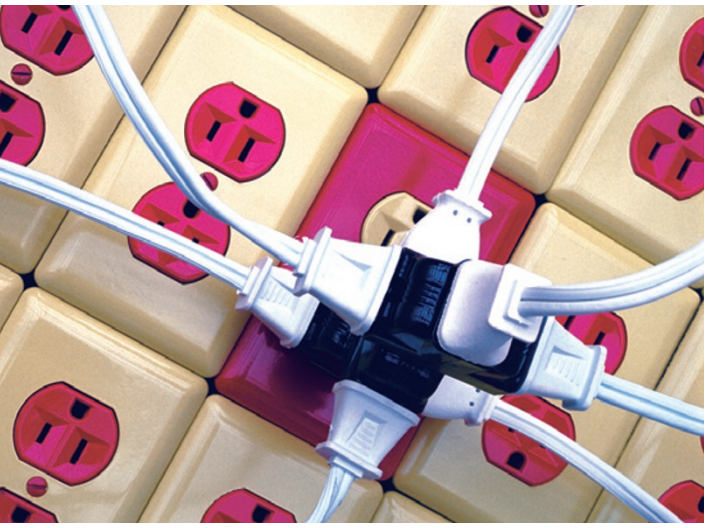
CANCER

Short-circuit to tumour cell apoptosis

Rationally designed molecularly targeted anticancer agents can provide high specificity and low toxicity compared with conventional chemotherapeutics. To date, most such agents target aberrant growth signals. In addition to inappropriate growth signals, many cancer cells have an inability to undergo apoptosis. Reporting in *Cancer Cell*, Petersen and colleagues now demonstrate that a small-molecule mimetic of a pro-apoptotic protein can restore apoptosis in a subset of cancer cells, and unravel the mechanism of its action.

The overexpression of anti-apoptotic genes, for example, members of the inhibitor of apoptosis (IAP) family, has been correlated with tumorigenesis and resistance to chemotherapy in numerous types of cancer. The authors had previously reported a small-molecule mimetic of second mitochondria-derived activator of apoptosis (Smac; also known as DIABLO), that was shown to induce apoptosis in synergy with other pro-apoptotic stimuli in cancer cells *in vitro* by binding to IAPs. Now, the authors demonstrate that the Smac mimetic can have single-agent activity in several different cancer cell lines, as well as in mice with human tumour xenografts derived from the sensitive cell lines. Importantly, 40% of the mice were tumour-free at the end of the experiment, without any signs of toxicity.



Investigating the underlying molecular mechanisms of this activity, the authors found that the Smac mimetic induced apoptosis only in cancer cells that use autocrine tumour necrosis factor-α (TNFα) as a growth factor (22% of the non-small-cell lung cancer cell lines tested). TNFα can activate both death and survival processes in a cell, and these aspects are mediated through two different complexes: a prosurvival complex containing members of the IAP family and a death-inducing complex that can activate the proteolytic caspase cascade. A key feature of regulated apoptosis is the release of Smac from mitochondria, its binding to cytosolic IAPs and the activation of the caspase cascade. The Smac mimetic was found to relieve the requirement for mitochondrial disruption in apoptosis induction. Further molecular analysis showed that it also alters the state of the TNFα receptor from one that signals survival to one that induces a death-inducing complex that kills the tumour cells, with TNF receptor 1 (TNFR1), receptor-interacting kinase 1 (RIPK1) and caspase 8 as central death-inducing players.

These results show that Smac mimetics can usurp autocrine TNFα signals, using the cell's own growth factor to induce apoptosis. It remains to be investigated whether co-treatment with TNFα or other factors may render Smac-mimetic resistant cancers sensitive, and whether molecular profiling can facilitate the identification of cancer patients who may respond to such treatments. Given the lack of toxicity and favourable response profile in animal models, Smac-mimetics are attractive candidates for new apoptosis-inducing anticancer strategies.

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ORIGINAL RESEARCH PAPER
Petersen, S.L. *et al.* Autocrine TNFα signaling renders human cancer cells susceptible to Smac-mimetic-induced apoptosis. *Cancer Cell* **12**, 445–456 (2007)