THERAPY

Restoration

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URLs

p53
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=7157

Lymphoma
http://www.cancer.gov/cancertopics/types/non-hodgkins-lymphoma

MYC
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=4609

ARF
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=1029

HRAS
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=3265

Restoration is a delicate business; you know how the finished product should look and feel, but whether you can achieve the outcome you want is not always certain. The same could be said for resurrecting the function of the tumour suppressor p53 in tumours; will this lead to tumour regression? Three papers from the laboratories of Gerard Evan, Tyler Jacks and Scott Lowe indicate that it will.

Evan and colleagues crossed heterozygous *Trp53*$^{KI/+}$ mice (which express a wild-type allele and an allele that produces a regulatable form of the p53 protein, p53ER^{TAM}) with *Eμ–Myc* mice to generate lymphomas. All of the lymphomas that developed had lost the function of the wild-type p53 protein. p53 expression was then reinstated through the administration of 4 hydroxytamoxifen (4OHT), which restored p53ER^{TAM} protein function.

Trp53$^{KI/+}$;*Eμ–Myc* mice treated with 4OHT showed increased survival compared with controls, owing to p53-induced tumour apoptosis. Interestingly, this treatment was not enough to prevent tumour recurrence, owing to the loss of either p53ER^{TAM} or the tumour suppressor ARF. ARF, an activator of p53, is activated in response to oncogenic stress, provided in this model by the deregulated expression of MYC. The ARF p53-activating signal is independent of the activation of p53 in response to DNA-damage signalling, and when these authors co-treated the mice with both 4OHT and a DNA-damaging agent they further increased the survival of the *Trp53*$^{KI/+}$;*Eμ–Myc* mice.

Jacks and colleagues used another approach to reactivate the function of p53 in tumours. Using a combination of the Cre-lox technology and the ER^{TAM} protein, they produced p53-null mice in which the expression of p53 could be restored by the addition of 4OHT. 4OHT enables the Cre recombinase–ER^{TAM} fusion protein to localize to the nucleus and excise a stop cassette in the first intron of *Trp53*, enabling the re-expression of the full length p53 protein. As these mice are p53 null until the addition of 4OHT, they develop both lymphomas and sarcomas. Re-expression of p53 in these tumours had different effects. The lymphomas regressed, owing to the induction of apoptosis, in line with the findings from the Evan laboratory. However, although the sarcomas regressed, they did so over a longer period of time, and this was not associated with the induction of apoptosis. Instead, the sarcoma cells became senescent.

So why did the sarcomas regress? Evidence from Lowe and colleagues indicates that the immune response might be involved. In another elegant approach, these authors used mouse liver progenitor cells transduced with retroviruses that expressed oncogenic HRASV12 and a tetracycline-responsive p53 miR30 short hairpin RNA (shRNA) to suppress p53 expression. These cells were injected into the livers of recipient mice, where they produced invasive hepatocarcinomas. Animals treated with doxycycline (Dox) to turn off the p53 shRNA showed tumour involution, and the tumours were barely detectable 12 days after starting Dox. In fact, just 2 days of Dox treatment were sufficient to stimulate tumour regression, and p53 induced senescence rather than apoptosis in these cells. As the tumours regressed they accumulated inflammatory cells. *In vivo* and *in vitro* data indicated that the senescent cells expressed inflammatory cytokines and other pro-inflammatory proteins, suggesting that senescent tumour cells might initiate an immune response through several mechanisms.

Although these data are clearly encouraging, achieving tumour regression through p53 restoration in humans will be a complex process that might require the co-administration of DNA damaging agents or agents to boost the immune response.

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ORIGINAL RESEARCH PAPERS Martins, C. P., Brown-Swigart, L. & Evan, G. I. Modeling the therapeutic efficacy of p53 restoration in tumours. *Cell* **127**, 1323–1334 (2006) | Ventura, A. *et al.* Restoration of p53 function leads to tumour regression *in vivo*. *Nature* **445**, 661–665 (2007) | Xue, W. *et al.* Senescene and tumour clearance triggered by p53 restoration in murine liver carcinomas. *Nature* **445**, 656–660 (2007)