The E2–UBL conjugate must now undock from E1, as E1 and E3 have overlapping binding sites on E2. The new structure provides insight into how E2–UBL might be released: freeing up of the T site allows the UFD to swing back to its A-site-only conformation. This clashes sterically with UBL–E2 and E2 is pushed out. The UFD neatly guards the free T site from UBL–E2 docking back on E1 and the UBL from being transferred in the reverse direction.

One part of the mechanism that remains unresolved is how UBLs move between the A and T sites, as the structure identifies a protein loop of E1 between the two sites that creates a restricted route of transfer. Future structural studies might reveal conformational changes that overcome this topological barrier.

James Pickett

ORIGINAL RESEARCH PAPER Huang, D. T. *et al.* Basis for a ubiquitin-like protein thioester switch toggling E1–E2 affinity. *Nature* **445**, 394–397 (2007)

catalysis. Instead, mutational analysis of Rtt109 showed that residue Asp89 is essential for HAT activity and that two additional Asp residues, although not essential, contribute to this activity.

Zhang and co-workers also showed that cells that lacked Rtt109 or contained a H3K56 mutant are sensitive to DNA-damaging agents and produce increased double-strand breaks predominantly during S phase. Furthermore, genetic interactions between Rtt109 and several proteins that function in DNA replication indicated that *rtt109Δ* cells are defective in certain aspects of DNA replication.

These findings establish Rtt109 as a member of a new class of HAT and provide a mechanism for how Rtt109 cooperates with Asf1 to promote H3 acetylation, maintain normal chromatin structure and promote genome stability in response to replicative stress.

Arianne Heinrichs

ORIGINAL RESEARCH PAPERS Driscoll, R. *et al.* Yeast Rtt109 promotes genome stability by acetylating histone H3 on lysine 56. *Science* **315**, 649–652 (2007) | Han, J. *et al.* Rtt109 acetylates histone H3 lysine 56 and functions in DNA replication. *Science* **315**, 653–655 (2007)

➡ CANCER

PTEN — a new guardian of the genome

10 years after its identification, the tumour suppressor phosphatase and tensin homologue (PTEN) still holds lots of surprises. Three studies, published in *Cell*, provide insights into how ubiquitylation regulates PTEN stability and its nuclear localization, as well as the role of nuclear PTEN in chromosomal integrity.

PTEN is a plasma-membrane lipid phosphatase that antagonizes the function of the phosphatidylinositol 3-kinase (PI3K)–AKT/protein kinase B (PKB) pathway. Various mutations in *PTEN* have been associated with primary tumours, and an inherited *PTEN* mutation causes Cowden syndrome — patients with this mutation have an increased risk of tumour development. Although this protein has been extensively studied, there are some unresolved questions. For example, some *PTEN* mutations occur in regions other than the phosphatase domain, which indicates that PTEN might have other functions in addition to the regulation of PI3K signalling. Intriguingly, this plasma-membrane phosphatase has also been found in cell nuclei, so what is the mechanism and function of this nuclear translocation?

Wang *et al.* showed that PTEN is ubiquitylated *in vitro* and *in vivo*, and purified its ubiquitin ligase as HECT-domain protein NEDD4-1. Although NEDD4-1 alone was not oncogenic, NEDD4-1 overexpression increased the efficiency of Ras-mediated transformation of *Trp53*-deficient mouse embryonic fibroblasts. Further analysis indicated that the aberrant upregulation of NEDD4-1 can post-translationally suppress PTEN activity in human and mouse cancer samples. The authors propose that NEDD4-1 is a potential proto-oncogene that negatively regulates PTEN through ubiquitylation, a paradigm that is analogous to that of MDM2 and p53.

Trotman *et al.* investigated a Lys to Glu mutation in *PTEN* (K289E) that was found in a family with Cowden syndrome. Using an intestinal polyp from a patient with this germline mutation, they showed that although PTEN retains catalytic activity, it fails to accumulate in the nuclei of dysplatic epithelial cells owing to an import defect. Residues Lys289 and Lys13 were identified as important monoubiquitylation sites that are essential for PTEN import. Small-interfering-RNA-mediated depletion of NEDD4-1 caused wild-type PTEN to redistribute in the cytoplasm, whereas the overexpression of NEDD4-1 increased the nuclear localization of PTEN. The authors also showed that polyubiquitylation leads to PTEN degradation in the cytoplasm. By contrast, nuclear monoubiquitylated PTEN is stable and antagonizes the AKT/PKB-mediated survival pathway.

So how does nuclear PTEN affect tumour suppression? Shen *et al.* found that the disruption of PTEN resulted in an increased number of chromosomal fragments with breakage at the centromeres and chromosomal translocations. PTEN is localized at the centromeres and is physically associated with CENP-C, an integral component of the kinetochore. Furthermore, *Pten*-null cells exhibited spontaneous DNA double-strand breaks and a decrease in mRNA and protein levels for the *Rad51* gene, which is involved in homologous recombination and DNA repair. Chromatin-immunoprecipitation assays revealed that PTEN acts on chromatin and regulates *Rad51* expression. Although the exact function of PTEN on the *Rad51* gene promoter remains to be clarified, this study shows a fundamental role for PTEN in the maintenance of chromosomal stability through a physical interaction with centromeres and the control of DNA repair. Therefore, PTEN, like p53, might function as a guardian of genomic stability.

Ekat Kritikou

ORIGINAL RESEARCH PAPERS Wang, X. *et al.* NEDD4-1 is a proto-oncogenic ubiquitin ligase for PTEN. *Cell* **128**, 129–139 (2007) | Trotman, L. C. *et al.* Ubiquitination regulates PTEN nuclear import and tumor suppression. *Cell* **128**, 141–156 (2007) | Shen, W. -H. *et al.* Essential roles for nuclear PTEN in maintaining chromosomal integrity. *Cell* **128**, 157–170 (2007)
FURTHER READING Baker S. J. PTEN enters the nuclear age. *Cell* **128**, 25–28 (2007)