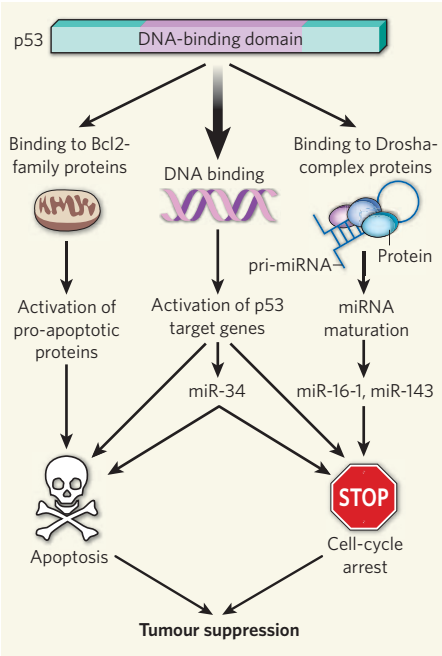

Figure 1 | Three antitumour functions. The DNA-binding domain of p53 lies in the core of the protein and has three antitumour functions. It binds to DNA and enables the activation of target genes (including the miR-34 gene family) to induce apoptosis or cell-cycle arrest; it stimulates apoptosis through an interaction with proteins of the Bcl2 family at the mitochondrion; and, as Suzuki *et al.*[3] show, it interacts with proteins of the Drosha complex to promote processing of a subset of miRNAs, including miR-16-1 and miR-143, which suppress cell proliferation. Most p53 mutations in human cancers lie in the DNA-binding domain and may affect all three functions.

Interestingly, p53 mutants that are frequently observed in human tumours — such as R175H and R273H — correlate with lower Drosha activity, whereas mutant C135Y, which is rarely found in cancers, has apparently less effect on Drosha[3]. Studies of additional p53 mutants will be required to further test whether there is an inverse correlation between the frequency of occurrence of a specific mutant p53 in human tumours and the magnitude of its effect on Drosha activity.

Mice with mutant p53 (ref. 6) have provided compelling evidence that some p53 mutants do not simply lose normal tumour-suppressor functions, but also acquire cancer-promoting (oncogenic) properties. Suzuki and colleagues' suggestion[3] that p53 mutants might reduce the interaction between pri-miRNAs and Drosha-complex proteins provides a possible, and previously unsuspected, mechanism by which mutant p53 could induce cancer. Together with previous studies[1,2], these findings suggest that, in human cancers, mutations that affect the DNA-binding domain of p53 essentially perform a hat-trick by hitting three tumour-suppressive functions at once: activation of target genes, induction of transcription-independent apoptosis, and processing of a subset of miRNAs (Fig. 1).

It will be important to establish the full repertoire of miRNAs that are upregulated by p53 through the mechanism described by Suzuki *et al.*, because this may provide clues about gene products whose function must be suppressed to promote tumour formation. Another member of the p53 family, p63, seems to be the main regulator of the DNA-damage response in female germ cells[7] — which were not studied by Suzuki and colleagues. It will be interesting to determine whether p63 regulates miRNA processing in germ cells.

TP53 is transcribed into nine different mRNAs, some of which are misregulated in human cancers[8]. Little is known about these different transcripts, including whether they are all efficiently translated into protein. However, the proteins they encode should contain most of the p53 DNA-binding domain, and so should have the potential to participate in the regulation of miRNA processing. The recent discovery of single nucleotide polymorphisms (SNPs) in several genes of the p53 pathway[9] adds another level of complexity. For example, a SNP in the promoter of *MDM2*, which encodes a major p53 inhibitor, alters p53 levels and affects the age at which people get certain tumours and the survival of patients after anticancer therapies[10]. Because it alters the amounts of p53, the same SNP probably also affects miRNA processing. This suggests the existence of distinct efficiencies of miRNA processing in human populations that may account, in part, for differences in the age and frequency of cancer onset or prognosis.

As more and more functions are ascribed to p53 (ref. 11), the mechanism identified by Suzuki *et al.*[3] has implications beyond the cell's response to DNA damage and cancer. The data suggesting that mutant p53 titrates the p68 RNA helicase[3] are particularly intriguing, because p68 is a transcriptional co-regulator that is also involved in RNA splicing[12]. Hence, mutant p53 could alter other aspects of RNA metabolism besides miRNA processing. In the ever-expanding universe of p53, the regulation of gene expression by p53–Drosha/p68 interactions may well be the next Big Bang. ■

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50 YEARS AGO

Puzzle-Math. By Dr. George Gamow and Dr. Marvin Stern — Books of the 'mathematics for fun' type are often neither very mathematical nor very funny, but those who know some of Dr. Gamow's earlier writings will expect this volume, in spite of its catchpenny title, to combine amusement with instruction, and they will not be disappointed. The thirty-three problems are entertainingly set out, and solved by honest mathematical processes, involving little or no manipulative technique. There are some 'chestnuts'... but many of the problems are new or not widely known ... A bright student might easily be led to a better appreciation of the fundamental logic of mathematics by reading this cheerful little book.
From *Nature* 25 July 1959.

100 YEARS AGO

In the July number of the *Reliquary*, Mr. E. H. Goddard continues the useful series of articles dealing with local collections of antiquities, his subject being Roman objects discovered in Wiltshire. Though the county possesses no Roman sites ranking in interest and importance with those of Dorchester, Silchester, Bath, or even Lydney or Woodchester, it contains Cunetio near Marlborough, villas at Box, Colerne, and Wraxall, and, in particular, Old Sarum.

...

On October 21, 1638, the Devil visited Widdecombe Church ... in Dartmoor, a full account of which remarkable event is recorded on a tablet in curious versification, the work of the village schoolmaster, which is preserved in the church. As a matter of fact, the place was the scene of a terrible thunderstorm, which caused the loss of several lives, damaged the tower, and caused such consternation that it was attributed to demoniacal agency. The original tablet, a curious instance of the popular beliefs current at the time, is reproduced by Mr. Le Blanc Smith in the July number of the *Reliquary*.
From *Nature* 22 July 1909.

50 & 100 YEARS AGO