HIGHLIGHTS

APOPTOSIS

Cheating death

The ability of p53 to induce apoptosis is a key defence against cancer. That cancer can, sometimes, occur indicates that this defence is not impenetrable, although the blame cannot always be laid on p53. Regulators of p53 are equally culpable, which makes their identification and characterization essential. Previously, Xin Lu's group identified two ASPP proteins — ASPP1 and ASPP2 — that act as potent activators of p53. Now, Lu and colleagues report, in *Nature Genetics*, the identification of a third member of this p53-regulating protein family — but, in this case, it acts as an inhibitor.

The authors recognized the importance of the ASPP proteins in regulating p53, so they turned to the worm as a more tractable biological model. However, homology searches with ASPP1 and ASPP2 revealed only one ASPP gene in *Caenorhabditis elegans*. Lu and co-workers knocked down the gene function using RNA interference (RNAi) and saw an increase in apoptotic germ cells — a surprising observation given the pro-apoptotic function of the previously known ASPPs. Similarly, the use of antisense RNA in human cell lines caused an increase in apoptosis. These findings indicated that the newly identified ASPP protein had an inhibitory effect on apoptosis, earning it the name iASPP.

The authors showed, using co-immunoprecipitation, that iASPP binds p53 and subsequently mapped the binding site to an SH3 domain. Given that this p53-binding domain is common to all three ASPP proteins, it seemed plausible that the proteins compete for p53. This turned out to be the case, as increased iASPP corresponded with reduced ASPP1 and ASPP2 co-immunoprecipitation with p53, and vice versa when ASPP1 and ASPP2 were increased. In addition, expression of iASPP *in vivo* abolished the pro-apoptotic function of ASPP1 and ASPP2.

The ability of iASPP to inhibit p53 implies that it has oncogenic properties, and the demonstration that its expression stimulated RAS-mediated transformation *in vitro* supports this claim. In addition, Lu and colleagues found that iASPP is overexpressed in several cancers containing wild-type p53 and normal levels of ASPP1 and ASPP2.

Binding of ASPP1 and ASPP2 enhances the capacity of p53 to turn on death-promoting genes. At the same time, binding to p53-regulated cell-cycle arrest genes is not enhanced. The authors observed the same specificity for the apoptosis programme with iASPP. Future studies will reveal whether iASPP has a dominant-negative effect on ASPP1 and ASPP2 or whether iASPP is a direct inhibitor of p53.

Regardless of how iASPP inhibits p53, it is now clear that the apoptotic function of p53 is stimulated by ASPP1 and ASPP2 and inhibited by iASPP — opposing roles for such close family members.

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References and links

ORIGINAL RESEARCH PAPER Bergamaschi, D. *et al.* iASPP oncoprotein is a key inhibitor of p53 conserved from worm to human. *Nature Genet.* **33**, 162–167 (2003)