P53 REGULATION

Another link in the chain

p53 — the guardian of the genome — is mutated in more than half of all human cancers, making it a prime therapeutic target. But p53 activity is regulated by many proteins; could any of these prove to be suitable candidates for cancer therapy? In the 19 October issue of *Cell*, Luo *et al.* and Vazri *et al.* identify another protein — Sir2 — that regulates p53's activity, and show that its inhibition potentiates p53's effects.

It has long been known that p53 activity is regulated by phosphorylation, but recent reports indicate that it is also regulated by a different type of modification — acetylation. Acetylation has previously been associated with the regulation of histones — the protein components of chromatin — but the Sir2 proteins are NAD-dependent deacetylases that are conserved in lower organisms that don't contain histones, so could they be involved in deacetylation of p53?

To investigate this, the groups isolated mammalian Sir2 homologues. Both human SIRT1 (also known as SIR2α) and mouse Sirt1 (also known as Sir2α) interacted with p53 *in vitro* and *in vivo*, and purified Sirt1 could deacetylate p53 *in vitro*. The *in vivo* deacetylase activity of SIRT1 was confirmed using an antibody that was specific for acetylated p53. Acetylated p53 could not be detected following transfection of SIRT1.

So why is p53 acetylated? Acetylation seems to be induced in response to cellular stress. Luo *et al.* showed that p53 acetylation was induced following treatment with the DNA-damaging drug etoposide, and Vaziri *et al.* showed that there was an increase in p53 acetylation following γ-irradiation. Acetylation could be abolished by expression of SIRT1.

As p53 is acetylated in response to stress, it is logical to assume that this would correlate with an increase in its activity, and that deacetylation by SIRT1 would inhibit p53's activity. The groups therefore tested the ability of p53 to activate transcription using a p53-activated luciferase reporter system. Luo *et al.* generated a construct with p53-binding sites upstream of the transcription start site, and Vaziri *et al.* used the promoter of a p53 transcriptional target — the *CDKN1A* gene, which encodes WAF1 — to drive transcription. p53 increased luciferase activity in a dose-dependent manner, and this activity was suppressed by SIRT1. Similar results were reported *in vivo*, as WAF1 was induced following exposure to γ-irradiation, and a fourfold overexpression of SIRT1 reduced this induction.

So, SIRT1 inhibits p53's ability to activate transcription, but what about its ability to induce apoptosis? Luo *et al.* treated $p53^{+/+}$ cells with either etoposide or hydrogen peroxide (oxidative stress), both of which induce apoptosis. However, expression of Sirt1 makes the cells more resistant to these types of cellular stress, so promoting cell survival.

These results indicate that p53 acetylation enhances its activity, and that this is attenuated by SIRT1. So could inhibition of SIRT1 prove a useful therapeutic approach for restoring p53 activity in cancer cells?

The answer seems to be yes. Luo *et al.* exploited the knowledge that Sirt1 was dependent on NAD hydrolysis for its activity to identify nicotinamide — a byproduct of this reaction — as an inhibitor of Sirt1. And both groups showed that SIRT1 was insensitive to inhibition by trichostatin A (TSA), which inhibits HDAC1, another deacetylase that acts on p53. Luo *et al.* showed that the two inhibitors cooperate in the induction of acetylated p53, and suggest that the combination of TSA and nicotinamide might act synergistically in cancer therapy to activate p53.

Vaziri *et al.* used a different approach to inhibit SIRT1 activity and potentiate that of p53. They constructed a dominant-negative SIRT1 mutant — that contained a histidine to tyrosine substitution at residue 363 and coded for a catalytically inactive protein — and showed that its expression increased the kinetics of accumulation of acetylated p53, the induction of WAF1 and apoptosis following transfection with p53.

So, with the characterization of SIRT1, we have discovered a new potential target for cancer therapy. Let's hope that this latest discovery will soon be capitalized on.

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References and links

ORIGINAL RESEARCH PAPER Luo, J. *et al.* Negative control of p53 by Sir2α promotes cell survival under stress. *Cell* **107**, 137–148 (2001) | Vaziri, H. *et al.* *hSIR2*^{SIRT1} functions as an NAD-dependent p53 deacetylase. *Cell* **107**, 149–159 (2001)

WEB SITES

Wei Gu's lab:
http://pathology.cpmc.columbia.edu/pbiowgu.html

Robert Weinberg's lab:
http://web.mit.edu/biology/www/Ar/weinberg.html

WEB WATCH

Chopping and changing

• http://www.infobiogen.fr/services/chromcancer/

Can a single web site catalogue all the genetic changes in every type of cancer? This is the ambitious aim of the Atlas of Genetics and Cytogenetics in Oncology and Haematology, although its editor, Jean-Loup Huret (University Hospital, Poitiers, France), admits that the task will never be complete. The peer-reviewed atlas allows users to search through several different headings. The 'genes' section contains concise summaries of oncogenes and tumour suppressors. Each gene has a 'card' listing its salient features, cancers in which the gene is implicated and links to other sources of information. The choice of entries belies a bias towards haematological malignancies, however, and there are some striking oversights (INK4A, ARF and MDM2 are missing, for example).

The 'leukaemias' section shuffles the cards according to chromosomal rearrangement. Here, you'll find notes on clinical features, treatment, other cytogenetic abnormalities that cluster with the rearrangement in question, the genes involved and references. There's a similar section for solid tumours, this time organized according to tumour type. Other sections include a deck of cards on cancer-prone disorders, 'deep insight' articles, which go into more detail than is possible for the standard database entries, and links to related resources.

The database provides an enormous amount of information in a user-friendly format, but perhaps it would be more successful if it was less ambitious. For the cytogeneticist, it provides a useful adjunct to the Mitelman Database of Chromosome Aberrations in Cancer. The Atlas also welcomes contributions, so if your favourite gene or translocation is missing, why not let the curators know?

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