CHROMATIN

RNA eviction by HP1

The formation of heterochromatin requires the conserved heterochromatin protein 1 (HP1), which can associate directly and dynamically with Lys9 trimethylated tails of histone H3 (H3K9me3). Bühler and colleagues find that, in fission yeast, this ensures local capture of heterochromatic mRNAs and their targeting for mRNA decay.

Although heterochromatin has traditionally been regarded as a region that is transcriptionally repressed, recent findings indicate that heterochromatin silencing can occur post-transcriptionally and that RNA processing is also important for this. For example, the non-canonical poly(A) polymerase Cid14 mediates heterochromatic mRNA processing. In this study, the authors first showed that, although loss of Cid14 results in higher levels of heterochromatic mRNAs, these are not translated into protein. They thus hypothesized that these mRNAs might be targeted into ribonucleoprotein particles that are refractory to translation.

In addition to having affinity for H3K9me3 tails, mammalian HP1 has been shown to bind RNA, suggesting that the HP1 homologue in fission

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yeast, HP1^{Swi6}, might have a role in diverting heterochromatic mRNAs away from the translation machinery. Indeed, in the absence of HP1^{Swi6}, heterochromatic mRNAs could be translated. Moreover, HP1^{Swi6} was found to directly bind RNA *in vitro*, as previously observed in mammalian cells, and the hinge region of HP1^{Swi6} is sufficient for this.

So what is the role of HP1^{Swi6} binding to mRNA? To answer this question, the authors constructed an HP1 protein that contained 25 mutations in the Lys and Arg residues of its hinge region (HP1^{Swi6}-KR25A) and thus could no longer bind RNA, although its overall protein folding was intact, as was its ability to bind an immobilized peptide corresponding to H3K9me3. Expression of HP1^{Swi6}-KR25A (fused with a nuclear localization sequence to ensure its localization to the nucleus) at the endogenous *swi6* locus revealed that, although RNA binding via the hinge region is not required for HP1^{Swi6} association with heterochromatin or for the overall structural integrity of heterochromatin, the affinity of HP1^{Swi6} for RNA is crucial for the repression of heterochromatic genes.

Next, the authors used fluorescence recovery after photobleaching (FRAP) experiments to confirm that the association of HP1^{Swi6} with chromatin is dynamic *in vivo*. By using a nuclear magnetic

resonance (NMR)-based assay they observed that binding of HP1^{Swi6} to RNA and methylated H3K9 occurs through multiple domains. Interestingly, further biophysical analysis revealed that RNA and H3K9me3 binding are competitive processes; the authors therefore concluded that HP1^{Swi6} association with heterochromatic RNAs actually triggers its release from heterochromatin owing to weakened H3K9me3 binding of HP1^{Swi6} when bound by RNA. Finally, chromatin profiling analysis also placed Cid14 nearby to heterochromatin, suggesting that a rapid 'hand-off' of mRNA from HP1^{Swi6} to Cid14 for processing might be possible.

Thus, although transcription can occur at heterochromatic loci, the methylation of Lys9 on histone H3 provides a local checkpoint through recruitment of HP1^{Swi6}. The association of HP1^{Swi6} with locally transcribed heterochromatic mRNAs results in its dissociation from chromatin and targeting of mRNAs for decay.

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