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APOPTOSIS

The p53 mafia

Courtesy of the Kobal Collection

At the heart of a report in *Nature* lies a tale of drugs and violent death. The leading role in this story goes to p53, which orders the apoptotic execution of cells in response to DNA-damaging agents such as doxorubicin. But as Elsa Flores, Tyler Jacks and co-workers now show, this is a family affair — for p53 needs its close relatives p63 and p73 to carry out the task.

The structural and functional similarities between p53 and its relatives led Jacks and colleagues to ask whether p63 and p73 are involved in the p53-dependent response to DNA-damaging agents. They studied this using mouse embryo fibroblasts (MEFs) that had been sensitized to undergo apoptosis by expression of the *E1A* oncogene and were deficient in various p53 family members.

As expected, after treatment with doxorubicin, the $p53^{-/-}$ MEFs were resistant to apoptotic death. The $p63^{-/-}$ and $p73^{-/-}$ cells showed only a partial resistance to apoptosis, but MEFs that lacked both of these genes were as resistant to apoptosis as were the $p53^{-/-}$ cells. Moreover, cells that lacked p53/p63 or p53/p73 were more resistant than MEFs that were deficient in p53 alone, and this indicated that p63 and p73 might act with p53 — or in a parallel pathway — to induce apoptosis after DNA damage. The authors confirmed these results in an *in vivo* system — the developing nervous system of day-13.5 mouse embryos, in which p53 has been shown to be important for γ-irradiation-induced apoptosis.

Although other mechanisms of p53-dependent apoptosis have been proposed, there is a general consensus that p53 acts in this process by the initiation of downstream target genes. So, Jacks and colleagues studied the induction of p53 target genes in MEFs that lacked the various p53 family members. The induction of some targets, such as *p21* and *mdm2*, was no different in wild-type cells than in cells that lacked p63, p73 or p63/p73. But other genes — *bax* and *PERP*, for example — were not expressed in MEFs that lacked p63 and p73. Notably, Bax and PERP are linked to apoptotic responses.

The authors had shown that both p53 and p63 are enriched in the nuclei of MEFs after DNA damage, so they tested whether these proteins can bind the promoters of p53 target genes. Both proteins associated with the *p21*, *mdm2*, *bax* and *PERP* promoters in wild-type MEFs. However, in cells that lacked p63 and p73, p53 could no longer associate with the *bax* or *PERP* promoters in response to DNA damage. Moreover, in p53-deficient MEFs, p63 was found specifically at the *bax* and *PERP* promoters.

These results indicate a model in which p63 and p73 regulate the ability of p53 to bind at certain promoters after its induction in response to DNA damage. And, as the authors speculate, they might "portend a greater role for these proteins in tumour suppression and chemosensitivity".

Alison Mitchell

References and links

ORIGINAL RESEARCH PAPER Flores, E. R. *et al*. p63 and p73 are required for p53-dependent apoptosis in response to DNA damage. *Nature* **416**, 560–564 (2002)

FURTHER READING Yang, A. & McKeon, F. p63 and p73: p53 mimics, menaces and more. *Nature Rev. Mol. Cell Biol*. **1**, 199–207 (2000)

WEB SITE

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