

cIAP1 and cIAP2 facilitate cancer cell survival by functioning as E3 ligases that promote RIP1 ubiquitination.

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Mol Cell. 2008 Jun 20;30(6):689-700.

The inhibitor of apoptosis (IAP) family of proteins enhances cell survival through mechanisms that remain uncertain. In this report, we show that cIAP1 and cIAP2 promote cancer cell survival by functioning as E3 ubiquitin ligases that maintain constitutive ubiquitination of the RIP1 adaptor protein. We demonstrate that AEG40730, a compound modeled on BIR-binding tetrapeptides, binds to cIAP1 and cIAP2, facilitates their autoubiquitination and proteosomal degradation, and causes a dramatic reduction in RIP1 ubiquitination. We show that cIAP1 and cIAP2 directly ubiquitinate RIP1 and induce constitutive RIP1 ubiquitination in cancer cells and demonstrate that constitutively ubiquitinated RIP1 associates with the prosurvival kinase TAK1. When deubiquitinated by AEG40730 treatment, RIP1 binds caspase-8 and induces apoptosis. These findings provide insights into the function of the IAPs and provide new therapeutic opportunities in the treatment of cancer.