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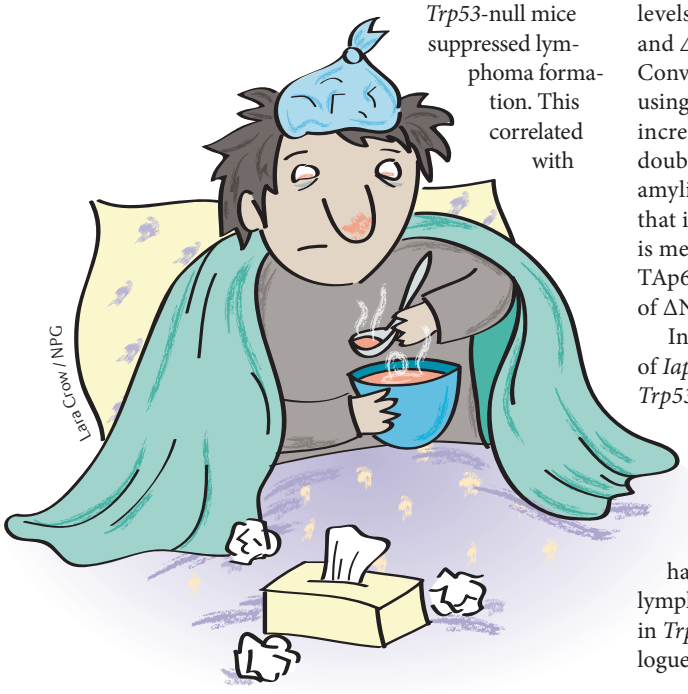
METABOLISM

Feed a cold, starve a tumour

> increased expression of *Iapp* is mediated by the expression of TAp63 and TAp73 in the absence of ΔNp63 and ΔNp73

Tumour cells have altered metabolic states, and it is hoped that these variations will provide new therapeutic windows for effective, tumour cell-specific therapies. Elsa Flores and colleagues have found that amylin, a pancreatic peptide co-secreted with insulin, can induce the regression of p53-deficient tumours in mice by reducing the rate of glycolysis.

The authors were initially interested in understanding the mechanisms in tumour cells that lead to the increased expression of ΔNp63 and ΔNp73, isoforms of the tumour suppressors p63 and p73, respectively. A Cre–*loxP* strategy was used to specifically delete the 3′ exon in both *Trp63* and *Trp73* genes to generate loss of the *ΔNp63* or *ΔNp73* isoforms and retention of the *TAp63* and *TAp73* isoforms. Acute ablation of *ΔNp63* or *ΔNp73* specifically in the thymus of *Trp53*-null mice suppressed lymphoma formation. This correlated with increased expression of the TAp63 and TAp73 isoforms and increased levels of apoptosis in thymic lymphoma cells. The authors also showed that the ΔN isoforms of p63 and p73 bind to the promoters of *TAp63* and *TAp73* and therefore probably repress the expression of these isoforms.



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RNA sequencing and pathway analyses of *Trp53*$^{-/-}$ lymphomas in which *ΔNp63* or *ΔNp73* had been acutely ablated revealed that metabolic pathways were perturbed in these tumours. The most significant change was a greater than five-fold increase in the expression of amylin (encoded by *Iapp*). Chromatin immunoprecipitation and luciferase reporter assays showed that *Iapp* is bound and transactivated by TAp63 and TAp73. Exogenous expression of *Iapp* reduced the levels of glycolysis in *Trp53*$^{-/-}$ mouse embryonic fibroblasts (MEFs) to levels evident in *ΔNp63*$^{-/-}$;*Trp53*$^{-/-}$ and *ΔNp73*$^{-/-}$;*Trp53*$^{-/-}$ MEFs. Conversely, knockdown of *Iapp* using short hairpin RNAs (shRNAs) increased glycolysis in these double-mutant cells, indicating that amylin suppresses glycolysis and that increased expression of *Iapp* is mediated by the expression of TAp63 and TAp73 in the absence of ΔNp63 and ΔNp73.

In mice, exogenous expression of *Iapp* resulted in the regression of *Trp53*-null lymphomas in which *ΔNp63* or *ΔNp73* had not been ablated. Moreover, expression of *Iapp*-targeted shRNAs in *Trp53*$^{-/-}$ lymphomas in which *ΔNp73* or *ΔNp63* had been acutely ablated restored lymphoma growth to levels evident in *Trp53*-null mice. Synthetic analogues of amylin are already being used for the treatment of patients with type I and type II diabetes, and one analogue, pramlintide, induced tumour regression when injected directly into the lymphomas or intravenously.

Are similar responses also evident in human tumour cells? The authors initially used a human lung cancer cell line deficient for *TP53* in which they knocked down *ΔNp63* or *ΔNp73* using small interfering RNAs (siRNAs) or cells transfected with *IAPP*, resulting in the inhibition of glycolysis and the induction of apoptosis. Treatment of these and other *TP53*-mutant human cancer cell lines with pramlintide also inhibited glycolysis and induced apoptosis. Moreover, inhibition of the calcitonin receptor (CALCR) and receptor activity modifying protein 3 (RAMP3), which bind to amylin, prevented amylin-induced inhibition of glycolysis both *in vitro* and *in vivo*. Data from The Cancer Genome Atlas indicated that expression of *IAPP*, *CALCR* and *RAMP3* in patients with various types of cancer with *TP53* mutations correlates with better survival.

The p53 pathway is disrupted in the majority of human cancers, and it will be interesting to see whether the effects of amylin analogues are evident in other tumour models in which p53 function is perturbed.

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ERRATUM

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In the version that was originally published, the competing interests statement for the author was omitted. This has now been added in the online version to state that the author declares no competing interests.