromeric heterochromatin.

Previous studies have established that transgenes inserted at the edges of centromeric heterochromatin domains also become silenced, but through an unknown mechanism. To test whether the RNAi machinery is recruited to these transgenes for silencing, Bühler and colleagues examined whether small interfering RNAs (siRNAs) are generated by the insertion of the marker gene *ura4*$^+$ to the edges of the centromeric region. Indeed, low abundances of siRNA were generated from inserted *ura4*$^+$, which indicates that silencing of inserted transgenes could occur through the recruitment and activation of the RNAi machinery. However, for some insertions, these siRNAs were predominantly of the sense orientation and, therefore, mostly unable to target Argonaute-1 (which binds siRNAs) and the RNAi machinery to the *ura4*$^+$ mRNA.

Suspecting that another mechanism might also be involved in the silencing of transgenes in heterochromatin regions, Bühler and colleagues next examined whether a non-canonical form of polyadenylation, which targets RNA for degradation in *Saccharomyces cerevisiae*, might also have a role in transgene silencing. Indeed, deletion of the poly(A) polymerase Cid14, or mutation of its catalytic core, resulted in the complete loss of *ura4*$^+$ silencing at centromeric heterochromatin domains. However, deletion of Cid14 did not affect the overall structural features of these heterochromatin regions, which suggests that Cid14 is more likely to have a downstream role in the silencing of genes from the heterochromatin domain than a direct role in the formation of heterochromatin.

The authors found that Cid14 resides in a complex that also includes Mtr4, a nuclear cofactor of the exosome. This complex resembles the TRAMP complex of *S. cerevisiae*, which promotes RNA degradation through the exosome. Taken together, it is likely that Cid14 polyadenylates RNA transcripts from the centromeric heterochromatin domains and targets them for degradation through the exosome, independently of the RNAi machinery.

These findings suggest that the centromeric heterochromatin regions, as well as the inserted transgenes, are silenced through both RNAi-dependent and -independent machineries. The interplay between these pathways now remains to be elucidated.

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ORIGINAL RESEARCH PAPER Bühler, M. *et al.* RNAi-dependent and -independent RNA turnover mechanisms contribute to heterochromatic gene silencing. *Cell* **129**, 707–721 (2007)
FURTHER READING Bayne, E. H. *et al.* DegrAAAded into silence. *Cell* **129**, 651–653 (2007)

STOCKBYTE

> …centromeric heterochromatin regions…are silenced through both RNAi-dependent and -independent machineries.