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Forward

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List of Abbreviations

AICD, activation-induced cell death
Apaf, apoptotic protease-activating factor
APC, antigen presenting cell
ASK, apoptosis signal-regulating kinase 1
BAL, broncho-alveolar lavage
BIR, baculovirus IAP repeat
c, cytochrome *c*
C-1, caspase-1
C-3, caspase-3
C-8, caspase-8
C-9, caspase-9
c-FLIP, cellular FLICE-inhibitory protein
c-IAP, cellular IAP
CARD, caspase-associated recruitment domain
CHX, cycloheximide
COMMD1, copper metabolism (Murr1) domain-containing 1
CYLD, cylindromatosis
DD, death domain
DISC, death-inducing signaling complex
DN, double negative
DP, double positive
EBV, Epstein-Barr Virus
ELISA, enzyme-linked immunosorbent assay
FADD, Fas-associated death domain protein
GAPDH,
IAP, inhibitor of apoptosis
IBM, IAP binding motif
I κ B α , inhibitor of κ B
IKK, I κ B kinase
ILP-2, IAP-like protein 2
INCENP, inner centromere protein
JNK, Jun N-terminal kinase
KO, knockout
LPS, lipopolysaccharide
LRR, leucine-rich repeat
MAD1, mitotic arrest deficient 1
MAX, myc-associated factor X
MAP3K, mitogen-activated kinase kinase kinase
MEF, murine embryonic fibroblast

MHC, major histocompatibility complex
MKK, mitogen-activated kinase kinase
ML-IAP, melanoma IAP
MYC, avian myelocytomatosis viral oncogene homolog
NAIP, neuronal apoptosis inhibitory protein
NF- κ B, nuclear factor- κ B
NIK, NF- κ B inducing kinase
NKT, natural killer T (cell)
NOD, nucleotide oligomerization domain
PAI-1, plasminogen activator inhibitor 1
PNA, peanut agglutinin
RING, really interesting new gene
RIP1, receptor interacting protein 1
RT-PCR, reverse transcription polymerase chain reaction
SAP, SLAM-associated protein
SLAM, second lymphocytic activation molecule
Smac, second mitochondrial activator of caspases
SRBC, sheep red blood cell
TAB, TAK1-binding protein
TAK1, TGF- β activated kinase 1
TCR, T cell receptor
TGF- β , transforming growth factor- β
TNF, tumor-necrosis factor
TNFR, TNF receptor
TRADD, TNFR1-associated death domain protein
TRAF2, TNFR associated factor 2
TRAIL, TNF-related apoptosis-inducing ligand
UBC, ubiquitin conjugation
WT, wild type
XIAP, X-linked IAP
XLP, X-linked Lymphoproliferative Syndrome

Abstract

Human X-linked inhibitor of apoptosis, or XIAP, is a member of the IAP family of proteins that has been shown to be a potent regulator of the cell death pathway, and has also been implicated as a mediator of other signal transduction pathways. Mutations in XIAP have been identified as a cause of X-linked lymphoproliferative disorder (XLP), a rare but fatal disease associated with aberrant response to Epstein-Barr virus (EBV). Surprisingly, mice that lack XIAP have not thus far been shown to have any major defects in apoptotic signaling, though JNK and NF- κ B-dependent transcription have been implicated in defective responses to bacteria. The studies presented here show that XIAP is not a universal mediator of TGF- β signaling or NF- κ B-dependent transcription. However, cells derived from *Xiap*-null mice exhibit increased sensitivity to apoptotic stimuli over their wildtype counterparts, but interestingly only under highly specific experimental conditions. A closely related family member, c-IAP2, is also shown to be protective from similar apoptotic stimuli, while another, c-IAP1, is not observed to protect cells from apoptosis. Our data also demonstrate that XIAP does not cause XLP in the same manner as another protein mutated in the same disease, SAP. Cells from *Xiap*-null mice respond differently to a murine γ -herpesvirus closely related to EBV, which may explain the role of XIAP in XLP. These studies will not only shed light on the function of XIAP in the regulation of the immune system, but will also help to understand the pathogenesis of XLP.