CELL CYCLE

Disposing of SETD8

SETD8 (also known as PRSET7) is a cell cycle-regulated enzyme that catalyses monomethylation of histone 4 at Lys20 (H4K20me1) to promote chromosome condensation and prevent DNA damage, among other functions. SETD8 expression decreases during S phase and peaks during mitosis, but what regulates this fluctuation was not clear. Now, three studies find that SETD8 is targeted for ubiquitin-mediated degradation by the $CRL4^{CDT2}$ ubiquitin ligase complex (made up of RBX1, cullin 4, DDB1 and CDT2) during S phase and following DNA damage.

$CRL4^{CDT2}$ regulates the cell cycle by degrading proteins that interfere with S phase progression. $CRL4^{CDT2}$ substrates contain a proliferating cell nuclear antigen (PCNA)-interacting motif, which, together with another two sequence elements, is known as the PCNA-interacting peptide (PIP) degron. SETD8 contains a PIP degron, so it could be a $CRL4^{CDT2}$ substrate. The three studies found that the SETD8 PIP degron was required for its interaction with PCNA, which has a role in promoting $CRL4^{CDT2}$-mediated degradation, as SETD8 with a mutation in its PIP degron fails to associate with PCNA. Furthermore, the mutant SETD8 is stable during S phase and following DNA damage caused by ultraviolet (UV) radiation, indicating that the interaction with PCNA is required for SETD8 proteasomal degradation.

The three groups then used small interfering RNAs to deplete the CDT2 subunit of $CRL4^{CDT2}$ to determine whether SETD8 is ubiquitylated by $CRL4^{CDT2}$, and observed inhibition of SETD8 degradation. *In vitro* ubiquitylation assays by all three groups confirmed that SETD8 ubiquitylation depends on $CRL4^{CDT2}$.

So why is SETD8 degraded? Abbas *et al.* and Centore *et al.* observed that cells expressing SETD8 PIP degron mutants showed defects in proliferation and progressed from S phase to mitosis more slowly than cells expressing wild-type SETD8. This delay in cell cycle progression was due to activation of the G2–M phase checkpoint. The subsequent cell cycle arrest was triggered by aberrant H4K20me1 levels, which may interfer with the dynamic changes in chromosome structure during the cell cycle and compromise genome integrity. Indeed, accumulation of H4K20me1 after a few hours of stable SETD8 resulted in chromatin compaction (Centore *et al.*), and repression of the histone gene promoters after a few cell cycles with stable SETD8 led to a marked loss of histones and global chromatin decompaction (Abbas *et al.*).

$CRL4^{CDT2}$-mediated SETD8 degradation also occurs following DNA damage by UV irradiation. Oda *et al.* found that monomethylation of H4K20 by SETD8 after DNA damage was required for the recruitment of p53-binding protein (p53BP) — which is involved in the DNA damage response — to these sites. Following p53BP recruitment, SETD8 was rapidly degraded, presumably because its continuous activity would inhibit cell cycle progression and lead to genome instability.

Together, these studies show that $CRL4^{CDT2}$-mediated ubiquitylation of SETD8 leads to its degradation during S phase and after DNA damage. This might occur to ensure appropriate changes in chromosome structure during the cell cycle or to preserve genome integrity after DNA damage.

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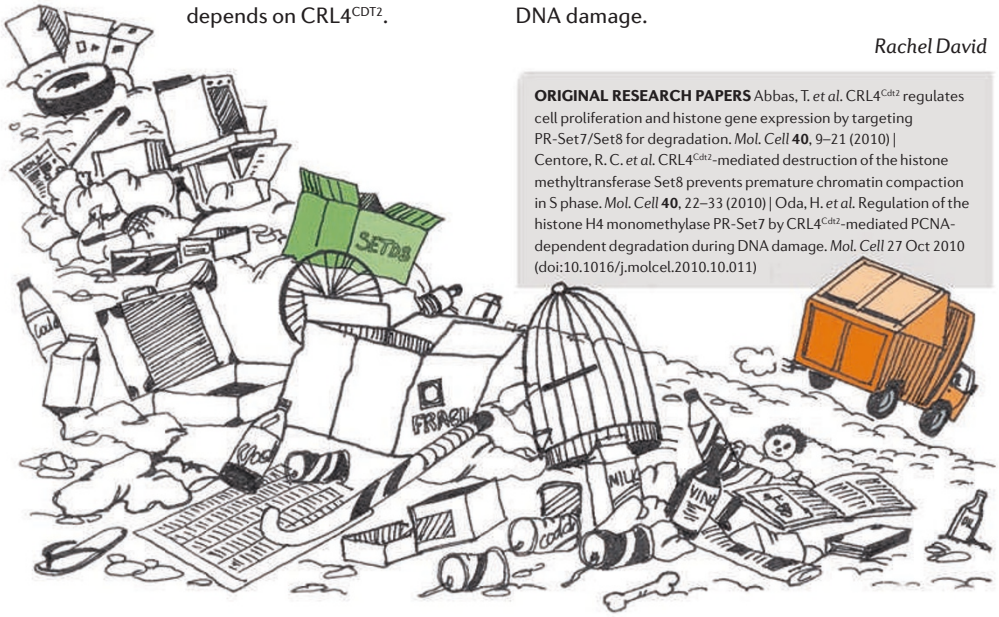

ORIGINAL RESEARCH PAPERS Abbas, T. *et al.* $CRL4^{Cdt2}$ regulates cell proliferation and histone gene expression by targeting PR-Set7/Set8 for degradation. *Mol. Cell* **40**, 9–21 (2010) | Centore, R. C. *et al.* $CRL4^{Cdt2}$-mediated destruction of the histone methyltransferase Set8 prevents premature chromatin compaction in S phase. *Mol. Cell* **40**, 22–33 (2010) | Oda, H. *et al.* Regulation of the histone H4 monomethylase PR-Set7 by $CRL4^{Cdt2}$-mediated PCNA-dependent degradation during DNA damage. *Mol. Cell* 27 Oct 2010 (doi:10.1016/j.molcel.2010.10.011)

ADDENDUM

Disposing of SETD8

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It has come to our attention that Tardat *et al.* reported similar findings in parallel to those discussed in this Research Highlight, showing that SETD8 is ubiquitylated by the CRL4 ubiquitin ligase complex, leading to its degradation during S phase. We apologize to the authors of this paper for the omission.

ORIGINAL RESEARCH PAPER Tardat, M. *et al.* The histone H4 Lys 20 methyltransferase PR-Set7 regulates replication origins in mammalian cells. *Nature Cell Biol.* **12**, 1086–1093 (2010)