CHROMATIN

A matter of inheritance

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The nucleosome composition of chromatin not only alters chromosome structure but also affects gene activity. How the chromatin structure of active genes is inherited following cell division is unknown. Tremethick and colleagues now show that the localization of the histone variant H2A.Z at active promoters is dynamic during the cell cycle and not maintained following DNA replication.

In mammalian cells, stable nucleosomes are absent from the transcriptional start site (TSS) of genes being transcribed by RNA polymerase II, and this may facilitate binding of the transcriptional machinery.

IMAGE SOURCE

This nucleosome-depleted region (NDR) is flanked on both sides by nucleosomes that contain the histone variant H2A.Z. To examine how this pattern might be inherited, the authors performed histone H2A.Z chromatin immunoprecipitation, followed by high-throughput sequencing experiments, and examined global gene expression at different stages of the cell cycle in mouse trophoblast stem cells. Interestingly, there was a specific loss of histone H2A.Z at active promoters in S phase and M phase compared with promoters that are active during G1 phase. Furthermore, this loss coincided with the formation of heterotypic H2A.Z–H2A nucleosomes at sites flanking the TSS rather than homotypic H2A.Z–H2A.Z nucleosomes.

Next, the authors asked whether depletion of H2A.Z in S and M phases might arise because there is not enough histone H2A.Z to restore normal patterns after DNA replication. Unexpectedly, the total amount of chromatin-bound H2A.Z was unchanged, suggesting this is not the case. Indeed, the authors found that during the transition from G1 to M phase, histone H2A.Z was redistributed to the centromere and subtelomeric regions in the form of homotypic H2A.Z–H2A.Z nucleosomes. This site-specific increase in H2A.Z supports previous findings suggesting that this histone variant has a structural role in organizing the centromere, and may indicate that H2A.Z also functions at subtelomeric regions.

The TSS has previously been shown to be marked by an unstable nucleosome that contains both H2A.Z and H3.3 histone variants. Tremethick and colleagues found that this site was also occupied by a heterotypic H2A.Z–H2A nucleosome in genes that are active in G1, and this may explain the instability of the nucleosome located at the TSS. This heterotypic nucleosome was lost during S phase and M phase, which suggests that it is not required for genes that are active in these cell cycle phases but is only necessary to facilitate transcription in G1. In addition, the authors report that the size of the NDR region increases during S phase. Interestingly, the size of the NDR did not correlate with transcription levels. This led the authors to propose that the cell cycle machinery has many effects on the structure and composition of active chromatin.

This work shows that remodelling of active chromatin occurs during the cell cycle, with histone H2A.Z being relocated to different regions of the genome at different phases. This challenges the view that active marks established in G1 phase may remain throughout M phase to facilitate the re-establishment of gene transcription after cell division. Furthermore, the formation of dynamic heterotypic H2A.Z–H2A nucleosomes during S and M phases may provide the cell with an opportunity to alter the composition of active chromatin by either restoring homotypic H2A.Z–H2A.Z in G1 or allowing H2A.Z to be lost.

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ORIGINAL RESEARCH PAPER Nekrasov, M. *et al.* Histone H2A.Z inheritance during the cell cycle and its impact on promoter organization and dynamics. *Nature Struct. Mol. Biol.* 21 Oct 2012 (doi:10.1038/nsmb.2424)