

# IAPS AND THEIR ANTAGONISTS - FROM BACULOVIRUS TO BEDSIDE

David L Vaux<sup>1</sup>

<sup>1</sup> La Trobe University, Melbourne, VIC, 3086, Australia

Inhibitor of Apoptosis Proteins (IAPs) were first identified in viruses that infect insect cells. These viruses use IAPs to prevent suicide of the host cell, thereby prolonging the time available for viral replication. Searches of host cell genomes revealed cellular IAP homologs throughout the metazoa. All IAPs bear from one to three zinc-binding domains termed a Baculoviral IAP Repeats (BIRs). While some IAPs are involved in innate immune responses and chromosome segregation, others, such as mammalian XIAP, cIAP1, cIAP2 and ML-IAP, appear, like the baculoviral IAPs, to be capable of inhibiting cell death.

Attention was initially focussed on XIAP because it was the only one of the of the mammalian IAPs capable of directly inhibiting caspase proteolytic activity. Co-immunoprecipitation of proteins that bound to XIAP led to the identification of Smac/Diablo and HtrA2/Omi, proteins that normally reside in the mitochondria, that when released into the cytosol can bind to XIAP, relieving its inhibition of caspases. The similarity of the N terminus of Smac/Diablo to that of insect IAP antagonists suggested that just the first few amino acids were critical for IAP binding. This led to the development of artificial IAP antagonist compounds, also known as “Smac-mimetics”, by pharmaceutical companies, with the hope that such compounds could promote apoptosis of cancer cells whose survival depended on high levels of XIAP.

Analysis of Smac-mimetic compounds showed that they did not function (as intended) by binding to XIAP, but instead acted by binding to the BIRs of cIAP1 and cIAP2. These two cIAPs were known to bind to TRAF1 and TRAF2, adaptor molecules required for activation of JNK and involved in activation of canonical NF- $\kappa$ B pathways downstream of the TNF receptor. Studies with the IAP antagonists and cells from IAP gene deleted mice show that the normal role of cIAP1 is to limit both transcription factor activation and caspase activation pathways downstream of TNFR superfamily members. cIAP2 is induced by ligation of TNF receptors, and functions as part of a negative feed-back loop to turn down TNF receptor signalling. When smac-mimetic compound is added, it causes dimerization of cIAPs, which autoubiquitylate in trans, and are degraded by the proteasome. When cells are depleted of IAPs in this way, NIK becomes stabilized, and non-canonical NF- $\kappa$ B pathways become activated. In some cell types, this leads to autocrine production of TNF that activates the now dis-inhibited TNF receptors, to cause caspase activation and apoptosis. In other cell types that do not produce TNF, cIAP depletion makes them much more sensitive to induction of apoptosis by addition of exogenous TNF family ligands, such as TNF itself, CD95L and TRAIL.

Experiments by a number of groups in which mice bearing xenograft tumours were treated with IAP antagonist compounds should that single agents could be curative. These results have encouraged some companies, such as Genentech, to commence Phase 1 human trials.