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Checks and Balances between Autophagy and Inflammasomes during Infection

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Abstract

Autophagy and inflammasome complex assembly are physiological processes that control homeostasis, inflammation, and immunity. Autophagy is a ubiquitous pathway that degrades cytosolic macromolecules or organelles, as well as intracellular pathogens. Inflammasomes are multi-protein complexes that assemble in the cytosol of cells upon detection of pathogen- or danger-associated molecular patterns. A critical outcome of inflammasome assembly is the activation of the serine protease caspase-1, which activates the pro-inflammatory cytokine precursors pro-IL-1β and pro-IL-18. Studies on chronic inflammatory diseases, heart diseases, Alzheimer's disease, and multiple sclerosis revealed that autophagy and inflammasomes intersect and regulate each other. In the context of infectious diseases, however, less is known about the interplay between autophagy and inflammasome assembly, although it is becoming evident that pathogens have evolved multiple strategies to inhibit and/or subvert these pathways and to take advantage of their intricate crosstalk. An improved appreciation of these pathways and their subversion by diverse pathogens is expected to help in the design of anti-infective therapeutic interventions.

Keywords

inflammasome; autophagy; bacterial and viral infection; inflammatory disease; therapeutic target

Introduction

Autophagy and inflammasome complex activation are physiological pathways that control tissue homeostasis and immunity. Like any other biological processes, if dysregulated, they can exert detrimental effects as exemplified by numerous inflammatory diseases and cancer

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[1,2]. It is now appreciated that autophagy and the inflammasomes intersect and regulate each other to maintain tissue homeostasis [3]. The goal of this review is to summarize current knowledge about the inflammasome complex and autophagy and their crosstalk in the context of infection.

Inflammasomes

Inflammasomes are multi-protein complexes that assemble in the cytosol of infected or damaged cells (recently reviewed in Refs. [4,5]). Assembly of these molecular platforms can be initiated by various signals, but they all converge toward the activation of the cysteine protease caspase-1, which ultimately orchestrates the elimination of pathogens and damaged cells. The assembly of an inflammasome is initiated upon engagement of sensor proteins (pattern recognition receptors, or PRRs) with pathogen-associated molecular patterns (PAMPs), or with damage-associated molecular patterns (DAMPs). These sensors are classified based on structural characteristics and include cytosolic nucleotide-binding oligomerization domain (NOD or NBD or NACHT) and leucine-rich repeat (LRR) receptors (NLRs), absent in melanoma 2 (AIM2)-like receptors (ALRs), and pyrin (Fig. 1). NLRs are further subdivided into NLRP and NLRC depending on the presence of a pyrin (PYD) or a caspase activation and recruitment (CARD) domains. The sensor recruits and nucleates an adaptor protein, the apoptosis-associated speck-like protein (ASC) containing CARD and PYD domains. Consequently, the association of pro-caspase-1 with the sensor-ASC complex promotes its auto-activation into a cysteine protease [6]. The assembly of an inflammasome relies on homotypic protein–protein interactions CARD–CARD or PYD–PYD domains located on sensors, the ASC adaptor, and pro-caspase-1. The adaptor ASC amplifies the signal through oligomerization into PYD filaments and recruitment of multiple pro-caspase-1 molecules via interaction with CARD. Different microbial products may engage distinct receptors giving rise to the activation of one or several canonical inflammasomes, among which the most studied are NLRP1, NLRP3, NLRC4, AIM 2, and pyrin. The NLRP3 inflammasome is also a master sensor of DAMPs, such as reactive oxygen species, adenosine 5′-triphosphate (ATP), mitochondrial DNA (mtDNA), and K^+ efflux. DAMPS form during tissue damage due to infection, or to non-infectious conditions such as disorders of autoimmunity, although the modalities of NLRP3 activation remain unsettled. The canonical inflammasomes may differ by their sensing receptors but converge toward the activation of caspase-1. Murine caspase-11 (caspase-4 and -5 in humans) forms a non-canonical inflammasome consisting of the lipid A portion of LPS interacting with the CARD domain of pro-caspase-11. Activated caspase-11 then controls caspase-1 activation via promoting the NLRP3 inflammasome and also exerts caspase-1-independent activities such as regulation of vesicular trafficking [7,8]. Once activated, caspase-1 processes several substrates, regulating numerous pathways. Caspase-1 major substrates include the pro-inflammatory cytokine precursors pro-IL-1β and pro-IL-18, which initial transcription and translation generally involve activation of Toll-like receptors (TLRs) by a process described as “priming.” Additional substrates include the pro-pyroptotic cell death molecule gasdermin, and molecules promoting fusion of bacteria-containing vesicles with lysosomes, tissue repair, membrane biogenesis, and metabolism [9–12]. Since the discovery that the common mouse used in caspase-1 research was indeed a double capase-$1^{-/-}$/caspase-$11^{-/-}$ knockout, the community is revisiting claimed downstream effectors of these caspases [13].

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Excessive activation and dysregulation of inflammasomes are associated with inflammatory and autoimmune diseases such as colitis, diabetes, multiple sclerosis, Alzheimer's disease, sepsis, and cancer. Therefore, tight regulation of inflammasome activation by the autophagy machinery is critical for tissue homeostasis and health.

Autophagy

Autophagy is a ubiquitous and versatile homeostatic pathway that disposes of intracellular macromolecules or organelles as well as infectious agents [14, 15]. Autophagy may be nonselective when cytosolic components are randomly captured to generate nutrients under starvation conditions, or can be selective when damaged organelles or intracellular pathogens must be targeted for their autophagic elimination. Autophagy involves over 30 proteins encoded by autophagy-related genes, or Atgs, including the highly studied class III phosphatidylinositol 3-kinase VPS34, the ubiquitin-like LC3 (Atg8 in yeast), and beclin-1 (Atg6 in yeast) proteins. This machinery sequentially recruits membranes to sequester a cargo into a double-membrane vesicle called the phagophore, which matures into an autophagosome (Fig. 2). Maturation of the autophagosome into an autophagolysosome then allows for the digestion and recycling of the cargo. Various forms of selective autophagy have been described based on the nature of the intracellular cargo to be degraded. For example, mitophagy clears damaged or senescent mitochondria and xenophagy eliminates intracellular pathogens whether they are cytosolic or reside within in a vacuole. Cargos can be targeted for selective autophagic degradation by both ubiquitin-dependent and -independent mechanisms [16]. The ubiquitinated cargo is recognized by adaptor proteins [p62/SQSTM1, NBR1, optineurin, nuclear domain 10 protein 52 (NDP52), TAX1BP1], which associate them with the forming phagophore via interaction with the autophagy protein LC3. Cytosolic receptors such as galectin-8 can also target some cargos for autophagy independently of prior ubiquiti-nation. In contrast to the assembly of inflammasomes, which occurs only when provoked, autophagy always proceeds at a constant low level in every eukaryotic cell to maintain a steady supply of nutrients. Basal autophagy also plays a housekeeping role by continuously removing damaged organelles, protein aggregates, and long-lived proteins. The resulting nutrients are recycled to participate in *de novo* macromolecule synthesis or energy production. Autophagy can be dramatically induced in response to various environmental stresses, such as starvation, hypoxia, oxidative stress, radiation, and infection [17,18]. The induction of autophagy is accompanied by increased synthesis of the autophagy proteins, increased autophagic degradation, or increased autophagic flux (defined as a measure of autophagic degradation activity [19]).

Autophagy is at the crossroad of multiple homeostatic pathways and is therefore critical for a diversity of physiological and pathological processes. Relevant to this review, autophagy is an innate immune mechanism that kills pathogens and controls inflammation. Xenophagy decreases pathogen burden and participates in the processing of antigens for activation of the adaptive immunity. On the other hand, mitophagy not only maintains normal production of energy and metabolism but also prevents inflammation by limiting both the release of mtDNA and the production of reactive oxygen species by damaged mitochondria, which would otherwise be potent activators of NLRP3 [20,21]. Therefore, by eliminating damaged

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mitochondria and other organelles, autophagy limits the release of pro-inflammatory cytokines.

Crosstalk between autophagy and the inflammasome machineries

Autophagy and inflammasomes are functionally interconnected; they both control cell homeostatic processes such as metabolism, energy production, maintenance of organelles, and critically control inflammation and the clearance of pathogens. It is therefore important to understand how autophagy and inflammasome machineries intersect and regulate each other.

TLRs, NLRs, and retinoic acid-inducible gene I (RIG-I)-like receptors have all been shown to activate autophagy by directly inducing posttranslational modifications of autophagy proteins, by increasing their synthesis, or by directing the localization of autophagy proteins [22]. In particular, recent studies have identified that NOD2-mediated induction of autophagy in intestinal epithelial cells was necessary to hold bacterial burden, thereby limiting inflammation [23]. NOD2 was identified as one of the inflammatory bowel disease susceptibility genes involved in autophagy [24,25]. NOD2 stimulation in dendritic cells also induces autophagy to promote bacterial clearance and antigen presentation [26]. In this process, NOD2 in conjunction with NOD1 recruits ATG16L1 to the site of bacterial entry to target the forming phagosome to the autophagy machinery [27]. Interestingly, p62 forms a complex with NOD2 and increases NOD2 signaling by stabilizing NOD2 oligomerization [28]. In the intestines, the NLRP6 inflammasome is important for mucus secretion by globlet cells. In NLRP6- or capase-1-deficient mice, mucus secretion and autophagy are impaired and mice are more susceptible to enteric infection. Notably, mucus secretion requires autophagy, thus linking inflammasome activity to autophagy in the intestines [29]. Activation of PRRs is also critical for cell priming for inflammasome activation. This priming involves the synthesis of inflammasome components and substrates. LPS is commonly used as a tool for cell priming via TLR4 and MyD88 signaling, increasing the synthesis of pro-IL-1β and other components necessary for the inflammasome pathways.

On the other hand, a number of PRRs and inflammasomes can inhibit autophagy. For example, NLRC4 and NLRP4 negatively regulate autophagy via association with and sequestration of the autophagy protein beclin1 [30]. Another mechanism of inhibition of autophagy involves caspase-1-mediated proteolytic cleavage of autophagy proteins and cytosolic transducers that are involved in autophagy activation. In particular, caspase-1 can degrade beclin 1 and the mitophagy-specific protein parkin [31].

Autophagy can promote inflammasome activity. The autophagosome has been proposed to promote the release of cytokines activated by caspase-1, thereby positively cooperating with the inflammasome. For example, recruitment of the autophagy machinery by the activated AIM2 inflammasome has been proposed to mediate the release of IL-1β via exocytosis of the autophagosome [32]. Thus, IL-1β can be released in an autophagy-dependent manner that requires SNAREs and syntaxins [33]. Additional studies showed that autophagy is required for the release of active IL-1β or IL-18 downstream of other inflammasomes [34]. Autophagy is also involved in the release of HMGB1 and secretory lysosomes [35,36].

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However, it is not clear how these substrates are selected for this secretion instead of degradation by autophagy. On the contrary, autophagy can suppress the activation of several inflammasomes by multiple mechanisms [37]. Autophagy can indirectly limit the activation of inflammasomes via removal of old/damaged organelles or pathogens, which decreases the release of PAMPs or DAMPs. In particular, mitochondria play a central role in the autophagy–inflammasome interplay. The capture and degradation of damaged mitochondria limits the accumulation mtDNA and reactive oxygen species. Reciprocally, autophagy genetic deficiencies, or autophagy inhibition by pharmacological compounds increases the activation of inflamma-somes via accumulation of PAMPs, DAMPs, cytokine precursors, and their downstream signaling pathways. The autophagosome may directly sequester and degrade activators, components, or products of inflammasomes. For example, autophagy controls IL-1β production by degrading the cytokine precursor pro-IL-1β [38]. More recently, basal autophagy was also shown to remove monomeric inactive MyD88 and degrade TRIF to limit pro-inflammatory signals mediated by TLR and IL-1R that produce pro-IL-1β and pro-IL-18 [39]. Autophagy can target and destroy AIM2 and NLRP3 in human macrophages, a process thought to limit inflammation [40]. In this process, the autophagy adaptor molecule p62 binds to ubiquitinated ASC or AIM2 and induces their degradation by selective autophagy (Fig. 3). In conclusion, autophagy and inflammasome are parts of complex regulatory networks and can inhibit or activate one another in multiple fashions.

Pathogens differentially interfere with the inflammasomes and autophagy machineries

Here we discuss how several intracellular pathogens including *Listeria monocytogenes*, *Salmonella enterica* serovar Typhimurium, *Francisella tularencis*, *Burkholderia cenocepacia, Mycobacterium tuberculosis (M.tb)*, non-tuberculous mycobacteria, and *Influenza* virus can modulate the activation of inflammasomes or autophagy machineries. It appears that each pathogen affects and is affected by inflammasomes and autophagy in a very unique mode.

Listeria monocytogenes

L. monocytogenes is a Gram-positive pathogen responsible for the foodborne disease listeriosis [41]. This facultative intracellular pathogen replicates in professional phagocytes and in normally non-phagocytic cells such as epithelial cells [42,43]. Its intracellular life cycle involves the secreted pore-forming toxin listeriolysin O (LLO) and two phospho-lipases C (PI-PLC and PC-PLC) that disrupt the membrane of the phagosome to allow bacterial replication in the cytosol [44]. In the cytosol, the bacterial surface protein ActA promotes the growth of F-actin at one bacterial pole, propelling the bacterium until it forms an extracellular protrusion [43,45]. The bacterium-containing protrusion is then taken up by a neighboring cell into a double-membrane vacuole that is disrupted by the concerted activities of LLO, PI-PLC and PC-PLC to initiate a new cycle of infection [46].

L. monocytogenes infection leads to the activation of caspase-1 as observed using *in vitro* and *in vivo* experimental models. In mice, this activation is necessary for early control of *L. monocytogenes* via production of IL-18 and interferon (IFN)γ. However, caspase-1 appears

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dispensable for acquisition of sterilizing adaptive immunity and no role for caspase-11 was identified in C57BL/6 mice [47–49]. Using cell culture models, several studies showed that *L. monocytogenes* activates NLRP3 and AIM2 inflammasomes. Activation of NLRP3 was reported to require LLO-mediated bacterial escape from the phagosome [47,50]. In the cytosol, *L. monocytogenes* components such as RNA and the secreted protein p60 activate NLRP3 [51,52]. Extracellular *L. monocytogenes* can also activate NLRP3 independently of host-cell invasion through secretion of LLO. Indeed, the efflux of K^+ subsequent to plasma membrane perforation by LLO leads to NLRP3 activation [53]. In addition, bacterial DNA released upon cytosolic lysis of *L. monocytogenes* activates the AIM2 inflammasome [54,55]. More recently, *L. monocytogenes* was proposed to activate the NLRP1B inflammasome, via causing energy stress in fibroblasts and macrophages [56]. It is thought that *L. monocytogenes* maintains a low-level of inflammasome activation in order to establish a successful infection. Hence, an *L. monocytogenes* strain engineered to activate the NLRC4 inflammasome was substantially attenuated in the murine model of infection [57,58].

Several studies report that *L. monocytogenes* can be targeted by the autophagy machinery and that autophagy limits its intracellular growth *in vivo* and *in vitro* [59–62]. Mice harboring $Atg5^{-/-}$-deficient monocyte/macrophages and granulocytes had increased *L. monocytogenes* burden and decreased survival [63]. Also, C57BL/6 $irf8^{-/-}$ mice displayed increased *L. monocytogenes* burden due to lower levels of autophagy, and it was proposed that the transcription factor IRF8 downstream from IFNγ controls the expression of seven of the autophagy genes during *Listeria* infection [64]. The autophagy adaptor optineurin is phosphorylated by the TANK binding kinase 1, which enhances its affinity for LC3 and *L. monocytogenes* degradation by autophagy in HeLa cells in an LLO-dependent fashion [65]. Macro-phage infection models suggested that autophagy can capture *L. monocytogenes* located in the phagosome, but after bacteria had started to replicate in the cytosol [62]. Furthermore, *L. monocytogenes* can activate autophagy at an early stage of infection in an LLO-dependent fashion and LLO is sufficient to activate autophagy in macrophages, which is consistent with the idea that the autophagy machinery recognizes damaged phagosomes [66]. However, an absence or low levels of autophagy during *L. monocytogenes* infection has been reported, unless the bacterial metabolic activity was affected by the antibiotic chloramphenicol [61]. Therefore, in order to survive within host cells, *L. monocytogenes* actively limits its recognition and destruction by the autophagy machinery. A strategy to avoid autophagy of the *L. monocytogenes*-containing phagosome is the secretion of phosphatidylinositol-specific phospholipase C (PI-PLC) that counteracts the synthesis of phosphatidylinositol 3-phosphate [59,67]. PI-PLC prevents LC3 lipidation, which is a key step in the formation of the autophagosome [66]. To limit selective autophagy in the cytosol, *L. monocytogenes* recruits host proteins that prevent ubiquitination of its surface and subsequent recruitment of p62 or NDP52 [68]. ActA recruits the host protein Ena/VASP and the Arp2/3 complex masking the bacterial surface, rather than via inducing bacterial motility, as it was initially thought [69]. This disguise strategy is exploited by a second virulence factor, the surface protein InlK, which recruits a conserved mammalian ribonucleo-protein, the major vault protein (MVP) [70].

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Taken together, *L. monocytogenes* has intrinsic features that can activate autophagy and multiple inflammasomes; however, this pathogen limits activation of these machineries to ensure its intracellular survival. To date, it is unknown if *L. monocytogenes* exploits or subvert the crosstalk between these two pathways. It would also be of interest to determine if treatments that potentiate autophagy or the inflammasomes facilitate elimination of *L. monocytogenes* and if this would involve beneficial co-regulation between both pathways.

Salmonella enterica serovar Typhimurium

S. enterica serovar Typhimurium is one of the most studied Gram-negative bacterium that causes gastroenteritis, typhoid fever, and enteric fever. This bacterium resides in the *Salmonella* containing vacuole within host cells. Two Type Three Secretion Systems (T3SS) play an essential role in mediating uptake and vacuole maturation for formation of the intracellular niche.

Salmonella has proved to be a valuable model system to dissect the different molecular pathways that contribute to inflammasome formation and activation. The necessity for inflammasome activation to control and clear *Salmonella* has been demonstrated through infection of caspase-$1^{-/-}$, IL-$18^{-/-}$, or IL-$1\beta^{-/-}$ mice, which are much more susceptible to oral infection than wild-type mice and succumb to *Salmonella* more rapidly with increased bacterial burden in the spleen and mesenteric lymph nodes [71,72]. Only NALP$3^{-/-}$ NLRC$4^{-/-}$ mice, but not NLRC$4^{-/-}$ or NLRP$3^{-/-}$ single knockout mice, were susceptible to infection similar to caspase-$1^{-/-}$, indicating that NLRP3 and NLRC4 are redundant or overlapping pathways for caspase-1 activation by *Salmonella* [73]. Critical to the host response to *Salmonella* is the recognition of ligands that activate these inflammasomes. Flagellin is a ligand for NAIP5 and 6 NLRC4 [9,72,74], the needle and inner rod of the T3SS are NAIP1 and NAIP2 ligands, respectively [55,75–77]. As an inflammasome evasion strategy, *Salmonella* can repress expression of PAMPs through the PhoP–PhoQ regulatory system. Interestingly, the consequences of inflammasome activation depend on the nature of the activated inflammasome. Activation of NLRP3 *by LPS* results in the production of IL-1β and IL-18. In contrast, activation of NLRC4 in response to *Salmonella* T3SS and/or LPS leads to rapid pyroptosis in a gasdermin D-dependent fashion. In the absence of gasdermin D, cells undergo mainly apoptosis instead of pyroptosis [78], which leads to increased infection benefiting *Salmonella*. In contrast to murine cells, human cells generate IL-1β in a caspase-1-dependent manner but also use caspase-4 for IL-1β release and the induction of cell death [79]. The process of pyroptosis is thought to bypass the beneficial induction of apoptosis by *Salmonella* [80]. Cytokine production and cell death by pyroptosis both contribute to the control or clearance of *Salmonella*, yet other mechanisms also exist. It is likely that during *Salmonella* infection, multiple receptors are engaged in tandem, generating a mixed response that is evident in the *in vivo* mouse models. In addition, *Salmonella* that lacks aconitase has attenuated virulence that is dependent on rapid NLRP3 inflammasome activation [81]. Neutrophils can also activate the NLRC4 inflammasome in response to *Salmonella* infection and make IL-1β but do not undergo pyroptosis (in contrast to macrophages) leading to sustained IL-1β production [82]. The GBP cytosolic proteins are host defense molecules whose expression is activated by the IFNs [83]. GBPs can target the *Salmonella*-containing vacuole causing its rupture and the release of PAMPs such as LPS

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leading to activation of the non-canonical NLRP3 [84]. It is important to note that GBPs also activate inflammasomes via multiple mechanisms [85].

Upon infection of epithelial cells, most *Salmonella* reside in a vacuole. However, due to damage of the vacuole by the T3SS or by host proteins, a significant fraction (around 15%–20%) of cytosolic bacteria or bacteria-containing damaged vacuoles are coated by ubiquitin and associate with LC3-positive nascent autophagosomes [86]. Depletion of a single autophagy receptor leads to hyperproliferation of *Salmonella* [87]. Three different autophagy receptors, p62 [88], NDP52 [87], and optineurin [89], recognize ubiquitinated *Salmonella* and target them to autophagosomes. In particular, the autophagy receptor optineurin is phosphorylated by protein kinase TANK binding kinase 1 (TBK1) to promote autophagy of *Salmonella* [90]. Linking inflammasome to autophagy during *Salmonella* infection, both processes can be activated by common pathways such as the damage of the *Salmonella*-containing vacuole by GBPs [22,91].

Francisella tularensis

F. tularensis is a highly infectious, facultative, intracellular, gram-negative bacterium, and is the causative agent of tularemia [92]. *F. tularensis* has been classified into four subspecies: *F. tularensis* subsp. *tularensis* (*F. tularensis*; Type A; includes Schu S4 strain), *F. tularensis* subsp. holarctica (*F. holarctica*; Type B; includes live vaccine strain), *F. mediasiatica*, and *F. tularensis* subsp. *novicida* (*F. novicida*). *Francisella* is characterized by its low infectious dose and ability to cause severe illness and death if untreated. The most life-threatening forms of tularemia are particularly associated with Type A infections (Schu S4) regardless of the host species [93], whereas *F. holarctica* is more virulent for mice than for humans. In contrast, *F. novicida* is highly virulent for mice but is almost completely avirulent for humans [94]. Of note, avirulent *F. novicida* can infect human monocytes and induce a more robust inflammatory response as compared to virulent *F. tularensis* and *F. holarctica* [95–97]. Macrophage infection by *Francisella* is characterized by a multifaceted life cycle that is essential for pathogenesis. It begins with recognition of the bacterium at the cell surface via the TLR2 receptor [98,99], followed by uptake by an asymmetrical exuberant pseudopod loop (looping phagocytosis) resulting in bacterium enclosure within a spacious vacuole [100]. Although the *Francisella*-containing phagosome acquires early endosomal markers, the bacterium arrests phagosome–lysosome fusion and rapidly escapes into the cytosol for extensive replication [101–103].

In the cytosol, intracellular *Francisella* subspecies can be recognized by intracellular PRRs including AIM2 [104,105], NLRP3 [106,107], and pyrin [108,109], depending on murine or human hosts. It is well established that AIM2 senses *Francisella* DNA [110], NLRP3 detects a broad range of signals, whereas no specific PAMP is identified for pyrin activation. Pyrin's role is controversial; originally, it was proposed as an anti-inflammatory molecule, but over the last several years, a growing body of evidence has demonstrated that the pyrin inflammasome is pro-inflammatory [111–115]. This leads to controlled active caspase-1 and IL-1β/IL-18 release followed by pyroptosis. At later stages of infection, some intracellular *Francisella* (in murine but not in human macro-phages) are found in autophagosomes but they are still intact and not degraded [116].

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To survive within an intracellular environment, bacteria should either avoid or suppress recognition by inflammasome or autophagy machineries. Schu S4, the most pathogenic strain of *Francisella*, can actively dampen and subvert the inflammatory response [96], reduce the expression of autophagy-related genes, and compromise relevant signaling pathways in human hosts. In particular, *F. tularensis* Schu S4, significantly downregulates the expression of autophagy related genes such as *BEC1, ATG5, ATG12, ATG16L2, ATG7, ATG4A*, and *PIK3R1* but increases expression of *IFNG* and *IFNB1* [117,118]. The observed downregulation of autophagy-related genes correlates with *Francisella's* ability to avoid degradation by autophagy during active cytosolic proliferation. In addition to the suppression of autophagy genes, *F. tularensis* SchuS4 may actively evade ubiquitination and subsequent recognition by the autophagy adaptors p62/SQSTM1 and NBR1 [119,120]. Interestingly, *Francisella's* O-antigen plays a protective role against uptake by the autophagy machinery [121]. Pyrin, which senses *Francisella*, directly interacts with essential autophagy molecules such as beclin1, ULK1, and ATL16L1 [122]. Autophagy proteins bind to pyrin's B-box and coiled-coil domain accompanied by the assembly of an autophagosome [122]. Homotypic interaction between PYD of pyrin, ASC, and other PYD-containing molecules (NLRP3) may bring the inflammasome's components into the autophagosome for degradation. It seems that *Francisella* modulates both pathways to establish a convenient niche for intracellular survival.

Burkholderia cenocepacia

Burkholderia pseudomallei is a facultative intracellular pathogen and the causative agent of melioidosis [123]. *B. cenocepacia* is a member of the *B. cepacia* complex and is frequently isolated from cystic fibrosis patients [124]. Acquisition of *B. cenocepacia* by cystic fibrosis patients leads to colonization and inflammation with two possible outcomes. *B. cenocepacia* can lead to moderate infection without severe change in pulmonary status, or severe infection with accelerated pulmonary deterioration accompanied by bacteremia, necrotizing pneumonia, and death. *B. cenocepacia* survives and may replicate within free-living amoebae [125] as well as in murine and human macrophages [126–131]. *B. cenocepacia* also survives in epithelial cells [132]. *B. cenocepacia* survives within a vacuole (phagosome) incystic fibrosis macrophages where the *B. cenocepacia*-containing vacuole acquires the early endosomal marker EEA1 and Rab5, and then slowly acquires LAMP-1 [126] while acquiring CD63 and Rab7 [133]. *B. cenocepacia* expresses one T3SS, two type 4 (T4SS-1 and T4SS-2), and one type 6 (T6SS) secretion systems [134–136]. *B. cenocepacia* employs its secretion systems, especially T6SS, to survive in macrophages. T6SS effectors are delivered into the cytosol where they affect the function of Rho-family GTPases. This disrupts the trafficking of the phagosome and causes a defect in the recruitment of soluble components of the NADPH oxidase to the membrane of the phagosome [128–130,137]. These functional defects, by a yet unidentified mechanism, lead to the activation of the NLRP3 and pyrin inflammasomes and subsequent cell death by pyroptosis and sustained inflammation [137]. *B. cenocepacia* infection of human mononuclear cells also leads to the production of IL-1β and IL-18 through NLRC4. In mouse macrophages, however, *B. cenocepacia* employs the NLRP3 inflammasome to induce IL-1β secretion and pyroptosis [138]. LPS is essential and sufficient for the production of IL-1β in macrophages [131].

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Autophagy has been implicated in the restriction of *B. pseudomallei* in macrophages [139]. Electron microscopy analyses of infected cells demonstrated that *B. pseudomallei* is sequestered in LC3-positive single-membrane phagosomes rather than double-membrane autophagosomes. On the other hand, engulfed *B. cenocepacia* resides in a vacuole that elicits the characteristic double membranes of typical autophagosomes [128,140]. The *B. cenocepacia*-containing phagosome also acquires LC3 [129]. However, even in wild-type murine macrophages, the bacteria-containing vacuoles remain in contact with newly formed endosomes and delays fusion with lysosomes [126]. Delay in acidification correlates with delayed recruitment of the phagosomal vacuolar ATPase [137,138]. Recent results have shown that in macrophages derived from cystic fibrosis (F508del CFTR) patients, and in a corresponding mouse model, *B. cenocepacia* persists in single-membrane vacuoles that lack LC3 and rarely fuse with lysosomes. These infected cells produce higher levels of IL-1β than infected CFTR-normal macrophages do [128]. Interestingly, *B. cenocepacia* infection leads to the downregulation of the expression of several autophagy-related genes [140]. This effect occurred in both human and mouse macrophages and was mediated through a specific microRNa cluster (Mir17-92) [140].

Mycobacterium tuberculosis

M.tb is the main causative agent of tuberculosis [141]. The main host cell harboring *M.tb* is the alveolar macrophage) [142]. Several mechanisms can be used by alveolar macrophage to control *M.tb* including bacterial degradation in the phagolysosomes, the oxidative response, TNF-induced apoptosis, and autophagy (reviewed in Ref. [143]). Studies have also shown that the inflammasome and autophagy contribute to the clearance of *M.tb* infection. Under some circumstances, *M.tb* is capable of bypassing all these killing mechanisms by using specific host-cell receptors and trafficking networks to create a safe intracellular niche [120–124]. *M.tb* has developed strategies to bypass the inflammatory process mediated by the assembly of the inflammasome. Initial reports indicated that *M.tb* infection does not activate IL-1β production [144]. Mechanistic *in vitro and in vivo* studies using a mutant strain lacking Zmp1 (Rv0198c), a putative Zn^{2+} metalloprotease, indicated that this mycobacterial protein is directly implicated in inhibiting caspase-1-dependent activation and secretion of IL-1β [144]. As is the case for non-flagellated *Shigella* [145], the production of IL-1β was observed via NLRC4-dependent- and ASC-inflammasome activation in macrophages only when using an *M.tb* zmp1-KO strain, resulting in a better control of the infection through increased acidification of *M.tb*-containing phagosomes [144]. In this model, the possibility of an alternate succession of NLRC4- and ASC-dependent inflammasomes was also suggested [144] as described in *Salmonella* infections [6]. Other reports indicate that *M.tb* is in fact capable of inflammasome activation and release of IL-1β employing the *M.tb* region of differentiation locus (RD1) encoding ESX-1 type VII secretion system [146–148]. *M.tb* inflammasome activation depends on the presence of bacterial DNA in the host-cell cytosol engaging AIM2 [149,150]. Further deletion of AIM2 and the observation of IL-1β and IL-18 production uncovered the role of NLRP3-dependent inflammasome system in *M.tb* infection in myeloid cells [151]. In this case, protein tyrosine kinase Syk is thought to participate in the *M.tb*-NLRP3-inflammasome activation [152], akin to what is observed for fungal pathogens [153]. The oxidative response generated by *M.tb* infection also plays a role, where radical oxygen intermediate-dependent NLRP-3 inflammasome activation depends on

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the generation of cardiolipin at the mitochondrial membrane [154], and generation of nitric oxide negatively regulates NLRP-3-inflammasome activation by directed *S*-nitrosylation of NLRP-3 [155]. The NLRP-3-mediated activation of the inflammasome involves potassium efflux [151]. However, *M.tb* is also capable of generating IL-1β independently of NLRP-3 and caspase-1 [151]. Subsequent studies indicate that *M.tb* is able to differentially engage the inflammasome/IL-1β pathway or the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS)/cyclic dinucleotide sensor STING/type-I IFN pathway during infection, and confirmed that this was directly dependent on the bacterium levels of EsXA and/or other EsxA/ESX-1 type VII secretion system-associated factors [151, 156–158], where less EsXA drives selective protective production of IL-1β [156]. Furthermore, as nitric oxide, IFN-β has being reported as a host factor induced by *M.tb* during infection to negatively regulate the NLRP3 inflammasome to bypass inflammation [159,160]. As IFN-β is reported to increase activity of the AIM2 inflammasome [161], induction of IFN-β at lower levels may suppress the NLRP3 inflammasome without activating the AIM2 inflammasome (concept extensively reviewed in Ref. [162]). Nonetheless, mechanisms behind regulation of the NLRP-3 inflammasome during *M.tb* infection need to be further explored, especially in the context of developing novel host mediated therapies looking at its link with the autophagy cellular process.

M.tb survives in infected host cells by blocking phagosome maturation or escaping from phagosomes to the cytosol [163]. Studies indicate that autophagy could also be subverted by *M.tb* to reside into an autophagosome that is not acidified [164]. Overall, the autophagy process depends on the activation status of Ser/Thr kinase Tor [165]. When Tor is active, autophagy is suppressed, but when Tor is inactivated, autophagy is promoted. Importantly, phosphatidylinositol 3-phosphate and hVPS34 are involved in phagosome and autophagosome maturation, only with a different autophagy-specific subunit termed Atg6 (or beclin 1) that is essential for autophagy [166]. Induction of autophagy can overcome phagosome maturation block imposed by *M.tb* [167]. Thus, physiological (nutrient starvation), pharmacological (rapamycin, sodium valproate, vitamin D), or immunological agonists of autophagy (TNF, IFN-α) stimulate mycobacterial phagosome maturation, allowing the host cell to control *M.tb* infection [163]. Specifically, IFN-γ acts on promoting autophagy via the induction of TNF and the immunity-related GTPase protein IRGM1 [49–51,167,168]. The role of IRGM1 in induction of autophagy has been well characterized in several human polymorphism studies, as well as the potential role of other closely related to autophagy genes such as *P_2X_7*, *VDR, NOD2*, and *TLR8* (summarized in Ref. [168]). Other cytokines such as IL-4, IL-10, and IL-13 have been shown to inhibit autophagy via the protein kinase B (Akt), signal transducer and activator of transcription (STAT)-3 and STAT-6 signaling pathways [169].

Recent *in vivo* studies, using a mouse strain lacking *Atg5* expression only in myeloid cells, showed that Atg5 is required to control of *M.tb* growth [170,171], thus indicating that this protein is important for restriction. However, subsequent *in vivo* studies looking at other autophagy proteins reported that except for Atg5, other proteins are not implicated in *M.tb* control. Thus, the role of autophagy in *M.tb* infection is uncertain. In this instance, several hypotheses can be put forward [172]. It is possible that *atg5* could be involved in a yet unrevealed autophagy-independent trafficking network contributing to the control of *M.tb*

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intracellular growth like other TAG proteins [173,174]. For instance, Atg5 is thought to be involved in controlling host-cell death via interactions with Bcl-xL and FADD [175,176]. An alternative explaination is the existence of an only *atg5*-dependent autophagy program [172,177]. Studies have demonstrated that treatment of *M tb*-infected human macrophages with ATP enhances intracellular killing of mycobacteria [178]. These anti-microbial responses appear to be dependent on both apoptosis and autophagy. Apoptosis of infected macrophages reduces intracellular viability of *M.tb* [179]. ATP is also an inducer of inflammasome activation and IL-1βsecretion in LPS-stimulated macrophages. The interplay between autophagy and the inflammasome during *M.tb* infection still needs extensive studies to discern their reciprocal interactions.

Nontuberculous mycobacteria

In contrast to *M tb*, few studies have examined inflammasome activation in cells infected with non-tuberculous mycobacteria (NTM). Nonetheless, *Mycobacterium marinum* has been shown to activate the NLRP3 inflammasome via the Esx-1 secretion system. Using both parental and *Esx-1* mutant bacteria and NRLP3- and ASC-deficient mice, Esx-1 was found to be necessary for increased caspase-1-dependent NRLP3 activation and increased IL-1β release. NLRP3 activation, however, did not restrict *M. marinum* growth, suggesting that inflammasome activation was not beneficial for the host [147]. In contrast, inflammasome activation and IL-1β secretion restricted growth by *Mycobacterium kansasii* in human macrophages [180]. *Mycobacterium abscessus* also activates NRLP3 in human macrophages via Syk kinase and the C-type lectin, Dectin-1 [181]. NLRP3 or ACS knockdown by RNA interference resulted in a significant reduction of IL-1β and a significant increase of viable *M. abscessus* in macrophages, suggesting that inflammasome activation is important in host defense with this pathogenic NTM. The diversity of NTM likely contributes to pathogen-specific effects and defining the mechanisms involved in regulating NTM-inflammasome activation requires further exploration.

A recent study showed that approximately 5% of *M. marinum* were found to be in autophagosomes in the zebrafish model [182]. Ubiquitinated cytosolic *M. marinum* is sequestered in LC3-negative double-membrane compartments that do not require ATG5 to assemble [183]. In one study, azithromycin appeared to impair autophagic and phagosomal degradation resulting in decreased mycobacterial clearance (including *M. abscessus*) by preventing lysosomal acidification and intracellular killing [184]. The smooth morphotype of *M. abscessus* was also recently shown to restrict intraphagosomal acidification resulting in reduced apoptosis and autophagy [185]. However, a detailed understanding of autophagy and/or inflammasome pathways as drivers of intracellular persistence and pathogenesis in NTM is still undefined and crosstalk between the two pathways is unknown. Given the recalcitrance of some NTM to antibiotic therapy, it would be of particular interest to determine if autophagy and/or inflammasome-potentiating treatments aid in the elimination of NTM and the involvement of possible co-regulation between these pathways.

Influenza virus

Influenza viruses are respiratory pathogens in humans that can cause both seasonal epidemics and global pandemics [186]. Distinguishing influenza virus from the bacterial

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pathogens discussed above, these viruses replicate their genomes in the cell nucleus and rely on host machinery to produce and organize the proteins needed for virus assembly and propagation. Likewise, the molecules detected by the innate immune system in influenza virus and bacterial infections are largely distinct, although similar pathways are activated, including the type I IFN system, inflammasomes, and autophagy, that determine the severity and ultimate outcome of infections.

Type I IFNs are a particularly critical component of the innate immune system for the early control of influenza virus infections, as mice deficient in the receptor for these antiviral cytokines succumb to virus doses that are sub-lethal in wild-type mice [187]. To induce IFNs, influenza virus RNAs possessing 5′-tri-phosphate ends are detected by RIG-I in most cell types [188–190]. This allows RIG-I interaction with mitochondrial antiviral signaling protein (MAVS) at the mitochondria and subsequent signaling that activates specific transcription factors required for induction of IFNs [191–194]. In addition, a minor role for the RNA sensor Melanoma Differentiation-Associated protein 5 (MDA5), which also signals through MAVS, has been reported recently [195], and TLR7 is the primary sensor for influenza virus leading to IFN production specifically in plasmacytoid DCs [190,196]. Double knockout of MAVS and TLR7 thus results in increased mortality during infection due to loss of type I IFN production [197]. In addition to IFNs, DCs and macrophages also secrete IL-1β when infected with influenza virus *in vitro*, indicating that inflammasome activation also occurs during infection [198,199]. Confirming the importance of this cytokine *in vivo*, the IL-1R is required for effective development of adaptive immunity during infection in the mouse model [199,200]. NLRP3 and caspase-1 were each found to be required for maximal IL-1β secretion by infected macrophages and DCs [199], and knockout of these molecules in mice results in enhanced lethality from influenza virus infection [201,202]. Linking the type I IFN induction system to inflammasome activation, RIG-I contributes to upregulation of NLRP3 inflammasome components through type I IFN signaling, and remarkably, RIG-I can also form a non-canonical inflammasome complex with ASC and caspase-1 [203]. Further highlighting the importance and connectivity of these pathways, the influenza virus NS1 protein directly binds to RIG-I and antagonizes cellular production of both IFNs and IL-1β [189,204–206]. Thus, the viral sensing pathways that lead to type I IFN and IL-1β secretion are interrelated and are both critically involved in anti-influenza virus immunity.

NLRP3 inflammasome activation during influenza virus infections occurs through at least four distinct and potentially redundant mechanisms that are largely virus specific. First, NLRP3 inflammasomes can be activated by viral ssRNA or dsRNA that are produced in abundance during infection [201]. Second, the matrix protein 2 (M2) of influenza virus, a proton-selective ion channel, can activate the NLRP3 inflammasome in a manner that is dependent on its ion channel activity and localization to the Golgi apparatus, indicating that aberrant intracellular proton gradients can serve to activate this inflammasome [207]. Third, the influenza virus PB1-F2 protein is able to activate the NLRP3 inflammasome, dependent on the formation of high-molecular-weight aggregates that disrupt mitochondria [208,209]. Fourth, the cellular protein RNase L, which is upregulated and activated by IFNs during influenza virus infection, produces RNA fragments possessing unusual termini that are capable of triggering activation of the NLRP3 inflammasome [210]. The relative

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contributions of each of these inflammasome activators during infection are unclear, although the varied mechanisms of inflammasome triggering further support the significance of this pathway in anti-influenza virus immunity.

Type I IFN production and inflammasome activation are also intricately intertwined with cellular autophagy in controlling the outcome of influenza virus infection. Interestingly, the production of specific influenza virus proteins (hemagglutinin and M2) stimulates autophagy [211], and the virus requires the autophagy pathway for optimal replication [212,213]. However, M2 concurrently limits autophagosome fusion with lysosomes [214,215]. Taken together, this suggests that inducing the formation of autophagosome membranes while dampening the degradative potential of these compartments is beneficial to the virus. Importantly, cells also respond to influenza virus infection by upregulating mitophagy through activation of the NOD2–RIPK2 signaling axis, which leads to phosphorylation and activation of the critical autophagy factor ULK1 [216]. In the absence of RIPK2 or ULK1, accumulation of damaged mitochondria during infection leads to further activation of the NLRP3 inflammasome during infection [216]. In addition to limiting NLRP3 activation, mitophagy can also decrease the number of mitochondrial signaling platforms for RIG-I, thus also reducing production of IFNs. The increased mortality of RIPK2 KO mice during influenza virus infection suggests that preventing excessive activation of type I IFN and inflammasome pathways is an essential role for autophagy in limiting virus-induced pathology [216]. Overall, the results of the studies discussed here demonstrate that complex interactions between type I IFN pathways, inflammasomes, and autophagy must be properly balanced to limit pathology while effectively clearing infection.

Conclusions

This review summarizes recent findings on the activation and subversion of the autophagy and inflammasome surveillance pathways during infection by a collection of pathogens. It is clear that each pathogen interacts with these pathways in a very unique fashion. While the autophagosome and the inflammasome implement checks and balances on each other, infectious agents likely employ their virulence factors to alter these checks and tip the balance toward a precise environment that favors their survival. As highlighted in this review, knowledge about the autophagy/inflammasome interconnection and their subversion is still lacking for many pathogens. We also realize that the way autophagy and inflammasomes interact is more sophisticated than previously expected. Therefore, each infectious disease still requires comprehensive studies to tease out the relationships between of autophagy and inflammasomes, which may lead to identification of therapeutic targets.

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Abbreviations

PRRs	pattern recognition receptors
PAMPs	pathogen-associated molecular patterns
DAMPs	damage-associated molecular patterns
NLRs	Nucleotide-binding domain, leucine-rich repeat containing family
AIM2	absent in melanoma 2
PYD	pyrin domain
CARD	caspase activation and recruitment domain
ASC	apoptosis-associated specklike protein
mtDNA	mitochondrial DNA
TLRs	Toll-like receptors
LLO	listeriolysin O
PI-PLC and PC-PLC	phospholipases C
NDP52	nuclear domain 10 protein 52
T3SS	Type three secretion system
M.tb	*Mycobacterium tuberculosis*
NTM	nontuberculous mycobacteria
IFN	interferon
RIG-I	retinoic acid-inducible gene I
MAVS	mitochondrial antiviral signaling protein
M2	matrix protein 2

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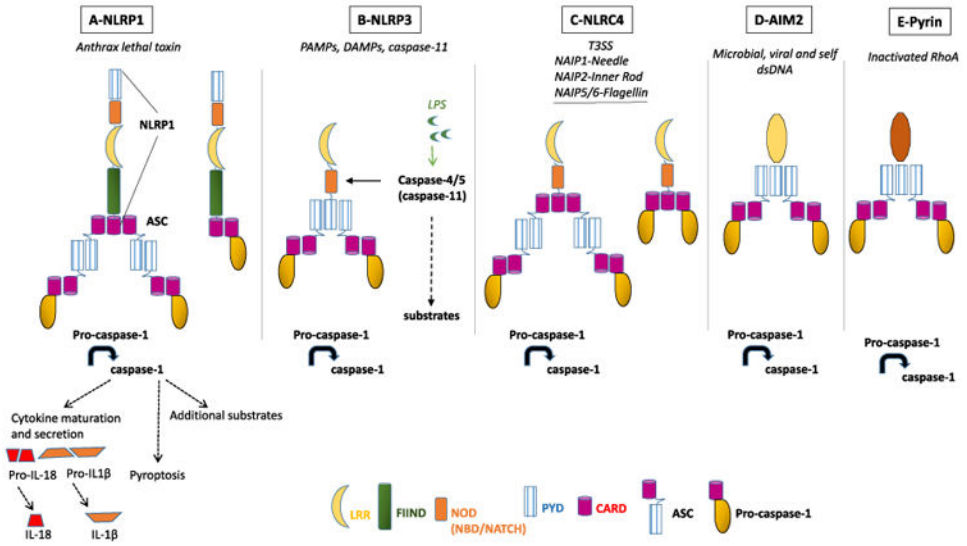

Fig. 1.

Canonical and non-canonical inflammasomes. (A) NLRP1 is activated by proteolysis consecutive to cell intoxication by the anthrax lethal toxin leading to the recruitment of the adaptor ASC and pro-caspase-1. Alternatively, activated NLRP1 can directly recruit pro-caspase-1 through its CARD domain. The drawing represents human NLRP1, and murine NLRP1 lacks the CARD domain. Note that NLRP1 carries both PYD and CARD domains and therefore can also recruit ASC via its PYD, as presented in panel B. (B) NLRP3 is activated in response to cell stress and infection, leading to the recruitment of ASC and pro-caspase-1. The non-canonical inflammasome consists of LPS-activated caspase-4/5 (in human), or caspase-11 (in mice), which then promotes NLRP3 activation. (C) NLRC4 inflammasome is activated by T3SS or by flagellin produced by Gram-negative bacteria. Activated NLRC4 can successively recruit ASC and pro-caspase-1, or can recruit directly pro-caspase-1. (D) AIM2 inflammasome is activated upon binding to double-stranded DNA. (E) Pyrin inflammasome is activated by bacterial toxins that inactivate the RhoA GTPase. Note: direct recruitment of pro-caspase-1 is not represented in panels D and E, but can proceed via CARD domain as presented in panels A and C.

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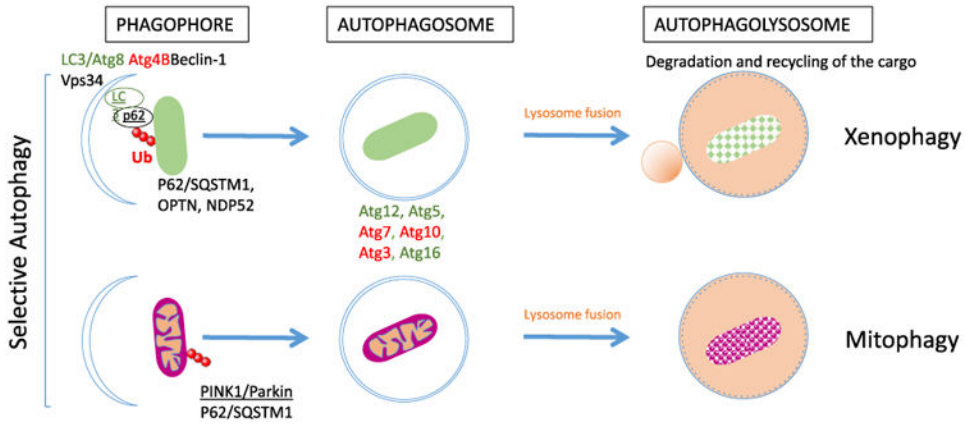

Fig. 2.

Selective autophagy. In selective autophagy, some molecular determinants or ubiquitin chains on the cargo are recognized by several autophagy receptors including p62 (or SQSTM1), which link the cargo to the autophagy machinery. PINK1/Parkin is a mitochondria-specific ubiquitination system, which can be recognized by autophagy receptors. Some Atgs are important to initiate formation of the phagophore as, for example, Beclin-1, Vps34, and LC3, whereas, additional Atgs are sequentially recruited for elongation and closure of the autophagosome including Atg3, Atg5, Atg7, Atg10, Atg12, and Atg16 (only a few molecules are presented here, reviewed in Ref. [15]). The autophagosome fuses with lysosomes to generate the autophagolysosome for degradation and recycling of the cargo.

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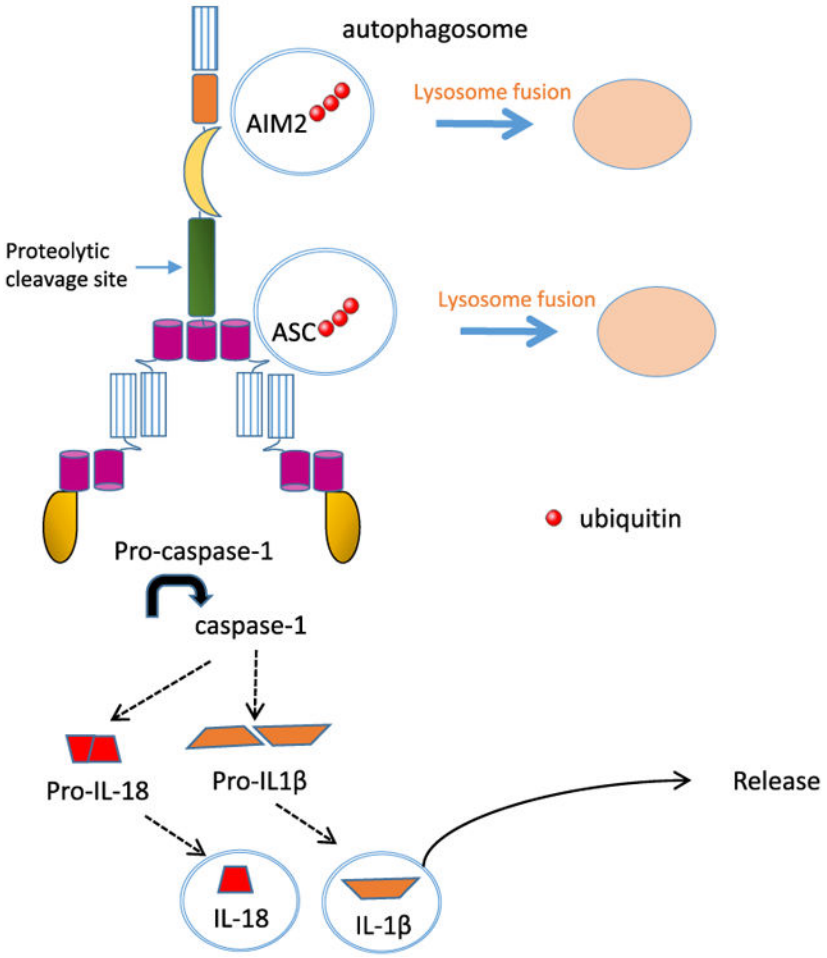

Fig. 3.

The mechanism by which autophagy controls activation of the inflammasome. Inflammasome sensors such as AIM2 and adaptor molecule ASC are ubiquitinated then targeted for degradation by autophagy. Similarly, the production of pro-IL-1β is regulated by autophagy. On the other hand, active IL-1β and IL-18 may exploit the autophagy machinery for packaging and release to extracellular milieu.