Discovery of potent antagonists of the anti-apoptotic protein XIAP for the treatment of cancer

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Apoptosis plays a critical role in the development and homeostasis of multicellular organisms. In many cancers the cell death machinery is inhibited by the upregulation of anti-apoptotic proteins, suggesting that the restoration of apoptotic activity might be an effective approach for treating these cancers. Inhibitor of apoptosis proteins (IAPs) are overexpressed in many cancers and have been implicated in tumor growth, pathogenesis and resistance to chemo- or radiotherapy. Human X-linked IAP (XIAP), the best-characterized among the IAPs, is believed to directly inhibit particular caspases via its 70-amino acid BIR domains. The BIR3 domain of XIAP binds directly to the small subunit of caspase-9, the initiator caspase in the mitochondrial pathway of apoptosis. Based on the NMR structure of a SMAC peptide complexed with the BIR3 domain of XIAP[1], a novel series of proteolytically stable XIAP antagonists was discovered and optimized using high-throughput parallel chemistry. The most potent compounds in this series bind to the BIR3 domain of XIAP with single-digit nanomolar affinity and promote cell death in several human cancer cell lines with EC₅₀ values as low as < 10 nM. In a breast cancer mouse xenograft model, these XIAP antagonists inhibited the growth of tumors. Results from cellular experiments are consistent with a mechanism in which ligands for the BIR3 domain of XIAP disrupt the XIAP-caspase 9 protein-protein complex, thereby activating downstream caspases and resulting in apoptosis. The present study validates the BIR3 domain of XIAP as a target and supports the use of small molecule XIAP antagonists as a potential therapy for cancers that overexpress XIAP.

References