TUMOUR SUPPRESSORS

# One faulty copy tips the balance

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TIP60 is an acetyl-transferase that co-regulates MYC and p53, and modulates the MYC-induced DNA-damage response (DDR). A new study shows that loss of a single copy of *Tip60* is associated with tumorigenesis, and that this is caused by impairment of the DDR and is independent of p53.

Mice that are homozygous *Tip60*-null are not viable, whereas heterozygotes have no observable phenotype. However, the authors showed that *Tip60* heterozygotes in the background of an overactive form of MYC, *Eμ-Myc*, had accelerated onset of MYC-induced B-cell lymphomas. Immunostaining of components of the DDR pathway showed that it was severely impaired in these heterozygotes. This observation was confirmed in a more controlled *in vitro* system in which RNA interference was used to downregulate *Tip60*, which also caused a downregulation of DDR. This impairment was specific to MYC-induced DDR, as mice heterozygous or wild type for *Tip60* did not differ in their response to ionizing radiation, which uses a different DDR pathway.

So, *Tip60* is haplo-insufficient in its tumour suppression through the DDR pathway, but what about its role in regulating MYC and p53? Transcriptional analysis of MYC and p53 targets showed no effect of *Tip60* heterozygosity, implying that the effects of TIP60 on DDR are independent of MYC and p53-induced transcription. However, this does not mean that TIP60 does not also have a tumour suppression role through p53 and MYC, only that such a role is not haplo-insufficient.

On the basis of these data in mice, the authors looked at TIP60 mRNA and protein levels in human tumours. In breast tumours, head and neck tumours, and various lymphomas, they found reduced TIP60 in around 40% of cases. Significantly, this proportion was much higher in high-grade breast tumours. Interestingly, immunostaining showed reduction in nuclear levels of TIP60 in tumour cells, but no reduction and even a possible increase in cytoplasmic TIP60, implying that delocalization as well as reduced expression might be important in tumorigenesis.

The results from mice had shown that the TIP60 DDR effect was independent of MYC and p53-regulated transcription. A similar phenomenon was observed in the human cells — loss of *TIP60* heterozygosity correlated with *TP53* mutations, showing that the two pathways act independently to promote tumorigenesis and that the effect of *TIP60* heterozygosity does not depend on functional p53.

To further understand tumorigenesis, it will be necessary to unravel the molecular mechanisms through which TIP60 affects DDR. Possible mediators include ataxia-telangiectasia mutated (ATM) and ARF, but the authors were unable to confirm any direct links, implying that the relationship might be complex. However, even without this understanding TIP60 status could become a useful indicator of tumour severity.

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**ORIGINAL RESEARCH PAPER** Gorrini, C. *et al.* Tip60 is a haplo-insufficient tumour suppressor required for an oncogene-induced DNA damage response. *Nature* **448**, 1063–1067 (2007)