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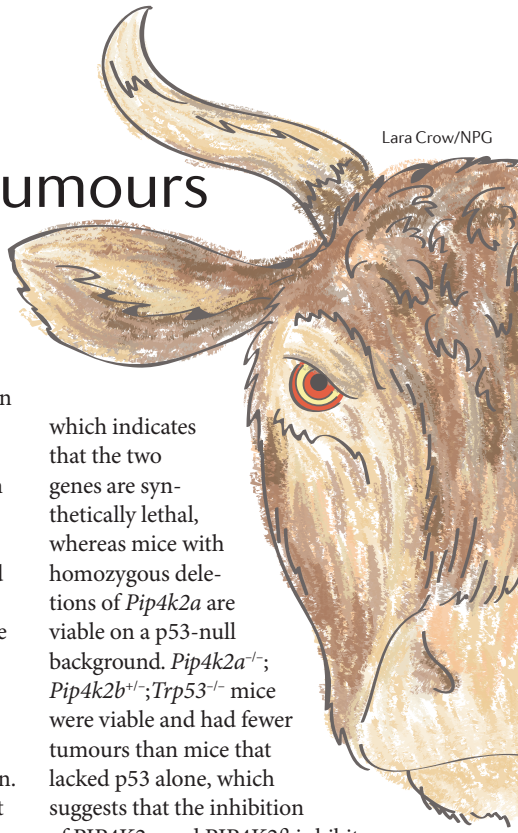
SIGNALLING

A new target for p53-null tumours



Lara Crow/NPG

> PIP4K2α and PIP4K2β are ideal drug targets for p53-negative tumours

The *TP53* tumour suppressor is the most commonly mutated gene across all cancers. However, directly targeting it pharmaceutically is challenging. A new study by Emerling and colleagues has shown that phosphatidylinositol 5-phosphate 4-kinase type-2α (PIP4K2α) and PIP4K2β are essential for growth of p53-null cells but not for p53 wild-type cells and thus may represent a pharmaceutical target in p53-mutated cancers.

The authors found that the gene encoding PIP4K2β (*PIP4K2B*) was amplified in breast tumour samples that encompassed a range of breast cancer subtypes. These *PIP4K2B* amplifications frequently occurred in tandem with p53 deletion or mutation. Interestingly, approximately 50% of tumours with *HER2* (also known as *ERBB2*) amplification also carried *PIP4K2B* amplifications. By contrast, *PIP4K2A* was only amplified in a small number of breast tumours. The authors also observed a significant increase of both PIP4K2α and PIP4K2β protein levels in breast tumours (43% higher for PIP4K2α and 38% higher for PIP4K2β) compared with normal tissue. The tumours with the highest expression of PIP4K2β were also HER2 positive, and this correlated with the gene amplification data.

Knockdown of either PIP4K2α or PIP4K2β in BT474 breast cancer cells, which also contain an inactivating p53 mutation, had little effect on cell growth, whereas knockdown of both kinases resulted in an 80% decrease in cell number. In addition, the knockdown of both kinases resulted in a significant increase in levels of reactive oxygen species (ROS) and in ROS-induced senescence, as shown by β-galactosidase staining. Similar results were seen in xenografts from BT474 cells in which PIP4K2α and PIP4K2β had been knocked down: knockdown of both kinases resulted in smaller tumours and a concomitant increase in the expression of the senescence marker p27.

The p53 mutation in BT474 cells is non-functional at 32 °C, and cells that are grown at this temperature have a partially restored p53 function. The authors showed that, in contrast to their results that were obtained at 37 °C, knockdown of PIP4K2α and PIP4K2β at 32 °C did not reduce cell proliferation. This suggests that knockdown of PIP4K2α and PIP4K2β only impairs growth in combination with non-functional p53. This result was further strengthened by knocking down PIP4K2α and PIP4K2β in other breast cancer cell lines with wild-type p53 and observing that this did not induce senescence or increase levels of ROS.

The authors clarified the results that were observed in cell culture by using genetic mouse models: *Pip4k2a*$^{-/-}$;*Pip4k2b*$^{+/-}$ mice develop normally but die soon after birth. Mice with homozygous deletions of *Trp53* and *Pip4k2b* died *in utero*, which indicates that the two genes are synthetically lethal, whereas mice with homozygous deletions of *Pip4k2a* are viable on a p53-null background. *Pip4k2a*$^{-/-}$;*Pip4k2b*$^{+/-}$;*Trp53*$^{-/-}$ mice were viable and had fewer tumours than mice that lacked p53 alone, which suggests that the inhibition of PIP4K2α and PIP4K2β inhibits the proliferation of tumour cells that lack p53.

Collectively, the results from this study suggest that PIP4K2α and PIP4K2β are ideal drug targets for p53-negative tumours because their inhibition in a p53-null context decreases proliferation but the inhibition of either kinase in a p53 wild-type background has no effect. In addition, the authors identified a link between *HER2* amplification and *PIP4K2β* overexpression, which merits further investigation.

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ORIGINAL RESEARCH PAPER Emerling, B. M. *et al.* Depletion of a putatively druggable class of phosphatidylinositol kinases inhibits growth of p53-null tumours. *Cell* **155**, 844–857 (2013)