ANTICANCER DRUGS

Overcoming inhibition

Ever since resistance to apoptosis emerged as an influential pathway in cancer development, targeting the mechanisms that allow tumours to avoid the same fate as normal cells has been proposed as a potent anticancer strategy. In *Cancer Cell*, John Reed and colleagues validate this principle by describing how small-molecule inhibitors that remove an important 'brake' in apoptosis can strip tumours of their immortality.

The ultimate effectors of programmed cell death are the caspase family of proteases. Normally, caspases are kept in check by members of the inhibitor of apoptosis (IAP) family, which bind to and inactivate caspases until they are needed. Caspases are overexpressed in tumours, but so are IAPs, and, therefore, failure to activate caspases could create resistance to apoptosis.

So, Reed and colleagues screened a library of around one million compounds for binding to one of the best characterized of the IAPs: XIAP. XIAP inhibits apoptosis at a distal step in the apoptosis pathway — at the convergence of cell-death pathways that are activated by mitochondria-dependent and mitochondria-independent stimuli.

Eight polyphenylurea-based compounds were identified that bind to the BIR2 domain of XIAP — which is responsible for the inactivation of caspase-3 and caspase-7 — and reversed caspase inhibition. (XIAP also suppresses an upstream initiator caspase-9 through the BIR3 region, but the authors decided to target a more downstream mechanism.)

The most active of these compounds induced apoptosis in a range of tumour cell lines and primary leukaemia cells *in vitro*, but showed little toxicity in normal cells. These compounds also sensitized tumour cells to the anticancer treatments etoposide (VP16), doxorubicin (Dox) and paclitaxel (Taxol). Inactive structural analogues had no effect on these tumour cells.

The induction of cell death by the XIAP antagonists was blocked by the universal caspase inhibitor zVAD-fmk and was reduced by overexpressing XIAP. Cell death was unaffected, however, by overexpression of the upstream apoptosis suppressors Bcl-X_L and CrmA, which shows that targeting such a distal point in the apoptosis pathway bypasses many upstream defects in apoptosis-regulatory mechanisms in tumours. Delivered at modest doses, the XIAP antagonists also suppressed growth of established tumours in mouse xenograft models, with little toxicity to normal cells.

The results indicate that tumours have an intrinsic drive to activate caspases, and that inhibition of IAPs allows apoptosis to occur in tumours with little or a lesser effect in normal cells. The compatibility of XIAP antagonists with established anticancer drugs, and their ability to suppress tumour growth *in vivo*, provides a rationale to investigate pharmacokinetic and toxicological profiles for these compounds as single agents or as combined therapy.

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References and links

ORIGINAL RESEARCH PAPER Schimmer, A. D. *et al.* Small-molecule antagonists of apoptosis suppressor XIAP exhibit broad antitumor activity. *Cancer Cell* **5**, 25–35 (2004)

FURTHER READING Reed, J. C. Apoptosis-based therapies. *Nature Rev. Drug Discov.* **1**, 111–121 (2002) | Salvesen, G. S. & Duckett, C. S. IAP proteins: blocking the road to death's door. *Nature Rev. Mol. Cell Biol.* **3**, 401–410 (2002)