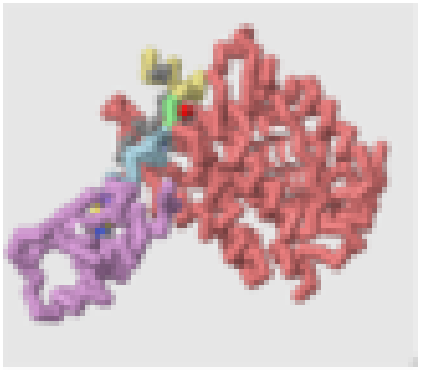
XIAP Summary Sheet Outline

X-linked inhibitor of apoptosis/Caspase 3

By Peter Sawyer



PDB: 1I30

Primary Citation: Reidl, S, Renatus, M, Schwarzenbacher, R, Zhou, Q, Sun, C, Fesik, S, Liddington, R and Salvensen, G. (2001). Structural basis of the inhibition of caspase-3 by XIAP. *Cell* 104:791-800.

Format: Alpha carbon backbone

RP: Zcorp with plaster

Description:

Apoptosis is defined as "programmed cell death." It is controlled by internal cellular processes. It differs from necrosis, which is cell death caused by external factors such as infection, toxins, or trama. Apoptosis is often illustrated in textbooks as the process that will eliminate cells in the interdigital regions of the developing plate-like hands and feet. In mammals, apoptotic pathways activate **c**ysteine-**asp**artic acid prote**ases (**caspases) because they cleave the peptide bonds at the end of a aspartic acid, glutamic acid, valine, aspartic acid sequence indiscriminately in cell proteins, leading to the distruction of the cell. The entire process is often initiated by the release of cytochrome *c* from the mitochondria. Cytochrome *c* functions in the electron transport chain in healthy cells, but in cells undergoing apoptosis, cytochrome *c* will activate caspase-9, one of 12 known caspases in humans.

XIAP is a protein that is coded for on the **X** chromosome and functions as an **i**nhibitor of **ap**optosis. The XIAP protein stops apoptotic cell death induced either by viral infection or by the overproduction of caspases. The XIAP protein binds to the active site of a caspase, preventing it from breaking down proteins. The XIAP protein is further characterized by three BIR (**b**aculoviral **I**AP **r**epeat) domains, which consist of approximately 70 amino acids each. There are three sections of the BIR domains known as the "hook," "line," and "sinker." The hook of the BIR interacts with the caspase enzyme through hydrophobic interactions that are further stabilized by hydrogen bonding. The line consists of two peptide bonds that stretch across the caspase substrate binding cleft. The BIR molecule is then stabilized in place by the sinker, which makes both hydrophobic and hydrogen bond interactions with the caspase just before the globular BIR domain. The globular BIR domain is stabilized by a zinc finger motif.

In the case of Nicholas Volker, a child in the Milwaukee, Wisconsin area with untreatable colitis, through a process of genetic sequencing and comparisons to known genetic maps, it was determined that he had a mutation on the second of three **b**aculoviral **I**AP **r**epeat domains,

(BIR2). Nicholas' DNA code for the XIAP protein had a single nucleotide substitution leading to a single amino acid change. The substitution of an adenine for the normal guanine led to a tyrosine being substituted for a cysteine in the critical stabilizing zinc finger motif in the BIR2 domain. This prevents Nicolas' XIAP protein from working properly.

Specific Model Information:

XIAP

- The hook of the BIR2 domain is colored khaki
- The line of the BIR2 domain is colored light green
- The sinker of the BIR2 domain is colored light blue
- The globular domain of BIR2 is colored plum
- The sidechains are displayed in CPK and represent the hydrophobic clusters that interact with caspase 3
- The globular domain of BIR2 contains a zinc finger. The zinc atom is coordinated by three cysteines and one histidine, displayed in ball and stick and colored CPK
- The backbone of cysteine 203 is colored a darker shade of purple. This is the cysteine is changed to a tyrosine in Nic Volker.

Caspase-3

- The active site (tyrosine) is colored red
- The sidechains are displayed in CPK and represent the hydrophobic clusters that interact with caspase 9