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A suppression switch

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The status of the protein p53 determines whether inhibiting the cellular autophagy pathway promotes or inhibits pancreatic cancer in mice. This finding serves as a cautionary tale for clinical trials of autophagy inhibitors.

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Autophagy is a fundamental process in which a cell cannibalizes itself, degrading and recycling cytoplasmic proteins and organelles. This pathway has a crucial role in promoting cellular homeostasis and survival in response to diverse forms of stress, so there is considerable interest in modulating autophagy in cancer cells. So far, clinical trials have focused predominantly on enhancing the efficacy of chemotherapy by inhibiting autophagy, using antimalarial drugs such as hydroxychloroquine[1]. But there is confusion as to whether inhibiting autophagy enhances or diminishes cancer therapy — current evidence suggests that both may be true. In an article published on *Nature*'s website today, Rosenfeldt *et al.*[2] identify the tumour-suppressor protein p53 as a determinant of whether autophagy suppresses or accelerates the progression of pancreatic cancer.

Pancreatic cancers, specifically pancreatic ductal adenocarcinomas (PDACs), are aggressive and lethal tumours that commonly display mutational activation of the signalling molecule Kras[3]. Recent work has established that tumours characterized by mutations in Kras or other Ras proteins rely on autophagy for growth and cell proliferation, making this pathway an attractive therapeutic target[4–7]. Rosenfeldt and colleagues used genetically engineered mice to investigate the role of autophagy in the progression and treatment of PDACs driven by the mutation Kras[G12D]. They demonstrate that silencing essential autophagy-regulating proteins (either ATG5 or ATG7) in Kras[G12D]-mutant pancreatic epithelial cells led to higher expression of p53, which was accompanied by decreased proliferation, increased apoptotic cell death and elevated cellular senescence, all of which are

important barriers to tumour formation[8].

The authors further show that this loss of autophagy is sufficient to prevent the progression of early stage precancerous lesions, termed pancreatic intraepithelial neoplasias (PanINs), into more advanced cancers (Fig. 1a). This finding is consistent with previous work demonstrating a requirement for autophagy in the growth of pancreatic cancer[9]. Interestingly, Rosenfeldt *et al.* also show that the engineered loss of autophagy in normal mouse pancreatic tissue led to elevated p53 expression and cell death, and that this resulted in pancreatic-tissue destruction and diabetes.

More than half of human PDACs exhibit silencing or mutation of the gene encoding p53 (ref. 10), raising the question of whether defective autophagy will still prevent PDAC progression when p53 is inactivated. The authors tested the effects of combined autophagy loss and p53 deficiency in Kras-mutant PDACs and, surprisingly, found that this accelerated, rather than impeded, PDAC progression (Fig. 1b). In a key experiment, the authors treated mice that had Kras[G12D]-driven, p53-deficient lesions with hydroxychloroquine and again observed significantly faster PDAC formation. This result contrasts with the previous observation[9] of delayed tumour progression following treatment of Kras[G12D]-driven, p53-normal PDACs with chloroquine, a hydroxychloroquine derivative.
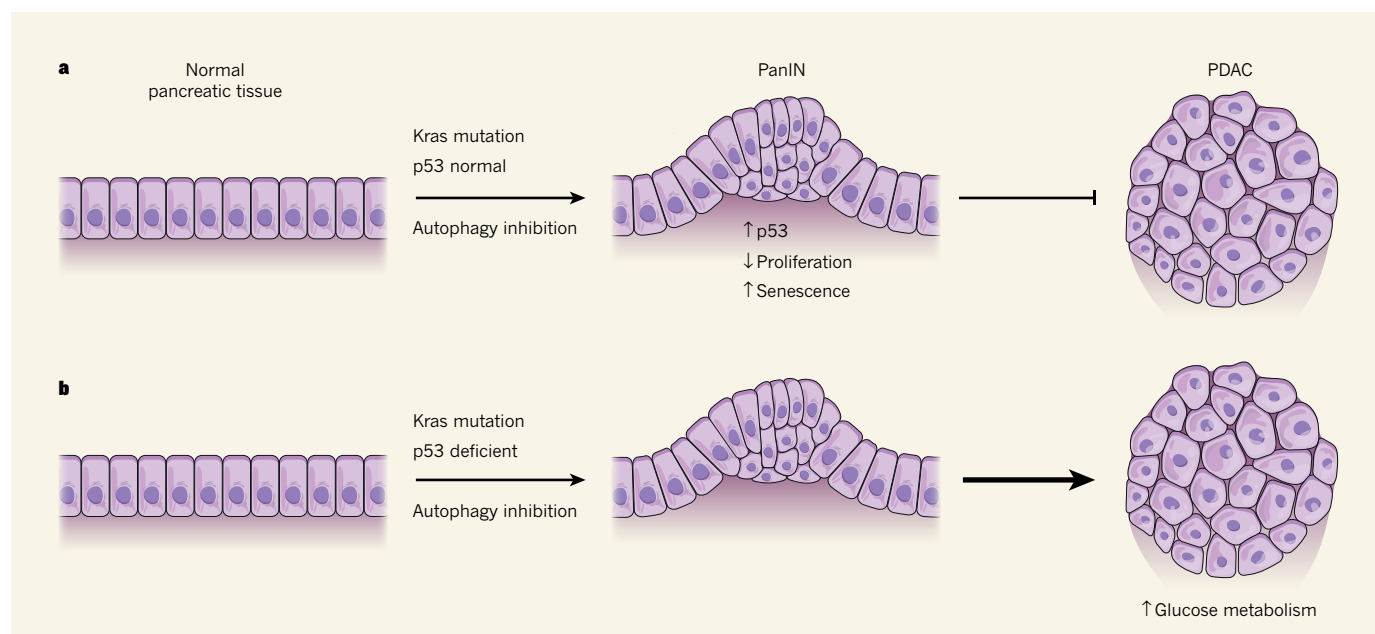

Figure 1 | Autophagy, p53 and cancer progression. Mutations that cause abnormal activation of the protein Kras are commonly associated with pancreatic cancer. The cell proliferation that results from these mutations leads to the development of precancerous lesions called pancreatic intraepithelial neoplasias (PanINs), which stochastically develop into invasive pancreatic ductal adenocarcinomas (PDACs). **a,** Rosenfeldt *et al.*[2] show that when this process is accompanied by normal activity of the tumour-suppressor protein p53, inhibiting autophagy blocks tumour progression at the PanIN stage, which is associated with p53 activation, suppression of proliferation and increased cellular senescence. **b,** However, if the Kras-mutant pancreatic cells lack p53, inhibition of autophagy accelerates the development of PDACs. The authors suggest that this acceleration may be due to enhanced glucose metabolism.

Thus it seems that p53 acts as a switch in pancreatic cancer that dictates whether therapeutic inhibition of autophagy slows or accelerates disease progression. It remains unclear whether p53 similarly regulates autophagy inhibition in other cancers, but it seems likely that there will be cancer-specific nuances — in Kras-mutant lung cancers, for example, silencing of ATG7 suppresses proliferation and alters tumour differentiation, irrespective of p53 status[6]. Nevertheless, Rosenfeldt and colleagues' findings have immense clinical implications, because they highlight the importance of determining the p53 status of pancreatic cancers before treatment with autophagy inhibitors.

The activation of Ras proteins elicits profound metabolic changes that drive energy production and biosynthetic capacity in rapidly proliferating tumour cells; previous studies[4–6] have demonstrated a requirement for autophagy in sustaining cellular metabolism during Ras mutation. In mouse models of lung cancers, autophagy-deficient precancerous tumours harbouring mutations in Kras or Braf (another signalling molecule commonly mutated in cancer) are unable to progress to the malignant stage and exhibit impaired mitochondrial metabolism[5,6]. By contrast, Rosenfeldt et al. propose that increased glucose metabolism is responsible for the accelerated progression of $Kras^{G12D}$-driven PDACs seen following concomitant inhibition of p53 and autophagy.

In support of this, the authors show that cells from PDACs growing in $Kras^{G12D}$ mice that also lacked p53 and ATG7 exhibited enhanced glucose uptake and increased metabolite levels compared with their autophagy-proficient $Kras^{G12D}$, p53-lacking counterparts. However, restoration of autophagy by re-expression of ATG7 did not reverse these metabolic alterations, so it remains unclear whether the metabolic changes are a cause or a consequence of the increased aggressiveness displayed by PDAC cells lacking both autophagy and p53. Furthermore, the loss of autophagy may have other metabolic consequences: in $Kras^{G12D}$-driven lung cancers, for example, the combined loss of ATG7 and p53 results in aberrant fatty-acid oxidation and profound lipid accumulation, suggesting a role for autophagy in lipid breakdown[5,6].

Finally, it is important to recognize that in human Kras-mutant PDAC cell lines with p53 mutations, the loss of autophagy reduces proliferation and tumour growth[9] — the opposite effects to those described by Rosenfeldt et al. in mice. This discrepancy may arise from the different effects of p53 mutation versus outright genetic deletion on metabolism in pancreatic cancers. Although further study is required to understand the mechanism underlying the ability of p53 to switch the clinical outcome of autophagy inhibition, Rosenfeldt and colleagues have illustrated the importance of defining the molecular contexts in which targeting autophagy may be beneficial for anticancer therapy. ∎

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1. Yang, Z. J., Chee, C. E., Huang, S. & Sinicrope, F. A. Mol. Cancer Therapeut. 10, 1533–1541 (2011).
2. Rosenfeldt, M. T. et al. Nature http://dx.doi.org/10.1038/nature12841 (2013).
3. Morris, J. P., Wang, S. C. & Hebrok, M. Nature Rev. Cancer 10, 683–695 (2010).
4. Guo, J. Y. et al. Genes Dev. 25, 460–470 (2011).
5. Guo, J. Y. et al. Genes Dev. 27, 1447–1461 (2013).
6. Strohecker, A. M. et al. Cancer Discov. 3, 1272–1285 (2013).
7. Lock, R. et al. Mol. Biol. Cell 22, 165–178 (2011).
8. Lowe, S. W., Cepero, E. & Evan, G. Nature 432, 307–315 (2004).
9. Yang, S. et al. Genes Dev. 25, 717–729 (2011).
10. Rozenblum, E. et al. Cancer Res. 57, 1731–1734 (1997).