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REVIEW ARTICLE

Autophagy and microbial pathogenesis

Matthew D. Keller[1,2] · Victor J. Torres[2] · Ken Cadwell[1,2,3]

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Abstract

Autophagy is a cell biological process that promotes resilience in the face of environmental perturbations. Given that infectious agents represent a major type of environmental threat, it follows that the autophagy pathway is central to the outcome of host–microbe interactions. Detailed molecular studies have revealed intricate ways in which autophagy suppresses or enhances the fitness of infectious agents, particularly intracellular pathogens such as viruses that require the host cell machinery for replication. Findings in animal models have reinforced the importance of these events that occur within individual cells and have extended the role of autophagy to extracellular microbes and immunity at the whole organism level. These functions impact adaptation to bacteria that are part of the gut microbiota, which has implications for the etiology of chronic disorders such as inflammatory bowel disease. Despite major advances in how autophagy regulates inflammatory reactions toward microbes, many challenges remain, including distinguishing autophagy from closely related pathways such as LC3-associated phagocytosis. Here, we review the role of autophagy in microbial pathogenesis at the level of organismal biology. In addition to providing an overview of the prominent function of autophagy proteins in host–microbe interactions, we highlight how observations at the cellular level are informing pathogenesis studies and offer our perspective on the future directions of the field.

Facts

- Removal of intracellular microbes and inhibition of inflammatory cytokine production are autophagy functions that work in concert to mediate the return to homeostasis.
- Autophagy promotes the replication of certain RNA viruses, yet other viruses block autophagy proteins to evade destruction or antigen presentation.
- Successful bacterial pathogens have evolved mechanisms to evade autophagic degradation, but other functions of autophagy proteins can still contribute to the outcome of an infection at the whole organism level.
- Defense against eukaryotic pathogens in particular is associated with non-autophagy functions of autophagy proteins.

Open questions

- Which functions attributed to autophagy proteins represent autophagy versus related pathways such as LC3-associated phagocytosis?
- For which pathogens and strains of pathogens are the detailed molecular mechanisms of autophagy-microbe interactions identified in vitro most relevant?
- Is targeting autophagy proteins a viable strategy for treating infectious disease in humans?

Introduction

The field of microbial pathogenesis seeks to understand how infectious agents contribute to disease events and lies at the intersection of cellular and molecular microbiology, immunology, and physiology. Cell biology has the potential to bridge these spheres of knowledge. From rewiring of the

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✉ Ken Cadwell
Ken.Cadwell@nyulangone.org

[1] Kimmel Center for Biology and Medicine, Skirball Institute, New York University School of Medicine, New York, NY 10016, USA

[2] Department of Microbiology, New York University School of Medicine, New York, NY 10016, USA

[3] Division of Gastroenterology and Hepatology, Department of Medicine, New York University Langone Health, New York, NY 10016, USA

cellular machinery by pathogens to multicellular communication in lymph nodes, certain cellular pathways are pervasive in host–microbe interactions. One such cell biological process that has captured the attention of many in the field is macroautophagy, more commonly referred to as autophagy.

Autophagy is a process by which substrates in the cytosol are sequestered in a double-membrane-bound vesicle termed the autophagosome and transported to the lysosome. This process is necessary for eliminating the unwanted material, such as damaged organelles and protein aggregates. Also, macromolecules (e.g., proteins) are broken down into their constituents (e.g., amino acids) by lysosomal hydrolases and exported back to the cytosol where they can replenish the nutrient pool. These functions of autophagy are mediated by conserved autophagy-related proteins (ATGs) that can be grouped into the following functional units (Fig. 1): (1) the preinitation complex downstream of autophagy-inducing signals, (2) the class 3 phosphatidylinositol kinase (PI3KC3) complex that nucleates the pre-autophagosomal structure, also known as the phagophore, and (3) the ATG16L1 complex that mediates the elongation of the phagophore around the cargo to seal the contents within the autophagosome [1]. Like other vesicle trafficking pathways, RAB GTPases and SNAREs mediate the fusion between the completed autophagosome and endosomes, multivesicular bodies (MVBs), or lysosomes.

Much of our understanding of how these steps are coordinated comes from studies examining the response of yeast and mammalian cells to nutrient starvation. The kinase function of the preinitation complex, which is restricted through inhibitory phosphorylation by mammalian target of rapamycin (mTOR) under nutrient replete conditions, activates the PI3KC3 complex to generate PI3Ps at the endoplasmic reticulum (ER) or sites associated with the ER [2, 3]. The multipass transmembrane molecule ATG9a cycles between vesicular compartments to recruit membrane-building material to this site of the nascent phagophore. ATG16L1 is recruited through interactions with FIP200 (part of the preinitiation complex) and the PI3P-binding protein WIPI2 [4, 5]. ATG16L1 non-covalently binds ATG5−ATG12, which is covalently linked to each other through a ubiquitination-like pathway involving other ATGs. This multimeric complex consisting of ATG16L1-ATG5−ATG12 serves as an E3 ubiquitin ligase-like enzyme that attaches a lipid, phosphatidylethanolamine (PE), to LC3 or homologs of LC3. PE-conjugated LC3 facilitates the efficient closure of the autophagosome and fusion with the lysosome [6, 7]. When autophagy mediates the degradation of mitochondria (mitophagy) or specific macromolecules, these substrates are recruited by autophagy receptors, such as SQSTM1 (also known as p62), that simultaneously interact with LC3 and the cargo, thereby adding specificity to the pathway.

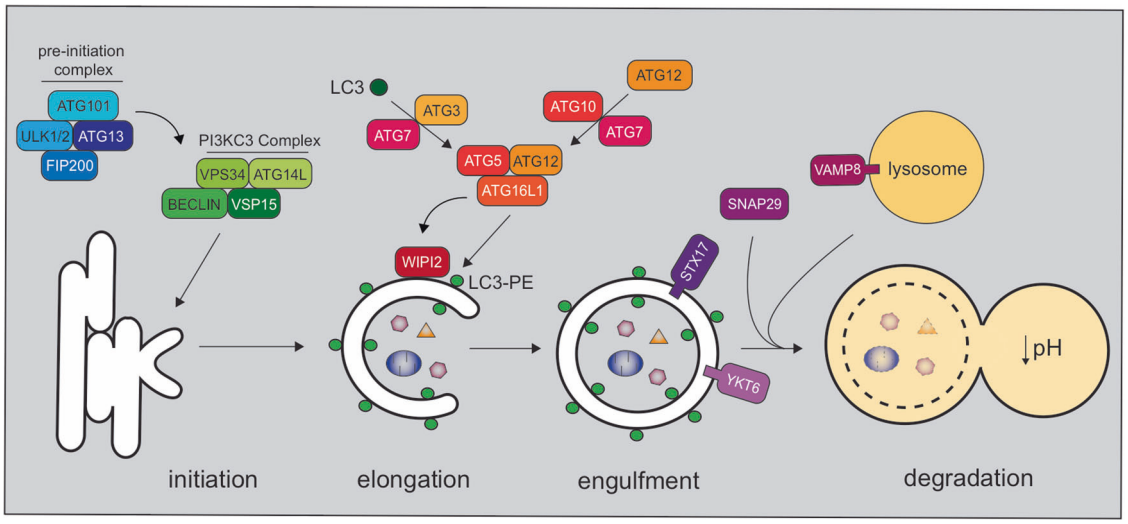

Fig. 1 Overview of the autophagy pathway. Autophagy is initiated when the preinitiation complex (ULK1 or ULK2, FIP200, ATG13, and ATG101) mediates the phosphorylation of Beclin-1 to activate the class 3 phosphatidylinositol kinase (PI3KC3) complex (VPS34, VPS15, Beclin-1, and ATG14L) to generate PI3Ps at the ER-Golgi intermediate compartment (ERGIC) and ER-mitochondria contact regions. The ATG16L1 complex (ATG16L1, ATG5, and ATG12) is generated through a ubiquitin-like pathway by ATG7 and ATG10 that covalently attaches ATG12 to ATG5. Following non-covalent binding between ATG5 and ATG16L1, the complex is recruited to these ER-associated sites by the PI3P-binding protein WIPI2. ATG7 also functions in a second ubiquitin-like pathway by activating and transferring the ubiquitin-like molecule LC3 to ATG3. The ATG16L1 complex then transfers LC3 from ATG3 onto the lipid phosphatidylethanolamine (PE) on the pre-autophagosomal structure. Through its fusogenic properties, LC3 mediates the elongation and closure of the autophagosome. STX17, VAMP8, SNAP29, YKT6 and other membrane integrated SNARE proteins and their cofactors mediate fusion between the autophagosome and endo-lysosomal vesicles. The acidic environment and enzymes mediate the degradation and recycling of cargo molecules such as mitochondria (blue oval), intracellular pathogens (purple hexagon), or protein aggregates (triangle).

Here, we review how the above ATGs contribute to microbial pathogenesis. We wish to distinguish this review article from previous, excellent ones written on immunity to infection by emphasizing multicellular and whole organism events, especially those that contribute to disease. We will first summarize the established role of autophagy in immunity. Then, we will discuss how autophagy relates to limiting the damage caused by pathogens, dividing the infectious agents into three major classes—viruses, bacteria, and eukaryotes. Infectious agents, including members of the gut microbiota, play a prominent role in chronic inflammatory disorders. Therefore, we will also discuss the role of autophagy in host–microbiota interactions by focusing on inflammatory bowel disease (IBD), a disorder associated with autophagy-related defects. Finally, we will examine the recurring themes presented in this article and offer our perspective on the future directions of the field.

Primer on autophagy and host defense

Autophagy functions as a form of cell autonomous defense when internalized microbes become substrates, a process referred to as xenophagy. *Salmonella enterica* serovar Typhimurium and *Mycobacterium tuberculosis* (*Mtb*), bacteria that cause gastroenteritis and tuberculosis, respectively, are the most extensively examined model pathogens for xenophagy. Host-encoded E3 ubiquitin ligases Parkin, LRSAM1, SMURF1, RNF166, and linear ubiquitin chain assembly complex (LUBAC) tag ubiquitin onto bacteria that escape into the cytoplasm or are exposed to the cytoplasm upon damage to the pathogen-containing vacuole (PcV) [8–14]. SQSTM1 and NDP52 are examples of autophagy receptors that can crosslink either mitochondria or bacteria to the autophagy machinery through ubiquitin and LC3 binding motifs. Hence, it is possible the mitophagy process was repurposed for xenophagy. NDP52 also binds galectin-8, a cytosolic lectin that recognizes the damaged PcVs [15]. These events are induced by pattern recognition receptors (PRRs) [16]. For example, toll-like receptor 4 (TLR4) recognition of lipopolysaccharide (LPS) activates two downstream kinases to target LC3 to *S.* Typhimurium: transforming growth factor beta-activated kinase 1 (TAK1) phosphorylates ULK1 in the preinitation complex to initiate autophagy [17], and TANK binding kinase 1 phosphorylates the autophagy receptor OPTN to enhance binding to ubiquitinated bacteria [18]. In another example, detection of cytosolic peptidoglycan by nucleotide-binding oligomerization domain protein-1 (NOD1) and NOD2 induces signaling that is favorable for autophagy and can directly recruit ATG16L1 to the internalized microbe [19–23].

Xenophagy may be a primordial effector function of PRRs that evolved earlier than cytokine production. Stimulator of interferon genes (STING) is best known for mediating antiviral type I interferon (IFN-I) production upon the binding of cyclic dinucleotides that are generated by cyclic GMP-AMP synthease (cGAS) in the presence of cytosolic DNA, such as during viral infection. However, the activation of STING in certain metazoans such as flies and the sea anemone induce autophagy but not interferons [24, 25]. Given that flies do not encode cGAS, STING is likely activated by cyclic dinucleotides that are directly made by bacteria. The observation that PRR-induced autophagy promotes defense against diverse viral and bacterial pathogens in fly, nematodes, zebrafish, and ameba models supports the concept that xenophagy is a conserved defense mechanism [25–30].

Counterintuitively, autophagy frequently inhibits production of cytokines that are important for host-pathogen interactions, most notably interleukin-1β (IL-1β) and IFN-I [31]. The NLRP3 inflammasome is a multimeric complex that induces an inflammatory form of cell death (pyroptosis) while simultaneously mediating the processing and the secretion of IL-1β [32]. Reactive oxygen species (ROS) and DNA from damaged mitochondria can activate the NLRP3 inflammasome. Mitophagy reduces IL-1β production by removing these inflammasome triggers [32, 33]. Similarly, mitophagy dampens IFN-I responses downstream of mitochondrial antiviral signaling protein (MAVS), an adapter molecule for the cytosolic RNA sensors retinoic acid inducible gene I and melanoma differentiation associated gene 5 (MDA5) [34–37]. These studies show autophagy can remove mitochondria that serve as a platform for MAVS signaling or directly target MAVS. When TLR3 or TLR4 are activated in macrophages, autophagy inhibits IFN-I production and cell death by removing the signaling adapter TRIF that is recognized by the autophagy receptor TAX1BP1 [38, 39]. Autophagy also inhibits IL-1β production through the caspase-11 inflammasome and IFN-I production through STING by reducing the availability of cytosolic LPS and DNA, respectively [40]. We propose the removal of intracellular microbes through xenophagy and the inhibition of inflammatory cytokine production are examples of autophagy functions working in concert to mediate a return to homeostasis and the swift resolution of infection. In the subsequent sections, we provide examples of how this regulation impacts the course of disease during an infection.

The same ATGs required for autophagy have autophagy-independent functions in immunity [41, 42]. This challenge in studying autophagy is illustrated by the finding that ATG5 protects against *Mtb* in mice by mediating neutrophil cell death, while other ATGs are dispensable for this function [43]. In contrast, ATGs function together to

mediate an alternate form of autophagy where antimicrobial granules, proteins lacking signal sequences such as certain cytokines, or other cargoes relevant to host defense are exocytosed from the cell [41]. The mechanism of secretory autophagy is not completely understood and may involve redirecting the autophagosome to the plasma membrane away from the lysosome by using different SNARE proteins than those involved in degradative autophagy [44]. Certain cargo may be placed within the intermembrane space of the autophagosome rather than the lumen, in which case the fusion of the double-membrane vesicle with the cell surface would lead to the release of soluble material in-between the outer and inner membranes [45]. Alternatively, it seems likely that there are instances such as exosome secretion in which ATGs act in an autophagosome-independent manner to induce trafficking of the multivesicular body and other endo-lysosomal vesicles [41]. For LC3-associated phagocytosis (LAP), ATGs that are part of the PI3KC and ATG16L1 complexes mediate the transport of cargo internalized from the extracellular environment to the endo-lysosomal compartment. LAP is distinguished by the absence of a double-membrane vesicle and its dependence on NADPH oxidase 2 (NOX2) and Rubicon, a protein that recruits the PI3KC complex to phagocytosed microbes, TLR ligands, and apoptotic corpses [46–49]. Internalized material processed through LAP induces cytokine expression and serves as a source of antigens for presentation on T cells [46, 49, 50]. For simplicity, a general rule is that autophagy targets cytosolic material while LAP is more likely to be relevant for cargo originating from the extracellular environment. ULK1 and ATG9a each have distinct autophagy-independent functions in inhibiting STING [51, 52], and the establishment of the *Brucella abortus* PcV is dependent on preinitiation and PI3K complex proteins but independent of the LC3 conjugation machinery [53]. Several other examples of non-autophagy roles of ATGs will be discussed below.

Viral pathogens

Autophagy at the whole organism level has been difficult to investigate for many medically important viruses due to the restricted host tropism and unavailability of practical animal models. Despite this limitation, several generalizable themes have emerged that are consistent with both in vitro and in vivo observations. First, viruses have evolved mechanisms to subvert autophagy, as exemplified by picornaviruses, a large family of single-stranded RNA viruses. Mice in which *Atg5* is deleted in pancreatic acinar cells display a striking decrease in the viral burden and disease in a model of coxsackievirus-induced pancreatitis [54], likely reflecting multiple stages of the life cycle impacted by ATGs. Upon entry into the host cell, the lipid-modifying enzyme PLA2G16 enables the delivery of the viral genome from the endosome to the cytosol through a pore before the damaged vesicle is targeted by the autophagy machinery for destruction [55]. During the generation of new virions, rather than target them for degradation, ATGs have been shown to be hijacked by multiple picornaviruses (coxsackievirus, poliovirus, and rhinovirus) to generate $LC3^{+}$ membranes that serve as a replication platform [56–58] (Table 1). In the case of coxsackievirus B3 and enterovirus D68, autophagosomes generated through this process are redirected to the plasma membrane in a manner similar to secretory autophagy by viral proteases that cleave the SNARE protein SNAP29, leading to the exocytosis of single-vesicles that cloak the virions [59, 60]. The phosphatidylserine decorating these pseudo-enveloped virions generated through an autophagy-like process facilitates entry into neighboring cells, especially macrophages [61, 62]. Therefore, ATGs aid the replication, egress, and subsequent entry of Picornaviruses. Herpesviruses, which are enveloped DNA viruses, also hijack LC3 for the maturation of viral particles and egress [63–65]. However, several herpesviruses related to these encode molecules that block autophagy to evade the immune system, which may be particularly important for chronic infections. Flaviviruses, which include medically important viruses like hepatitis C virus, have also been shown to depend on autophagy at various steps in their life cycles. One study provided evidence that this dependence represents a therapeutic opportunity by showing that inhibiting autophagy reduces Zika virus (ZIKV) replication in human trophoblasts and limits transmission from the pregnant mother to fetus in mice [66].

For other viruses, autophagy can protect the host. Therapeutically enhancing autophagy by inoculating mice with a Beclin-1 peptide decreases viral burden and improves survival during chikungunya virus and West Nile virus infections [67]. Herpesviruses actively block autophagy. Murine gammaherpesvirus 68 (MHV68) and herpes simplex virus type 1 (HSV-1) engineered to lack viral Bcl-2 and ICP34.5, Beclin-1 inhibitors encoded by the respective viruses, display impaired virulence and fail to establish chronic infections [68, 69] (Table 1). Autophagy also has an essential role in protecting against tissue injury and cell death during viral infection. The capsid protein of Sindbis virus is degraded by selective autophagy through autophagy receptors, which prevents virus-induced death of neurons during infection of the central nervous system [70, 71]. In addition, ATG5 is required to control HSV-1 replication in dorsal root ganglionic neurons following intra-vaginal inoculation of mice [72], and for control of ZIKV in the fly brain [25]. ATGs also prevent necrotic cell death in the intestinal epithelium in response to TNFα produced during

Table 1 Examples of autophagy modulating virulence factors produced by pathogens.

Pathogen	Virulence factor	Target	Model system	Citation
Virus				
HSV-1	ICP34.5	Beclin-1	Cell culture and animal	[69, 81]
MHV68	vBcl-2	Beclin-1	Cell culture and animal	[68, 158, 159]
Influenza A virus	M2	LC3	Cell culture	[160, 161]
HPIV3	Matrix protein	LC3	Cell culture	[76]
Coxsackievirus B3	2A, 3C	SQSTM1, SNAP29, PLEKHM1	Cell culture	[59, 162]
Enterovirus D68	3C	SNAP29 and SQSTM1	Cell culture	[60]
Poliovirus	2BC and 3A	LC3	Cell culture	[163]
HIV	Nef	Beclin-1	Cell culture	[164, 165]
Bacteria				
Group A Streptococcus	SpeB	P62, NDP52, and NBR1	Cell culture	[92]
L. monocytogenes	LLO	NLRX1	Cell culture and animal	[87]
L. monocytogenes	ActA	Prevent recognition by p62 and LC3	Cell culture	[88]
L. pneumophila	RavZ	LC3	Cell culture	[7]
S. flexneri	IcsP	C3-ATG16L1	Cell culture and animal	[85]
S. flexneri	IcsB	ATG5	Cell culture	[90, 91]
S. Typhimurium	PgtE	C3-ATG16L1	Cell culture and animal	[85]
S. Typhimurium	SopF	V-ATPase-ATG16L1	Cell culture and animal	[84]
Fungus				
Aspergillus fumigatus	Melanin	LAP (NADPH oxidase)	Cell culture and animal	[108]
Parasite				
Toxoplasma gondii	Micronemal proteins	EGFR	Cell culture	[114]
Plasmodium berghei	UIS3	LC3	Cell culture and animal	[113]

HSV-1 herpes simplex virus 1, *MHV68* murine γ-herpesvirus 68, *HPIV3* human parainfluenza virus type 3, *L. monocytogenes* Listeria monocytogenes, *L. pneumophila* Legionella pneumophila, *S. flexneri* Shigella flexneri, *S. Typhimurium* Salmonella enterica serovar Typhimurium, *A. fumigatus* Aspergillus fumigatus, *T. gondi* Toxoplasma gondii

persistent murine norovirus (MNV) infection [73]. Although we focus on mammalian autophagy in this review, it is worth noting that similar paradigms are observed in plants where autophagy binds viral proteins or regulates cell death during infections, which can be pro- or antiviral depending on the virulence strategies employed by the virus [74].

In many of the above examples, autophagy functions within parenchymal cells such as epithelia and neurons to protect the tissue from damage. In other cases, ATGs function in immune cells to limit immune-mediated injury. Mitophagy is induced following the recognition of cytosolic influenza virus RNA to dampen the NLRP3 inflammasome and prevent an over-exuberant immune response that causes lung pathology [75]. This mechanism in place to restrict tissue injury is a double-edged sword because the human parainfluenza virus type 3 (HPIV3) matrix protein induces mitophagy to inhibit IFN-I production downstream of MAVS, leading to the evasion of antiviral immunity and increased viral replication [76]. In other studies examining the response to influenza virus or MHV68 infection, mice harboring deletions in one of any number of ATGs in myeloid cells were found to display a striking increase in the production of multiple cytokines that impact tissue injury and viral replication through a mechanism that is not easily explained by currently known autophagy functions [77, 78].

Finally, autophagy and LAP have essential roles in adaptive immunity during viral infections. The deletion of *Atg5* in $CD11c^+$ cells (i.e., dendritic cells and some macrophages) leads to compromised antigen presentation to T cells in response to HSV-2 and yellow fever virus vaccine challenges [79, 80]. In a model of corneal infection, an ICP34.5 mutant HSV-1 that fails to inhibit Beclin-1 generates a stronger $CD4^+$ T cell response, reinforcing a role for the autophagy machinery in MHC-II antigen presentation [81]. In addition, ATGs in T and B lymphocytes help adapt to changing metabolic needs and stress during differentiation and proliferation [1]. For example, autophagy is upregulated during the contraction phase when clonal expansion has ended and is essential for the persistence of memory $CD8^+$ T cells following the infection by LCMV, MCMV, and influenza virus [82, 83]. T cells from older mice display a decrease in autophagy, potentially

contributing to decreases in immunity that occur with aging [83]. To summarize, autophagy or related processes promote the replication of certain RNA viruses or dampen the antiviral response, but other viruses block the function of ATGs to evade direct destruction or antigen presentation. Then, during the resolution of viral infection, autophagy continues to be important in lymphocytes for sustaining the memory of the infection.

Bacterial pathogens

Successful pathogens that depend on intracellular replication have evolved strategies to avoid xenophagy. *S.* Typhimurium [84, 85], *Legionella pneumophila* [7], *Listeria monocytogenes* [86–90], *Shigella flexneri* [90, 91], and contemporary isolates of Group A *Streptococcus* [92], encode virulence factors that block the recruitment of ATG16L1 to the PcV, inactivate LC3 and autophagy receptors through enzymatic cleavage, or facilitate escape from the autophagy machinery through motility (Table 1). Despite these evasive tactics, autophagy mutant mice are generally susceptible to infection, suggesting that ATGs are performing other functions in addition to xenophagy. Such complex or tissue-specific roles are difficult to investigate in cell lines. One example where the animal model revealed a role of autophagy that is distinct from the role established in cell culture experiments is in studies of *Staphylococcus aureus*, a Gram-positive bacterium that causes a range of life-threatening illnesses including pneumonia, endocarditis, and sepsis. While initial tissue culture studies using HeLa cells highlight how *S. aureus* highjacks autophagy to promote bacterial survival [93], autophagy does not contribute to *S. aureus* burden during lung and blood stream infections in vivo [94]. Instead, ATG16L1 and other autophagy components are involved in the protection of host cells from the lethal effects mediated by a potent pore-forming toxin (α-toxin) produced by the bacterium [94]. Thus, in this scenario, the autophagy machinery prevents excessive tissue damage and is involved in the "tolerance" or a host resilience response [95]. In another recent example, the ATG16L1 complex, but not other steps of autophagy, was shown to mediate plasma membrane repair in response to listeriolysin O (LLO), a pore-forming toxin produced by *L. monocytogenes* [86]. Rather than controlling replication in the cytosol, the ATG16L1 complex restricts cell-to-cell spread of bacteria by maintaining the integrity of the plasma membrane [86, 96]. Thus, ATGs may have a general role in countering damage to the plasma membrane during infections (Fig. 2).

Mouse experiments confirm a membrane repair function of ATG16L1 in the intestinal epithelium during *L. monocytogenes* infection [86] and also reveal other mechanisms by which the autophagy pathway participates in defense against this agent of food poisoning. ATG5 has a non-xenophagy function in myeloid cells that protects animals from lethal *L. monocytogenes* infection [97], a process that may be related to a novel IFN-γ effector mechanism observed during protozoan infection (see "Eukaryotic pathogens" section below). Also, a recent

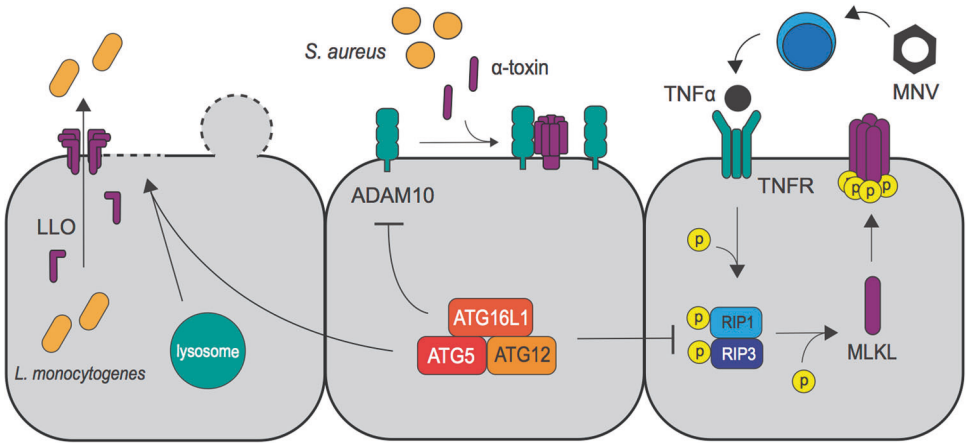

Fig. 2 The ATG16L1 complex defends the plasma membrane from pore-forming molecules during infections. In the first example, Listeriolysin O (LLO) produced by *Listeria monocytogenes* mediates pore formation in the plasma membrane that facilitates cell-to-cell spread of the bacterium. The ATG16L1 complex restricts this spread by promoting plasma membrane repair through an autophagy-independent mechanism involving the exocytosis of lysosomes that confines the damage to surface blebs. In the second example, α-toxin secreted by *Staphylococcus aureus* binds ADAM10 on the surface of target cells such as the endothelium leading to cell death. The ATG16L1 complex downregulates ADAM10 levels, limiting the availability of the receptor for α-toxin binding and promotes cell survival. In the third example, TNFα produced by immune cells in the gut in response to murine norovirus (MNV) infection is tolerated by intestinal epithelial cells when autophagy is intact. However, upon the disruption of the ATG16L1 complex and inhibition of mitophagy, the accumulation of reactive oxygen species (ROS) licenses signaling through RIPK1 and RIPK3 downstream of the TNFα receptor (TNFR) resulting in the activation of MLKL, the pore-forming executioner molecule of the necroptosis pathway of programmed cell death.

study showed LLO specifically induces mitophagy in macrophages via the mitochondria-localized autophagy receptor NLRX1 to rid the cells of ROS generated by damaged mitochondria upon infection, thereby dampening the inflammatory response and promoting intracellular bacterial survival [87]. This elegant study does not preclude other important ways in which ATGs promote intracellular survival of *L. monocytogenes* through establishment of a protective niche [98], but it demonstrates the power of using recently developed tools to inhibit specific autophagy functions with precision.

Approaches in which pathogens are introduced through artificial routes of infection could miss key autophagy functions at barrier sites. In the gastrointestinal tract, epithelial cells act as sentinels that respond to different bacteria by activating autophagy [99, 100]. Using intestinal epithelial cell (IEC)-specific ATG deficient mice, autophagy downstream of Myd88 (adapter for TLRs and IL-1 receptor) was shown to control extraintestinal dissemination of *S.* Typhimurium following oral infection. Work with *Citrobacter rodentium*, a rodent pathogen used as a model for Enteropathogenic *Escherichia coli* (EPEC) infection of humans, highlights how the contribution of autophagy cannot be automatically extended to similar bacterial pathogens. Although both bacterial species are members of the Enterobacteriaceae family of gut pathogens, *C. rodentium* is an extracellular bacterium that does not establish the intracellular vacuole characteristic of *S.* Typhimurium. Mice with decreased expression of *Atg16L1* or specific deletion in IECs are hyper-resistant to oral challenge by *C. rodentium* because of enhanced IFN-I signaling associated with unrestricted MAVS and STING activation [101, 102]. *Atg16L1* mutant mice are also resistant to uropathogenic *E. coli* (UPEC) in a model of urinary tract infections due to increased IL-1β production downstream of the NLRP3 inflammasome in myeloid cells [103, 104]. Observations with these three related pathogens, when introduced via their natural route of infection, underscore the context-specific role of autophagy.

Eukaryotic pathogens

LAP in phagocytic cells appears to be the dominant mechanism by which ATGs promote immunity toward eukaryotic pathogens (Fig. 3). β-glucan moieties on the fungal cell wall triggers the recruitment of LC3 to the internalized fungi following ROS production via NOX2 upon recognition by TLR2 or the C-type lectin receptor Dectin-1 [46, 105]. Inhibiting LAP during the fungal infection can lead to decreased fungicidal activity, altered cytokine production, and reduced antigen presentation [47, 50, 105–107]. These functions may be particularly important for *Aspergillus fumigatus*, an opportunistic pathogen that causes life-threatening pulmonary infections. Germination of *A. fumigatus* spores exposes β-glucan and induces the release of Ca^{2+} from ER stores, which activates LAP to reduce the fungal burden and airway inflammation in the mouse model [108, 109]. Chronic granulomatous disease (CGD) patients who carry mutations in *NOX2* are susceptible to *A. fumigatus* and display defective LC3 recruitment to fungi internalized by macrophages [110, 111]. Blocking IL-1β in CGD patients or an animal model improves colitis, one of the consequences of invasive infection, indicating that excess inflammasome activity due to defective autophagy may also be important during aspergillosis [110]. Similar to CGD patients, aspergillosis incidence is higher in hematopoietic stem cell transplant recipients who have a polymorphism in *death-associated protein kinase 1 (DAPK1)*, an IFN-γ inducible gene that is necessary for LAP and proteasomal degradation of NLRP3 [111]. Thus, LAP represents a promising pharmacological target for treating fungal infections.

ATGs may have similar functions during the infection by protozoan parasites. Like fungal infection of macrophages, IFN-γ induced LAP in hepatocytes kills *Plasmodium* species, the causative agent of malaria [112]. However, the parasite can avoid killing through production of UIS3C, a PcV membrane-associated molecule that binds and inhibits LC3 [113] (Table 1). Similarly, invasion by *Toxoplasma gondii* activates the epidermal growth factor receptor to prevent LC3 recruitment by inhibiting PKR and eIF2α, known activators of autophagy [114, 115] (Table 1). Conversely, the causative agent of Chagas disease, *Trypanosoma cruzi*, requires acidification of the PcV for its virulence, which was shown to depend on the host autophagy machinery in fibroblasts [116]. Although the role of ATGs in these examples likely reflects LAP, another IFN-γ inducible non-degradative (lysosome-independent) function of the LC3 conjugation machinery called targeting by AutophaGy proteins (TAG) can mediate parasite killing by recruiting molecules that disrupt membranes (Fig. 3). The ATG16L1 complex restricts *T. gondii* through TAG by mediating lipidation of LC3 homologs, especially GATE-16 (also known as GABARAPL2), which then recruit interferon-inducible GTPases (IRGs) and guanylate binding proteins (GBPs) to the PcV and compromises the replicative niche [117–123]. TAG also disrupts the membrane-associated replication complex of MNV [124, 125] and may explain why ATG5 restricts *L. monocytogenes* in macrophages in vivo [97], suggesting that recruiting IRGs and GBPs by ATGs is a defense response to a broad range of pathogens that target host membranes. The mechanism by which ATGs are directed toward TAG rather than autophagy and how IRGs and GBPs disrupt membranes are two key questions that will need to be addressed. Also,

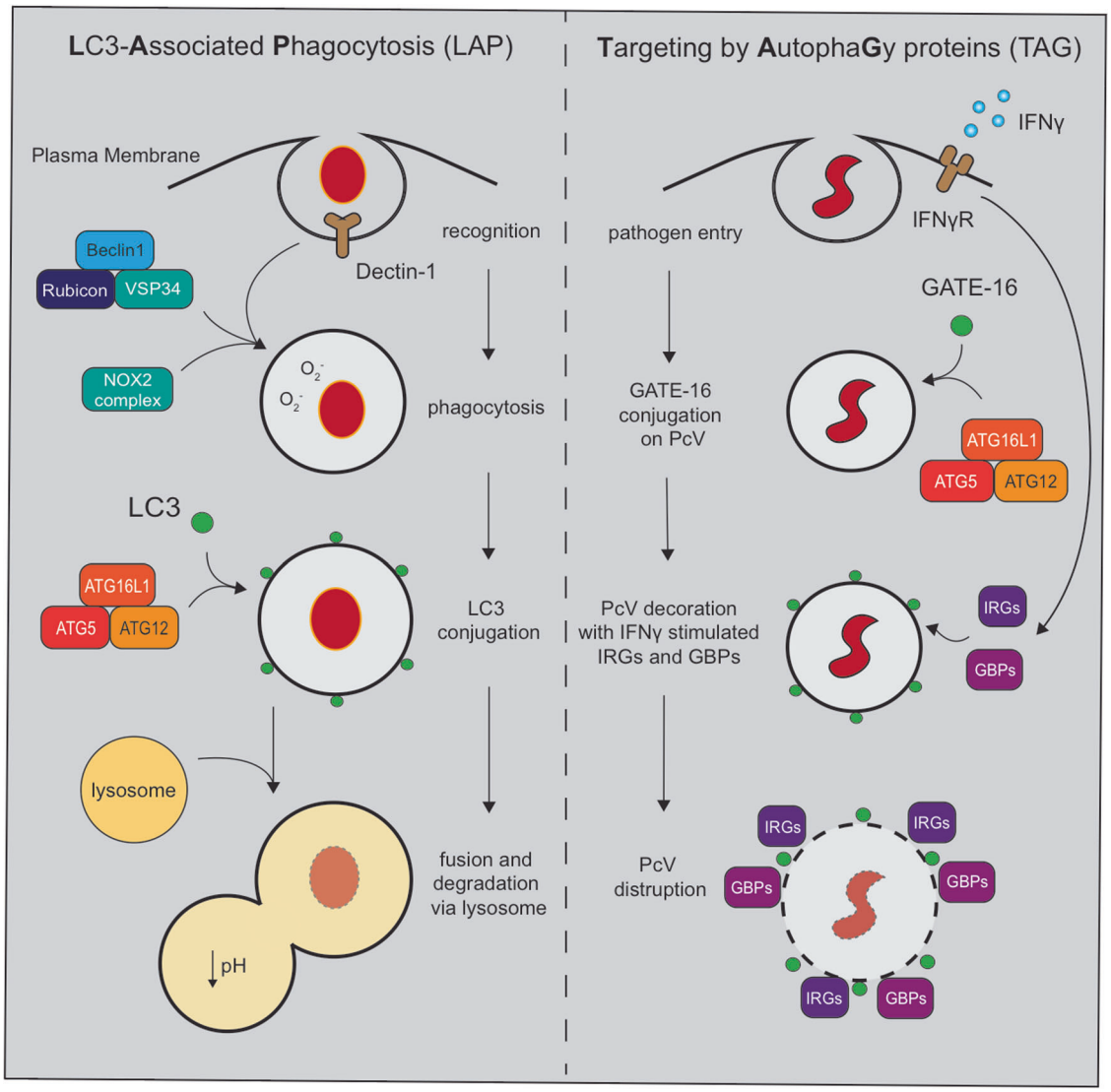

Fig. 3 Non-autophagy functions of ATGs mediate cell autonomous defense against eukaryotic pathogens. During LC3-associated phagocytosis (LAP), internalized microbes are recognized by pattern recognition receptors, such as Dectin-1 binding of β-glucan from *Aspergillus fumigatus*, leading to the recruitment of a PI3KC3 complex. In contrast to autophagy, the PI3KC3 complex assembled during LAP is distinguished by the presence of Rubicon and the concurrent recruitment of the NADPH oxidase 2 (NOX2) complex that generates ROS. LC3 lipidation by the ATG16L1 complex then mediates the maturation of the single-membrane phagosome through fusion with the lysosome and degradation of the contents. Targeting by Autophagy Proteins (TAG) is initiated by IFNγ and involves the decoration of the pathogen-containing vacuole (PcV) by the LC3 homolog GATE-16 during *Toxoplasma gondii* infection. Although dependent on the ATG16L1 complex, the downstream autophagy factors involved in lysosomal degradation are dispensable. Instead, IFNγ inducible GTPase belonging to the IRG and GBP families are recruited and contribute to the disruption of the PcV membrane.

ATG5 is essential for maintaining the intestinal barrier during *T. gondii* infection by preventing epithelial cell death [126], indicating the role of ATGs in tissue injury and repair during parasitic infection requires additional investigation.

Gut microbiota and IBD

The trillions of bacteria and other infectious agents that are part of the gut microbiota achieve a balanced co-existence with a healthy host. Disruption of this balance has been implicated in the origin of immune and metabolic disorders including IBD, a chronic and relapsing inflammatory condition affecting millions worldwide [127]. Although no single etiologic agent has been identified, decades of observations in patients and animal models suggest a microbial origin of IBD [128]. There has been intense interest in examining the role of autophagy in mediating host–microbe interactions in the gut following the identification of a coding variant in *ATG16L1* (T300A) associated with risk of acquiring Crohn's disease, a type of IBD that

commonly affects the small intestine as well as other parts of the gastrointestinal tract [127]. The *ATG16L1*^{T300A} protein product is susceptible to cleavage by caspase-3 induced by cellular stressors such as TNFα and nutrient deprivation [129, 130]. Consistent with the role of ATG16L1 in autophagy, macrophages and DCs from mice and humans expressing the *ATG16L1*^{T300A} variant are defective in xenophagy, antigen presentation, and control of IL-1β and IFN-I production [22, 129–131]. Animal models provide evidence that an uncontrolled cytokine response is a particularly important function of macrophage ATG16L1 during intestinal inflammation. The anti-inflammatory cytokine IL-10 induces mitophagy in macrophages to promote oxidative phosphorylation and inhibit glycolysis in the presence of LPS [132]. Deleting *Atg16l1* in macrophages, therefore, leads to a pro-inflammatory metabolic state associated with damaged mitochondria and NLRP3 activity that exacerbate disease in mouse models of colitis [32, 132, 133].

These findings do not exclude a role for LAP. ATG16L1 has a WD40 C-terminal domain outside the region necessary for complex formation with ATG5-12, and this domain is required for recruitment of LC3 to endosomal membranes for MHC-II antigen presentation [134]. The T300A substitution interferes with binding TMEM59, an interaction that mediates the recruitment of LC3 to internalized *S. aureus* through a process resembling LAP [135]. Outer membrane vesicles derived from *B. fragilis* induce LAP in DCs, which can enhance the differentiation of co-cultured T cells into IL-10 producing Tregs. Monocyte-derived DCs from individuals with the *ATG16L1*^{T300A} variant fail to promote Treg differentiation, and a similar loss of tolerance was observed in an analogous animal model [136]. Thus, the genetic association between *ATG16L1* and Crohn's disease could reflect a defect in autophagy, LAP, or both that leads to an exaggerated cytokine responses toward microbes that are otherwise managed.

ATG16L1 also has an essential role in IECs. Crohn's disease patients homozygous for the *ATG16L1*^{T300A} variant display defects in granule production by Paneth cells [137], antimicrobial epithelial cells in the small intestine that maintain barrier function [138]. Mutation of *Atg16l1*, *Atg4b*, *Atg5*, and *Atg7* in mice all lead to similar Paneth cell defects [137, 139–142]. A specific role for the microbial pathogenesis is supported by the observation that an infectious trigger is required for intestinal disease in three independently generated *Atg16l1* mutant mice: mice with a hypomorphic allele of *Atg16l1*, an IEC-specific knockout, or a T300A mutation develop Paneth cell defects and an exacerbated intestinal injury response following infection by MNV [73, 143]. In other situations, MNV infection promotes the differentiation and function of the mucosal immune system similar to beneficial bacteria, and protects against vancomycin resistant *Enterococcus* and *C. rodentium* infections by inducing the epithelial regenerative cytokine IL-22 [144, 145]. The anaerobic bacterium *Bacteroides ovatus*, a common member of the human gut microbiota that has garnered some interest as a probiotic, induces inflammatory T cell differentiation in the intestines of *Atg16l1*^{T300A} knock-in mice when transferred from Crohn's disease patients [146]. Hence, viruses and bacteria that are potentially beneficial in other settings evoke inflammatory responses in the gut of *Atg16l1* mutant mice. These observations are consistent with a model of IBD in which genetically susceptible individuals lose tolerance to commensal agents.

Mechanistically, the role of ATG16L1 in IECs could be explained by the link between autophagy, organelle homeostasis, and secretion. Unmitigated ER stress upon the inhibition of IKKα signaling in IECs leads to ATG16L1 instability and intestinal inflammation [147]. Individuals with the *ATG16L1*^{T300A} variant and aged *Atg16l1* mutant mice display signs of ER stress in Paneth cells [148, 149], which is associated with a compensatory upregulation of IgA production by B cells [150]. Simultaneous deletion of *Atg16l1* and the ER stress transcription factor *X-box binding protein-1* (*Xbp-1*) leads to a dramatic loss of Paneth cells and severe intestinal inflammation [151]. In contrast to colonic IECs that die from apoptosis upon autophagy inhibition [152, 153], *Atg16l1* mutant Paneth cells accumulate defective mitochondria and die from necroptosis, a form of programmed necrosis in which mixed lineage kinase domain like protein induces pore formation in the plasma membrane [73, 154] (Fig. 2). The selective effects of *ATG* mutation on Paneth cells may reflect the vulnerability of cells with a high secretory burden. In addition to resolving organelle stress through autophagy, ATG proteins can compensate for ER-Golgi trafficking defects that occur in Paneth cells during *S.* Typhimurium infection by mediating exocytosis of the antimicrobial molecule lysozyme [155]. ATGs are necessary for mucus secretion by goblet cells [156], another secretory epithelial cell subset that produces the mucus necessary to prevent invasion by commensal and pathogenic microbes [138]. The loss of ATG16L1 is counterbalanced by a binding partner, the cytokine signaling inhibitor and deubiquitinase A20, and deleting both together leads to severe epithelial cell death and intestinal inflammation [157]. When taken together, these studies show that ATG16L1 has a fundamental role in promoting the viability and function of Paneth cells and other IECs in response to stressful conditions associated with colonization by benign bacteria and viruses. This role of ATG16L1 is linked to organelle homeostasis and could reflect both autophagy and related events such as unconventional protein secretion.

Concluding remarks

A key frontier in infection biology is to apply the molecular level knowledge of autophagy gained from sophisticated cell biological experiments toward elucidating mechanisms of pathogenesis. The pioneering studies that investigated ATG function in simplified models have generated an array of hypotheses, many of which have been supported. In addition, coinciding with the generation of mutant mice, research from this past decade has extended the way in which autophagy intersects host defense. Tissue and cell type-specific activities have become more apparent, and multicellular and multi-organ mechanisms are being discovered.

A few themes have emerged that are consistent across multiple studies. At the individual cell level, ATGs are central players in the battle over membranes. Intracellular pathogens seek to subvert membranes to establish replicative niches, pass through membranes to access various compartments, or to simply avoid degradation. In a pathogen-specific manner, autophagy and related pathways can limit these processes or be hijacked to complete the life cycle. Outside the infected cell, autophagy restricts the damage caused by infections, especially by extracellular pathogens, either by supporting the viability of key cell types or restraining inflammatory cytokine production. Applying the brakes to the inflammatory cascade comes at a cost because it dampens antimicrobial immunity but is essential for preventing chronic immune responses associated with a litany of diseases including IBD. After the initial events associated with infection, autophagy and LAP are critically important for adaptive immunity by mediating antigen presentation and lymphocyte differentiation.

These immune functions of autophagy represent generalities. Mechanisms revealed by examination of one pathogen cannot be extended to others because even closely related microbes use distinct virulence strategies. Similarly, the literature on ATG16L1 highlights the importance of distinguishing the function of ATGs in leukocytes versus parenchymal cell types. It may be particularly interesting to test whether the ability of certain viruses to exploit the autophagy machinery in one cellular compartment is a liability in another cell type or tissue, and how this might determine disease outcomes. Also, the ability to discriminate autophagy from related ATG-dependent pathways remains a challenge, especially when relying on animal models in which genetically inhibiting multiple parts of the pathway is cost prohibitive. Therefore, great care must be taken when considering how autophagy can be targeted for therapeutic purposes. It is clear that additional research is needed before we can harness the benefit of this multistep cellular process to promote immunity toward disease-causing microbes. We suggest that the use of clinical isolates of pathogens, advanced cell culture models, and human specimens can bridge the gap between in vitro studies and the increasing repertoire of animal models.

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Compliance with ethical standards

Conflict of interest VJT is an inventor on patents and patent applications filed by New York University, which are currently under commercial license to Janssen Biotech Inc. KC has consulted for or received an honorarium from Puretech Health, Genentech, and AbbVie, Inc., has received research support from Puretech Health and Pfizer, Inc, and has a provisional patent, US Patent Appln. No. 15/625,934.

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