cIAP antagonists and IFNγ activate novel caspase and RIPK1 dependent death pathways

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Peptido-mimetic IAP antagonists (smac-mimetics) have been shown to kill tumour cells as single agents or sensitisise them to existing anti-cancer treatments. We have previously shown that one such smac-mimetic, compound A, has similar effects on cells as TWEAK, a ligand of the TNF superfamily. Because some cancer lines can be sensitised to TWEAK cytotoxicity by co-treatment with IFNγ, we hypothesised that IFNγ might also synergise with compound A to kill cells. Consistent with our hypothesis, tumor cell lines that are sensitive to TWEAK/IFNγ were killed when treated with IFNγ and compound A. Both JAK/STAT and NF-kB signaling were required for cell death because synergistic killing could be blocked by either SOCS1 or dominant negative IκBα overexpression. Smac-mimetics kill some cell lines by inducing autocrine TNF in an NF-kB dependent manner but compound A/IFNγ killing did not require TNF-R1 signalling. Another distinguishing feature of this IAP antagonist/IFNγ death was that in some cell lines it could not be blocked by caspase inhibition alone even though cells displayed classic apoptotic features. Surprisingly, caspase inhibition together with a RIPK1 inhibitor (Nec1) blocked synergistic killing by Compound A and IFNγ, as did RIPK1 knockdown. Our results suggest that smac-mimetics can activate both apoptotic and non-apoptotic cell death which may extend their clinical use.

IAP antagonists target cIAP1 to induce TNFalpha-dependent apoptosis.


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TAK1 is required for survival of mouse fibroblasts treated with TRAIL, and does so by NF-kappaB dependent induction of cFLIPL.