Inflammasome-dependent Mechanisms Involved in Sensing and Restriction of Bacterial Replication

Warrison A. Andrade and Dario S. Zamboni*

Department of Cell Biology, Ribeirão Preto Medical School, University of São Paulo (FMRP-USP), Ribeirão Preto, Brazil.

*Correspondence: dszamboni@fmrp.usp.br

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Abstract

Inflammasomes are multiprotein platforms assembled in the cytosol in response to pathogens and cell stress. Inflammasomes are recognized by their important role on defences against bacterial infections and have been also implicated in a range of human inflammatory disorders. Intracellular sensors such as NLRP1, NLRP3, NLRC4, AIM2 and Pyrin induce assembly of inflammasomes, while caspase-11 induces the non-canonical pathway for activation of the NLRP3 inflammasome. The formation of the inflammasome leads to caspase-1 activation that triggers pyroptosis and activation of interleukin 1β (IL-1β) and IL-18. Pyroptotic cell death and cytokines production are involved in restriction of bacterial replication by limiting the replication niche of intracellular bacteria and by inducing inflammatory responses. In this review we focus on the mechanisms mediated by inflammasome activation that leads to inflammatory responses and restriction of bacterial infection.

Introduction

Invading pathogens have been interacting with their hosts during evolution. Vertebrates from fish to mammals have selected several defence strategies to protect against invading bacteria, parasites and viruses. The first line of host defence is the innate immune system, which relies on the recognition of conserved pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs), by germline-encoded pattern-recognition receptors (PRRs) that survey the intracellular and extracellular spaces and initiate signalling cascades leading mainly to the induction of pro-inflammatory cytokines (Jack, 2015; Kawai and Akira, 2011).

PRRs are classified into five major families, including the Toll-like receptors (TLRs), retinoic acid-inducible (RIG-I)-like receptors (RLRs), absent of melanoma 2 (AIM2)-like

receptors (ALRs), C-type lectin receptors (CLRs) and nucleotide-binding domain (NBD), leucine-rich repeat (LRR)-containing receptor (NLRs). TLRs and CLRs are bound to the plasma membrane to survey the extracellular space, or to the endosomal compartment. RLRs, ALRs and NLRs are intracellular receptors located in the cytosol, where they sense the presence of intracellular pathogens or danger signals (Broz and Dixit, 2016; Kawai and Akira, 2011).

The activation of NLRs usually results in the formation of a large multimeric protein complex, named inflammasome by Tschopp and co-workers (Martinon *et al.*, 2002; Tschopp *et al.*, 2003). After the recognition of the inflammatory stimulus by the NLRs, including ligands from pathogens (DNA, RNA, flagellin, muramyl dipeptide) self-antigens (ATP, amyloid β, cholesterol crystals) or environmental stimulus (silica, asbestos, alum), it leads to the NLR self oligomerization allowing the binding to the adaptor apoptosis-associated speck-like protein containing a CARD (ASC). Nucleation of ASC allows the recruitment of pro-caspase-1, and through proximity-induced auto processing, results in caspase-1 activation and inflammasome formation. Active caspase-1 can cleave pro-interleukin 1β (IL-1β) and pro-IL-18 into the mature cytokines, and induce a specific inflammatory cell death called pyroptosis (Fig. 5.1) (Latz *et al.*, 2013; Man and Kanneganti, 2015).

Thus, inflammasome activation provides two different outcomes, the release of mature cytokines and the removal of infected cells by pyroptosis, important features of the innate immune system that are involved in restriction of pathogen replication. Mutations on the NLRs are associated to human inflammatory diseases including gout and periodic fever syndromes, which include cryopyrin-associated periodic fever syndromes (CAPS) and Familial Mediterranean fever (FMF), both characterized by IL-1β overproduction (Broz and Dixit, 2016; Hoffman *et al.*, 2001; Rigante *et al.*, 2016).

NLR family members are characterized by a central NOD domain, a C-terminal leucine-rich domain (LRRs) and a N-terminal effector domain. The C-terminal domain is involved on the recognition of the ligand and sensing of the stimulus, while the N-terminal domain is involved on the interaction with other proteins from the complex (Sharma and Kanneganti, 2016). The NLR family members are grouped into two categories, NLRC and NLRP, depending on whether the N-terminal domain contains caspase activation and recruitment domain (CARD) or a pyrin domain, respectively. NLRP1, NLRP3, and NLRC4 are well studied NLRs that assemble the canonical inflammasomes, and several reports characterized their function on pathogen and stress recognition, which leads to cytokine production and pyroptosis. Caspase-11 was also demonstrated to play an important role on the secretion of mature IL-1β and pyroptosis induced by Gram-negative bacteria, forming the non-canonical inflammasome (Fig. 5.1) (de Vasconcelos *et al.*, 2016; Kayagaki *et al.*, 2011; Sharma and Kanneganti, 2016). In this review we provide an overview of inflammasome activation and mechanisms used by the host to control bacterial replication.

Canonical and non-canonical inflammasomes

NLRP1 inflammasome

NLRP1 was the first NLR described to its capacity to form a platform able to activate caspase-1 (Martinon *et al.*, 2002). The human proteome harbours only one NLRP1 that was described to be involved in Vitiligo, autoimmune Addison's disease, type I diabetes,

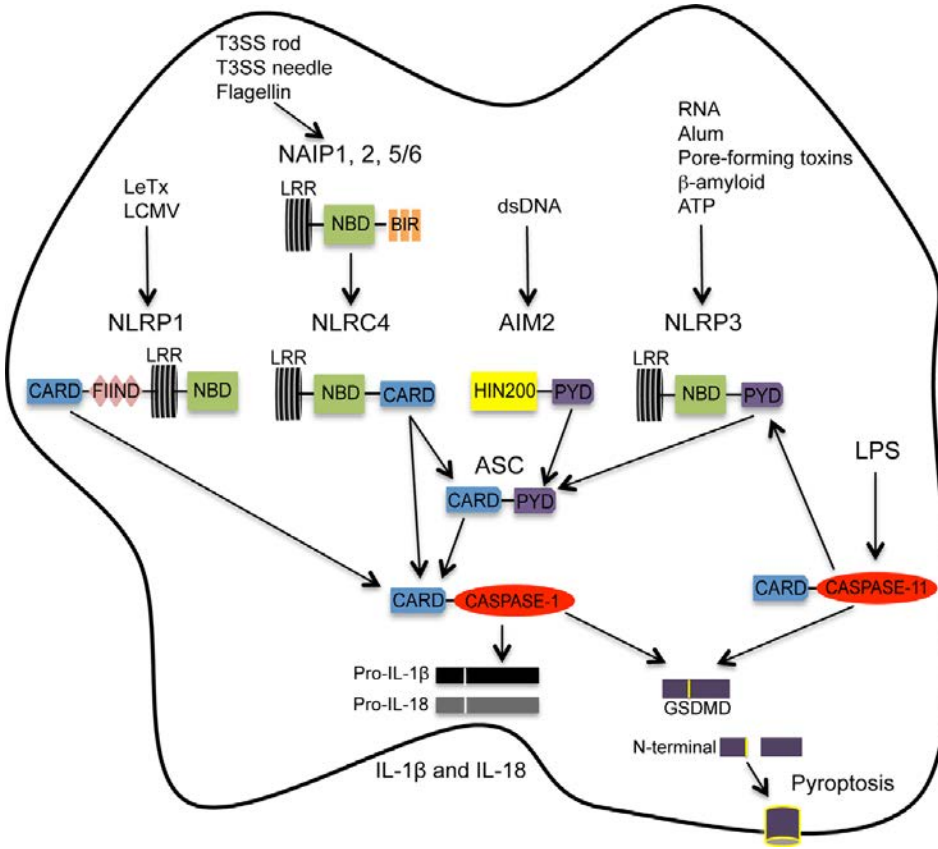

Figure 5.1 Inflammasome components and caspase-1 activation by canonical and non-canonical pathways. NOD-like receptors (NLRs) (NLRP1, NLRP3 and NLRC4) and AIM2-like receptors (ALRs) (AIM2) are depicted with individual domains and activate the canonical inflammasome pathway by sensing several intracellular bacterial ligands and cell stress. Caspase-11 directly senses LPS and activates NLRP3/caspase-1 through the non-cannonical inflammasome pathway. Activation of both canonical and non-cannonical pathways induce the secretion of mature IL-1β and IL-18, and pyroptosis by cleaving gasdermin D (GSDMD) leading to pore formation and cell death. For CARD-containing inflammasomes, pyroptosis and cytokine secretion occurs independently and dependently of ASC, respectively. Cytokine secretion by NLRP1 does not require ASC. CARD, caspase recruitment domain; NBD, nucleotide binding domain; PYD, pyrin domain; LRR, leucine-rich repeat domain; FIIND- function to find domain; HIN-HIN200 domain; BIR, baculovirus inhibitor of apoptosis protein repeat.

multiple self-healing palmoplantar carcinoma and familial keratosis lichenoides chronica (Jin *et al.*, 2007; Magitta *et al.*, 2009; Zhong *et al.*, 2016). On the other hand, mouse genome encodes three paralogues, NLRP1a, NLRP1b and NLRP1c. Human NLRP1 contains an amino terminal PYD, a NOD and LRR domains, a function-to-find and also a C-terminal CARD domain, whereas all murine NALP1 lack the PYD (Hiller *et al.*, 2003; Martinon *et al.*, 2001; Tschopp *et al.*, 2003).

Different studies have shown that NLRP1a and NLRP1b can form a functional inflammasome that activate caspase-1. NLRP1a is activated in progenitor cells infected by

lymphocytic choriomeningitis virus (LCMV), and a mutation in the NLRP1a gene leads to a systemic inflammatory disease mediated by caspase-1 and IL-1β (Masters *et al*., 2012). NLRP1b is activated by anthrax lethal toxin (LeTx) produced by *Bacillus anthrax*. LeTx consists of a protective antigen that generates pore in the membrane and lethal factor that enters the cell and cleave NLRP1b at the N-terminal site (Boyden and Dietrich, 2006; Chavarría-Smith and Vance, 2013). Macrophages from NLRP1b deficient mice are defective in caspase-1 activation, IL-1β secretion and pyroptosis in response to LeTx (Kovarova *et al*., 2012), thus NLRP1b inflammasome is important to control *B. anthrax* infection in mice (Moayeri *et al*., 2010). Interesting, NLRP1b is also involved in the control and protection against *Toxoplasma gondii* infection, although NLRP1b cleavage is not required (Ewald *et al*., 2014; Gorfu *et al*., 2014; Zamboni and Lima-Junior, 2015).

NLRP3 inflammasome

NLRP3 (cryopyrin) was first shown to be associated with autoinflammatory syndromes called CAPS, including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS), and also in gout, diabetes and atherosclerosis (Duewell *et al*., 2010; Guo *et al*., 2015; Hoffman *et al*., 2001). NLRP3 is now implicated in the pathogenesis of several neuroinflammatory diseases, including Alzheimer's, Parkinson's and Prion diseases (Guo *et al*., 2015; Heneka *et al*., 2013; Shi *et al*., 2015a).

NLRP3 respond to a wide range of stimulus, including ligand derived from pathogens (microbial cell-wall components, RNA, DNA and pore-forming toxins), environmental ligands (silica, asbestos and alum) and endogenous danger signals (ATP, β-amyloid and uric acid crystals) (Latz *et al*., 2013; Man and Kanneganti, 2015). The lack of similarity between the diversity of stimulus, raise the possibility that NLRP3 senses an endogenous signal that is triggered after the cell gets in contact with the stimulus. In fact, several mechanisms have being proposed to be involved in NLRP3 activation. For example, the production of reactive oxygen species (ROS), oxidized mitochondrial DNA, potassium efflux, lysosomal release of cathepsins, changing in intracellular calcium levels (Cassel *et al*., 2008; Cruz *et al*., 2007; Hornung *et al*., 2008; Lee *et al*., 2012; Misawa *et al*., 2013; Muñoz-Planillo *et al*., 2013; Shimada *et al*., 2012; Zhou *et al*., 2010), but no unifying mechanism was identified. There are some evidences from several groups that potassium efflux is a common mechanism for NLRP3 activation, but it was also demonstrated to be involved in NLRP1b activation (Munñoz-Planillo *et al*., 2013; Pétrilli *et al*., 2007); thus this is not specific for NLRP3 activation. Despite this controversy, it is clear that NLRP3 activation requires two signals; the first stimulus is an NF-κB activator that is responsible for pro-IL1β expression and NLRP3 induction (Bauernfeind *et al*., 2009), and a second stimulus that induces NLRP3 inflammasome assembly (Latz *et al*., 2013). NLRP3 deubiquitination mediated by the k63-specific deubiquitinase BRCC3 is also required for NLRP3 assembly and activation (Juliana *et al*., 2012; Lopez-Castejon *et al*., 2013; Py *et al*., 2013). Recently, a new report about NLRP3 in human monocytes is challenge the dogma for NLRP3 activation. Gaidt and co-workers identified a new alternative NLRP3 inflammasome activation pathway. LPS alone activates caspase-1 and induces IL-1β production through a TLR4/TRIF/RIP1/FADD/caspase-8-dependent pathway. This inflammasome activation leads to IL-1β secretion but no pyropstosis, and is independent of potassium efflux (Gaidt *et al*., 2016). New insights into NLRP3 activation came from reports demonstrating an important role for NIMA-related kinase 7 (NEK7), a protein involved in cell-cycle progression, in NLRP3 activation. NEK7

interacts with the LRR domain of NLRP3 and it is important to its oligomerization and activation (He *et al.*, 2016; Schmid-Burgk *et al.*, 2016; Shi *et al.*, 2016). Under resting conditions, NLRP3 is localized at the endoplasmic reticulum (ER), and ASC is found in the nucleus, cytosol and mitochondria. Due to this different spatial localization, protein translocation is necessary for inflammasome assembly, and this is mediated by dynein that transports the mitochondria to the ER, bringing ASC and NLRP3 to the same location, demonstrating also a role for microtubules on the activation (Misawa *et al.*, 2013).

Due to the wide diversity of stimulus able to activate NLRP3, this is the best-studied inflammasome, and its role was described in a variety of infections and inflammatory diseases, but a lot of important information about NLRP3 activation and inhibition are still unclear.

NLRP12 inflammasome

Wang and co-workers described NLRP12 as a protein that could function as an inflammasome component (Wang *et al.*, 2002). It was first demonstrated that NLPR12 would act as NFκB signalling inhibitor (Williams *et al.*, 2005), and other studies suggested a role for NLRP12 as a negative regulator of colon inflammation and tumorigenesis in a DSS colitis model (Allen *et al.*, 2012; Zaki *et al.*, 2011). On the other hand, a pro-inflammatory role for NLRP12 was described on *Plasmodium* and *Yersinia pestis* infection, having an important role in IL-1β and IL-18 production and infection control (Ataide *et al.*, 2014; Vladimer *et al.*, 2012).

It is possible that NLRP12 can play a different role depending on the ligand source or on the cell type involved, but further studies are required to fully understand the mechanism of NLRP12 activation and signalling.

AIM2 inflammasome

The presence of DNA from pathogens or host into the cytosol is a danger signal sensed by the cell. It was observed that the presence of intracellular DNA induced caspase-1 activation in a ASC-dependent manner (Muruve *et al.*, 2008). The absent in melanoma 2 (AIM2) assembles a well-characterized inflammasome involved in the recognition of cytosolic double-stranded DNA (dsDNA) (Bürckstuümmer *et al.*, 2009; Fernandes-Alnemri *et al.*, 2009; Hornung *et al.*, 2009). AIM2 features a N-terminal PYD domain able to interact with the PYD of ASC and a C-terminal HIN domain involved in ligand binding and dsDNA recognition, that is sequence independent but requires about 80 pb length (Hornung *et al.*, 2009; Jin *et al.*, 2012; Roberts *et al.*, 2009).

AIM2 is involved in the recognition and host defence against several DNA viruses and bacteria, and its activation is important to infection control (Fernandes-Alnemri *et al.*, 2010; Jones *et al.*, 2010; Kim *et al.*, 2010; Rathinam *et al.*, 2010; Sauer *et al.*, 2010). It was suggested that AIM2 could be involved in some human autoimmune disorders, and increased AIM2 expression is associated with systemic lupus erythematosus, psoriasis and abdominal aortic aneurysm (Dihlmann *et al.*, 2014; Dombrowski *et al.*, 2011; Javierre *et al.*, 2010; Zhang *et al.*, 2013).

Pyrin

Pyrin was the latest PRR described as capable to assemble a canonical inflammasome. Pyrin was first described as an inflammasome involved in a mouse model of familial Mediterranean

fever (FMF), an autoinflammatory disorder mediated by ASC and IL-1β (Chae *et al.*, 2011). Mutations in the C-terminal domain B30.2 from human pyrin are linked to FMF, and are associated to high levels of caspase-1 activation and IL-1β release (Chae *et al.*, 2011; Hesker *et al.*, 2012).

It was recently shown the definitive role of pyrin as an inflammasome platform. It was demonstrated that bacterial toxins produced by various species trigger pyrin inflammasome activation in response to Rho-GTPase modifications (Gavrilin *et al.*, 2012; Xu *et al.*, 2014).

NLRC4 inflammasome

NLRC4 contains a CARD domain on the N-terminal portion that mediates caspase-1 activation via CARD–CARD domain interaction. This probably explains why ASC is dispensable for pyroptosis induction by NLRC4. On the other hand, cytokine maturation and secretion by the NLRC4 inflammasome is dependent on ASC (Broz *et al.*, 2010b; Mariathasan *et al.*, 2004; Miao *et al.*, 2010a; Poyet *et al.*, 2001).

A number of bacteria induce caspase-1 activation via NLRC4 (Brodsky *et al.*, 2010; Miao *et al.*, 2008; Miao *et al.*, 2010b; Ren *et al.*, 2006; Zamboni *et al.*, 2006; Zhao *et al.*, 2011). NLRC4 is activated by three different bacterial components that enter the cytosol; flagellin, the monomeric subunit from bacteria flagellum (Franchi *et al.*, 2006; Mariathasan *et al.*, 2004; Miao *et al.*, 2006; Molofsky *et al.*, 2006); type III secretion (T3SS) rod proteins and T3SS needle proteins (Miao *et al.*, 2010b; Yang *et al.*, 2013a; Zhao *et al.*, 2011). Activation of NLRC4 is not direct mediated by the ligand; instead, a family of proteins called NAIPs (NLR family apoptosis inhibitory proteins) binds to the ligand and mediate NLRC4 activation (Cunha and Zamboni, 2013).

The NAIP family encodes seven NAIPs in mice, but only one NAIP in humans (Endrizzi *et al.*, 2000). Murine NAIP1 binds to the needle component of T3SS (Rayamajhi *et al.*, 2013; Yang *et al.*, 2013a), NAIP2 binds to the T3SS rod protein (Kofoed and Vance, 2011; Zhao *et al.*, 2011), flagellin binds to NAIP5 and NAIP6 and induces NLRC4 oligomerization (Ren *et al.*, 2006). The homologue human NAIP can sense the needle subunit of the T3SS (Yang *et al.*, 2013a), and the role of human NAIP in flagellin recognition is controversial (Kortmann *et al.*, 2015; Zhao *et al.*, 2011). However, a recent report elegantly demonstrated that a specific isoform of the human NAIP senses flagellin and trigger responses against flagellated intracellular bacteria (Kortmann *et al.*, 2015). Phosphorylation of NLRC4 on the Ser^{533} was also described to be important for NLRC4 activation (Qu *et al.*, 2012). NLRC4 is kept in an inactive state on the cytosol, and contains a winged-helix domain that stabilizes the protein in a closed conformation. A substantial reorganization is required for oligomerization and NLRC4 activation (Hu *et al.*, 2013; Hu *et al.*, 2015; Tenthorey *et al.*, 2014; Zhang *et al.*, 2015). Upon flagellin binding, NAIP5 recruits 11/12 NLRC4 molecules and forms a disk-like structure with a diameter of 28 nm. A rotation of the LRR domain is required for NAIP5/NLRC4 structure assembly (Diebolder *et al.*, 2015; Halff *et al.*, 2012).

Human genetic studies have shown gain-of-functions mutations on NLRC4 associated to autoinflammation (Canna *et al.*, 2014). One striking report showed that activation of NLRC4 inflammasome by intraperitoneal injection of flagellin induces high mortality independent of IL-1β and IL-18. The death was caused by the production of eicosanoids, including prostaglandins and leukotrienes, that led to a rapid vascular fluid loss (von Moltke *et al.*, 2012).

Caspase-11 and the non-canonical pathway for activation of the NLRP3 inflammasome

Caspase-11, an orthologue of human caspases-4 and caspase-5, was described as a binding partner and mediator of caspase-1 activation in a model of endotoxic shock by LPS (Wang *et al.*, 1998). The role of caspase-11 was masked in the mouse models used for years due to the lack of a functional caspase-11 on the strains engineered for caspase-1 deficiency (Kayagaki *et al.*, 2011). Recently, it was demonstrated that mouse caspase-11 is involved in a caspase-1-independent cell death in response to Gram-negative bacteria infection (Broz *et al.*, 2012; Case *et al.*, 2013; Hagar *et al.*, 2013; Rathinam *et al.*, 2012), but not Gram-positive bacteria (Rathinam *et al.*, 2012). Caspase-11 plays a dual role, acting as a sensor, by direct binding to LPS, and a pyroptosis inducer mediated by LPS (Kayagaki *et al.*, 2011; Shi *et al.*, 2014). Once caspase-11 activation is mediated by intracellular LPS, extracellular LPS present in Gram-negative bacteria need to gain access to the cytosol to activate caspase-11. Outer membrane vesicles (OMV) carry LPS to the cytosol by clathrin-mediated endocytosis, and LPS gains access to the cytosol from early endosomes (Vanaja *et al.*, 2016). Interestingly, LPS-mediated septic shock, first described to be TLR4 dependent, was demonstrated to be dependent on caspase-11. TLR4 was required only for type I interferon production that drives caspase-11 induction (Hagar *et al.*, 2013; Kayagaki *et al.*, 2011; Kayagaki *et al.*, 2013; Rathinam *et al.*, 2012; Shi *et al.*, 2014).

Pyroptosis induced via caspase-11 by Gram-negative bacteria is independent of ASC and NLRP3, whereas cytokine processing depends on both ASC and NLRP3 (Hagar *et al.*, 2013; Kayagaki *et al.*, 2011; Shi *et al.*, 2014). Until recently it was not known how activation of caspase-1 and caspase-11 lead to cell death. Three different groups identified gasdermin (GSDMD) as the link between caspase activation and cell death (He *et al.*, 2015; Kayagaki *et al.*, 2015; Shi *et al.*, 2015b). The inflammatory caspases 1, 4, 5 and 11 cleave GSDMD on the same site, and the N-terminal portion is required and sufficient to induce pyroptosis (Kayagaki *et al.*, 2015; Shi *et al.*, 2015b). Now, it was demonstrated that the GSDMD N-terminal portion binds to phosphatidylinositol phosphates, phosphatidylserine and cardiolipin present on the plasma membrane forming the pore and inducing pyroptosis (Aglietti *et al.*, 2016; Ding *et al.*, 2016; Liu *et al.*, 2016).

The mechanism by which caspase-11 induces NLRP3 activation is not described, and the lack of caspase-11 does not affect the canonical activation of NLRP3. Once NLRP3 inflammasome assembly is not fully understood, there are different hypotheses trying to explain how caspase-11 leads to NLRP3 activation. For example, caspase-11 activation leads to potassium efflux and drop in the intracellular levels, that could be responsible for NLRP3 activation (Rühl and Broz, 2015). Yang and collaborators showed that pannexin-1 channel is also cleaved by caspase-11, leading to ATP release and P2X7 activation, that ultimately leads to intracellular potassium levels drop and NLRP3 activation (Yang *et al.*, 2015). Another hypothesis that now can be postulated is the induction of pyroptosis and NLRP3 activation through the GSDMD pores, by which potassium could freely move to the extracellular space and induce NLRP3 activation. New studies will be required to confirm the link between caspase-11, intracellular potassium levels and NLRP3 activation.

Inflammasome activation during bacterial infections

Legionella

Legionella pneumophila is a Gram-negative intracellular bacterium that can be found in freshwater and soil, where they normally infect unicellular protozoa including several amoebae species (Newton *et al.*, 2010). *L. pneumophila* infection occurs by the inhalation of contaminated water and is normally controlled by the innate immune response, but if not controlled in the early stages have the potential to cause a form of pneumonia known as Legionnaires' disease (Parr *et al.*, 2015; Sabrià and Campins, 2003). In the lung, *L. pneumophila* initially infects alveolar macrophages using a type IV secretion system (T4SS), termed Dot/Icm, to inject bacterial proteins into the cytosol (Copenhaver *et al.*, 2014; Finsel and Hilbi, 2015; Hubber and Roy, 2010). These effectors block phagosomal maturation and fusion with lysosomes, thus preventing *L. pneumophila* degradation, and promoting the establishment of a *Legionella*-containing vacuole (LCV), a favourable niche for *Legionella* replication.

It was extensively demonstrated that *L. pneumophila* strongly activates different inflammasomes, including the canonical NLRC4 and NLRP3 (Case and Roy, 2011; Cerqueira *et al.*, 2015; Pereira *et al.*, 2011a; Pereira *et al.*, 2011b; Silveira and Zamboni, 2010) and non-canonical inflammasomes (Aachoui *et al.*, 2013; Akhter *et al.*, 2012; Case *et al.*, 2013; Casson *et al.*, 2013). *L. pneumophila* flagellin secretion is dependent on the Dot/Icm system that along with the effector proteins is secreted into the host cell cytosol. Flagellin recognition is mediated by NAIP5/NLRC4, which activates caspase-1 and triggers pyroptosis and IL-1β secretion in an ASC-independent and ASC-dependent manner, respectively (Amer *et al.*, 2006; Broz *et al.*, 2010b; Case *et al.*, 2009; Jamilloux *et al.*, 2013; Molofsky *et al.*, 2006). The recognition of flagellin and activation of NAIP5/NLRC4/caspase-1 is the main mechanism responsible for the control of *Legionella* infection both *in vivo* and *in vitro* (Coers *et al.*, 2007; Molofsky *et al.*, 2006; Pereira *et al.*, 2011b; Ren *et al.*, 2006). Caspase-7 also plays a role in restriction of *L. pneumophila* replication in murine macrophages. Caspase-7 activation downstream of NLRC4 was required for caspase-1 activation, and cells deficient for caspase-7 have an increased bacterial replication (Akhter *et al.*, 2009).

L. pneumophila deficient for the flagellin, encoded by the gene *flaA*, bypass NLRC4 inflammasome activation and replicates in macrophages (Molofsky *et al.*, 2006; Ren *et al.*, 2006). The use of the bacteria mutant for *flaA*, enabled the identification of NAIP5/NLRC4-independent pathways that are also involved in control of bacterial replication. Caspase-11 is activated by *L. pneumophila* and leads to pyroptosis independent of flagellin, but dependent on Dot/Icm (Case *et al.*, 2013), which is mediated by the release of LPS into the cytosol triggering caspase-11 activation (Kayagaki *et al.*, 2011; Shi *et al.*, 2014). Activation of caspase-11 leads to NLRP3/ASC/Caspase-1 activation and IL-1β secretion.

Activation of NAIP5/NLRC4 by flagellin induces caspase-1 activation. On this platform ASC is not present, and caspase-1 is present in an active state, but not cleaved. The dogma was that caspase-1 autoprocessing was required for its activity, but it was demonstrated that during the induction of pyroptosis by NAIP5/NLRC4/caspase-1, caspase-1 is not processed into the p10 and p20 forms (Broz *et al.*, 2010b). But ASC is required for IL-1β processing and cleavage of caspase-1. Until recently, the mechanism behind the control of *Legionella* replication was unknown. Miao and co-works demonstrated that in the case of *L. pneumophila*, caspase-1-induced pyroptosis, but not IL-1β and IL-18, is the main mechanism for restriction of bacterial replication, releasing bacteria to the extracellular space to

be killed by neutrophils. Infection of IL-1/IL-18 double deficient mice did not recapitulate the phenotype from caspase-1 deficient mice, which was also observed for *Burkholderia thailandensis* (Miao *et al*., 2010a).

L. pneumophila evolved in direct contact with unicellular protozoans and probably encountered almost no pressure to evade the recognition by the innate immune system, including inflammasome activation (Massis and Zamboni, 2011). Strains lacking SdhA are defective for intracellular replication and activate host cell death (Laguna *et al*., 2006). The effector protein SdhA is responsible for maintaining the LCV architecture, and mutants lacking SdhA are unable to control vacuole integrity, leading to vacuole rupture and bacteria release to the cytosol, triggering host responses (Creasey and Isberg, 2012). *L. pneumophila* SdhA deficient is detected by caspase-11 (Aachoui *et al*., 2013), and also by AIM2 through the detection of cytoplasmic bacteria DNA and induction of pyroptosis and IL-1β (Ge *et al*., 2012).

After uptake, *L. pneumophila* creates the LCV that allows bacteria replication and survival. Through the T4SS, the bacteria secrete more than 300 effector proteins that are important to manipulate the host response, including delaying phagosome maturation (Hubber and Roy, 2010; Isberg *et al*., 2009; Kagan and Roy, 2002). Rab proteins are involved in vesicular trafficking and phagosome maturation, and are regular target of intracellular pathogens to avoid phagosome acidification (Bhuin and Roy, 2014; Fratti *et al*., 2003; Stein *et al*., 2012; Via *et al*., 1997). It was demonstrated that Rab1 is involved in phagosome acidification by *L. pneumophila;* Rab1 recruitment to the LCV avoids phagosome acidification and bacterial killing (Connor *et al*., 2015). ER stress is a common response to infection by intracellular bacteria, and activation or inhibition of unfolded protein response (UPR) is used by pathogens to manipulate host defence (Lee *et al*., 2008; Zhang and Kaufman, 2008). Recently two groups demonstrated that *L. pneumophila* manipulate UPR response by inhibiting the expression of immunoglobulin binding protein (BiP) and C/EBP homologous transcription factor protein (CHOP), and also by the inhibition of X-box binding protein 1 (XBP1) splicing, controlling host protein translation (Hempstead and Isberg, 2015; Treacy-Abarca and Mukherjee, 2015). While *L. pneumophila* triggers ER stress, inhibition of UPR responses may allow bacteria survival by limiting immune response and apoptosis.

Salmonella

Salmonella belongs to the Enterobacteriaceae family of Gram-negative bacteria, which consists of a large group with the ability to infect animal hosts (Baker and Dougan, 2007; Costa *et al*., 2012). A prime example of an infectious agent is the pathogen *Salmonella enterica*, a facultative intracellular bacterium that is responsible for an estimated 90 million cases of human gastroenteritis (Majowicz *et al*., 2010). The majority of clinical disease in animals and humans is caused by serovars within the *Salmonella enterica* subspecies and this can range from local gastroenteritis to a fatal disseminated disease. After oral ingestion, *Salmonella* invade intestinal epithelial cells in the distal ileum. *Salmonella* usually interacts first with epithelial cells, which can recognize pathogenic bacteria and initiate an inflammatory response (Jones *et al*., 1994; Tam *et al*., 2008).

Salmonella Typhimurium have two distinct pathogenic islands, SPI-1 and SPI-2 T3SS, which are expressed on different phase of the infection. During epithelial cells invasion, *Salmonella* utilizes the SPI-1 to invade cells. After invasion, bacteria reside in the *Salmonella*-containing vacuole (SCV) and expresses SPI-2 inside epithelial cells and macrophages,

altering the vacuolar membrane and limiting lysosomal fusion (Drecktrah *et al.*, 2007; Figueira and Holden, 2012; Ibarra and Steele-Mortimer, 2009). The initial immune response to *Salmonella* involves the recruitment of neutrophils and monocytes, and TLRs and NLRs play a pivotal role (Broz *et al.*, 2010a; Hayashi *et al.*, 2001; Rydström and Wick, 2007; Sivick *et al.*, 2014). TLR4 and TLR5 play a role in the recognition of *Salmonella* by sensing LPS and flagellin, respectively (Feuillet *et al.*, 2006), and TLRs involved in the recognition of nucleic acids are also involved in *Salmonella* infection control (Sivick *et al.*, 2014). *Salmonella* is detected by NLRP3 and NLRC4, and activation of both NLRs is associated with host protection (Broz *et al.*, 2010a).

NLRP3 activation under *Salmonella* infection occurs on late time points, and the mechanism of activation is unknown. Activation of NLRP3 by some bacteria is dependent on T3SS (Brodsky *et al.*, 2010), but in *Salmonella* infection NLRP3 activation is independent of SPI-1 and SPI-2 T3SS (Broz *et al.*, 2010a). In a model of *Salmonella* infection, NLRP3 and ASC play a role in cytokine maturation, but bacterial counts and inflammation were not affected on the absence of NLRP3 and ASC (De Jong *et al.*, 2014).

NLRC4 is activated by the recognition of flagellin or T3SS and T4SS proteins from a variety of bacteria (Amer *et al.*, 2006; Franchi *et al.*, 2006; Miao *et al.*, 2006; Suzuki *et al.*, 2014; Zhao *et al.*, 2011). Macrophages can detect *Salmonella* flagellin and rod protein PrgJ translocated to the cytosol by SPI-1. *Salmonella* flagellin is recognized by NAIP5 and NAIP6, while PrgJ is sensed by NAIP2 (Kofoed and Vance, 2011; Zhao *et al.*, 2011). A mechanism of exclusion of *Salmonella*-infected enterocytes is used by the host to remove infected cells, expulsing them to the lumen. This response depends on NAIPs, NLRC4 and caspase1/11, but is independent of IL-1β and IL-18 (Sellin *et al.*, 2014). *Salmonella* is also detected by caspase-11, assembling the non-canonical inflammasome. SifA is a SPI-2 effector that is vital for SCV stabilization (Cirillo *et al.*, 1998). A *Salmonella* SifA mutant strongly induces pyroptosis dependent on caspase-11, but independent of NLRP3 and NLRC4 (Aachoui *et al.*, 2013). Caspase-11 recognizes *Salmonella* after it escapes from the SCV to the cytosol, but it can also detect when the vacuole is compromised (Broz *et al.*, 2012; Rathinam *et al.*, 2012). GBP2 expression induced by type I interferon and SCV destabilization mediated by GBP2 are required for caspase-11 activation in *Salmonella* infection (Meunier *et al.*, 2014). Caspase-11 and its human orthologue caspase-4 were also involved on the control of *S.* Typhimurium in intestinal epithelial cells by IL-18 secretion and cell death (Knodler *et al.*, 2014). Recently, a new report showed that growth of cytosolic *Salmonella* in a subpopulation of host cells is inhibited prior to pyroptosis, and requires caspase-1 and caspase-11 enzymatic activity (Thurston *et al.*, 2016). Macrophages are the major cell involved in *Salmonella* recognition and inflammasome activation, but neutrophils also play an important role. During acute *S.* Typhimurium infection, neutrophils are the main source of IL-1β, and different from macrophages, neutrophils do not undergo pyroptosis, sustaining IL-1β production on the site of infection (Chen *et al.*, 2014). On the other hand, NLRP6 and NLRP12 were also described in *Salmonella* infection, but in an opposite way. Mice deficient for NLRP6 and NLRP12 have a decreased bacterial burden and produce elevated levels of IL-6 and TNF-α, (Anand *et al.*, 2012; Zaki *et al.*, 2014). The mechanism of NLRP6 and NLRP12 activation by *Salmonella* still needs to be determined.

Caspase-1-deficient mice are highly susceptible to *S.* Typhimurium infection (Lara-Tejero *et al.*, 2006; Raupach *et al.*, 2006), and mice double deficient for NLRP3 and NLRC4 recapitulate this phenotype (Broz *et al.*, 2010a). However, IL-1β deficient mice have a mild

phenotype. *Salmonella* control is largely mediated by IL-18, once IL-18 deficient mice are as susceptible as caspase-1 deficient mice (Raupach *et al.*, 2006). IL-18 is important to induce IFN-γ production by NK cells and T lymphocytes, a cytokine extremely important in the control of *Salmonella* infection (Eckmann and Kagnoff, 2001; Kupz *et al.*, 2014). A *S.* Typhimurium engineered to continuously express flagellin induces pyroptosis mediated by NLRC4 and caspase-1, and bacteria control was mediated by pyroptosis, removing the replicative niche and allowing extracellular bacteria to be killed by neutrophils. However, IL-18 and IL-1β did not play an important role in the control of this modified strain (Miao *et al.*, 2010a). Thus, IL-18 plays an important role in the control of WT *S.* Typhimurium, but in the case of a bacteria persistently expressing flagellin, pyroptosis is the main mechanism involved in the control. This discrepancy maybe is explained by the strong NLRC4 activation by this modified strain that leads to pyroptosis and bacteria killing by neutrophils. On the other hand, wild-type *S.* Typhimurium evades NLRC4 recognition by inhibiting flagellin expression and modifying T3SS rod protein (Miao *et al.*, 2010a; Miao and Rajan, 2011). Recently, another study from Ed Miao's group demonstrated that pore formation induced by *S.* Typhimurium infected cells leads to pyroptosis that traps live bacteria inside pyroptotic cell corpses, which ultimately are phagocytosed by neutrophils by efferocytose and killed via ROS. On this model, neutrophil recruitment to pyroptotic macrophages is dependent on IL-1β, IL-18 and eicosanoids (Jorgensen *et al.*, 2016a; Jorgensen *et al.*, 2016b).

As bona fide mammalian pathogen, *Salmonella* have developed strategies to dampen inflammasome activation and persist on the host. For example, it was identified two enzymes, aconitase and isocitrate dehydrogenase, involved on the bacterial tricarboxylic acid cycle. Mutations on these genes led to high intracellular citrate and elevated mitochondrial ROS, resulting in NLRP3 activation (Wynosky-Dolfi *et al.*, 2014). *Salmonella* also evades NLRC4 recognition by inhibiting flagellin expression in the intracellular environment when SPI-2 T3SS is active. *Salmonella* also expresses a T3SS rod protein termed Ssa1 that evades NAIP2 binding (Miao *et al.*, 2010b). Modifications on several amino acids on the Ssa1 protein inhibit NAIP2 recognition and NLRC4 activation (Jorgensen and Miao, 2015).

Francisella

Francisella tularensis is a Gram-negative intracellular bacterium and the causative agent tularemia, a life-threatening infectious disease of the respiratory tract. Depending on the route of infection, various organs and tissues can be colonized by *F. tularensis*, including lungs, liver, skin, and spleen (Carvalho *et al.*, 2014). Phagocytosis of *Francisella* by macrophages has been extensively studied and involves the engagement of different phagocytic receptors. Following uptake, *Francisella* resides within an initial vacuolar compartment on the endocytic pathway that would normally change to a bactericidal phagolysosome (Chong *et al.*, 2008; Clemens *et al.*, 2004, 2005; Santic *et al.*, 2006). However, *F. tularensis* escapes from the phagosome to the cytosol, and in contrast to other intracellular bacteria, it does not depend on T3SS or T4SS for virulence and secretion of effector proteins (Larsson *et al.*, 2005).

The role of inflammasome in the recognition and control of *F. novicida* in mouse infection was initially demonstrated by Denise Monack's group. Recognition of *F. novicida* in the cytosol induces a host response dependent on ASC and caspase-1, and is required for bacterial control and resistance to infection (Mariathasan *et al.*, 2005). Later on, three different groups reported the AIM2 inflammasome as responsible for *F. tularensis and F.*

novicida recognition and inflammasome activation *in vitro* and *in vivo*. AIM2 is involved on the recognition of *Francisella* DNA and is required for ASC oligomerization, caspase-1 activation, IL-1β maturation and cell death (Fernandes-Alnemri *et al*., 2010; Jones *et al*., 2010; Rathinam *et al*., 2010). On the other hand, NLRP3 is dispensable for inflammasome activation by *F. novicida* (Fernandes-Alnemri *et al*., 2010).

It was previously reported a role for type I Interferon in AIM2 activation by *F. novicida*. Macrophages knockout for type I IFN receptor or IRF3 are defective in caspase-1 activation, IL-1β and IL-18 secretion during *F. novicida* infection (Henry *et al*., 2007). These data were confirmed by other results demonstrating that mice deficient for the DNA sensor cGAS and the adaptor STING are defective in both IFN-β and IL-1β production (Jones *et al*., 2010; Storek *et al*., 2015). Until recently, the mechanism by which type I IFN controls AIM2 inflammasome activation by *Francisella* was not described. Once bacterial DNA needs to be released to activate AIM2, and type I IFN is not required for AIM2 activation by synthetic dsDNA, it was proposed that type I IFN would be involved in bacteriolysis and DNA release. It was also reported that the IFN-inducible transcription factor IRF1 is involved in AIM2 activation by *F. novicida* downstream of IFN-β (Man *et al*., 2015). IRF1 is required for the induction of guanylate-binding proteins Gbp2 and Gbp5, which are involved in intracellular bacteria killing and DNA release. Gbp2 and Gbp5 knockdown reduced AIM2 inflammasome activation by *F. novicida* infection (Man *et al*., 2015; Meunier *et al*., 2015). Recently, Man and collaborators identified IRGB10, together with GBPs, as essential for the disruption of *F. novicida* membrane, DNA release and AIM2 recognition. IRGB10 also plays a partial role on the activation of the non-canonical inflammasome by *Escherichia coli* and *Citrobacter rodentium*, supposedly by making LPS more available for caspase-11 recognition (Man *et al*., 2016). On the other hand, *in vivo* infection by *F. novicida*, type I IFN has a detrimental role (Henry *et al*., 2010), and IFN-γ is important for Gbps induction and infection control (Pierini *et al*., 2013).

Cytosolic localization of *F. novicida* is also required for IL-1β release by human monocytes (Gavrilin *et al*., 2006), and heat-killed bacteria is unable to induce IL-1β maturation (Li *et al*., 2006). Several groups have described that AIM2, but not NLRP3, plays a role in *F. novicida* infection in murine cells. However, in human cells, both NLRP3 and AIM2 are involved in *F. novicida* recognition and IL-1β induction, once knockdown of NLRP3 or AIM2 reduces IL-1β secretion by THP-1 cells (Atianand *et al*., 2011). NLRP3 also forms a speck with ASC in 293T cells infected by *F. novicida* (Bedoya *et al*., 2007), but how the bacteria triggers NLRP3 activation is unknown.

Both caspase-1 activation, and IL-1β and IL-18 cytokines are involved in the control of *Francisella* infection. IL-18 is important for IFN-γ production by NK cells, which is essential for bacterial control. IL-18 deficient mice are susceptible to *F. tularensis* infection, but the treatment with recombinant IFN-γ rescues the phenotype. The same group also demonstrated that IL-1β is important for anti-LPS IgM production that increases opsonization and bacterial killing (del Barrio *et al*., 2015). A nice set of experiments using mice deficient for caspase-1 and for both IL-1β and IL-18, showed a role for both cytokines and caspase-1 in the control of *F. novicida* infection. Mice double deficient for IL-1β and IL-18 have an intermediate phenotype when compared to WT and caspase-1 deficient (Henry and Monack, 2007). Similar results were reported for *S.* Typhimurium, *L. pneumophila* and *B. thailandensis* (Miao *et al*., 2010a).

Bacteria from the genus *Francisella* express a modified LPS that does not engage TLR4 activation (Hajjar *et al.*, 2006). Despite the induction of caspase-11 by *F. novicida* (Akhter *et al.*, 2012), the bacterium is not able to activate caspase-11 mostly due to its tetra-acylated lipid A, evading the non-canonical inflammasome activation (Hagar *et al.*, 2013). Mutations in the gene FTL_0325 from *F. tularensis*, which encodes an OmpA-like protein, interferes with NF-κB signalling and reduces cytokine production (Mahawar *et al.*, 2012), and the same mutant also delays AIM2 inflammasome activation and cell death at the early stages of infection (Dotson *et al.*, 2013).

Listeria

Listeria monocytogenes, the causative agent of listeriosis, a life-threatening food-borne disease, is a Gram-positive facultative intracellular pathogen that survives in different environments and infects several hosts (Hernandez-Milian and Payeras-Cifre, 2014). Infection with *L. monocytogenes* is usually caused by ingestion of contaminated food such as dairy products, meat, vegetables and seafood. *L. monocytogenes* can infect and survive in a variety of cells, including myeloid cells through phagocytosis or through invasion of epithelial cells by its virulence factor internalin A (Mengaud *et al.*, 1996). After entering the cell, *L. monocytogenes* is initially present inside a phagocytic vacuole, and through the pore-forming toxin listeriolysin-O (LLO, encoded by the gene *hly*), *L. monocytogenes* escapes from the phagosome and gains access to the cytosol (Hamon *et al.*, 2012; Portnoy *et al.*, 1988). *L. monocytogenes* is detected *in vitro* by the NLRP3, NLRC4 and AIM2 inflammasomes. NLRP3 activation, caspase-1 activation and cytokine production are dependent on the adaptor ASC in *L. monocytogenes* infection (Kim *et al.*, 2010; Mariathasan *et al.*, 2006; Wu *et al.*, 2010). The induction of mature IL-1β is also dependent on TLR2, required for the first signal, transcription of pro-IL-1β (Ozören *et al.*, 2006). LLO-mediated pore formation is essential for NLRP3 activation through potassium efflux that induces its oligomerization (Hamon and Cossart, 2011; Kanneganti *et al.*, 2006; Meixenberger *et al.*, 2010). Vacuole escaping by *L. monocytogenes* mediated by LLO leads to cathepsin B release from the phagosome, and cathepsin B and phagosome disruption is also sensed by NLRP3. Infection by mutants lacking LLO or an avirulent *Listeria innocua*, had impaired IL-1β production (Hamon and Cossart, 2011; Meixenberger *et al.*, 2010). However, different reports demonstrated no role for NLRP3 in *L. monocytogenes* infection (Franchi *et al.*, 2007; Sauer *et al.*, 2010).

Another platform that senses *L. monocytogenes* is the AIM2 inflammasome (Kim *et al.*, 2010). After escaping from the phagosome, bacteriolysis occurs in the cytosol and the released DNA activates AIM2 (Sauer *et al.*, 2010). Macrophages AIM2 deficient have reduced caspase-1 activation and IL-1β production after *L. monocytogenes* infection (Rathinam *et al.*, 2010; Warren *et al.*, 2010), but the combined deficiency of both NLRP3 and AIM2 totally abrogates inflammasome activation (Kim *et al.*, 2010).

L. monocytogenes activates NLRC4 *in vitro*, but is a poor inducer *in vivo*. It was demonstrated an important role for NLRC4 in non-primed macrophages infected with *L. monocytogenes*. In cells NLRC4 deficient, caspase-1 activation and cell death are not induced after infection, but after LPS priming, NLRC4 is not required for cell death and caspase-1 activation (Wu *et al.*, 2010). Sauer and co-workers engineered a flagellin-expressing *L. monocytogenes* strain and investigated the role of this inflammasome *in vivo*. This strain activates NLRC4 and was highly attenuated *in vivo*, and restriction of bacterial replication was independent

of IL-1β and IL-18 (Sauer *et al.*, 2011). *In vivo*, caspase-1/11 deficient mice have increased susceptibility to *L. monocytogenes* infection, but this feature is not corroborated by other groups (Sauer *et al.*, 2011; Tsuji *et al.*, 2004).

L. monocytogenes is able to evade the immune system through different mechanisms. It avoids the activation of NLRC4 inflammasome by suppressing flagellin expression at 37°C via the transcriptional regulator MogR (Grundling *et al.*, 2004; Shen and Higgins, 2006). NLRP3 activation is avoided by controlling LLO expression transcriptionally or post transcriptionally through the activity of the transcriptional factor PrfA (Schnupf *et al.*, 2006; Shen and Higgins, 2006), and also by the limited activity of LLO in acidic pH compartments, preventing the damage of infected cells (Glomski *et al.*, 2003; Glomski *et al.*, 2002).

Mycobacterium

Mycobacterium tuberculosis (Mtb) causes a chronic bacterial disease called tuberculosis (TB). The majority of people infected by Mtb do not display symptoms. Many individuals contain Mtb confined in structures of immune cells termed granulomas (Nowag and Hartmann, 2016). The innate immune response is critical for host resistance against TB, where pro-inflammatory cytokines as IL-12, IFN-γ and TNF-α plays an important role (Dorhoi and Kaufmann, 2014; Sia *et al.*, 2015). Murine models of TB have demonstrated an important role for these cytokines in defence against Mtb. Cytokines from the IL-1 family have emerged as key players in the Mtb control. IL-1R-deficient mice infected by Mtb succumbed to the infection (Di Paolo *et al.*, 2015; Fremond *et al.*, 2007).

One important characteristic of virulent strains of Mtb is the presence of type VII secretion system (T7SS), among them ESX-1, that exports bacterial proteins into the host and is involved in the escape from the phagosome to the cytosol (de Jonge *et al.*, 2007; Houben *et al.*, 2012; Simeone *et al.*, 2012). Mutants lacking ESX-1 are severely attenuated in murine infection models (Hsu *et al.*, 2003). ESX-1 is important to activate PRR including the inflammasome. Mtb mutant strains that lack ESX-1 are poor IL-1β inducers in both human and mouse macrophages (Dorhoi *et al.*, 2012; Koo *et al.*, 2008; Mishra *et al.*, 2010).

The role of NLRP3, ASC and caspase-1 in *Mycobacterium* infection is controversial. Some reports show a role for NLRP3 in Mtb IL-1β induction and ESX-1 plays a key role, but other reports showed no role for NLRP3 and caspase-1 in IL-1β production (Dorhoi *et al.*, 2012; Koo *et al.*, 2008; Kurenuma *et al.*, 2009; Netea *et al.*, 2015). A human study showed that individuals carrying a gain-of-function mutation on the *NLRP3* gene, in combination with mutations on *CARD8*, have an improved Mtb control by macrophages (Eklund *et al.*, 2014). *In vivo* Mtb murine models found that both ASC and caspase-1 are not required for IL-1β production, and almost no increase in bacteria load was observed (Dorhoi *et al.*, 2012; McElvania Tekippe *et al.*, 2010). IL-1β and IL-1R deficient mice are more susceptible than ASC and caspase-1 knockout mice, and caspase-1-independent IL-1β cleavage was already described (Mayer-Barber *et al.*, 2010; Netea *et al.*, 2015). Recognition of *Mycobacterium leprae* by Dectin-1 in DC leads to IL-1β production mediated by caspase-8 and ASC (Gringhuis *et al.*, 2012), and macrophages could also induce IL-1β secretion independent of caspase-1 through RIPK3 (Vince *et al.*, 2012). It was also recently described that *Mycobacterium bovis* induces IL-1β secretion to a mechanism dependent on NLRP7 that also leads to pyroptosis (Zhou *et al.*, 2016).

The AIM2 inflammasome have also been described as involved in Mtb recognition. DNA from *Mycobacterium* can reach the cytosol through ESX-1, where it can activate AIM2 and

induce IL-1β. Mice AIM2 knockout are more susceptible to Mtb infection (Saiga *et al.*, 2012; Yang *et al.*, 2013b).

Mtb can modulate inflammasome activation to escape from this response. *Mycobacterium smegmatis* induces AIM2 inflammasome activation dependent on IFN-β production; in contrast Mtb inhibits AIM2 activation by blocking type I interferon induction (Shah *et al.*, 2013). ZMP-1, an effector molecule produced by Mtb can diminish inflammasome activation, IL-1β production and phagosome maturation, increasing Mtb survival (Master *et al.*, 2008).

Yersinia

The *Yersinia* genus consists of Gram-negative coccobacilli or rod-shaped bacteria, and three species within the genus *Yersinia* are pathogenic for humans, *Yersinia pestis*, *Yersinia pseudotuberculosis*, and *Yersinia enterocolitica*. *Y. pestis* is the causative agent of the plague, and the other two species are enteric pathogens that cause a self-limiting gastroenteritis. They share a common virulence plasmid that encodes the T3SS (Fällman and Gustavsson, 2005). Translocation of *Yersinia* effector proteins (YopE, YopM, YpkA/YopO, YopH, YopT and YopP/J) into the cytosol of host cells results in immune response modulation and cell death. Both epithelial cells and macrophages have been shown to respond to *Yersinia* infection, and massive of immune cells is hallmark of infection by *Yersinia* species (Cornelis, 2002; Trosky *et al.*, 2008; Wren, 2003). It is believed that *Yersinia* primarily replicates extracellularly and evades phagocytosis in lymphoid tissues, but intracellular replication was already described (Grabenstein *et al.*, 2004). Distinct types of cell death including apoptosis, pyroptosis and even necrosis were described in *Yersinia* infection, but their contribution to pathogenesis or bacteria control is still debatable, especially *in vivo* (Monack *et al.*, 1998; Philip *et al.*, 2014; Ruckdeschel *et al.*, 1998; Ruckdeschel *et al.*, 1997; Zheng *et al.*, 2012). Cell death was described as a mechanism used by *Yersinia* for phagocyte elimination (Monack *et al.*, 1998), but some reports suggested that *Yersinia* induced cell death could trigger immune responses against the bacteria (Bergman *et al.*, 2009; Zauberman *et al.*, 2009).

The effector YopJ, called YopP in *Y. enterocolitica*, induces caspase-1-dependent apoptosis during infection (Brodsky *et al.*, 2010; Zheng *et al.*, 2011). YopJ is a MAPK and NFκB signalling inhibitor (Ruckdeschel *et al.*, 1998; Ruckdeschel *et al.*, 2001), and was also described as an ubiquitin-like protein protease and also as a deubiquitinase (Orth *et al.*, 2000; Sweet *et al.*, 2007; Zhou *et al.*, 2005). TLR activation and signalling through MAPK and NFκB induces up-regulation of pro-survival genes that limit caspase-8-dependent apoptosis, thus inhibition of MAPK and NFκB by YopJ induces caspase-8/caspase-1 activation and cell death. Recently, a caspase-independent cell death, mediated by Receptor Interacting Protein Kinases 1 and 3 (Ripk1 and Ripk3) was also described in *Yersinia* infection (Philip *et al.*, 2014; Weng *et al.*, 2014).

Despite the mechanism of inflammasome activation by *Yersinia* is still unknown, the induction of IL-1β and IL-18 by YopJ requires NLRP3, ASC and caspase-1, but caspase-1 activation is independent of NLRP3 and ASC. Moreover, T3SS recognition induces caspase-1 activation and IL-1β secretion dependent on NLRP3, NLRC4 and ASC, but the mechanism is unclear (Brodsky *et al.*, 2010; Zheng *et al.*, 2011). NLRP12 was also demonstrated to play a role in *Y. pestis* infection, and both NLRP12 and NLRP3 were involved in host defence against *Yersinia in vivo*, probably via caspase-1-dependent IL-1β and IL-18

induction (Vladimer *et al.*, 2012). In contrast to other Gram-negative bacteria such as *Salmonella*, *Yersinia* do not strongly activate the NLRC4 inflammasome, possibly because bacteria inhibits flagellin expression (Brodsky *et al.*, 2010; Minnich and Rohde, 2007).

Although the precise role of cell death in *Yersinia* infections is not entirely clear, evasion of inflammasome activation might be beneficial to the bacteria in some circumstances. YopM was originally described to play a role in IL-10 induction and immune response suppression (McPhee *et al.*, 2010; McPhee *et al.*, 2012; Nemeth and Straley, 1997). One isoform of YopM from *Y. pestis* is able to bind and inhibits caspase-1. YopM can bind directly to caspase-1 acting as a pseudosubstrate, or to interact with the small GTPase IQGAPI to inhibit inflammasome activation. The decreased virulence of YopM mutant was reversed in caspase-1 -deficient mice (Chung *et al.*, 2014; LaRock and Cookson, 2012), but the mechanism was unclear. A new report demonstrated a role for YopM in the inhibition of pyrin inflammasome in *Yersinia* infection. *In vivo* infection by *Yersinia* activates pyrin inflammasome that is important for bacteria control and host survival, and *Yersinia* YopM mutant was unable to inhibit pyrin inflammasome. These data suggest that YopM promotes virulence by inhibiting pyrin through its phosphorylation by protein kinase C-related kinases, PRK1 and PRK2 (Chung *et al.*, 2016). Recently, two reports showed that YopJ, that induces inflammasome activation, is also involved in inflammasome inhibition by acting together with YopM (Ratner *et al.*, 2016; Schoberle *et al.*, 2016).

A secreted effector protein called YopK prevents inflammasome activation. YopK deficient bacteria inject increased amount of proteins (YopB and YopD) into the host cell and activates the inflammasome (Zwack *et al.*, 2015). YopE and YopT, which are involved in Rho GTPase inactivation (Black and Bliska, 2000; Shao *et al.*, 2003), are also involved in IL-1β inhibition in *Y. enterocolitica* infection (Schotte *et al.*, 2004). Recently it was demonstrated that *Yersinia* modifies its own LPS from the hexa-acylated form to a tetra-acylated form when grew at 37°C. This hypoacylated LPS evades TLR4 recognition (Matsuura, 2013), and probably caspase-11 activation (Kayagaki *et al.*, 2011; Shi *et al.*, 2014).

Shigella

Shigella is a Gram-negative intracellular pathogen and is the causative agent of the acute recto-colitis shigellosis, otherwise known as bacillary dysentery. Children living in endemic areas of poor countries are the most affected by this disease (Raqib *et al.*, 2000). Strong acute inflammation is a characteristic of the host innate immune response to *Shigella* infection, marked by a rapid influx of neutrophils that leads to tissue destruction (Parsot and Sansonetti, 1996; Perdomo *et al.*, 1994). The pathogenesis of *Shigella* relies on the expression of a T3SS, through which the delivery of bacterial effectors into host cell cytosol promotes pathogenesis (Ogawa *et al.*, 2008; Parsot, 2009; Schroeder and Hilbi, 2008). The main response against intracellular pathogens, including *Salmonella*, *Legionella* and also *Shigella* is mediated by the activation of NLRC4 inflammasome. As such, *S. flexneri* is detected by NLRC4 and induces caspase-1 activation and IL-1β and IL-18 secretion (Suzuki *et al.*, 2014). However, *S. flexneri* is non-flagellated bacteria, thus NLRC4 do not respond to flagellin during *Shigella* infection. The bacterial T3SS rod protein MxiI and the needle component MxiH are detected by NAIP2 and NAIP1 respectively (Miao *et al.*, 2010b; Yang *et al.*, 2013a; Zhao *et al.*, 2011). The T3SS effector protein invasion plasmid antigen B (IpaB) that is required for virulence also induces pyroptosis and IL-1β secretion dependent on

caspase-1 (Chen *et al.*, 1996; Hilbi *et al.*, 1998). IpaB oligomerizes and forms an ion channel allowing potassium influx and endolysosomal destabilization, leading to caspase-1 activation (Senerovic *et al.*, 2012). An NLRC5/NLRP3 inflammasome was also involved in the recognition and caspase-1 activation in *S. flexneri* infection. Cells knockdown for NLRC5 or NLRP3 have a decreased caspase-1 activation and IL-1β secretion (Davis *et al.*, 2011). Inflammasome activation by *S. flexineri* leads to caspase-1 activation and Il-1β and IL-18 secretion. Experiments using caspase-1 deficient mice, and also IL-1β and IL-18 deficient mice demonstrated an important role for both cytokines in inducing inflammation and infection control (Sansonetti *et al.*, 2000).

Recently, a guinea pig model of *S. flexneri* infection reported a caspase-4-dependent cell death, suggesting a role for human caspase-4 in *S. flexineri* infection. The *S. flexneri* effector OspC3 inhibits caspase-4 activation by interacting with the p19 subunit preventing its heterodimerization. Bacteria deficient in OspC3 induced higher cell death and showed decreased bacterial burden (Kobayashi *et al.*, 2013). Another mechanism described for *S. flexineri* to dampen IL-1β production is the modification of its own LPS structure. *S. flexneri* expresses a hypoacylated LPS that differs from the LPS of bacteria growing in laboratory. This hypoacylated LPS induces lower levels of IL-1β and has reduced priming capacity (Paciello *et al.*, 2013).

Concluding remarks

In the past few years we have vastly increased our knowledge about the mechanisms involved in inflammasome activation and suppression by intracellular bacteria (Table 5.1), but a number of unanswered questions still remains. For example, the molecular mechanisms responsible for NLRP3 activation, the role of pyroptotic cell death in restriction of pathogen replication *in vivo*, and the mechanism by which IL-1β is secreted still need to be determined. Inflammasome activation and downstream innate immune responses present a strong host immune defence against pathogens, and successful pathogens evolved mechanisms to avoid inflammasome activation, or in some cases to induce cell death. The identification and characterization of the pyrin inflammasome and the non-canonical inflammasome gave new insights on how the innate immune system recognize and respond to intracellular pathogens.

Inflammasomes mediate host defence by two major mechanisms. First, the induction and secretion of IL-1β and IL-18, which are important to trigger cellular responses mediated mostly by macrophages and neutrophils. Second, pyroptosis is important for the removal of the bacterial replicative niche and bacteria release to the extracellular milieu and killing mostly by neutrophils.

In addition, inflammasome biology has been extensively studied in murine models, facilitated by new techniques for genetic manipulation, allowing the study of hundreds of genes. But some of these discoveries cannot be easily translated to human inflammasome biology, and there is a need for more investigation on inflammasome biology in human cells. Future studies shall determine the precise role of cytokines and pyroptosis, and also other mechanisms operating downstream of the inflammasome for the control of bacterial infections. On the other hand, new strategies used by pathogens to escape and inhibit inflammasome activation will also be identified.

Table 5.1 Putative inflammasome activators and suppressors in bacterial infection

Pathogen	Inflammasome sensor	Putative inflammasome activator	Role *in vivo*	Putative inflammasome suppressor	References
Legionella	NLRC4	Flagellin	Yes	SdhA	Ren *et al*. (2006)
	NLRP3	ND	No		Case *et al*. (2013)
	Caspase-11	LPS	No		Silveira and Zamboni (2010)
	AIM2	DNA	ND		Ge *et al*. (2012)
Salmonella	NLRP3/NLRC4	T3SS	Yes	Ssa1	Broz *et al*. (2010a)
	NLRC4	Flagellin, PrgJ	Yes		Zhao *et al*. (2011)
	Caspase-11	LPS	Yes		Aachoui *et al*. (2013)
	NLRP6	ND	No		Anand *et al*. (2012)
	NLRP12	ND	No		Zaki *et al*. (2014)
Francisella	AIM2	DNA	Yes	FTL_0325	Fernandes-Alnemri *et al*. (2010)
	NLRP3	ND	No	Tetra-acylated lipid A	Rathinam *et al*. (2010)
					Atianand *et al*. (2011)
Listeria	NLRP3	LLO	ND	PrfA	Kanneganti *et al*. (2006)
	NLRC4	Flagellin	No	MogR	Kim *et al*. (2010)
	AIM2	DNA	Yes		Wu *et al*. (2010)
Mycobacterium	NLRP3	ESX-1	No	ZMP-1	Dorhoi *et al*. (2012)
	AIM2	DNA	Yes		Saiga *et al*. (2012)
	NLRP7	ND	ND		Zhou *et al*. (2016)
Yersinia	NLRP3	YopJ	Yes	YopK	Brodsky *et al*. (2010)
	Naip/NLRC4	T3SS	No	YopT	Zheng *et al*. (2011)
	NLRP12	T3SS, YopJ	Yes	YopE	Vladimer *et al*. (2012)
			Yes	YopM	Ratner *et al*. (2016)
				Tetra-acylated lipid A	Matsuura (2013)
Shigella	NLRC4	MxiI, MxiH, IpaB	Yes	OspC3	Suzuki *et al*. (2014)
	NLRC5/NLRP3	ND	ND		Yang *et al*. (2013a)
					Davis *et al*. (2011)

ND, not determined.

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