DNA REPAIR

Making the cut

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URLs
PCNA:
http://ca.expasy.org/uniprot/P12004
USP1:
http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?db=protein&val=63053524

DNA-damage-repair pathways allow for the identification, excision and sometimes even the bypass of lesions to ensure DNA replication and cell survival. The regulation of these pathways is highly involved, and includes, among other mechanisms, post-translational modifications such as ubiquitylation. D'Andrea and colleagues, reporting in *Nature Cell Biology*, now demonstrate how auto-cleavage of a deubiquitylation enzyme is central in the regulation of translesion DNA synthesis (TLS), an important DNA-damage-repair pathway.

In specific cases of DNA damage, such as those that are induced by ultraviolet (UV) radiation, the best hope for cell survival lies in the bypass of the lesion, as attempts at repairing the lesion might result in prolonged cell-cycle arrest and eventual apoptosis. TLS, a pathway that involves specialized polymerases that can bypass lesions, is involved in some of these cases. TLS polymerases are recruited to DNA in times of damage by monoubiquitylated PCNA (proliferating cell nuclear antigen). These TLS polymerases are crucial in coping with lesions, but most are error prone and therefore not desirable under healthy replication conditions. So, in the absence of DNA damage, PCNA is deubiquitylated, through a previously unknown mechanism, to prevent the recruitment of error-prone TLS polymerases to DNA. But how is PCNA deubiquitylation regulated?

By carrying out protein-overexpression and small interfering RNA (siRNA)-mediated knockdown studies, D'Andrea and colleagues first demonstrated that PCNA is deubiquitylated by overexpressed USP1 (a deubiquitylation enzyme) and over-ubiquitylated in its absence. Next, they examined the effects of UV exposure on USP1 mutants. Western blots of wild-type USP1 revealed that the protein is cleaved immediately following a conserved C-terminal Gly–Gly motif. By contrast, when the catalytic domain is mutated, the degradation of mutant USP1 is inhibited. This indicates that USP1 is degraded through an auto-cleavage event.

In an *in vivo* siRNA knockdown of USP1, the authors demonstrated that UV irradiation of USP1-depleted cells resulted in an approximately two-fold increase in DNA-mutation frequency. The cumulative evidence supports a model in which UV radiation causes DNA damage and USP1 auto-cleavage. Subsequent to USP1 auto-cleavage, mono-ubiquitylated PCNA can no longer be deubiquitylated, and so recruits error-prone TLS polymerases that can bypass the UV-induced DNA lesions.

How UV exposure causes USP1 to auto-cleave, whether USP1 auto-cleavage has a role in DNA-damage sensing, and the possibility that auto-cleavage might be a recurring mechanism in the regulation of ubiquitylation and ubiquitin-like modifications all need further investigation. But, when it comes to DNA-damage repair, it seems that for cells to make the cut, sometimes they have to make the auto-cut.

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ORIGINAL RESEARCH PAPER Huang, T. T. *et al.* Regulation of monoubiquitinated PCNA by DUB autocleavage. *Nature Cell Biol.* **8**, 341–347 (2006)
FURTHER READING Huang, T. T. & D'Andrea, A. D. Regulation of DNA repair by ubiquitlyation *Nature Rev. Mol. Cell Biol.* **7**, 323–334 (2006)