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Review

The diverse roles of RIP kinases in host-pathogen interactions

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ABSTRACT

Receptor Interacting Protein Kinases (RIPKs) are cellular signaling molecules that are critical for homeostatic signaling in both communicable and non-communicable disease processes. In particular, RIPK1, RIPK2, RIPK3 and RIPK7 have emerged as key mediators of intracellular signal transduction including inflammation, autophagy and programmed cell death, and are thus essential for the early control of many diverse pathogenic organisms. In this review, we discuss the role of each RIPK in host responses to bacterial and viral pathogens, with a focus on studies that have used pathogen infection models rather than artificial stimulation with purified

Abbreviations: $3C^{pro}$, viral non-structural protein 3C; AEC, airway epithelial cell; AIM2, absent in melanoma 2; ALRs, AIM2-like receptors; AP-1, activator protein 1; ATG16L1, autophagy-related 16-like 1; ASC, apoptosis-associated speck-like protein; BAV, BeAn 58058 poxvirus; Bcl-2, B-cell lymphoma 2; BclxL, Bcl-extra large; BMDMs, bone marrow-derived macrophages; BVDV, bovine viral diarrhoea virus; CA6, coxsackievirus A6; CARD, caspase activation and recruitment domain; CD, Crohn's disease; c-FLIP, cellular FLICE inhibitory protein; cIAPs, cellular inhibitor of apoptosis proteins; Cif, cycle inhibiting factor; CMV, cytomegalovirus; CNF1, cytotoxic necrotising factor 1; CNS, central nervous system; COR, C-terminal of Roc; COTV, Cotia poxvirus; COVID-19, coronavirus disease 2019; CVB, coxsackievirus B3; DAI, DNA-dependent activator of IRFs; DAMPs, danger-associated molecular patterns; DAP, diaminopimelic acid; DENV, dengue virus; DISCs, death-inducing signaling complexes; DR, death receptor; DRP1, dynamin-related protein 1; dsRNA, double stranded RNA; E3L, vaccinia virus protein E3 long; EBV, Epstein-Barr virus; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinases; GEF, guanidine exchange factor; GSDMD, gasdermin D; HAEC, human aortic endothelial cells; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HFMD, hand foot and mouth disease; HIV-1, human immunodeficiency virus type 1; HMGB1, high mobility group box 1; HPV, human papilloma virus; HSV, Herpes simplex virus; IAV, influenza A virus; ID, intermediate domain; iE-DAP, γ-D-glutamyl-mesodiaminopimelic acid; IFI44L, IFN-induced protein 44-like; IFN, interferon; IL, interleukin; IκB, inhibitor of κB; IKK, IκB kinase; IRFs, IFN regulatory factors; IRG1, immunoresponsive gene 1; ISGF3, IFN-stimulated gene factor 3; ISGs, interferon stimulated genes; JEV, Japanese encephalitis virus; JNK, c-Jun N-terminal kinase; KD, kinase domain; Kgp, lysine-specific protease gingipain; KO, knockout; LMP1, latent membrane protein; LPS, lipopolysaccharide; LRR, leucine-rich repeat; LUBAC, linear ubiquitin chain assembly complex; M45, murine CMV virion associated protein M45; MAPKs, mitogen-activated protein kinases; MAVS, mitochondrial antiviral signaling proteins; MCMV, murine cytomegalovirus; MDA5, melanoma differentiation-associated protein 5; MDP, muramyl dipeptide; MLKL, mixed-lineage kinase-domain like protein; MKKs, MAPK kinases; Mtb, *Mycobacterium tuberculosis*; MyD88, myeloid differentiation factor 88; NAIPs, NLR family apoptosis inhibitory proteins; Nec-1, necrostatin-1; NET, neutrophil extracellular traps; NF-κB, nuclear factor-κB; NK, natural killer; NleB, non-LEE encoded effector protein B; NLRs, nucleotide-binding domain–like receptors; NLRC4, NLR family CARD domain containing 4; NLRP3, NLR family pyrin domain containing 3; NO, nitric oxide; NOD, nucleotide-binding oligomerization domain; NoV, norovirus; NP, nucleoprotein; NSA, necrosulfonamide; NSP, non-structural protein; OMV, outer membrane vesicle; ORF, open reading frame; PAMPs, pathogen associated molecular patterns; PD, Parkinson disease; PFT, pore-forming toxins; PGN, bacterial peptidoglycan; PKR, protein kinase R; PI3P, phosphatidylinositol 3-phosphate; PI3K, PI3 kinase; PnCW, pneumococcal cell wall; Poly (I:C), polyinosinic:polycytidylic acid; PR, protease; PRRs, pattern recognition receptors; PVM, pneumonia virus of mice; RDA, RIPK1-dependent apoptosis; RHIM, RIP homotypic interaction motif; RIG-I, cytosolic retinoic acid-inducible gene I; RIPKs, receptor interacting protein kinases; Roc, Ras-of-complex; ROS, reactive oxygen species; RR, ribonucleotide reductase; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome; SARS-3a, SARS-CoV ORF protein 3a; SDH, succinate dehydrogenase; siRNA, small interfering RNA; SNPs (line 657) ssRNA, single-stranded RNA; T3SS, type III secretion system; T4SS, type IV secretion system; TAK1, TGFβ-activated kinase 1; TBK1, TANK-binding kinase 1; TGFβ, transforming growth factor beta; Th1, T helper 1; TLR, toll-like receptor; TNF, tumour necrosis factor; TNFR1, TNF receptor type 1; TRADD, TNFR1-associated death domain protein; TRAF, TNFR associated factors; TRAILR, TNF-related apoptosis-inducing ligand receptor; TRAM, translocating chain-associated membrane protein; TRIF, TIR-domain-containing adapter-inducing interferon-β; TRPM7, transient receptor potential cation channel subfamily M member 7; UBE2N, ubiquitin-conjugating enzyme E2N; UL45/UL48, human CMV envelope protein 45/48; UPR, unfolded protein response; vICA, viral inhibitor of caspase-8 activation; vIRA, viral inhibitor of RIP activation; vMLKL, viral MLKL-like proteins; VSV, vesicular stomatitis virus; VV, vaccinia virus; WNV, West Nile virus; WT, wild-type; XIAP, X-linked inhibitor of apoptosis protein; Yop, Yersinia outer protein; ZBP1, Z-DNA binding protein; ZIKV, Zika virus.

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pathogen associated molecular patterns. We also discuss the intricate mechanisms of host evasion by pathogens that specifically target RIPKs for inactivation, and finally, we will touch on the controversial issue of drug development for kinase inhibitors to treat chronic inflammatory and neurological disorders, and the implications this may have on the outcome of pathogen infections.

1. Introduction

Pathogen infection initiates multiple innate immune signaling pathways via the stimulation of pattern recognition receptors (PRRs) with pathogen-associated molecular patterns (PAMPs). The outcomes of PAMP-PRR signaling are diverse, and often dependent on pathogen-specific virulence factors as well as host factors including, cell type, species, existing gene polymorphisms or pre-existing co-morbidities. Nevertheless, the signal transduction that follows pathogen recognition elicits numerous defence mechanisms, including the induction of inflammatory cytokine, chemokine and interferon production, activation of programmed cell death pathways, and inevitably an adaptive immune response, all of which contribute to pathogen control and elimination [1].

There are seven members of the Receptor Interacting Protein Kinase (RIPK) family, RIPK1-7, some of which have emerged as critical effectors of immunity to infection with a diverse array of bacterial, viral and protozoal pathogens. Structurally and functionally, all members of the RIPK family share a homologous serine-threonine kinase domain (KD) with a catalytic site [2], with RIPK2 boasting additional tyrosine kinase activity [3]. RIPK1 has a C-terminal death domain (DD), and an intermediate domain (ID) which harbors a RIP homotypic interaction motif (RHIM). RIPK2 contains a C-terminal CARD (caspase activation and recruitment domain) and an ID. RIPK3 has a C-terminal RHIM domain alongside the N-terminal KD. RIPK4 and RIPK5 are characterized by C-terminal ankyrin repeats, and RIPK6 and RIPK7 each harbor a leucine-rich repeat (LRR) motif, ankyrin repeats, a Ras-of-complex (Roc) domain followed by a C-terminal of Roc (COR) domain, and a WD40 domain.

To date, the most studied RIPKs in relation to inflammation of host immune responses are RIPK1, 2 and 3, with RIPK7 following steadily behind. This rapidly moving field has brought the biochemical functions of RIPKs to the forefront of cellular immunity. Here, model pathogens including *Listeria monocytogenes*, *Shigella flexneri*, *Mycobacterium tuberculosis*, influenza A virus (IAV) and cytomegaloviruses (CMV) have been instrumental in dissecting the role of RIPKs in host immunity. Furthermore, research over the past decade has revealed multiple pathogenic mechanisms of bacteria and viruses that specifically target RIPKs or their downstream signaling networks for inactivation. Despite the volume of research on RIPKs and host responses to infection, there is a long way to go in understanding the physiological role of each RIPK and their functional domains in specific infection settings. This is partly due the fact that RIPK1 and RIPK3 are implicated in pro-survival transcriptional pathways as well as cell death, but also due to the ongoing discovery of novel virulence mechanisms of pathogens.

In this review, we will provide an up to date account of RIPK-mediated host responses to bacterial and viral infections as well as the mechanisms pathogens have evolved to evade RIPK signaling outcomes. Importantly, we have focused on studies that have utilised in vitro or in vivo infections with pathogenic organisms to stimulate physiological immune responses, rather than those that have used purified or synthetic stimulants, for example lipopolysaccharide (LPS) or polyinosinic: polycytidylic acid (Poly I:C). We note that although we were not able to discuss all relevant pathogens, including protozoal organisms, we have generated a comprehensive list of pathogens, the associated RIPK signaling pathways and relevant references in Table 1.

1.1. RIPK1 and RIPK3-mediated pro-survival inflammatory signaling in pathogen infection

RIPK1 regulates inflammation in response to death receptors (DR), including tumour necrosis factor receptor 1 (TNFR1), TNF-related apoptosis-inducing ligand receptors 1 and 2 (TRAILR1/2) and Fas [4–6], as well as toll-like receptor (TLR)3 and TLR4 [7,8] (Fig. 1). RIPK3, although best known for its role in necroptosis (discussed later), can act in concert with RIPK1 to engage in pro-inflammatory, non-cell death signaling [9]. Here we will focus on research that indicate direct RIPK1 and/or RIPK3 involvement in pathways specifically described to be cell death-independent during host infection.

1.1.1. RIPK1/3 in inflammatory responses to viral infections

West Nile virus (WNV) and Zika virus (ZIKV) are medically important arboviruses that cause severe neurological disease in humans [23,24]. Control of WNV requires robust neuroinflammation and infiltration of peripheral leukocytes into the central nervous system (CNS), mediated by RIPK1 and RIPK3 [23,25]. Daniels et al. [25] demonstrated that *Ripk3*$^{-/-}$ and RIPK1 kinase-dead (*Ripk1*$^{K45A/K45A}$) mice have suppressed TLR-induced chemokine expression, as well as reduced recruitment of T lymphocytes and myeloid cells into the CNS, resulting in accelerated virus-induced mortality. Similarly, direct ZIKV infection in the CNS of *Ripk3*$^{-/-}$, *Ripk1*$^{K45A/K45A}$ and *Dai*$^{-/-}$ mice induces rapid mortality and elevated viral titres within the brain [26]. Pharmacological blockade of RIPK3 also enhances ZIKV replication in human neuroblastomas. This intrinsic neuronal cell defect results from disrupted DAI/RIPK-mediated transcription of immunoresponsive gene 1 (IRG1) required for itaconate production. Itaconate inhibits succinate dehydrogenase (SDH) activity and subsequently reprograms neuronal metabolism into an antiviral state [26–28]. As such, these results highlight the contribution of RIPK1/3 in defence against neurovirulent viruses, independently of cell death.

CMVs are large double-stranded DNA viruses that have the capacity to encode viral effectors that directly manipulate components of host immune pathways. Murine CMV (MCMV) expresses the M45 protein, which interacts with RIPK1 through its catalytically inactive ribonucleotide reductase (RR) domain and inhibits RIPK1 ubiquitylation [29]. This process blocks pathways dependent on polyubiquitylated RIPK1, including TNF-induced NF-κB and p38 MAPK activation, as well as TLR3-induced NF-κB activation, thus facilitating immune evasion. M45 is also shown to bind RIPK1, RIPK3 and DAI via its N-terminal RHIM domain, which interferes with DAI-induced NF-κB signaling [22]. Similarly, human CMV (HCMV) is able to inhibit RIPK1-mediated NF-κB signaling through synergistic function of its encoded UL48 and UL45 proteins [30]. During the late stages of infection, UL48 cleaves the K63-polyubiquitin chains on RIPK1, thus preventing TNF-induced NF-κB activation [30,31]. UL45 supports this process by enhancing UL48-RIPK1 interaction and re-localization of RIPK1 to the cytoplasmic virion assembly complex.

Conversely, RIP kinases can also be utilised to promote viral propagation. Following Japanese encephalitis virus (JEV) infection, *Ripk3* gene expression is upregulated in primary neurons of wild-type (WT) mice, which corresponds to heightened viral titres [32]. RNA-sequencing of infected brain tissues revealed *Ripk3*$^{-/-}$ mice upregulate a number of IFN-stimulated genes (ISGs), independently of RIPK3 and MLKL phosphorylation. Silencing of the ISG, IFI44 L, in both WT and *Ripk3*$^{-/-}$ neurons increases viral RNA levels, suggesting that the elevated RIPK3 assists with JEV immune evasion.

Table 1
List of pathogens that are controlled by RIPK signaling or those that manipulate RIPK signaling processes.

Microorganism	Classification	RIPK	Inhibits/activates RIPK signaling	Virulence factor	Model	Reference
Bacteria						
Borrelia burgdorferi	Spirochete	RIPK2	Activates	–	Mouse	[165–167]
Brucella abortus	Gram-negative	RIPK2	Activates	VceC	Mouse, human	[194]
Chlamydia muridarum	Gram-negative	RIPK2	Activates	–	Mouse, human	[194,195]
Citrobacter rodentium	Gram-negative	RIPK1, RIPK3	Inhibits	EspL	Mouse	[113]
Enteropathogenic *Escherichia coli*	Gram-negative	RIPK1	Inhibits	NleB1	Human	[45,46]
		RIPK1, RIPK3	Inhibits	EspL	Human	[113]
Helicobacter pylori	Gram-negative	RIPK2	Activates	–	Human	[149]
Klebsiella pneumoniae	Gram-negative	RIPK1, RIPK3	Activates	–	Mouse	[17]
Legionella pneumophila	Gram-negative	RIPK2	Activates	–	Mouse	[145,162]
		RIPK1	Inhibits	MavC	Human	[42]
Listeria monocytogenes	Gram-positive	RIPK1, RIPK3	Activates	PFT	Mouse, human	[115]
		RIPK2, RIPK7	Activates	–	Mouse	[137,151,184,217]
Mycobacterium leprae	Acid-fast	RIPK2, RIPK7	Activates	–	Human	[152,219,220]
Mycobacterium tuberculosis	Acid-fast	RIPK3, RIPK7	Activates	–	Mouse, human	[119,120,222,223]
		RIPK2	Activates	–	Mouse	[147]
Porphyromonas gingivalis	Gram-negative	RIPK1, RIPK2	Inhibits	Kgp	Human	[209]
Salmonella enterica serovar Typhimurium	Gram-negative	RIPK1, RIPK3, RIPK7	Activates	–	Mouse	[117,118,216]
		RIPK2	Activates	SipA, SopE	Human	[185,188,189]
Serratia marcescens	Gram-negative	RIPK1, RIPK3	Activates	PFT	Mouse, human	[115]
Shigella flexneri	Gram-negative	RIPK2	Activates	IpgB2, OspB	Human	[177,187]
		RIPK2	Inhibits	–	Human	[199]
Staphylococcus aureus	Gram-positive	RIPK1, RIPK3	Activates	PFT	Mouse, human	[114,116]
Streptococcus pneumoniae	Gram-positive	RIPK1, RIPK3	Activates	PFT	Mouse, human	[115]
		RIPK2	Activates	–	Mouse	[157]
Uropathogenic *Escherichia coli*	Gram-negative	RIPK1, RIPK2	Activates	CNF1	Flies, human	[192]
		RIPK1, RIPK3	Activates	PFT	Mouse, human	[115]
Yersinia pestis	Gram-negative	RIPK1	Activates	–	Mouse	[39]
Yersinia pseudotuberculosis	Gram-negative	RIPK1, RIPK3	Activates	–	Mouse	[17,79,80]
Virus						
BeAn 58058 poxvirus, Cotia poxvirus	dsDNA virus (Poxvirus)	RIPK3	Inhibits	vMLKL	Mouse, human	[101]
Bovine viral diarrhoea virus	ssRNA virus (Flavivirus)	RIPK6	Inhibits	–	Goat	[213]
Coxsackievirus A6	ssRNA virus (Picornavirus)	RIPK3	Activates	Nsp-3D	Human	[105]
Coxsackievirus B3	ssRNA virus (Picornavirus)	RIPK3	Activates non-necrotic signaling, inhibits necroptosis	Nsp-3C ($3C^{pro}$)	Human	[37]
Dengue virus	ssRNA virus (Flavivirus)	RIPK1	Activates	–	Human	[130]
Epstein-Barr virus	dsDNA virus (γ-herpesvirus)	RIPK1, RIPK3	Activates pro-survival signaling, inhibits necroptosis	LMP1	Human	[35]
Hepatitis B virus	dsDNA virus (Hepadnavirus)	RIPK2	Inhibits	HBeAg	Human	[208]
Hepatitis C virus	ssRNA virus (Flavivirus)	RIPK2	Activates	NS5B	Mouse, human	[207]
Herpes simplex virus-1/2	dsDNA virus (α-herpesvirus)	RIPK1,RIPK3	Inhibits	ICP6/10	Human	[73,97,98]
		RIPK1,RIPK3	Activates	ICP6/10	Mouse	[98,99]
Human cytomegalovirus	dsDNA virus (β-herpesvirus)	RIPK1	Inhibits	UL48, UL45	Human	[30]
		RIPK1,RIPK3	Inhibits	IE1	Human	[96]
Human immunodeficiency virus	ssRNA virus (Retrovirus)	RIPK1, RIPK2	Inhibits	PR	Human	[102]
Influenza A virus	ssRNA virus (Orthomyxovirus)	RIPK1, RIPK3	Activates	–	Mouse, human	[33,75,78]
		RIPK2	Activates	–	Mouse	[205]
Japanese encephalitis virus	ssRNA virus (Flavivirus)	RIPK3	Activates	–	Mouse	[32]
Murine cytomegalovirus	dsDNA virus (β-herpesvirus)	RIPK1, RIPK3	Inhibits	M45 (vIRA)	Mouse	[22,29,90,91,93]
Pneumonia virus of mice	ssRNA virus (Paramyxovirus)	RIPK1	Activates	–	Mouse	[107]
Respiratory syncytial virus	ssRNA virus (Paramyxovirus)	RIPK1	Activates	–	Human	[107]
SARS-CoV	ssRNA virus (Coronavirus)	RIPK3	Inhibits	SARS 3a	Human	[110]
SARS-CoV-2		RIPK1	Unknown	Nsp-12	Human	[109]

(*continued on next page*)

RIPK3-regulated type I IFN signaling is also shown to be crucial in anti-IAV immunity. Indeed, infected *Ripk3*$^{-/-}$ mice exhibit increased pulmonary viral load and enhanced immunopathology and mortality [33]. This susceptibility is largely attributed to defective IFN production from infected *Ripk3*$^{-/-}$ macrophages, independent of IAV-associated cell death outcomes. Specifically, RIPK3 controls type I IFN signaling at the transcriptional level, where virus-induced upregulation of RIPK3 disrupts RIPK1-MAVS interaction and reduces IFN-β mRNA expression, which facilitates IAV persistence [19,33]. Interestingly, the increased RIPK3 also activates protein kinase R (PKR) that stabilises IFN-β transcripts [34], thus elevating IFN-β production and type I IFN protection [33]. This is presumed to have been counter-evolved by hosts in response to viral evasion and represents a potential avenue for therapy against pathogenic IAV.

Several other viruses are known to modulate RIPK1/3 signaling in non-cell death pathways to benefit pathogenesis. For example, the common cause for infectious mononucleosis, Epstein-Barr virus (EBV), encodes a latent membrane protein (LMP1) that binds both RIPK1 and RIPK3, and recruits E3 ligases to regulate protein ubiquitylation [35]. Consequently, LMP1 promotes RIPK1 polyubiquitylation, while RIPK3 polyubiquitylation is suppressed through yet undefined means, which switches cell fate from necroptosis to survival. Human immunodeficiency virus type 1 (HIV-1) protease (PR) cleaves RIPK1 with high specificity in human T lymphocytes, resulting in failure to activate NF-κB [35]. Conversely, coxsackievirus B3 (CVB) employs RIPK3 to promote autophagic flux for viral assembly [36], and as such, silencing of RIPK3 in human intestinal epithelial cells restricts early viral replication [37].

1.1.2. RIPK1/3 in inflammatory responses to bacterial infections

Yersinia pestis, the etiological agent of bubonic plague, produces an array of *Yersinia* outer protein (Yop) virulence effectors that are translocated into host cells via a type III secretion system (T3SS) to alter host cell signaling [38]. Infection of macrophages with *Y. pestis* results in TNF, IL-6 and IL-1β secretion, mediated through a RIPK1 and caspase-8 dependent, but RIPK3-independent mechanism [39]. As a result, RIPK1 deletion in murine myeloid cells causes defective cytokine release, associated with decreased IκBα degradation and NF-κB nuclear translocation. In the absence of caspase activity, *Y. pseudotuberculosis* is also shown to induce RIPK1/RIPK3/TRIF-mediated synthesis of IFN-β in macrophages, similar to *Klebsiella pneumoniae* [17]. This process requires the kinase activity of both RIPKs but operates independently of MLKL-mediated necroptosis and caspase-8 apoptosis. To counter host inflammation, *Y. pestis* encodes YopJ, which acetylates MAPKs, IKKβ and TAK1 within their activation loops, thus dampening host MAPK and NF-κB signaling [40].

Legionella pneumophila is an environmental organism and accidental human pathogen that causes Legionnaires' disease, a severe form of acute pneumonia [41]. Following infection, *L. pneumophila* effector MavC (also known as Lpg2147) deamidates the human ubiquitin-conjugating enzyme E2N (UBE2N), which disrupts UBE2N-mediated formation of Lys63 polyubiquitin chains [42]. This prevents RIPK1 polyubiquitylation, thus suppressing downstream NF-κB signaling in infected cells in vitro. Given the presence of MavC homologues in the cycle inhibiting factor (Cif) effector family of T3SS pathogens [43,44], there may be similar routes for RIPK1 inhibition in other bacterial contexts.

Bacterial effectors can also directly manipulate RIPKs. Enteropathogenic *Escherichia coli* (EPEC) encodes an arginine glycosyltransferase, NleB1, that modifies RIPK1 following infection of human cells [45,46]. This activity inhibits the recruitment of ubiquitinated RIPK1 to TNFR1, thus disrupting the assembly of Complex I required for TNF-induced NF-κB signaling [45]. Although transient expression of NleB1 inhibits NF-κB activation [47], NleB1 alone is not sufficient to inhibit NF-κB-mediated IL-8 production during EPEC infection in vitro [46], as multiple effectors are required to achieve this outcome [48].

1.2. RIPK1 and RIPK3-mediated apoptotic signaling in pathogen infection

Apoptosis is a common host response to infection that helps restrict the replicative niche of pathogens, and facilitates phagocytosis and antigen presentation through the production of apoptotic bodies [49]. Many pathogens however, have evolved mechanisms to manipulate apoptotic processes to benefit survival and virulence (Fig. 2).

Table 1 (*continued*)

Microorganism	Classification	RIPK	Inhibits/activates RIPK signaling	Virulence factor	Model	Reference
	ssRNA virus (Coronavirus)					
Swine influenza virus	ssRNA virus (Orthomyxovirus)	RIPK1	Activates	–	Pig	[131]
		RIPK1, RIPK3	Activates	B13R/Spi2	Mouse	[82]
Vaccinia virus	dsDNA virus (Poxvirus)	RIPK3	Inhibits	E3L	Mouse, human	[87]
Vesicular stomatitis virus	ssRNA virus (Rhabdovirus)	RIPK1, RIPK3	Activates	–	Mouse, human	[129]
West Nile Virus	ssRNA virus (Flavivirus)	RIPK1, RIPK3	Activates	–	Mouse	[25]
Zika virus	ssRNA virus (Flavivirus)	RIPK1, RIPK3	Activates	–	Mouse	[26]
Pathogens not covered in this review						
Adenovirus type 5	dsDNA virus (Adenovirus)	RIPK3	Activates	–	Human	[230]
Murine gammaherpesvirus-68	dsDNA virus (γ-herpesvirus)	RIPK1, RIPK3	Activates	–	Mouse	[231]
Murine hepatitis virus type 3	ssRNA virus (Coronavirus)	RIPK1	Activates	–	Mouse	[232]
Murine norovirus-1	ssRNA virus (Calicivirus)	RIPK2	Activates	–	Mouse	[201]
Reovirus	dsRNA virus	RIPK1, RIPK3	Activates	–	Mouse	[233,234]
Sendai virus	ssRNA virus (Paramyxovirus)	RIPK1, RIPK3	Activates	Y1, Y2	Mouse	[231]
Chlamydophila pneumoniae	Gram-negative	RIPK2	Activates	–	Mouse	[235]
Pasteurella multocida	Gram-negative	RIPK1, RIPK3	Activates	–	Chicken	[236]
Leishmania braziliensis	Trypanosomatid	RIPK3	Inhibits	–	Human	[237]
Leishmania infantum	Trypanosomatid	RIPK1, RIPK3	Activates	–	Mouse, human	[238,239]
Plasmodium falciparum	Plasmodiidae	RIPK2	Activates	–	Mouse	[240]
Trypanosoma cruzi	Trypanosomatid	RIPK2	Activates	–	Mouse	[241]

1.2.1. RIPK1/3 in apoptotic responses to viral infections

The execution of apoptosis is heavily reliant on host caspases, thus most large DNA viruses encode effectors for inhibiting caspase activity [70], however, few viral factors target RIPKs directly. Herpes simplex virus (HSV) contains numerous proteins that can interact with apoptotic signaling components, including ICP6 and ICP10 encoded by HSV-1 and HSV-2 respectively [71]. These proteins possess a C-terminal RR domain that inhibits caspase-8 function, thus suppressing TNF and Fas-induced apoptosis [72]. Curiously, this C-terminal RR, and not its N-terminal RHIM-like domain, also binds RIPK1 and prevents poly(I:C)-induced apoptosis in human cells [73]. Moreover, ICP6 and ICP10 can disrupt the RHIM-dependent interaction between TRIF and RIPK1, which may contribute to the disabling of apoptosis. Although the role of this cell death inhibition in viral pathogenesis has not been examined, it appears HSV has a strategy for managing dsRNA mediated apoptosis.

Similarly, initiation of IAV-induced PAN-optosis (pyroptosis, apoptosis, necroptosis) requires DAI sensing of viral RNA through its second Zα domain [74,75], though DAI is recently reported to also detect IAV nucleoprotein (NP) and polymerase subunit (PB1), as a collective unit of viral ribonucleoprotein [76,77]. Upon stimulation, DAI associates with RIPK3, which recruits RIPK1, FADD and MLKL to form a "ripoptosome" complex [75,78]. Here, the apoptotic arm operates under

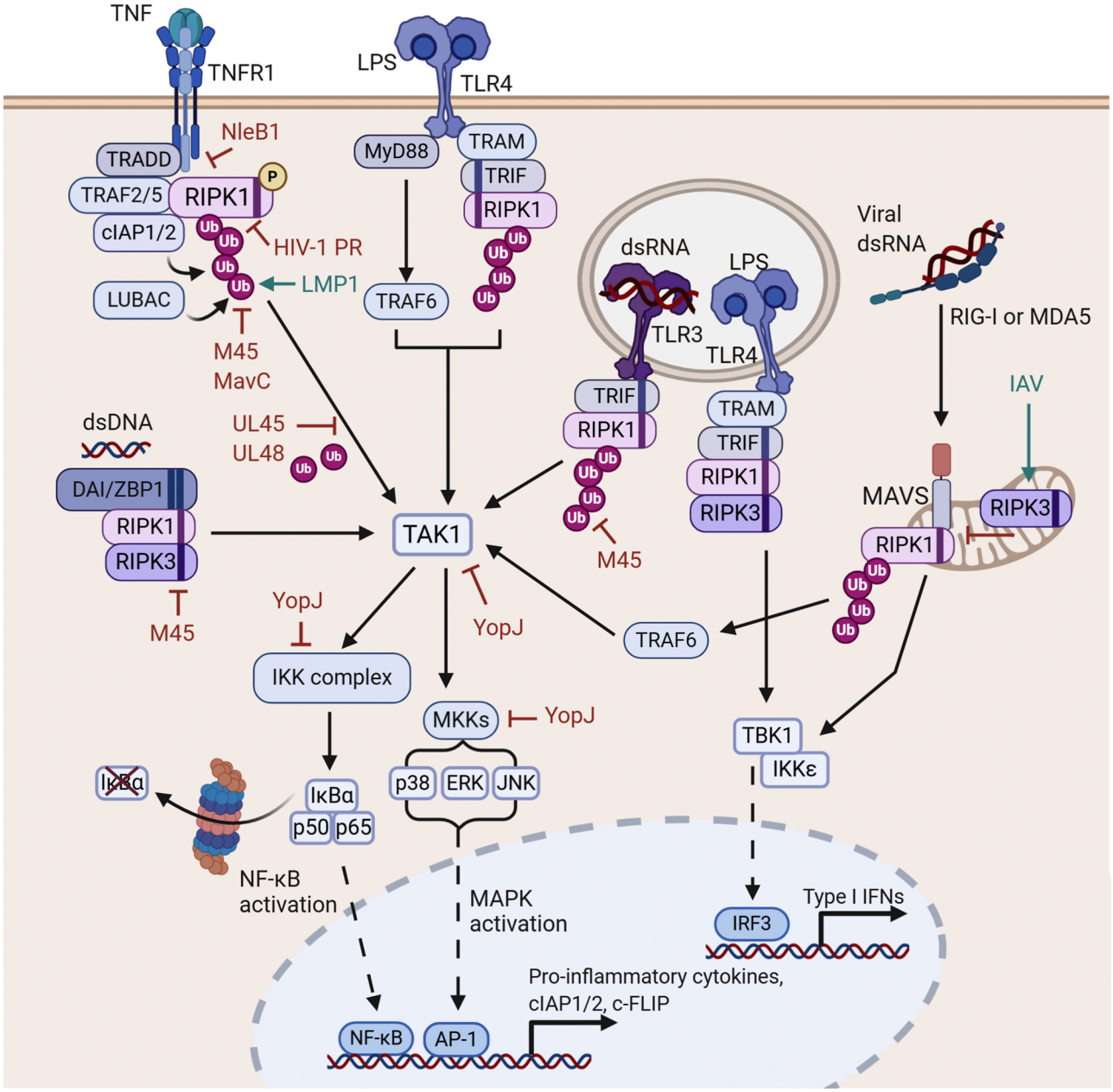

Fig. 1. Inflammatory pathways mediated by RIPK1/3 in response to pathogen sensing. Upon stimulation with TNF, TNFR1 recruits TRADD and RIPK1 via the DD, then subsequently TRAF2/5 and cIAP1/2 to form a membrane-bound pro-inflammatory signaling complex [10,11]. Ubiquitylation of RIPK1 by cIAP1/2 and LUBAC enables recruitment of TAK1 and the IKK complex, which promotes activation of MAPK and canonical NF-κB signaling [12–15]. Ligation of TLR3/4 reinforces these pathways through RHIM-mediated interactions between TRIF and RIPK1, with subsequent RIPK1 ubiquitylation continuing to drive NF-κB activation [7,16]. TLR4-TRIF interactions can also induce Type I IFN signaling via recruitment of RIPK1 and RIPK3, which activates TBK1 and IKKε to promote nuclear translocation of IRF3 [17]. In response to dsRNA sensing by cytosolic RIG-I or MDA5, MAVS-RIPK1 interactions additionally drive IRF3 and NF-κB transcription pathways [18–20]. Finally, cytosolic dsDNA sensing by DAI/ZBP1 promotes NF-κB induction via RHIM-mediated recruitment of RIPK1, with RIPK3 kinase activity also required for synergistic activation [21,22]. Virulence factors that interact with these pathways are indicated, and have been discussed in text the main body of text.

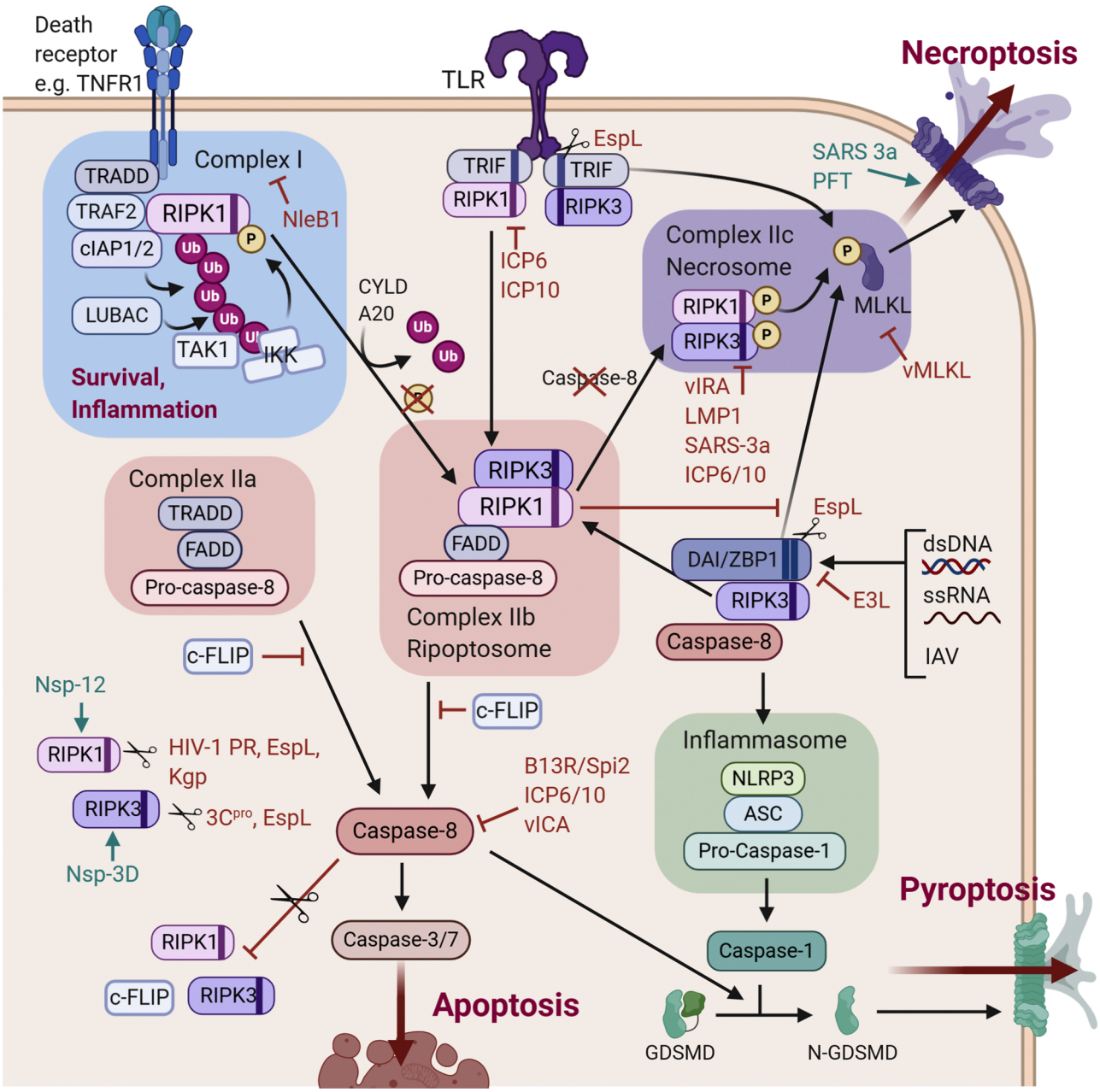

Fig. 2. Programmed cell death pathways regulated by RIPK1/3. Following the TNFR1-mediated assembly of pro-inflammatory complex I, deubiquitinases (CYLD or A20) remove polyubiquitin chains from RIPK1 to terminate inflammation and enable downstream death signaling [50,51]. RIPK1 (with RIPK3) interacts with FADD and pro-caspase-8 to form complex IIb (ripoptosome) [52,53], and can initiate extrinsic apoptosis [54,55]. Active caspase-8 facilitates repression of necroptosis and NF-κB signaling by cleaving RIPK1 and RIPK3 [56–58]. In the absence of caspase activity, RIPK1 and RIPK3 oligomerize to form complex IIc (necrosome) that phosphorylates MLKL and induces necroptosis [59–61]. TLR-driven TRIF-RIPK1 interactions can also promote ripoptosome formation [62], while TRIF-RIPK3 phosphorylates MLKL for necroptosis [63]. Following nucleic acid sensing, RHIM interactions between DAI/ZBP1 and RIPK3 induces ripoptosome formation or direct phosphorylation of MLKL [64,65]. However, the resulting necroptosis can be suppressed by RIPK1 RHIM [66,67]. DAI/ZBP1-RIPK3 complexing also promotes NLRP3 inflammasome activation and death via pyroptosis [68,69]. Virulence factors that interact with these pathways are indicated, and have been discussed in the main body of the text.

a RIPK1-FADD-caspase-8 axis, in a manner independent of RIPK1 kinase activity [78]. Neither caspase inhibition through z-VAD nor FADD deletion in mouse fibroblasts rescues cell viability, but pre-treatment of these cells with RIPK3 kinase inhibitors grants significant protection, thus highlighting the importance of RIPK3 in regulating the parallel cell death pathways. Surprisingly, DAI also triggers RIPK3-independent apoptosis, where DAI engages RIPK1 directly to recruit FADD and caspase-8, which deploys an alternative, delayed apoptotic cell death [75,78]. As inhibition of necroptosis does not affect IAV control, while *Mlkl-/-Fadd-/-* mice exhibit marked susceptibility to IAV-induced lethality [78], it signifies that RIPK1/3-mediated apoptosis is a major form of host protection against IAV infection.

1.2.2. RIPK1/3 in apoptotic responses to bacterial infections

In response to YopJ-mediated abrogation of inflammation during *Yersinia* infection [40], infected macrophages engage TLR4/TRIF and TNFR1 to induce apoptotic cell death [39]. Both cell death pathways occur in a non-redundant manner and rely on RIPK1-mediated activation of caspase-8 for downstream signaling [39,79]. The RIPK1-dependent apoptosis provides a cell-extrinsic signal required for

cytokine production by inflammatory monocytes and neutrophils [80]. Consequently, *Ripk1*$^{K45A/K45A}$ mice orally infected with *Y. pseudotuberculosis* exhibit decreased caspase-3 staining within the mesenteric lymph nodes, as well as reduced levels of IL-12-producing monocytes and TNF-producing neutrophils. These mice are unable to restrict bacterial replication and systemic dissemination, resulting in rapid mortality.

1.3. RIPK1 and RIPK3-mediated necroptotic signaling in pathogen infection

Necroptosis has largely been studied in the context of antiviral responses, often as an alternate form of cell death for restricting viral replication. Necroptosis is a form of regulated lytic cell death that operates independent of caspases, and requires both RIPK3 and MLKL function (Fig. 2). It is important to note that although the studies discussed below have specified necroptosis as the specific cell death outcome involved in the infection process, some have only documented RIPK3 dependence but have not directly shown involvement of MLKL or pMLKL. Therefore, we have noted whether experimental evidence has been provided for dependence on MLKL within the text.

1.3.1. RIPK1/3 in necroptotic responses to viral infections

Mouse fibroblasts infected with vaccinia virus (VV), which is a poxvirus strain that encodes the caspase inhibitor B13R/Spi2, are shown to have resistance to TNF-induced apoptosis but increased sensitivity to RIPK3-dependent necroptosis [81,82]. VV-infected WT mice exhibit extensive inflammation and necrotic tissue damage within the liver, associated with formation of RIPK1-RIPK3 complexes [82]. *Ripk3*$^{-/-}$ mice fail to initiate virus-induced necroptosis, resulting in elevated viral titres and mortality [83,84]. The requirement for RIPK1 kinase activity remains unclear however, as groups have reported either increased [84] or unchanged [85] VV loads within the liver and spleen of infected *Ripk1*$^{D138N/D138N}$ mice. VV also encodes E3L, which contains an N-terminal Z-DNA binding domain that competes with DAI to inhibit DAI/RIPK3 necroptosis [86,87]. Administration of an E3L mutant lacking this domain in mouse fibroblasts and human epithelial cells results in increased IFN-induced necroptosis, featuring increased MLKL phosphorylation, and fails to elicit disease in WT mice [87].

Similarly, MCMV encodes a viral inhibitor of caspase-8 activation (vICA), which blocks DR-induced apoptosis but sensitises cells to necroptosis [88,89]. To combat this, MCMV expresses the viral inhibitor of RIP activation (vIRA), that binds RIPK1 and RIPK3 through its N-terminal RHIM domain [90]. vIRA is a potent inhibitor for MCMV-triggered necroptosis that is dependent on DAI/RIPK3 signaling [91]. MCMV mutants lacking vIRA or its RHIM domain are severely attenuated in WT mice, but unaffected in *Ripk3*$^{-/-}$ and *Dai*$^{-/-}$ mice [91–93]. Phosphorylation of MLKL occurs within hours during in vitro infection with vIRA RHIM mutant MCMV, and is reliant on IE3-mediated transcription of its genome [94]. Briefly, HCMV also elicits DAI-mediated production of IFNs and TNF-induced necroptosis in a RIPK-regulated manner [21,95,96]. Notably, the TNF-driven cell death is inhibited by HCMV-encoded IE1 through a yet unknown process that occurs after RIPK3 activation and MLKL phosphorylation, thus distinguishing the immunosuppressive strategies of HCMV from its murine counterpart [96].

HSV-1 and HSV-2 modulate immune responses in a manner similar to MCMV. They carry ICP6 and ICP10 respectively, which expresses an N-terminal RHIM domain that mediates RIPK1 and RIPK3 interaction, leading to anti-necroptotic signaling in human cells, but pro-necroptotic death in mice [97–99]. Expression of ICP6/10 or HSV challenge in human cells causes competitive RHIM binding that prevents RIPK1-RIPK3 necrosome formation and subsequent TNF-induced MLKL phosphorylation and necroptosis [97,98]. In contrast, ICP6 interaction with RIPKs in mouse cells promotes RIPK3-RIPK3 complex formation for MLKL recruitment and execution of necroptosis, independent of DR, DAI and TLR signaling [98,99]. This RIPK3-dependent necroptosis is crucial for controlling HSV-1 propagation, as *Ripk3*$^{-/-}$ mice present with markedly elevated susceptibility to infection and death, not seen in WT mice.

As mentioned previously, human γ-herpesvirus EBV binds RIPK1 and RIPK3 through the C-terminal activation region of its encoded LMP1 effector, which prevents RIPK1-RIPK3 complex formation in human nasopharyngeal cells [35]. Moreover, LMP1 promotes K63-linked polyubiquitylation of RIPK1 that forms the scaffolding required for TNF-induced NFκB signaling [13], while inhibiting K63-linked polyubiquitylation of RIPK3 that typically supports necrosome assembly [35,100]. These post-translational modifications drive a switch from necroptotic death to a pro-survival cell fate, as indicated by the suppressed RIPK3 and MLKL phosphorylation following EBV infection in TNF-induced necroptotic cells [35].

As opposed to targeting the RHIM sequences of RIPKs, BeAn 58058 poxvirus (BAV) and Cotia poxvirus (COTV) carry viral MLKL-like proteins (vMLKL) that block necroptosis by interacting with the RIPK3 kinase domain [101]. In both human and mouse epithelial cells, vMLKL and RIPK3 bind via a pseudokinase to kinase domain interface, such that it overlaps the site typically engaged by cellular MLKL. In particular, this process in human cells prevents RIPK1 interaction, but drives RIPK3 phosphorylation despite pharmacological kinase inactivation of both RIPK1 and RIPK3 [101], which suggests that vMLKL alters RIPK3 in a manner that nulls kinase inhibitor treatment or promotes phosphorylation by another yet unknown kinase. However, in mouse cells, vMLKL inhibits RIPK3 phosphorylation, thus preventing RIPK3 activation and subsequent catalytic activity [101]. Regardless, vMLKL is capable of sequestering both mouse and human RIPK3 upon expression, which disrupts downstream TNF-induced necroptosis.

In contrast to DNA viruses, the mechanisms surrounding manipulation of necroptosis by RNA viruses are less explored. The HIV-1-encoded PR, previously described to inhibit NF-κB activation, also disrupts RIPK1-RIPK3 interaction in CD4 + T cells via RIPK1 cleavage [102]. This may contribute to necroptosis suppression, but no study has confirmed this observation. Additionally, necroptosis is implicated in the proliferative defect of HIV-specific CD8 + T lymphocytes in patients with progressive infection [103]. This defect is successfully reversed following pre-treatment of antigen-stimulated CD8 + T cells with necrosis inhibitor NecroX-5 or RIPK3 silencing. However, as MLKL dependence was not explored in this study, it would be appropriate to address this in further studies targeting necroptosis for HIV therapy.

Coxsackieviruses are the etiological agent of hand, foot and mouth disease [104]. Coxsackievirus A6 (CA6) infection of human cells triggers upregulation of RIPK3 via its non-structural protein (Nsp)-3D, which increases subsequent necrotic death [105]. This cell death can be inhibited by Nec-1, which dramatically reduces virus production, suggesting that necroptosis is required for CA6 infection. It should be specified that although the study attributes necroptosis to CA6 pathogenesis, no changes in MLKL nor pMLKL expression was found. In contrast, at late stages of human intestinal epithelial cell infection with coxsackievirus B3 (CVB), Nsp-3C (3C^{pro}) proteolytically cleaves RIPK3 and disrupts necroptosis, as determined by lack of HMGB1 release [37]. Intriguingly, the cleaved RIPK3 interacts with RIPK1 to induce a non-necrotic death [37], implying that CVB manipulates RIPK3 to redirect the host cell into a more favourable but yet undefined death pathway.

Respiratory syncytial virus (RSV) triggers necroptosis without direct modulation of RIPK1/3. RSV causes bronchiolitis in children, typically characterised by airway epithelial cell (AEC) death and massive cytokine release [106]. In response to infection, primary human AECs exhibit increased levels of pRIPK1, pMLKL and HMGB1 release, which correlates with increased necroptotic death [107]. Pharmacological inhibition of RIPK1 and MLKL reduces viral titres, suggesting that necroptosis promotes viral persistence. These results are recapitulated in a mouse model using pneumonia virus of mice (PVM). Here, inhibition of RIPK1 or MLKL lowered viral loads and prevented severe bronchiolitis,

also seen in *Ripk1*$^{K45A/K45A}$ mice [107]. The necrosome is also reported to trigger neutrophil extracellular traps (NET) release in RSV-stimulated human neutrophils or neutrophils co-incubated with RSV-infected AECs [108], which facilitates RSV containment.

The topic of viral respiratory illness has gained much attention recently due to the emergence of the hypervirulent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for COVID-19. In an effort to identify potential therapeutic targets, Gordon et al. [109] have mapped the interactions between SARS-CoV-2 proteins and human proteins. Amidst the phenomenal set of results, RIPK1 was shown to associate with the viral Nsp-12, which is inferred to be an RNA polymerase. Perhaps unsurprisingly, the 2002 SARS-CoV has been shown to interact with RIPK3 via its open reading frame (ORF)-3a protein (SARS 3a) to promote SARS 3a oligomerization and subsequent necrotic death in human lung cells [110]. This process operates independently of RIPK3 kinase activity and MLKL [110], with SARS 3a likely replacing the latter as the necroptotic executioner due to its ability to function as an ion channel following membrane insertion [111]. However, SARS 3a also reduces RIPK3 and MLKL phosphorylation [110]. Infection with a SARS 3a-deletion mutant rescued mice from virus-induced mortality, suggesting an antiviral role for necroptosis in SARS-CoV infection [112].

1.3.2. RIPK1/3 in necroptotic responses to bacterial infections

Compared to viral pathogens, far fewer bacterial effectors have been identified to directly interact with RIPKs for necroptosis modulation. EPEC employs a cysteine protease, EspL, that directly cleaves the RHIM domain of RIPK1 and RIPK3, which prevents MLKL membrane complex formation during infection [113]. This inhibits TNF and TLR3/4-induced necroptosis in vitro. Furthermore, mice orally challenged with an *espL* deletion mutant of the EPEC-like mouse pathogen, *Citrobacter rodentium*, exhibit attenuated bacterial colonization in the intestine [113]. This suggests that EspL-mediated blockade of necroptosis contributes to bacterial persistence.

Staphylococcus aureus is an opportunistic pathogen that causes pneumonia and bacteraemia in immunosuppressed patients. Its pore-forming toxin (PFT) induces necroptosis in both human and murine pulmonary macrophages, and as such, inhibition of RIPK1 or MLKL in vitro, or genetic deletion of RIPK3 in vivo, significantly reduces cytotoxicity and improves *S. aureus* clearance in the lungs [114]. Other PFT-carrying bacterial pathogens, such as *Serratia marcescens*, *Streptococcus pneumoniae*, *Listeria monocytogenes* and uropathogenic *E. coli* (UPEC) also trigger RIPK1/RIPK3/MLKL-dependent necroptosis in macrophages, highlighting necroptosis as a promising target for PFT-associated disease intervention [115]. In contrast, in models of skin infection or sepsis, inhibition of RIPK1 or MLKL results in exacerbated disease, due to excessive IL-1β-induced inflammation [116]. This is not seen in *Ripk3*$^{-/-}$ mice, likely due to RIPK3 influence on inflammasome activation. These results indicate tissue-specific roles for RIPKs during *S. aureus* infection.

Similarly, *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium) triggers necroptosis in macrophages to benefit bacterial survival. This process is dependent on initial type I IFN signaling following injection of *S.* Typhimurium in mice, as well as pathogen-mediated caspase-8 inactivation, which enables RIPK1 recruitment to IFNAR1 for phosphorylation and subsequent association with RIPK3 [117]. The resulting necroptotic cell death facilitates macrophage elimination, leading to compromised pathogen control. Alternatively, Ro et al. [118] reported that microRNA (miR)-155 upregulation following *S.* Typhimurium infection drives necroptotic macrophage death. Transfection of miR-155 in vitro induces RIPK1 and RIPK3 activation and subsequent necroptosis, which is partly inhibited following Nec-1 treatment. It is worth noting that although the authors describe the mode of cell death in both of the above *S.* Typhimurium infection studies as necroptosis, no experimental evidence showing MLKL phosphorylation or dependence on MLKL presence was provided.

Thus far, studies on mycobacterial-induced necroptosis in macrophages have been largely divisive. *Mycobacterium tuberculosis* triggers RIPK3-dependent necroptosis in both human and murine macrophages in a pathway reliant on reactive oxygen species (ROS) production and the mitochondrial Bcl-2 family member protein B-cell lymphoma-extra large (Bcl-xL) [119,120]. The ensuing macrophage death is suggested to assist bacterial pathogenesis, as *Ripk3*$^{-/-}$ macrophages display enhanced restriction of bacterial replication in vitro and in vivo. However, despite increased MLKL expression, pMLKL is not detected in infected macrophages, suggesting that the signaling process utilises an alternative executioner or is non-necroptotic. This is further complicated by results from Stutz et al. [121,122], which argue that deletion of MLKL or RIPK3 does not rescue macrophages from death during *M. tuberculosis* infection. In fact, the macrophage population and bacterial burden in infected *Ripk3*$^{-/-}$ mice are indistinguishable from WT controls. Further research is required to ascribe a role for necroptosis in mycobacterial infections.

1.4. RIPK1 and RIPK3-mediated inflammasome signaling in pathogen infection

Host cell death and inflammation can also be induced independently of death receptors through inflammasome signaling, as depicted in Fig. 2. RIPK1 and RIPK3 are primarily involved in alternative inflammasome activation pathways, which remain largely unexplored. A number of studies have used purified pathogen components such as LPS to investigate the outcomes of RIPK1/3-mediated inflammasome signaling, which appear to be largely dependent on cell type, stimulus, and the availability or functional activity of certain host signaling proteins [65,123–127]. Here we will discuss RIPK1 and RIPK3 involvement in inflammasome signaling during pathogen-specific infections.

1.4.1. RIPK1/3 in inflammasome responses to viral infections

Vesicular stomatitis virus (VSV) is a rhabdovirus that causes vesicular lesions on the mucosa of livestock [128]. VSV-infected mice exhibit NLRP3 inflammasome activation, characterised by elevated levels of cleaved caspase-1, as well as IL-1β and IL-18 secretion [129]. Here, RIPK1 complexes with RIPK3 following stimulation of a yet unidentified RNA sensor, which enables RIPK1-mediated activation of dynamin-related protein 1 (DRP1). Subsequent translocation of DRP1 to the mitochondria promotes aberrant fission and ROS production in both mouse and human cells, thus activating NLRP3 inflammasome. This DRP1-mediated inflammasome signaling is reported to also occur in response to dengue virus [130] and swine influenza virus infection [131]. Some studies contradict these observations [132–134], likely due to different experimental models, therefore additional research is necessary to conclusively define this form of NLRP3 signaling.

1.4.2. RIPK1/3 in inflammasome responses to bacterial infections

Yersinia is capable of inducing caspase-1 processing and cell death following infection of mouse macrophages [39,135,136]. This is driven by YopJ-mediated suppression of TAK1, which enables RIPK1, FADD and caspase-8 recruitment, and subsequent activation of caspase1. The resulting cell death exhibits significant RIPK1/caspase-8-mediated GSDMD cleavage, implicating pyroptosis in this process [136]. Notably, NLRP3 and caspase-1/11 are not involved in this pyroptotic pathway, but instead activated following potassium efflux to promote IL-1β processing and release. These observations illustrate an alternative NLRP3-independent mechanism for caspase-1 and GSDMD activation during *Yersinia* infection.

2. RIPK2 signaling in pathogen infection

RIPK2 (also known as RIP2, RICK and CARDIAK) is an essential scaffold for signal transduction via the nucleotide-binding oligomerization domain (NOD) proteins, NOD1 and NOD2 [137–140], and is thus frequently implicated in innate inflammatory responses to pathogens.

NOD proteins are cytosolic pattern-recognition receptors (PRRs) that activate pro-inflammatory and antimicrobial responses when exposed to pathogen associated molecular patterns (PAMPs). NOD1 recognizes Ɣ-D-glutamyl-mesodiaminopimelic acid (iE-DAP) from Gram-negative bacteria and some Gram-positive bacteria, whereas NOD2 recognizes a conserved component of bacterial peptidoglycan (PGN) consisting of muramyl dipeptide (MDP) from both Gram-positive and Gram-negative bacteria [141–144] (Fig. 3). These stimulatory agents are released from bacteria upon cell wall fragmentation in bacterial killing, bacterial division, or they can be co-injected into host cells with virulence proteins by bacterial secretion systems [145]. Alternative mechanisms of NOD/RIPK2 activation will be discussed in context within the review.

2.1. RIPK2 in host responses to bacterial pathogens

To date, much of the research on NOD1/NOD2/RIPK2 signaling mechanisms has relied on purified PGN components as a cellular stimulus. This has been useful for the identification of cellular mechanisms, however can have limitations when considering the physiological role of signaling mediators in the context of pathogen infection, especially when many pathogens encode virulence factors that can inactivate innate immune signaling. Although many studies have assessed mechanisms of NOD signaling in bacterial control, especially in the context of autophagy, this review will focus on studies with direct experimental evidence of RIPK2 involvement, and where live bacterial agents have been utilised.

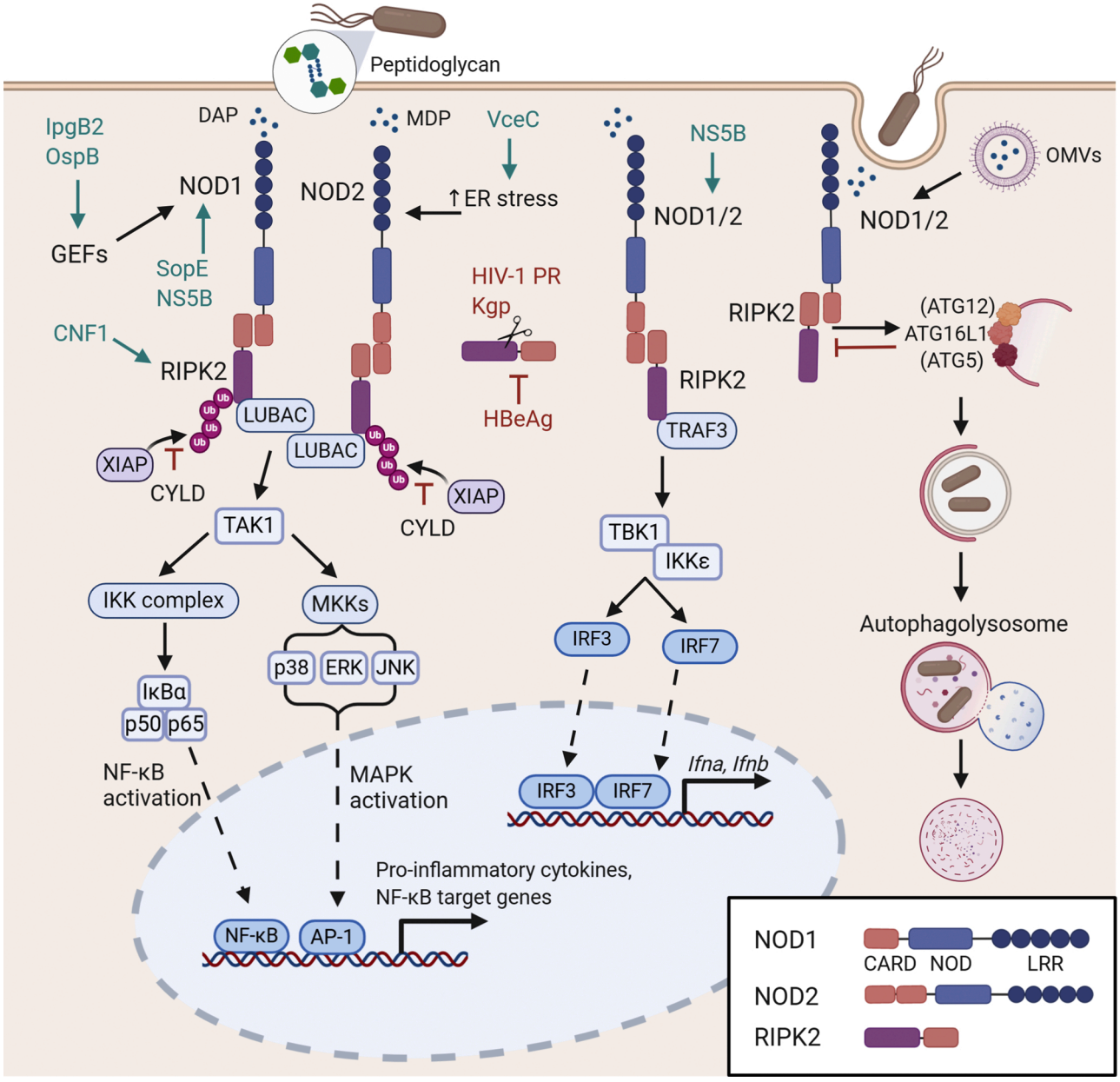

Fig. 3. RIPK2 regulation of NOD1 and NOD2 signaling in response to PAMP sensing. Upon activation by bacterial peptidoglycan components, NOD1 and NOD2 oligomerize and interact with RIPK2 via homotypic CARD-CARD interactions [137]. Once engaged, RIPK2 is activated by autophosphorylation, then ubiquitylated by E3 ligases including XIAP and LUBAC, which further activates both NF-κB and MAPK pathways and promotes pro-inflammatory cytokine production [146]. Alternatively, TRAF3 can interact with RIPK2 following NOD1/2 ligation, redirecting signaling to TBK1 and IKKε to promote downstream IFN production [147]. Other roles of RIPK2 include mediating interactions between NOD1/2 and key autophagy protein ATG16L1, which enables autophagic bacterial clearance following NOD sensing of peptidoglycan or bacterial OMVs [148–150]. Virulence factors that interact with these pathways are indicated, and have been discussed in the main body of the text.

Some of the earliest studies that characterised the role of RIPK2 in host responses to infections utilised *L. monocytogenes*, the causative agent of listeriosis. Initial studies showed macrophages from *Ripk2*$^{-/-}$ mice were defective in NF-κB signaling and produced significantly less pro-inflammatory cytokines than WT macrophages following infection [137,151]. Furthermore, *Ripk2*$^{-/-}$ mice were unable to control *L. monocytogenes* infection due to decreased NF-κB activation, and impaired IFNγ production in T helper 1 (Th1) and natural killer (NK) cells. Overall this suggests that RIPK2 plays an important role in both innate and adaptive immunity to infection [137,151], and that RIPK2 was mediating these responses via NOD1/2 and not directly via TLR activation [140].

RIPK2 has since been shown to play a role in controlling a diverse array of bacterial pathogens, particularly those with an intracellular lifestyle (Table 1). Single nucleotide polymorphisms (SNPs) in *RIPK2* increase susceptibility to mycobacterial infections, for example, multibacillary leprosy caused by *M. leprae* [152], and *M. tuberculosis* infections within the Western Chinese Han population [153]. Although the mechanisms underlying susceptibility are unclear, *M. tuberculosis* activates NOD2/RIPK2, which stimulates the activity of IRF5 to induce transcription of type I IFNs [147]. Furthermore, IFNγ production by Th1 cells induces macrophage maturation and anti-mycobacterial molecules important for resistance against mycobacterial infections [154,155]. Zhang et al. [152] suggested RIPK2 and NOD2 may regulate IFNγ which could explain increased susceptibility to mycobacterial infections in those with RIPK2 polymorphisms.

Streptococcus pneumoniae (pneumococcus) is a an opportunistic pathogen associated with pneumonia, ear infections, sinus infections, meningitis and bacteremia [156]. NOD2/RIPK2 are critical for anti-inflammatory signaling in response to the purified pneumococcal cell wall (PnCW) of *S. pneumoniae*. PnCW induces intensive inflammatory responses by macrophages and dendritic cells during systemic infection in a TLR2-dependent, NOD2/RIPK2-independent manner [157,158]. This inflammation is critically modulated by IL-10 [159], as IL-10 deficiency increases mortality in *S. pneumoniae* infection in vivo [160]. Curiously, this IL-10 production is TLR2, NOD2 and RIPK2-dependent, whereby RIPK2 or NOD2-deficient BMDMs have compromised IL-10 production in response to PnCW [157]. Although the mechanism is not clear, this suggests that there is cell-specific and stimulus-specific crosstalk between TLR2 and NOD2/RIPK2 pathways [161].

During *L. pneumophila* infection, RIPK2 mediates NF-κB activation independently of TLR/MyD88 activation, but in response to bacterial factors (likely PGN) delivered directly into the host cell cytosol by the *Legionella* T4SS [145]. in vivo studies have shown that RIPK2-deficiency results in poor neutrophil recruitment into the lung, a significant reduction in proinflammatory cytokine and chemokine secretion, and increased bacterial burden [162]. While one study suggested only NOD1 was involved in these responses in *Ripk2*$^{-/-}$ mice [163], another implicated both NOD1 and NOD2 [162]. Overall, it appears NOD signaling plays a role in RIPK2-mediated responses to *L. pneumophila,* however it doesn't rule out involvement of other signaling pathways initiated by TLR2, IL-1R or IL-18R [137].

Borrelia burgdorferi is the causative agent of Lyme disease, a tick-borne infection that causes multi-systemic illness [164]. Early studies showed that RIPK2 expression is increased in astrocytes and microglia exposed to *Borrelia* spirochetes [165,166]. Subsequent work showed that peritoneal macrophages from *Ripk2*$^{-/-}$ mice exhibit a significant reduction in IL-1β, IL-6 and IL-8 production following stimulation with heat-killed *Borrelia*, compared to WT mice [167]. Here, through an unknown mechanism, uptake and degradation of *Borrelia* in lysosomes introduces PGN to the cytosol and stimulates NOD2/RIPK2-mediated NF-κB activation and inflammatory cytokine production [167].

2.1.1. RIPK2 and autophagy as a host response to bacterial infection

RIPK2 induces antibacterial autophagic responses by signaling between NODs and the autophagy factor ATG16L1 [148] (Fig. 3). Mutations in ATG16L1 disrupt an inhibitory interaction with NOD2 and consequently increase the activation of RIPK2 [150]. Excessive RIPK2 activation has been reported in pediatric Crohn's disease (CD) [168,169] and there is a strong link between resident intestinal bacteria and CD pathogenesis; therefore, it has been proposed that ineffective bacterial clearance due to impaired anti-bacterial autophagy is an important contributor to the pathogenesis of this chronic inflammatory disease [170,171]. Autophagy has an essential role in innate immunity and the elimination of pathogens that have escaped into the cytoplasm, as it forms a double-layered membrane that envelopes cytosolic bacteria for degradation via fusion with lysosomes [172–174].

The invasive gastrointestinal pathogen, *Shigella flexneri*, is a major cause of morbidity and mortality in children under 5 years in developing countries [175], and is an emerging sexually transmitted infection of men who have sex with men [176]. *S. flexneri* induces NF-κB and JNK activation in a NOD1/RIPK2-dependent manner to limit bacterial replication in intestinal epithelial cells [177]. Although early studies did not investigate mechanisms of *S. flexneri* killing, it was pivotal in understanding the mechanisms of NOD/RIPK2-mediated autophagy in future infection studies.

The gastric pathogen *Helicobacter pylori* is subject to degradation by autophagy via the NOD1/RIPK2 signaling axis. *H. pylori* infection has long been implicated in the development of gastric cancer [178–180], and recently, polymorphisms in *RIPK2* were found to be associated with increased susceptibility to gastric cancer in Japanese populations [181] where the prevalence of this disease is very high. Indeed, *Nod1*$^{-/-}$ mice are highly susceptible to *H. pylori* infection [182], and mechanistically, Irving et al. [149] demonstrated that in gastric epithelial cells, RIPK2 mediates NOD1-dependent IL-8 production and autophagosome formation in early endosomes in response to *H. pylori*-derived outer membrane vesicles (OMVs) containing PGN. Overall, NOD1/RIPK2 signaling protects against *H. pylori* infection and subsequent malignancies.

NOD2/RIPK2-mediated autophagy aids in the control of a number of pathogens including *L. monocytogenes*, *S.* Typhimurium and *Shigella* spp. [183]. *L. monocytogenes* undergoes autophagosomal degradation in phagocytic cells in mouse BMDMs and in vivo via ERK activation, in a process mediated by TLR2, NOD2 and RIPK2 [184]. In *S.* Typhimurium infected intestinal epithelial cells, NOD2/RIPK2 is required for autophagy induction [185]. This in vitro model of *Salmonella* infection demonstrated a dual role for RIPK2 tyrosine kinase activity in NOD2-dependent autophagy through activation of p38 MAPK and indirect repression of PP2A phosphatase activity [185].

2.1.2. Alternative mechanisms of NOD/RIPK2 stimulation in bacterial infections

In addition to PGN stimulation, there is increasing evidence that NOD/RIPK2 signaling can be activated by pathogen-induced modifications to the host actin cytoskeleton [186–189]. Cytoskeletal dynamics are mediated via a balance of active GTP-bound and inactive GDP-bound forms of small Rho GTPases [190]. *Salmonella* and *Shigella* spp. utilise T3SS to translocate bacterial effector proteins into host cells, and manipulate host cytoskeletal proteins and innate immune responses [191]. *Shigella* infection induces the recruitment of GEF-H1, a guanidine exchange factor (GEF) for the small Rho GTPase RhoA, to the site of invasion to promote host cell entry. Following invasion, the *Shigella* effectors IpgB2 and OspB induce RIPK2-dependent NF-κB activation mediated by the interaction of recruited GEF-H1 with NOD1 [187]. The *S.* Typhimurium effector SipA drives NOD1/NOD2/RIPK2 dependent NFκB activation via an unknown mechanism [189], whereas, SopE, functions as a GEF for the small Rho GTPases Rac1 and Cdc42. In this setting, Rac1 and Cdc42 interact with the NOD1/RIPK2 signaling complex in the absence of PGN to mediate NF-κB-dependent inflammation [188]. In addition, the *Escherichia coli* cytotoxic necrotising factor 1 (CNF1) activates the small Rho GTPase Rac2, which then interacts with

RIPK1 and RIPK2 to induce a potent inflammatory response, independent of NOD1/2 [192]. Many other bacterial pathogens have also been shown to induce changes to Rho GTPases [193], overall highlighting the role of pathogen-induced small Rho GTPase activation in NOD1/RIPK2-mediated inflammation.

Pathogen-activated endoplasmic reticulum (ER)-stress also drives NOD/RIPK2-induced inflammation [194]. The intracellular pathogen *Brucella abortus* induces ER stress via the IRE1α pathway of the unfolded protein response (UPR). IRE1α acts as a receptor that is stimulated upon binding of the *Brucella* T4SS effector VceC to the ER chaperone BiP, and subsequently recruits TRAF2 to activate NOD2/RIPK2-mediated NF-κB activation [194]. Although the precise mechanism is not yet established, the intracellular pathogen *Chlamydia muridarum* also induces NOD1/-NOD2/RIPK2 signaling in response to ER stress in vitro [194], however *in vivo* studies have shown that RIPK2 deletion has a limited effect on chlamydial infection in terms of bacterial burden, immune responses and pathology [195]. Given that many pathogens including IAV [196] and HCMV [197] activate ER-stress followed by induction of the UPR, it could be likely that NOD/RIPK2 signaling has an underappreciated role in host immunity via this pathogen-induced mechanism.

2.1.3. Regulation of RIPK2 and implications for bacterial infection outcomes

Regulation of RIPK2-mediated inflammatory responses to infection is dependent upon the deubiquitinating enzyme CYLD [198]. During in vitro infection of mouse bone marrow-derived macrophages (BMDMs) with *L. monocytogenes*, CYLD binds and deubiquitylates RIPK2, resulting in decreased activation of NF-κB and ERK1/2 signaling. Thus, inhibition of RIPK2 by CYLD leads to impaired pathogen control due to a reduction in antimicrobial responses including pro-inflammatory cytokine production, ROS and nitric oxide (NO) production.

Another recent study used kinase inhibitors to demonstrate functional specificity of the kinase domain of RIPK2 in controlling bacterial pathogens. WEHI-345 is a potent inhibitor of RIPK2 that specifically targets serine/threonine kinase activity [146] and pre-treatment of $CD11\beta^{+}$ monocytes with this inhibitor significantly reduces TNF production during in vitro infection with *L. monocytogenes* [146], suggesting a role for the serine/threonine kinase activity of RIPK2 in protection against bacterial infection.

RIPK2 signaling may also be regulated via the formation of RIPosomes, which are high molecular weight cytoplasmic complexes comprised of RIPK2 [199,200]. Ellwanger et al. [199] showed RIPosomes form post-NF-κB activation, and suggest that sequestration of RIPK2 in these complexes may act to dampen RIPK2 signaling. Intriguingly, RIPosomes form in the cytosol of epithelial cells upon invasion with *S. flexneri*, suggesting the pathogen may actively prevent RIPK2 signaling via an unknown process. Given that inhibition of XIAP was shown to promote deposition of RIPK2 in RIPosomes, it may be that *Shigella* encodes a virulence factor that targets XIAP for cleavage or degradation, or actively inhibits XIAP-designated sites of ubiquitylation on RIPK2 to inhibit inflammatory signaling [199].

2.2. RIPK2-mediated inflammatory responses in the control of viral pathogens

It is now established that NOD1 and NOD2 respond to viral infections, thus participating in the coordinated host defense against viruses [201–204]. Activation of NOD1, NOD2 and RIPK2 during viral infection depends on type I IFN, synthesized as a result of activation of other PRRs. One of the first studies to assess the role of NOD2/RIPK2 activation in viral infection showed that RIPK2 was critical for dampening inflammasome activation during H1N1 IAV infection [205]. Here, $Ripk2^{-/-}$ mice were highly susceptible IAV infection, whereby enhanced NLRP3 inflammasome activation and increased IL-18 secretion were potent drivers of disease progression and mortality in vivo. Negative regulation of inflammasome activity by RIPK2 is dependent its kinase-mediated activation of the mitophagy inducer, ULK1. Thus NOD2 and RIPK2 respond to IAV infection by promoting ULK1 phosphorylation and inducing mitophagy, which dampens inflammasome activation and IL-18 production. In addition, both NK cells and CD8 + T cells isolated from IAV-infected $Ripk2^{-/-}$ mice are highly activated and exhibit increased IFN-γ production despite the total numbers of these cells being similar in WT mice. These results indicate that increased IL-18 in $Ripk2^{-/-}$ mice subsequently leads to increased IFN-γ production from innate and adaptive cell populations [205].

Hepatitis B and C virus (HBV and HCV) are associated with the development of hepatocellular carcinoma [206]. NOD1/RIPK2 signaling is activated by the viral polymerase NS5B of HCV [207], thus deletion of RIPK2 in HepaRG cells expressing NS5B, results in significantly reduced MAPK activation, proinflammatory cytokine production, and IFNβ production. In HBV infection, the Hepatitis B e-antigen (HBeAg) inhibits RIPK2 expression and also interacts with RIPK2 in HepG2 cells in vitro, resulting in inhibition of NOD1/RIPK2-mediated NF-κB activation and subsequent IL-6 production [208]. These studies highlight the importance of RIPK2 in controlling chronic Hepatitis infections.

2.3. Pathogens targeting RIPK2 for inactivation

To date, the only known pathogens to directly target RIPK2 during infection are HIV-1 and the primary etiologic agent of periodontal disease, *Porphyromonas gingivalis*. The HIV-1 protease PR cleaves RIPK2 within the N-terminus, although its outcomes in infection have not been tested [102]. Similarly, *P. gingivalis* infection of human aortic endothelial cells results in rapid direct cleavage of RIPK2, and is dependent upon the lysine-specific protease, gingipain (Kgp) [209]. Given the mounting evidence for pathogens targeting RIP kinases, it would not be surprising if other pathogens were found to specifically inactivate RIPK2 in future studies.

3. The role of RIPK4, RIPK5, RIPK6 and RIPK7 in pathogen infection

There is currently relatively little published on RIPK4-6 and their role in host responses to pathogen infection, however RIPK7 is emerging as an important mediator of immunity to intracellular pathogens.

3.1. RIPK4 (DIK/PKK) and RIPK5 (SgK288)

RIPK4 has a well-described role in cellular differentiation, but also mediates proinflammatory cytokine production in keratinocytes via direct stimulation of IRF6 [210]. Furthermore, overexpression of RIPK4 leads to NF-κB and MAPK activation [211]. Although no study has reported a direct role for RIPK4 in host responses to pathogens, it would not be surprising to find RIPK4 mediates inflammation during infection. RIPK5 on the other hand, has no reported association with innate or adaptive immune responses in mammals.

3.2. RIPK6 (LRRK1) and RIPK7 (LRRK2)

Pathogenic variants of RIPK7 are one of the most prominent genetic causes of Parkinson disease (PD) [212], whereas *RIPK6* variants have been shown to have no association with the development of PD. As for infection, the only reported data for RIPK6 is in relation to bovine viral diarrhoea virus (BVDV), where RIPK6 is downregulated in PBMCs infected with BVDV-2 [213]. RIPK7 however, has been shown to play a role in numerous cellular processes associated with pathogen control, including vesicular trafficking, microtubule binding, autophagy and mitophagy [214]. One of the first studies to examine the role of RIPK7 in innate immunity found that RIPK7 contributes to the restriction of *S.* Typhimurium by macrophages in vitro [215]. This was supported in vivo as $Ripk7^{-/-}$ mice are more susceptible to *S.* Typhimurium intraperitoneal infection, exhibiting decreased IL-1β secretion, reduced

neutrophil infiltration, high bacterial load in the peritoneal cavity and overall increased mortality [216]. Mechanistically, this study showed RIPK7 forms a complex with the NLRC4 inflammasome in a kinase dependent manner, which then promotes inflammasome activation and restriction of bacterial growth during infection [216]. Similarly, *Ripk7*$^{-/-}$ mice are more susceptible to oral infection with *L. monocytogenes* than WT mice [217]. This study showed that RIPK7 is highly expressed in lysozyme-positive Paneth cells and myeloid cells within the lamina propria of the ileum, suggesting RIPK7 plays a protective role at the intestinal mucosa. This is further supported by the fact that mutations in RIPK7 are associated with increased severity of inflammatory bowel disease [218].

Similar to RIPK2, polymorphisms in *RIPK7* are associated with the development of multibacillary leprosy caused by *M. leprae* [152,219,

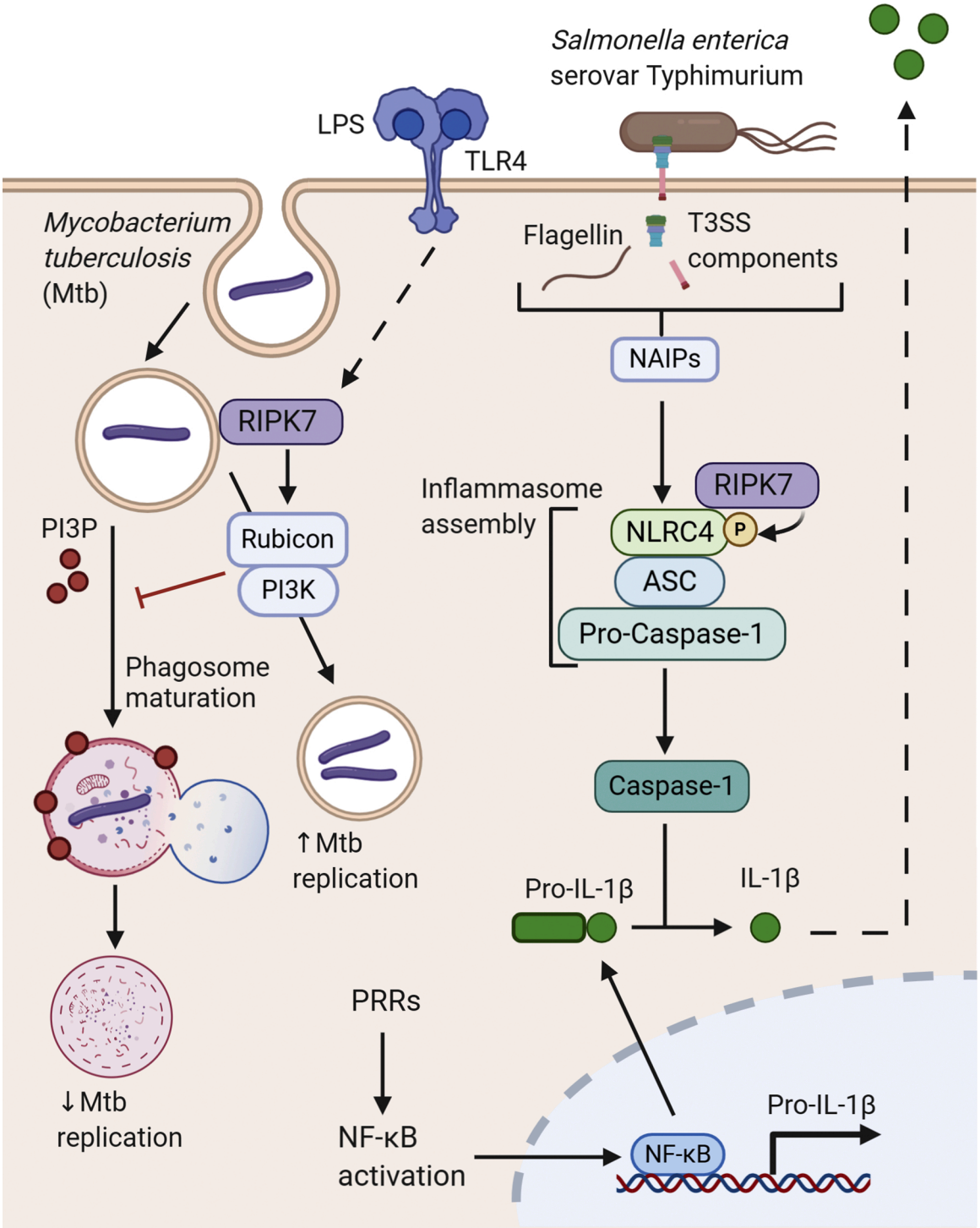

Fig. 4. Cellular responses to bacterial infection mediated by RIPK7 (LRRK2). Sensing of LPS by TLR4 promotes localization of RIPK7 to endosomal membranes [225, 226]. Here, RIPK7 can be exploited by *M. tuberculosis* (Mtb) to promote bacterial replication, as RIPK7 recruits Rubicon to the endosome, where this complexes with PI3K to prevent further phagosome maturation [222]. Following priming by PRRs, detection of *S.* Typhimurium bacterial components such as flagellin (or Type III Secretion System rod proteins) by NAIP family members induces NLRC4 activation [227]. In contrast to RIPK7's role in Mtb infection, kinase-dependent interactions between RIPK7 and NLRC4 promote efficient inflammasome assembly and aid downstream restriction of bacterial growth [216].

220] and Mtb infection [221]. A recent study identified a mechanism whereby RIPK7 negatively regulates phagosome maturation in macrophages by controlling Rubicon/PI3K activity on phagosomes in a kinase dependent manner, resulting in impaired immune responses and promotion of Mtb replication [222] (Fig. 4). Contradictory to the requirement of RIPK7 for the control of *Salmonella* and *Listeria* infection, RIPK7-deficiency in macrophages or mice results in improved control of Mtb infection, which supports a specific role for RIPK7 in mycobacterial control via the regulation of degradative pathways [222]. *Ripk7*$^{-/-}$ mice exhibit increased transcription of type II IFN, but decreased transcription of type I IFN during Mtb infection [222], and *RIPK7*-deficient macrophages fail to induce type I IFN in vitro when infected with Mtb [223]. Mechanistically, RIPK7 regulates type I IFN gene expression by maintaining mitochondrial homeostasis [223]. Given that production of type I IFNs during Mtb infection have been shown to promote disease [224], this may explain why Mtb infection is limited in the absence of RIPK7. Thus, RIPK7 acts as a regulator of early clearance of Mtb and given its function is kinase dependent, there may be therapeutic potential for RIPK7-specific kinase inhibitors in tuberculosis.

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4. Concluding remarks and future perspectives

RIPK1, 2, 3 and 7 have emerged as critical mediators of inflammation and innate immunity in response to multiple diverse pathogens. Not surprisingly, many pathogens have evolved highly specific mechanisms to either directly or indirectly target RIPK signaling networks to benefit replication and survival, and have thus provided invaluable knowledge on the physiological role of RIPK signaling in the context of infection. One of the major challenges that remain in the field of host-pathogen interactions is the consistency of experimental conditions, whereby factors including genetic background of animal models, specific pathogen strains (lab adapted vs currently circulating clinical isolates), cell types (primary, site specific vs immortalised carcinoma cell lines) and the use of inhibitors (e.g. Nec-1 vs Nec-1 stable) heavily influence experimental outcomes. The more unified this becomes globally, the more reliable the data will become.

Finally, RIPKs are currently under critical review as potential therapeutic targets, as dysregulation of RIPK signaling is closely associated with hyperinflammation and pathology. Multiple studies are investigating various classes of kinase inhibitors for RIPK1-3 [228], however given the importance of kinase-dependent cell-death responses to infection, it is critical that we understand the impact of these therapeutic interventions on infection outcomes before introduction to the clinic. The same goes for the recently identified small molecule therapy, Proteolysis-Targeting Chimeras (PROTACs), for the selective degradation of RIPK2 [229]; given the importance of RIPK2 in detection of multiple intracellular pathogens, what would be the effect on infection outcome?

Overall, there has been significant progress made in the field of RIPK biology, and continued efforts on this front will help to bolster our understanding of host-pathogen interactions and potential therapeutic development for infectious diseases. To this end, we must continue to develop a comprehensive understanding the of 1) the biochemical function of each RIPK domain and the role they play in response to specific pathogens, and 2) biochemical mechanisms of virulence factors in currently circulating pathogenic organisms.

Declaration of competing interest

We, the authors declare no competing interests.

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