ANTICANCER DRUGS

Reactivating p53

Mutant tumour suppressor p53 proteins are expressed in and regulate tumour biology in many human cancers, and so restoration of p53 function could be a viable anticancer strategy. Writing in *Cancer Cell*, Yu and colleagues used data from the US National Cancer institute (NCI) drug screen (known as the NCI60 screen) to identify a compound that restored the structure and function of one of the most common p53 mutants.


PHOTODISC

Because the p53 status of the cell lines used in the NCI60 screen — which determined the IC_{50} (half-maximal inhibitory concentration) values of over 48,000 compounds on 60 cell lines — was known, the authors thought these data could be used to identify compounds that target tumours expressing mutant p53. They first used an *in silico* methodology that normalized the IC_{50} values to statistically define a good response, and then scored compounds based on whether they produced a good response against mutant p53 while not having a good response against wild-type p53.

Three compounds with high scores were thiosemicarbazone compounds, of which two (NSC319725 and NSC319726) were shown to inhibit the growth of mouse fibroblasts expressing mutant p53. NSC319726 was then assayed in tumour cell lines expressing different p53 mutations (in amino acid positions 175, 248 or 273 of the DNA-binding domain). These studies showed that NSC319726 inhibited cellular growth the most in cells expressing the $p53^{R175}$ mutant. Further work showed that the NSC319726-mediated reduction in cell growth was mediated by apoptosis, which was at least partially dependent on the presence of the $p53^{R175}$ mutant protein.

Next, the authors investigated the mechanism of action of NSC319726. Using conformation-specific antibodies, they showed that NSC319726 could restore the conformation of mutant $p53^{R175}$ protein to that of the wild-type protein. Furthermore, this conformational change restored the DNA-binding properties of $p53^{R175}$ and increased levels of p53 target genes, indicating that NSC319726 restored the transcriptional functions of $p53^{R175}$.

Thiosemicarbazone compounds are metal ion chelators and redox modulators. Indeed, the authors found that chelation of zinc ions and modulation of cellular redox states had a role in the NSC319726-mediated inhibition of cellular growth, and hypothesized that NSC319726 could act as a source of zinc to allow the $p53^{R175}$ mutant to adopt a correct conformation. When the authors investigated the effects of NSC319726 in mice expressing xenograft tumours derived from human cell lines expressing different p53 alleles, NSC319726 (delivered by injection) inhibited the growth of $p53^{R175H}$ xenografts but not of xenografts expressing other mutant p53 alleles.

These data further highlight that reactivation of mutant p53 using a small molecule is a potential anticancer strategy. The authors note that, unlike previous studies, NSC319726 was identified from a screen that used many different cell lines with diverse genetic backgrounds, which could better reflect the tumour heterogeneity observed in the clinic.

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ORIGINAL RESEARCH PAPER Yu, X. *et al.* Allele-specific p53 mutant reactivation. *Cancer Cell* **21**, 614–625 (2012)