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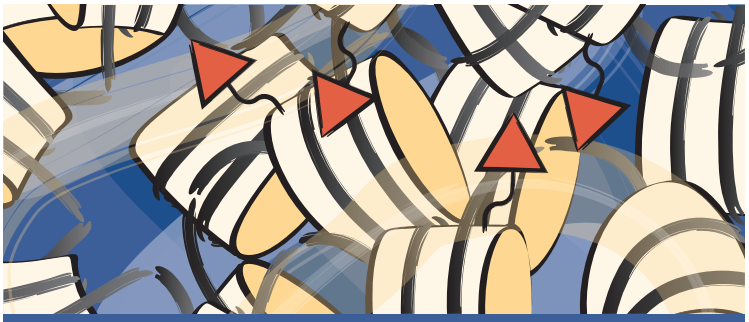

Vicky Summersby/NPG

GENE EXPRESSION

Buffering newly replicated DNA

> “cells with H3K56 mutation had significantly increased expression of replicated genes”

Replication of the genome during the S phase of the cell cycle increases the DNA dose of newly replicated genes, but in eukaryotic cells, the mRNA expression levels of these genes do not increase accordingly. This has led to the hypothesis that mRNA transcription of newly replicated DNA is transiently suppressed during S phase to buffer changes in DNA dose. A new study in *Science* describes a role for histone 3 (H3) acetylation in the maintenance of this expression homeostasis during DNA replication.

In cell cycle-synchronized budding yeast, the mRNA expression levels of genes that replicate early during S phase were increased by only ~20% compared with genes that replicate late during S phase, despite a 70% increased DNA content of early- versus late-replicating genes. This is in line with previous studies showing that the DNA dose has a limited effect on mRNA synthesis during S phase.

Although the increased binding of RNA polymerase II (Pol II) to replicated genes was less than would be expected on the basis of DNA dose alone, Pol II binding to DNA did correlate to some extent with the DNA content of cells. Thus, reduced binding of Pol II to replicated DNA is not the only factor that accounts for buffering of gene expression.

To identify chromatin regulators that could suppress the transcription of replicated DNA, the authors looked at a published data set describing changes in gene expression associated with individual deletion of 165 chromatin-associated factors. Based on the assumption that deleting a factor that is normally involved in expression homeostasis would increase the expression of early-replicated genes relative to late-replicated genes, they identified from this data set a role for the H3 acetyltransferase Rtt109 and its cofactor Asf1, as well as the putative transcription factor Tos4. They went on to show that in *rtt109*-, *asf1*- or *tos4*-deleted synchronized budding yeast cells, the buffering of mRNA synthesis during DNA replication was lost. The effect of double deletion of *rtt109* and *asf1*, or *rtt109* and *tos4*, was similar to that of single deletion, which suggests that the three genes function in the same pathway.

Rtt109 and Asf1 are involved in the acetylation of two H3 residues, K56 and K9. Whereas mutating K9 did not affect the buffering of gene expression, cells with H3K56 mutation had significantly increased expression of replicated genes. Similarly, cells overexpressing the H3K56-specific histone deacetylases Hst3 and Hst4 lost the relative suppression of early-replicated gene transcription, which confirms a requirement for H3K56 acetylation to buffer the expression of newly replicated DNA. This complements the previously known role of H3K56 acetylation in nucleosome assembly and genome stability.

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