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> PTPN14 functions within the p53 pathway

TUMOUR SUPPRESSORS

Digging deeper into p53's functions

Although the tumour suppressor p53 (encoded by *Trp53* in mice and *TP53* in humans) has been extensively studied for many years, the mechanisms by which p53 prevents tumour formation are still unclear. Mello *et al.* analysed the effects of various p53 transactivation domain (TAD) mutants in pancreatic ductal adenocarcinoma (PDAC) and uncovered a crucial tumour-suppressive pathway in which p53 mediates inhibition of the transcriptional co-activator YAP.

Using mice that express oncogenic $Kras^{G12D}$ in the pancreas, the authors showed that expression of a *Trp53* allele with both TADs mutated functions as a *Trp53*-null allele and promotes PDAC development. By contrast, mice that express $Kras^{G12D}$ and a *Trp53* allele with only the second TAD mutated ($Trp53^{53,54}$) are protected from PDAC development, suggesting that $Trp53^{53,54}$ functions as a 'super' tumour suppressor. Transcriptomic and chromatin immunoprecipitation followed by sequencing (ChIP–seq) data indicated that $Trp53^{53,54}$ hyperactivates target genes in mouse embryonic fibroblasts (MEFs).

Of the genes with potential relevance in PDAC, the authors selected protein tyrosine phosphatase non-receptor type 14 (*Ptpn14*) for further study. PTPN14 directly binds to and negatively regulates YAP, a protein that promotes PDAC progression. ChIP–seq data indicated that p53 binds to the *PTPN14* locus in primary human fibroblasts and MEFs, and PTPN14 expression was p53-dependent in a variety of different oncogene-expressing mouse and human cells. In addition, PTPN14 expression was hyperactivated by $Trp53^{53,54}$.

In $Kras^{G12D}$;$Trp53^{-/-}$ mouse PDAC cells and in *TP53*-mutant human PDAC cells, PTPN14 overexpression inhibited proliferation, clonogenic potential and anchorage-independent growth. Knockdown of PTPN14 in p53-expressing PDAC cells promoted clonogenic and anchorage-independent growth *in vitro* and subcutaneous growth in mice, whereas knockdown of PTPN14 in p53-deficient PDAC cells had no effect, indicating that PTPN14 functions within the p53 pathway. Importantly, knockdown of PTPN14 or p53 had similar effects, suggesting a crucial role for PTPN14 in this tumour-suppressive pathway.

Mutants of PTPN14 that could not bind to YAP were unable to mediate PDAC cell growth arrest. Furthermore, the clonogenic growth of PDAC cells lacking either p53 or PTPN14 was attenuated by treatment with the YAP inhibitor verteporfin, indicating the importance of YAP signalling in p53-mediated tumour suppression. Indeed, nuclear localization of YAP and a YAP transcriptional signature were induced in $Trp53^{-/-}$ early-stage pancreatic intraepithelial neoplasia (PanIN) lesions in mice.

In human samples, PTPN14 expression was reduced in PDACs relative to PanINs, and *TP53*-null lesions had a substantial loss of PTPN14 expression as well as nuclear YAP localization. *PTPN14* mutations in human gastrointestinal tumours were mutually exclusive with *TP53* mutations, and increased *PTPN14* expression correlated with increased survival in patients with PDAC.

Data from The Cancer Genome Atlas indicated that a YAP transcriptional signature occurs in many different types of tumours with p53 deficiency, suggesting that this tumour-suppressive p53–PTPN14–YAP pathway might be relevant in a wide range of p53-deficient tumours. Furthermore, verteporfin is under clinical development and could potentially be therapeutically active against these tumours.

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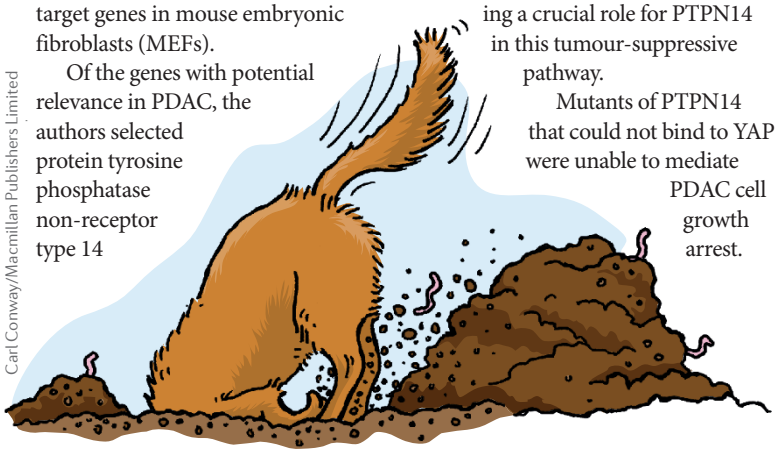

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ORIGINAL ARTICLE Mello, S. S. *et al.* A p53 super-tumor suppressor reveals a tumor suppressive p53–Ptpn14–Yap axis in pancreatic cancer. *Cancer Cell* **32**, 460–473 (2017)

FURTHER READING Bieging, K. T., Mello, S. S. & Attardi, L. D. Unravelling mechanisms of p53-mediated tumour suppression. *Nat. Rev. Cancer* **14**, 359–370 (2014)