



Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Lalaoui, N;Vaux, DL

Title:

Recent advances in understanding inhibitor of apoptosis proteins.

Date:

2018-01-01

Citation:

Lalaoui, N. & Vaux, D. L. (2018). Recent advances in understanding inhibitor of apoptosis proteins.. F1000research, 7, pp.F1000 Faculty Rev-1889-. <https://doi.org/10.12688/f1000research.16439.1>.

Persistent Link:

<https://hdl.handle.net/11343/253670>

License:

[CC BY](#)



REVIEW

Recent advances in understanding inhibitor of apoptosis proteins [version 1; referees: 2 approved]

Najoua Lalaoui ^{1,2}, David Lawrence Vaux^{1,2}

¹Cell Signalling and Cell Death, The Walter and Eliza Hall Institute of Medical Research, Melbourne, Victoria, 3052, Australia

²Department of Medical Biology, The University of Melbourne, Melbourne, Victoria, 3050, Australia

v1 First published: 03 Dec 2018, 7(F1000 Faculty Rev):1889 (<https://doi.org/10.12688/f1000research.16439.1>)

Latest published: 03 Dec 2018, 7(F1000 Faculty Rev):1889 (<https://doi.org/10.12688/f1000research.16439.1>)

Abstract

The inhibitor of apoptosis proteins (IAPs) are a family of proteins that were chiefly known for their ability to inhibit apoptosis by blocking caspase activation or activity. Recent research has shown that cellular IAP1 (cIAP1), cIAP2, and X-linked IAP (XIAP) also regulate signaling by receptors of the innate immune system by ubiquitylating their substrates. These IAPs thereby act at the intersection of pathways leading to cell death and inflammation. Mutation of IAP genes can impair tissue homeostasis and is linked to several human diseases. Small-molecule IAP antagonists have been developed to treat certain malignant, infectious, and inflammatory diseases. Here, we will discuss recent advances in our understanding of the functions of cIAP1, cIAP2, and XIAP; the consequences of their mutation or dysregulation; and the therapeutic potential of IAP antagonist drugs.

Keywords

IAP, cell death, innate receptors signalling, inflammation, smac-mimetic

Open Peer Review

Referee Status:  

	Invited Referees	
	1	2
version 1 published 03 Dec 2018		

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

- 1 **Christine J Hawkins**, La Trobe University, Australia
- 2 **Mads Gyrd-Hansen**, University of Oxford, UK

Discuss this article

Comments (0)

Corresponding authors: Najoua Lalaoui (lalaoui@wehi.edu.au), David Lawrence Vaux (vaux@wehi.edu.au)

Author roles: **Lalaoui N:** Conceptualization, Funding Acquisition, Writing – Original Draft Preparation, Writing – Review & Editing; **Vaux DL:** Funding Acquisition, Writing – Review & Editing

Competing interests: DLV was on the scientific advisory board of TetraLogic, and he and NL have patent applications related to birinapant.

Grant information: This work was supported by project grant #1145588 from the Cancer Australia and Cure Cancer Australia Foundation (to NL), Victorian Cancer Agency Mid-career Fellowship #17030 (to NL), Australian National Health and Medical Research Council (NHMRC) Program Grant #1113133 (to DLV), NHMRC Fellowship #1020136 (to DLV), and Leukemia and Lymphoma Society SCOR grant #7001-13 (to DLV). This work was made possible by operational infrastructure grants through the Australian government's Independent Research Institute Infrastructure Support Scheme and the Victorian state government's Operational Infrastructure Support.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2018 Lalaoui N and Vaux DL. This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Lalaoui N and Vaux DL. **Recent advances in understanding inhibitor of apoptosis proteins [version 1; referees: 2 approved]** *F1000Research* 2018, 7(F1000 Faculty Rev):1889 (<https://doi.org/10.12688/f1000research.16439.1>)

First published: 03 Dec 2018, 7(F1000 Faculty Rev):1889 (<https://doi.org/10.12688/f1000research.16439.1>)

Introduction

The inhibitor of apoptosis proteins (IAPs) are a family of proteins that were first identified in insect baculoviruses^{1,2}. These viral IAPs were found to block defensive apoptosis in order to facilitate viral replication^{1,2}. Subsequently, cellular homologs have been identified in both invertebrates and vertebrates. Like viral IAPs, some cellular IAPs can inhibit apoptosis. Cellular and viral IAPs are characterized by the presence of baculoviral repeat domain (BIR) repeats. This review will focus on the most intensively studied mammalian IAPs, which are cellular IAP1 (cIAP1), cIAP2, and X-linked IAP (XIAP).

Mammalian IAPs were initially thought to inhibit cell death only by directly binding to caspases. However, only XIAP is able to bind caspase-3 and -9^{3,4}. Upon apoptotic stimuli, IAP inhibitors, including Smac/Diablo and HtrA2/Omi, are released from the mitochondria and bind to XIAP's BIR domains, releasing active caspases into the cytosol⁵. Unlike XIAP, cIAP1 and 2 are poor direct caspase inhibitors⁶. Instead, they bind to tumor necrosis factor (TNF) receptor-associated factors (TRAFs) via their BIR1 domains⁷ to block cell death induced by TNF receptor 1 (TNFR1) by promoting the activation of signaling pathways that induce the expression of pro-survival proteins.

Recent advances in understanding of IAP function from genetics, biochemistry, structural biology, and medicinal chemistry have shown that IAPs have roles beyond inhibiting cell death. All three IAPs have a carboxy-terminal RING (really interesting new gene) domain that allows them to act as ubiquitin E3 ligases that can ubiquitylate associated proteins as well as themselves. IAPs can regulate innate immune responses by limiting non-canonical nuclear factor kappa B (NFκB) signaling, promoting canonical NFκB and mitogen-activated protein kinase (MAPK) signaling, and inhibiting both caspase-dependent and -independent cell death. Drugs that antagonize IAPs, termed "Smac-mimetics", have been developed to promote the death of cancer cells and those bearing intracellular infections. Use of these drugs in pre-clinical models has revealed additional roles of IAPs that might be exploited to treat certain inflammatory conditions and to enhance anti-tumor immunity.

IAP and TNF signaling

TNF-induced survival

Despite its name, TNF does not induce cell death in the majority of cell types. However, cell death can occur when canonical NFκB activation is delayed or blocked. Binding of TNF to TNFR1 induces the recruitment of TRADD, RIPK1, TRAF2, and cIAP1 and 2 to form complex I at the plasma membrane. cIAP1 binds to TRAF2 through both its BIR1 and its UBA domains^{8–11}. Within complex I, cIAP1 and 2 conjugate K11-, K48-, and K63-linked ubiquitin chains to themselves and other complex I components such as RIPK1^{12–16}. cIAP-mediated ubiquitylation of components of complex I leads to the recruitment of the linear ubiquitin chain assembly complex (LUBAC), which in turn linearly ubiquitylates several components of the complex I, including TNFR1, TRADD, RIPK1, or NEMO^{17–22}. Both K63-linked and linear ubiquitin chains serve as docking sites for TAB2/3/TAK1 and the IKK subunit NEMO^{23–27}. Subsequently, TAK1

phosphorylates IKK2 and MAPK kinases²⁸, leading to the transcription of NFκB-dependent and MAPK-dependent genes that induce inflammation, proliferation, and cell survival (Figure 1).

According to this model, ubiquitylation of RIPK1 mediated by cIAP1 and 2 and LUBAC serves as a scaffold to activate NFκB and MAPK, providing inflammatory and survival outcomes (Figure 1). However, several reports have questioned parts of this model. For instance, in Jurkat T cells lacking RIPK1, there was no activation of NFκB in response to TNF, suggesting a requirement for RIPK1 so that TNF could activate NFκB. In contrast, in primary fibroblasts and T cells, TNF was able to activate NFκB in the absence of TRADD or RIPK1^{24,29–32}. Similarly, the deletion of cIAP1/2 genes markedly delayed, but did not prevent, TNF-induced activation of NFκB in mouse embryonic fibroblasts (MEFs)^{11,33}. Observations such as these have led to a proposal that TNF induces two waves of IKK activation occurring a few minutes apart³⁴. The first is dependent on RIPK1 ubiquitylation and the second on LUBAC recruitment, which allows further recruitment of IKKs³⁴. It is therefore plausible that the first early wave has at times been missed and this could explain why in some cell types RIPK1 has been found to be dispensable for canonical NFκB activation³⁴. It also might account for why the loss of LUBAC components reduces or delays the activation of NFκB by TNF^{18–21,35–39}. However, because both waves depend on TRAF2 and cIAP1, this does not explain how canonical NFκB is activated in the absence of cIAP1 and 2. Perhaps, in some cell types, in the absence of cIAP1 and 2, there are backup signaling mechanisms to ensure the transcription of survival and inflammatory genes. In other cell types, the absence of backup signaling would terminate the inflammatory response.

TNF-induced cell death

While there remains uncertainty about whether cIAP1 and 2 are absolutely necessary for activation of the canonical NFκB pathway, there is general agreement that IAPs prevent TNF-induced cell death. Internalization of complex I leads to the recruitment of FADD, caspase-8, and RIPK3, forming a cytosolic cell death-promoting platform referred to as complex II^{40,41}. Signaling from complex I stimulates transcription of the *CFLAR* gene encoding cFLIP, a structural homolog of caspase-8 that lacks caspase activity. Binding of cFLIP to caspase-8 limits caspase-8 activity so that a restricted number of substrates, such as RIPK1, are cleaved whereas others, such as pro-caspase-3 or Bid, are not^{42–45} (Figure 1).

Cleavage of RIPK1 is believed to allow the dissociation of complex II and also prevents RIPK1 from oligomerizing with RIPK3 (another substrate of the cFLIP/caspase-8 heterodimer). Accordingly, if caspase-8 activity is compromised, uncleaved RIPK1 and 3 oligomerize to form a complex called the necrosome, in which RIPK3 is auto-phosphorylated and in turn phosphorylates MLKL, which causes a form of cell death known as necroptosis^{41,46,47}. Consistent with the role for cIAP1 and 2 as ubiquitin ligases for RIPK1, the absence of, a decrease in, or mutation of the BIR or UBA domains of cIAP1 and 2 allows RIPK1 to remain or become deubiquitylated, so that complex I more rapidly transitions into complex II, promoting cell death^{11,15,48}.

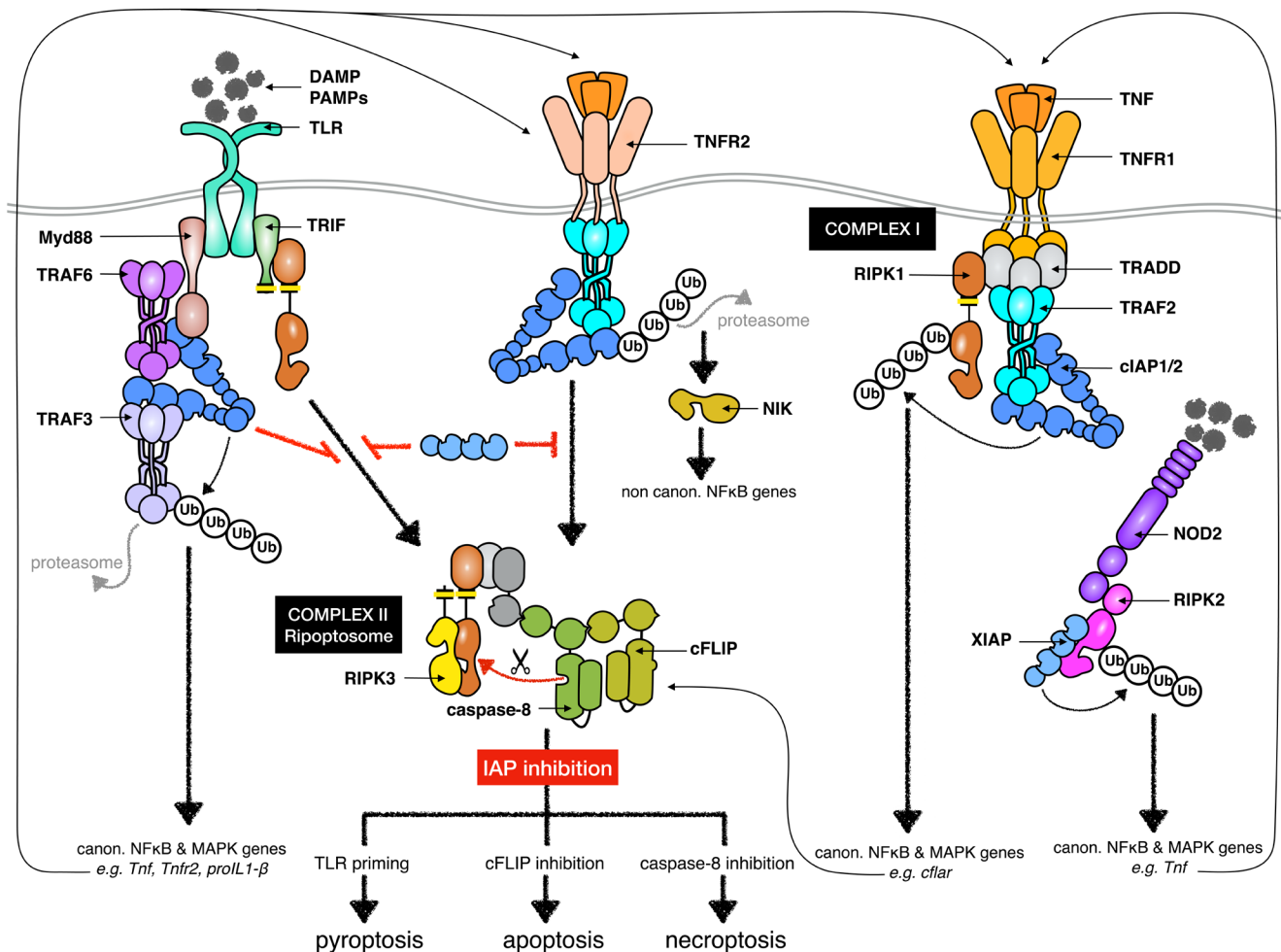


Figure 1. Regulation of innate receptor signaling pathways by inhibitors of apoptosis proteins (IAPs). Tumor necrosis factor (TNF) binding to TNF receptor 1 (TNFR1) triggers complex I formation, in which cIAP1 and 2 ubiquitylate RIPK1. This leads to the induction of canonical (canon.) nuclear factor kappa B (NFκB)- and mitogen-activated protein kinase (MAPK)-dependent genes, including *cflar* encoding cFLIP. Subsequently, cytosolic complex II containing FADD, caspase-8, RIPK1, RIPK3, and cFLIP is formed. In this complex, cFLIP inhibits caspase-8 activation to block apoptosis and necroptosis. Inhibition of cIAP1 and 2 by Smac-mimetic drugs impairs canonical NFκB activation and accelerates the formation of complex II, which leads to apoptosis. When caspase-8 activation is blocked within complex II, RIPK1 and 3 are not cleaved and necroptosis is activated. Stimulation of nucleotide-binding oligomerization domain 1/2 (NOD1/2) receptors induces RIPK2 ubiquitylation by XIAP and activates the transcription of NFκB- and MAPK-dependent cytokines such as TNF, which amplifies the inflammatory signal. Binding of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) to Toll-like receptors (TLRs) leads to the recruitment of the Myd88/TRAF3/6/cIAP1/2 complex. Within this complex, cIAP1 and 2 ubiquitylate TRAF3, inducing its degradation and increasing the expression of cytokines and chemokines. The other TLR adaptor, TRIF, recruits RIPK1 via its RIP homotypic interaction motif (RHIM) domain (yellow). Upon TLR activation, inhibition of IAPs by Smac-mimetics promotes the formation of the ripoptosome, which has a composition similar to that of complex II. TLR-induced expression of TNF and TNFR2 triggers cIAP1/2 degradation and a subsequent accumulation of NFκB-inducing kinase (NIK), which activates non-canonical (non canon.) NFκB-dependent genes. In the context of XIAP deficiency, the degradation of cIAP1 and 2 by TNFR2 leads to the formation of complex II. Activation of complex II or the ripoptosome can activate pyroptosis after TLR priming. TRAF, tumor necrosis factor receptor-associated factor.

This would have an immediate effect in addition to the slower effect of reduced activation of NFκB leading to less production of cFLIP (Figure 1).

In some circumstances, the absence of just XIAP can also allow TNF to induce cell death, but less is known about how this occurs, compared with induction of cell death in the absence of

cIAP1 and 2^{49,50}. It has been speculated that XIAP blocks RIPK1 ubiquitylation within complex II in a RIPK3-dependent manner⁵⁰. Consistent with this, ubiquitylated RIPK1 species are present in complex II or the necrosome when all IAPs are inhibited⁵¹. Perhaps cIAP1 and 2 ubiquitylate RIPK1 in complex I, thus limiting RIPK1's entry into complex II, whereas XIAP limits RIPK1's ubiquitylation within complex II to block its activation.

It is important to note that, in some cells, inhibition of cIAP1 and 2 can allow spontaneous formation of a RIPK1/FADD/caspase-8/FLIP complex called the “riposome” independently of the addition of TNF or other death ligands such as TRAIL and FasL^{52,53}. Formation and activation of this complex are further enhanced in the absence of XIAP^{52–54} (Figure 1). Whereas the role of cIAP1 and 2 in limiting riposome formation is likely to be due to decreased RIPK1 ubiquitylation, the exact role of XIAP in inhibiting riposome formation is not known.

IAPs and microbial sensors

Toll-like receptors and inflammasomes

Toll-like receptors (TLRs) recognize pathogen-associated and damage-associated molecular patterns known as PAMPs and DAMPs, respectively. TLRs transduce signals through the adaptor proteins MyD88 and TRIF⁵⁵. When PAMPs and DAMPs bind TLRs, those dependent on MyD88 recruit TRAF6, and the TRIF-dependent TLRs recruit both TRAF6 and TRAF3. TRAF6 activates NFκB and MAPK, whereas TRAF3 is believed to decrease activity of the MAPK signaling pathway and mediate IRF3-dependent production of type I interferon (IFN)⁵⁵. It has been proposed that, in the MyD88 complex, TRAF6 K63 ubiquitylates cIAP1 and 2^{56,57}. By K48 ubiquitylating TRAF3, cIAP1/2 cause its degradation and limit MAPK-dependent production of cytokines and chemokines without affecting the production of type I IFN⁵⁶ (Figure 1). Another study suggested that cIAP1 and 2 function in concert with TRAF2/3 to mediate the degradation of c-Rel and IRF5, limiting the production of pro-inflammatory cytokines⁵⁸.

Although there are only a few reports on the role of IAPs in regulating TLR-induced production of cytokines, there is a substantial body of work showing that IAPs block cell death induced by TLRs. IAPs prevent TLR-dependent riposome formation and a TLR-dependent, inflammasome-induced form of cell death termed “pyroptosis”. TRIF is the adaptor that links TLRs to the riposome, mediated by its RIP homotypic interaction motif (RHIM) domain that binds to the RHIM domains of RIPK1/3⁵⁹. Upon TLR stimulation, formation and activation of the riposome are limited by IAPs^{52,60}. Accordingly, inhibition of IAPs by Smac-mimetics sensitizes cells to TLR-induced apoptosis and necroptosis^{54,59–63} (Figure 1).

IAPs also play key roles in limiting pyroptosis, but there are conflicting views on how they do so. The nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family constitutes some of the sensors that trigger the formation of inflammasomes when they are bound by PAMPs or DAMPs in the cytoplasm. Their oligomerization results in (a) caspase-1 activation leading to pyroptosis to clear stressed cells and pathogens and (b) cleavage of interleukin-1 beta (IL-1β) to alert the immune system. Whereas Labbé *et al.*⁶⁴ found that cIAP1 and 2 are obligatory for IL-1β processing, other groups failed to find a role for cIAP1 and 2 in IL-1β maturation but instead showed that XIAP together with cIAP1 and 2 acted in the opposite way by preventing the cleavage of IL-1β^{50,54,63–66}. Labbé *et al.* showed that in macrophages cIAP1 and 2 K63 ubiquitylate caspase-1 to enhance NLRP3 and NLRC4 inflammasome activity⁶⁴. In contrast, other groups found that all three IAPs limit caspase-8-dependent activation of IL-1β processing^{50,54,63,65,66}.

In macrophages, dendritic cells, and neutrophils bearing XIAP-null or -RING mutations, TLR ligation was sufficient to drive IL-1β maturation and NLRP3 activation^{50,54,63,65,66}. TLR stimulation promoted the expression of both TNF and TNFR2⁶³. Binding of TNF to TNFR2 caused cIAP degradation^{63,67}. Thus, in the absence of XIAP, TNFR2-induced cIAP degradation allows the formation of TNFR1-dependent complex II as well as the TRIF-dependent riposome^{50,54,63,65,66}. In these complexes, activated caspase-8 leads to IL-1β processing by both NLRP3-dependent and -independent mechanisms^{50,54,63,65,66} (Figure 1). Accordingly, combined depletion of XIAP and cIAP1 and 2 profoundly enhanced IL-1β cleavage^{50,54,63,65,66}. Importantly, RIPK3 was also required for IL-1β processing when IAPs were inhibited^{50,54,65,66}. Upon IAP inhibition, RIPK3 seems to enhance caspase-8 activity and the consequent processing of IL-1β^{63,65}.

The differences in these observations could be due to the different genetic backgrounds of the knockout mice. Labbé *et al.* used cIAP1/2 knockout mice generated in a 129/sv background. 129/sv strains also carry a passenger mutation that inactivates caspase-11. cIAP1 and caspase-11 genes are too close in the genome to be segregated by recombination, even after extensive backcrossing⁶⁸. Therefore, all cIAP1 (and potentially cIAP2) knockout mice generated in a 129/sv background are likely to be mutant for caspase-11⁶⁸. Because caspase-11 can cleave IL-1β in the NLRP3 non-canonical inflammasome, the effect seen in 129/Sv cIAP1 (and potentially cIAP2) knockouts might be due to non-functional caspase-11⁶⁹.

Although the main activator of IL-1β is caspase-1, a role for caspase-8 in IL-1β maturation has been supported by several studies. Caspase-8 can mediate cleavage and secretion of IL-1β downstream of TLR and Fas signaling pathways, in the context of bacterial or fungal infections, during endoplasmic reticulum stress, or upon chemotherapeutic drugs^{70–77}. None of these reports showed that IAPs had to be absent for caspase-8 to process IL-1β. However, it is worth keeping in mind that TLR signaling drives the expression of TNFR2, which in turn induces the degradation of cIAP1 and 2⁶³. Therefore, it is plausible that bacteria or fungi that trigger TLRs reduce cIAP1/2 levels, leading to activation of complex II and the riposome. In addition, some pathogens, such as *Shigella*, can both directly and indirectly inhibit cIAP1/2 functions, leading to activation of the inflammasome^{78,79}. Similarly, it has been shown that chemotherapeutic drugs, such as etoposide, decrease IAP levels and trigger riposome formation⁵³. A role for RIPK3 in promoting IL-1β processing has also been reported by others^{73,80}. The exact molecular mechanism by which RIPK3 regulates IL-1β processing is still under investigation, but there is evidence that, in the absence of IAPs, RIPK3 favors ubiquitylation of RIPK1 and caspase-8, which presumably facilitates their activation within complex II or the riposome^{50,51,63,65,81}. All together, these studies indicate that IAPs not only restrict RIPK1's cytotoxic function but also prevent RIPK3 from enhancing IL-1β secretion.

NOD signaling

NOD1 and NOD2 are intracellular members of the NLR family that recognize bacterial peptidoglycan derivatives. Their ligation leads to NFκB- and MAPK-dependent production of inflammatory mediators. IAPs regulate the NOD1/2 signaling

pathway, and XIAP is the key player. Just as TNFR1 triggers cIAP1/2-mediated ubiquitylation of RIPK1 in complex I, NOD2 stimulation induces XIAP-mediated RIPK2 polyubiquitylation, which serves as a platform to recruit TAK1 and the IKKs^{82–84}. XIAP interacts via its BIR2 with the kinase domain of RIPK2 to ubiquitylate RIPK2, presumably on lysines 209, 410, and 538^{84–88}. RIPK2 ubiquitylation by XIAP recruits LUBAC, which in turn linearly ubiquitylates RIPK2, increasing the recruitment of IKK subunits⁸⁹ (Figure 1). Accordingly, deficiency of XIAP in mice completely abrogates NOD1/2 signaling and reduces responses to *Listeria* and *Chlamydomonas pneumoniae* infections^{49,89,90}. Importantly, several studies have demonstrated that the ortholog of XIAP in *Drosophila*, DIAP2, is essential to resist Gram-negative bacterial infection^{91–95}. These studies in flies demonstrated an evolutionarily conserved function of XIAP in regulating innate immunity.

It has been reported that, in addition to XIAP, cIAP1 and 2 can mediate the ubiquitylation of RIPK2; however, the exact role of this ubiquitylation in NOD2 signaling is still under debate^{86,89,96–98}. Although there is general agreement that cIAP1 regulates NOD1/2 signaling, the mechanisms proposed differ. Bertrand *et al.* proposed that cIAP1/2-mediated ubiquitylation of RIPK2 favors activation of NFκB and MAPK induced by NOD2⁹⁶. In contrast, although several studies showed that loss of cIAP1 and 2 affects RIPK2 ubiquitylation^{86,89,96}, two groups did not find evidence that cIAP1 and 2 directly regulate NOD2-induced NFκB and MAPK activation^{86,98}. Instead, it has been proposed that cIAP1 increases NOD2-induced cytokine production through a TNFR1 signaling pathway⁹⁸ (Figure 1). Consistent with this, TNFR1 knockout mice have a blunted response to NOD2 stimulation⁹⁸. As with the discordant views of how cIAP1 and 2 regulate the inflammasome, these discrepancies might be due to the use of cIAP knockouts generated in different genetic backgrounds (129/sv versus C57BL/6J) and the use of different methods to stimulate NOD signaling (DOTAP versus IFNγ priming)^{96,98}.

Conversely, there is no doubt that XIAP plays an essential role in NOD signaling. Its importance is reflected by the existence of XIAP mutations contributing to human diseases in which defects in NOD signaling play a role in the pathogenesis^{86,99–101}. XIAP deficiency in humans causes a rare immunodeficiency syndrome characterized by high susceptibility to viruses such as Epstein–Barr virus (EBV), cytomegalovirus (CMV), or herpesvirus 6¹⁰². This syndrome is frequently referred to as X-linked lymphoproliferative disease 2 (XLP2) because the first reported XLP2 patients showed a susceptibility to EBV infections like that in XLP1 patients¹⁰³. However, this classification is currently under debate because so far no reported XIAP-deficient/XLP2 patient has developed lymphomas^{104–107}. XIAP-deficient patients are affected with a range of immunological defects that can occur independently of each other. These include hemophagocytic lymphohistiocytosis, recurrent splenomegaly, and inflammatory bowel disease (IBD) resembling Crohn's disease¹⁰². Given that NOD2 mutations are the strongest genetic factor associated with Crohn's disease^{108,109}, the pathological mechanism underlying IBD in XIAP deficiency is likely to be due to impaired

NOD signaling. Accordingly, like those from NOD2-associated Crohn's patients, cells from XIAP-deficient patients have reduced responses to NOD2 activation^{86,99–101}. On the other hand, it has been shown that NOD signaling can sense viral products^{110,111}. Thus, the impaired response to NOD signaling in XIAP-deficient patients might contribute to their susceptibility to viral infections.

Nevertheless, defects in NOD signaling do not account for all of the signs and symptoms seen in XIAP deficiency. The role for XIAP in regulating apoptosis and the inflammasome also appears in other clinical manifestations. For instance, adaptive and innate-like T lymphocytes from XIAP patients are more sensitive to cell death induced by death receptors *in vitro*^{103,104,106}. This propensity to apoptosis might compromise immune responses during viral infections. In addition, it is important to note that, although there is no direct proof of a role in aberrant inflammasome activation, some XIAP patients had high levels of IL-18 in their bloodstream¹¹². Like IL-1β, IL-18 is cleaved and released upon inflammasome activation. Given that loss of XIAP in mice can activate the inflammasome, it is plausible that loss of XIAP function in these patients drives the secretion of IL-18 and the consequent associated inflammatory phenotypes.

IAPs and tissue homeostasis

Gene deletion

Different genetic knockouts and mutants of murine genes for XIAP, cIAP1, and cIAP2 have revealed that they work in overlapping and partially redundant ways to ensure proper embryonic development and tissue homeostasis. Mice lacking cIAP1 or 2 or XIAP are viable with no overt phenotype^{48,113,114}. However, unlike the co-deletion of *Xiap/Birc4* and *Ciap2/Birc3*, which leads to viable mice, co-deletion of *Ciap1/Birc2* and *Ciap2/Birc3*, or co-deletion of *Ciap1/Birc2* and *Xiap/Birc4*, results in early embryonic lethality on a pure C57BL/6 background⁴⁸. This suggests that cIAP1 alone is enough to achieve all essential IAP functions and also that XIAP can co-operate with cIAP2 to accomplish cIAP1's functions. The lethality of mice lacking both XIAP and cIAP1 was nevertheless surprising. Because of the close linkage of cIAP1 and 2 genes (~15 kb), it has been assumed that they were the result of gene duplication and therefore might have redundant functions. Consistent with this idea, mice lacking XIAP and cIAP1 in a 129/Sv background are viable¹¹⁵. These opposite results might be due to the different genetic background of the mice. Thus, it is plausible that passenger mutations such as the mutation on *caspase-11* account for 129/Sv *Xiap^{-/-}Ciap1^{-/-}* viability. Conversely, Heard *et al.* found that the level of cIAP2 in the C57BL/6J *Xiap^{-/-}Ciap1^{-/-}* MEFs was greatly reduced, which could explain why C57BL/6J *Xiap^{-/-}Ciap1^{-/-}* mice were not viable¹¹⁵. The reason for the difference in cIAP2 levels between these two sets of *Xiap^{-/-}Ciap1^{-/-}* MEFs is still unclear. The use of CRISPR/Cas9 technology might help to determine whether cIAP2 can compensate cIAP1 when XIAP is absent^{115,116}.

The lethality of *Ciap1^{-/-}Ciap2^{-/-}* and *Xiap^{-/-}Ciap1^{-/-}* mice (on a pure C57BL/6J background) occurs at E10.5 and is caused by hemorrhages and cardiovascular failure⁴⁸. Similar lethal defects arose in *Fadd^{-/-}*, *Cflar^{-/-}*, *Casp8^{-/-}*, *Hoip^{-/-}*, and *Hoil^{-/-}* mutant

mice^{35,38,48,117–119}. Importantly, loss of *Casp8* or *Hoip* just in the endothelia phenocopied the E10 lethality, demonstrating that the cardiac defect and hemorrhages were due to an endothelial defect^{35,120}. Because IAPs, FADD, FLIP, caspase-8, and HOIP/HOIL all participate in the regulation of cell death induced by TNFR1, a common mechanism dependent on TNFR1 might account for the lethality in all of these knockouts. Accordingly, loss of *Tnfr1* delayed *Fadd*^{-/-}, *Casp8*^{-/-}, *Hoil*^{-/-}, *Hoip*^{-/-}, and *Ciap1*^{-/-}*Ciap2*^{-/-} lethality, suggesting that the TNFR1-mediated endothelial cell death is responsible for some defects during embryogenesis in all of these knockouts^{35,38,48,120,121}. It is important to note that deletion of cIAP1 in zebrafish leads to endothelial cell death, implying an evolutionary conservation of the functions of IAPs¹²².

Since cIAP1 and 2 ubiquitylate RIPK1, it seemed likely that lethality in IAP knockouts was due to aberrant TNFR1-mediated RIPK1 activation. Surprisingly, *Ripk1* loss rescued *Ciap1*^{-/-}*Ciap2*^{-/-} mice only to E12. Several subsequent reports helped explain why *Ripk1* loss did not prevent the defects seen in cIAP1/2 double mutants. Within complex II, cleavage of RIPK1 by the caspase-8/cFLIP heterodimers prevents RIPK1 from triggering full processing and activation of caspase-8⁴⁴. Furthermore, binding of RIPK1 to RIPK3 via their RHIM domains prevents RIPK3 activation by other RHIM domain-containing proteins such as TRIF or DAI^{123,124}. This implies that the *Ciap1*^{-/-}*Ciap2*^{-/-}*Ripk1*^{-/-} mice might die because of overwhelming caspase-8-dependent apoptosis and RIPK3-dependent necroptosis. Consistent with this idea, mutants lacking the other RIPK1 E3 ligases, *Hoil* and *Hoip*, which die at E10 from a cardiac defect similar to that in the *Ciap1*^{-/-}*Ciap2*^{-/-} mice, are rescued by co-deletion of genes for RIPK1, RIPK3, and caspase-8³⁸. Whether the combined absence of RIPK1, RIPK3, and caspase-8 would rescue *Ciap1*^{-/-}*Ciap2*^{-/-} double mutants needs to be determined but would show whether cIAP1 and 2 act at the same level as HOIL/HOIP.

Although XIAP deficiency causes primary immunodeficiencies in humans, *Xiap*^{-/-} mice are healthy¹¹³. This difference might be due to the fact that environmental factors such as pathogens also play a role in the pathogenesis of human diseases. Accordingly, unchallenged *Xiap*^{-/-} mice housed in clean facilities with controlled environments had no phenotype, but when they were challenged with pathogens they developed syndromes resembling those in XIAP-deficient patients, such as splenomegaly and increased cytokine production^{49,50,90,125}. The role for cIAP1 and 2 in the gut was recently investigated. The authors showed that levels of IAPs were particularly low in enterocytes, consistent with their susceptibility to TNF-induced cell death¹²⁶. Whereas responses to TNF were similar in intestinal epithelial cells from wild-type, *Xiap*^{-/-}, and *Ciap2*^{-/-} mice, those from *Ciap1*^{-/-} mice died much more readily, highlighting a critical role for cIAP1 in intestinal homeostasis during infection¹²⁶. This implies that although an association of cIAP1 mutations with IBD has not been reported, low levels of cIAP1 might contribute to TNF-mediated enteropathies.

Insights from tissue-specific knockouts

Tissue-specific IAP knockout mice have provided insights into how IAPs regulate inflammation in particular tissues. For instance,

combined deletion of genes for cIAP1 and 2 in the myeloid lineage is sufficient to cause a mild inflammatory phenotype characterized by splenomegaly with disrupted splenic architecture and arthritis^{63,127}. Although the loss of both XIAP and cIAP1 in mice did not cause any overt phenotype, the combined loss of both cIAP1/2 and XIAP severely worsened the pathology seen in myeloid-specific *Ciap1*^{-/-}*Ciap2*^{-/-} mice^{63,127}. The sterile inflammation was associated with abnormally high levels of cytokines and chemokines in the bloodstream^{63,127}. *In vitro* studies in macrophages revealed that the absence of IAPs leads to the spontaneous production of cytokines, including TNF¹²⁷. Furthermore, this cytokine production depended on the presence of both RIPK1 and 3, which subsequently activated apoptosis and necroptosis^{63,65,127}. In addition, lipopolysaccharide challenge of *Ciap1*^{-/-}*Ciap2*^{-/-} macrophages triggered IL-1 β secretion and pyroptosis in a RIPK3-dependent manner^{63,65}. All together, these findings demonstrated that all three IAPs repress RIPK1/3-mediated cytokine production and cell death. Many other studies have proposed that RIPK1 and 3 control cytokine production in different inflammatory settings, yet the exact molecular mechanisms remain enigmatic^{127–131}.

Strikingly, the deletion of both cIAP1 and 2 in the epidermis induced a lethal skin inflammation that occurred in the first week after birth¹³². Although the loss of cIAP1 in the skin combined with the loss of XIAP did not induce a lethality, these mice developed skin inflammation in adulthood¹³². Similarly, injection of a pan Smac-mimetic into the skin of adult mice led to the development of inflammatory skin lesions¹³². These findings highlight a vital role for these proteins in skin development and homeostasis, in which cIAP1 plays a major role. Interestingly, the early lethality of mice lacking both cIAP1 and 2 in the skin phenocopied the effects observed in skin-specific knockout of *Fadd*, *Casp8*, *Hoil*, and *Hoip*^{39,133,134}. All of these skin knockout mice developed epidermal hyperplasia accompanied by the death of keratinocytes and high levels of cytokines in the skin^{132–134}. Remarkably, the loss of one allele of *Ripk1* delayed the death of the *Ciap1*^{-/-}*Ciap2*^{-/-} epidermal knockouts to weaning and completely inhibited skin inflammation caused by Smac-mimetic injection¹³². Importantly, like the loss of cFLIP in the skin of adult mice, depletion of all IAPs with Smac-mimetic in adult mice led to skin lesions resembling a human inflammatory skin disease called toxic epidermal necrolysis^{132,135}. On one hand, an inactivating mutation on the gene encoding the LUBAC component SHARPIN caused a form of dermatitis with features seen in psoriasis and eczema¹³⁶. Just as the deletion of one allele of *Ripk1* greatly reduced the severity of the lesions in skin lacking cIAP1 and 2, it also significantly delayed the *Sharpin* mutant skin phenotype¹³². Importantly, crossing to mice bearing a mutation that inactivated RIPK1's kinase activity provided a complete rescue of the *Sharpin* mutant phenotype¹³⁷. Collectively, these findings provide the rationale to test RIPK1 inhibitors in inflammatory skin diseases. In this line, GlaxoSmithKline (Brentford, UK) has an ongoing clinical trial testing RIPK1 inhibitors for the treatment of psoriasis (ClinicalTrials.gov Identifier: NCT02776033).

The deletion of genes for cIAP1 and 2 in B cells did not induce lymphocyte cell death but instead provided a survival advantage¹³⁸. The accumulation of B cells *in vivo* was thought to be

caused by the activation of the non-canonical NF κ B pathway. This pathway is activated by a subset of TNFR members and relies on the stability of the NF κ B-inducing kinase (NIK). In cells not exposed to cytokine, the degradation of NIK is triggered by its ubiquitylation by a complex of TRAF2 and 3 and cIAP1 and 2^{56,139–142}. Consistent with this, the mutation or deletion of genes for TRAF2 or 3 or cIAP2 has increased levels of NIK, leading to spontaneous activation of non-canonical NF κ B and abnormal accumulation of B cells^{138,143,144}.

Therapeutic interventions targeting IAPs

Targeting IAPs to treat inflammatory and infectious diseases

Activating mutations in NOD2 have been associated with early onset sarcoidosis and Blau syndrome as well as early onset IBD^{145,146}. Different strategies have been proposed to target NOD2 signaling to treat these diseases. Several groups showed that kinase inhibitors targeting RIPK2 can inhibit NOD signaling *in vitro* and *in vivo* and provide therapeutic responses in mouse models of multiple sclerosis and Crohn's disease-like ileitis and also in Crohn's and colitis patient samples^{147–152}. The primary assumption was that these kinase inhibitors act by blocking RIPK2's kinase activity. However, RIPK2 kinase-dead expressing cells had normal responses to NOD stimulation^{88,152}. Thus, these inhibitors might act via an allosteric mechanism to interfere with the interaction of RIPK2 with IAPs^{148,152}. These studies highlighted the IAP–RIPK2 interaction as a pharmacological target and prompted other researchers to generate XIAP antagonists to disrupt this interaction to block NOD signaling⁸⁸. In contrast to pan IAP antagonists, Smac-mimetics that preferentially target XIAP's BIR2 domain did not induce cell death⁸⁸. Instead, these compounds affected XIAP–RIPK2 binding and inhibited NOD2 signaling⁸⁸. The promiscuity of many kinase inhibitors compared with the specificity with which the XIAP BIR2 domain regulates NOD signaling¹⁵³ renders XIAP antagonists particularly attractive for therapeutic intervention. However, given the role for XIAP in limiting IL-1 β secretion (see the “Toll-like receptors and inflammasomes” section), it will be important to test the effect of targeting XIAP BIR2 on inflammasome activity.

Suicide of infected cells is one of the strategies that the immune system uses to limit pathogen dissemination and latent reservoirs. Recently, some studies suggested that targeting IAPs could be a therapeutic approach to kill human immunodeficiency virus (HIV)- and hepatitis B virus (HBV)-infected cells. Despite the success of anti-viral therapies, HIV persists because of long-lived, latently infected cells that hide from the immune system. The “shock and kill” treatment strategy consists of reactivating the viral replication of latent virions. The infected cells then would be killed either by the virus itself or by the patient's immune system. It has been shown that Smac-mimetics can kill long-lived HIV infected CD4⁺ T cells or HIV-infected macrophages^{154,155}. In addition, one study suggested that the activation of the non-canonical NF κ B pathway because of inhibition of cIAP1 and 2 by a Smac-mimetic is able to reactivate the replication of latent viruses¹⁵⁶. Pache *et al.* showed that the non-canonical transcription factor RELB associates with the viral long terminal repeat to directly influence HIV transcription¹⁵⁶.

The combination of a Smac-mimetic and latency-reversing agents can synergistically reverse latency in resting CD4⁺ T cells, providing the opportunity for these cells to be attacked by the immune system and/or killed by Smac-mimetics themselves^{156,157}. All together, these findings suggest that Smac-mimetics might be used to eliminate latent HIV reservoirs, as they can simultaneously “shock” and “kill” latent infected cells.

Viral latency is also a challenge in HBV infection, as it predisposes to cirrhosis and hepatocellular carcinoma. TNF is an important cytokine promoting HBV clearance^{158,159}. Taking advantage of the importance of TNF in HBV, Ebert *et al.* explored IAP inhibition to switch TNF-induced viral clearance to TNF-induced cell death^{158,160}. They found that the deletion of IAP genes or treatment with Smac-mimetics induced early viral clearance^{158,160}. IAP inhibition led to cell death of HBV-infected hepatocytes in a TNF-dependent manner with no collateral damage or liver failure. In addition, Smac-mimetics enhanced the efficacy of the standard drug used to treat HBV, entecavir¹⁵⁸. These findings led to a phase I/IIa study of the Smac-mimetic birinapant for the treatment of HBV carriers (ClinicalTrials.gov Identifier: NCT02288208). Unfortunately, this trial had to stop because of temporary cranial nerve palsies observed in the first cohort. This adverse event has also been observed in patients with cancer treated with two Smac-mimetics including birinapant, suggesting that it might not be due to HBV infection^{161,162} (ClinicalTrials.gov Identifier: NCT01188499).

Targeting IAPs to treat cancer

The ability of IAPs to promote cell survival, and their elevated expression in many cancers, prompted efforts to target them to treat cancers^{163,164}. Different approaches were adopted to inhibit IAPs. One was to develop peptidomimetics based on the region of Smac/Diablo that binds to XIAP's BIR domains, so-called “Smac-mimetics”. Although these drugs were initially designed to target the BIR domains of XIAP because of the similarity to the BIRs of other IAPs, most Smac-mimetics also bind to cIAP1 and 2. It was originally thought that Smac-mimetics would induce cell death because their binding to IAPs would release active caspases in the cytosol. However, their mode of action is mainly via their ability to induce auto-ubiquitylation and degradation of cIAP1 and 2, which leads to activation of the non-canonical NF κ B pathway with reduced signals activating canonical NF κ B. Although there is no clear experimental proof, it is believed that the non-canonical NF κ B pathway is responsible for autocrine TNF secretion. In the absence of cIAP1 and 2, binding of autocrine TNF to TNFR1 triggers the formation of complex II, which kills the cancer cells. To improve the efficacy of Smac-mimetics, several groups used the strategy of combining them with drugs that increase TNF secretion. Cytokines induced by some chemotherapeutic agents would be expected to act synergistically with Smac-mimetics. Similarly, the cytokine storm induced by non-pathologic oncolytic viruses increased Smac-mimetic killing¹⁶⁵. In addition, our group found that p38 inhibitors and caspase inhibitors increased TNF production in response to Smac-mimetics and consequently increased the amount of cell killing^{166,167}. Although high levels of TNF can be a safety concern, these three combinations were proven to be well tolerated in mice^{165–167}.

Mice mutant for IAPs helped determine which IAP would be best to target to find a safe therapeutic window. Targeting all three IAPs is highly inflammatory because it unleashes the inflammatory functions of RIPK1 and 3 which leads to the secretion of not only TNF but also the inflammasome-related cytokines IL-1 β and IL-18^{50,54,63,65,66}. The inflammatory phenotypes observed in the different IAP mutant mice and cells suggest that an ideal Smac-mimetic should strongly target cIAP1 and less cIAP2 or XIAP or both. This has been exemplified by the comparison of two Smac-mimetics presenting different affinities to each IAP¹⁶⁸. Indeed, the pan Smac-mimetic CompA (K_d <1 nM for all IAPs) was not tolerated in mice, as it caused widespread severe weight loss and skin lesions^{132,168}. In contrast, the Smac-mimetic birinapant, which binds strongly to cIAP1 but has lower affinity for cIAP2 and XIAP, was generally well tolerated in mice and humans¹⁶⁸.

Another issue to consider is the malignancy of cell types that depend on the non-canonical NF κ B pathway to survive or to proliferate or both. Like the deletion of genes for cIAP1 and 2 in B cells that caused the proliferation of B cells, the depletion of IAPs by a Smac-mimetic enhanced the survival of B lymphoma cells because of activation of the non-canonical NF κ B pathway^{138,169}. Nevertheless, this survival advantage is potentially reversed by combining the Smac-mimetic with a proteasome inhibitor¹⁷⁰.

It is unlikely that Smac-mimetics will be used on their own to treat cancer. Several combination treatments have been reported to enhance Smac-mimetic-induced apoptosis and necroptosis^{163,164}. Necroptosis has recently emerged as a mechanism to allow killing of cells in which apoptotic pathways are blocked. Combined inhibition of IAPs and caspases triggered necroptosis in leukemia, pancreatic, colorectal, and ovarian cancer cells^{166,171–174}. Consistent with genetic studies, combining a Smac-mimetic with inhibition of caspase-8/cFLIP_L heterodimers using the clinical caspase inhibitor emricasan strongly triggered necroptosis in leukemic cells^{44,45,166}. Interestingly, in some samples of patients with acute lymphocytic leukemia (ALL), Smac-mimetics alone triggered necroptosis, possibly indicating that some ALL cases do not efficiently activate caspase-8¹⁷⁵. This suggests that Smac-mimetics might provide an alternative treatment for cancers that have silenced caspase-8¹⁷⁶.

Because it is a pro-inflammatory form of cell death, necroptosis can help trigger the immune system to attack cancers in a RIPK1-dependent manner^{177,178}. Smac-mimetics have been shown to play a role in anti-tumor immunity in different ways. Because these drugs promote RIPK1 activation, they might promote anti-tumor immunity in part by RIPK1-dependent cytokine production and necroptosis. Accordingly, Smac-mimetics can increase the production of death ligands, IFN γ and IL-2 by immune cells, as well as sensitizing cancer cells to the produced death ligands^{179–182}. Smac-mimetics can also enhance cytotoxic lymphocyte killing of tumor cells, decrease expression of the immune checkpoint PD1, polarize M2 macrophages into M1 macrophages, and reduce immunosuppressive T-cell functions^{181,183–186}. In contrast, inhibition of IAPs can increase the expression of the immune checkpoint PDL1, affect memory T cells, and polarize M1 macrophages into M2 macrophages, supporting the invasion and metastasis of tumor cells^{183,187,188}. All together, these

findings suggest that Smac-mimetics can act as a double-edged sword in anti-tumor immunity. The challenge now is to determine which combinations are best applied to specific tumor types.

Conclusions

The generation of IAP mutant mice has offered further insights into how these proteins coordinate innate immune responses. A large body of work has shown that, at the molecular level, IAPs regulate inflammation mainly through the ubiquitylation of RIPK1 and 2. Relatively little is known about other IAP substrates that might play important roles in inflammatory or other signaling pathways. Nevertheless, early findings suggest that IAPs regulate not only the ripoptosome, inflammasome, and apoptosome but also the autophagosome^{189,190}. The pleiotropic roles for IAPs mean that Smac-mimetics are not simply “killer drugs” but also induce cytokine production that impacts on immune anti-tumor responses. Although several Smac-mimetics have entered clinical trials to treat cancer and infectious diseases, the identification of molecular and immune biomarkers of response to Smac-mimetics is still lacking.

Abbreviations

ALL, acute lymphocytic leukemia; BIR, baculoviral repeat domain; cIAP1, cellular inhibitor of apoptosis 1; cIAP2, cellular inhibitor of apoptosis 2; DAMP, damage-associated molecular pattern; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IAP, inhibitor of apoptosis; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; LUBAC, linear ubiquitin chain assembly complex; MAPK, mitogen-activated protein kinase; MEF, mouse embryonic fibroblast; NF κ B, nuclear factor kappa B; NIK, NF κ B-inducing kinase; NLR, NOD-like receptor; NOD, nucleotide-binding oligomerization domain; PAMP, pathogen-associated molecular pattern; RHIM, RIP homotypic interaction motif; RING, really interesting new gene; TLR, Toll-like receptor; TNF, tumor necrosis factor; TNFR1, tumor necrosis factor receptor 1; TRAF, tumor necrosis factor receptor-associated factor; XIAP, X-linked IAP; XLP2, X-linked lymphoproliferative disease 2

Grant information

This work was supported by project grant #1145588 from the Cancer Australia and Cure Cancer Australia Foundation (to NL), Victorian Cancer Agency Mid-career Fellowship #17030 (to NL), Australian National Health and Medical Research Council (NHMRC) Program Grant #1113133 (to DLV), NHMRC Fellowship #1020136 (to DLV), and Leukemia and Lymphoma Society SCOR grant #7001-13 (to DLV). This work was made possible by operational infrastructure grants through the Australian government's Independent Research Institute Infrastructure Support Scheme and the Victorian state government's Operational Infrastructure Support.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

We apologize to the many people whose work we could not cite here because of space restrictions.

References



1. Crook NE, Clem RJ, Miller LK: **An apoptosis-inhibiting baculovirus gene with a zinc finger-like motif.** *J Virol.* 1993; 67(4): 2168–74.
[PubMed Abstract](#) | [Free Full Text](#)
2. Birnbaum MJ, Clem RJ, Miller LK: **An apoptosis-inhibiting gene from a nuclear polyhedrosis virus encoding a polypeptide with Cys/His sequence motifs.** *J Virol.* 1994; 68(4): 2521–8.
[PubMed Abstract](#) | [Free Full Text](#)
3. **F** Shiozaki EN, Chai J, Rigotti DJ, *et al.*: **Mechanism of XIAP-mediated inhibition of caspase-9.** *Mol Cell.* 2003; 11(2): 519–27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
4. Scott FL, Denault JB, Riedl SJ, *et al.*: **XIAP inhibits caspase-3 and -7 using two binding sites: evolutionarily conserved mechanism of IAPs.** *EMBO J.* 2005; 24(3): 645–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. Silke J, Vucic D: **IAP family of cell death and signaling regulators.** *Methods Enzymol.* 2014; 545: 35–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Eckelman BP, Salvesen GS: **The human anti-apoptotic proteins cIAP1 and cIAP2 bind but do not inhibit caspases.** *J Biol Chem.* 2006; 281(6): 3254–60.
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Rothe M, Pan MG, Henzel WJ, *et al.*: **The TNFR2-TRAF signaling complex contains two novel proteins related to baculoviral inhibitor of apoptosis proteins.** *Cell.* 1995; 83(7): 1243–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Samuel T, Welsh K, Lober T, *et al.*: **Distinct BIR domains of cIAP1 mediate binding to and ubiquitination of tumor necrosis factor receptor-associated factor 2 and second mitochondrial activator of caspases.** *J Biol Chem.* 2006; 281(2): 1080–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
9. Vince JE, Pantaki D, Feltham R, *et al.*: **TRAF2 must bind to cellular inhibitors of apoptosis for tumor necrosis factor (tnf) to efficiently activate nf-(kappa)b and to prevent tnf-induced apoptosis.** *J Biol Chem.* 2009; 284(51): 35906–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
10. **F** Zheng C, Kabaleeswaran V, Wang Y, *et al.*: **Crystal structures of the TRAF2: cIAP2 and the TRAF1: TRAF2: cIAP2 complexes: affinity, specificity, and regulation.** *Mol Cell.* 2010; 38(1): 101–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
11. Annibaldi A, Wicky John S, Vanden Berghie T, *et al.*: **Ubiquitin-Mediated Regulation of RIPK1 Kinase Activity Independent of IKK and MK2.** *Mol Cell.* 2018; 69(4): 566–580.e5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
12. Park S, Hatanpaa KJ, Xie Y, *et al.*: **The receptor interacting protein 1 inhibits p53 induction through NF-kappaB activation and confers a worse prognosis in glioblastoma.** *Cancer Res.* 2009; 69(7): 2809–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
13. Varfolomeev E, Goncharov T, Fedorova AV, *et al.*: **c-IAP1 and c-IAP2 are critical mediators of tumor necrosis factor alpha (TNFalpha)-induced NF-kappaB activation.** *J Biol Chem.* 2008; 283(36): 24295–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
14. **F** Mahoney DJ, Cheung HH, Mrad RL, *et al.*: **Both cIAP1 and cIAP2 regulate TNFalpha-mediated NF-kappaB activation.** *Proc Natl Acad Sci U S A.* 2008; 105(33): 11778–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
15. **F** Bertrand MJ, Milutinovic S, Dickson KM, *et al.*: **cIAP1 and cIAP2 facilitate cancer cell survival by functioning as E3 ligases that promote RIP1 ubiquitination.** *Mol Cell.* 2008; 30(6): 689–700.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
16. **F** Dynek JN, Goncharov T, Dueber EC, *et al.*: **c-IAP1 and UbcH5 promote K11-linked polyubiquitination of RIP1 in TNF signalling.** *EMBO J.* 2010; 29(24): 4198–209.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
17. **F** Tokunaga F, Sakata S, Saeki Y, *et al.*: **Involvement of linear polyubiquitylation of NEMO in NF-kappaB activation.** *Nat Cell Biol.* 2009; 11(2): 123–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
18. **F** Haas TL, Emmerich CH, Gerlach B, *et al.*: **Recruitment of the linear ubiquitin chain assembly complex stabilizes the TNF-R1 signaling complex and is required for TNF-mediated gene induction.** *Mol Cell.* 2009; 36(5): 831–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
19. **F** Tokunaga F, Nakagawa T, Nakahara M, *et al.*: **SHARPIN is a component of the NF-kB-activating linear ubiquitin chain assembly complex.** *Nature.* 2011; 471(7340): 633–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
20. **F** Gerlach B, Cordier SM, Schmukle AC, *et al.*: **Linear ubiquitination prevents inflammation and regulates immune signalling.** *Nature.* 2011; 471(7340): 591–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
21. Ikeda F, Deribe YL, Skánland SS, *et al.*: **SHARPIN forms a linear ubiquitin ligase complex regulating NF-kB activity and apoptosis.** *Nature.* 2011; 471(7340): 637–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
22. Emmerich CH, Bakshi S, Kelsall IR, *et al.*: **Lys63/Met1-hybrid ubiquitin chains are commonly formed during the activation of innate immune signalling.** *Biochem Biophys Res Commun.* 2016; 474(3): 452–61.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. Kanayama A, Seth RB, Sun L, *et al.*: **TAB2 and TAB3 activate the NF-kappaB pathway through binding to polyubiquitin chains.** *Mol Cell.* 2004; 15(4): 535–48.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. **F** Ea CK, Deng L, Xia ZP, *et al.*: **Activation of IKK by TNFalpha requires site-specific ubiquitination of RIP1 and polyubiquitin binding by NEMO.** *Mol Cell.* 2006; 22(2): 245–57.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
25. **F** Wu CJ, Conze DB, Li T, *et al.*: **Sensing of Lys 63-linked polyubiquitination by NEMO is a key event in NF-kappaB activation [corrected].** *Nat Cell Biol.* 2006; 8(4): 398–406.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
26. Komander D, Reyes-Turcu F, Licchesi JD, *et al.*: **Molecular discrimination of structurally equivalent Lys 63-linked and linear polyubiquitin chains.** *EMBO Rep.* 2009; 10(5): 466–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
27. Rahighi S, Ikeda F, Kawasaki M, *et al.*: **Specific recognition of linear ubiquitin chains by NEMO is important for NF-kappaB activation.** *Cell.* 2009; 136(6): 1098–109.
[PubMed Abstract](#) | [Publisher Full Text](#)
28. **F** Wang C, Deng L, Hong M, *et al.*: **TAK1 is a ubiquitin-dependent kinase of MKK and IKK.** *Nature.* 2001; 412(6844): 346–51.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
29. Ermolaeva MA, Michallet MC, Papadopolou N, *et al.*: **Function of TRADD in tumor necrosis factor receptor 1 signaling and in TRIF-dependent inflammatory responses.** *Nat Immunol.* 2008; 9(9): 1037–46.
[PubMed Abstract](#) | [Publisher Full Text](#)
30. Pobezińska YL, Kim YS, Choksi S, *et al.*: **The function of TRADD in signaling through tumor necrosis factor receptor 1 and TRIF-dependent Toll-like receptors.** *Nat Immunol.* 2008; 9(9): 1047–54.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
31. **F** Wong WW, Gentle IE, Nachbur U, *et al.*: **RIPK1 is not essential for TNFR1-induced activation of NF-kappaB.** *Cell Death Differ.* 2010; 17(3): 482–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
32. Devin A, Cook A, Lin Y, *et al.*: **The distinct roles of TRAF2 and RIP in IKK activation by TNF-R1: TRAF2 recruits IKK to TNF-R1 while RIP mediates IKK activation.** *Immunity.* 2000; 12(4): 419–29.
[PubMed Abstract](#) | [Publisher Full Text](#)
33. Feltham R, Moulin M, Vince JE, *et al.*: **Tumor necrosis factor (TNF) signaling, but not TWEAK (TNF-like weak inducer of apoptosis)-triggered cIAP1 (cellular inhibitor of apoptosis protein 1) degradation, requires cIAP1 RING dimerization and E2 binding.** *J Biol Chem.* 2010; 285(23): 17525–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
34. Blackwell K, Zhang L, Workman LM, *et al.*: **Two coordinated mechanisms underlie tumor necrosis factor alpha-induced immediate and delayed IκB kinase activation.** *Mol Cell Biol.* 2013; 33(10): 1901–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
35. Peltzer N, Rieser E, Taraborrelli L, *et al.*: **HOIP deficiency causes embryonic lethality by aberrant TNFR1-mediated endothelial cell death.** *Cell Rep.* 2014; 9(1): 153–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
36. Draber P, Kupka S, Reichert M, *et al.*: **LUBAC-Recruited CYLD and A20 Regulate Gene Activation and Cell Death by Exerting Opposing Effects on Linear Ubiquitin in Signaling Complexes.** *Cell Rep.* 2015; 13(10): 2258–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
37. Hrdinka M, Fill BK, Zucca M, *et al.*: **CYLD Limits Lys63- and Met1-Linked Ubiquitin at Receptor Complexes to Regulate Innate Immune Signaling.** *Cell Rep.* 2016; 14(12): 2846–58.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
38. **F** Peltzer N, Darding M, Montinaro A, *et al.*: **LUBAC is essential for embryogenesis by preventing cell death and enabling haematopoiesis.** *Nature.* 2018; 557(7703): 112–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
39. **F** Taraborrelli L, Peltzer N, Montinaro A, *et al.*: **LUBAC prevents lethal dermatitis by inhibiting cell death induced by TNF, TRAIL and CD95L.** *Nat Commun.* 2018; 9(1): 3910.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
40. **F** Micheau O, Tschopp J: **Induction of TNF receptor I-mediated apoptosis via two sequential signaling complexes.** *Cell.* 2003; 114(2): 181–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

41. **F** Cho YS, Challa S, Moquin D, *et al.*: Phosphorylation-driven assembly of the RIP1-RIP3 complex regulates programmed necrosis and virus-induced inflammation. *Cell*. 2009; 137(6): 1112–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
42. Micheau O, Thome M, Schneider P, *et al.*: The long form of FLIP is an activator of caspase-8 at the Fas death-inducing signaling complex. *J Biol Chem*. 2002; 277(47): 45162–71.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. Boatright KM, Deis C, Denault JB, *et al.*: Activation of caspases-8 and -10 by FLIP_L. *Biochem J*. 2004; 382(Pt 2): 651–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
44. **F** Oberst A, Dillon CP, Weinlich R, *et al.*: Catalytic activity of the caspase-8-FLIP complex inhibits RIPK3-dependent necrosis. *Nature*. 2011; 471(7338): 363–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
45. Pop C, Oberst A, Drag M, *et al.*: FLIP_L induces caspase 8 activity in the absence of interdomain caspase 8 cleavage and alters substrate specificity. *Biochem J*. 2011; 433(3): 447–57.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
46. **F** Sun L, Wang H, Wang Z, *et al.*: Mixed lineage kinase domain-like protein mediates necrosis signaling downstream of RIP3 kinase. *Cell*. 2012; 148(1–2): 213–27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
47. Murphy JM, Czabotar PE, Hildebrand JM, *et al.*: The pseudokinase MLKL mediates necroptosis via a molecular switch mechanism. *Immunity*. 2013; 39(3): 443–53.
[PubMed Abstract](#) | [Publisher Full Text](#)
48. **F** Moulin M, Anderton H, Voss AK, *et al.*: IAPs limit activation of RIP kinases by TNF receptor 1 during development. *EMBO J*. 2012; 31(7): 1679–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
49. Prakash H, Albrecht M, Becker D, *et al.*: Deficiency of XIAP leads to sensitization for *Chlamydia pneumoniae* pulmonary infection and dysregulation of innate immune response in mice. *J Biol Chem*. 2010; 285(26): 20291–302.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
50. **F** Yabal M, Müller N, Adler H, *et al.*: XIAP restricts TNF- and RIP3-dependent cell death and inflammasome activation. *Cell Rep*. 2014; 7(6): 1796–808.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
51. **F** de Almagro MC, Goncharov T, Newton K, *et al.*: Cellular IAP proteins and LUBAC differentially regulate necrosome-associated RIP1 ubiquitination. *Cell Death Dis*. 2015; 6: e1800.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
52. Feoktistova M, Geserick P, Kellert B, *et al.*: cIAPs block Ripoptosome formation, a RIP1/caspase-8 containing intracellular cell death complex differentially regulated by cFLIP isoforms. *Mol Cell*. 2011; 43(3): 449–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
53. Tenev T, Bianchi K, Darding M, *et al.*: The Ripoptosome, a signaling platform that assembles in response to genotoxic stress and loss of IAPs. *Mol Cell*. 2011; 43(3): 432–48.
[PubMed Abstract](#) | [Publisher Full Text](#)
54. Lawlor KE, Feltham R, Yabal M, *et al.*: XIAP Loss Triggers RIPK3- and Caspase-8-Driven IL-1 β Activation and Cell Death as a Consequence of TLR-MyD88-Induced cIAP1-TRAF2 Degradation. *Cell Rep*. 2017; 20(3): 668–82.
[PubMed Abstract](#) | [Publisher Full Text](#)
55. De Nardo D: Toll-like receptors: Activation, signalling and transcriptional modulation. *Cytokine*. 2015; 74(2): 181–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
56. Vallabhapurapu S, Matsuzawa A, Zhang W, *et al.*: Nonredundant and complementary functions of TRAF2 and TRAF3 in a ubiquitination cascade that activates NIK-dependent alternative NF- κ B signaling. *Nat Immunol*. 2008; 9(12): 1364–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
57. Xiao Y, Jin J, Chang M, *et al.*: Peli1 promotes microglia-mediated CNS inflammation by regulating Traf3 degradation. *Nat Med*. 2013; 19(5): 595–602.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
58. Jin J, Xiao Y, Hu H, *et al.*: Proinflammatory TLR signalling is regulated by a TRAF2-dependent proteolysis mechanism in macrophages. *Nat Commun*. 2015; 6: 5930.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
59. Kaiser WJ, Sridharan H, Huang C, *et al.*: Toll-like receptor 3-mediated necrosis via TRIF, RIP3, and MLKL. *J Biol Chem*. 2013; 288(43): 31268–79.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
60. Weber A, Kirejczyk Z, Besch R, *et al.*: Proapoptotic signalling through Toll-like receptor-3 involves TRIF-dependent activation of caspase-8 and is under the control of inhibitor of apoptosis proteins in melanoma cells. *Cell Death Differ*. 2010; 17(6): 942–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
61. Kaiser WJ, Offermann MK: Apoptosis induced by the toll-like receptor adaptor TRIF is dependent on its receptor interacting protein homotypic interaction motif. *J Immunol*. 2005; 174(8): 4942–52.
[PubMed Abstract](#) | [Publisher Full Text](#)
62. **F** He S, Liang Y, Shao F, *et al.*: Toll-like receptors activate programmed necrosis in macrophages through a receptor-interacting kinase-3-mediated pathway. *Proc Natl Acad Sci U S A*. 2011; 108(50): 20054–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
63. Lawlor KE, Khan N, Mildenhall A, *et al.*: RIPK3 promotes cell death and NLRP3 inflammasome activation in the absence of MLKL. *Nat Commun*. 2015; 6: 6282.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
64. Labbé K, McIntire CR, Doiron K, *et al.*: Cellular inhibitors of apoptosis proteins cIAP1 and cIAP2 are required for efficient caspase-1 activation by the inflammasome. *Immunity*. 2011; 35(6): 897–907.
[PubMed Abstract](#) | [Publisher Full Text](#)
65. Vince JE, Wong WW, Gentile I, *et al.*: Inhibitor of apoptosis proteins limit RIP3 kinase-dependent interleukin-1 activation. *Immunity*. 2012; 36(2): 215–27.
[PubMed Abstract](#) | [Publisher Full Text](#)
66. Wicki S, Gurzeler U, Wei-Lynn Wong W, *et al.*: Loss of XIAP facilitates switch to TNF α -induced necroptosis in mouse neutrophils. *Cell Death Dis*. 2016; 7(10): e2422.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
67. Fotin-Mleczek M, Henkler F, Samel D, *et al.*: Apoptotic crosstalk of TNF receptors: TNF-R2 induces depletion of TRAF2 and IAP proteins and accelerates TNF-R1-dependent activation of caspase-8. *J Cell Sci*. 2002; 115(Pt 13): 2757–70.
[PubMed Abstract](#)
68. Kenneth NS, Younger JM, Hughes ED, *et al.*: An inactivating caspase 11 passenger mutation originating from the 129 murine strain in mice targeted for c-IAP1. *Biochem J*. 2012; 443(2): 355–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
69. **F** Kayagaki N, Warming S, Lamkanfi M, *et al.*: Non-canonical inflammasome activation targets caspase-11. *Nature*. 2011; 479(7371): 117–21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
70. Maelfait J, Vercammen E, Janssens S, *et al.*: Stimulation of Toll-like receptor 3 and 4 induces interleukin-1 β maturation by caspase-8. *J Exp Med*. 2008; 205(9): 1967–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
71. Bossaller L, Chiang PI, Schmidt-Lauber C, *et al.*: Cutting edge: FAS (CD95) mediates noncanonical IL-1 β and IL-18 maturation via caspase-8 in an RIP3-independent manner. *J Immunol*. 2012; 189(12): 5508–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
72. Antonopoulos C, El Sanadi C, Kaiser WJ, *et al.*: Proapoptotic chemotherapeutic drugs induce noncanonical processing and release of IL-1 β via caspase-8 in dendritic cells. *J Immunol*. 2013; 191(9): 4789–803.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
73. Kang TB, Yang SH, Toth B, *et al.*: Caspase-8 blocks kinase RIPK3-mediated activation of the NLRP3 inflammasome. *Immunity*. 2013; 38(1): 27–40.
[PubMed Abstract](#) | [Publisher Full Text](#)
74. Gurung P, Anand PK, Malireddi RK, *et al.*: FADD and caspase-8 mediate priming and activation of the canonical and noncanonical Nlrp3 inflammasomes. *J Immunol*. 2014; 192(4): 1835–46.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
75. Philip NH, Dillon CP, Snyder AG, *et al.*: Caspase-8 mediates caspase-1 processing and innate immune defense in response to bacterial blockade of NF- κ B and MAPK signaling. *Proc Natl Acad Sci U S A*. 2014; 111(20): 7385–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
76. Shenderov K, Riteau N, Yip R, *et al.*: Cutting edge: Endoplasmic reticulum stress licenses macrophages to produce mature IL-1 β in response to TLR4 stimulation through a caspase-8- and TRIF-dependent pathway. *J Immunol*. 2014; 192(5): 2029–33.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
77. **F** Karki R, Man SM, Malireddi RKS, *et al.*: Concerted activation of the AIM2 and NLRP3 inflammasomes orchestrates host protection against *Aspergillus* infection. *Cell Host Microbe*. 2015; 17(3): 357–68.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
78. Andree M, Seeger JM, Schüll S, *et al.*: BID-dependent release of mitochondrial SMAC dampens XIAP-mediated immunity against *Shigella*. *EMBO J*. 2014; 33(19): 2171–87.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
79. Suzuki S, Suzuki T, Mimuro H, *et al.*: Shigella hijacks the glomulin-cIAPs-inflammasome axis to promote inflammation. *EMBO Rep*. 2018; 19(1): 89–101.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
80. **F** Duong BH, Onizawa M, Oses-Prieto JA, *et al.*: A20 restricts ubiquitination of pro-interleukin-1 β protein complexes and suppresses NLRP3 inflammasome activity. *Immunity*. 2015; 42(1): 55–67.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
81. **F** Jin Z, Li Y, Pitti R, *et al.*: Cullin3-based polyubiquitination and p62-dependent aggregation of caspase-8 mediate extrinsic apoptosis signaling. *Cell*. 2009; 137(4): 721–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
82. Inohara N, Koseki T, Lin J, *et al.*: An induced proximity model for NF- κ B activation in the Nod1/RICK and RIP signaling pathways. *J Biol Chem*. 2000; 275(36): 27823–31.
[PubMed Abstract](#) | [Publisher Full Text](#)
83. Yang Y, Yin C, Pandey A, *et al.*: NOD2 pathway activation by MDP or *Mycobacterium tuberculosis* infection involves the stable polyubiquitination of Rip2. *J Biol Chem*. 2007; 282(50): 36223–9.
[PubMed Abstract](#) | [Publisher Full Text](#)

84. Hasegawa M, Fujimoto Y, Lucas PC, *et al.*: **A critical role of RICK/RIP2 polyubiquitination in Nod-induced NF-kappaB activation.** *EMBO J.* 2008; 27(2): 373–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
85. Krieg A, Correa RG, Garrison JB, *et al.*: **XIAP mediates NOD signaling via interaction with RIP2.** *Proc Natl Acad Sci U S A.* 2009; 106(34): 14524–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
86. Damgaard RB, Fiil BK, Speckmann C, *et al.*: **Disease-causing mutations in the XIAP BIR2 domain impair NOD2-dependent immune signalling.** *EMBO Mol Med.* 2013; 5(8): 1278–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
87. Chirieleison SM, Marsh RA, Kumar P, *et al.*: **Nucleotide-binding oligomerization domain (NOD) signaling defects and cell death susceptibility cannot be uncoupled in X-linked inhibitor of apoptosis (XIAP)-driven inflammatory disease.** *J Biol Chem.* 2017; 292(23): 9666–79.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
88. **F** Goncharov T, Hedayat S, Mulvihill MM, *et al.*: **Disruption of XIAP-RIP2 Association Blocks NOD2-Mediated Inflammatory Signaling.** *Mol Cell.* 2018; 69(4): 551–565.e7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
89. **F** Damgaard RB, Nachbur U, Yabal M, *et al.*: **The ubiquitin ligase XIAP recruits LUBAC for NOD2 signaling in inflammation and innate immunity.** *Mol Cell.* 2012; 46(6): 746–58.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
90. **F** Bauler LD, Duckett CS, O'Riordan MX: **XIAP regulates cytosol-specific innate immunity to *Listeria* infection.** *PLoS Pathog.* 2008; 4(8): e1000142.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
91. **F** Gesellchen V, Kutenkeuler D, Steckel M, *et al.*: **An RNA interference screen identifies *Inhibitor of Apoptosis Protein 2* as a regulator of innate immune signalling in *Drosophila*.** *EMBO Rep.* 2005; 6(10): 979–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
92. **F** Kleino A, Valanne S, Ulvila J, *et al.*: **Inhibitor of apoptosis 2 and TAK1-binding protein are components of the *Drosophila* Imd pathway.** *EMBO J.* 2005; 24(19): 3423–34.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
93. Leulier F, Lhocine N, Lemaître B, *et al.*: **The *Drosophila* inhibitor of apoptosis protein DIAP2 functions in innate immunity and is essential to resist gram-negative bacterial infection.** *Mol Cell Biol.* 2006; 26(21): 7821–31.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
94. Huh JR, Foe I, Muro I, *et al.*: **The *Drosophila* inhibitor of apoptosis (IAP) DIAP2 is dispensable for cell survival, required for the innate immune response to gram-negative bacterial infection, and can be negatively regulated by the reaper/hid/grim family of IAP-binding apoptosis inducers.** *J Biol Chem.* 2007; 282(3): 2056–68.
[PubMed Abstract](#) | [Publisher Full Text](#)
95. Valanne S, Kleino A, Myllymäki H, *et al.*: **lap2 is required for a sustained response in the *Drosophila* Imd pathway.** *Dev Comp Immunol.* 2007; 31(10): 991–1001.
[PubMed Abstract](#) | [Publisher Full Text](#)
96. **F** Bertrand MJ, Doiron K, Labbé K, *et al.*: **Cellular inhibitors of apoptosis ciAP1 and ciAP2 are required for innate immunity signaling by the pattern recognition receptors NOD1 and NOD2.** *Immunity.* 2009; 30(6): 789–801.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
97. Bertrand MJ, Lippens S, Staes A, *et al.*: **ciAP1/2 are direct E3 ligases conjugating diverse types of ubiquitin chains to receptor interacting proteins kinases 1 to 4 (RIP1–4).** *PLoS One.* 2011; 6(9): e22356.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
98. **F** Stafford CA, Lawlor KE, Heim VJ, *et al.*: **IAPs Regulate Distinct Innate Immune Pathways to Co-ordinate the Response to Bacterial Peptidoglycans.** *Cell Rep.* 2018; 22(6): 1496–508.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
99. Aguilar C, Lenoir C, Lambert N, *et al.*: **Characterization of Crohn disease in X-linked inhibitor of apoptosis-deficient male patients and female symptomatic carriers.** *J Allergy Clin Immunol.* 2014; 134(5): 1131–41.e9.
[PubMed Abstract](#) | [Publisher Full Text](#)
100. Christiansen M, Ammann S, Speckmann C, *et al.*: **XIAP deficiency and MEFV variants resulting in an autoinflammatory lymphoproliferative syndrome.** *BMJ Case Rep.* 2016; 2016: pii: bcr2016216922.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
101. Amininejad L, Charlotteaux B, Theatre E, *et al.*: **Analysis of Genes Associated With Monogenic Primary Immunodeficiency Identifies Rare Variants in XIAP in Patients With Crohn's Disease.** *Gastroenterology.* 2018; 154(8): 2165–77.
[PubMed Abstract](#) | [Publisher Full Text](#)
102. Latour S, Aguilar C: **XIAP deficiency syndrome in humans.** *Semin Cell Dev Biol.* 2015; 39: 115–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
103. **F** Rigaud S, Fondanèche MC, Lambert N, *et al.*: **XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome.** *Nature.* 2006; 444(7115): 110–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
104. Marsh RA, Madden L, Kitchen BJ, *et al.*: **XIAP deficiency: a unique primary immunodeficiency best classified as X-linked familial hemophagocytic lymphohistiocytosis and not as X-linked lymphoproliferative disease.** *Blood.* 2010; 116(7): 1079–82.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
105. Pachlopnik Schmid J, Canioni D, Moshous D, *et al.*: **Clinical similarities and differences of patients with X-linked lymphoproliferative syndrome type 1 (XLP-1/SAP deficiency) versus type 2 (XLP-2/XIAP deficiency).** *Blood.* 2011; 117(5): 1522–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
106. Yang X, Kanegane H, Nishida N, *et al.*: **Clinical and genetic characteristics of XIAP deficiency in Japan.** *J Clin Immunol.* 2012; 32(3): 411–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
107. Speckmann C, Lehmberg K, Albert MH, *et al.*: **X-linked inhibitor of apoptosis (XIAP) deficiency: the spectrum of presenting manifestations beyond hemophagocytic lymphohistiocytosis.** *Clin Immunol.* 2013; 149(1): 133–41.
[PubMed Abstract](#) | [Publisher Full Text](#)
108. **F** Ogura Y, Bonen DK, Inohara N, *et al.*: **A frameshift mutation in *NOD2* associated with susceptibility to Crohn's disease.** *Nature.* 2001; 411(6837): 603–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
109. **F** Hugot JP, Chamaillard M, Zouali H, *et al.*: **Association of *NOD2* leucine-rich repeat variants with susceptibility to Crohn's disease.** *Nature.* 2001; 411(6837): 599–603.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
110. **F** Sabbah A, Chang TH, Harnack R, *et al.*: **Activation of innate immune antiviral responses by Nod2.** *Nat Immunol.* 2009; 10(10): 1073–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
111. Kapoor A, Forman M, Arav-Boger R: **Activation of nucleotide oligomerization domain 2 (NOD2) by human cytomegalovirus initiates innate immune responses and restricts virus replication.** *PLoS One.* 2014; 9(3): e92704.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
112. Wada T, Kanegane H, Ohta K, *et al.*: **Sustained elevation of serum interleukin-18 and its association with hemophagocytic lymphohistiocytosis in XIAP deficiency.** *Cytokine.* 2014; 65(1): 74–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
113. Harlin H, Refey SB, Duckett CS, *et al.*: **Characterization of XIAP-deficient mice.** *Mol Cell Biol.* 2001; 21(10): 3604–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
114. Conze DB, Albert L, Ferrick DA, *et al.*: **Posttranscriptional downregulation of c-IAP2 by the ubiquitin protein ligase c-IAP1 *in vivo*.** *Mol Cell Biol.* 2005; 25(8): 3348–56.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
115. Heard KN, Bertrand MJ, Barker PA: **ciAP2 supports viability of mice lacking ciAP1 and XIAP.** *EMBO J.* 2015; 34(19): 2393–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
116. Moulin M, Voss AK, Thomas T, *et al.*: **Response to Heard *et al.*** *EMBO J.* 2015; 34(19): 2396–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
117. Varfolomeev EE, Schuchmann M, Luria V, *et al.*: **Targeted disruption of the mouse Caspase 8 gene ablates cell death induction by the TNF receptors, Fas/Apo1, and DR3 and is lethal prenatally.** *Immunity.* 1998; 9(2): 267–76.
[PubMed Abstract](#) | [Publisher Full Text](#)
118. Yeh WC, de la Pompa JL, McCurrach ME, *et al.*: **FADD: essential for embryo development and signaling from some, but not all, inducers of apoptosis.** *Science.* 1998; 279(5358): 1954–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
119. Yeh WC, Itie A, Elia AJ, *et al.*: **Requirement for Casper (c-FLIP) in regulation of death receptor-induced apoptosis and embryonic development.** *Immunity.* 2000; 12(6): 633–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
120. **F** Kang TB, Ben-Moshe T, Varfolomeev EE, *et al.*: **Caspase-8 serves both apoptotic and nonapoptotic roles.** *J Immunol.* 2004; 173(5): 2976–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
121. **F** Dillon CP, Weinlich R, Rodriguez DA, *et al.*: **RIPK1 blocks early postnatal lethality mediated by caspase-8 and RIPK3.** *Cell.* 2014; 157(5): 1189–202.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
122. Santoro MM, Samuel T, Mitchell T, *et al.*: **Birc2 (clap1) regulates endothelial cell integrity and blood vessel homeostasis.** *Nat Genet.* 2007; 39(11): 1397–402.
[PubMed Abstract](#) | [Publisher Full Text](#)
123. **F** Newton K, Wickliffe KE, Maltzman A, *et al.*: **RIPK1 inhibits ZBP1-driven necroptosis during development.** *Nature.* 2016; 540(7631): 129–33.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
124. **F** Lin J, Kumari S, Kim C, *et al.*: **RIPK1 counteracts ZBP1-mediated necroptosis to inhibit inflammation.** *Nature.* 2016; 540(7631): 124–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
125. Hsieh WC, Chuang YT, Chiang IH, *et al.*: **Inability to resolve specific infection generates innate immunodeficiency syndrome in *Xiap*^{-/-} mice.** *Blood.* 2014; 124(18): 2847–57.
[PubMed Abstract](#) | [Publisher Full Text](#)
126. **F** Grabinger T, Bode KJ, Demgenski J, *et al.*: **Inhibitor of Apoptosis Protein-1 Regulates Tumor Necrosis Factor-Mediated Destruction of Intestinal Epithelial**

- Cells.** *Gastroenterology*. 2017; **152**(4): 867–79.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
127. Wong WW, Vince JE, Lalaoui N, *et al.*: **ciAPs and XIAP regulate myelopoiesis through cytokine production in an RIPK1- and RIPK3-dependent manner.** *Blood*. 2014; **123**(16): 2562–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
 128. Christofferson DE, Li Y, Hitomi J, *et al.*: **A novel role for RIP1 kinase in mediating TNF α production.** *Cell Death Dis*. 2012; **3**(6): e320.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 129. Lukens JR, Vogel P, Johnson GR, *et al.*: **RIP1-driven autoinflammation targets IL-1 α independently of inflammasomes and RIP3.** *Nature*. 2013; **498**(7453): 224–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 130. Najjar M, Saleh D, Zelic M, *et al.*: **RIPK1 and RIPK3 Kinases Promote Cell-Death-Independent Inflammation by Toll-like Receptor 4.** *Immunity*. 2016; **45**(1): 46–59.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 131. Kang TB, Jeong JS, Yang SH, *et al.*: **Caspase-8 deficiency in mouse embryos triggers chronic RIPK1-dependent activation of inflammatory genes, independently of RIPK3.** *Cell Death Differ*. 2018; **25**(6): 1107–17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 132. Anderton H, Rickard JA, Varigos GA, *et al.*: **Inhibitor of Apoptosis Proteins (IAPs) Limit RIPK1-Mediated Skin Inflammation.** *J Invest Dermatol*. 2017; **137**(11): 2371–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 133. Kovalenko A, Kim JC, Kang TB, *et al.*: **Caspase-8 deficiency in epidermal keratinocytes triggers an inflammatory skin disease.** *J Exp Med*. 2009; **206**(10): 2161–77.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 134. **F** Bonnet MC, Preukschat D, Welz PS, *et al.*: **The adaptor protein FADD protects epidermal keratinocytes from necroptosis *in vivo* and prevents skin inflammation.** *Immunity*. 2011; **35**(4): 572–82.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 135. Panayotova-Dimitrova D, Feoktistova M, Ploesser M, *et al.*: **cFLIP regulates skin homeostasis and protects against TNF-induced keratinocyte apoptosis.** *Cell Rep*. 2013; **5**(2): 397–408.
[PubMed Abstract](#) | [Publisher Full Text](#)
 136. HogenEsch H, Gijbels MJ, Offerman E, *et al.*: **A spontaneous mutation characterized by chronic proliferative dermatitis in C57BL mice.** *Am J Pathol*. 1993; **143**(3): 972–82.
[PubMed Abstract](#) | [Free Full Text](#)
 137. Berger SB, Kasparova V, Hoffman S, *et al.*: **Cutting Edge: RIP1 kinase activity is dispensable for normal development but is a key regulator of inflammation in SHARPIN-deficient mice.** *J Immunol*. 2014; **192**(12): 5476–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 138. Gardam S, Turner VM, Anderton H, *et al.*: **Deletion of ciAP1 and ciAP2 in murine B lymphocytes constitutively activates cell survival pathways and inactivates the germinal center response.** *Blood*. 2011; **117**(15): 4041–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
 139. Liao G, Zhang M, Harhaj EW, *et al.*: **Regulation of the NF-kappaB-inducing kinase by tumor necrosis factor receptor-associated factor 3-induced degradation.** *J Biol Chem*. 2004; **279**(25): 26243–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
 140. He JQ, Saha SK, Kang JR, *et al.*: **Specificity of TRAF3 in its negative regulation of the noncanonical NF-kappa B pathway.** *J Biol Chem*. 2007; **282**(6): 3688–94.
[PubMed Abstract](#) | [Publisher Full Text](#)
 141. Zarnegar BJ, Wang Y, Mahoney DJ, *et al.*: **Noncanonical NF-kappaB activation requires coordinated assembly of a regulatory complex of the adaptors ciAP1, ciAP2, TRAF2 and TRAF3 and the kinase NIK.** *Nat Immunol*. 2008; **9**(12): 1371–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 142. Lee S, Challa-Malladi M, Bratton SB, *et al.*: **Nuclear factor- κ B-inducing kinase (NIK) contains an amino-terminal inhibitor of apoptosis (IAP)-binding motif (IBM) that potentiates NIK degradation by cellular IAP1 (c-IAP1).** *J Biol Chem*. 2014; **289**(44): 30680–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 143. Grech AP, Amesbury M, Chan T, *et al.*: **TRAF2 differentially regulates the canonical and noncanonical pathways of NF-kappaB activation in mature B cells.** *Immunity*. 2004; **21**(5): 629–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
 144. **F** Conze DB, Zhao Y, Ashwell JD: **Non-canonical NF- κ B activation and abnormal B cell accumulation in mice expressing ubiquitin protein ligase-inactive c-IAP2.** *PLoS Biol*. 2010; **8**(10): e1000518.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 145. Uhlig HH, Schwerdt T: **From Genes to Mechanisms: The Expanding Spectrum of Monogenic Disorders Associated with Inflammatory Bowel Disease.** *Inflamm Bowel Dis*. 2016; **22**(1): 202–12.
[PubMed Abstract](#) | [Publisher Full Text](#)
 146. Negroni A, Pierdomenico M, Cucchiara S, *et al.*: **NOD2 and inflammation: current insights.** *J Inflamm Res*. 2018; **11**: 49–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 147. Shaw PJ, Barr MJ, Lukens JR, *et al.*: **Signaling via the RIP2 adaptor protein in central nervous system-infiltrating dendritic cells promotes inflammation and autoimmunity.** *Immunity*. 2011; **34**(1): 75–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 148. Nachbur U, Stafford CA, Bankovacki A, *et al.*: **A RIPK2 inhibitor delays NOD signalling events yet prevents inflammatory cytokine production.** *Nat Commun*. 2015; **6**: 6442.
[PubMed Abstract](#) | [Publisher Full Text](#)
 149. Canning P, Ruan Q, Schwerdt T, *et al.*: **Inflammatory Signaling by NOD-RIPK2 Is Inhibited by Clinically Relevant Type II Kinase Inhibitors.** *Chem Biol*. 2015; **22**(9): 1174–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 150. **F** Haile PA, Votta BJ, Marquis RW, *et al.*: **The Identification and Pharmacological Characterization of 6-(tert-Butylsulfonyl)-N-(5-fluoro-1H-indazol-3-yl)quinolin-4-amine (GSK583), a Highly Potent and Selective Inhibitor of RIP2 Kinase.** *J Med Chem*. 2016; **59**(10): 4867–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 151. **F** He X, Da Ros S, Nelson J, *et al.*: **Identification of Potent and Selective RIPK2 Inhibitors for the Treatment of Inflammatory Diseases.** *ACS Med Chem Lett*. 2017; **8**(10): 1048–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 152. Hrdinka M, Schlicher L, Dai B, *et al.*: **Small molecule inhibitors reveal an indispensable scaffolding role of RIPK2 in NOD2 signaling.** *EMBO J*. 2018; **37**(17): pii: e99372.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 153. Chirieleison SM, Rathkey JK, Abbott DW: **Unique BIR domain sets determine inhibitor of apoptosis protein-driven cell death and NOD2 complex signal specificity.** *Sci Signal*. 2018; **11**(539): pii: eaao3964.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 154. Busca A, Saxena M, Kumar A: **Critical role for antiapoptotic Bcl-xL and Mcl-1 in human macrophage survival and cellular IAP1/2 (ciAP1/2) in resistance to HIV-Vpr-induced apoptosis.** *J Biol Chem*. 2012; **287**(18): 15118–33.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 155. Campbell GR, Bruckman RS, Chu YL, *et al.*: **SMAC Mimetics Induce Autophagy-Dependent Apoptosis of HIV-1-Infected Resting Memory CD4+ T Cells.** *Cell Host Microbe*. 2018; **24**(5): 689–702.e7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 156. Pache L, Dutra MS, Spivak AM, *et al.*: **BIRC2/cIAP1 Is a Negative Regulator of HIV-1 Transcription and Can Be Targeted by Smac Mimetics to Promote Reversal of Viral Latency.** *Cell Host Microbe*. 2015; **18**(3): 345–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 157. Hattori SI, Matsuda K, Tsuchiya K, *et al.*: **Combination of a Latency-Reversing Agent With a Smac Mimetic Minimizes Secondary HIV-1 Infection *in vitro*.** *Front Microbiol*. 2018; **9**: 2022.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 158. Ebert G, Preston S, Allison C, *et al.*: **Cellular inhibitor of apoptosis proteins prevent clearance of hepatitis B virus.** *Proc Natl Acad Sci U S A*. 2015; **112**(18): 5797–802.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 159. Yang PL, Althage A, Chung J, *et al.*: **Immune effectors required for hepatitis B virus clearance.** *Proc Natl Acad Sci U S A*. 2010; **107**(2): 798–802.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 160. Ebert G, Allison C, Preston S, *et al.*: **Eliminating hepatitis B by antagonizing cellular inhibitors of apoptosis.** *Proc Natl Acad Sci U S A*. 2015; **112**(18): 5803–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 161. **F** Amaravadi RK, Schilder RJ, Martin LP, *et al.*: **A Phase I Study of the SMAC-Mimetic Birinapant in Adults with Refractory Solid Tumors or Lymphoma.** *Mol Cancer Ther*. 2015; **14**(11): 2569–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 162. Noonan AM, Bunch KP, Chen JQ, *et al.*: **Pharmacodynamic markers and clinical results from the phase 2 study of the SMAC mimetic birinapant in women with relapsed platinum-resistant or -refractory epithelial ovarian cancer.** *Cancer*. 2016; **122**(4): 588–97.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 163. Fulda S: **Smac mimetics as IAP antagonists.** *Semin Cell Dev Biol*. 2015; **39**: 132–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 164. Fulda S: **Smac Mimetics to Therapeutically Target IAP Proteins in Cancer.** *Int Rev Cell Mol Biol*. 2017; **330**: 157–69.
[PubMed Abstract](#) | [Publisher Full Text](#)
 165. **F** Beug ST, Tang VA, LaCasse EC, *et al.*: **Smac mimetics and innate immune stimuli synergize to promote tumor death.** *Nat Biotechnol*. 2014; **32**(2): 182–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 166. Brumatti G, Ma C, Lalaoui N, *et al.*: **The caspase-8 inhibitor emricasan combines with the SMAC mimetic birinapant to induce necroptosis and treat acute myeloid leukemia.** *Sci Transl Med*. 2016; **8**(339): 339ra69.
[PubMed Abstract](#) | [Publisher Full Text](#)
 167. Lalaoui N, Hänggi K, Brumatti G, *et al.*: **Targeting p38 or MK2 Enhances the Anti-Leukemic Activity of Smac-Mimetics.** *Cancer Cell*. 2016; **29**(2): 145–58.
[PubMed Abstract](#) | [Publisher Full Text](#)
 168. Condon SM, Mitsunuchi Y, Deng Y, *et al.*: **Birinapant, a smac-mimetic with improved tolerability for the treatment of solid tumors and hematological malignancies.** *J Med Chem*. 2014; **57**(9): 3666–77.
[PubMed Abstract](#) | [Publisher Full Text](#)
 169. **F** West AC, Martin BP, Andrews DA, *et al.*: **The SMAC mimetic, LCL-161, reduces survival in aggressive MYC-driven lymphoma while promoting**

- susceptibility to endotoxic shock. *Oncogenesis*. 2016; 5: e216.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
170. Bhatti IA, Abhari BA, Fulda S: Identification of a synergistic combination of Smac mimetic and Bortezomib to trigger cell death in B-cell non-Hodgkin lymphoma cells. *Cancer Lett*. 2017; 405: 63–72.
[PubMed Abstract](#) | [Publisher Full Text](#)
 171. McCabe KE, Bacos K, Lu D, *et al.*: Triggering necroptosis in cisplatin and IAP antagonist-resistant ovarian carcinoma. *Cell Death Dis*. 2014; 5: e1496.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 172. Hannes S, Abhari BA, Fulda S: Smac mimetic triggers necroptosis in pancreatic carcinoma cells when caspase activation is blocked. *Cancer Lett*. 2016; 380(1): 31–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 173. Safferthal C, Rohde K, Fulda S: Therapeutic targeting of necroptosis by Smac mimetic bypasses apoptosis resistance in acute myeloid leukemia cells. *Oncogene*. 2017; 36(11): 1487–502.
[PubMed Abstract](#) | [Publisher Full Text](#)
 174. **F** He GW, Günther C, Thonn V, *et al.*: Regression of apoptosis-resistant colorectal tumors by induction of necroptosis in mice. *J Exp Med*. 2017; 214(6): 1655–62.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 175. **F** McComb S, Aguadé-Gorgorió J, Harder L, *et al.*: Activation of concurrent apoptosis and necroptosis by SMAC mimetics for the treatment of refractory and relapsed ALL. *Sci Transl Med*. 2016; 8(339): 339ra70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 176. Stupack DG: Caspase-8 as a therapeutic target in cancer. *Cancer Lett*. 2013; 332(2): 133–40.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 177. Yatim N, Jusforgues-Saklani H, Orozco S, *et al.*: RIPK1 and NF- κ B signaling in dying cells determines cross-priming of CD8⁺ T cells. *Science*. 2015; 350(6258): 328–34.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 178. **F** Aaes TL, Kaczmarek A, Delvaeye T, *et al.*: Vaccination with Necroptotic Cancer Cells Induces Efficient Anti-tumor Immunity. *Cell Rep*. 2016; 15(2): 274–87.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 179. Dougan M, Dougan S, Slisz J, *et al.*: IAP inhibitors enhance co-stimulation to promote tumor immunity. *J Exp Med*. 2010; 207(10): 2195–206.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 180. Fischer K, Tognarelli S, Roesler S, *et al.*: The Smac Mimetic BV6 Improves NK Cell-Mediated Killing of Rhabdomyosarcoma Cells by Simultaneously Targeting Tumor and Effector Cells. *Front Immunol*. 2017; 8: 202.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 181. Pan W, Luo Q, Yan X, *et al.*: A novel SMAC mimetic APG-1387 exhibits dual antitumor effect on HBV-positive hepatocellular carcinoma with high expression of cIAP2 by inducing apoptosis and enhancing innate anti-tumor immunity. *Biochem Pharmacol*. 2018; 154: 127–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
 182. Clancy-Thompson E, Ali L, Bruck PT, *et al.*: IAP Antagonists Enhance Cytokine Production from Mouse and Human iNKT Cells. *Cancer Immunol Res*. 2018; 6(1): 25–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 183. **F** Chesi M, Mirza NN, Garbitt VM, *et al.*: IAP antagonists induce anti-tumor immunity in multiple myeloma. *Nat Med*. 2016; 22(12): 1411–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 184. Kearney CJ, Lalaoui N, Freeman AJ, *et al.*: PD-L1 and IAPs co-operate to protect tumors from cytotoxic lymphocyte-derived TNF. *Cell Death Differ*. 2017; 24(10): 1705–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 185. Xiao R, Allen CT, Tran L, *et al.*: Antagonist of cIAP1/2 and XIAP enhances anti-tumor immunity when combined with radiation and PD-1 blockade in a syngeneic model of head and neck cancer. *Oncotarget*. 2018; 7(9): e1471440.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 186. Kim DS, Dastidar H, Zhang C, *et al.*: Smac mimetics and oncolytic viruses synergize in driving anticancer T-cell responses through complementary mechanisms. *Nat Commun*. 2017; 8(1): 344.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 187. Giardino Torchia ML, Munitic I, Castro E, *et al.*: c-IAP ubiquitin protein ligase activity is required for 4-1BB signaling and CD8⁺ memory T-cell survival. *Eur J Immunol*. 2015; 45(9): 2672–82.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 188. Nadella V, Mohanty A, Sharma L, *et al.*: Inhibitors of Apoptosis Protein Antagonists (Smac Mimetic Compounds) Control Polarization of Macrophages during Microbial Challenge and Sterile Inflammatory Responses. *Front Immunol*. 2018; 8: 1792.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 189. Ebner P, Poetsch I, Deszcz L, *et al.*: The IAP family member BRUCE regulates autophagosome-lysosome fusion. *Nat Commun*. 2018; 9(1): 599.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 190. Gradzka S, Thomas OS, Kretz O, *et al.*: Inhibitor of apoptosis proteins are required for effective fusion of autophagosomes with lysosomes. *Cell Death Dis*. 2018; 9(5): 529.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Referee Status:



Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

- 1 **Mads Gyrd-Hansen** Nuffield Department of Clinical Medicine, Ludwig Institute for Cancer Research, University of Oxford, Oxford, UK
Competing Interests: No competing interests were disclosed.
- 2 **Christine J Hawkins** Department of Biochemistry and Genetics, La Trobe Institute for Molecular Science, La Trobe University, Melbourne, Australia
Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research