CANCER

Taming Puma

Controlling the activity of p53 after DNA damage is essential for the appropriate execution of cell death and the regulation of cell survival. But how does p53 decide whether to induce cell-cycle arrest or apoptosis in different cell types? Reporting in *Cell*, Wen-Shu Wu and colleagues now show that the transcription factor slug determines the fate of haematopoietic progenitors by repressing the gene that encodes puma (*Bbc3*) — a BCL2-homology domain-3 (BH3)-only protein.

Slug (which is encoded by the *Snai2* gene) belongs to the highly conserved slug/snail family of transcription factors, which have numerous roles at different stages of development, in *Caenorhabditis elegans* to humans. In the haematopoietic system, slug functions as a survival factor to protect the progenitor cells from DNA damage. Intriguingly, slug is expressed in stem cells and progenitors of the myeloid lineage, which undergo cell-cycle arrest and DNA repair upon DNA damage, but not in differentiated cells, which undergo apoptosis after genotoxic stress. So, assuming that slug could provide the switch between the cell-cycle arrest and cell death, what might be the mechanism that drives such a decision?

The authors tested the genetic interaction of slug with p53 — the key mediator of DNA-damage-induced apoptosis — and found that slug protects haematopoietic progenitors from DNA-damage-induced apoptosis by antagonizing the p53-mediated apoptotic pathway. As slug contains a potent SNAG transcriptional-repressor domain, it might antagonize p53 by repressing a p53-responsive gene. By using a combination of numerous techniques, Wu and colleagues showed that slug selectively downregulates puma — a downstream effector of p53-induced apoptosis — by binding specifically to a conserved binding site in the first intron of *Bbc3*.

The evidence that slug functions downstream of p53, and the existence of p53-responsive elements in the mouse and human *Snai2* genes, prompted the authors to test whether slug could be a potential p53 target. *In vitro* experiments indicated that p53 not only interacts with each of the putative p53-responsive elements in *Snai2,* but it directly upregulates slug expression after γ-irradiation. Furthermore, analysis of mice that lacked either both slug and p53, or slug and puma confirmed that slug functions downstream of p53 and upstream of puma to control the fate of progenitor cells that are exposed to genotoxic stress *in vivo*.

The ability of slug to repress *Bbc3* transcription has important implications for tumorigenesis — slug is aberrantly expressed in various tumours, and it might contribute to tumorigenesis by repressing the expression of puma or other BH3-only proteins. The authors propose that their findings are also relevant to cancer therapy, as the selective upregulation of slug before cancer treatment might be advantageous for the survival of haematopoietic progenitor cells.

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Links
p53
http://us.expasy.org/cgi-bin/niceprot.pl?P04637
Bbc3
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=170770
slug
http://us.expasy.org/uniprot/O43623
snail
http://us.expasy.org/uniprot/O95863

ORIGINAL RESEARCH PAPER Wu, W.-S. *et al.* Slug antagonizes p53-mediated apoptosis of hematopoietic progenitors by repressing *puma*. *Cell* **123**, 641–653 (2005)
FURTHER READING Zilfou, J. T. *et al.* Slugging it out: fine tuning the p53–PUMA death connection. *Cell* **123**, 545–548 (2005)