p53

Solving a MYSTery

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The tumour suppressor p53 protects cells from malignant transformation by inducing either cell-cycle arrest or apoptosis following DNA damage. However, how cells choose between these two pathways is not well understood. Now, two studies have identified a new post-translational modification in the DNA-binding domain of p53 that has an important role in determining cell fate during the p53-mediated DNA-damage response.

Both the groups of Gu and McMahon identified a previously unknown acetylation site at lysine 120 (K120) in the DNA-binding domain of p53 by mass-spectrometric analysis of acetylated forms of p53. The acetylation site is conserved in all known homologues of p53 and is a rare p53 mutation site in human cancers, which implies that this residue is important for p53 function. In addition, K120 acetylation was significantly increased in U2OS osteosarcoma cells after DNA damage.

Interestingly, none of the histone acetyltransferases that are known to target p53 were found to acetylate K120. Instead, TIP60, a member of the MYST family of acetyltransferases, was shown to bind and acetylate p53 both *in vitro* and *in vivo*. Moreover, depleting U2OS cells of TIP60 by RNA interference (RNAi) significantly reduced the levels of K120-acetylated p53 following DNA damage, without affecting the DNA-damage-induced accumulation of p53.

p21 and *PUMA* are transcriptional targets of p53 that mediate cell-cycle arrest and apoptosis, respectively. DNA-damage-induced expression of both genes was significantly impaired in TIP60-depleted cells. However, although cells that expressed the tumour-derived mutant p53 K120R (which cannot be acetylated by TIP60) were defective for *PUMA* transcription and induction of apoptosis, their ability to induce p21 and cell-cycle arrest was equivalent to cells that expressed wild-type p53. TIP60-mediated acetylation of K120 is therefore thought to be required for the p53-mediated apoptotic response, but not for the p53-induced cell-cycle arrest.

McMahon and colleagues found that, in addition to TIP60, the related MYST histone acetyltransferase MOF was able to acetylate p53 at K120, and that mutating K120 to arginine (K120R) abrogated MOF-mediated acetylation of p53. RNAi-mediated depletion of either MOF or TIP60 in U2OS cells caused a reduction in the levels of K120-acetylated p53 after DNA-damage by 28% or 52%, respectively. And, the simultaneous knockdown of *MOF* and *TIP60* decreased the level of K120 acetylation to that observed in cells before DNA damage.

Depletion of either MOF or TIP60 partially blocked p53-mediated transcription of the pro-apoptotic genes *BAX* and *PUMA* in the breast-cancer cell line MCF7 following treatment with ultraviolet light, but did not affect the p53-mediated induction of p21. Furthermore, K120-acetylated p53 was found to accumulate at the promoters of *BAX* and *PUMA*, but not of *p21*, in MCF7 cells upon DNA damage, perhaps providing a mechanistic explanation for the defect in apoptosis, but not cell-cycle arrest, in the K120R tumour mutant.

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FURTHER READING Tyteca, S. *et al.* To die or not to die: a HAT trick. *Mol. Cell* **24**, 807–808 (2006)