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DNA DAMAGE

Limiting 53BP1

Chromatin modifications regulate the ordered assembly of repair proteins at the site of DNA double-strand breaks (DSBs) to direct repair mechanisms. Tang *et al.* now show that acetylation at histone H4 has a central role in balancing the differential localization of the DNA damage response proteins BRCA1 and 53BP1 to damaged chromatin.

They showed that increased H4 acetylation through the inhibition of histone deacetylases (HDACs) led to decreased 53BP1 but increased BRCA1 occupancy at DSB chromatin, whereas knockdown of the acetyltransferase TIP60 had the opposite effect, limiting 53BP1 access to defined endogenous genomic sites. This suggests that the balance between acetylation and deacetylation regulates the localization of BRCA1 and 53BP1 to DSB chromatin and thus the repair mechanism.

So, how does increased H4 acetylation regulate 53BP1 localization at DSBs? 53BP1 binds dimethylated Lys20 of H4 (H4K20me2) via its Tudor domains at sites of DNA damage. The authors found that TIP60-dependent Lys16 acetylation of H4 (H4K16ac) decreased binding of 53BP1 to H4K20me2 sites. Structural analysis revealed that H4K16ac reduced the binding affinity of 53BP1 towards H4K20me2, potentially by disrupting a salt bridge formed between the negatively charged Glu1551 of the 53BP1 Tudor domain and the positively charged unmodified Lys16 residue of H4. Deletion of TIP60 impaired homology-directed repair, and this effect was rescued by knockdown of 53BP1.

Thus, TIP60-dependent acetylation exerts opposing control on the association of BRCA1 and 53BP1 to promote homologous recombination.

Andrea Du Toit

ORIGINAL RESEARCH PAPER Tang, J. *et al.* Acetylation limits 53BP1 association with damaged chromatin to promote homologous recombination. *Nature Struct. Mol. Biol.* 3 Feb 2013 (doi:10.1038/nsmb.2499)