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Review

Targeting RIP Kinases in Chronic Inflammatory Disease

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Abstract: Chronic inflammatory disorders are characterised by aberrant and exaggerated inflammatory immune cell responses. Modes of extrinsic cell death, apoptosis and necroptosis, have now been shown to be potent drivers of deleterious inflammation, and mutations in core repressors of these pathways underlie many autoinflammatory disorders. The receptor-interacting protein (RIP) kinases, RIPK1 and RIPK3, are integral players in extrinsic cell death signalling by regulating the production of pro-inflammatory cytokines, such as tumour necrosis factor (TNF), and coordinating the activation of the NOD-like receptor protein 3 (NLRP3) inflammasome, which underpin pathological inflammation in numerous chronic inflammatory disorders. In this review, we firstly give an overview of the inflammatory cell death pathways regulated by RIPK1 and RIPK3. We then discuss how dysregulated signalling along these pathways can contribute to chronic inflammatory disorders of the joints, skin, and gastrointestinal tract, and discuss the emerging evidence for targeting these RIP kinases in the clinic.

Keywords: apoptosis; necroptosis; RIP kinases; chronic inflammatory disease; tumour necrosis factor; interleukin-1

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1. Introduction

Common chronic inflammatory and autoinflammatory diseases are caused by immune dysregulation, the aetiology of which involves a complex interplay between genetic and environmental factors that is incompletely understood [1]. Unmistakably, however, the underlying cause of distinct tissue pathologies is a failure to resolve inflammation arising from the excessive production of inflammatory cytokines and chemokines, as well as danger-associated molecular patterns (DAMPs) that are released from dying cells. Tumour necrosis factor (TNF) is the archetypal death ligand and a pivotal pathogenic cytokine in many common inflammatory diseases. Accordingly, a number of TNF antagonists, as well as other anti-inflammatory biological agents that dampen its activity, have met with considerable success in the clinic. Yet, many patients still fail to respond, or else develop severe adverse reactions to these therapies, highlighting the need for a both a greater understanding of TNF signalling on a cell-by-cell level and also the need for alternative strategies to target TNF signalling pathways in disease.

Over the last decade, the serine-threonine receptor-interacting protein (RIP) kinases -1 and -3 have emerged as key regulators of innate immunity via their integral roles in cell death signalling during cellular stress and following exposure to inflammatory and infectious stimuli [2–4]. RIPK1 has a critical scaffolding role in tumour necrosis factor receptor-1 (TNFR1) and Toll-like receptor 3/4 (TLR3/4) pro-inflammatory signalling [5–7], as well as a kinase-dependent role in both apoptotic and necroptotic cell death [8]. The carboxy-terminal death domain (DD) of RIPK1 can facilitate its interaction with other DD-containing proteins to promote formation of death receptor signalling complexes [9–11], while its RIP homotypic interaction motif (RHIM) domain (also shared with RIPK3) enables

RIPK1/3 interactions with other cell death and/or immune adaptors [12], e.g., TIR domain-containing adaptor-inducing IFN-β (TRIF) [5,13] and the dsDNA receptor Z-DNA binding protein-1 (ZBP1; also known as DAI) [14].

TNF ligation of TNFR1 typically recruits RIPK1 into a membrane bound receptor signalling complex, referred to as complex I, that activates NF-κB-mediated transcription of pro-survival genes (Figure 1). Along with RIPK1, TNFR1-associated death domain protein (TRADD) is recruited to TNFR1 via their common DD [15,16]. The adaptor TNFR-associated factor 2 (TRAF2) subsequently binds to TRADD and recruits the cellular inhibitor of apoptosis proteins (cIAP)-1 and cIAP2 [17,18]. The E3 ubiquitin ligase activity of cIAP1/2 attaches K63- and K11-linked polyubiquitin chains to RIPK1, allowing for the recruitment of the linear ubiquitin chain assembly complex (LUBAC), which is a heterotrimeric complex made up of haeme-oxidized IRP2 ubiquitin ligase 1 (HOIL-1), HOIL-1-interacting protein (HOIP), and SHANK-associated RH domain-interacting protein (SHARPIN). Subsequent M1-linked ubiquitylation of complex I components by LUBAC stabilises the complex and promotes the TAK1- and IKK-dependent activation of canonical NF-κB transcription [19–21]. Post-translational modification of RIPK1 within complex I, as well as the selective cleavage of RIPK1 and RIPK3 (and cylindromatosis [CYLD]) by caspase-8, maintain TNF-mediated pro-survival signalling and block the transition to pro-apoptotic cell death complex II [22–29]. This critical pro-survival scaffolding role for RIPK1 is evidenced by the fact that RIPK1-deficient mice die shortly after birth due to systemic multi-organ inflammation mediated by unrestrained apoptosis and necroptosis [30–36].

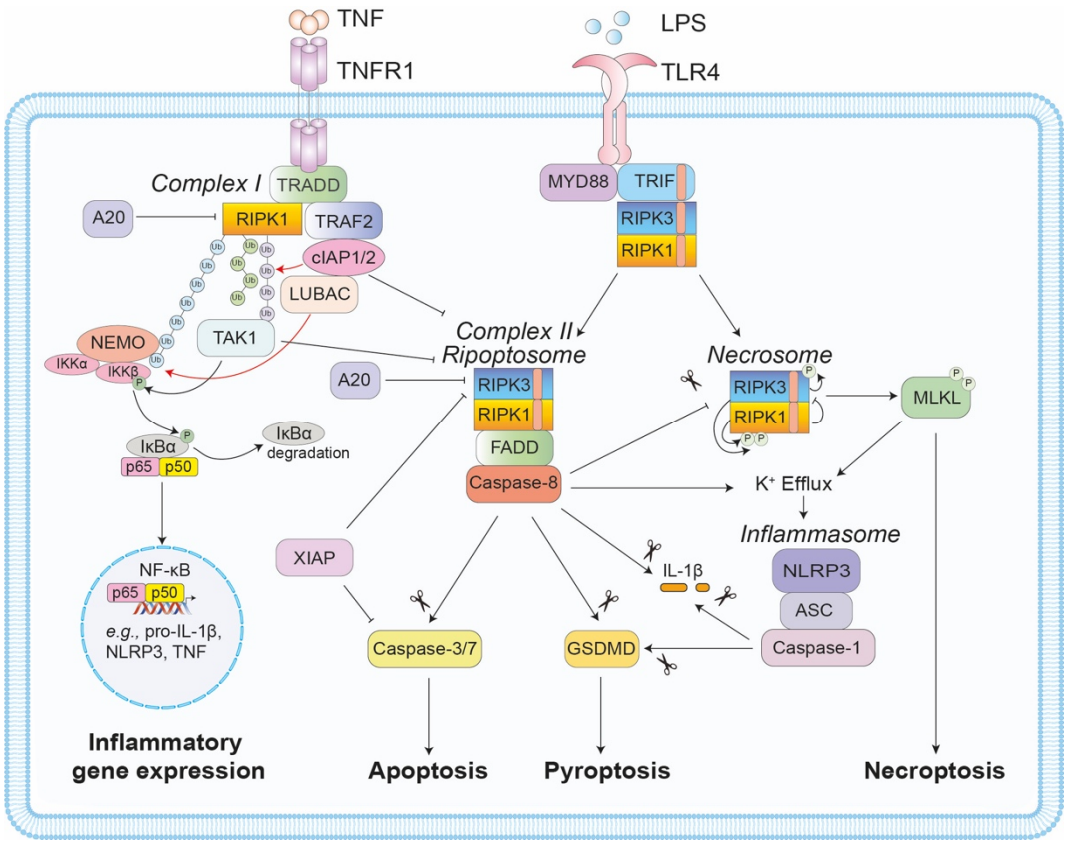

Figure 1. Regulation of RIPK1- and RIPK3-mediated cell death and inflammation. TNF ligation of its receptor, TNFR1, typically induces complex 1 formation, where TNFR1 associates with RIPK1 and TRADD. TRADD subsequently interacts with TRAF2 to facilitate cIAP1 and LUBAC recruitment to the complex. The cIAPs and LUBAC ubiquitylate RIPK1 to facilitate a signalling cascade that induces pro-survival and pro-inflammatory gene expression. If either RIPK1 phosphorylation or ubiquitylation are impaired, FADD-RIPK1(RIPK3)-caspase-8 associate to form the pro-apoptotic complex II (or the ripoptosome). If caspase-8 activity is compromised, a further complex, termed the necrosome, forms in a RIPK1- and RIPK3

kinase-dependent manner. Within this complex, RIPK3-mediated phosphorylation and activation of MLKL induces necroptosis, a lytic inflammatory form of cell death. Of note, TLR4 ligation can also induce similar inflammatory (e.g., RIPK3-caspase-8-mediated cytokine transcription) and cell death events via RHIM-RHIM interactions between the adaptor TRIF and RIPK1/3. In addition to cell death and cytokine transcription, it is now appreciated that both the ripoptosome and the necrosome can promote inflammasome assembly, i.e., caspase-8 and MLKL activity can trigger NLRP3 inflammasome activation, via K^+ efflux, while caspase-8 can also directly cleave IL-1β and GSDMD to induce inflammation.

Complex II, and the related ripoptosome complex that can form in the absence of death receptor ligation [37,38], are essentially comprised of the adaptor protein Fas-associated protein with death domain (FADD), RIPK1, RIPK3, and pro-caspase-8 (Figure 1). Known triggers of complex II/ripoptosome include cIAP loss, via the natural IAP antagonist second mitochondria-derived activator of caspases (Smac; also known as DIABLO), or genetic/chemical depletion [25,37–40], as well as loss/inhibition of TRAF2, TAK1, or IKK-β/γ [18,29,41]. Once formed, catalytically active caspase-8 within complex II triggers apoptosis by cleaving and activating the downstream effector caspases-3 and -7. Caspase-8 can also cleave and truncate Bid to engage the mitochondrial apoptosis pathway and amplify death in certain cell types (i.e., type II cells, including hepatocytes) [42–44]. It is worth mentioning, that while antagonism of X-linked IAP (XIAP) by Smac is thought to promote apoptosis indirectly by unleashing caspase-3, -7, and -9 activity, the ubiquitin E3 ligase activity of XIAP also critically represses TNFR1 and TLR3/4-induced cell death in myeloid cells [45–49].

When the activity of caspase-8 is compromised, either genetically or by viral/chemical inhibition, both TNFR1 and TLR-TRIF signalling can trigger a RIP kinase-dependent, caspase-independent form of lytic cell death called necroptosis (Figure 1) [50,51]. In the case of TNF signalling, loss of both the IAPs and caspase-8 activity promotes full-length RIPK1 and RIPK3 interactions via their RHIM domains to form a functional oligomeric amyloid structure, termed the necrosome [52]. Next, autophosphorylation of RIPK3 facilitates the recruitment of the terminal necroptotic effector, the pseudokinase mixed-lineage kinase domain-like (MLKL). Subsequent phosphorylation of the MLKL activation loop by RIPK3 triggers a conformational change that exposes its N-terminal 4-helix bundle (4HB) killing domain and promotes the assembly of pore-forming oligomers within the plasma membrane and the lytic release of the cellular contents, including inflammatory DAMPs, e.g., interleukin (IL)-1α, IL-33, high-mobility group box 1 (HMGB1), ATP, uric acid, and heat shock proteins (HSPs) [53–58]. Of note, while the kinase activity of RIPK1 is essential for TNF-mediated necroptosis, it is not required for TLR-TRIF signalling. Moreover, RIPK1 inhibits the necroptotic activity of RIPK3 in response to TLR-TRIF signalling [45], and its RHIM domain also acts as a brake on ZBP1-RIPK3-mediated necroptosis during development, via an unknown mechanism [59–61].

It has recently emerged that significant crosstalk exists between extrinsic cell death and inflammatory signalling, particularly with regard to the NOD-like receptor protein 3 (NLRP3) inflammasome (reviewed in [42,62]). The multimeric cytosolic NLRP3 inflammasome complex comprises the sensor protein NLRP3 that is triggered by a number of host and pathogen danger molecules and instigates stepwise inflammasome assembly via recruitment of the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD) and pro-caspase-1. Active caspase-1 then cleaves pro-IL-1β and pro-IL-18 into their mature bioactive forms and activates the pore-forming effector, gasdermin D (GSDMD), to induce pyroptotic cell death. A number of studies have now highlighted how cell death machinery can regulate NLRP3 inflammasome activity via effects on transcriptional responses and post-translational events that facilitate complex assembly [63]. For example, TLR-induced NLRP3 inflammasome priming (i.e., induction of core inflammasome machinery NLRP3 and pro-IL-1β) and post-translational activity was suggested to be dependent on a FADD-caspase-8 complex in response to both canonical and non-canonical caspase-11 inflammasome stimuli [64]. Whilst the defective transcriptional pathway associated specifically with blunted enzymatic caspase-8 activity upon TLR ligation in *Ripk3*$^{-/-}$*Caspase-8*$^{-/-}$, *Ripk3*$^{-/-}$*Fadd*$^{-/-}$, and *Fadd*$^{-/-}$*Mlkl*$^{-/-}$ bone marrow-derived macrophages (BMDM) and

bone marrow-derived dendritic cells (BMDC) remains controversial [64–68], it is now appreciated that a FADD-RIPK1-caspase-8 scaffolding complex supports inflammasome responses [69,70], and that caspase-8 can also interact with ASC to coordinate cell death and IL-1β activation (in the absence of caspase-1) [71–73].

It is now also becoming increasingly clear that RIPK1 and RIPK3 can coordinate alternative and cell death-induced pathways to NLRP3 inflammasome and IL-1β activation [42,74,75] (Figure 1). Loss of key negative regulators of cell death, such as the IAPs, the NF-κB inhibitor and deubiquitinase A20, and TAK1, which promotes phosphorylation events that prevent RIPK1 death signalling [76,77], can also induce modes of RIPK1 (RIPK3)-FADD-caspase-8-mediated NLRP3 inflammasome activation [45–47,49,78–85]. For example, the potassium efflux (K^+) associated with necroptotic cell death in IAP- and/or caspase-8-deficient cells can potently activate the NLRP3 inflammasome in a cell intrinsic manner [45,86,87]. Likewise, RIPK1 can act as a repressor of RIPK3/MLKL-mediated necroptotic activation of NLRP3 [45]. Additionally, TLR4-TRIF (or TNFR) signalling in IAP-depleted myeloid cells can induce the direct caspase-8-mediated proteolysis of IL-1β, as well as NLRP3 inflammasome activation that is dependent on K^+ efflux linked to caspase-8-mediated apoptosis occurring upstream [45,78,88].

TNFR1 signalling via RIPK1 has been long recognised for its role in driving pathogenic pro-inflammatory cytokine and chemokine production in common diseases, such as Rheumatoid arthritis (RA), psoriasis, ankylosing spondylitis, and inflammatory bowel disease (IBD). Hence, TNF antagonists with different mechanisms of action have been used extensively, and with considerable success, to treat these disorders [89–91]. Intriguingly, recent evidence shows that pathology in a number of rare autoinflammatory syndromes is driven by excessive RIPK1/3-mediated cell death and inflammasome-associated IL-1β and IL-18 production [92]. Consequently, RIP kinase inhibitors have significant therapeutic potential beyond simply limiting TNF-induced inflammation. To date, small-molecule inhibitor development has preferentially focused on targeting the kinase activity of RIPK1 [93,94], as RIPK3 kinase inhibitor development has been thwarted by the fact they can promote apoptosis via a RIPK1-FADD-caspase-8-cFLIP complex. This phenomenon is analogous to the embryonic lethality observed in RIPK3 kinase dead (*Ripk3*$^{D161N/D161N}$) mice [95,96]. Since knock-in mice expressing a kinase dead form of RIPK1 are healthy [96,97], it is predicted that inhibitors targeting the kinase activity of RIPK1 will be well tolerated and not disrupt its critical pro-survival scaffolding role. It is also worth acknowledging that, unlike RIPK1-deficient mice that die perinatally, patients with biallelic loss-of-function mutations in RIPK1 survive into early adulthood but do develop primary immunodeficiency typified by recurrent infections, as well as clinical manifestations including oral/skin lesions, arthritis, and early-onset IBD [98,99]. This partial redundancy in humans again highlights RIPK1 as a suitable druggable target for disease.

Current efforts to generate RIPK1 inhibitors have yielded small molecules that bind within the hydrophobic pocket of RIPK1, located between the N- and C-terminus of the kinase domain, and stabilise RIPK1 in an inactive conformation [100]. Pre-clinical studies using RIPK1 kinase dead mice and the first generation indole-hydantoin RIP1 kinase inhibitors, Necrostatin-1s (Nec-1s), and less-specific analogue Nec-1, have demonstrated the potential to target RIPK1 signalling in numerous injury (e.g., renal ischaemic reperfusion, hypoxic brain injury), acute (e.g., systemic inflammatory response syndrome), and chronic inflammatory disease models (e.g., multiple sclerosis) (comprehensively reviewed in [42,94,101]). Now, a number of more specific, small-molecule RIPK1 inhibitors have been developed by Glaxo-Smith Kline (GSK), Sanofi/Denali (DNL), Takeda, and Genentech, which are either undergoing pre-clinical testing or have entered early-phase clinical trials, including the benzoxazepinone GSK2982772 for the treatment of psoriasis, ulcerative colitis (UC), and RA, and brain-penetrant DNL747 for the treatment of the neurodegenerative disease Amyotrophic Lateral Sclerosis (ALS) [94,101,102].

This review will explore the evidence for a role for RIP kinase-regulated cell death and inflammation in rare autoinflammatory syndromes and how mechanistic insights from these conditions can be extrapolated into chronic inflammatory diseases of the gastrointestinal tract, joints, and skin (Table 1), which are triggered by ill-defined environmental and genetic factors. It will also address the therapeutic potential of targeting RIPK1 in the clinic to treat these disorders.

2. Multi-Organ—Autoinflammatory Syndromes

To date, mutations in cell death regulatory genes, including TNFR1, XIAP, A20, OTULIN, LUBAC components (HOIL-1, HOIP and SHARPIN), RIPK1, and caspase-8, cause primary immunodeficiency, autoimmunity, and/or trigger autoinflammation reminiscent of NLRP3 autoactivating mutation-associated cryopyrin-associated periodic syndromes (CAPS). In the case of TNFR-associated periodic syndrome (TRAPs), XIAP deficiency (i.e., hemophagocytic lymphohistiocytosis), haploinsufficiency in A20 (HA20), LUBAC deficiency, otulipenia, and biallelic RIPK1 deficiency common overlapping clinical manifestations include recurrent fever and infection, arthritis and arthralgia/myalgia (i.e., joint and musculoskeletal pain), skin lesions, and intestinal inflammation and/or diarrhoea, as well as on occasion hepatosplenomegaly [63,98,103–108]. Often, mutation of these genes in mice causes embryonic or perinatal lethality associated with multi-organ inflammation and/or excessive cell death that precludes analysis of common disease manifestations, but cell-specific gene targeting is beginning to establish disease mechanisms and therapeutic targets [107,109–113]. Moreover, despite the variability in death modalities that may drive autoinflammation, therapeutics targeting TNF, IL-6, or IL-1β itself are comparatively effective, although responses can be unpredictable [114]. Hence, targeting upstream signalling pathways may yield a more uniform therapeutic responsiveness and this approach will be discussed in more detail below.

3. Joints—Rheumatoid Arthritis

Historically, RA development and chronicity have been linked to a lack of apoptosis due to the expression of intrinsic and extrinsic pro-survival proteins in inflamed synovial joints [115–119]. This prompted interest in examining the cell-specific survival requirements of pathogenic cells [120–123] and the repurposing and pre-clinical testing of anti-cancer small-molecule drugs (e.g., BH3 mimetics, pegylated TRAIL) to treat arthritis, albeit with limited to moderate therapeutic success [124–127]. In fact, the generation of conditional mutant mice lacking key extrinsic cell death regulatory machinery, namely A20 ($A20^{\text{LysM.cre}}$), cIAP1/2 ($cIap1^{\text{LysM.cre}}cIap2^{-/-}$), or XIAP/cIAP1/2 ($cIap1^{\text{LysM.cre}}Xiap^{-/-}cIap2^{-/-}$) in myeloid cells, and caspase-8 inhibitor c-FLIP ($c\text{-}flar^{\text{CD11c.cre}}$) in dendritic cells, revealed how perturbation of cell death signalling pathways can induce multi-organ inflammation characterised by severe inflammatory arthritis (Table 1). Moreover, a dominant inflammasome-associated IL-1β signature was observed in all arthritic mutant mice; with the exception of the myeloid-specific cIAP1/2 knockout mouse (that exhibited TNF as the main biomarker) [45,82,128,129]. Notably, pathogenicity of disease in these spontaneous arthritis models is complex as, in some cases, disease is rescued by NLRP3 inflammasome deficiency rather than TNF loss, and vice versa. Therefore, the contribution of apoptotic versus necroptotic signalling, particularly in IL-1β activation, remains ill defined. For example, while in vitro evidence suggests that NLRP3 inflammasome and IL-1β activation in the absence of A20 (encoded by *TNFAIP3*) is regulated by RIPK3-caspase-8 signalling, a recent study in $A20^{\text{LysM.cre}}$ mice showed that loss of RIPK3, MLKL, or the kinase activity of RIPK1, dampened IL-1β activity and alleviated arthritis symptoms [130].

Examination of genetic knockout mice lacking central cell death repressors, the IAPs, in experimental arthritis models has also revealed potential overlap between monogenic disease and inflammatory arthritis pathogenesis. Reconstitution of wild-type mice with bone marrow lacking XIAP/cIAP1/2 or cIAP1/2 in the myeloid compartment not only transferred a mild form of spontaneous arthritis but also promoted exaggerated innate

immune cell-driven K/BxN serum-induced arthritic responses that were associated with enhanced IL-1β and TNF activity, respectively. Noting that single cIAP1-, cIAP2-, and XIAP-deficient, as well as XIAP/cIAP2 doubly-deficient mice behaved akin to wild-type animals [45]. Further mechanistic insight into how TNFR1 and TLR signalling may regulate inflammatory arthritis has also been gained using mice deficient in core cell death signalling machinery and kinase inhibitors. For example, in the acute K/BxN serum-induced arthritis model, signalling via TLR4-MyD88, as well as IL-1α and IL-1β activity, play a more crucial role in disease progression and chronicity than TNF itself [34]. Remarkably, studies examining *Trif*$^{-/-}$, *Ripk3*$^{-/-}$, *Mlkl*$^{-/-}$, and *Ripk3*$^{-/-}$*caspase-8*$^{-/-}$ (where caspase-8 is deleted on a RIPK3-deficient background to avoid lethal necroptotic signalling [43,44]) mice revealed that a TLR-TRIF-RIPK3-caspase-8 signalling axis regulates caspase-1-independent IL-1β secretion during the late macrophage-driven phase of this disease model. Surprisingly, MLKL was redundant for arthritis development or resolution in this context [45]. Fitting with the idea that dysregulated caspase-8 activity may drive disease progression, mice lacking the extrinsic death receptor Fas in myeloid cells also exhibited enhanced disease resolution, although this was not associated with a blunted IL-1β response [123]. Intriguingly, a further study showed that conditional deletion of caspase-8 in dendritic cells (*Caspase-8*$^{CD11c.cre/+}$) exacerbated arthritis, whilst, conversely, myeloid cell-specific caspase-8 loss (*Caspase-8*$^{LysM.cre/cre}$) enhanced disease resolution. Disease perturbations were suggested to be caused by altered RIPK3-mediated signalling and the development of innate immune cell populations, as co-deletion of RIPK3 reversed overall disease responses [131]. This work points to RIPK1/3-caspase-8 signalling having differential effects in specific myeloid populations, as previously evidenced by the distinct role for RIPK1 versus RIPK3 in repressing cytokine production in the *Caspase-8*$^{CD11c.cre/+}$ and *Caspase-8*$^{LysM.cre}$ mice [132]. It is also worth noting that in our hands, *Caspase-8*$^{LysM.cre/+}$ (hemizygous Cre) mice developed comparable, if not mildly enhanced, levels of arthritis compared to *Caspase-8*$^{lox/lox}$ mice (Lawlor KE, unpublished data), which is more reminiscent of the *Caspase-8*$^{CD11c.cre/+}$ mice. Overall, differences in RIPK-caspase-8 signalling requirements in arthritis pathogenesis could be due to differential cell-specific effects, levels of Cre recombinase expression, absolute levels of caspase-8 that can act as scaffolding for multiple modes of cell death [45,69,70,87,132,133], as well as environmental and genetic differences (e.g., *Caspase-8*$^{lox/lox}$ derived on a 129 [131] versus C57BL/6 [45] background).

RIPK1 kinase inhibitors are an attractive therapeutic avenue for RA, as they may limit TNF-induced inflammation in addition to blocking cell death that also has the propensity to be pro-inflammatory. Indeed, two groups have documented the therapeutic efficacy of RIPK1 kinase inhibitors in acute and chronic arthritis models. In the case of chronic autoimmune collagen-induced arthritis, prophylactic treatment with the RIPK1 kinas inhibitor necrostatin-1s (Nec-1s) modestly reduced the incidence and severity of arthritis and was associated with reduced cytokine and necroptotic activity in the synovium, a skewing of the CD4^{+} T-cell response towards a T_H2 and regulatory T-cell profile, and attenuated osteoclastogenesis [134]. In comparison, both RIPK1 kinase dead mice and mice receiving the RIPK1 kinase inhibitor, GNE684, were shown to have reduced acute innate immune cell-driven collagen antibody-induced arthritis (CAIA). This effect was directly attributable to GNE684 inhibiting TNF signalling, as blocking TNF using TNFR2-Fc caused an equivalent effect and failed to further dampen responses upon co-therapy [135]. On the surface, these results suggest that RIPK1 kinase inhibitors are likely to be as efficacious as TNF biologicals for the treatment of RA. However, a Phase II clinical trial in patients with moderate to severe RA using the first-in-class small-molecule RIPK1 inhibitor GSK2982772 (NCT02858492) failed to see significant clinical improvement beyond potential reductions in bone erosions [136]. It remains to be seen whether improved bioavailability, or treatment of mild RA cases, will reveal therapeutic efficacy.

4. Skin—Psoriasis and Dermatitis

RIPK1 has an established role in preventing apoptosis and necroptosis of murine epithelial cells, and *Ripk1*$^{-/-}$ neonates have elevated levels of inflammatory cytokines in their skin, as well as keratinocyte hyperplasia that is a hallmark of excessive cell death [30,35,36,59,61,137]. RIPK1 also appears to play a protective role in human keratinocytes, albeit less dominantly. Patients with biallelic mutations in RIPK1 can present with inflammatory skin lesions among a number of more debilitating pathologies (Table 1) [98,99]. In contrast, patients with cleavage-resistant RIPK1 autoinflammatory (CRIA) syndrome caused by heterozygous mutations in the caspase-8 cleavage site (D324) do not display a skin phenotype, although mice harbouring a homozygous mutation (*Ripk1*$^{D325A/D325A}$) of this conserved site do exhibit skin hyperplasia [138]. In fact, a number of mouse models with dysregulated complex I signalling present with lethal inflammatory skin disorders, often linked to RIPK1 activity [139,140]. In humans, autoinflammatory skin disorders, such as psoriasis, are multi-factorial [141]. However, inflammation-associated keratinocyte cell death does appear to major contributor to disease pathology.

The heterotrimeric linear ubiquitin chain assembly complex (LUBAC; composed of HOIP that harbours the essential enzymatic activity, and HOIL-1 and SHARPIN that promote complex assembly and stability) coordinates NF-κB activation via linear ubiquitylation of RIPK1 and NEMO within complex I. As briefly touched on above, HOIL-1- and HOIP-deficient patients survive but present with immunodeficiency and multi-organ autoinflammation, including dermatitis [106,142,143]. In contrast, the absence of HOIL-1 or HOIP in mice, and the ensuing lack of linear ubiquitylation in complex I, results in early-mid-gestational lethality due to aberrant TNFR1-mediated endothelial apoptotic and necroptotic cell death that is only partially dependent on the kinase activity of RIPK1 [144]. Intriguingly, whilst combined MLKL and caspase-8 deficiency rescues the HOIL-1 and HOIP-deficient mice from embryonic lethality, co-deletion of RIPK3 and caspase-8 results in late-gestation lethality due to RIPK1-induced haematopoietic defects [144]. Examination of the role of LUBAC selectively in skin homeostasis, via conditional deletion of HOIL-1 and HOIP in mouse keratinocytes (keratin 14 promoter), revealed the onset of lethal postnatal dermatitis at 4–6 days-of-age, which was partially attributable to exaggerated TNFR1-mediated apoptotic caspase-8 activity but largely RIPK1-independent [145]. Interestingly, however, the skin lesions that developed in the absence of both TNFR1 and HOIL-1 were delayed by MLKL loss and completely rescued by RIPK1 kinase inhibition using GSK'547, suggesting a combination of RIPK1 kinase-dependent apoptosis and necroptosis is triggered in the absence of LUBAC and TNFR1 [145]. Additionally, in the absence of TNFR1, dermatitis was induced redundantly by TNF-related apoptosis-inducing ligand (TRAIL) or Fas (CD95), suggesting that multiple death receptors mediate skin disease in the absence of linear ubiquitylation signals [145].

In contrast to HOIL-1- and HOIP-deficiency, mice deficient in SHARPIN (*Sharpin*$^{cpdm/cpdm}$) are viable but present with severe multi-organ inflammation and progressive dermatitis with alopecia that develops from 3–4 weeks of age [146]. Viability is attributed to the fact that, in the absence of SHARPIN, decoration of TNFR1 signalling components with linear ubiquitin chains is merely reduced, rather than absent [144]. Dermatitis in *Sharpin*$^{cpdm/cpdm}$ mice is driven by TNF/TNFR signalling in keratinocytes and is dependent on the kinase activity of RIPK1, and also partly dependent on NLRP3 inflammasome-mediated IL-1β activity and IL-1 receptor signalling [19,113,140,147–150]. Caspase-8 heterozygosity significantly delays dermatitis onset, while co-deletion of FADD (in the skin) and RIPK3 was required to entirely ablate skin inflammation, implying that inflammation is primarily driven by apoptosis, with a minor role for necroptosis [113,151]. Interestingly, in line with the late-gestation lethality observed in HOIL-1- and HOIP-deficient mice, *Sharpin*$^{cpdm/cpdm}$*Ripk3*$^{-/-}$*caspase-8*$^{-/-}$ mice exhibited perinatal lethality due to defects in haematopoiesis [113,144]. Mirroring genetic studies, small-molecule RIPK1 inhibitor GNE684 therapy in *Sharpin*$^{cpdm/cpdm}$ mice with established dermatitis reduced inflammation and caspase-3 cleavage in the skin [135,152].

As discussed above, the inhibitor of apoptosis proteins (cIAP1, cIAP2, and XIAP) also regulate cell fate in a RIPK1 and/or RIPK3-dependent manner. Loss of IAP activity in the skin, via injection of a pan-IAP-targeting Smac mimetic (SM), Compound A or 911, leads to more extensive skin lesions than those observed in *Sharpin*$^{cpdm/cpdm}$ mice. Noting that disease manifestations were linked to TNFR1 and/or FasL-mediated apoptotic cell death and inflammation, with necroptosis appearing to drive secondary damage [139]. Genetic loss of specific IAP family members was also found to trigger distinct skin phenotypes. For example, while *cIap1*$^{K14.cre/K14.cre}$*Xiap*$^{-/-}$ mice develop a spongiotic dermatitis with psoriasis-like features affecting the ears and face from around 10 weeks of age, *cIap1*$^{K14.cre/K14.cre}$*cIap2*$^{-/-}$ mice become moribund at postpartum day 10 due to widespread dermatoses that, like the *Sharpin*$^{cpdm/cpdm}$ mice, are prevented by *Ripk1* heterozygosity [139]. In humans, IAPs are abundantly expressed in the skin and their levels are potently reduced by SM administration [153], so one could envisage unwanted inflammation could present during systemic therapies. However, SM have in general been well tolerated during Phase1/II clinical trials for haematological and solid cancer malignancies; with only high doses inducing adverse events (e.g., cytokine release syndrome, diarrhoea, vomiting, fatigue, anorexia, and occasionally a pruritic rash [93,154]).

Neutrophilic dermatoses, such as Sweet's syndrome and pyoderma gangrenosum, are often associated with mutant forms of protein tyrosine phosphatase-6 (PTPN6) that trigger cell death-induced tissue inflammation [155,156]. In mice, conditional deletion of *Ptpn6* in neutrophils is sufficient to initiate a severe IL-1α/β-mediated cutaneous inflammatory disease driven by both caspase-8-dependent apoptotic and RIPK3/MLKL-dependent necroptotic signalling, suggesting that mutant forms of PTPN6 may fail to restrict RIPK1 pro-death activity [157,158]. Remarkably, genetic loss of RIPK1, or its kinase activity (*Ripk1*^{D138N}), actually accelerated disease onset in this context, suggesting divergent signalling in neutrophilic dermatoses compared to psoriasiform conditions caused by LUBAC and IAP mutations [158].

Despite genetic evidence that the IAPs and RIPK1 can repress inflammatory skin lesions, studies into RIPK1 and RIPK3 function in the context of psoriasis are limited. RIPK1 expression was reported to be decreased in lesions of plaque-type psoriasis patients, thereby sensitizing keratinocytes to TRAIL. Correspondingly, TRAIL neutralisation in an imiquimod (IMQ)-induced murine model of psoriasis improved skin inflammation and led to a decrease in inflammatory cytokines [159]. In contrast, a more recent study observed increased levels of RIPK1, RIPK3, MLKL, and phosphorylated (p)MLKL in psoriatic lesions from patients, suggesting that the skin pathology may be driven by necroptosis [160]. Consistent with this notion, treatment with the RIPK1 inhibitor, Nec-1s, or the MLKL inhibitor necrosulfonamide (NSA) reduced IMQ-induced psoriasis, with the caveats that NSA targets GSDMD rather than MLKL in mice, and the fact that a further study found no role genetically for the kinase activity of RIPK1 or RIPK3 [161,162]. Overall, the complexity of RIPK1's role in skin inflammation suggests that caution should be taken when targeting RIPK1 in all hyperinflammatory disorders, or that rationally designed drugs targeting other cell death machinery may have merit [158]. Encouragingly, a recent Phase II clinical trial using RIPK1 inhibitor GSK2982772 in plaque-type psoriasis has shown therapeutic benefit but there is still a lack of data surrounding RIPK1 inhibitors and their long-term use in the clinic [163,164].

5. Gut—Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), which includes the chronic relapsing inflammatory disorders Crohn's Disease (CD) and ulcerative colitis (UC), is characterised by intestinal inflammation and epithelial cell injury affecting the gastrointestinal (GI) lining [165]. The GI tract harbours an enormous bacterial load and disruption of mucosal barrier integrity due to aberrant intestinal epithelial cell (IEC) death allows luminal bacteria to enter the lamina propria and trigger inflammation [166–168].

Germline loss-of-function mutations in XIAP pre-dispose males to very-early-onset (VEO)-IBD [169–171]. Additionally, approximately 50–70% of patients with X-linked lymphoproliferative disease 2 (XLP2), caused by mutations that limit XIAP expression/function, develop hemophagocytic lymphohistiocytosis (HLH) with symptoms that include hyperinflammation and early-onset chronic haemorrhagic colitis [172–175]. In addition to its critical role in suppressing ripoptosome formation and subsequent NLRP3 inflammasome activation in innate immune cells [45–49,78], XIAP also ubiquitylates the nucleotide-binding oligomerisation domain (NOD)-2 adaptor, RIPK2 [176]. NOD2 responds to the bacterial cell wall component, muramyl dipeptide (MDP), and signalling via this pathway has been implicated in IBD pathogenesis [177–179]. The fact that both XLP2 and very early-onset (VEO)-IBD *XIAP* variants confer increased sensitivity to cell death [180] suggests the possibility of a combined role for perturbed NOD2-RIPK2 signalling and RIPK1-mediated cell death in IBD pathogenesis.

TNFR1 signalling is unequivocally connected with IBD pathogenesis, as best demonstrated by the wide-spread use of anti-TNF therapeutics in IBD patients [181,182], and the clinical benefits observed in pre-clinical IBD models using drugs targeting downstream TLR/TNFR1 inflammatory signalling molecules [183]. Interestingly, despite a clear role for TNFR1 complex I signalling, evidence now suggests that TNFR1-mediated cell death also contributes to IBD (Table 1). Mutations in mice that derepress RIPK1-dependent apoptotic and/or necroptotic IEC death elicit severe chronic intestinal inflammation, akin to that seen in IBD in humans. For example, loss of IKK complex component NEMO in IECs (*Villin* cre) results in spontaneous colitis mediated by TNFR1 signalling and RIPK1 kinase-dependent cell death [135,184,185], while IKKβ protects against colitis induced by *Clostridium difficile* or dextran sodium sulphate (DSS) [186,187]. Loss of upstream TAK1 in IECs triggers TNFR1-dependent (presumably RIPK1-dependent) apoptosis and intestinal inflammation, although colitis and ileitis ultimately develop in the absence of TNFR1 [188]. Whilst deficiencies in IKK or NF-κB have not yet been reported in human IBD patients, patients with ecto-dermal dysplasia with immunodeficiency (EDA-ID) caused by hypomorphic NEMO mutations often suffer from colitis [189–192]. In addition, *TNFAIP3*, which encodes A20, is a susceptibility locus for CD and UC in humans [193]. Exactly how A20 expression contributes to IBD development is still unclear but, in contrast to other spontaneous diseases caused by conditional A20 loss, deletion of A20 in both IECs and myeloid cells is required to induce spontaneous colitis and ileitis, as well as apoptosis of crypt cells [194,195]. Different groups have also reported that overexpression of A20 in IECs is protective in lipopolysaccharide (LPS) and DSS-induced colitis models [196,197] but promotes RIPK1-dependent IEC death in response to TNF [198].

Both apoptotic caspase-8 and its adaptor protein FADD have been revealed to be vital to maintaining intestinal homeostasis [43,44,199,200]. Mice lacking FADD in IECs ($Fadd^{\text{Villin.cre}}$) develop severe colitis and ileitis, as well as Paneth cell loss [201]. $Caspase\text{-}8^{Villin.cre}$ mice also present with ileitis and Paneth cell loss, but colitis only develops in the presence of certain microbiota [202,203]. Colitis in both the $Fadd^{\text{Villin.cre}}$ and $Caspase\text{-}8^{\text{Villin.cre}}$ mice is caused by RIPK1 kinase activity-dependent IEC necroptosis and is primarily mediated by TNFR1, with a minor role for ZBP1 [201,204,205]. In contrast, TNFR1 and ZBP1 act redundantly to trigger ileitis in the $Caspase\text{-}8^{\text{Villin.cre}}$ and $Fadd^{\text{Villin.cre}}$ mice, which is also driven by necroptotic IEC death. It is worth noting that FADD-deficient IECs can also reportedly utilise RIPK3 scaffolding to undergo caspase-8-mediated apoptosis and a 'pyroptotic-like' death [204]. Surprisingly, humans with loss-of-function mutations in the *CASP8* gene develop VEO-IBD that is refractory to TNF treatment [206], suggesting that ZBP1 (or possibly TLR signalling) may also drive intestinal inflammation in human patients. The importance of RIPK1 kinase activity in inflammation arising from loss FADD or caspase-8 loss underscores the therapeutic potential of targeting the kinase activity of RIPK1 in *CASP8* mutant patients with VEO-IBD.

Table 1. Spontaneous tissue pathologies linked to RIPK signalling.

Gene Name	Mutation	RIP Kinase Signalling	Joint	Skin	Gut	Ref.
Tnfaip3 **Mouse**	Myeloid-specific A20 knockout ($Tnfaip3^{LysM.cre}$)	RIPK1 kinase/RIPK3/MLKL-dependent necroptosis and NLRP3 inflammasome activation	Arthritis			[82,128,130]
	Intestinal epithelium- and myeloid-specific A20 knockout [B] ($Tnfaip3^{Villin.cre}Tnfaip3^{LysM.cre}$)	⇑ TNF-induced IEC apoptosis [C]			Severe colitis	[194,195]
cIAP1, cIAP2 **Mouse**	Myeloid-specific cIAP1 and global knockout of cIAP2 [A,B] ($cIap1^{LysM.cre}cIap2^{-/-}$)	⇑ TNF serum levels	Arthritis			[45]
	Epidermal-specific cIAP1 and global knockout of cIAP2 ($cIap1^{E\text{-}KO}cIap2^{-/-}$)	TNF-mediated RIPK1-dependent apoptosis		Severe dermatitis		[139]
cIAP1, XIAP **Mouse**	Epidermal-specific cIAP1 and global knockout of XIAP ($cIap1^{E\text{-}KO}$ $Xiap^{-/-}$)	RIPK1-dependent cell death		Severe dermatitis		[139]
cIAP1, cIAP2, XIAP **Mouse**	Myeloid-specific cIAP1 and global knockout of cIAP2 and XIAP [B] ($cIap1^{LysM.cre}cIap2^{-/-}$ $Xiap^{-/-}$)	⇑ TNF, IL-1 RIPK3-dependent apoptosis or necroptosis	Arthritis	Inflammation		[45]
Fadd **Mouse**	Intestinal epithelial cell-specific knockout of FADD ($Fadd^{Villin.cre}$)	TNF-induced RIPK3-dependent necroptosis Caspase-8/GSDMD-dependent pyroptosis			Colitis, ileitis	[201,204]
Caspase-8 **Mouse**	IEC-specific knockout of Caspase 8 ($Caspase\text{-}8^{Villin.cre}$)	TNF-induced RIPK3-dependent necroptosis			Ileitis, susceptible to colitis	[202,203]
Human	Loss of function mutations in Caspase-8	⇑ IL-1 (patient-derived monocytes) [C]			VEO-IBD	[206]
RIPK1 **Mouse**	Global RIPK1 knockout [A,B] ($Ripk1^{-/-}$)	Apoptosis and RIPK3-dependent necroptosis		Epidermal hyperplasia		[35,97]
	Epithelial-specific knockout of RIPK1 ($Ripk1^{E\text{-}KO}$)	TNFR1-induced RIPK3- and ZBP1-RIPK3-MLKL-dependent necroptosis		Psoriasis-like disease		[30,61,137]
	RHIM domain mutation [A] ($Ripk1^{RHIM/RHIM}$)	Overactive ZBP1-RIPK3-MLKL-dependent necroptosis		Dermatitis		[59]
	IEC-specific knockout of RIPK1 [A] ($Ripk1^{Villin.cre}$)	TNF/FADD-dependent apoptosis or RIPK3-dependent necroptosis (when FADD is absent)			Inflammation	[30,36]
	Caspase-8 cleavage-resistant RIPK1 [B] ($Ripk1^{D325A/D325A}$)	TNF-induced apoptosis and necroptosis		Skin hyperplasia		[138]
Human	Homozygous loss-of-function or missense mutations [B]	⇑ IL-1β signalling Aberrant TNFR and TLR signalling	Early-onset poly-arthritis	Skin lesions	IBD	[98,99,138,207]
HOIL-1 **Mouse**	Keratinocyte-specific deletion of HOIL [A] ($Hoil^{E\text{-}KO}$)	TNFR1-induced Caspase-8-dependent apoptosis (RIPK1 independent)		Dermatitis		[145]
Human	Autosomal recessive loss-of-function [B]	⇓ RIPK1 polyubiquitination		Dermatitis	IBD	[143]
Hoip **Mouse**	Keratinocyte-specific deletion of HOIP [A] ($Hoip^{E\text{-}KO}$)	TNFR1-induced Caspase-8-dependent RIPK-independent apoptosis		Lethal dermatitis		[145,112]
Sharpin **Mouse**	Global knockout ($Sharpin^{cpdm/cpdm}$) [B]	TNFR1-induced cell death ⇓ NF-κB signalling	Arthritis	Severe dermatitis	Loss of Peyer's patches in gut	[19,113,135,140,147]

Genetic models of spontaneous disease in the joints, skin, or gastrointestinal tract where loss of factors targeting RIPK1/3 directly have been clearly implicated. Key: [A] Embryonic or postnatal lethality; [B] multi-organ inflammation; [C] direct role for RIP kinase signalling is unclear.

RIPK1 has a critical pro-survival scaffolding role and patients with biallelic mutations in RIPK1 present with early-onset IBD involving the upper and lower GI tract that is triggered by environmental insults [98,99,207]. It is clear from these studies that RIPK1-deficient human cells have aberrant TNFR and TLR signalling responses and a potential increase in the number of apoptotic bodies within crypts. However, how RIPK1 regulates intestinal homeostasis (i.e., IEC death versus cytokine production) remains ill defined. Interestingly, the presence of necrotic lesions in CD patients [202,208], combined with the fact that elevated pRIPK1, pRIPK3, and pMLKL levels in the terminal ileum and colon correlate with severe disease in both CD and UC patients [209–212], indicates that RIPK1-dependent necroptosis may contribute to pathology in human IBD. Indeed, pharmacological inhibition of RIPK1 kinase activity has been shown to be effective in the murine $CD4^{+}CD45RB^{HI}$ T-cell transfer model of colitis and provided dose-dependent protection from inflammatory cell death in $Nemo^{Villin.cre/+}$ mice [213]. Yet, curiously, despite some groups reporting that MLKL-deficient mice are protected from DSS-induced colitis and colitis-associated tumourigenesis [214,215], other studies, including those using littermate control animals, found little-to-no role for RIPK1 kinase, RIPK3- or MLKL-dependent necroptotic signalling in DSS-induced colitis and/or colorectal cancer [162,216]. Nonetheless, RIPK1 may still mediate deleterious non-necroptotic signalling in IBD and other related disorders. In fact, pre-clinical studies have shown that the small-molecule RIPK1 kinase inhibitor, GSK2982772, blocks spontaneous cytokine production in explants derived from UC patients and reduces inflammation in a DSS-induced colitis model in mice [164,217]. It will be interesting to see the published results from a recently completed Phase II clinical trial examining the efficacy of GSK2982772 in UC patients [NCT02903966].

6. Conclusions

This review gives an overview of the role of RIPK1 and RIPK3 activity in inflammatory diseases associated with the skin, gut, lung, and joints. RIPK1 and RIPK3 are central regulators of inflammatory signalling and control multiple modalities of cell death downstream of death receptor and TLR ligation. As such, perturbations in RIPK-dependent signalling networks are a feature of many auto-inflammatory and chronic inflammatory disorders. Existing therapeutics largely focus on targeting pro-inflammatory cytokines, such as TNF, IL-1β, and IL-6. However, many patients experience treatment failures or severe adverse reactions, supporting the need for new drug development in this space. Small-molecule RIP kinase inhibitors are now emerging in the clinic. Although a large number of pre-clinical studies have shown that targeting RIPK1 kinase activity limits deleterious inflammation in models of acute and chronic inflammation [101], early results from Phase I/II clinical trials with RIPK1 kinase inhibitors have revealed that, although well tolerated, they may not hold up to their full therapeutic promise [136]. As such, much more information is required in order to fully understand the multi-faceted roles these kinases play in regulating cell fate and innate immunity during homeostasis, as well as during infectious and inflammatory disease in humans. Ultimately, this knowledge will enable better rational drug design and the development of co-therapeutic strategies that maximise clinical benefit whilst ameliorating the risk of treatment failures and unwanted side-effects.

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Abbreviations

ASC	apoptosis-associated speck-like containing a CARD
CAIA	collagen antibody-induced arthritis
CAPS	cryopyrin-associated periodic syndromes
CARD	caspase activation and recruitment domain
caspase	cysteine-dependent aspartic acid-specific protease
CD	Crohn's Disease
cFLIP	cellular FLICE-like inhibitory protein
cIAP	cellular inhibitor of apoptosis protein
CRIA	cleavage-resistant RIPK1-induced autoinflammatory syndrome
CYLD	cylindromatosis
DAI	DNA-dependent activator of IFN regulatory transcription factors
DAMP	damage-associated molecular pattern
DNA	deoxyribonucleic acid
EDA-ID	ecto-dermal dysplasia with immunodeficiency
ER	endoplasmic reticulum
GI	gastrointestinal
GSDMD	gasdermin D
HA20	haploinsufficiency in A20
HLH	hemophagocytic lymphohistiocytosis
HMGB1	high-mobility group box 1
HOIL-1	haeme-oxidized IRP2 ubiquitin ligase 1
HOIP	HOIL1-interacting protein
HSP	heat shock protein
IBD	inflammatory bowel disease
IAV	Influenza A virus
IEC	intestinal epithelial cell
IFN	interferon
IL	interleukin
IMQ	imiquimod
LOF	loss of function
LRR	leucine-rich repeat
LUBAC	linear ubiquitin chain assembly complex
MAPK	mitogen-activated protein kinase
MDP	muramyl dipeptide
MLKL	mixed lineage kinase domain-like
NEMO	NF-κB essential modulator (IKK)
NF-κB	nuclear factor-kappa B
NLR	NOD-like receptor
NLRP3	NOD-like protein receptor 3
NOD	nucleotide-binding oligomerization domain
NSA	necrosulfonamide
PAMP	pathogen-associated molecular pattern
PRR	pattern recognition receptor
RA	rheumatoid arthritis
RIPK	receptor-interacting protein kinase
RNA	ribonucleic acid
ROS	reactive oxygen species
RSV	respiratory syncytial virus
SHARPIN	SHANK-associated RH domain-interacting protein
PTPN6	protein tyrosine phosphatase-6
SMAC	second mitochondrial activator of caspases
SM	Smac mimetic
TAK1	transforming growth factor—activated kinase
TLR	Toll-like receptor
TNF	tumour necrosis factor

TNFR	tumour necrosis factor receptor
TRADD	TNFR1-associated death domain protein
TRAF2	TNF receptor-associated factor 2
TRAIL	TNF-related apoptosis-inducing ligand
TRAPS	TNFR-associated periodic syndrome
TRIF	TIR-domain-containing adapter-inducing interferon-β
UC	ulcerative colitis
VEO	very-early onset
XIAP	X-linked inhibitor of apoptosis protein
XPL2	X-linked lymphoproliferative disease 2
ZBP1	Z-DNA binding protein 1

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