THERAPY

Restraint required

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URLs

p53

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

MDM2

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&md=Retrieve&dopt=full_report&list_uids=4193

ARF

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

Components of the **p53** tumour-suppressor pathway are often mutated in human tumours, making them potential therapeutic targets. As p53 is continuously degraded through its interaction with the ubiquitin ligase **MDM2**, removing this restraint has been one obvious means of increasing p53 expression levels in tumours with wild-type p53. Although small-molecule inhibitors that achieve this aim are now in preclinical trials, recent results from Gerard Evan and colleagues have indicated that this approach could be problematic.

In vitro data indicate that tumour cells can activate p53 if its expression is restored because signals that activate p53 are maintained in these cells, whereas such signals are likely to be low in normal cells, providing a window of therapeutic opportunity. Evan and colleagues, using their p53ER^{TAM} knockin mice (*Trp53^{KI/KI}*), which express a regulatable form of the p53 protein that can be switched (through the administration of 4-hydroxytamoxifen; 4OHT) between a null and wild-type state, have examined the activity of p53 *in vivo* in normal tissues of mice that lack MDM2.

The restoration of p53 functionality in all tissues — through the systemic administration of 4OHT — in adult *Trp53^{KI/-}* mice on an *Mdm2*-null background results in

their death within 5–6 days. High levels of apoptosis are induced in tissues that are radiosensitive, such as bone marrow, thymus and spleen, and profound growth arrest is induced in radioresistant tissues such as the liver. There is no evidence that DNA-damage signalling pathways are active in these tissues, nor is p53 activity being mediated through the tumour suppressor **ARF**, which activates p53 in response to oncogenic stress. Moreover, under these conditions p53 is not subject to serine 18 phosphorylation, a post-translational modification that is typically associated with p53 activation. Therefore, the complete absence of MDM2 seems to be all that is needed for p53 to be fully and lethally active in tissues, suggesting that a complete blockade of the p53–MDM2 interaction is probably not a good idea therapeutically.

Nonetheless, small molecules such as Nutlin 3, which inhibit the interaction between p53 and MDM2, have shown significant anti-tumour effects in mice with no obvious side effects. This might be because Nutlin 3 does not completely inhibit the interaction of p53 with MDM2, leaving p53 susceptible to some degree of regulation.

Clearly, we need to know more about the interaction and regulation of p53 by MDM2 to better understand how to manipulate this component of the p53 pathway.

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ORIGINAL RESEARCH PAPERS Ringshausen, I., O'Shea, C. C., Finch, A. J., Brown-Swigart, L. & Evan, G. I. Mdm2 is critically and continuously required to suppress lethal p53 activity *in vivo*. *Cancer Cell* **10**, 501–514 (2006)