TUMOUR SUPPRESSION

The burning issue of p63

The involvement of the p53 family member p63 in tumour suppression and in promoting tumorigenesis has been a matter of debate, and a new paper in *Nature* now clarifies the tumour suppressor function of p63.

The full-length isoform of p63 that contains the transactivation (TA) domain, TAp63, is thought to be a tumour suppressor; so Su, Chakravarti and colleagues investigated this further with cohorts of knockout mice. Aged *TAp63*$^{+/-}$ and *TAp63*$^{-/-}$ mice spontaneously developed metastatic sarcomas and carcinomas and had a shorter lifespan than wild-type mice. More of the *TAp63*$^{+/-}$ mice developed tumours than the *TAp63*$^{-/-}$ mice, and tumours from the heterozygous mice still had the wild-type gene, which suggested that *TAp63* is a haploinsufficient tumour suppressor. They also found that more sarcomas were metastatic in the *TAp63*$^{+/-}$ mice than in the *TAp63*$^{-/-}$ mice, whereas the number of metastatic carcinomas was the same in both mice. To further investigate the haploinsufficiency of *TAp63*, the authors examined the interaction between p53 and TAp63. *TAp63* heterozygosity increased the number of metastatic and invasive sarcomas in *Trp53*$^{+/-}$ mice compared with *TAp63*$^{-/-}$;*Trp53*$^{+/-}$ mice, whereas carcinomas from *TAp63*$^{-/-}$;*Trp53*$^{+/-}$ mice were more metastatic than carcinomas from *TAp63*$^{+/-}$;*Trp53*$^{+/-}$ mice. The authors also observed markers of senescence in osteosarcomas and rhabdomyosarcomas from *TAp63*$^{-/-}$;*Trp53*$^{+/-}$ mice, but not in the same tumour types from *TAp63*$^{+/-}$;*Trp53*$^{+/-}$ mice, suggesting that the induction of senescence as a result of *TAp63* homozygous ablation could account for the more severe phenotype of *TAp63* heterozygosity. Furthermore, senescence markers were not observed in carcinomas from *TAp63*$^{-/-}$;*Trp53*$^{+/-}$ mice, and these mice had increased polyploidy and chromosome aberrations, which indicated a tissue-specific response to loss of *TAp63*.

Interestingly, the authors found that dicer expression was reduced in tumours from *TAp63*$^{-/-}$ mice, and chromatin immunoprecipitation experiments revealed that all isoforms of TAp63 — but not p53 — bind the *Dicer1* promoter and activate its transcription. Moreover, re-expression of *Dicer1* in *TAp63*$^{-/-}$ mouse embryonic fibroblasts (MEFs) prevented the ability of these cells to invade, and *Dicer1* knockdown in wild-type MEFs increased their invasiveness *in vitro*, suggesting that reduced levels of dicer increase cell invasion. The authors also found that microRNAs that have been associated with metastasis and are processed by dicer were not processed correctly in *TAp63*$^{-/-}$ MEFs and that re-expression of *TAp63* rescued this. TAp63 also transactivates *mir-130b*, and further investigation showed that regulation of *Dicer1* and *mir-130b* by TAp63 is important for suppressing metastasis.

These data reveal that TAp63 is a haploinsufficient tumour suppressor with context-specific roles in the suppression of metastasis.

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ORIGINAL RESEARCH PAPER Su, X. *et al.* *TAp63* suppresses metastasis through coordinate regulation of *Dicer* and miRNAs. *Nature* **467**, 986–990 (2010)