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Targeting the inhibitor of apoptosis (IAP) proteins

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The IAP proteins are major regulators of apoptosis that bind to and inhibit caspases-3, -7, and/or -9. Overexpression of IAP proteins has been demonstrated to confer protection against a variety of pro-apoptotic stimuli, including chemotherapies, and is a marker for poor prognosis in a variety of solid tumors and hematologic malignancies. All IAP proteins contain one to three copies of the baculoviral IAP repeat (BIR) domain, zinc-binding domains of about 80 amino acids, that are necessary for their interactions with a number of cytosolic target proteins, including activated caspases-3, -7, and/or -9.

Antagonism of the IAP protein mediated inhibition of these caspases is required for caspase dependent cell death, and can be achieved by the mitochondrial protein second mitochondria-derived activator of caspases/direct IAP-binding protein with low pI (Smac/DIABLO), which is released into the cytoplasm in response to pro-apoptotic stimuli. The pro-apoptotic function of Smac/DIABLO is dependent on a conserved four-residue IAP protein-interaction motif (A−V/I–P/A−I/F/Y) found at the N-terminus of the mature, post-translationally processed, protein. Structural studies have shown that such N-terminal peptides bind to a surface groove on the BIR domains. The Smac-binding groove of XIAP-BIR3 also makes critical contacts with an IAP protein-interacting motif located at the N-terminus of the small subunit of caspase-9. Accordingly, Smac-derived peptides and Smac mimetics have been shown to sensitize a number of different tumor cell lines to apoptosis induced by a variety of pro-apoptotic drugs, both in vitro and in vivo. Efforts to develop Smac mimetics that target the IAP proteins will be discussed.