

## **Cytoprotective effects of IAPs revealed by a small molecule antagonist**

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Deregulated expression of members of the IAP (inhibitor of apoptosis) family has been identified in a wide variety of neoplastic cells, and synthetic IAP antagonists represent a promising novel class of chemotherapeutic agents. Early work focused on the ability of these compounds to block the caspase-inhibitory function of XIAP (X-linked IAP). However, recent studies have shown that IAP antagonists, although primarily designed to target XIAP, trigger ubiquitin-mediated degradation of two related proteins, c-IAP (cellular IAP) 1 and c-IAP2, and through this process potentiates the death of tumour cells via autocrine cellular-signalling pathways. In this context, the relative contribution of XIAP as a target of this class of compounds is unclear. In the present study, we examine the involvement of XIAP using a recently described synthetic IAP antagonist, AEG40730, and through comparison of a human XIAP-depleted tumour cell line with its isogenic wild-type control line. Treatment with nanomolar concentrations of AEG40730 resulted in the loss of both XIAP and c-IAP1 proteins, albeit with different kinetics. Although XIAP-deficient HCT116 cells retained some sensitivity to external apoptotic stimuli, the results suggest that IAP antagonists, such as AEG40730, exert their apoptosis-enhancing effects through XIAP in addition to the c-IAPs. These results indicate that IAP antagonists can target multiple IAPs to augment distinct pro-apoptotic signalling pathways, thereby revealing the potential for these compounds in cancer therapy and underscoring the promise of IAP-targeted therapies.