CHAPTER FIVE

The involvement of regulated cell death forms in modulating the bacterial and viral pathogenesis

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Abstract

Apoptosis, necroptosis and pyroptosis represent three distinct types of regulated cell death forms, which play significant roles in response to viral and bacterial infections. Whereas apoptosis is characterized by cell shrinkage, nuclear condensation, bleb formation and retained membrane integrity, necroptosis and pyroptosis exhibit osmotic imbalance driven cytoplasmic swelling and early membrane damage. These three cell death forms exert distinct immune stimulatory potential. The caspase driven apoptotic cell demise is considered in many circumstances as anti-inflammatory, whereas the two lytic cell death modalities can efficiently trigger immune response by releasing damage associated molecular patterns to the extracellular space. The relevance of these cell death modalities in infections can be best demonstrated by the presence of viral proteins that directly interfere with cell death pathways. Conversely, some pathogens

hijack the cell death signaling routes to initiate a targeted attack against the immune cells of the host, and extracellular bacteria can benefit from the destruction of intact extracellular barriers upon cell death induction. The complexity and the crosstalk between these cell death modalities reflect a continuous evolutionary race between pathogens and host. This chapter discusses the current advances in the research of cell death signaling with regard to viral and bacterial infections and describes the network of the cell death initiating molecular mechanisms that selectively recognize pathogen associated molecular patterns.
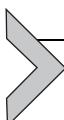
1. Introduction

In the late 1960s, it was recognized that cell death could be considered as a regulated process. For the genetically programmed, regulated cell demise the term apoptosis (from Greek: "*falling off*") was coined, which exhibited distinctive morphological and molecular patterns (Kerr et al., 1972). That time necrosis was interpreted as a total counterpart of apoptosis, a non-physiological and non-regulated, lytic cell death modality. In the recent decades, additional newly discovered regulated cell death modalities have been added to the list of cell death types (Galluzzi et al., 2018), and it became evident that necrotic-like, lytic cell death can also take place in a regulated manner. Apoptosis is a non-lytic form of cell death characterized by nuclear condensation, shrinkage of the cell, formation of apoptotic bodies and preservation of the cytoplasm membrane integrity until the late stages of the process (Kerr et al., 1972). Importantly, apoptosis actively labels itself by translocating phosphatidylserine (PS) to the outer leaflet of the membrane lipid bilayer. The PS exposure on the outer surface provides a so-called "eat me" signal for the neighboring monocytes and macrophages and ensuring the clearance of the apoptotic debris (Fadok et al., 1992). These two main attributes qualify apoptosis as a non-inflammatory cell death. In contrast, necroptosis and pyroptosis are lytic cell death modalities, accompanied by early membrane rupture and osmotic imbalance, which provoke inflammatory signals by releasing damage associated molecular patterns (DAMPs) to the extracellular space (Galluzzi et al., 2018). It is important to note that the immunogenicity of the cell death is a more complex process than above outlined. The lytic property of a cell demise does not necessarily result in an immune stimulation, while the caspase-8 driven apoptosis may lead to immunogenic processes (Yatim et al., 2015). This also clearly indicates that the release of DAMPs is a signaling-dependent, actively regulated process.

The human body developed elaborate strategies to efficiently avoid and eliminate infectious pathogens. Two corner stones of this response are the innate and the adaptive immune signaling, which also include controlled killing/self-killing mechanisms of the infected host cells (Jorgensen et al., 2017). This review focuses on the infection related aspects of regulated cell death forms, which in many instances provide benefit for the hosts by destroying the intracellular niche of the pathogen. Nevertheless, it is evident that some extracellular pathogens—and also intracellular ones—can benefit from the death of the host cells. In this chapter, based on the current advances in the research, we give a detailed description about the key cell death modalities, including apoptosis, necroptosis and pyroptosis emerging in response to pathogenic insults, and we discuss how bacterial and viral infections can modulate these signaling pathways.

2. Role of apoptosis in bacterial and viral infection

2.1 The apoptotic core machinery

Apoptosis is conducted by caspase activation. Caspases are cysteine-driven and aspartate-directed peptidases, which present in inactive forms, and become cleaved and activated upon selective apoptotic stimulation (Cohen, 1997). The initiator caspases (for instance caspase-8 and -9) are the upstream components of the caspase-cascade. Their structurally unique feature is the large pro-domain, that enables the recruitment to multimeric protein complexes (Mace and Riedl, 2010). Extrinsic and intrinsic pathways represent the two major routes of initiator caspase activation. In the extrinsic pathway, extracellular ligands from the tumor necrosis factor (TNF) super-family interact with transmembrane death receptors (DR) of the TNF superfamily. Consequently, by the help of an adaptor protein, caspase-8 and -10 are recruited into the DR containing cell death inducing signaling complex (DISC), which leads to proximity induced cleavage and activation of these initiator caspases (Wilson et al., 2009). The intrinsic pathway can be triggered by intracellular perturbations, for instance by genotoxic stress, star-vation and ER-stress. Upon stimulus, two pro-apoptotic members of the B cell lymphoma 2 (BCL-2) protein family BCL-2-associated X protein (BAX) and BCL-2-antagonistic killer (BAK) go through conformational changes and translocate into the mitochondria (Tait and Green, 2010). In turn, these proteins oligomerize and form large pores throughout the mitochondrial membrane (Große et al., 2016). This event initiates the mitochondrial outer membrane permeabilization (MOMP). Caspase-9

activation takes place in the apoptosome protein complex. Formation of this complex is dependent on the MOMP-driven release of mitochondrial pro-apoptotic proteins, such as cytochrome-C (Riedl and Salvesen, 2007). The activation of initiator caspases in both pathways culminates in the cleavage of executioner caspase-3, -6 and -7. In turn, the effector caspases cleave selective substrates, including poly ADP-ribose polymerase (PARP), inhibitor of caspase activated DNAse (ICAD) and lamins calling forth the biochemical and morphological features of apoptosis (Cohen, 1997; Tewari et al., 1995).

2.2 Apoptosis in virus infection

Viruses are obligatory intracellular pathogens and their propagation is fully dependent on the intracellular milieu of the host cell. The host organisms developed various strategies to detect and destroy the invading viral pathogens. The immunological responses, involving the transcription of anti-viral genes (e.g., interferons and cytokines) given to a specific virus infection are well characterized. It is widely accepted view that apoptosis can be beneficial for the host by destroying the intracellular niche of the pathogen (Evavold et al., 2018). The most striking evidence for the anti-viral advantage of apoptosis is the observation that many viruses produce anti-apoptotic/ necroptotic proteins that block cell death signals (Thome et al., 1997; Zhou et al., 1997). However, based on recent studies, it is obvious that the picture is more complex than originally expected, and whether the cell death is beneficial or detrimental for the host seems to be dependent on multiple factors, including timing, cell type and the effectiveness of the cell death modality to trigger or suppress immune response.

2.2.1 The role of death receptors and the extrinsic apoptotic pathway
The TNF ligand superfamily acts via transmembrane TNF receptors. Specific members of these receptor family, also called death receptors (DR), possess a cytoplasmic 80 amino acid motif, termed death effector domain. These receptors, including TNFR1, first apoptosis signal (FAS, also called CD95) and the TNF-related apoptosis-inducing ligand receptor-1/2 (TRAILR1/2) can unleash various signaling pathways, such as proliferation, survival, immune response and apoptosis (Wilson et al., 2009). In response to ligand binding, the trimerized DRs can recruit one of the two death domain (DD) containing adaptor proteins: TNFR associated DD (TRADD) or FAS associated DD (FADD). Recruitment of TRADD leads to the assembly of a complex containing several proteins, including the DD containing receptor interacting protein kinase-1 (RIPK1) (Hsu et al., 1996), the cellular FLICE/Casp8

inhibitory protein (cFLIP), the TNFR associated factor-2 (TRAF2) and the E3 ubiquitin ligase cellular inhibitor of apoptosis (cIAP) (Varfolomeev and Vucic, 2008). This protein complex conveys a non-apoptotic signal via the activation of the NF-κB signaling. In contrast, the binding of FADD triggers the interaction of caspase-8 and -10, leading to apoptotic signaling either via the mitochondrial amplification loop or via direct caspase-3/-7 cleavage in immune cells. TNFR stimulation primarily results in the recruitment of TRADD, leading to non-apoptotic signals via NF-κB activation and expression of pro-survival genes such as cFLIP. Once this primary signal is compromised by the inhibition of the expression of anti-apoptotic cFLIP, the apoptotic signal can proceed. Conversely, activation of FAS and TRAILR predominately transduces FADD dependent apoptotic signaling (Wilson et al., 2009). Signaling through DRs represents one of the major forms of the immune cell directed host cell killing in infection.

Cytotoxic T cells (CTL) are key components of the adaptive immune response and natural killer (NK) cells play analogous role in the innate immune response. CTLs express FAS ligands (FASL) on their surface (Fig. 1) (Halle et al., 2017). The trimerized ligands bind the DRs expressed on the cell surface, leading to DR clustering and binding of the adaptor protein FADD, which consequently results in the recruitment of initiator caspase-8/-10. This cell killing mechanism can reduce the spreading of the virus by eliminating the intracellular niche of the pathogen (Halle et al., 2017). This occurs in human vascular endothelial cells in response to Dengue virus (DV), where the cells exhibit increased FASL and FAS expression and increased number of FAS on the cell surface. This phenomenon is accompanied by elevated rate of apoptosis (Liao et al., 2010). Similarly, influenza A virus (IAV) infection leads to the expression of FASL, FADD and caspase-8, and downregulates the expression of cFLIP in human lung epithelial cell lines. However, it is not entirely clear if the host or the virus profits from the apoptosis induction. For instance, the replication of the IAV can be amplified by overexpression of pro-apoptotic genes and is blocked by the upregulation of anti-apoptotic genes (Wang et al., 2014). This study suggests that an initially protective apoptotic over-activation can turn against the host in some instances. TNFα, the ligand of TNFR1 can also be expressed paracrine or in autocrine manner as the part of the anti-viral immune response. Hepatitis B virus x protein (HBx) sensitizes host cells to TNF driven apoptosis by interfering the anti-apoptotic function of cFLIP, thereby resulting in caspase-8 over-activation upon stimuli (Kim and Seong, 2003).
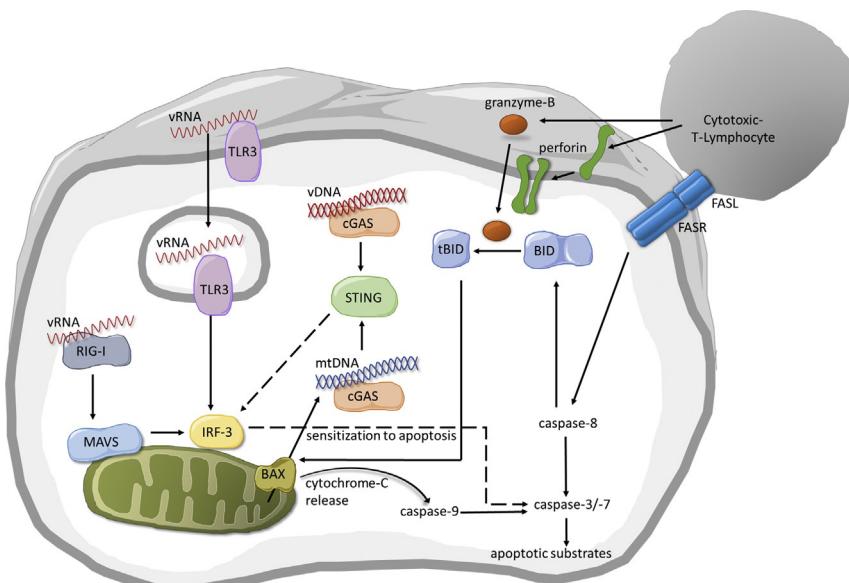
Fig. 1 Apoptosis signaling in response to infection. Extracellular and intracellular Viral RNA (vRNA) fragments (left) activate TLR3 and RIG-I, respectively, resulting in IRF-3 activation. Cytoplasmic viral, bacterial or mitochondrial DNA (mtDNA) is detected by cGAS, which in turn activates the STING pathway, leading to apoptotic signaling via a putative IRF-3 driven mechanism. Apoptosis can be triggered by effector cells of the immune system. Ligation of the FASR (right) leads to the assembly of the adaptor FADD and caspase-8 containing DISC, resulting in the activation of caspase-8. Activation of caspase-8 either results in the direct cleavage of caspase-3/7 or leads to the BID cleavage (tBID) driven amplification loop of the intrinsic pathway. The secretion of the pro-apoptotic perforin and granzyme-B (middle) triggers the activation of the intrinsic apoptotic pathway.

2.2.2 Intrinsic apoptosis triggered by immune cells: Granzyme-B

In addition, CTLs and NK cells induce apoptosis in virus infected target cells through the action of secreted effector molecules. Granzyme–B enters the cells along with another secreted protein called perforin (Fig. 1) (Lowin et al., 1994; Shresta et al., 1995). Granzyme–B is a serine protease that has been shown to induce mitochondrial apoptosis by inducing Bid cleavage and subsequent mitochondrial cytochrome–C release, leading to caspase–9 activation (Pinkoski et al., 2001).

2.2.3 Virus induced direct self-destruction in infected cells

Apart from the significant role of immune system driven apoptotic responses, a plethora of evidence demonstrates the relevance of apoptosis,

unleashed directly by the viral pathogens intracellularly. Enterovirus 71 (EV71), a virus in the family of Picornaviridae, is one of the main causative agents of hand, foot and mouth disease in infected infants and young children. EV71 can directly induce the intrinsic apoptotic pathway by activating BAX and the subsequent MOMP, leading to the caspase-9 driven apoptotic signal. Importantly, depletion of caspase-8 has no influence on the cell death initiated by the virus, excluding the role of a DR driven external stimulation (Han and Cong, 2017). Analogously, Coxsackievirus A16 (CA16) can trigger both the extrinsic and the intrinsic way of apoptosis in human neuronal and muscle cell lines accompanied by the typical apoptotic features: caspase cleavage, DNA fragmentation, and PS translocation (Li et al., 2014). The West Nile virus (WNV) is a mosquito born single-stranded RNA virus, causing West Nile encephalitis in humans. The non-structural proteins 2B and 3 (NS2B and NS3) conduct the proteolytic cleavage and the processing of the large viral polyprotein, that is formed directly from the RNA of the virus. Besides, NS3 initiates apoptosis in a caspase-8 dependent way, which then results in typical apoptotic features in multiple human cell lines (Ramanathan et al., 2006).

The virus-host co-evolution is well demonstrated by the examples, where the pathogen has developed strategies to hijack the originally protective apoptotic signaling of the host. Chikungunya virus (CHIKV) was reported to infect macrophages and induce apoptosis by triggering the intrinsic apoptotic pathway via the caspase-9/-3 axis (Nayak et al., 2017). Intriguingly, CHIKV virus exploits the formation of the apoptotic blebs to transport the virus particles into neighboring macrophages (Krejbich–Trotot et al., 2011). The apoptosis can be beneficial for the pathogen, if the defensive immune cells are selectively deleted by the virus-driven cell death signals. The human immunodeficiency virus (HIV) protease cleaves procaspase-8 to a 41 kDa fragment, called casp8p41, which lacks the catalytic site of the caspase. Interestingly, the catalytically inactive fragment can facilitate BAX oligomerization and apoptosis in the host CD4 cells (Sainski et al., 2014).

2.2.4 Viral RNA sensors involved in apoptosis

Probably one of the most thrilling question, emerging from the studies on the host–pathogen interactions, is how the host organisms differentiate between friend and foe. Detection of intracellular pathogens in mammalian cells is a multifaceted mechanism, which involves the recognition of various signals deriving from the pathogens, collectively termed pathogen associated

molecular patterns (PAMPs). For instance, the viral RNA and DNA fragments represent a prominent group of PAMPs. PAMPs are detected by PAMP recognition receptors (PRR) (Chow et al., 2015), which mediate the expression and activation of immunomodulatory cytokines, chemokines, and interferons. Furthermore, the signaling through PRRs leads to cell death signals primarily via the transcriptional activation of apoptotic genes.

Depending on the spatial localization of the viral RNA fragments, RNA viruses can either stimulate Toll-like receptors (TLRs) or activate the retinoic acid inducible gene-I (RIG-I) pathway. TLR3, which resides in the cytoplasmic and endosomal membranes (Fig. 1), recognizes extracellular double-stranded viral RNA (vRNA) fragments (Alexopoulou et al., 2001). TLR3 utilizes the adaptor protein Toll/interleukin-1 receptor (TIR) domain containing adaptor inducing interferon (TRIF) (Yamamoto et al., 2003) to recruit the inhibitor of kappa B kinase (IKK), subsequently leading to the activation of transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and the TANK binding kinase 1 (TBK1) (Fitzgerald et al., 2003), which in turn induces the interferon regulatory factor-3 (IRF3).

Intracellular dsRNA, produced by replicating viruses is detected by cytoplasmic RNA helicases, RIG-I and melanoma differentiation–associated gene 5 (MDA5) (Fig. 1). RIG-I plays important role in recognizing RNAs from RNA viruses, including Newcastle disease virus (NDV), Sendai virus (SeV) and Vesicular stomatitis virus (VSV) (Kato et al., 2006). They recruit members of the TRAF family via the mitochondrial anti-viral-signaling protein (MAVS). In turn, MAVS, analogously to the TLR3 pathway activates the transcription factors IRF3 and NF-κB. Importantly, cells lacking the IRF3 gene are not susceptible to apoptosis upon SeV infection (Peters et al., 2008). Conversely, MAVS is shown to induce apoptosis via caspase-8 but not via IRF3 upon Semliki Forest virus infection (El Maadidi et al., 2014). Infection of a genetically engineered Vaccinia virus strain, lacking the viral BCL-2 analog F1L protein induces apoptosis via the activation of IRF3, which in turn mediates the expression of the pro-apoptotic protein Noxa (from Latin: "*damag*e") in monocytes and lymphocytes (Eitz Ferrer et al., 2011), whereas the wild type strain, possessing the F1L protein cannot stimulate the same response, indicating that the Vaccinia virus successfully adapted in an evolutionary race to overcome the apoptotic inducing capacity of the host.

It was recognized that TLR3 stimulation was able to trigger apoptosis via the adaptor protein TRIF (Kaiser and Offermann, 2005) and that TLR3

mediated direct caspase-8 activation, primarily depending on the presence of cFLIP isoforms (Feoktistova et al., 2011; Weber et al., 2010). Along with this, immunoprecipitation experiments of TLR3 demonstrate the formation of a TLR3 associated DISC-like complex, including TRIF, RIPK1, FADD, cFLIP and caspase-8 in response to IAV infection. The administration of interleukin-24 (IL-24) facilitates the caspase-8 activation by decreasing the presence of cFLIP in the complex and renders the cells to apoptosis (Weiss et al., 2013). The relevance of TLR-3/caspase-8 dependent apoptosis is further confirmed in mouse intestinal epithelial cells, where the apoptosis is independent from the TNFR signaling and from the effect of external cytokines (McAllister et al., 2013).

2.2.5 Viral DNA sensors inducing apoptosis

The cyclic GMP-AMP (cGAMP) synthase (cGAS) has been shown to interact with viral DNA (vDNA) molecules. Upon interaction, cGAS produces its second messenger cGAMP and this in turn activates the stimulator of interferon gene (STING) protein (Fig. 1), which is located in the endoplasmic reticulum (ER). Consequently, STING can activate IRF3 (Ishikawa and Barber, 2008; Sun et al., 2013) and result in mitochondrial apoptosis (Diner et al., 2016). Intriguingly, mitochondrial DNA (mtDNA) that is released upon the apoptotic mitochondrial membrane permeabilization can also activate cGAS. This can trigger IRF3 activation and consequently result in anti-viral responses even in circumstances where viruses efficiently block apoptosis downstream of MOMP, for example at the level of caspase activation. It has been demonstrated that apoptotic caspases not only mediate an anti-inflammatory cell death pathway, but also directly block the mtDNA triggered STING-mediated IFN production in mice (White et al., 2014). A recent study provides evidence that apoptotic caspases cleave the cytoplasmic anti-viral sensors cGAS, MAVS and IRF3 to limit cytokine production. In this study caspase-3 deficient mice exerts increased resistance to virus infection, suggesting that caspase activation may contribute to virus propagation by cutting off the pro-inflammatory signals deriving from the infected cells (Ning et al., 2019).

2.2.6 When apoptosis does not work: Anti-apoptotic proteins encoded by viruses

The viruses developed elaborate countermeasures to avoid or delay a premature apoptotic demise, which consequently would eliminate the

essential environment of the virus replication. These strategies include the expression of apoptosis inhibitor proteins. The majority of the anti-apoptotic factors are encoded by large DNA viruses, which generally replicate with slower kinetics than RNA viruses. A broad group of inhibitors attack the extrinsic pathway of apoptosis, which is triggered by an anti-viral immune response. Viral FLICE-like inhibitory protein (vFLIP) is encoded by the Molluscum contagiosum virus and several gamma Herpes viruses, including Kaposi's sarcoma-associated herpes virus (KSHV). The vFLIP exerts its inhibitory activity by binding the adaptor protein FADD and forming inactive caspase-8/vFLIP heterodimers (Thome et al., 1997). Human cytomegalovirus (CMV) is a common infection in humans, which does not lead to disease in healthy individuals, whereas it causes severe infections or death in patients with immunodeficiencies. The mouse CMV (MCMCV) is the experimental model of human CMV infection. The M36 protein of the virus blocks caspase-8 driven apoptosis and thus contributing to the pathogenicity of the microbe (Ebermann et al., 2012; Skaletskaya et al., 2001). The large subunit of the herpes simplex virus (HSV) ribonucleotide reductase ICP10 demonstrates caspase-8 inhibitory potential by directly interacting with the initiator caspase (Dufour et al., 2011; Langelier et al., 2002). The cytokine response modifier A (CrmA), a product of the Cowpox virus, prevents apoptosis by blocking the activity of caspase-8 (Zhou et al., 1997). Other group of viral anti-apoptotic proteins modulates the expression of cellular anti-apoptotic proteins. The human T-cell leukemia virus type-1 (HTLV-1)-associated adult T-cell leukemia/lymphoma (ATL) is a malignancy of infected mature CD4 T cells in humans (Matsuoka and Jeang, 2007). The transactivator protein TAX of HTLV-1 upregulates the expression of cFLIP by binding to the inhibitor of κB kinase (IKK) and inducing the NF-κB pathway in the host cells, and thereby the virus efficiently amplifies the apoptosis resistance in infected cells (Okamoto et al., 2006). A further group of virally encoded anti-apoptotic factors target the intrinsic apoptosis signaling. The Vaccinia virus encoded F1L protein inhibits the mitochondrial apoptotic signaling in two distinct ways. F1L functions both as an inhibitor of pro-apoptotic BCL-2 family proteins and as a direct caspase-9 inhibitor (Zhai et al., 2010). Human papillomavirus (HPV), a double-stranded DNA virus has been associated with cervical cancer developments in humans (Dürst et al., 1983). The early gene-coding region protein 6 (E6) of HPV is reported to interfere with apoptosis signaling at the level of p53 and by interacting with the pro-apoptotic BAK protein.

2.3 Bacterial infection driven apoptosis

2.3.1 Canonical caspase-8 activation in response to bacterial infection

In contrast to viruses, bacteria are not essentially dependent on the intracellular environment. Moreover, intact cellular layers exhibit physical barriers against bacterial penetration. Therefore, extracellular bacteria developed strategies to efficiently destroy these barrier functions. A novel study presents the bacterial qourum-sensing autoinducer of the *Pseudomonas aeruginosa* N-(3-oxo-dodecanoyl) homoserine lactone (3oc), a small chemical released to control microbial communication, as an inducer of TNFR1. It is demonstrated that 3oc directly disrupts the lipid domain structures, containing sphingolipids and cholesterol, and induces the translocation of TNFR1 into the disordered lipid phase of the membrane, which in turn triggers the trimerization of the TNFR and leads to subsequent apoptosis in human and mice monocytes (Song et al., 2019). This type of TNFR activation ensures a ligand independent induction of the extrinsic pathway. Another type of cell killing involves neighboring immune cells. The Gram-positive bacteria *Listeria monocytogenes* conducts the sorting of the bacterial DNA into extracellular vesicles, which in turn are delivered to bystander T cells, where they trigger the DNA sensor cGAS-STING pathway mediated apoptosis (Nandakumar et al., 2019).

2.3.2 TLR mediated caspase activation upon bacterial infection

Yersinia pestis, the causative agent of pest, induces significant cytotoxicity. The type three secretion system (T3SS) is a host sensor and effector system, which can be found in several Gram-negative bacteria. This system promotes the virulence of the bacteria by injecting effector proteins into the cytosol (Ashida et al., 2011). Structurally, TT3S consists of a base embedded in the bacterial membrane, the needle, which directly interacts with the host membrane, and the rod, which connects the base to the needle. Yersinia outer protein J (YopJ), an effector protein of the T3SS, rapidly kills macrophages in a caspase-8 dependent way, which occurs independent of the canonical inducers of extrinsic apoptosis. In this model, TLR4 stimulation by the pathogen activates the TRIF/RIPK1/caspase-8 axis, which leads to caspase-1 cleavage and cell death. Consistently, mice lacking caspase-8 and RIPK3 are more susceptible to the infection, pinpointing the importance of caspase-8 and RIPK driven signaling in tackling this disease (Gröbner et al., 2007; Weng et al., 2014). *Mycobacterium (M.) tuberculosis* triggers caspase-8

dependent apoptosis in human monocytes, which is induced by extracellular bacterial RNA fragments detected by TLR3 (Obregón-Henao et al., 2012). The polymorphic GC-rich repetitive sequence containing PE_PGRS33, a surface exposed protein and the 19-kDa glycolipoprotein (p19) of the *M. tuberculosis* can both engage TLR2 and initiate apoptosis signal–regulating kinase-1 (ASK1) driven TNF and TNFR expression in mouse macrophages (Basu et al., 2007; López et al., 2003). Finally, group B streptococcus, a pathogen causing neonatal meningitis, induces apoptosis via the activation of TLR2, which engages its adaptor protein myeloma differentiation primary response-88 (MyD88), and consequently results in caspase-8 activation in microglial cells (Lehnardt et al., 2007).

2.3.3 Role of caspase-2 in bacterial infection

Caspase-2 is unique among caspases. It exhibits initiator characteristics structurally, since it has an N-terminal caspase activation and recruitment domain (CARD). In addition, caspase-2 represents executioner features functionally, because it can selectively cleave substrates similar to that of caspase-3 or –7 (Olsson et al., 2015). Caspase-2, along with caspase-1 plays a significant role in *Brucella abortus* and *Brucella suis* induced cell death (Bronner et al., 2013; Chen et al., 2011). One possible mechanism of activation is derived from the studies on bacterial pore forming toxins (PFT), alpha toxin and aerolysin secreted by the human pathogens *Staphylococcus aureus* and *Pseudomonas aeruginosa*, respectively. Based on this study, caspase-2 activation can be triggered by the PFT driven potassium efflux in epithelial cells, which facilitates the assembly of a caspase-2 containing high molecular weight protein complex (Imre et al., 2012). Importantly, the low potassium concentration triggered activation of caspases is not without precedent in the literature. Though, the role of potassium efflux has been demonstrated in terms of the pro-inflammatory caspase-1 activation in immune cells (see pyroptosis), it is not clear whether caspase-2 activation takes place in an inflammasome-like complex in response to pathogen insults in epithelial cells.

2.3.4 Anti-apoptotic strategies of the bacteria

Several pathogenic bacteria developed strategies to evade the apoptotic demolition. *Francisella tularensis*, a highly virulent Gram–negative pathogen inhibits apoptosis by retaining mitochondrial integrity via the inhibition of BID processing and BAX translocation, and successfully extends the lifespan of the infected neutrophils (McCracken et al., 2016). *Helicobacter pylori* leads to a persistent, yet asymptomatic infection, which, however, can increase

the incidence of the chronic gastritis and the gastric adenocarcinoma. This pathogen inhibits the anti-bacterial and cell death responses simultaneously by enhancing the level of ubiquitin-editing enzyme A20, which in turn bi-functionally blocks both the NF-κB activity and the caspase-8 activity (Lim et al., 2017). Enteropathogenic *Escherichia coli* (EPEC) transports effector proteins directly into the cytosol of infected cells by utilizing the T3SS. One of these effector proteins is the non-locus of enterocyte effacement encoded effector B1 (NLeB1). NleB1 transfers an *N*-acetyl-glucosamine residue to Arg117 in the death domain of FADD and inhibits the FADD dependent caspase-8 activation (Pearson et al., 2013). *Chlamydia trachomatis* is an obligate intracellular pathogen with medical relevance, which interferes with apoptosis by blocking the internalization of the cell death receptor TNFR1. This mechanism renders the specific blockage of the apoptotic signaling but preserves the function of the NF-κB signaling of the TNFR1 (Waguia Kontchou et al., 2016).

3. Role of necroptosis in bacterial and viral infection

3.1 Necroptosis signaling

In the previous chapter, we have seen several examples for apoptosis being induced in response to PAMPs. Nevertheless, apoptosis in many circumstances does not support the immune stimulation, which on the long run assists the pathogen to evade the counterattacks of the immune system. Necroptosis represents an immunogenic cell death modality. This non-apoptotic programmed cell death form, that morphologically resembles necrosis, has gained attention in the past 2 decades (Degterev et al., 2005; Vercammen et al., 1998), and its relevance in infection has been recognized only recently (Pan et al., 2014). In contrast to apoptosis, necroptosis is characterized by swelling of the cytoplasm, osmotic perturbations and the early rupture of the cytoplasm membrane, resulting in the release of DAMPs into the extracellular space. Receptor interacting protein kinase-1 and -3 (RIPK1 and RIPK3) play indispensable role in conducting necroptosis signaling. RIPKs interact via their RIPK homotypic interaction motif (RHIM) domains. The most studied pathway, by which RIPK dependent necroptosis can be triggered is the TNFR1 induced pathway. TNFR1 activation primarily results in NF-κB dependent pro-proliferative response. Upon the ligation of TNFR1 the formation of the so-called complex-I takes place, consisting of the adaptor proteins TRADD, TRAF2, cIAP and ubiquitinated RIPK1 (Fig. 2) (Wilson et al., 2009). Once, the pro-proliferative signal is blocked,
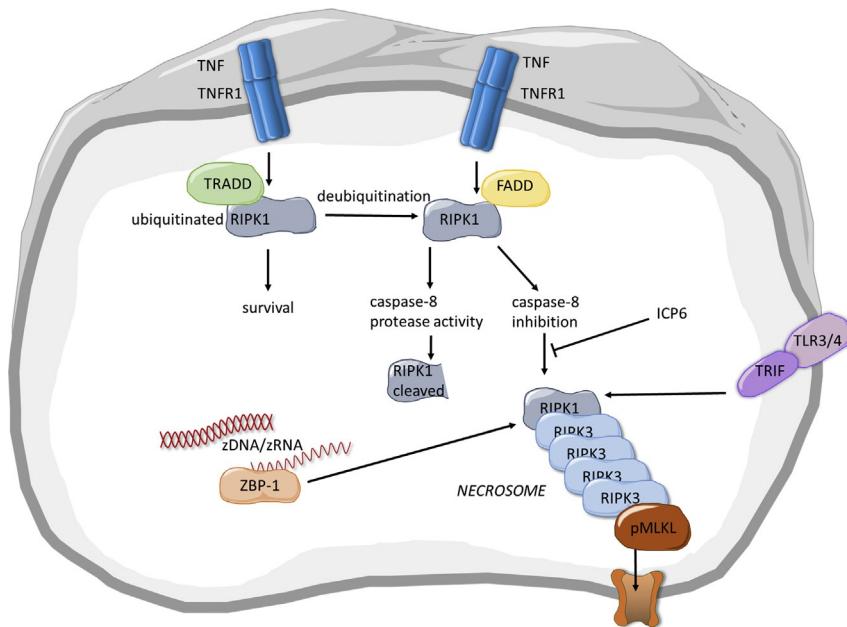
Fig. 2 Necroptosis signaling pathways. Necroptosis can be triggered by TNF ligation (top). RIPK1 deubiquitination promotes the cytotoxic function of RIPK1. Active caspase-8 cleaves RIPK1. Inhibition of caspase-8 leads to RIPK1 dependent assembly of the RIPK3 and MLKL containing necrosome. Phosphorylation of the MLKL in the necrosome results in MLKL oligomerization and its translocation into the cytoplasm membrane. TLR3 and 4 ligation (right) recruits the adaptor protein TRIF, which in turn activates RIPK3 and triggers the oligomerization of the MLKL. ZBP1 detects z-DNA and z-RNA fragments, subsequently leading to the binding of the RIPK3 and to the oligomerization of the MLKL.

the FADD containing apoptotic signal takes over, leading to caspase-8 activation. Surprisingly, the inhibition of the TNFR induced apoptosis by caspase inhibitors results in a necrotic-like cell demise. This programmed necrotic cell death, also termed necroptosis can be inhibited by RIPK1 inhibitor necrostatin-1 (Xie et al., 2013). It is also acknowledged that the proteolytic activity of caspase-8 acts against the necroptotic activity of three key components of the pathway: RIPK1, RIPK3 and cylindromatosis (CYLD) (O'Donnell et al., 2011; Tenev et al., 2011), hence inhibition of caspase-8 activity is a prerequisite for the induction of the TNFR1 driven necroptosis (Fig. 2). Once caspase-8 activity is blocked, RIPK1 is enabled to recruit RIPK3. Consequently, RIPK3 activation can lead to the phosphorylation of the necroptotic effector mixed lineage kinase-like protein (MLKL) (Fig. 2) (Sun et al., 2012). Upon the phosphorylation driven conformational

changes, MLKL oligomerizes and forms pores throughout the cytoplasm membrane, resulting in membrane integrity loss. In the past decade, it became clear that RIPK1 is a multifaceted scaffold protein. If ubiquitinated, RIPK1 inhibits the caspase-8 driven apoptosis and the RIPK3/MLKL dependent necroptosis. However, as a deubiquitinated protein, RIPK1 can promote the stimulation of both cell death signaling pathways (Varfolomeev and Vucic, 2018). Apart from the decisive role of ubiquitination, phosphorylation at Ser89 by protein kinase A, C, and phosphorylation at several sites by IKKs have been found to be important to attenuate the cytotoxic potential of this signaling protein (Dondelinger et al., 2019; McQuade et al., 2013).

3.2 Necroptosis modulation in response to viral infections

3.2.1 Virus induced necroptosis via extracellular factors

The current observations indicate that the majority of the human pathogen viruses developed strategies to avoid the necroptotic signaling of the host. Conversely, human immunodeficiency virus type 1 (HIV-1) induces TNFα dependent necroptotic cell death in CD4+ T lymphocytes, which can be inhibited by necrostatin-1. Unlike apoptosis, this cell death occurs in infected cells and spares the bystander cells (Pan et al., 2014). Nevertheless, the HIV triggered necroptosis is considered detrimental for the host by targeting the defensive mechanisms of the immune system. Another example, where necroptosis is triggered by viruses, takes places in response to human corona-virus (HCoV) infection. HCoV is a neuroinvasive respiratory pathogen, which induces a cell death pathway dependent on RIPK1 and MLKL in human neuroblastoma cells (Meessen-Pinard et al., 2017).

3.2.2 Necroptosis via ZBP1

The protein z-DNA/RNA binding protein-1 (ZBP1; also known as DAI) recognizes z-RNA or z-DNA structures, which are common as a conse-quence of a rapid viral RNA and DNA synthesis, but distinct from the B structure of the eukaryotic RNA or DNA. ZBP1 can activate RIPK3 (Upton et al., 2012), since it is capable to interact the RIPKs via its RHIM (Fig. 2). Intriguingly, MEFs, liver cells, lymphoid cells and skin cells isolated from mice exhibiting catalytically inactive RIPK1 die early and exert RIPK3 auto-phosphorylation, a hallmark of the necroptotic activa-tion, whereas RIPK3 and MLKL deficient mice are protected from the cell death ex vivo and in vivo. Furthermore, the ZBP1-RIPK3 interaction can be blocked in macrophages from wild type mice, whereas the interaction takes place in mouse macrophages that express a RHIM deficient RIPK1.

These results indicate that RIPK1 acts as a negative regulator of ZPB1–RIPK3 interaction during development in order to prevent premature necroptosis (Newton et al., 2016). To date, IAV infection is the only example, where ZBP1 dependent necroptosis occurs in response to viral infections employing non-engineered (wild type) virus strains. IAV induces RIPK3 and MLKL dependent, but TNFα and TLR independent necroptosis (Nogusa et al., 2016). This pathway is mediated through ZBP1 by sensing viral genomic RNA segments (Thapa et al., 2016). A recent study (Wang et al., 2019b) performed in mice further confirms the role of ZBP-1 as the key necroptosis modulator protein in response to IAV infection in vivo. Aside from the necroptosis stimulatory effects of the viral RNA fragments, the NS1 protein of the IAV is suggested as a direct interactor of MLKL (Gaba et al., 2019). Finally, the transcriptional regulation of ZBP1 seems to be dependent on the interferon regulatory factor 1 (IRF1), which is activated in mouse bone marrow-derived macrophages in response to IAV infection (Kuriakose et al., 2018). Consequently, depletion of IRF1 can reduce the level of ZBP1 and diminish the IAV induced necroptotic features, including MLKL phosphorylation and membrane integrity loss.

Murine cytomegalovirus (MCMV) lacking the viral M45-encoded inhibitor of RIPK (vIRA) triggers premature cell death in mice. Importantly, RIPK3 knockout can rescue the premature death phenotype, indicating that the MCMV infection induces a RIPK3 dependent necroptotic cell death (Upton et al., 2010). Similar to IAV infection, the RIPK3 driven necroptosis is independent of the effect of RIPK1 and the TNF stimulation, but ZBP1 is activated via its putative RNA binding domain Zα (Sridharan et al., 2017). Analogously, the Vaccinia virus (VACV) encoded innate immune evasion protein-3 (E3) can directly interact with the Zα domain of the ZBP1. Along with this, E3 deleted VACV strain triggers immediate necroptosis in interferon treated mouse L292 and human embryonal kidney (HEK293T) cells. The cytotoxic effect of the engineered VACV strain is attributed to necroptotic signaling, because the pathogenicity of the virus can be restored in vivo by the depletion of either RIPK3 or ZBP1 in mice (Koehler et al., 2017).

3.2.3 Species-specific dual role of the viral ICP6 in necroptosis regulation

The large subunit of the viral ribonucleotide reductase ICP6 (Fig. 2) is capable to engage both RIPK1 and RIPK3 through its RHIM-like domain upon herpes simplex virus type 1 (HSV-1) infection and to result in necroptosis,

which also contributes to the limited viral propagation in mice. Intriguingly, ICP6 inhibits the necroptosis signaling in its natural host, in human cells. This observation points out the species-specific differences in cell death signaling pathways and indicates that viruses in their natural hosts evolved to overcome host defense mechanisms (Huang et al., 2015). HSV-1 induces necroptosis not only via its ICP6 protein, but also by triggering the ZBP1 pathway in mice. Conversely, in order to induce the necroptotic pathway in human cells, the expression of ZBP1 has to be first enhanced (Guo et al., 2018). Moreover, ICP10, the virally encoded large subunit of the ribonucleotide reductase of HSV-2, can efficiently prevent necroptosis that is induced by TNFα (Guo et al., 2015). One possible explanation for the difference between mice and human responses might be provided by a recent study on HSV-1 demonstrating that ICP6 blocks TNFR1 induced MLKL necrosome assembly in membrane vesicles (Ali et al., 2019). This compartmentalization process of the necrosome represents a critical step for the progression of necroptosis in human cells. Consistent with this, RHIM domain deficient RIPK3 can efficiently phosphorylate MLKL but does not lead to necroptosis in human cells. Thus, one can speculate that ICP6 can trigger necrosome formation in mice, because the compartmentalization step may not be required for the effector mechanisms of necroptosis. Additionally, inositol phosphate (IP) kinases largely contribute to the oligomerization of MLKL. IP kinase mutants are unable to achieve the MLKL oligomerization and membrane localization despite a functioning RIPK3 in response to a genetically engineered ICP-6 mutant HSV-1 infection (Dovey et al., 2018). This study suggests that the RIPK3 dependent phosphorylation at the C-terminal Ser358 and the subsequent events, such as oligomerization and membrane localization are separately regulated in human cells. Accordingly, in order to accomplish necroptosis, MLKL activation requires a highly phosphorylated IP product to bind to the N-terminal domain. It is currently not clear what the exact role of the highly phosphorylated product can be, nevertheless the stabilization of the oligomerized MLKL complex can serve as one plausible explanation.

3.2.4 Viral inhibitors of necroptosis

The latent membrane protein-1 (LMP1) of the γ-herpes virus Epstein–Barr virus (EBV) is considered as the major transforming factor of the pathogen. Initially, this transmembrane protein has been reported to exert anti-apoptotic effects in B cells (Henderson et al., 1991). Later, LMP1 has been associated with necroptosis inhibition in EBV-infected human

nasopharyngeal epithelial cells and nasopharyngeal carcinoma cells. LMP1 can interact both RIPKs and can successfully mediate the polyubiquitination of them, which in turn leads to the inhibition of the kinase function of the RIPK3 and activates the pro-survival pathway (Liu et al., 2018). As previously discussed, the vIRA protein of MCMV can efficiently block RIPKs and hamper the necroptotic signaling. Though, distinct from the necroptosis inhibitory mechanism of the vIRA protein, the human CMV has also developed a strategy to suppress necroptosis upstream of MLKL phosphorylation (Omoto et al., 2015). Furthermore, Rhinoviruses, the causative agents of common cold can actively suppress both apoptosis and necroptosis. The viral 3C protease directly interacts and cleaves RIPK1 and blocks necroptosis stimulated by Poly(I:C) in human airway epithelial cells (Lötzerich et al., 2018). It is therefore somewhat surprising that the viral protease still triggers a lytic cell death pathway, which is distinct from necroptosis and apoptosis.

3.3 The role of necroptosis in bacterial infection

Whereas the relevance of necroptosis initiation in viral infection has been proven only in few cases, for instance in response to IAV, the connection between necroptosis and bacterial infection seems to be more obvious. The significance of type I interferons in initiating necroptosis is demonstrated during *Salmonella typhimurium* infection. Mice deficient in the receptor for type I interferons (Ifnar1) exhibit improved survival, and macrophages derived from these mice exert resistance to the bacteria triggered cell death. Consistently, RIPK3 deficient macrophages can similarly evade the cell death upon infection. This study gives an example for a necroptosis induction, which is detrimental for the host and beneficial for the bacteria (Robinson et al., 2012). Similarly, *Staphylococcus (S.) aureus* infection induced cytotoxicity can be prevented by RIPK3 depletion or inhibition of RIPK1 and MLKL in primary human macrophages. Surprisingly, necroptosis induction by pore forming toxins (PFT) of *S. aureus* occurs without employing any external caspase inhibition, which suggests that the caspase-8 signal remains inactive throughout the whole infection process (Kitur et al., 2015). In concordance with this, several PFT producing bacterial strains, including *Streptococcus pneumoniae* and *Staphylococcus marcescens* induce necroptotic cell death in mouse macrophages, which can be arrested by necroptosis inhibitors (e.g., necrostatins) but not by the depletion/inhibition of caspases (González-Juarbe et al., 2015). Surprisingly, a PFT secreted by *S. marcescens* can trigger MLKL dependent necroptosis in mouse lung epithelial cells in the absence of TNFR1/2 or

TLR4 signaling (González-Juarbe et al., 2017). Potassium efflux, as a key event, has been previously studied in necroptosis initiation. However, how this osmotic imbalance orchestrates the necroptotic process still needs to be elucidated. An in vivo study describes the PFT driven activation of caspase-2, -4 and -10, which facilitates the release of alarmins to the extracellular space (Gonzalez-Juarbe et al., 2018). *Mycobacterium tuberculosis* infection induces NAD+ depletion triggered necroptosis via the RIPK3-MLKL axis, which is initiated by the tuberculosis necrotizing toxin (TNT) in human macrophages (Pajuelo et al., 2018). In contrast to the observation in human macrophages, the pathogenesis of *Mycobacterium tuberculosis* infection is independent from the role of RIPK3 and necroptosis in mice (Stutz et al., 2018).

Yersinia pestis outer protein J (YopJ) is required for the lymphatic spread of the bacteria, which leads to the formation of swollen and necrotic structures called buboes. YopJ suppresses the downregulators of the RIPK1 driven necroptosis, resulting in necroptotic spread of the pathogen. In concordance with this, necrostatin treatment efficiently protects the mice from lethal infections of the bacteria (Arifuzzaman et al., 2018). It is demonstrated that YopJ interferes with the pro-survival activity of the FLIPs in the DISC, thereby promoting the necroptotic feature of the RIPKs.

In contrast to the previous examples, some bacteria have developed countermeasures to inhibit the necroptotic signals of the host. The enterophatogenic *E. coli* (EPEC) directly interferes with the elements of the necroptotic signal transduction. Espl, an effector component of the EPEC T3SS is identified as a protease, that can target and cleave host proteins containing a RHIM domain, including RIPK1/3, TRIF and ZBP1 (Pearson et al., 2017). Further example for necroptosis inhibition is demonstrated in a study employing the Salmonella induced colitis model. The salmonella outer protein B (SopB) attenuates the necroptotic cell death by decreasing the level of MLKL phosphorylation in the cells (Hu et al., 2019).

3.3.1 Necroptosis via TLR signaling

TLR-3 and TLR-4 are PAMP recognition receptors and engage dsRNA and bacterial lipopolysaccharide (LPS), respectively, which in turn initiate the recruitment of Toll/IL-1R (TIR) domain containing adapters to activate gene expression via transcription factors, such as NF-κB and IRF3/7. Over the last years, the role of TLR receptors in mediating cell death pathways has been intensively studied. Induction of TLRs can induce caspase-8 activation (Kaiser and Offermann, 2005) and the inhibition of caspase-8 activity leads to a RIPK3 dependent necrotic-like cell death in

mouse macrophages (He et al., 2011). The adaptor protein TRIF is necessary to transduce signals from TLR3 stimulation, whereas activation of TLR4 can engage both TRIF and MyD88. These pathways proceed independent of RIPK1 in mouse fibroblasts, but can efficiently trigger MLKL activation downstream of RIPK3 (Kaiser et al., 2013) (Fig. 2). In response to TNFR ligation, the ubiquitination status of RIPK1 is defined as the key factor in the decision making between survival and death. Upon TNF stimulation, the activated caspase-8 cleaves CYLD, the deubiquitinase enzyme of RIPK1 (O'Donnell et al., 2011). The LPS induced TLR-4 ligation recruits FADD and caspase-8 in a complex and initiates the cleavage of CYLD (Legarda et al., 2016). The non-histone chromatin binding protein high mobility group box-1 (HMGB1) is released into the extracellular space (Lu et al., 2012) during necroptosis and functions as a pro-inflammatory DAMP (Scaffidi et al., 2002). Interestingly, HMGB1 can form a complex with LPS upon infection, which leads to an amplified activation of TRIF dependent immune responses (Meng et al., 2019).

4. Role of pyroptosis in bacterial and viral infections

4.1 The pyroptotic machinery

Pyroptosis is an inflammatory and regulated cell death modality (Fink and Cookson, 2006) that partially shares features with apoptosis, because it requires caspase activation. On the other hand, the pyroptotic membrane rupture occurs rapidly in the affected cells, which is a common feature shared with necroptosis. Pyroptosis has been observed in monocytes, macrophages, dendritic cells, lymphocytes, epithelial cells, and endothelial cells (Man et al., 2017). Contrary to apoptosis, induction of pyroptosis activates inflammatory caspases, which, similarly to apoptotic initiator caspases, possess a large pro-domain structure. The inflammatory caspase-1, caspase-4/5 in humans and caspase-11 in mice are being activated in large molecular weight complexes, termed inflammasomes (van Opdenbosch and Lamkanfi, 2019). In general, inflammasomes consist of sensors that can recognize pathogenic insults, also termed PAMPs. Depending on the nature of a PAMP signal, different sensors are triggered. The nucleotide binding oligomerization domain (NOD)-like receptors represent the best studied inflammasome components, that recognize PAMPs (Fig. 3), but various other PAMP receptors have also been identified in the last years. These pathogen sensors can recruit caspases either directly or via an adaptor molecule. Once, the inflammatory caspase-1 is activated, it can process interleukin (IL) 1β and 18 into their mature forms.
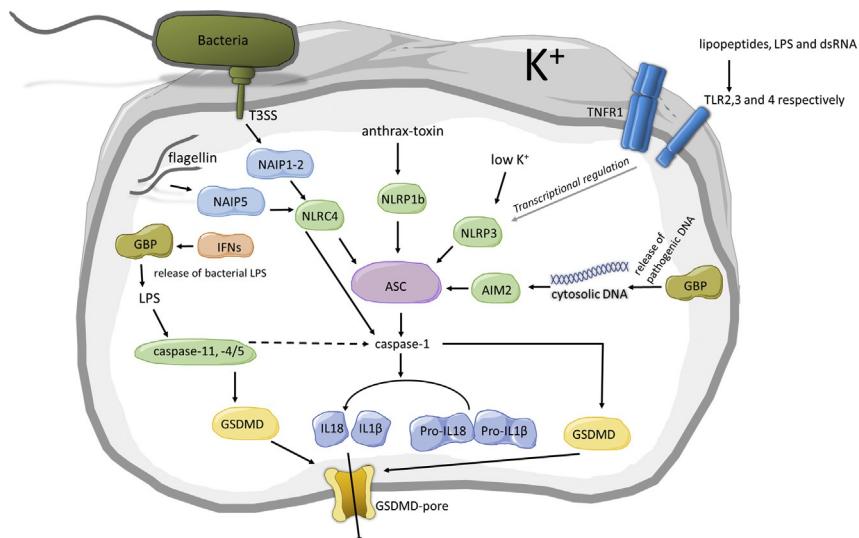
Fig. 3 Inflammasome activation and pyroptosis signaling. Components of the bacterial T3SS and bacterial flagellins can activate the NAIPs. In turn, NAIPs stimulate the NLRC-4 inflammasome (top left), leading to caspase-1 activation. Anthrax lethal toxin (top middle) directly interacts with NLRP1b and triggers the recruitment of ASC. Intracellular perturbations culminating in potassium efflux stimulate the assembly of the NLRP3 inflammasome (top right), leading to the recruitment of the adaptor protein ASC. NLRP3 requires priming signals via the ligation of TNF or TLRs. The IFN-stimulated GBPs facilitate the release of the pathogenic DNA fragments into the cytosol, which in turn can stimulate the AIM2 inflammasome. Caspase-11 and caspase-4/5 (left) can directly detect LPS, released by the GBPs into the cytosol. Active caspase-1 can process pro-IL1β/IL18 and cleave GSDMD, subsequently leading to GSDMD pore formation and release of the ILs into the extracellular space.

Furthermore, both caspase-1 and caspase-11 can process gasdermin-D (GSDMD), a member of the less studied gasdermin protein family (Kayagaki et al., 2015). The N-terminal leaflet of GSDMD inserts into the lipid bilayer and forms oligomer pores with an inner diameter of approximately 20 nm (Sborgi et al., 2016), leading to IL-1β/-18 release (He et al., 2015) and to osmotic imbalance driven swelling of the cells (Fig. 3). Several studies conclude the role of GSDMD as a key factor for IL secretion. In this setup, the pyroptotic membrane integrity loss, the swelling and the cell death are interpreted as the collateral damage of the pore formation. In fact, GSDMD driven IL release can proceed without any cell destruction (Evavold et al., 2018). In contrast, a recent study on mice infected with *Burkholderia thailandensis* leads to the conclusion that the action of GSDMD on bacterial killing occurs in a pyroptosis dependent manner

and is entirely independent from an indirect effect of IL production (Wang et al., 2019a). Interestingly, GSDMD is also capable to insert into the bacterial membrane and to kill extracellular bacteria (Liu et al., 2016). Thus, it seems that GSDMD is represented at three different layers of defense depending on the localization of the pathogen. Besides, gasdermin E, another member of the gasdermin family, is also reported to participate in pyroptosis and in post-apoptotic secondary necrosis (Rogers et al., 2017).

4.2 Pyroptosis in virus infection

Whereas, virus triggered inflammasome activation is a common event, inflammasome induced pyroptosis cannot be observed in all circumstances. Nevertheless, inflammasome dependent pyroptosis has been reported in response to infection by several viral pathogens, including HIV, DV (Tan and Chu, 2013), IAV (Kuriakose et al., 2016), Coxsacivirus (CV) (Wang et al., 2018), Parvovirus (Deng et al., 2017), hepatitis C virus (Kofahi et al., 2016), and Enterovirus 71 (EV71) (Huang et al., 2015; Zhu et al., 2018). An in vivo study on attenuated Rabies strain provides evidence for the beneficial role of pyroptosis against viral infections. The infection with the attenuated Rabies virus strain, which normally leads to the onset of mild symptoms, can be aggravated by caspase-1/-11 depletion, but not by caspase-3/7 or by IL-1β/IL-18 depletion (Kip et al., 2017). These observations suggest that the pyroptosis can be necessary to limit the Rabies infection. Further argument for the anti-viral nature of pyroptosis is provided by the observation that some viruses developed strategies in order to inhibit the effector mechanisms of this lytic cell death modality. EV71 triggers GSDMD by the viral protease 3C, and the cleaved fragments fail to unleash pyroptosis in THP-1 macrophages, HEK293T embryonal kidney and rhabdomyosarcoma cell lines (Lei et al., 2017).

The nature of the viral PAMPs determines which inflammasome mediated pyroptotic pathway is activated in response to a specific stimulus. In accordance with this, viral nucleotide patterns can lead to the activation of absent in melanoma-2 (AIM2) and interferon-γ-inducible protein 16 (IFI16) inflammasome activation, whereas various virally triggered stress signals can result in the assembly of the NOD-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasome (Fig. 3).

4.2.1 The role of NLRP3 inflammasome

NLRP3 protein is the major component of the NLRP3 inflammasome, which is the most studied inflammasome to date. NLRP3 consist of a pyrin

domain, a nucleotide binding site, and a leucine-rich repeat motif. Upon activation by PAMPs, NLRP3 interacts with the apoptosis–associated speck–like protein (ASC) via its pyrin domain (Fig. 3). This in turn induces ASC polymerization and the assembly of the ASC specks. The adaptor protein ASC possesses a caspase recruitment CARD domain and is therefore capable to recruit pro-inflammatory caspases, such as caspase–1 (Martinon, 2008). Consequently, caspase–1 is dimerized and auto-processed based on the principle of the induced proximity.

Several PAMP signals have been demonstrated to culminate in NLRP3 activation. For instance, lytic cell death induced potassium efflux is proposed as the major mechanism of the NLRP3 inflammasome activation following Encephalomyocarditis virus (EMCV) and VSV infection (da Costa et al., 2019). In these infections, the lytic cell death precedes the inflammasome formation, whereas the infection with IAV results in rapid NLRP3 dependent pyroptosis in dendritic cells (Fernandez et al., 2016; Kuriakose et al., 2016), indicating that other mechanism can also trigger NLRP3 assembly. It is of note, that IAV infection results in pyroptosis with a delayed kinetic in respiratory epithelial cells (Lee et al., 2018). In the activation of NLRP3 inflammasome in DV infection, the cytoplasmic membrane surface C–type lectin 5A (CLEC5A) is found to be critical, which interacts directly the DV virion and serves as a pathogen sensing receptor in human inflammatory macrophages (Wu et al., 2013). A highly pathogenic avian influenza A (H5N1) results in pneumonia and acute respiratory distress syndrome in humans. The depletion of galectin–B, a b–galactosidase binding protein leads to a striking reduction of inflammation in lungs of the infected mice compared to that of the wild type mice. Consequently, co-immunoprecipitation experiments demonstrate the interaction of galectin–B, NLRP3 and ASC in bone marrow–derived macrophages upon infection (Chen et al., 2018). The gp120 envelop protein of the HIV is the major contributing factor of the HIV-associated neurocognitive disorder accompanied by neuroinflammation. The gp120 triggered neuropathy is NLRP3 dependent and the administration of a selective NLRP3 inhibitor can alleviate the neuronal death and the impaired cognitive functions in gp120 transgenic mice. In a recent study, the role of the Purinergic 2X4 (P2X4), a cationic ion channel involved in neuropathic pain, is shown to mediate the gp120 dependent inflammasome activation and the caspase–1 cleavage in glial cells (Zhao et al., 2019). Most of these studies indicate the role of osmotic imbalances, such as potassium efflux as one of the major causative of NLRP3 inflammasome stimulation, however, how the low potassium concentration renders

changes in the NLRP3 structure and whether this is a direct or an indirect effect still needs to be clarified.

4.2.2 The role of IFI16 in the HIV induced T lymphocyte pyroptosis

HIV triggers bystander pyroptosis in non-infected T lymphocytes (Doitsh et al., 2014). The bystander CD4 T cells, that are not permissive to HIV infection, play a crucial role in the acquired immunodeficiency syndrome (AIDS). These cells go through an incomplete virus replication cycle, resulting in aberrant transcripts of the viral genome. These transcripts have been demonstrated to stimulate the DNA sensor interferon-γ-inducible protein 16 (IFI16), leading to caspase-1 activation mediated pyroptosis (Monroe et al., 2014) (Fig. 3). The immune stimulatory dying of the T lymphocytes initiates a pathogenic positive feedback loop by recruiting more immune cells to the site of infections, which leads to even more accelerated propagation of the virus. Cell free virions are unable to trigger pyroptosis. Thus, a cell to cell transmission of the virions is required for the induction of this lytic inflammatory cell death (Galloway et al., 2015). A clinical antiretroviral therapy study in humans demonstrates that the non-responding individuals have increased level of NLRP3 and caspase-1. In addition, the non-responding group exhibits significantly lower levels of CD4 T lymphocytes in comparison to that of the responder patients. Though, this patient data supports the previous in vitro and mouse experiments, which suggest the relevance of CD4 lymphocyte loss in the pathogenesis of HIV infection (Bandera et al., 2018), it does not provide direct evidence for an IFI16 driven pyroptotic cell death.

4.2.3 AIM2 inflammasome

AIM2 has been shown to bind DNA and engage the caspase-1–activating adaptor protein ASC to form an inflammasome. AIM2 conducts the maturation of IL-1β/IL-18 and induces pyroptosis in response to exposure of synthetic double-stranded DNA (Fig. 3). In natural situations, AIM2 dependent pyroptosis is observed in response to MCMV, Vaccinia virus (Rathinam et al., 2010) and EV71 infections (Yogarajah et al., 2017). Zika virus (ZIKV), an RNA virus, has gained increased attention over the last years due to its association with severe birth defects, including microcephaly. Infection with this flavivirus triggers higher expression levels of NLRP1, 3, AIM2 and caspase-1 in brain tissues collected from fatal human cases (de Sousa et al., 2018). It is, however, not clear whether the accompanied brain tissue damage is the direct consequence of the GSDMD driven

pyroptosis or the detected higher inflammasome expression levels represent a completely unrelated phenomenon.

4.2.4 Alternative inflammasomes in virus infection

Virus induced pyroptosis can be triggered cell type specifically for instance in Rotavirus infection, a leading cause of gastroenteritis and diarrhea in small children. NLRP9 is a member of the NLR family that is specifically expressed in intestinal epithelial cells in the site of the Rotavirus infection. NLRP9 can recognize dsRNA fragments and form inflammasome with ASC to initiate caspase-1 cleavage and GSDMD driven pyroptosis (Zhu et al., 2017). Moreover, Caspase-4, the human homolog of the mouse caspase-11 has been reported to function as a PAMP receptor. In response to DV infection, caspase-4 is activated and can process caspase-1 in order to accomplish pyroptosis (Cheung et al., 2018).

4.3 Pyroptosis in response to bacterial infection

The first report describing infection driven pyroptosis was performed in *Salmonella enterica serovar Typhimurium* (also called *Salmonella typhimurium*) infected mouse macrophages (Fink and Cookson, 2006), although caspase-1 dependent cell death in response to bacterial infection was mentioned in the literature earlier (Chen et al., 1996; Monack et al., 2001). The detection of PAMPs in bacterial infections includes the recognition of bacterial LPS, flagellins, components of the bacterial T3SS and the detection of cytoplasmic bacterial DNA.

4.3.1 Detection of bacterial proteins by the NLRC4 inflammasome

The components of the bacterial T3SS trigger inflammasome formation and pyroptotic cell death in Shigella infected macrophages through the activation of the NLR family CARD domain containing protein 4 (NLRC4) (Fig. 3). NLRC4 possess a CARD domain, therefore this NLR family member can directly engage and process caspase-1 (Suzuki et al., 2007). Besides, flagellins of various bacterial strains, including *Listeria (L.) monocytogenes* (Cervantes et al., 2008; Warren et al., 2008), *Legionella pneumophila* and *Burkholderia thailandensis* (Miao et al., 2010) can lead to the assembly of the NLRC4 inflammasome (Case et al., 2009). The activation of NLRC4 inflammasome has been shown to lead to bacterial clearance independent from the effect of IL-1 and IL-18 production, since this process functioned efficiently in IL-1/IL-18 knockout mice (Miao et al., 2010), thus implicating the primary role of pyroptosis in the bacterial clearance. This process involves the pyroptotic

release of the intracellular pathogens from the macrophages and leads to the uptake of the bacteria by neutrophil granulocytes. In contrast, pyroptosis can be also detrimental for the host organisms. The extracellular opportunistic pathogen *Pseudomonas aeruginosa* infection in mice leads to NLRC4 inflammasome activation, pyroptosis and increased mortality, whereas depletion of NLRC4 results in improved bacterial clearance and increased survival (Cohen and Prince, 2013).

The NLRC4 inflammasome utilizes various sensors in order to recognize PAMPs. The human NLR family apoptosis inhibitory protein 2 (NAIP2) and the mouse counterpart Naip5 prevent apoptosis by inhibiting caspases. The flagellin of the *Legionella pneumophila* can result in caspase-1 activation and cell death in a NAIP2 dependent manner in macrophages (Fig. 3) (Katagiri et al., 2012). Importantly, not all bacterial strains express flagellins constantly. Nevertheless, the inner rod of the T3SS needle complex of the non-flagellated Shigella bacteria results in the engagement of mouse Naip2 and leads to the NLRC4 inflammasome mediated pyroptosis in primary mouse macrophages (Suzuki et al., 2014). The hNAIP and the mouse counterpart Naip1 (Fig. 3) can recognize the needle component of the Salmonella T3SS in dendritic cells, and to less extent in macrophages (Yang et al., 2013). NLRC4 activation is mediated by NAIP independent phosphorylation events, which suggest a biphasic model for the stimulation of this intracellular pathogen sensor (Matusiak et al., 2015; Qu et al., 2012). The existence of a second stimulatory signal is further supported by the observations on the T3SS effector protein YopJ of the *Yersinia pestis*, which translocates into the cytoplasm upon infection and induces a rapid apoptosis in macrophages. In contrast, a preceding activation by LPS or by the ligation of the PRRs TLR2, 3 and 4 leads to a YopJ independent pyroptosis (Bergsbaken and Cookson, 2007). Furthermore, interferon regulatory factor 8 (IRF8) is required for the activation of the NLRC4 inflammasome in bone marrow-derived macrophages infected with *Salmonella typhimurium*, *Burkholderia thailandensis* and *Pseudomonas aeruginosa*. In these infections, IRF8 conducts the transcription of the NAIPs (Karki et al., 2018). These results implicate that the activation of NLRC4 relies on a second PAMP signal, which then initiate transcriptional priming and can mediate further stimulatory phosphorylation steps.

4.3.2 The NLRP3 inflammasome
NLRP3 indirectly senses pathogen associated signals such as extracellular ATP and uric acid crystals (Martinon et al., 2006), which then leads to a

conformational change, resulting in the binding and the oligomerization of the adaptor molecule ASC. Bacterial PFTs, including the hemolysin of the bacteria *Vibrio cholerae*, or the M surface protein of the group A Streptococcus can efficiently induce potassium efflux, which has been defined as the unified trigger of the NLRP3 inflammasome activation (Muñoz-Planillo et al., 2013; Queen et al., 2015; Valderrama et al., 2017). Alternatively, disruption of the glycolysis, leading to mitochondrial ROS production is also proposed as the intracellular mechanism of the NLRP3 activation (Sanman et al., 2016). Besides, a TLR triggered second priming event by ubiquitination is necessary to stimulate the NLRP3 inflammasome in mice myeloid cells (Humphries et al., 2018).

4.3.3 NLRP1B and the anthrax lethal toxin

Anthrax lethal toxin (LT), the critical virulence factor of the *Bacillus anthracis* induces caspase-1 activation and lytic cell death through the cytosolic NLR family member NLRP1B in macrophages (Boyden and Dietrich, 2006) and dendritic cells (Fink et al., 2008) (Fig. 3). In humans, NLRP1B possess a pyrin domain and lacks the CARD domain, therefore ASC is required as an adaptor protein to activate caspase-1. It has been demonstrated that LT was transported to the cytosol, where it could interact with additional factors, however the question whether NLRP1B directly interacted the LT remained elusive. This question was answered few years later in a study where the direct proteolytic cleavage of NLRP1B could activate NLRP1B driven pyroptosis in mice and rat cells (Chavarría-Smith and Vance, 2013).

4.3.4 The role of caspase-11 and caspase-4/-5

The mouse caspase-11 and its duplicated human homologs caspase-4 and -5 are often referred as non-canonical inflammasome, since they function as direct LPS sensors in the cytosol (Fig. 3). The CARD domain of the caspase-4 is capable to bind LPS molecules and, surprisingly, can directly cleave LPS micelles (An et al., 2019). The advantage of the caspase-11 and caspase-4/5 inflammasome can be understood in situations in which the pathogen attempts to evade caspase-1 activation, for instance by blocking the NLRC-4 inflammasome activation. It has been recently shown that the Shiga toxin from the pathogenic enterohemorrhagic *Escherichia coli* could lead to the activation of caspase-4 and result in the cleavage of GSDMD upstream of the NLRP3 activation in human THP-1 cells (Platnich et al., 2018). Furthermore, the Gram-negative *Burkholderia thailandensis* infection triggers the activation of caspase-11 in mice (Aachoui et al., 2013) and

Legionella (L.) pneumophila similarly elicits the activation of caspase-11, which in this scenario is dependent on the IFN signaling. Interestingly, loss of IFNs does not lead to the inhibition of caspase-11 expression, but it hampers the caspase-11 dependent pyroptosis in macrophages (Case et al., 2013). The requirement of IFNs leads us to the problem of the cytosolic LPS detection. The Gram-negative bacteria *Salmonella typhimurium* and *L. pneumophila* are normally located in vacuoles, hence they are protected from cytoplasmic pathogen sensors as for instance caspase-11. The guanylate-binding proteins (GBPs) represent a family of IFN-inducible GTPases. It has been demonstrated that IFN-stimulated GBP members were capable to bind the vacuoles and initiate the rupture of the membrane, which in turn resulted in the release of the bacterial LPS, exposing it to the cytoplasmic caspase-11 (Meunier et al., 2014; Rupper and Cardelli, 2008). Conversely, IFNs can also directly regulate the transcription of the pro-inflammatory caspases. Based on a new genome-wide screen, the interferon regulatory factor 2 (IRF2) seems to act as the main transcription factor directly regulating caspase-4 expression upon LPS stimulus in human monocytes (Benaoudia et al., 2019).

4.3.5 AIM2 inflammasome in bacterial infection: DNA sensing

The role of the AIM2 inflammasome in the recognition of the intracellular bacteria has been demonstrated in response to *Listeria monocytogenes*, *Francisella (F.) tularensis* (Kim et al., 2010; Rathinam et al., 2010) and *Brucella abortus* infection (Costa Franco et al., 2019). Since the recognition by AIM2 is fully dependent on the availability of cytosolic DNA, strains engineered to lyse in the cytosol can induce pyroptosis more efficiently (Sauer et al., 2010). Conversely, in response to a naturally-occurring infection by non-lysing strains, including *F. novicida* (Man et al., 2016), *F. tularensis* (Man et al., 2015) and *Chlamydia trachomatis* (Finethy et al., 2015) the cytosolic release of the bacterial DNA is facilitated by the TLR mediated GBPs, hence supporting the relevance of the IFN dependent priming events to activate this inflammasome.

4.3.6 Cross talk between inflammatory and apoptotic cell death pathways

A study on caspase-1 deficient murine macrophages implicates the existence of the cross talk between pyroptosis and apoptotic caspases. In the absence of caspase-1, the stimulation of the AIM2/ASC axis by *F. tularensis* leads to caspase-8 cleavage and apoptosis, which can restrict bacterial replication

in vitro (Pierini et al., 2012). The mechanistic details of the activation, however, still need to be elucidated. Surprisingly, the loss of caspase-1 results in faster kinetics of the AIM-2 speck formation, indicating the presence of a caspase-1 dependent negative feedback loop (Juruj et al., 2013). We therefore speculate that an over-activation of the AIM2 speck formation may result in the loss of specificity, consequently leading to the recruitment of other initiator caspases into the complex. In fact, the recruitment of caspase-8 into the NLRP3-ASC inflammasome has been demonstrated in LPS and nigericin stimulated murine bone marrow-derived dendritic cells in the absence of caspase-1 and -11 (Antonopoulos et al., 2015). Furthermore, the Yersinia effector protein YopJ has been shown to inhibit TAK1 and IKK, which in turn led to RIPK1 and caspase-8 activation in macrophages. This and another group simultaneously published the finding that caspase-8 could directly cleave GSDMD, leading to pyroptotic cell death (Orning et al., 2018; Sarhan et al., 2018). Finally, in a third study the NLRC4 dependent assembly of the ASC caspase-8 inflammasome has been demonstrated in *Salmonella typhimurium* infected cells (Man et al., 2013).

5. Concluding remarks

In this review, we discussed the role of three major cell death pathways: apoptosis, necroptosis, and pyroptosis in the context of viral and bacterial infections. The past few years of research in the field of host-pathogen interaction demonstrates us that the connection between the pathogens and the host cell death signaling is more complex than previously expected. The complexity of the apoptotic, necroptotic, and pyroptotic signaling pathways, the presence of the cross talks and the feedback mechanisms reflect the significance of a continuously running evolutionary race between the pathogens and their natural hosts. This is best proven by the observations that successful human pathogens developed counter measures to attenuate the cell death induction potential of the host, whereas other pathogens developed strategies to hijack the cell death machinery in order to accomplish the targeted destruction of the defense mechanism of the host. Thus, looking it from an evolutionary perspective, the different layers of cell death pathways can be interpreted as different evolutionary steps built upon each other in response to a selective pathogen insult. The better understanding of these mechanisms can provide us novel strategies to more efficiently treat infectious diseases in the future.

Acknowledgments

References

Aachoui, Y., Leaf, I.A., Hagar, J.A., Fontana, M.F., Campos, C.G., Zak, D.E., Tan, M.H., Cotter, P.A., Vance, R.E., Aderem, A., Miao, E.A., 2013. Caspase-11 protects against bacteria that escape the vacuole. Science (New York, NY) 339 (6122), 975–978.

Alexopoulou, L., Holt, A.C., Medzhitov, R., Flavell, R.A., 2001. Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. Nature 413 (6857), 732–738.

Ali, M., Roback, L., Mocarski, E.S., 2019. Herpes simplex virus 1 ICP6 impedes TNF receptor 1-induced necrosome assembly during compartmentalization to detergent-resistant membrane vesicles. J. Biol. Chem. 294 (3), 991–1004.

An, J., Kim, S.H., Hwang, D., Lee, K.E., Kim, M.J., Yang, E.G., Kim, S.Y., Chung, H.S., 2019. Caspase-4 disaggregates lipopolysaccharide micelles via LPS-CARD interaction. Sci. Rep. 9 (1), 826.

Antonopoulos, C., Russo, H.M., El Sanadi, C., Martin, B.N., Li, X., Kaiser, W.J., Mocarski, E.S., Dubyak, G.R., 2015. Caspase-8 as an effector and regulator of NLRP3 inflammasome signaling. J. Biol. Chem. 290 (33), 20167–20184.

Arifuzzaman, M., Ang, W.X.G., Choi, H.W., Nilles, M.L., St John, A.L., Abraham, S.N., 2018. Necroptosis of infiltrated macrophages drives Yersinia pestis dispersal within buboes. JCI insight 3, 18.

Ashida, H., Ogawa, M., Kim, M., Mimuro, H., Sasakawa, C., 2011. Bacteria and host interactions in the gut epithelial barrier. Nat. Chem. Biol. 8 (1), 36–45.

Bandera, A., Masetti, M., Fabbiani, M., Biasin, M., Muscatello, A., Squillace, N., Clerici, M., Gori, A., Trabattoni, D., 2018. The NLRP3 inflammasome is upregulated in HIV-infected antiretroviral therapy-treated individuals with defective immune recovery. Front. Immunol. 9, 214.

Basu, S., Pathak, S.K., Banerjee, A., Pathak, S., Bhattacharyya, A., Yang, Z., Talarico, S., Kundu, M., Basu, J., 2007. Execution of macrophage apoptosis by PE_PGRS33 of *Mycobacterium tuberculosis* is mediated by Toll-like receptor 2-dependent release of tumor necrosis factor-alpha. J. Biol. Chem. 282 (2), 1039–1050.

Benaoudia, S., Martin, A., Puig Gamez, M., Gay, G., Lagrange, B., Cornut, M., Krasnykov, K., Claude, J.-B., Bourgeois, C.F., Hughes, S., Gillet, B., Allatif, O., Corbin, A., Ricci, R., Henry, T., 2019. A genome-wide screen identifies IRF2 as a key regulator of caspase-4 in human cells. EMBO Rep. 20 (9), e48235.

Bergsbaken, T., Cookson, B.T., 2007. Macrophage activation redirects yersinia-infected host cell death from apoptosis to caspase-1-dependent pyroptosis. PLoS Pathog. 3 (11), e161.

Boyden, E.D., Dietrich, W.F., 2006. Nalp1b controls mouse macrophage susceptibility to anthrax lethal toxin. Nat. Genet. 38 (2), 240–244.

Bronner, D.N., O'Riordan, M.X.D., He, Y., 2013. Caspase-2 mediates a *Brucella abortus* RB51-induced hybrid cell death having features of apoptosis and pyroptosis. Front. Cell. Infect. Microbiol. 3, 83.

Case, C.L., Shin, S., Roy, C.R., 2009. Asc and Ipaf inflammasomes direct distinct pathways for caspase-1 activation in response to *Legionella pneumophila*. Infect. Immun. 77 (5), 1981–1991.

Case, C.L., Kohler, L.J., Lima, J.B., Strowig, T., de Zoete, M.R., Flavell, R.A., Zamboni, D.S., Roy, C.R., 2013. Caspase-11 stimulates rapid flagellin-independent pyroptosis in response to *Legionella pneumophila*. Proc. Natl. Acad. Sci. U. S. A. 110 (5), 1851–1856.

Cervantes, J., Nagata, T., Uchijima, M., Shibata, K., Koide, Y., 2008. Intracytosolic Listeria monocytogenes induces cell death through caspase-1 activation in murine macrophages. Cell Microbiol. 10 (1), 41–52.

Chavarría-Smith, J., Vance, R.E., 2013. Direct proteolytic cleavage of NLRP1B is necessary and sufficient for inflammasome activation by anthrax lethal factor. PLoS Pathog. 9 (6), e1003452.

Chen, Y., Smith, M.R., Thirumalai, K., Zychlinsky, A., 1996. A bacterial invasin induces macrophage apoptosis by binding directly to ICE. EMBO J. 15 (15), 3853–3860.

Chen, F., Ding, X., Ding, Y., Xiang, Z., Li, X., Ghosh, D., Schurig, G.G., Sriranganathan, N., Boyle, S.M., He, Y., 2011. Proinflammatory caspase-2-mediated macrophage cell death induced by a rough attenuated Brucella suis strain. Infect. Immun. 79 (6), 2460–2469.

Chen, Y.-J., Wang, S.-F., Weng, I.-C., Hong, M.-H., Lo, T.-H., Jan, J.-T., Hsu, L.-C., Chen, H.-Y., Liu, F.-T., 2018. Galectin-3 enhances avian H5N1 influenza A virus-induced pulmonary inflammation by promoting NLRP3 inflammasome activation. Am. J. Pathol. 188 (4), 1031–1042.

Cheung, K.T., Sze, D.M., Chan, K.H., Leung, P.H., 2018. Involvement of caspase-4 in IL-1 beta production and pyroptosis in human macrophages during dengue virus infection. Immunobiology 223 (4–5), 356–364.

Chow, J., Franz, K.M., Kagan, J.C., 2015. PRRs are watching you: localization of innate sensing and signaling regulators. Virology 479–480, 104–109.

Cohen, G.M., 1997. Caspases: the executioners of apoptosis. Biochem. J. 326 (Pt 1), 1–16.

Cohen, T.S., Prince, A.S., 2013. Activation of inflammasome signaling mediates pathology of acute *P. aeruginosa* pneumonia. J. Clin. Invest. 123 (4), 1630–1637.

Costa Franco, M.M.S., Marim, F.M., Alves-Silva, J., Cerqueira, D., Rungue, M., Tavares, I.P., Oliveira, S.C., 2019. AIM2 senses *Brucella abortus* DNA in dendritic cells to induce IL-1β secretion, pyroptosis and resistance to bacterial infection in mice. Microbes Infect. 21 (2), 85–93.

da Costa, L.S., Outlioua, A., Anginot, A., Akarid, K., Arnoult, D., 2019. RNA viruses promote activation of the NLRP3 inflammasome through cytopathogenic effect-induced potassium efflux. Cell Death Dis. 10 (5), 346.

de Sousa, J.R., Azevedo, R.D.S.D.S., Martins Filho, A.J., de Araujo, M.T.F., Cruz, E.D.R.M., Vasconcelos, B.C.B., Cruz, A.C.R., de Oliveira, C.S., Martins, L.C., Vasconcelos, B.H.B., Casseb, L.M.N., Chiang, J.O., Quaresma, J.A.S., Vasconcelos, P.F.D.C., 2018. In situ inflammasome activation results in severe damage to the central nervous system in fatal Zika virus microcephaly cases. Cytokine 111, 255–264.

Degterev, A., Huang, Z., Boyce, M., Li, Y., Jagtap, P., Mizushima, N., Cuny, G.D., Mitchison, T.J., Moskowitz, M.A., Yuan, J., 2005. Chemical inhibitor of nonapoptotic cell death with therapeutic potential for ischemic brain injury. Nat. Chem. Biol. 1 (2), 112–119.

Deng, X., Zou, W., Xiong, M., Wang, Z., Engelhardt, J.F., Ye, S.Q., Yan, Z., Qiu, J., 2017. Human parvovirus infection of human airway epithelia induces pyroptotic cell death by inhibiting apoptosis. J. Virol. 91 (24), e01533–17.

Diner, B.A., Lum, K.K., Toettcher, J.E., Cristea, I.M., 2016. Viral DNA sensors IFI16 and cyclic GMP-AMP synthase possess distinct functions in regulating viral gene expression, immune defenses, and apoptotic responses during herpesvirus infection. mBio 7 (6), e01553-16.

Doitsh, G., Galloway, N.L.K., Geng, X., Yang, Z., Monroe, K.M., Zepeda, O., Hunt, P.W., Hatano, H., Sowinski, S., Muñoz-Arias, I., Greene, W.C., 2014. Cell death by pyroptosis drives CD4 T-cell depletion in HIV-1 infection. Nature 505 (7484), 509–514.

Dondelinger, Y., Delanghe, T., Priem, D., Wynosky-Dolfi, M.A., Sorobetea, D., Rojas-Rivera, D., Giansanti, P., Roelandt, R., Gropengiesser, J., Ruckdeschel, K., Savvides, S.N., Heck, A.J.R., Vandenabeele, P., Brodsky, I.E., Bertrand, M.J.M., 2019. Serine 25 phosphorylation inhibits RIPK1 kinase-dependent cell death in models of infection and inflammation. Nat. Commun. 10 (1), 1729.

Dovey, C.M., Diep, J., Clarke, B.P., Hale, A.T., McNamara, D.E., Guo, H., Brown, N.W., Cao, J.Y., Grace, C.R., Gough, P.J., Bertin, J., Dixon, S.J., Fiedler, D., Mocarski, E.S., Kaiser, W.J., Moldoveanu, T., York, J.D., Carette, J.E., 2018. MLKL requires the inositol phosphate code to execute necroptosis. Mol. Cell 70 (5), 936–948.

Dufour, F., Sasseville, A.M.-J., Chabaud, S., Massie, B., Siegel, R.M., Langelier, Y., 2011. The ribonucleotide reductase R1 subunits of herpes simplex virus types 1 and 2 protect cells against TNFα- and FasL-induced apoptosis by interacting with caspase-8. Apoptosis 16 (3), 256–271.

Dürst, M., Gissmann, L., Ikenberg, H., zur Hausen, H., 1983. A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions. Proc. Natl. Acad. Sci. U. S. A. 80 (12), 3812–3815.

Ebermann, L., Ruzsics, Z., Guzmán, C.A., van Rooijen, N., Casalegno-Garduño, R., Koszinowski, U., Čičin-Šain, L., 2012. Block of death-receptor apoptosis protects mouse cytomegalovirus from macrophages and is a determinant of virulence in immunodeficient hosts. PLoS Pathog. 8 (12), e1003062.

Eitz Ferrer, P., Potthoff, S., Kirschnek, S., Gasteiger, G., Kastenmüller, W., Ludwig, H., Paschen, S.A., Villunger, A., Sutter, G., Drexler, I., Häcker, G., 2011. Induction of Noxa-mediated apoptosis by modified vaccinia virus Ankara depends on viral recognition by cytosolic helicases, leading to IRF-3/IFN-β-dependent induction of proapoptotic Noxa. PLoS Pathog. 7 (6), e1002083.

El Maadidi, S., Faletti, L., Berg, B., Wenzl, C., Wieland, K., Chen, Z.J., Maurer, U., Borner, C., 2014. A novel mitochondrial MAVS/Caspase-8 platform links RNA virus-induced innate antiviral signaling to Bax/Bak-independent apoptosis. J. Immunol. 192 (3), 1171–1183.

Evavold, C.L., Ruan, J., Tan, Y., Xia, S., Wu, H., Kagan, J.C., 2018. The pore-forming protein gasdermin D regulates interleukin-1 secretion from living macrophages. Immunity 48 (1), 35–44.

Fadok, V.A., Voelker, D.R., Campbell, P.A., Cohen, J.J., Bratton, D.L., Henson, P.M., 1992. Exposure of phosphatidylserine on the surface of apoptotic lymphocytes triggers specific recognition and removal by macrophages. J. Immunol. 7 (148), 2207–2216.

Feoktistova, M., Geserick, P., Kellert, B., Dimitrova, D.P., Langlais, C., Hupe, M., Cain, K., MacFarlane, M., Häcker, G., Leverkus, M., 2011. cIAPs block Ripoptosome formation, a RIP1/caspase-8 containing intracellular cell death complex differentially regulated by cFLIP isoforms. Mol. Cell 43 (3), 449–463.

Fernandez, M.V., Miller, E., Krammer, F., Gopal, R., Greenbaum, B.D., Bhardwaj, N., 2016. Ion efflux and influenza infection trigger NLRP3 inflammasome signaling in human dendritic cells. J. Leukoc. Biol. 99 (5), 723–734.

Finethy, R., Jorgensen, I., Haldar, A.K., de Zoete, M.R., Strowig, T., Flavell, R.A., Yamamoto, M., Nagarajan, U.M., Miao, E.A., Coers, J., 2015. Guanylate binding proteins enable rapid activation of canonical and noncanonical inflammasomes in Chlamydia-infected macrophages. Infect. Immun. 83 (12), 4740–4749.

Fink, S.L., Cookson, B.T., 2006. Caspase-1-dependent pore formation during pyroptosis leads to osmotic lysis of infected host macrophages. Cell. Microbiol. 8 (11), 1812–1825.

Fink, S.L., Bergsbaken, T., Cookson, B.T., 2008. Anthrax lethal toxin and Salmonella elicit the common cell death pathway of caspase-1-dependent pyroptosis via distinct mechanisms. Proc. Natl. Acad. Sci. U. S. A. 105 (11), 4312–4317.

Fitzgerald, K.A., McWhirter, S.M., Faia, K.L., Rowe, D.C., Latz, E., Golenbock, D.T., Coyle, A.J., Liao, S.-M., Maniatis, T., 2003. IKKepsilon and TBK1 are essential components of the IRF3 signaling pathway. Nat. Immunol. 4 (5), 491–496.

Gaba, A., Xu, F., Lu, Y., Park, H.-S., Liu, G., Zhou, Y., 2019. The NS1 protein of influenza A virus participates in necroptosis by interacting with MLKL and increasing its oligomerization and membrane translocation. J. Virol. 93 (2), e01835–18.

Galloway, N.L., Doitsh, G., Monroe, K.M., Yang, Z., Muñoz-Arias, I., Levy, D.N., Greene, W.C., 2015. Cell-to-cell transmission of HIV-1 is required to trigger pyroptotic death of lymphoid-tissue-derived CD4 T cells. Cell Rep. 12 (10), 1555–1563.

Galluzzi, L., Vitale, I., Aaronson, S.A., Abrams, J.M., Adam, D., Agostinis, P., Alnemri, E.S., Altucci, L., Amelio, I., Andrews, D.W., Annicchiarico-Petruzzelli, M., Antonov, A.V., Arama, E., Baehrecke, E.H., Barlev, N.A., Bazan, N.G., Bernassola, F., Bertrand, M.J.M., Bianchi, K., Blagosklonny, M.V., Blomgren, K., Borner, C., Boya, P., Brenner, C., Campanella, M., Candi, E., Carmona-Gutierrez, D., Cecconi, F., Chan, F.K.-M., Chandel, N.S., Cheng, E.H., Chipuk, J.E., Cidlowski, J.A., Ciechanover, A., Cohen, G.M., Conrad, M., Cubillos-Ruiz, J.R., Czabotar, P.E., D'Angiolella, V., Dawson, T.M., Dawson, V.L., de Laurenzi, V., de Maria, R., Debatin, K.-M., DeBerardinis, R.J., Deshmukh, M., Di Daniele, N., Di Virgilio, F., Dixit, V.M., Dixon, S.J., Duckett, C.S., Dynlacht, B.D., El-Deiry, W.S., Elrod, J.W., Fimia, G.M., Fulda, S., García-Sáez, A.J., Garg, A.D., Garrido, C., Gavathiotis, E., Golstein, P., Gottlieb, E., Green, D.R., Greene, L.A., Gronemeyer, H., Gross, A., Hajnoczky, G., Hardwick, J.M., Harris, I.S., Hengartner, M.O., Hetz, C., Ichijo, H., Jäättelä, M., Joseph, B., Jost, P.J., Juin, P.P., Kaiser, W.J., Karin, M., Kaufmann, T., Kepp, O., Kimchi, A., Kitsis, R.N., Klionsky, D.J., Knight, R.A., Kumar, S., Lee, S.W., Lemasters, J.J., Levine, B., Linkermann, A., Lipton, S.A., Lockshin, R.A., López-Otín, C., Lowe, S.W., Luedde, T., Lugli, E., MacFarlane, M., Madeo, F., Malewicz, M., Malorni, W., Manic, G., Marine, J.-C., Martin, S.J., Martinou, J.-C., Medema, J.P., Mehlen, P., Meier, P., Melino, S., Miao, E.A., Molkentin, J.D., Moll, U.M., Muñoz-Pinedo, C., Nagata, S., Nuñez, G., Oberst, A., Oren, M., Overholtzer, M., Pagano, M., Panaretakis, T., Pasparakis, M., Penninger, J.M., Pereira, D.M., Pervaiz, S., Peter, M.E., Piacentini, M., Pinton, P., Prehn, J.H.M., Puthalakath, H., Rabinovich, G.A., Rehm, M., Rizzuto, R., Rodrigues, C.M.P., Rubinsztein, D.C., Rudel, T., Ryan, K.M., Sayan, E., Scorrano, L., Shao, F., Shi, Y., Silke, J., Simon, H.-U., Sistigu, A., Stockwell, B.R., Strasser, A., Szabadkai, G., Tait, S.W.G., Tang, D., Tavernarakis, N., Thorburn, A., Tsujimoto, Y., Turk, B., Vanden Berghe, T., Vandenabeele, P., Vander Heiden, M.G., Villunger, A., Virgin, H.W., Vousden, K.H., Vucic, D., Wagner, E.F., Walczak, H., Wallach, D., Wang, Y., Wells, J.A., Wood, W., Yuan, J., Zakeri, Z., Zhivotovsky, B., Zitvogel, L., Melino, G., Kroemer, G., 2018. Molecular mechanisms of cell death: recommendations of the nomenclature committee on cell death 2018. Cell Death Differ. 25 (3), 486–541.

González-Juarbe, N., Gilley, R.P., Hinojosa, C.A., Bradley, K.M., Kamei, A., Gao, G., Dube, P.H., Bergman, M.A., Orihuela, C.J., 2015. Pore-forming toxins induce macrophage necroptosis during acute bacterial pneumonia. PLoS Pathog. 11 (12), e1005337.

González-Juarbe, N., Bradley, K.M., Shenoy, A.T., Gilley, R.P., Reyes, L.F., Hinojosa, C.A., Restrepo, M.I., Dube, P.H., Bergman, M.A., Orihuela, C.J., 2017. Pore-forming toxin-mediated ion dysregulation leads to death receptor-independent necroptosis of lung epithelial cells during bacterial pneumonia. Cell Death Differ. 24 (5), 917–928.

Gonzalez-Juarbe, N., Bradley, K.M., Riegler, A.N., Reyes, L.F., Brissac, T., Park, S.-S., Restrepo, M.I., Orihuela, C.J., 2018. Bacterial pore-forming toxins promote the activation of caspases in parallel to necroptosis to enhance alarmin release and inflammation during pneumonia. Sci. Rep. 8 (1), 5846.

Gröbner, S., Schulz, S., Soldanova, I., Gunst, D.S.J., Waibel, M., Wesselborg, S., Borgmann, S., Autenrieth, I.B., 2007. Absence of Toll-like receptor 4 signaling results in delayed Yersinia enterocolitica YopP-induced cell death of dendritic cells. Infect. Immun. 75 (1), 512–517.

Große, L., Wurm, C.A., Brüser, C., Neumann, D., Jans, D.C., Jakobs, S., 2016. Bax assembles into large ring-like structures remodeling the mitochondrial outer membrane in apoptosis. EMBO J. 35 (4), 402–413.

Guo, H., Omoto, S., Harris, P.A., Finger, J.N., Bertin, J., Gough, P.J., Kaiser, W.J., Mocarski, E.S., 2015. Herpes simplex virus suppresses necroptosis in human cells. Cell Host Microbe 17 (2), 243–251.

Guo, H., Gilley, R.P., Fisher, A., Lane, R., Landsteiner, V.J., Ragan, K.B., Dovey, C.M., Carette, J.E., Upton, J.W., Mocarski, E.S., Kaiser, W.J., 2018. Species-independent contribution of ZBP1/DAI/DLM-1-triggered necroptosis in host defense against HSV1. Cell Death Dis. 9 (8), 816.

Halle, S., Halle, O., Förster, R., 2017. Mechanisms and dynamics of T cell-mediated cytotoxicity in vivo. Trends Immunol. 38 (6), 432–443.

Han, X., Cong, H., 2017. Enterovirus 71 induces apoptosis by directly modulating the conformational activation of pro-apoptotic protein Bax. J. Gen. Virol. 98 (3), 422–434.

He, S., Liang, Y., Shao, F., Wang, X., 2011. Toll-like receptors activate programmed necrosis in macrophages through a receptor-interacting kinase-3-mediated pathway. Proc. Natl. Acad. Sci. U. S. A. 108 (50), 20054–20059.

He, W.-T., Wan, H., Hu, L., Chen, P., Wang, X., Huang, Z., Yang, Z.-H., Zhong, C.-Q., Han, J., 2015. Gasdermin D is an executor of pyroptosis and required for interleukin-1β secretion. Cell Res. 25 (12), 1285–1298.

Henderson, S., Rowe, M., Gregory, C., Croom-Carter, D., Wang, F., Longnecker, R., Kieff, E., Rickinson, A., 1991. Induction of bcl-2 expression by epstein-barr virus latent membrane protein 1 protects infected B cells from programmed cell death. Cell 65 (7), 1107–1115.

Hsu, H., Huang, J., Shu, H.-B., Baichwal, V., Goeddel, D.V., 1996. TNF-dependent recruitment of the protein kinase RIP to the TNF receptor-1 signaling complex. Immunity 4 (4), 387–396.

Hu, G.-Q., Yang, Y.-J., Qin, X.-X., Qi, S., Zhang, J., Yu, S.-X., Du, C.-T., Chen, W., 2019. Salmonella outer protein b suppresses colitis development via protecting cell from necroptosis. Front. Cell. Infect. Microbiol. 9, 87.

Huang, Z., Wu, S.-Q., Liang, Y., Zhou, X., Chen, W., Li, L., Wu, J., Zhuang, Q., Chen, C.A., Li, J., Zhong, C.-Q., Xia, W., Zhou, R., Zheng, C., Han, J., 2015. RIP1/RIP3 binding to HSV-1 ICP6 initiates necroptosis to restrict virus propagation in mice. Cell Host Microbe 17 (2), 229–242.

Humphries, F., Bergin, R., Jackson, R., Delagic, N., Wang, B., Yang, S., Dubois, A.V., Ingram, R.J., Moynagh, P.N., 2018. The E3 ubiquitin ligase Pellino2 mediates priming of the NLRP3 inflammasome. Nat. Commun. 9 (1), 1560.

Imre, G., Heering, J., Takeda, A.-N., Husmann, M., Thiede, B., zu Heringdorf, D.M., Green, D.R., van der Goot, F.G., Sinha, B., Dötsch, V., Rajalingam, K., 2012. Caspase-2 is an initiator caspase responsible for pore-forming toxin-mediated apoptosis. EMBO J. 31 (11), 2615–2628.

Ishikawa, H., Barber, G.N., 2008. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. Nature 455 (7213), 674–678.

Jorgensen, I., Rayamajhi, M., Miao, E.A., 2017. Programmed cell death as a defence against infection. Nat. Rev. Immunol. 17 (3), 151–164.

Juruj, C., Lelogeais, V., Pierini, R., Perret, M., Py, B.F., Jamilloux, Y., Broz, P., Ader, F., Faure, M., Henry, T., 2013. Caspase-1 activity affects AIM2 speck formation/stability through a negative feedback loop. Front. Cell. Infect. Microbiol. 3, 14.

Kaiser, W.J., Offermann, M.K., 2005. Apoptosis induced by the Toll-like receptor adaptor TRIF is dependent on its receptor interacting protein homotypic interaction motif. J. Immunol. 174 (8), 4942–4952.

Kaiser, W.J., Sridharan, H., Huang, C., Mandal, P., Upton, J.W., Gough, P.J., Sehon, C.A., Marquis, R.W., Bertin, J., Mocarski, E.S., 2013. Toll-like receptor 3-mediated necrosis via TRIF, RIP3, and MLKL. J. Biol. Chem. 288 (43), 31268–31279.

Karki, R., Lee, E., Place, D., Samir, P., Mavuluri, J., Sharma, B.R., Balakrishnan, A., Malireddi, R.K.S., Geiger, R., Zhu, Q., Neale, G., Kanneganti, T.-D., 2018. IRF8 regulates transcription of Naips for NLRC4 inflammasome activation. Cell 173 (4), 920–933.e13.

Katagiri, N., Shobuike, T., Chang, B., Kukita, A., Miyamoto, H., 2012. The human apoptosis inhibitor NAIP induces pyroptosis in macrophages infected with *Legionella pneumophila*. Microbes Infect. 14 (13), 1123–1132.

Kato, H., Takeuchi, O., Sato, S., Yoneyama, M., Yamamoto, M., Matsui, K., Uematsu, S., Jung, A., Kawai, T., Ishii, K.J., Yamaguchi, O., Otsu, K., Tsujimura, T., Koh, C.-S., Reis e Sousa, C., Matsuura, Y., Fujita, T., Akira, S., 2006. Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. Nature 441 (7089), 101–105.

Kayagaki, N., Stowe, I.B., Lee, B.L., O'Rourke, K., Anderson, K., Warming, S., Cuellar, T., Haley, B., Roose-Girma, M., Phung, Q.T., Liu, P.S., Lill, J.R., Li, H., Wu, J., Kummerfeld, S., Zhang, J., Lee, W.P., Snipas, S.J., Salvesen, G.S., Morris, L.X., Fitzgerald, L., Zhang, Y., Bertram, E.M., Goodnow, C.C., Dixit, V.M., 2015. Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. Nature 526 (7575), 666–671.

Kerr, J.F., Wyllie, A.H., Currie, A.R., 1972. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br. J. Cancer 26 (4), 239–257.

Kim, S., Bauernfeind, F., Ablasser, A., Hartmann, G., Fitzgerald, K.A., Latz, E., Hornung, V., 2010. *Listeria monocytogenes* is sensed by the NLRP3 and AIM2 inflammasome. Eur. J. Immunol. 40 (6), 1545–1551.

Kim, K.-H., Seong, B.L., 2003. Pro-apoptotic function of HBV X protein is mediated by interaction with c-FLIP and enhancement of death-inducing signal. EMBO J. 22 (9), 2104–2116.

Kip, E., Nazé, F., Suin, V., Vanden Berghe, T., Francart, A., Lamoral, S., Vandenabeele, P., Beyaert, R., van Gucht, S., Kalai, M., 2017. Impact of caspase-1/11, -3, -7, or IL-1β/IL-18 deficiency on rabies virus-induced macrophage cell death and onset of disease. Cell Death Discov. 3, 17012.

Kitur, K., Parker, D., Nieto, P., Ahn, D.S., Cohen, T.S., Chung, S., Wachtel, S., Bueno, S., Prince, A., 2015. Toxin-induced necroptosis is a major mechanism of *Staphylococcus aureus* lung damage. PLoS Pathog. 11 (4), e1004820.

Koehler, H., Cotsmire, S., Langland, J., Kibler, K.V., Kalman, D., Upton, J.W., Mocarski, E.S., Jacobs, B.L., 2017. Inhibition of DAI-dependent necroptosis by the Z-DNA binding domain of the vaccinia virus innate immune evasion protein, E3. Proc. Natl. Acad. Sci. U. S. A. 114 (43), 11506–11511.

Kofahi, H.M., Taylor, N.G.A., Hirasawa, K., Grant, M.D., Russell, R.S., 2016. Hepatitis C virus infection of cultured human hepatoma cells causes apoptosis and pyroptosis in both infected and bystander cells. Sci. Rep. 6, 37433.

Krejbich-Trotot, P., Denizot, M., Hoarau, J.-J., Jaffar-Bandjee, M.-C., Das, T., Gasque, P., 2011. Chikungunya virus mobilizes the apoptotic machinery to invade host cell defenses. FASEB J. 25 (1), 314–325.

Kuriakose, T., Man, S.M., Malireddi, R.K.S., Karki, R., Kesavardhana, S., Place, D.E., Neale, G., Vogel, P., Kanneganti, T.-D., 2016. ZBP1/DAI is an innate sensor of influenza virus triggering the NLRP3 inflammasome and programmed cell death pathways. Sci. Immunol. 1 (2), aag2045.

Kuriakose, T., Zheng, M., Neale, G., Kanneganti, T.-D., 2018. IRF1 is a transcriptional regulator of ZBP1 promoting NLRP3 inflammasome activation and cell death during influenza virus infection. J. Immunol. 200 (4), 1489–1495.

Langelier, Y., Bergeron, S., Chabaud, S., Lippens, J., Guilbault, C., Sasseville, A.M.-J., Denis, S., Mosser, D.D., Massie, B., 2002. The R1 subunit of herpes simplex virus ribonucleotide reductase protects cells against apoptosis at, or upstream of, caspase-8 activation. J. Gen. Virol. 83 (Pt 11), 2779–2789.

Lee, S., Hirohama, M., Noguchi, M., Nagata, K., Kawaguchi, A., 2018. Influenza A virus infection triggers pyroptosis and apoptosis of respiratory epithelial cells through the type I interferon signaling pathway in a mutually exclusive manner. J. Virol. 92, 14.

Legarda, D., Justus, S.J., Ang, R.L., Rikhi, N., Li, W., Moran, T.M., Zhang, J., Mizoguchi, E., Zelic, M., Kelliher, M.A., Blander, J.M., Ting, A.T., 2016. CYLD proteolysis protects macrophages from TNF-mediated auto-necroptosis induced by LPS and licensed by type I IFN. Cell Rep. 15 (11), 2449–2461.

Lehnardt, S., Wennekamp, J., Freyer, D., Liedtke, C., Krueger, C., Nitsch, R., Bechmann, I., Weber, J.R., Henneke, P., 2007. TLR2 and caspase-8 are essential for group B Streptococcus-induced apoptosis in microglia. J. Immunol. 179 (9), 6134–6143.

Lei, X., Zhang, Z., Xiao, X., Qi, J., He, B., Wang, J., 2017. Enterovirus 71 inhibits pyroptosis through cleavage of gasdermin D. J. Virol. 91 (18), pii: e01069-17.

Li, Z., Yu, J., Liu, L., Wei, Z., Ehrlich, E.S., Liu, G., Li, J., Liu, X., Wang, H., Yu, X.-F., Zhang, W., 2014. Coxsackievirus A16 infection induces neural cell and non-neural cell apoptosis in vitro. PLoS One 9 (10), e111174.

Liao, H., Xu, J., Huang, J., 2010. FasL/Fas pathway is involved in dengue virus induced apoptosis of the vascular endothelial cells. J. Med. Virol. 82 (8), 1392–1399.

Lim, M.C.C., Maubach, G., Sokolova, O., Feige, M.H., Diezko, R., Buchbinder, J., Backert, S., Schlüter, D., Lavrik, I.N., Naumann, M., 2017. Pathogen-induced ubiquitin-editing enzyme A20 bifunctionally shuts off NF-κB and caspase-8-dependent apoptotic cell death. Cell Death Differ. 24 (9), 1621–1631.

Liu, X., Zhang, Z., Ruan, J., Pan, Y., Magupalli, V.G., Wu, H., Lieberman, J., 2016. Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. Nature 535 (7610), 153–158.

Liu, X., Li, Y., Peng, S., Yu, X., Li, W., Shi, F., Luo, X., Tang, M., Tan, Z., Bode, A.M., Cao, Y., 2018. Epstein-Barr virus encoded latent membrane protein 1 suppresses necroptosis through targeting RIPK1/3 ubiquitination. Cell Death Dis. 9 (2), 53.

López, M., Sly, L.M., Luu, Y., Young, D., Cooper, H., Reiner, N.E., 2003. The 19-kDa *Mycobacterium tuberculosis* protein induces macrophage apoptosis through Toll-like receptor-2. J. Immunol. 170 (5), 2409–2416.

Lötzerich, M., Roulin, P.S., Boucke, K., Witte, R., Georgiev, O., Greber, U.F., 2018. Rhinovirus 3C protease suppresses apoptosis and triggers caspase-independent cell death. Cell Death Dis. 9 (3), 272.

Lowin, B., Beermann, F., Schmidt, A., Tschopp, J., 1994. A null mutation in the perforin gene impairs cytolytic T lymphocyte- and natural killer cell-mediated cytotoxicity. Proc. Natl. Acad. Sci. U. S. A. 91 (24), 11571–11575.

Lu, B., Nakamura, T., Inouye, K., Li, J., Tang, Y., Lundbäck, P., Valdes-Ferrer, S.I., Olofsson, P.S., Kalb, T., Roth, J., Zou, Y., Erlandsson-Harris, H., Yang, H.,

Ting, J.P.-Y., Wang, H., Andersson, U., Antoine, D.J., Chavan, S.S., Hotamisligil, G.S., Tracey, K.J., 2012. Novel role of PKR in inflammasome activation and HMGB1 release. Nature 488 (7413), 670–674.

Mace, P.D., Riedl, S.J., 2010. Molecular cell death platforms and assemblies. Curr. Opin. Cell Biol. 22 (6), 828–836.

Man, S.M., Tourlomousis, P., Hopkins, L., Monie, T.P., Fitzgerald, K.A., Bryant, C.E., 2013. Salmonella infection induces recruitment of Caspase-8 to the inflammasome to modulate IL-1β production. J. Immunol. 191 (10), 5239–5246.

Man, S.M., Karki, R., Malireddi, R.K.S., Neale, G., Vogel, P., Yamamoto, M., Lamkanfi, M., Kanneganti, T.-D., 2015. The transcription factor IRF1 and guanylate-binding proteins target activation of the AIM2 inflammasome by Francisella infection. Nat. Immunol. 16 (5), 467–475.

Man, S.M., Karki, R., Sasai, M., Place, D.E., Kesavardhana, S., Temirov, J., Frase, S., Zhu, Q., Malireddi, R.K.S., Kuriakose, T., Peters, J.L., Neale, G., Brown, S.A., Yamamoto, M., Kanneganti, T.-D., 2016. IRGB10 liberates bacterial ligands for sensing by the AIM2 and caspase-11-NLRP3 inflammasomes. Cell 167 (2), 382–396.e17.

Man, S.M., Karki, R., Kanneganti, T.-D., 2017. Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases. Immunol. Rev. 277 (1), 61–75.

Martinon, F., 2008. Detection of immune danger signals by NALP3. J. Leukoc. Biol. 83 (3), 507–511.

Martinon, F., Pétrilli, V., Mayor, A., Tardivel, A., Tschopp, J., 2006. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature 440 (7081), 237–241.

Matsuoka, M., Jeang, K.-T., 2007. Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation. Nat. Rev. Cancer 7 (4), 270–280.

Matusiak, M., van Opdenbosch, N., Vande Walle, L., Sirard, J.-C., Kanneganti, T.-D., Lamkanfi, M., 2015. Flagellin-induced NLRC4 phosphorylation primes the inflammasome for activation by NAIP5. Proc. Natl. Acad. Sci. U. S. A. 112 (5), 1541–1546.

McAllister, C.S., Lakhdari, O., Pineton de Chambrun, G., Gareau, M.G., Broquet, A., Lee, G.H., Shenouda, S., Eckmann, L., Kagnoff, M.F., 2013. TLR3, TRIF, and caspase 8 determine double-stranded RNA-induced epithelial cell death and survival in vivo. J. Immunol. 190 (1), 418–427.

McCracken, J.M., Kinkead, L.C., McCaffrey, R.L., Allen, L.-A.H., 2016. Francisella tularensis modulates a distinct subset of regulatory factors and sustains mitochondrial integrity to impair human neutrophil apoptosis. J. Innate Immun. 8 (3), 299–313.

McQuade, T., Cho, Y., Chan, F.K.-M., 2013. Positive and negative phosphorylation regulates RIP1- and RIP3-induced programmed necrosis. Biochem. J. 456 (3), 409–415.

Meessen-Pinard, M., Le Coupanec, A., Desforges, M., Talbot, P.J., 2017. Pivotal role of receptor-interacting protein kinase 1 and mixed lineage kinase domain-like in neuronal cell death induced by the human neuroinvasive coronavirus OC43. J. Virol. 91, 1.

Meng, R., Gu, L., Lu, Y., Zhao, K., Wu, J., Wang, H., Han, J., Tang, Y., Lu, B., 2019. High mobility group box 1 enables bacterial lipids to trigger receptor-interacting protein kinase 3 (RIPK3)-mediated necroptosis and apoptosis in mice. J. Biol. Chem. 294 (22), 8872–8884.

Meunier, E., Dick, M.S., Dreier, R.F., Schürmann, N., Kenzelmann Broz, D., Warming, S., Roose-Girma, M., Bumann, D., Kayagaki, N., Takeda, K., Yamamoto, M., Broz, P., 2014. Caspase-11 activation requires lysis of pathogen-containing vacuoles by IFN-induced GTPases. Nature 509 (7500), 366–370.

Miao, E.A., Leaf, I.A., Treuting, P.M., Mao, D.P., Dors, M., Sarkar, A., Warren, S.E., Wewers, M.D., Aderem, A., 2010. Caspase-1-induced pyroptosis is an innate immune effector mechanism against intracellular bacteria. Nat. Immunol. 11 (12), 1136–1142.

Monack, D.M., Navarre, W.W., Falkow, S., 2001. Salmonella-induced macrophage death: the role of caspase-1 in death and inflammation. Microbes Infect. 3 (14–15), 1201–1212.

Monroe, K.M., Yang, Z., Johnson, J.R., Geng, X., Doitsh, G., Krogan, N.J., Greene, W.C., 2014. IFI16 DNA sensor is required for death of lymphoid CD4 T cells abortively infected with HIV. Science (New York, NY) 343 (6169), 428–432.

Muñoz-Planillo, R., Kuffa, P., Martínez-Colón, G., Smith, B.L., Rajendiran, T.M., Núñez, G., 2013. K$^+$ efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. Immunity 38 (6), 1142–1153.

Nandakumar, R., Tschismarov, R., Meissner, F., Prabakaran, T., Krissanaprasit, A., Farahani, E., Zhang, B.-C., Assil, S., Martin, A., Bertrams, W., Holm, C.K., Ablasser, A., Klause, T., Thomsen, M.K., Schmeck, B., Howard, K.A., Henry, T., Gothelf, K.V., Decker, T., Paludan, S.R., 2019. Intracellular bacteria engage a STING-TBK1-MVB12b pathway to enable paracrine cGAS-STING signalling. Nat. Microbiol. 4 (4), 701–713.

Nayak, T.K., Mamidi, P., Kumar, A., Singh, L.P.K., Sahoo, S.S., Chattopadhyay, S., Chattopadhyay, S., 2017. Regulation of viral replication, apoptosis and pro-inflammatory responses by 17-AAG during chikungunya virus infection in macrophages. Viruses 9 (1), 3.

Newton, K., Wickliffe, K.E., Maltzman, A., Dugger, D.L., Strasser, A., Pham, V.C., Lill, J.R., Roose-Girma, M., Warming, S., Solon, M., Ngu, H., Webster, J.D., Dixit, V.M., 2016. RIPK1 inhibits ZBP1-driven necroptosis during development. Nature 540 (7631), 129–133.

Ning, X., Wang, Y., Jing, M., Sha, M., Lv, M., Gao, P., Zhang, R., Huang, X., Feng, J.-M., Jiang, Z., 2019. Apoptotic caspases suppress type I interferon production via the cleavage of cGAS, MAVS, and IRF3. Mol. Cell 74 (1), 19–31.

Nogusa, S., Thapa, R.J., Dillon, C.P., Liedmann, S., Oguin, T.H., Ingram, J.P., Rodriguez, D.A., Kosoff, R., Sharma, S., Sturm, O., Verbist, K., Gough, P.J., Bertin, J., Hartmann, B.M., Sealfon, S.C., Kaiser, W.J., Mocarski, E.S., López, C.B., Thomas, P.G., Oberst, A., Green, D.R., Balachandran, S., 2016. RIPK3 activates parallel pathways of MLKL-driven necroptosis and FADD-mediated apoptosis to protect against influenza A virus. Cell Host Microbe 20 (1), 13–24.

Obregón-Henao, A., Duque-Correa, M.A., Rojas, M., García, L.F., Brennan, P.J., Ortiz, B.L., Belisle, J.T., 2012. Stable extracellular RNA fragments of Mycobacterium tuberculosis induce early apoptosis in human monocytes via a caspase-8 dependent mechanism. PLoS One 7 (1), e29970.

O'Donnell, M.A., Perez-Jimenez, E., Oberst, A., Ng, A., Massoumi, R., Xavier, R., Green, D.R., Ting, A.T., 2011. Caspase 8 inhibits programmed necrosis by processing CYLD. Nat. Cell Biol. 13 (12), 1437–1442.

Okamoto, K., Fujisawa, J.-I., Reth, M., Yonehara, S., 2006. Human T-cell leukemia virus type-I oncoprotein Tax inhibits Fas-mediated apoptosis by inducing cellular FLIP through activation of NF-kappaB. Genes Cells 11 (2), 177–191.

Olsson, M., Forsberg, J., Zhivotovsky, B., 2015. Caspase-2: the reinvented enzyme. Oncogene 34 (15), 1877–1882.

Omoto, S., Guo, H., Talekar, G.R., Roback, L., Kaiser, W.J., Mocarski, E.S., 2015. Suppression of RIP3-dependent necroptosis by human cytomegalovirus. J. Biol. Chem. 290 (18), 11635–11648.

Orning, P., Weng, D., Starheim, K., Ratner, D., Best, Z., Lee, B., Brooks, A., Xia, S., Wu, H., Kelliher, M.A., Berger, S.B., Gough, P.J., Bertin, J., Proulx, M.M., Goguen, J.D., Kayagaki, N., Fitzgerald, K.A., Lien, E., 2018. Pathogen blockade of TAK1 triggers caspase-8-dependent cleavage of gasdermin D and cell death. Science (New York, NY) 362 (6418), 1064–1069.

Pajuelo, D., Gonzalez-Juarbe, N., Tak, U., Sun, J., Orihuela, C.J., Niederweis, M., 2018. NAD + depletion triggers macrophage necroptosis, a cell death pathway exploited by *Mycobacterium tuberculosis*. Cell Rep. 24 (2), 429–440.

Pan, T., Wu, S., He, X., Luo, H., Zhang, Y., Fan, M., Geng, G., Ruiz, V.C., Zhang, J., Mills, L., Bai, C., Zhang, H., 2014. Necroptosis takes place in human immunodeficiency virus type-1 (HIV-1)-infected CD4 + T lymphocytes. PLoS One 9 (4), e93944.

Pearson, J.S., Giogha, C., Ong, S.Y., Kennedy, C.L., Kelly, M., Robinson, K.S., Lung, T.W.F., Mansell, A., Riedmaier, P., Oates, C.V.L., Zaid, A., Mühlen, S., Crepin, V.F., Marches, O., Ang, C.-S., Williamson, N.A., O'Reilly, L.A., Bankovacki, A., Nachbur, U., Infusini, G., Webb, A.I., Silke, J., Strasser, A., Frankel, G., Hartland, E.L., 2013. A type III effector antagonizes death receptor signalling during bacterial gut infection. Nature 501 (7466), 247–251.

Pearson, J.S., Giogha, C., Mühlen, S., Nachbur, U., Pham, C.L.L., Zhang, Y., Hildebrand, J.M., Oates, C.V., Lung, T.W.F., Ingle, D., Dagley, L.F., Bankovacki, A., Petrie, E.J., Schroeder, G.N., Crepin, V.F., Frankel, G., Masters, S.L., Vince, J., Murphy, J.M., Sunde, M., Webb, A.I., Silke, J., Hartland, E.L., 2017. EspL is a bacterial cysteine protease effector that cleaves RHIM proteins to block necroptosis and inflammation. Nat. Microbiol. 2, 16258.

Peters, K., Chattopadhyay, S., Sen, G.C., 2008. IRF-3 activation by Sendai virus infection is required for cellular apoptosis and avoidance of persistence. J. Virol. 82 (7), 3500–3508.

Pierini, R., Juruj, C., Perret, M., Jones, C.L., Mangeot, P., Weiss, D.S., Henry, T., 2012. AIM2/ASC triggers caspase-8-dependent apoptosis in Francisella-infected caspase-1-deficient macrophages. Cell Death Differ. 19 (10), 1709–1721.

Pinkoski, M.J., Waterhouse, N.J., Heibein, J.A., Wolf, B.B., Kuwana, T., Goldstein, J.C., Newmeyer, D.D., Bleackley, R.C., Green, D.R., 2001. Granzyme B-mediated apoptosis proceeds predominantly through a Bcl-2-inhibitable mitochondrial pathway. J. Biol. Chem. 276 (15), 12060–12067.

Platnich, J.M., Chung, H., Lau, A., Sandall, C.F., Bondzi-Simpson, A., Chen, H.-M., Komada, T., Trotman-Grant, A.C., Brandelli, J.R., Chun, J., Beck, P.L., Philpott, D.J., Girardin, S.E., Ho, M., Johnson, R.P., MacDonald, J.A., Armstrong, G.D., Muruve, D.A., 2018. Shiga toxin/lipopolysaccharide activates caspase-4 and gasdermin D to trigger mitochondrial reactive oxygen species upstream of the NLRP3 inflammasome. Cell Rep. 25 (6), 1525–1536.

Qu, Y., Misaghi, S., Izrael-Tomasevic, A., Newton, K., Gilmour, L.L., Lamkanfi, M., Louie, S., Kayagaki, N., Liu, J., Kömüves, L., Cupp, J.E., Arnott, D., Monack, D., Dixit, V.M., 2012. Phosphorylation of NLRC4 is critical for inflammasome activation. Nature 490 (7421), 539–542.

Queen, J., Agarwal, S., Dolores, J.S., Stehlik, C., Satchell, K.J.F., 2015. Mechanisms of inflammasome activation by Vibrio cholerae secreted toxins vary with strain biotype. Infect. Immun. 83 (6), 2496–2506.

Ramanathan, M.P., Chambers, J.A., Pankhong, P., Chattergoon, M., Attatippaholkun, W., Dang, K., Shah, N., Weiner, D.B., 2006. Host cell killing by the West Nile Virus NS2B-NS3 proteolytic complex: NS3 alone is sufficient to recruit caspase-8-based apoptotic pathway. Virology 345 (1), 56–72.

Rathinam, V.A.K., Jiang, Z., Waggoner, S.N., Sharma, S., Cole, L.E., Waggoner, L., Vanaja, S.K., Monks, B.G., Ganesan, S., Latz, E., Hornung, V., Vogel, S.N., Szomolanyi-Tsuda, E., Fitzgerald, K.A., 2010. The AIM2 inflammasome is essential for host defense against cytosolic bacteria and DNA viruses. Nat. Immunol. 11 (5), 395–402.

Riedl, S.J., Salvesen, G.S., 2007. The apoptosome: signalling platform of cell death. Nat. Rev. Mol. Cell Biol. 8 (5), 405–413.

Robinson, N., McComb, S., Mulligan, R., Dudani, R., Krishnan, L., Sad, S., 2012. Type I interferon induces necroptosis in macrophages during infection with Salmonella enterica serovar Typhimurium. Nat. Immunol. 13 (10), 954–962.

Rogers, C., Fernandes-Alnemri, T., Mayes, L., Alnemri, D., Cingolani, G., Alnemri, E.S., 2017. Cleavage of DFNA5 by caspase-3 during apoptosis mediates progression to secondary necrotic/pyroptotic cell death. Nat. Commun. 8, 14128.

Rupper, A.C., Cardelli, J.A., 2008. Induction of guanylate binding protein 5 by gamma interferon increases susceptibility to Salmonella enterica serovar Typhimurium-induced pyroptosis in RAW 264.7 cells. Infect. Immun. 76 (6), 2304–2315.

Sainski, A.M., Dai, H., Natesampillai, S., Pang, Y.-P., Bren, G.D., Cummins, N.W., Correia, C., Meng, X.W., Tarara, J.E., Ramirez-Alvarado, M., Katzmann, D.J., Ochsenbauer, C., Kappes, J.C., Kaufmann, S.H., Badley, A.D., 2014. Casp8p41 generated by HIV protease kills CD4 T cells through direct Bak activation. J. Cell Biol. 206 (7), 867–876.

Sanman, L.E., Qian, Y., Eisele, N.A., Ng, T.M., van der Linden, W.A., Monack, D.M., Weerapana, E., Bogyo, M., 2016. Disruption of glycolytic flux is a signal for inflammasome signaling and pyroptotic cell death. eLife, 5, e13663.

Sarhan, J., Liu, B.C., Muendlein, H.I., Li, P., Nilson, R., Tang, A.Y., Rongvaux, A., Bunnell, S.C., Shao, F., Green, D.R., Poltorak, A., 2018. Caspase-8 induces cleavage of gasdermin D to elicit pyroptosis during Yersinia infection. Proc. Natl. Acad. Sci. U. S. A. 115 (46), E10888–E10897.

Sauer, J.-D., Witte, C.E., Zemansky, J., Hanson, B., Lauer, P., Portnoy, D.A., 2010. Listeria monocytogenes triggers AIM2-mediated pyroptosis upon infrequent bacteriolysis in the macrophage cytosol. Cell Host Microbe 7 (5), 412–419.

Sborgi, L., Rühl, S., Mulvihill, E., Pipercevic, J., Heilig, R., Stahlberg, H., Farady, C.J., Müller, D.J., Broz, P., Hiller, S., 2016. GSDMD membrane pore formation constitutes the mechanism of pyroptotic cell death. EMBO J. 35 (16), 1766–1778.

Scaffidi, P., Misteli, T., Bianchi, M.E., 2002. Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature 418 (6894), 191–195.

Shresta, S., MacIvor, D.M., Heusel, J.W., Russell, J.H., Ley, T.J., 1995. Natural killer and lymphokine-activated killer cells require granzyme B for the rapid induction of apoptosis in susceptible target cells. Proc. Natl. Acad. Sci. U. S. A. 92 (12), 5679–5683.

Skaletskaya, A., Bartle, L.M., Chittenden, T., McCormick, A.L., Mocarski, E.S., Goldmacher, V.S., 2001. A cytomegalovirus-encoded inhibitor of apoptosis that suppresses caspase-8 activation. Proc. Natl. Acad. Sci. U. S. A. 98 (14), 7829–7834.

Song, D., Meng, J., Cheng, J., Fan, Z., Chen, P., Ruan, H., Tu, Z., Kang, N., Li, N., Xu, Y., Wang, X., Shu, F., Mu, L., Li, T., Ren, W., Lin, X., Zhu, J., Fang, X., Amrein, M.W., Wu, W., Yan, L.-T., Lü, J., Xia, T., Shi, Y., 2019. Pseudomonas aeruginosa quorum-sensing metabolite induces host immune cell death through cell surface lipid domain dissolution. Nat. Microbiol. 4 (1), 97–111.

Sridharan, H., Ragan, K.B., Guo, H., Gilley, R.P., Landsteiner, V.J., Kaiser, W.J., Upton, J.W., 2017. Murine cytomegalovirus IE3-dependent transcription is required for DAI/ZBP1-mediated necroptosis. EMBO Rep. 18 (8), 1429–1441.

Stutz, M.D., Ojaimi, S., Ebert, G., Pellegrini, M., 2018. Is receptor-interacting protein kinase 3 a viable therapeutic target for Mycobacterium tuberculosis infection? Front. Immunol. 9, 1178.

Sun, L., Wang, H., Wang, Z., He, S., Chen, S., Liao, D., Wang, L., Yan, J., Liu, W., Lei, X., Wang, X., 2012. Mixed lineage kinase domain-like protein mediates necrosis signaling downstream of RIP3 kinase. Cell 148 (1–2), 213–227.

Sun, L., Wu, J., Du, F., Chen, X., Chen, Z.J., 2013. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. Science 339 (6121), 786–791.

Suzuki, T., Franchi, L., Toma, C., Ashida, H., Ogawa, M., Yoshikawa, Y., Mimuro, H., Inohara, N., Sasakawa, C., Nuñez, G., 2007. Differential regulation of caspase-1 activation, pyroptosis, and autophagy via Ipaf and ASC in Shigella-infected macrophages. PLoS Pathog. 3 (8), e111.

Suzuki, S., Franchi, L., He, Y., Muñoz-Planillo, R., Mimuro, H., Suzuki, T., Sasakawa, C., Núñez, G., 2014. Shigella type III secretion protein MxiI is recognized by Naip2 to induce Nlrc4 inflammasome activation independently of Pkcδ. PLoS Pathog. 10 (2), e1003926.

Tait, S.W.G., Green, D.R., 2010. Mitochondria and cell death: outer membrane permeabilization and beyond. Nat. Rev. Mol. Cell Biol. 11 (9), 621–632.

Tan, T.Y., Chu, J.J.H., 2013. Dengue virus-infected human monocytes trigger late activation of caspase-1, which mediates pro-inflammatory IL-1β secretion and pyroptosis. J. Gen. Virol. 94 (Pt 10), 2215–2220.

Tenev, T., Bianchi, K., Darding, M., Broemer, M., Langlais, C., Wallberg, F., Zachariou, A., Lopez, J., MacFarlane, M., Cain, K., Meier, P., 2011. The Ripoptosome, a signaling platform that assembles in response to genotoxic stress and loss of IAPs. Mol. Cell 43 (3), 432–448.

Tewari, M., Quan, L.T., O'Rourke, K., Desnoyers, S., Zeng, Z., Beidler, D.R., Poirier, G.G., Salvesen, G.S., Dixit, V.M., 1995. Yama/CPP32β, a mammalian homolog of CED-3, is a CrmA-inhibitable protease that cleaves the death substrate poly(ADP-ribose) polymerase. Cell 81 (5), 801–809.

Thapa, R.J., Ingram, J.P., Ragan, K.B., Nogusa, S., Boyd, D.F., Benitez, A.A., Sridharan, H., Kosoff, R., Shubina, M., Landsteiner, V.J., Andrake, M., Vogel, P., Sigal, L.J., tenOever, B.R., Thomas, P.G., Upton, J.W., Balachandran, S., 2016. DAI senses influenza A virus genomic RNA and activates RIPK3-dependent cell death. Cell Host Microbe 20 (5), 674–681.

Thome, M., Schneider, P., Hofmann, K., Fickenscher, H., Meinl, E., Neipel, F., Mattmann, C., Burns, K., Bodmer, J.L., Schröter, M., Scaffidi, C., Krammer, P.H., Peter, M.E., Tschopp, J., 1997. Viral FLICE-inhibitory proteins (FLIPs) prevent apoptosis induced by death receptors. Nature 386 (6624), 517–521.

Upton, J.W., Kaiser, W.J., Mocarski, E.S., 2010. Virus inhibition of RIP3-dependent necrosis. Cell Host Microbe 7 (4), 302–313.

Upton, J.W., Kaiser, W.J., Mocarski, E.S., 2012. DAI/ZBP1/DLM-1 complexes with RIP3 to mediate virus-induced programmed necrosis that is targeted by murine cytomegalovirus vIRA. Cell Host Microbe 11 (3), 290–297.

Valderrama, J.A., Riestra, A.M., Gao, N.J., LaRock, C.N., Gupta, N., Ali, S.R., Hoffman, H.M., Ghosh, P., Nizet, V., 2017. Group A streptococcal M protein activates the NLRP3 inflammasome. Nat. Microbiol. 2 (10), 1425–1434.

van Opdenbosch, N., Lamkanfi, M., 2019. Caspases in cell death, inflammation, and disease. Immunity 50 (6), 1352–1364.

Varfolomeev, E., Vucic, D., 2008. (Un)expected roles of c-IAPs in apoptotic and NFkappaB signaling pathways. Cell Cycle 7 (11), 1511–1521.

Varfolomeev, E., Vucic, D., 2018. Intracellular regulation of TNF activity in health and disease. Cytokine 101, 26–32.

Vercammen, D., Brouckaert, G., Denecker, G., van de Craen, M., Declercq, W., Fiers, W., Vandenabeele, P., 1998. Dual signaling of the Fas receptor: initiation of both apoptotic and necrotic cell death pathways. J. Exp. Med. 188 (5), 919–930.

Waguia Kontchou, C., Tzivelekidis, T., Gentle, I.E., Häcker, G., 2016. Infection of epithelial cells with Chlamydia trachomatis inhibits TNF-induced apoptosis at the level of receptor internalization while leaving non-apoptotic TNF-signalling intact. Cell. Microbiol. 18 (11), 1583–1595.

Wang, X., Tan, J., Zoueva, O., Zhao, J., Ye, Z., Hewlett, I., 2014. Novel pandemic influenza A (H1N1) virus infection modulates apoptotic pathways that impact its replication in A549 cells. Microbes Infect. 16 (3), 178–186.

Wang, Y., Jia, L., Shen, J., Wang, Y., Fu, Z., Su, S.-A., Cai, Z., Wang, J.-A., Xiang, M., 2018. Cathepsin B aggravates coxsackievirus B3-induced myocarditis through activating the inflammasome and promoting pyroptosis. PLoS Pathog. 14 (1), e1006872.

Wang, J., Deobald, K., Re, F., 2019a. Gasdermin D protects from melioidosis through pyroptosis and direct killing of bacteria. J. Immunol. 202 (12), 3468–3473.

Wang, Y., Hao, Q., Florence, J.M., Jung, B.-G., Kurdowska, A.K., Samten, B., Idell, S., Tang, H., 2019b. Influenza virus infection induces ZBP1 expression and necroptosis in mouse lungs. Front. Cell. Infect. Microbiol. 9, 286.

Warren, S.E., Mao, D.P., Rodriguez, A.E., Miao, E.A., Aderem, A., 2008. Multiple Nod-like receptors activate caspase 1 during *Listeria monocytogenes* infection. J. Immunol. 180 (11), 7558–7564.

Weber, A., Kirejczyk, Z., Besch, R., Potthoff, S., Leverkus, M., Häcker, G., 2010. Proapoptotic signalling through Toll-like receptor-3 involves TRIF-dependent activation of caspase-8 and is under the control of inhibitor of apoptosis proteins in melanoma cells. Cell Death Differ. 17 (6), 942–951.

Weiss, R., Sachet, M., Zinngrebe, J., Aschacher, T., Krainer, M., Hegedus, B., Walczak, H., Bergmann, M., 2013. IL-24 sensitizes tumor cells to TLR3-mediated apoptosis. Cell Death Differ. 20 (6), 823–833.

Weng, D., Marty-Roix, R., Ganesan, S., Proulx, M.K., Vladimer, G.I., Kaiser, W.J., Mocarski, E.S., Pouliot, K., Chan, F.K.-M., Kelliher, M.A., Harris, P.A., Bertin, J., Gough, P.J., Shayakhmetov, D.M., Goguen, J.D., Fitzgerald, K.A., Silverman, N., Lien, E., 2014. Caspase-8 and RIP kinases regulate bacteria-induced innate immune responses and cell death. Proc. Natl. Acad. Sci. U. S. A. 111 (20), 7391–7396.

White, M.J., McArthur, K., Metcalf, D., Lane, R.M., Cambier, J.C., Herold, M.J., van Delft, M.F., Bedoui, S., Lessene, G., Ritchie, M.E., Huang, D.C.S., Kile, B.T., 2014. Apoptotic caspases suppress mtDNA-induced STING-mediated type I IFN production. Cell 159 (7), 1549–1562.

Wilson, N.S., Dixit, V., Ashkenazi, A., 2009. Death receptor signal transducers: nodes of coordination in immune signaling networks. Nat. Immunol. 10 (4), 348–355.

Wu, M.-F., Chen, S.-T., Yang, A.-H., Lin, W.-W., Lin, Y.-L., Chen, N.-J., Tsai, I.-S., Li, L., Hsieh, S.-L., 2013. CLEC5A is critical for dengue virus-induced inflammasome activation in human macrophages. Blood 121 (1), 95–106.

Xie, T., Peng, W., Liu, Y., Yan, C., Maki, J., Degterev, A., Yuan, J., Shi, Y., 2013. Structural basis of RIP1 inhibition by necrostatins. Structure 21 (3), 493–499.

Yamamoto, M., Sato, S., Hemmi, H., Hoshino, K., Kaisho, T., Sanjo, H., Takeuchi, O., Sugiyama, M., Okabe, M., Takeda, K., Akira, S., 2003. Role of adaptor TRIF in the MyD88-independent Toll-like receptor signaling pathway. Science (New York, NY) 301 (5633), 640–643.

Yang, J., Zhao, Y., Shi, J., Shao, F., 2013. Human NAIP and mouse NAIP1 recognize bacterial type III secretion needle protein for inflammasome activation. Proc. Natl. Acad. Sci. U. S. A. 110 (35), 14408–14413.

Yatim, N., Jusforgues-Saklani, H., Orozco, S., Schulz, O., da Barreira Silva, R., Reis e Sousa, C., Green, D.R., Oberst, A., Albert, M.L., 2015. RIPK1 and NF-κB signaling in dying cells determines cross-priming of CD8^{+} T cells. Science (New York, NY) 350 (6258), 328–334.

Yogarajah, T., Ong, K.C., Perera, D., Wong, K.T., 2017. AIM2 inflammasome-mediated pyroptosis in enterovirus A71-infected neuronal cells restricts viral replication. Sci. Rep. 7 (1), 5845.

Zhai, D., Yu, E., Jin, C., Welsh, K., Shiau, C.-W., Chen, L., Salvesen, G.S., Liddington, R., Reed, J.C., 2010. Vaccinia virus protein F1L is a caspase-9 inhibitor. J. Biol. Chem. 285 (8), 5569–5580.

Zhao, S., Zhou, Y., Fan, Y., Gong, Y., Yang, J., Yang, R., Li, L., Zou, L., Xu, X., Li, G., Liu, S., Zhang, C., Li, G., Liang, S., 2019. Involvement of P2X4 receptor in gp120-induced pyroptosis in dorsal root ganglia. J. Neurochem. 151 (5), 584–594.

Zhou, Q., Snipas, S., Orth, K., Muzio, M., Dixit, V.M., Salvesen, G.S., 1997. Target protease specificity of the viral serpin CrmA. Analysis of five caspases. J. Biol. Chem. 272 (12), 7797–7800.

Zhu, S., Ding, S., Wang, P., Wei, Z., Pan, W., Palm, N.W., Yang, Y., Yu, H., Li, H.-B., Wang, G., Lei, X., de Zoete, M.R., Zhao, J., Zheng, Y., Chen, H., Zhao, Y., Jurado, K.A., Feng, N., Shan, L., Kluger, Y., Lu, J., Abraham, C., Fikrig, E., Greenberg, H.B., Flavell, R.A., 2017. Nlrp9b inflammasome restricts rotavirus infection in intestinal epithelial cells. Nature 546 (7660), 667–670.

Zhu, X., Wu, T., Chi, Y., Ge, Y., Wu, B., Zhou, M., Zhu, F., Ji, M., Cui, L., 2018. Pyroptosis induced by enterovirus A71 infection in cultured human neuroblastoma cells. Virology 521, 69–76.