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DNA REPAIR

Histones have got to go

> DNA damage induces the degradation of core histones

Homologous recombination comprises a series of reactions that allow high-fidelity template-based repair of complex DNA lesions such as double-strand breaks (DSBs). Previous studies demonstrated that induction of DNA damage is associated with increased physical dynamicity of chromatin, in particular enhanced mobility of chromosome regions (both damaged and undamaged), and this was predicted to facilitate homologous recombination. Hauer *et al.* now show that this increase in chromatin dynamicity is governed by the proteasome-mediated degradation of core histones.

Chromatin properties are greatly modulated by the nucleosome occupancy levels. Using a radiometric mass spectrometry approach in budding yeast, the authors noted that protein levels of core histones (but not of histone variants) decrease considerably following the induction of DSBs by the chemical compound zeocin or by ionizing radiation. Genome-wide nucleosome mapping revealed that this was associated with widespread reduction of nucleosome occupancy in chromatin, which occurred rapidly — within 30 minutes — after the induction of DSBs. Inhibition of the proteasome complex suppressed these effects, collectively indicating that DNA damage induces the degradation of core histones, leading to a genome-wide decrease in nucleosome occupancy.

High-speed, super-resolution imaging of yeast cells with fluorescently labelled chromatin domains revealed the volumetric expansion of these domains following zeocin treatment, showing that DNA damage promotes chromatin decompaction. Furthermore, zeocin enhanced the mobility of chromatin domains as well as increased the average distances between individual domains, demonstrating that DNA damage is associated with increased chromatin fibre flexibility and, confirming previous results, with increased chromosome mobility. Reducing core histone expression could induce chromatin decompaction and chromosome mobility even in the absence of DNA damage, suggesting that decreased histone levels are directly linked to increased chromatin dynamicity.

Previous studies linked the increase in chromatin dynamicity following DNA damage to the activation of the DNA damage checkpoint (DDC) and the chromatin remodeller complex INO80-C. In line with this, zeocin treatment did not induce chromatin decompaction and chromosome mobility in yeast strains lacking the main DDC kinases as well as in strains deficient for INO80-C subunits. In addition, histone levels were unchanged in these strains, providing evidence that histone degradation following DNA damage is mediated by chromatin remodellers, most likely acting downstream of DDC kinases.

INO80-C-deficient yeast strains showed reduced recombination rates, whereas recombination was promoted in mutants with decreased histone expression. In addition, reduction of histone expression increased the recovery of yeast cells from acute DNA damage and partially rescued the zeocin sensitivity of INO80-C-mutant strains. Finally, reduced histone levels were associated with an increased turnover of the recombination machinery.

In summary, this study reveals that DNA damage induces the degradation of core histones, resulting in a genome-wide reduction in nucleosome occupancy and, as a consequence, increased chromatin dynamicity, which appears to be important for sustaining robust homologous recombination and thus error-free DNA repair.

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ORIGINAL ARTICLE Hauer, M. H. *et al.* Histone degradation in response to DNA damage enhances chromatin dynamics and recombination rates. *Nat. Struct. Mol. Biol.* http://dx.doi.org/10.1038/nsmb.3347 (2017)

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