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CHROMATIN

Lys36 sets limits for histone exchange

RNA polymerase II elongation is linked to histone exchange and an enrichment of histone H3 Lys36 methylation (H3K36me) across the open reading frames (ORFs) of transcribed genes in *Saccharomyces cerevisiae*. In two new studies, Workman and colleagues show that the H3K36me mark actually represses histone exchange to allow accurate transcription, and that this also requires cooperation from chromatin-remodelling factors.

The Lys methyltransferase Set2 methylates Lys36 on histone H3 in coding regions in *S. cerevisiae*. To assess the role of the H3K36me mark, Venkatesh *et al.* measured whether changes in histone exchange occur in Set2 deletion mutants (*set2*Δ) using chromatin immunoprecipitation followed by microarray analysis (ChIP–chip). They found that histone exchange was increased across ORFs in *set2*Δ mutants compared with wild-type strains but was not affected at intergenic regions where Set2-mediated H3K36me marks are absent. Furthermore, loss of Set2 activity resulted in increased histone acetylation, which disrupted chromatin organization and resulted in an accumulation of cryptic transcripts owing to inappropriate transcription initiation. Thus, the H3K36me mark seemed to repress histone exchange and thereby prevent the incorporation of acetylated histones.

> “H3K36me … represses histone exchange to allow accurate transcription”

What other mechanisms underlie the control of this exchange? Smolle *et al.* focused on the role of chromatin-remodelling factors from the ISWI (imitation switch) and CHD (chromodomain helicase DNA-binding) families, which are relatively conserved from yeast to humans. They found that Isw1 and Chd1 associate with the H3K36me nucleosomes *in vitro*, that the Isw1b complex directly recognized this mark and that Isw1b and Chd1 were important for preventing intragenic transcription. By using ChIP–chip analysis, the authors then tested whether the chromatin remodellers were also involved in transcription-coupled exchange of histones. Indeed, although histone exchange in wild-type yeast was high at the promoters and low across coding regions, *isw1*Δ and *chd1*Δ mutants had increased levels of histone exchange from the middle of the ORF to the 3′ ends of genes, areas that are associated with Lys36 methylation. Increased levels of histone acetylation on Lys56 were also observed across this region in these mutants. So, they conclude that these chromatin remodellers are recruited to sites of H3K36me in ORFs to repress histone exchange and cryptic transcription.

Taken together, these studies suggest that Set2-mediated methylation of

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Lys36 provides a determining mark in ORFs that normally represses histone exchange promoted by histone chaperones and thereby limits incorporation of acetylated histones in coding regions. Furthermore, chromatin remodelling factors such as Isw1 and Chd1 are recruited to the H3K36me mark and cooperate with the Set2 pathway to antagonize histone exchange. Together, this ensures that chromatin integrity is maintained during transcription elongation and that transcriptional initiation is spatially controlled.

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ORIGINAL RESEARCH PAPERS
Venkatesh, S. *et al.* Set2 methylation of histone H3 lysine 36 suppresses histone exchange on transcribed genes. *Nature* 22 Aug 2012 (doi:10.1038/nature11326) | Smolle, M. *et al.* Chromatin remodelers Isw1 and Chd1 maintain chromatin structure during transcription by preventing histone exchange. *Nature Struct. Mol. Biol.* 26 Aug 2012 (doi:10.1038/nsmb.2312)