Chapter 6
The Interplay Between Pattern Recognition Receptors and Autophagy in Inflammation

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Abstract Pattern recognition receptors (PRRs) are sensors of exogenous and endogenous "danger" signals from pathogen-associated molecular patterns (PAMPs), and damage associated molecular patterns (DAMPs), while autophagy can respond to these signals to control homeostasis. Almost all PRRs can induce autophagy directly or indirectly. Toll-like receptors (TLRs), Nod-like receptors (NLRs), retinoic acid-inducible gene-I-like receptors (RLRs), and cyclic guanosine monophosphate–adenosine monophosphate synthase (cGAS)-stimulator of interferon genes (STING) pathway can induce autophagy directly through Beclin-1 or LC3-dependent pathway, while the interactions with the receptor for advanced glycation end products (RAGE)/high mobility group box 1 (HMGB1), CD91/Calreticulin, and TLRs/HSPs are achieved by protein, $Ca2^{+}$, and mitochondrial homeostasis. Autophagy presents antigens to PRRs and helps to clean the pathogens. In addition, the induced autophagy can form a negative feedback regulation of PRRs-mediated inflammation in cell/disease-specific manner to maintain homeostasis and prevent

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excessive inflammation. Understanding the interaction between PRRs and autophagy in a specific disease will promote drug development for immunotherapy. Here, we focus on the interactions between PRRs and autophagy and how they affect the inflammatory response.

Keywords PRRs · Autophagy · TLRs · NLRs · cGAS-STING · RLRs · RAGE · HMGB1 · Calreticulin · HSPs

6.1 Introduction

6.1.1 Pattern Recognition Receptors

Pattern recognition receptors (PRRs) are host sensors of exogenous and endogenous "danger" signaling existed in cells of innate immune systems, such as dendritic cells (DCs), macrophages, monocytes, neutrophils, and epithelial cells [150]. They can recognize molecules typically from microbial pathogens called pathogen-associated molecular patterns (PAMPs) [83] and components of host cells released during cell damage or death, which are damage associated molecular patterns (DAMPs). PRRs are key components of the innate immune system [104] evolving before adaptive immunity and also distinguish complex molecular architecture to activate down-regulatory signaling to promote homeostasis in immunologic responses [191]. Upon the binding of PRRs with PAMPs or DAMPs, the downstream signaling is activated to release the inflammatory cytokines, thereby initiating an adaptive immune response [83, 160].

6.1.2 Classification of PRRs

Diverse PRR families have been identified as mediators of PAMPs or DAMPs recognition. Toll-like receptors (TLRs) are the most prominent PRRs with the capacity to recognize the widest range of PAMPs or DAMPs. While TLR1, 2, 4, 5, 6, and 10 are located on the cell surface, TLR3, 7, 8, and 9 present in intracellular membranes. TLR signaling can induce pro-inflammatory cytokines and type I interferons (IFNs) depending on the myeloid differentiation factor 88 (MyD88) or the Toll/IFN response factor (TRIF) [68]. In contrast, NOD-like receptors (NLRs) are cytoplasmic PRRs made up of three subfamilies: NODs, NLRPs, and the IPAF [82, 150]. NOD1 and NOD2 can initiate pro-inflammatory signaling by activating NF-κB dependent pathway. NLRP3 induces the formation of the inflammasomes in response to the stimulation from DAMPs including extracellular ATP, hyaluronan, uric acid, and so on, which can activate caspase-1 for the release of IL-1β, and IL-18.

There are also several other PRRs that can recognize more specific types of PAMPs or DAMPs. Cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS) can sense the cytoplasm DNA and catalyze the formation of second messenger cGAMP for recruiting the adaptor protein stimulator of IFN gene (STING) [65], which induces the production of IFNs and other pro-inflammatory cytokines through NF-κB, TBK1, and IRF3 dependent pathway [165]. RIG-like receptors (RLRs), including RIG-I, MDA5, and LGP2, can detect cytoplasmic RNA, such as viral RNA and self RNA [98]. RLR signaling induces the production of IFNs through MAVS dependent pathway and can also cross talk with cGAS-STING and inflammasome signaling pathway for the regulation of immune response. Scavenger receptors such as CD36, CD44, CD68, CD91, CXCL16, and the receptor for advanced glycation end products (RAGE) expressed on macrophages or other cell types are mainly responsible for the recognition of DAMPs including HMGB1, Calreticulin, HSP, ATP, S100, and host DNA, as well as some PAMPs, and mediate inflammation, oxidative stress, and apoptosis [135].

6.1.3 PRRs and Inflammatory Disease

PRRs-mediated inflammation contributes to the clearance of microbial infection or tissue damage [2, 9], but also causes autoimmune disease. Overproduction of pro-inflammatory cytokines by immune cells can be fatal and is also critical for the pathogenesis of autoimmune diseases [109]. It is well known that septic shock is caused by acute inflammation from the activation of TLR signaling in response to bacterial components. cGAS-STING can sense self-DNA that is released or leaked from the nucleus and mitochondria into the cytoplasm and trigger autoimmunity in Aicardi-Gourtieres syndrome [46, 102]. TLR9 and non-canonical autophagy also play vital roles in mediating systemic lupus erythematosus [52]. In the mouse model, the lack of negative control of PRRs signaling is associated with autoimmune disease. Loss of TANK, an inhibitor of TLR signaling results in autoimmune glomerular nephritis [77]; while the loss of A20, a negative regulator of NF-κB activator, can result in multi-organ inflammatory disorders [13, 56]. In addition, TLR-mediated inflammation contributes to the pathogenesis of ischemia-reperfusion myocardial injury [6].

In contrast, triggering the PRRs-mediated immune response is a strategy for cancer immunotherapy. One of the ideal targets is the cGAS-STING pathway. STING mediates multiple types of tumor killing effects by recognizing self-DNA from dying tumor cells [24]. The combination of cGAMP with irradiation or immune system-checkpoint inhibitors provides a promising outcome for tumor immunotherapy [25, 27]. In addition, CD91/Calreticulin on plasma membrane promotes an “eat” me signal in tumor cells [119]. Any drug/therapy designed to promote calreticulin escape of ER retention to the plasma membrane can enhance tumor immunity and trigger CD91/calreticulin-mediated tumor killing effects.

6.1.4 Autophagy and Innate Immunity

Autophagy is a conserved "self-eaten" cellular activity in response to starvation. In this activity, cytosolic material is delivered into double-membrane vesicles (autophagosomes) and fused with late endosomes or lysosomes [112]. However, cytosolic bacteria damaged organelles or protein aggregates could also be eliminated through selective autophagy, which indicates the potential of autophagy in regulating innate immunity [180]. Autophagy plays important roles in host cell defense to bacteria invasion including *Shigella flexneri* [121], *Listeria monocytogenes* [136], *Salmonella Typhimurium* [11], and *Mycobacterium tuberculosis* [47]. The importance of autophagy in innate immunity is proven by the fight of bacteria against autophagy [62]. Some bacteria such as *S. Typhimurium*, *M. tuberculosis*, and *Bacillus anthracis* can express some genes or toxins to inhibit autophagy initiation signaling through blocking pro-autophagy signals such as mTOR and reactive oxygen species (ROS) or promoting anti-autophagy signal through a second messenger called cyclic AMP [8, 38, 154]. The bacterium can inactivate autophagy components. For example, *Legionella pneumophila* can produce RAVZ protein, an ATG4B-like cysteine protease to degrade LC3 [20]. *Shigella flexneri* can invade epithelial cells and escape from autophagy by T3SS effector VirA to inactivate RAB GTPases [36]. The most interesting pathway of evasion of autophagy recognition is through masking the bacterial surface by either recruiting host cytoskeleton proteins on their surface in *Listeria monocytogenes* [189] or abolish the binding of ATG5 in *S. flexneri* [121]. Recently, a T3SS effector SopF that potently blocked *Salmonella* autophagy was reported. V-ATPase can recruit ATG16L1 onto bacteria containing vacuole after bacteria caused vacuolar damage, which was blocked by SopF, leading to autophagy inhibition and enhanced *S. Typhimurium* proliferation in vivo. In addition, some bacterium can block autophagosome fusion with the lysosome, although the mechanism remains unclear. Therefore, PRR induced autophagy could be a promising target for drug design in the treatment of bacterial infection.

6.1.5 Autophagy Contributes to Regulate PRRs-Mediated Inflammation

The connection between PRRs and autophagy is well-demonstrated in Crohn's disease. Susceptible genes for Crohn's disease are NOD2 and ATG16L1, which are core autophagy genes [31]. Functional studies show that NOD2 can recruit ATG16L1 to the bacterial entry site for inducement of autophagy [171]. Unexpectedly, the hypomorphic ATG16 allele can enhance the resistance of mice to *Citrobacter rodentium* and uropathogenic *Escherichia coli* [107, 175]. These results might suggest not only the cooperation between PRRs and autophagy but also the negative feedback regulation.

Currently, two different types of autophagy which are LC3- or Beclin 1-dependent autophagy involve the interaction with PRRs. LC3-dependent autophagy is achieved by recognition of 'eat-me' signals of cargoes (e.g., galectin-8 from bacteria, poly-ubiquitin) by cargo receptor p62 and its paralog NBR1, NDP52, T6BP, and optineurin for the association with LC3/GABARAP on phagophores [14, 70]. The generation of ubiquitin "eat-me'"signal is PRR signaling-dependent [64]. More interestingly, Beclin-1/Bcl-2 complex is a toggle switch regulating autophagy/apoptosis. Beclin-1, a Bcl-2 homology 3 (BH3) domain only protein [120], can initiate autophagy through recruiting other autophagic proteins and forming Beclin-1-Vps34-Vps15 core complex [51]. Also, the interaction of Beclin-1 with anti-apoptotic Bcl-2 family members prevents Beclin-1-mediated initiation of autophagy [91].

Most PRRs can affect autophagy directly or indirectly. TLRs, NLRs, RLRs, and cGAS-STING can induce autophagy directly through Beclin-1 or LC3-dependent pathway, but the interactions with RAGE/HMGB1, CD91/Calreticulin, and TLRs/HSPs are achieved by protein, $Ca2^{+}$, and mitochondrial homeostasis. Through the close interaction with PRRs, autophagy presents antigens to PRRs that helps in destroying pathogens. Also, autophagy-mediated PRR inflammation prevents the over-reaction of the immune response. Therefore, the focus of this write-up is to discuss the association between PRRs and autophagy which is a promising therapy in the management of infection concerning the inflammatory response.

6.2 Pathogen-Dependent PRR Signaling and Autophagy

6.2.1 TLRs

The TLRs are integral transmembrane proteins with N-terminal ectodomain of leucine-rich repeats (LRRs) and intracellular Toll/IL-1 receptor (TIR) domain. It contains 6 members (TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10) located on the plasma membrane and 4 (TLR3, TLR7, TLR8, and TLR9) in the lumen of endocytic compartments that uptake microbial components [161]. Extracellular LRRs of different TLRs with diversity in length, number, and N-linked glycosylation can form a horseshoe-shaped structure for pathogen recognition and shape the recognition specificity. The TLR heterodimers can also regulate the recognition specificity or versatility of PAMPs. TLR4 and TLR5 recognize LPS from Gram-negative bacterial and bacterial flagellin from flagellated bacteria, respectively, but TLR10 can sense the influenza virulence from influenza A virus. However, TLR2/TLR10 heterodimers can sense Listeria proteins. TLR2 combined with TLR1 or TLR6 can recognize most of extracellular PAMPs such as lipopeptides, peptidoglycans, lipoteichoic acid, zymosan, and mannan. In endocytic compartments, endocytic TLRs mainly recognize RNA, TLR3 for viral dsRNA and siRNAs, TLR7/8 for both viral and bacterial single-stranded RNA (ssRNA), TLR9 for unmethylated CpG DNA motif from bacteria [161].

6.2.1.1 TLRs Signaling Pathway

Upon binding with PAMPs, intracellular TIR domain recruits adaptor proteins to activate NF-κB, MAPK signaling for the production of pro-inflammatory cytokines and type I IFNs [118]. Although there are several adaptor proteins reported in TLRs pathways including MyD88, TRIF, MyD88 adapter-like (Mal/TIRAP), Trif-related adaptor molecule (TRAM), and sterile α and armadillo motif-containing protein (SARM). TRIF is recruited by TLR3 and TLR4, and for the rest TLRs, MyD88 is commonly used.

6.2.1.2 TLRs and Autophagy

Cytosolic TLRs such as TLR7/8 and TLR9 exist in the endosome. How endosomal TLRs recognizes cytosolic viral components remains unclear. Endosomal TLRs may "find" and "eat" the viruses through autophagy. For instance, TLR7 recognizes the replicating vesicular stomatitis virus (VSV) in the cytosol of plasmacytoid dendritic cells (pDCs) that are delivered in the lysosomes through autophagy for activating TLR7 signaling [87]. The essential role of autophagy in activating TLR7/9 signaling is confirmed in autophagy-deficient mice or cells. Atg5-deficient mice are susceptible to systemic VSV infection. Without Atg5, pDCs does not secrete IFN-α and IL-12, which are downstream pro-inflammatory cytokines of TLRs signaling [163].

Autophagy does not just passively deliver the PAMPs to TLRs. It also utilizes TLR signaling to promote phagosome maturation, which is observed by the co-occurrence of TLR activation and fusion with lysosomes. Phagocytosis of the fungal cell wall component zymosan can induce Atg proteins-dependent LC3 recruitment to phagosomes and fusion with lysosomes [147].

In the case of extracellular TLRs, they do not need the help of the autophagy to "find" the PAMPs but induce the autophagy for "eating" pathogens. Autophagy inducement is firstly observed in TLR4 [184], then in various TLRs including TLR1-7, which enhanced the microbial clearance. Interestingly, this process is mediated by a relatively conserved mechanism through the TRIF/MyD88 axis. TRIF/MyD88 can be recruited to TLRs after TLR binding with its ligand for the activation of AP-1/IRF3/NF-κB mediated pro-inflammatory cytokines and IFNs as well as regulating Beclin-1/Bcl-2 interaction for the induction of autophagy [152] (Fig. 6.1).

6.2.1.3 TLRs and Autophagy in Autoimmune Disease

The cooperation between autophagy and endosomal TLRs is not always favorable for health but contribute to autoimmune disease. The recruitment of TLR9-containing endosomes to the autophagosomes with DNA-containing antigens through BCR signals can result in B cells hyper-responses [23]. Another study reports different mechanism for TLR9 and non-canonical autophagy-mediated systemic lupus erythematosus, which is caused by uncontrolled production of type I IFNs. Recruitment of TLR9 and LC3 in response to DNA immune complexes results in LC3-associated phagocytosis, thus producing IFN-α [52].

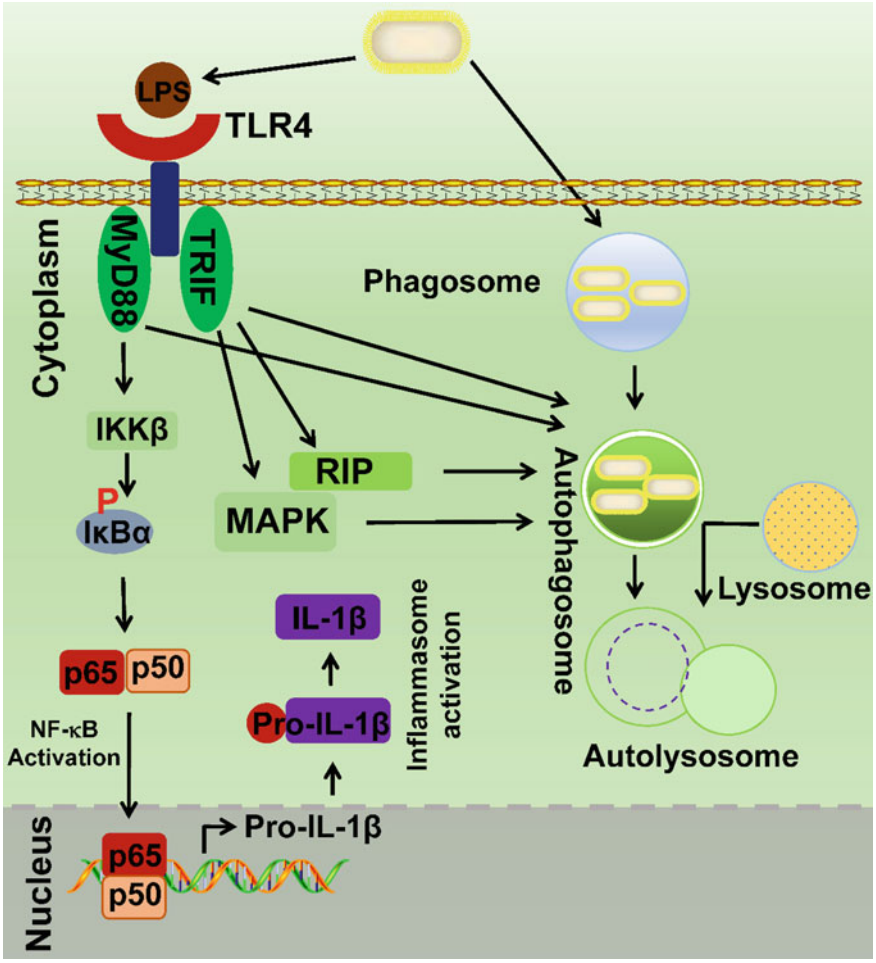

Fig. 6.1 TLRs and autophagy. TLR4 induces autophagosome formation via TRIF-mitogen-activated protein kinase (MAPK)/RIP signaling axis. TLR4 also triggers the myeloid differentiation primary response gene 88 (MyD88)-dependent signaling pathway to activate the transcription factor nuclear factor κB (NF-κB), and promotes pro-IL-1β expression. These processes facilitate fusion of the autophagosomes with the lysosomes, which in turn finally results in the killing of intracellular bacteria

6.2.2 NLRs

Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are intracellular sensors of PAMPs and DAMPs including ATP, mtDNA, and ROS that are primarily expressed in macrophages and other professional antigen-presenting cells (APCs). NLRs are signal transduction ATPases with three domains, including a C-terminal leucine-rich repeat (LRR) domain for ligand sensing, a central NATCH,

telomerase-associated protein 1 that mediates self-oligomerization and is essential for activation of NLRs, and an N-terminal effector domain for adapter recruitment [80]. NLRs are classified into three subfamilies according to the nature of the N-terminal domains: NLRC subfamily such as NOD1, NOD2, NLRC3, NLRC4, and NLRC5 with caspase activation and recruitment domain (CARD), NLRP subfamily with pyrin domain including NLRP1-10 for inflammasome assembly, and NAIP subfamily with three baculovirus inhibitors (BIRs) of the apoptosis protein repeat domain such as NAIPs [79, 115].

6.2.2.1 NLR Signaling Pathway

NLR signaling can regulate the production of pro-inflammatory cytokines, and assembly of inflammasomes. NOD1 and NOD2 can sense bacterial peptidoglycan in epithelial cells of the gastrointestinal tract for recruitment of receptor-interacting protein kinase 2 (RIP2), leading to activation of NF-κB and AP-1 signaling for the production of type I INFs and pro-inflammatory cytokines [129]. Unexpectedly, some NLR members such as NLRP4, NLRP6, and NLRP12 can also inhibit NF-κB signaling cascades, although the mechanism is unclear. NLRC3 are reported to inhibit NF-κB signaling through cross talk with TLR4-mediated NF-κB signaling [149]. In addition, NLRs are essential for the assembly of inflammasomes, which can mediate the activation of caspase-1 for the maturation of inactive cytokine from pro-inflammatory stimuli [108, 150]. Upon the detection of PAMPs with NLRs, self-oligomerization occurs followed by recruitment of apoptosis-associated speck-like protein containing a CARD (ASC) as an adaptor for caspase-1 activation. Currently, NLR inflammasomes are reported to mediate the inflammatory response of different DAMPs or PAMPs, e.g., NLRC4 inflammasomes for flagellin, T3SS and T4SS [45, 155, 195], NLRP1 for anthrax lethal toxin [113] and NLRP3 for ATP, amyloid, monosodium urate crystals and silica [16]. Interestingly, these cytosol PAMPs might be generated by IFN inducible protein IRGB10, which can damage the bacterial membrane for the release of DNA and LPS [106].

6.2.2.2 NLRs and Autophagy

NLRs are very important to clear the cytosol-dwelling bacteria. NLRs can also directly induce autophagy in response to bacterial invasion [23, 171]. Different from TLRs, RIP2, and ATG16L1 play an essential role in the inducement of autophagy. Atg16L1 is recruited to the plasma membrane by NOD2 at the first site of bacterial invasion for bacterial trafficking to the autophagosomes and fusion with the lysosomes [171]. NOD2 mutation and Atg16L1 SNPs are associated with Crohn's disease, which is likely to be inflammatory bowel disease due to immunodeficiency. RIP2 is essential for NOD2-dependent autophagy through recognition of muramyl dipeptide from Gram-positive bacteria [57].

NLR inflammasomes can reciprocally regulate autophagy in cell context and antigen-dependent manner. NLRP4 signalosome can induce autophagy in phagosomes in response to group A *Streptococcus* infection through dissociation from Beclin-1 [71]. NLRP3 inflammasome can trigger autophagy for the promotion of *Pseudomo aeruginosa* phagocyte destruction [29]. However, TLR2/TLR4 can activate autophagy but degrade NLRP3 and reduce IL-1β production [21] (Fig. 6.2).

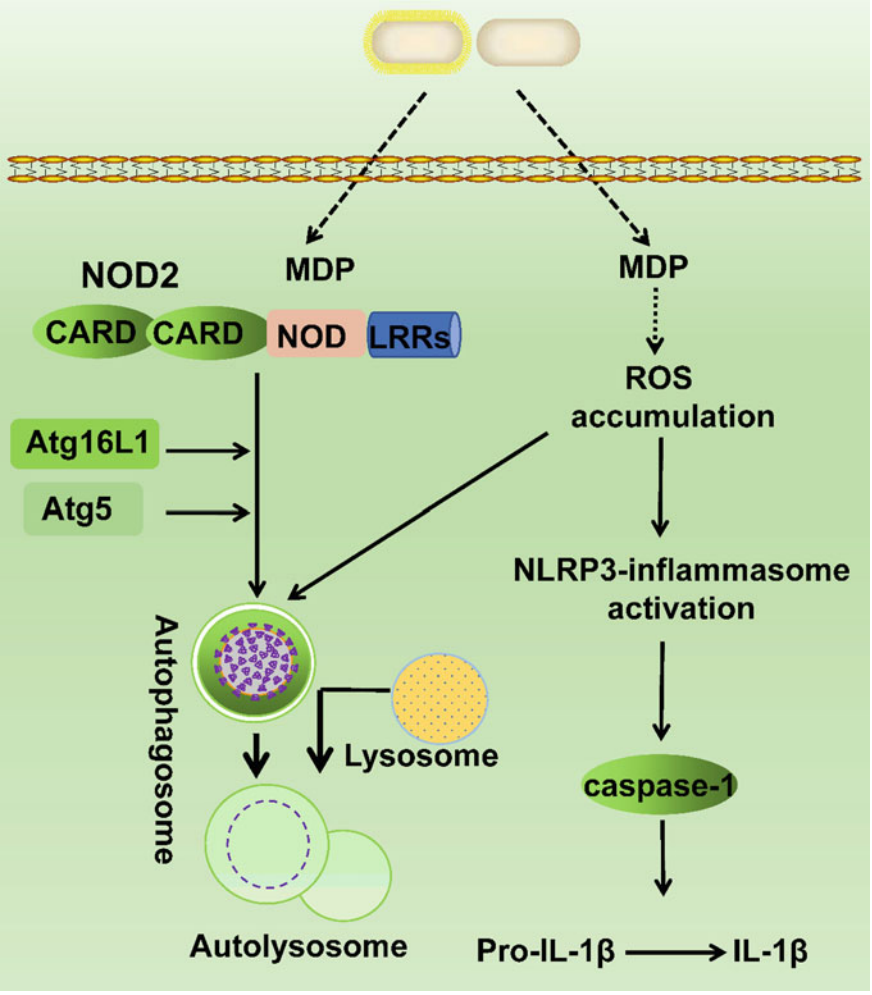

Fig. 6.2 NLRs and autophagy. Activation of NOD2 by bacteria induces autophagosome formation. NOD2 is activated by muramyl dipeptide (MDP) which is found in both Gram-negative and Gram-positive bacteria. In this process, autophagy proteins such as Atg5 and Atg16L1 are required. Autophagy also regulates NLRP3 inflammasome-induced inflammatory responses. MDP released by bacterial infection regenerates ROS, leading to NLRP3 inflammasome activation, which finally activates caspase-1 and results in the maturation and secretion of pro-IL-1β and pro-IL-18

6.2.3 cGAS-STING Pathway

6.2.3.1 The cGAS-STING Pathway of Cytosolic DNA Sensing

cGAS-STING is a cytosolic DNA sensing pathway for triggering immune responses. cGAS can sense the cytosolic DNA and catalyze the formation of second messenger cGAMP which is an endogenous high-affinity ligand for the adaptor protein STING [65]. Upon the binding with cGAMP, the conformation of STING changes and translocates from the endoplasmic reticulum (ER) to the Golgi apparatus for protein modification [145]. The modified STING can recruit and activate TANK-binding kinase 1 (TBK1) and IFN regulatory factor 3 (IRF3) [165]. In addition, STING also activates NF-κB for the production of type I IFNs and other pro-inflammatory cytokines.

6.2.3.2 cGAS Activation

cGAS can bind to the sugar–phosphate backbone of dsDNA and is activated upon binding with dsDNA [159]. Therefore, oxidation of DNA bases caused by ultraviolet irradiation does not change the binding ability with cGAS [43]. ssDNA can also activate cGAS through the formation of internal duplex or Y-shaped structure [53]. Although short dsDNA with 15 bp can activate cGAS, long DNA is more essential for cGAS activation. dsRNA can not activate cGAS although it can bind with cGAS [193].

6.2.3.3 Functions of the GAS-STING Pathway

The cGAS-STING pathway can sense DNA released from microbial pathogens including DNA viruses, retroviruses, endogenous retroviruses and retroelements, and DNA producing bacteria. In cGAS-deficient mice, IFN induction is absent in response to the infection of several DNA viruses including herpes simplex virus, vaccinia virus, adenovirus, cytomegalovirus and Kaposi's sarcoma-associated herpesvirus (KSHV) [92, 101, 125, 182, 192]. Retroviruses HIV-1 and HIV-2 might also be detected by cGAS [85]. HIV can reversely transcribe viral RNA into cDNA and inject the cDNA into the nucleus for the integration to the host genome. However, if the cDNA leak into the cytoplasm due to broken viral capsid, the cDNA can be sensed by cGAS for triggering the induction of IFNs and other inflammatory cytokines. cGAS-deficient mice also cannot respond to multivalent antigens such as bacterial capsular polysaccharides that activate the transcription of endogenous retroviral RNA and is reversely transcribed to DNA by the RNA helicase RIG-I for cGAS sensing [190]. Many intracellular bacteria including *Mycobacteria*, *Legionella*, *Listeria*, *Shigella*, *Francisella*, *Chlamydia*, *Neisseria*, group B *Streptococcus* and so on induce IFNs through the cGAS-STING pathway although it is unclear how bacterial DNA might gain access to the cytoplasm [4, 5, 22, 48, 157, 194].

6.2.3.4 cGAS-STING Pathway in Autoimmune Diseases

Self-DNA that released or leaked from the nucleus and mitochondria into cytoplasm can activate cGAS and trigger autoimmunity. In Aicardi-Gourtieres syndrome, a collection of monogenic autoimmune disease, the mutation in TREX1 which is an exonuclease of dsDNA and ssDNA or RNase H2 which degrades RNA in RNA–DNA hybrid leads to elevated expression of type I IFNs. Mice lacking TREX1 or RNase H2 activates cGAS-STING pathway and exhibits elevated expression IFNs [46, 102]. In patients with early-onset vasculopathy and pulmonary inflammation, gain-of-function mutations of the gene encoding STING are identified, which can render the protein constitutively active and result in IFN production [95]. These genetic studies support the role of the cGAS-STING pathway in autoimmune diseases.

6.2.3.5 cGAS-STING Pathway in Cancer

Self-DNA from dying tumor cells can also trigger the cGAS-STING pathway to induce IFNs [24]. Interestingly, STING mediates multiple types of tumor killing effects. STING is required for priming $CD8^+$ T cells against tumor-associated antigens and is also essential for the anti-tumor effects of radiation. CD47 antibody, a phagocytosis-inhibitory protein, exerts STING-dependent anti-tumor effects [28, 94]. The anti-tumor effect mediated by STING probably through tumor-derived DNA, which delivers to the cytoplasm of DCs and facilitates the activation of $CD8^+$ T cells. Therefore, activation of the cGAS-STING pathway is applied in anti-tumor therapy. One common strategy is the combination of cGAMP with irradiation or immune system-checkpoint inhibitors [25, 27]. However, in some cases, activation of STING facilitates tolerogenic response and metastasis [18, 63]. Optimal combination of different treatments may be essential to achieve a good clinical outcome.

6.2.3.6 cGAS-STING and Autophagy

The cytosolic DNA sensor cGAS can sense cytosolic DNA from bacteria or virus and activate ubiquitin-mediated autophagy for microbe clearance. During *M. tuberculosis* infection, the STING-dependent cytosolic pathway can recognize mycobacterial DNA, which exposed to the host through extra-embryonic spermatogenic homeobox 1 (ESX-1) secretion system, resulting in the recruitment of ubiquitin chains, LC3-binding autophagic adaptors p62 and NDP52 for targeting the mycobacteria to the selective autophagy pathway [179]. Also, cGAS-STING can interact with Beclin-1 to promote PI3 KC3-induced autophagy [159]. Autophagy can also repress STING-dependent IFN responses through Atg9a [145]. Lack of Atg9a induces overactivation of type I IFN through promoting the interaction between STING and TBK1. In the cGAS sensing pathway, the negative feedback control by autophagy occurs through the release of Rubicon, which enhances the autophagy-mediated degradation of pathogen DNA [90] (Fig. 6.3).

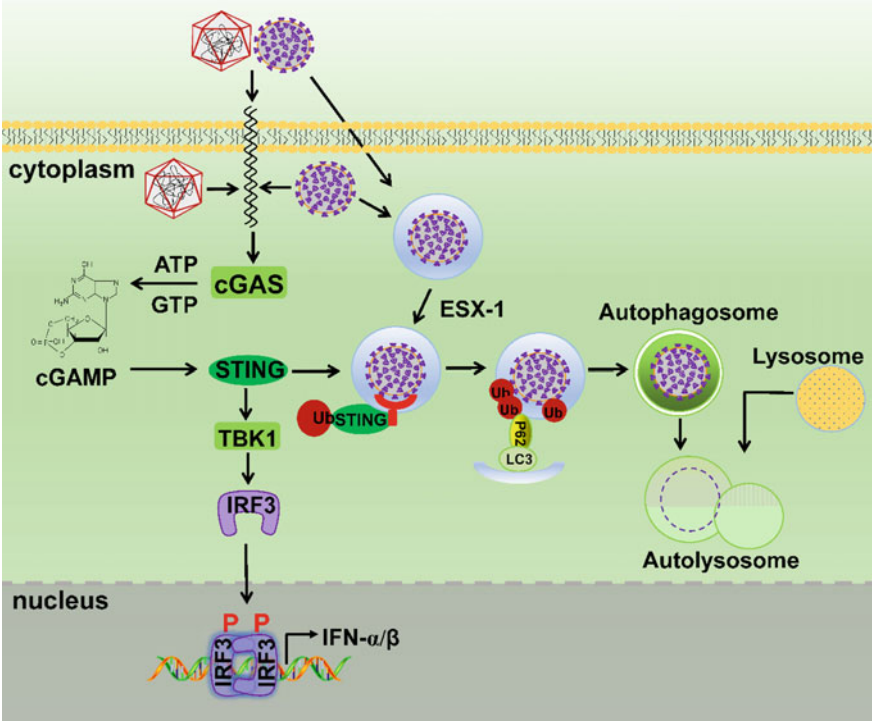

Fig. 6.3 cGAS-STING signaling and autophagy. cGAS-STING pathway mediates anti-microbial innate immunity by inducing the production of type I IFNs and inflammatory cytokines upon recognition of microbial DNA. During bacterial clearance, bacterial extracellular DNA, which is exposed to the host through ESX-1-mediated permeabilization of the phagosomal membrane, is recognized by the STING-dependent cytosolic pathway. The ubiquitinated bacterial DNA, which binds to the autophagosome-associated protein LC3 via adaptor protein p62 and NDP52, is targeted to the selective autophagy pathway

6.2.4 RIG-I-like Receptors (RLRs)

Retinoic acid-inducible gene (RIG-I)-I-like receptors (RLRs) are cytoplasmic sensors of viral RNA [122]. RLRs includes three members: RIG-I, melanoma differentiation associated factor 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2). They are a family of DExD/H box RNA helicases with the capacity to hydrolyze ATP, bind and possibly unwind RNA. RIG-I and MDA5 have two additional domains, an N-terminal region consisting of tandem CARDs, and a C-terminal repressor domain embedded within the C-terminal domain for autoregulation. However, LGP2 can only work as a regulator of RIG-I and MDA5 signaling due to lack of N-terminal CARDs [188].

6.2.4.1 RLRs Signaling Pathway

Upon the detection of viral RNA, RLRs are recruited to a membrane-associated CARD-containing adaptor protein MAVS through homotypic CARD interactions [78]. The interaction with MAVS can accumulate the downstream signaling molecules to form a MAVS signalosome, which can drive IRF3, IRF7, and NF-κB mediated IFN production [55]. In another study, IRF3, IRF7, NF-κB, ATF-2, c-Jun, and transcriptional enhancer CBP-p300 can form a complex to enhance the expression of IFN-β [127]. However, IRF3 and NF-κB might play an essential role in inducing the complex formation, as in most cases, IRF3 and components of the NF-κB activation program constitute MAVS signalosome [55]. The secreted IFN-β can amplify the IFN response by inducing the ISGF3-dependent expression of IFN-stimulated genes for increasing the expression of IFN-α subtypes in a positive feedback loop [97, 133]. In addition to IFN-α/β, RLRs also induce the expression of IFN-λ following the infection of a paramyxovirus Newcastle disease virus through IRFs and NF-κB binding [123]. RIG-1 also associates with ASC protein and triggers caspase-1-dependent inflammasome activation for promoting the mature of pro-IL-1β and pro-IL-18, which involves a MAVS independent signaling [133].

6.2.4.2 Cross talk with Other PRRs Signaling

RLR signaling intersects with TLR signaling probably through the shared components such as IRF3, IRF7, and NF-κB. RLRs can also apply STING as a cofactor, which passes RLR-mediated immune response to virus RNA and STING-mediated immune response to virus DNA [65]. RLR and NLR signaling have direct interactions in terms of regulation of inflammasome signaling. NLRX1 can disrupt the interaction between MAVS and RLR and inhibit the RLR-mediated IFN induction. NLRX1 depletion can rescue the RLR-mediated elimination of virus [114]. Another NLR member, NLRC5 can directly interact with RIG-I and MDA5 and disrupt the RLR-mediated activation of NF-κB. Knockdown of NLRC5 gene can enhance IFN production and antiviral response [26].

6.2.4.3 RLRs and Autophagy

RLR signaling is also reported to induce autophagy but through cross talk with STING [141] (Fig. 6.4). Autophagy can also inhibit RLR signaling [37, 69, 183]. Atg5 deficiency leads to the overproduction of type I IFNs in RIG-I/MDA-5-mediated pro-inflammatory response to VSV infection. On the other hand, with the overexpression of Atg5, the IFN signaling is also suppressed [72]. There are different explanations for how Atg5 can inhibit RLR signaling. One study showed that Atg5 can interact directly with RIG-I for repression of RLR signaling. Another study has emphasized the indirect role of autophagy in the regulation of RLR signaling. Atg5 deficiency causes more dysfunctional mitochondria and ROS production, which can enhance RLR signaling [164].

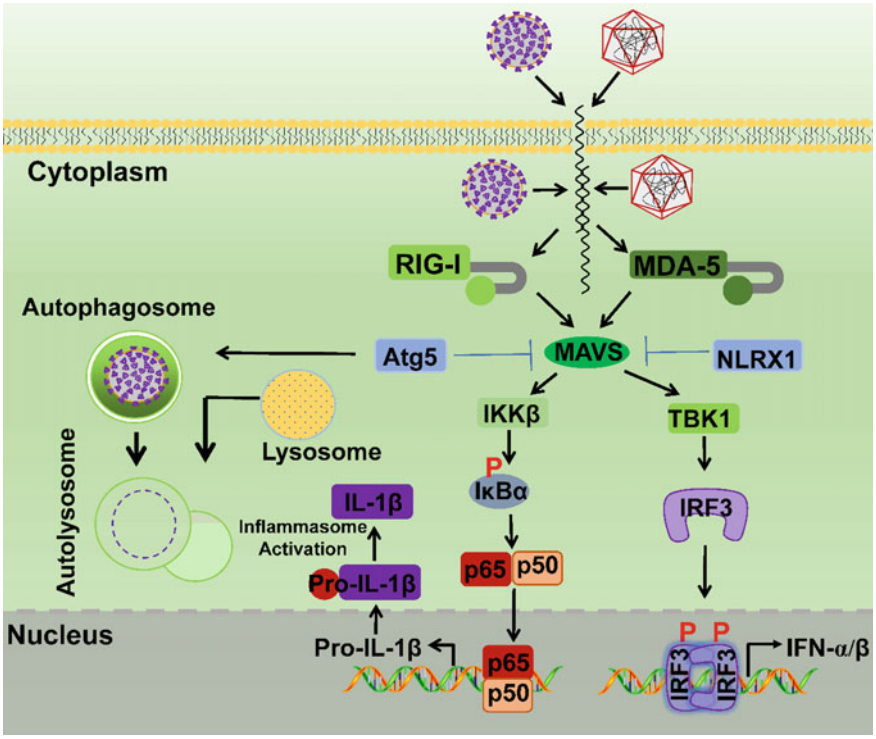

Fig. 6.4 RLRs and autophagy. RIG-1and MDA5 can be activated by bacteria and virus via the adaptor protein MAVS located at mitochondria, leading to the activation of IRF-3 and NF-κB, and promoting pro-IL-1β and IFN expression. Atg5, the autophagy protein, can interact with RIG-I for repression of RLR signaling

6.3 Non-pathogens-Associated PRRs and Autophagy

In addition to PAMPs from pathogens, DAMPs has been identified as ligands of PRRs which induce inflammatory response and autophagy. DAMPs are cell-derived molecules that can initiate non-pathogen-driven immunity such as in response to trauma, ischemia, cancer or other tissue damage. These DAMPs come from various cell components, including cell-derived HMGB1 and S100, heat shock proteins (HSP) from exosomes, hyaluronic acid from the extracellular matrix, in plasma components such as complement, and non-protein ATP, heparin sulfate, RNA and DNA. DAMPs can interact with TLRs and RAGE for activating downstream inflammation through mitogen-activated protein kinases (MAPKs), NF-κB, and PI3K/AKT. Increased serum levels of these DAMPs are associated with inflammatory diseases, including sepsis, arthritis, atherosclerosis, systemic lupus erythematosus, Crohn's disease, and cancer. Several DAMPs such as HMGB1, ATP, S100, and host DNA have been well-characterized [12, 15, 44, 162].

6.3.1 RAGE/HMGB1

RAGE is a multiligand member of the immunoglobulin superfamily. It is first described as a receptor for the products of non-enzymatic glycation and oxidation of proteins or advanced glycation end products (AGE) [67]. However, in addition to AGEs, RAGE can bind with a variety of DAMPs such as HMGB1, S100 [156] as well as in vitro dsDNA and dsRNA [128]. Ligands-RAGE interaction activates MAPK, p38, JNK signaling [89, 186], JAK/STAT pathways, rho and rac GTPases, and p21ras [3, 88, 116].

HMGB1 is chromatin-associated proteins, which is released from the nucleus or the cell in response to various stress, such as bacterial products [66, 177], virus infection [17], inflammatory stimuli [169] or apoptotic cells [139], necrotic cells [148]. Release of HMGB1 is closely associated with autophagy induction through positive feedback regulation. On one hand, HMGB1 localization and release can be regulated by autophagy through ROS [166, 167]. On the other hand, HMGB1 is a direct regulator of Bcl2-Beclin-1 complex for competing Bcl2 or promoting Bcl2 phosphorylation for induction of Beclin-1-dependent autophagy [167]. In colorectal cancer, cytosolic p53 or HMGB1 competes to regulate apoptosis or autophagy [96]. In contrast, in the nucleus, histone deacetylase (HDACs) regulate the nuclear location of HMGB1, which might suggest HMGB1 is linked to HDAC-autophagy pathway [143]. HMGB1 may also regulate mitophagy [168] through HSPB1 as well as mediating PAMP-induced autophagy [10]. These pieces of evidence suggest HMGB1 acts as a universal factor for inducement of autophagy.

6.3.1.1 RAGE/HMGB1 and Autophagy

RAGE/HMGB1 can activate autophagy through increasing Beclin-1-PI3KC3 interaction and decreasing mTOR phosphorylation, which limits apoptosis thus promoting tumor cell survival [73, 74]. Knockdown of RAGE diminishes HMGB1-induced autophagy in cancer cells [166]. In Lung ischemia-reperfusion injury, HMGB1 and HSP60 aggravate lung tissue damage through triggering inflammatory cytokine production and activation of the autophagy flux. However, autophagy inhibition by knockdown of Atg7 or Beclin-1 can markedly reduce the inflammatory cytokine production, which dependents on ubiquitination of TRAF6 [93].

Another mechanism for RAGE/HMGB1-mediated autophagy is through the modulation of mitochondrial activity. Knockdown of RAGE decreases mitochondrial respiratory chain complex I activity and ATP production through IL-6/STAT3 [74]. It is also reported that HSPB1, a cytoskeleton regulator critical for dynamic intracellular trafficking during autophagy and mitophagy, is required for HMGB1-dependent mitochondrial homeostasis [168]. In addition to HMGB1, other ligands, S100 are also reported to induce autophagy [44]. In macrophages, RAGE can enhance phagocytosis-dependent clearance of apoptosis through binding with phosphatidylserine receptor.

In addition to RAGE, other DAMPs receptors are also reported to induce pro-inflammation response but whether the mediated innate immune response depends on autophagy remains unclear. For instance, AIM2-like receptors (ALR) can sense the vaccinia virus and induce the processing of pro-IL-1β into the mature IL-1β form [58].

6.3.2 CD91/Calreticulin

Endoplasmic reticulum (ER) chaperones such as calreticulin and oxidoreductases can be exposed on the plasma membrane in stressed, damaged or dying cells and tumor cells, thus work as one type of DAMP [42, 144]. Calreticulin on plasma membrane promotes an "eat" me signal in tumor cells [119]. In the tumor, chemotherapeutic stimuli, e.g., cisplatin and anthracyclines doxorubicin, idarubicin, and mitoxantrone can trigger calreticulin exposure on plasma membrane [119, 185]. The calreticulin receptor CD91 on DCs and other APCs can recognize calreticulin and induce phagocytotic signal [119]. The Calreticulin-CD91 complex activity could be interfered by CD47 [39, 140]. Injection of Calreticulin coated cancer cells can activate tumor-specific immune response [181]. Interestingly, overexpression of calreticulin is observed in tumor tissue and is associated with the development and progression of pancreatic cancer [151]. In hepatocellular carcinoma, high levels of circulating anti-calreticulin antibodies have been found [132]. In bladder cancer, serum anti-calreticulin autoantibodies can mark cancer progression [111]. These pieces of evidence suggest calreticulin can be an indicator of tumor immunogenicity and may provide avenues of cancer treatment.

In addition to calreticulin, immunoglobulin binding protein (BiP/GRP78), a major ER-lumenal chaperone, can regulate protein folding and ER stress by triggering the unfolded protein response (UPR) to activate the transcription of other ER chaperones and oxidoreductases [40]. Therefore, surface BiP/GRP78 indicates inhibition of tumor cell apoptosis and immunorecognition. High expression of BiP/GRP78 inhibits apoptosis not only through repression of UPR [99] but also through sequestering pro-apoptotic Bcl2 family proteins [196]. In addition, pro-apoptotic Ca^{2+} transfer from ER to mitochondria is also inhibited by BiP/GRP78 [50, 124]. Overexpression of BiP/GRP78 is observed in various cancers and associated with tumor proliferation and invasion as well as therapeutic resistance [86].

6.3.2.1 Cell Surface Calreticulin-Mediated Autophagy

Cell surface calreticulin can induce "eat" me signal for phagocytic uptake and immunogenicity of cells [119]. Several mechanisms have been proposed to explain the escape of calreticulin from ER and exposure on the cell surface. One mechanism suggests that calreticulin needs to bind with phosphatidylserine to expose in a calcium-dependent manner [1, 39, 170]. In cells exposed to anthracycline chemotherapeutics, calreticulin-ERp57 complexes are exposed on cell surface with activation of

pancreatic ER kinase (PERK), leading to the induction of ROS, pro-apoptotic cleavage of caspase-8, activation of pro-apoptotic molecules such as Bcl-2-associated X protein (BAX) and Bcl-2-homologous antagonist/killer (BAK), and ER calcium efflux [126]. In addition, ERp57-independent secretory pathway might contribute to calreticulin cell surface expression in cells through the inactivation of SERCA-2 and disruption of ER calcium homeostasis [41]. Therefore, ER stress can perturb Ca^{2+} homeostasis and glucose transport and may be a key factor for cell surface calreticulin-mediated autophagy [75].

6.3.2.2 ER Chaperones in Cancer Treatment

Cell surface ER chaperones as critical hallmarks of cancer cells which insights the development of new drugs for cancer treatment. Modulation of UPR is a common approach with a diversity of drugs attempting to prevent the pro-survival role of UPR in preclinical studies [54]. These drugs can prevent cancer growth in the myeloma xenograft model [158], especially combined with bortezomib, an inducer of ER stress through blocking proteasome [110]. In addition to UPR, interference of ER Ca^{2+} content by SERCA inhibitor can promote calreticulin escape of ER retention for enhanced tumor immunity, and at the same time promote tumor growth through increasing surface BIP/GRP78 [34, 137, 178]. Mitoxantrone, an anthracycline with promising potential to promote calreticulin plasma membrane exposure, is currently in clinical trials against lymphoma [174]. In contrast, the oncogenic role of BiP/GRP78 makes it an inhibitory target for testing cancer drug. Antibody-based experimental therapies targeting BiP/GRP78 is under development [142, 173]. In addition, inhibitory agents targeting BiP/GRP78 has been developed. One strategy is the application of bacterial toxin subAb to selective destruction of surface BiP/GRP78 [131], which inhibits the cancer xenografts in mice [7]. BiP/GRP78 ATPase inhibitor such as epigallocatechin gallate can also work as tumor repressor [30]. BiP/GRP78-binding peptides also obstruct Xenograft growth of tumors [103].

Autophagy is a basic catabolic process, serving as an internal engine during responses to various cellular stresses. As regards cancer, autophagy may play a tumor-suppressive role by preserving cellular integrity during tumor development and by possible contribution to cell death. However, autophagy may also exert oncogenic effects by promoting tumor cell survival thereby preventing cell death. Autophagy modulation might be promising in anticancer therapies, however, it is a context-dependent matter if inhibition or activation of autophagy leads to tumor cell death.

6.3.3 TLRs/HSPs

HSPs are functional molecular chaperones which facilitate the synthesis and folding of proteins, induce proteasomal degradation, and prevent apoptosis. In addition to maintaining protein homeostasis, HSPs can be released in response to cell stress

and injury for promoting pro-inflammatory cytokine and APC activation. HSPs is upregulated in various tumors and correlated with tumor proliferation, lymph node metastases, and drug resistance to chemotherapies. Conversely, knockdown of HSPs inhibit tumor growth and increase drug response. HSPs are recognized by TLR4, TLR2, CD40, CD91, and CCR5, facilitating intracellular antigen processing and presentation with the exertion of immunoregulatory effects [59].

6.3.3.1 TLRs/HSPs and Autophagy

More importantly, HSPs can cooperate with autophagy to protect protein homeostasis, which can be disrupted by intracellular problems such as translational errors as well as extracellular stressors such as radiation, toxic chemicals, endotoxins, and osmotic pressure through altering the folding capacity [105]. Dysregulation of homeostasis is associated with diseases such as Huntington, amyloidosis, Alzheimer, Parkinson, and cancers [134, 60, 100]. Cells employ several systems to ensure protein homeostasis, including cellular chaperones, the ubiquitin-proteasome system, and autophagy. Interestingly, autophagy is ubiquitous in eukaryotic cells, but the HSP chaperone system is available for both prokaryotes and eukaryotes [49, 81]. Although HSPs and autophagy represent the distinct system of protein homeostasis, the cooperation between HSP and autophagy can be shown in a type of autophagy called chaperone-mediated autophagy [19, 33]. In chaperone-mediated autophagy, HSPA8/HSC70 can recognize cytosolic proteins with signature exposed pentapeptide motif (KFERQ) and target them to undergo unfolding and translocation into lysosomal lumen for degradation [76]. In mouse embryonic fibroblasts, HSP70 is required for panobinostat-induced autophagosomes formation [187]. HSF1 knockdown prevents a chemotherapeutic agent carboplatin-induced autophagy [32]. In addition, rapamycin activated autophagy also accompany with activation of HSF1 and HSP expression in brain and improvement of protein homeostasis [32].

Some recent studies provide evidence that in certain stress conditions, HSP inhibits autophagy, which might reflect the priority of the HSP response over autophagy by certain conditions. For instance, overexpression of the HSP70 protein inhibits starvation- or rapamycin-induced autophagy [35], heat-induced autophagy [61], and pro-apoptotic agent OSU-03012-induced autophagy in colorectal cancer cells [130]. In contrast, inhibition of the HSP70-dependent proteasomal pathway induces autophagy [176]. Mechanism study reveals that downregulation of AKT-TSC-mTOR pathway may be responsible for the repression role of HSPs system in the regulation of autophagy [138].

6.4 Conclusions and Perspectives

In the light of the afore evidence, PRRs are sensors of "danger" signals, while autophagy responds to these signals to maintain homeostasis. Therefore, PRRs and autophagy have close cooperation to enhance mycobacterial clearance as autophagy presents antigens to PRRs and helps to clean the pathogens while PRRs promote autophagy mature. Their roles in innate immunity are quite distinctive and best illustrated by the negative feedback regulation of PRR-mediated inflammation.

Autophagy deficiency such as Atg16L1 deficiency results in enhanced production of pro-inflammatory cytokine secretion [146]. In Crohn's disease, Atg16L1-deficiency is present with endotoxin-induced inflammasome activation suggesting the negative feedback regulation of inflammasomes by autophagy. Increasing studies reveal the mechanism of how autophagy regulates cytokine secretion. A study reveals blocking mitophagy leads to the activation of NLRP3 inflammasome with the accumulation of ROS but the inhibition of mitochondrial activity suppresses inflammasome activation [197]. In another report, depletion of autophagic proteins increases dysfunctionality of mitochondria, cytosolic translocation of mitochondrial DNA (mtDNA) and LPS, thereby activating NLRP3 inflammasome [117]. From these studies, autophagy can regulate inflammasome in a quantitively negative feedback mechanism via the manipulation of mitochondrial integrity.

Another way that autophagy limits the inflammatory response is ubiquitination of inflammasomes. Autophagic adaptor p62 can recognize ubiquitinated inflammasomes into autophagy pathways, which limits IL-1β production [153]. In RIG-I/MDA5-mediated pro-inflammatory response to VSV infection, Atg5 deficiency results in overproduction of type I IFNs following VSV infection, while IFN signaling is suppressed when overexpressing Atg5 [72]. There are different explanations for how Atg5 inhibits RLR signaling. A study revealed that Atg5 can interact directly with RIG-I for repression of RLR signaling. Another study emphasized the indirect role of autophagy in the regulation of RLR signaling. With Atg5 deficiency, more dysfunctional mitochondria and ROS production are generated which may enhance RLR signaling [164]. In addition, autophagy can also repress STING-dependent IFN responses through Atg9a [145]. Also, lack of Atg9a induces overactivation of type I IFN through the promotion of STING and TBK1 assembly. In cGAS-mediated DNA sensing signaling, Rubicon is released to establish negative feedback controlled by autophagy by enhancing the autophagy-mediated degradation of pathogen DNA [90].

Autophagy induced by PRR activation can negatively regulate the PRR signaling through various mechanisms depending on the configuration of PRRs and cell contexts. The activation of the negative feedback regulation of inflammation helps to maintain homeostasis and prevent excessive inflammation. There are also other reports which are inconsistent with the above regulatory relation between PRRs and autophagy. Exploring the distinctive roles of PRRs and autophagy will promote the understanding of microenvironment-dependent regulatory relations between PRRs

and autophagy. Also, investigating interactions between PRRs and autophagy in specific disease microenvironments, e.g., specific cancers will benefit drug development for immunotherapy.

As a key to maintain homeostasis, autophagy can respond to almost all the "danger" signals from PAMPs or DAMPs, with the aid of various types of PRRs. Almost all PRRs can induce autophagy directly for PRRs/PAMPs, but indirectly for PRRs/DAMPs. TLRs, NLRs, RLRs, and cGAS-STING can induce autophagy directly through Beclin 1 or LC3-dependent pathway, while the interactions with RAGE/HMGB1, CD91/Calreticulin, and TLRs/HSPs are achieved by protein, Ca^{2+}, mitochondrial or ROS homeostasis. As autophagy already existed before the emergence of PRRs/PAMPs, it might regulate PRRs/DAMPs through indirect response to "host-danger" signals more efficiently than the direct interaction response to PRRs/PAMPs. However, before the presence of PRRs/PAMPs, autophagy may already attend to host defense against pathogens, which contributes to the formation of the interaction with PRRs/DAMPs. Mitochondria is supposed to derive from autophagy of a *Rickettsia*-like α-*Protobacterium* [84]. In addition, mitochondria are prime autophagic targets and eliminating the damaged or dysfunctional mitochondrial occurs in all cells at all times [172]. This hypothesis also suggests that although autophagy is the oldest and conserved system, it may be easily regulated by various environmental signals probably due to its role in maintaining homeostasis, which is also supported by the increasing number of new types of autophagy identified. However, a more difficult question is how the autophagy coordinate various signals for its action. Further studies should be conducted to investigate these mechanisms, which can ultimately unravel the rebuilding of homeostasis to cure the disease and therapeutic purposes.

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