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REVIEW

Bacteria Exploit Autophagy For Their Own Benefit

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Abstract: Autophagy is a lysosomal degradation pathway to clear long-lived proteins, protein aggregates, and damaged organelles. Certain microorganisms can be eliminated by an autophagic degradation process termed xenophagy. However, many pathogens deploy highly evolved mechanisms to evade autophagic degradation. What is more, series of pathogens have developed different strategies to exploit autophagy to ensure their survival. These bacteria could induce autophagy and/or prevent autophagosomes fusion with lysosomes through secreted effector proteins or utilizing host components, thereby maintaining the localization of the bacteria within the autophagosomes where they replicate. Here, we review the current knowledge of the mechanisms developed by the bacteria to benefit from autophagy for their survival.

Keywords: bacteria, autophagy, exploit, benefit

Introduction

Autophagy was first described as a response to starvation by the liver, with the term "autophagy" derived from the Greek words for "self" and "eating". It involves the sequestration and transport of complete regions of the cytoplasm, including both soluble proteins and entire organelles within double-membrane vacuoles called autophagosomes, to the lysosomal system for degradation and recycling by lysosomal hydrolases.[1] Autophagy is the lysosomal degradation process which regulates levels of long-lived proteins and organelles.[1] The general autophagy is bulk autophagy which appears to randomly sequester cytosolic content, while selective autophagy requires cargo adaptors specifically enrich forming autophagosomes for certain cargos. So far, selective autophagy has given rise to terms such as mitophagy, ribophagy, aggrephagy, lipophagy, endoplasmic reticulum (ER)-phagy, and pexophagy according to the engulfed material.[2]

Autophagy pathways can be broken down into five basic phases: initiation, elongation, closure, maturation, and degradation.[3] Autophagy is regulated at the molecular level by a family of dedicated genes called autophagy-related (*ATG*) genes.[4] The first *ATG* gene was identified in yeast by Ohsumi in 1993.[5] To date, at least 37 *ATG*s were identified.[6] Among them, one subset has been referred to as the "core" autophagic machinery as they are required for autophagosome formation in all autophagy subtypes.[7] These core ATGs can be subdivided into four subgroups: 1) the ATG1/ULK1 complex, composed of ATG1/ULK1, ATG13, ATG101 and FIP200; 2) the class III PI3K complex, composed of Vps34, Vps15, ATG6/Beclin1 and ATG14; 3) two ubiquitin-like protein conjugation systems which consist of

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ATG12, ATG5, ATG16L1, ATG8/LC3, ATG7, ATG10, ATG3 and ATG4; and 4) two transmembrane proteins, ATG9 (and associated proteins ATG2 and ATG18/WIPI2) and VMP1.[7,8] The first and second subgroups of core ATGs regulate the initiation phase of autophagy, the third subgroup involves in autophagosome formation and membrane elongation, and the fourth subgroup is important for autophagosome formation and maturation.[2,8]

In 2005, Levine defined xenophagy as a process that host cells direct the cell's digestive machinery to the breakdown of invading microorganisms to address the risk of pathogen invasion.[9] Autophagy is the first line of host innate immune system to eliminate invasive pathogens, however, pathogens have evolved countermeasures to either evade or reconfigure the autophagy pathway for their own survival.[10] Furthermore, autophagy or autophagy-related proteins also could be exploited by the pathogens. Studies have demonstrated that some viruses, such as poliovirus (PV), hepatitis C virus (HCV), dengue virus (DENV), human immunodeficiency virus (HIV), hepatitis B virus (HBV) and so on, could use autophagy for their replication, assembly and release.[11–13] In 2011, Ogawa et al reviewed the strategies of some bacteria to manipulate autophagy for their own benefit, however, many bacterial effectors and host factors which were involved in the utilization of host autophagy by pathogens were identified during these years.[10] Understanding how bacterial pathogens achieve this at the molecular level will provide new potential targets for therapeutic intervention. In this review, we will focus on the bacterial pathogens and summarize the current knowledge of the mechanisms developed by the bacteria to hijack autophagy for their own benefit.

Anaplasma phagocytophilum

A. phagocytophilum is a Gram-negative obligate intracellular bacterium that causes human granulocytic anaplasmosis. After invasion of the host cells, *A. phagocytophilum* replicates in a membrane-bound compartment contains autophagy-related proteins LC3 and Beclin1 but is endosomal or lysosomal markers are absent. Induction of autophagy facilitates *Anaplasma* infection while inhibition of autophagy arrests its growth.[14] The secreted effector *Anaplasma* translocated substrate 1 (Ats-1) stimulates autophagy nucleation by interacting with Beclin1 therefore facilitates autophagosome formation and subsequently promotes its own growth by using the nutrients contained in the autophagosomes (Table 1, Figure 1).[15,16]

Brucella

Bacteria of the genus *Brucella*, contains six classic species, are the causative agent of brucellosis, a worldwide zoonosis with significant health and economic consequences.[17] The internalized bacterium *Brucella abortus* traffics from the endocytic compartment to the ER to form *Brucella*-containing vacuole (rBCV), where the bacterium proliferates.[18,19] Taguchi et al showed that the formation of rBCV required the autophagy protein ATG9, WIPI1 and rBCV conversion into a compartment with autophagic features (aBCV) accompany *Brucella* replication.[20,21] The formation of aBCV required the autophagy-initiation proteins ULK1, Beclin1, ATG14L and PI3K but independent of the proteins involve in autophagosome membrane elongation such as ATG5, ATG16L1, ATG7, ATG4B, and LC3B. aBCV formation completes the *Brucella* intracellular cycle and promotes subsequent cell-to-cell spreading.[21,22] Further, *B. abortus* induces autophagy and prevents *Brucella*-containing phagosomes fusion with lysosomes.[22–24] Similar to *B. abortus, B. melitensis* infection triggers autophagosome formation, and autophagy favors *B. melitensis* survival.[25,26] Deletion of host autophagy system ULK1, ATG9 and Beclin1 resulted in striking disruption of *B. melitensis* intracellular trafficking and replication.[27] Thus, *Brucella* selectively co-opts autophagy-initiation complexes to subvert host clearance and facilitate the bacterium persist and replicate within aBCV, eventually promote infection.

Coxiella burnetii

C. burnetii, the causative agent of human Q fever, is a highly infectious Gram-negative bacterium. *Coxiella* hijacks the autophagosomes and redirect the nutrient by-products of the autophagolysosomes toward microbial replication rather than for the use by the host cell.[28–30] After infection, *C. burnetii* establishes large acidic vacuoles containing multiple replicating bacteria that were labeled with autophagy protein LC3.[31] Induction of autophagy by starvation or overexpression of LC3, Rab24 or Beclin1 promotes the formation of *Coxiella*-replicative vacuoles.[32,33] The clathrin heavy chain (CLTC), a scaffolding protein of clathrin-coated vesicles, facilitating the fusion of autophagosomes with the *Coxiella*-containing vacuoles (CCVs) (Table 1, Figure 1).[34] Intracellular *Coxiella* has two morphologically, compositionally and functionally distinct forms: the metabolically dormant, less replicating and environmentally stable small cell variants (SCVs) and the metabolically active, replicating and more fragile large cell variants (LCVs).[35] It is believed

Table 1 Effectors And Host Targets Involve In Bacterial Exploitation Of Autophagy

Bacteria	Effector	Host target	Outcome	Reference
A. phagocytophilum	Ats-1	Beclin1	Stimulates autophagy nucleation	15
C. burnetii	– Cig2 CvpB	CLTC – PIKfyve	Facilitates the fusion of autophagosomes with CCVs Facilitates the fusion of autophagosomes with CCVs Facilitates the homotypic fusion of CCVs	34 40,41 42
C. trachomatis	pORF5	HMGB1	Induces mitophagy and inhibits apoptosis to generate enough nutrients for bacterial survival	
H. pylori	VacA VacA VacA	LRP1 mTORC1 –	Prevents autophagosome-lysosome fusion Induces autopahgy Decreases the level of cathepsin D	55 56 54
L. pneumophila	DrrA/SidM, LidA, RalF	–	Inhibit the immediate delivery to lysosomes	62
L. monocytogenes	LLO	NLRX1	Induce mitophagy and decrease the production of mtROS	65
M. tuberculosis	SapM, PknG, PtpA	–	Prevents phagosomes fusion with lysosomes	68–70
M. avium	–	Cholesterol	Inhibits phagosomes maturation and fusion with lysosomes	71
P. gingivalis	PG0717 LPS	– –	Induces autophagy Induces autophagy	75 79
Pst	HopM1	–	Activates proteaphagy	83
S. marcescens	ShlA	–	Induces autophagy	93
S. aureus	– Hla	TMEM59 –	Facilitates recruitment of ATG16L1 and promotes LC3 labelling of *S. aureus*-containing phagosomes Induces autophagy	95 96
UPEC	–	Ferritin	Increased iron availability for UPEC	104
Y. pseudotuberculosis	_	VAMP7	Promotes LC3 recruitment to *Y. pseudotuberculosis*-containing autophagosomes	109

that the differentiation from SCV to LCV is triggered by a nutrient-rich environment as induction of autophagy increases the number of LCVs in HeLa cells.[36] Moreover, the CCVs acquire certain lysosomal characteristics, the low pH conditions favorable to *Coxiella* replication, while increasing the phagolysosomal pH inhibited the multiplication of the bacteria.[37–39] The *Coxiella* effector proteins Cig2 and CvpB facilitate CCVs fusion with autophagosomes. Cig2 promotes fusion of the CCVs with autophagosomes by continuously maintaining LC3 on the CCVs membranes which delays autophagosome maturation and promotes constitutive fusion between autophagosome and CCVs (Table 1, Figure 1).[40,41] CvpB can bind phosphatidylinositol 3-phosphate (PI3P) and perturb the activity of the phosphatidylinositol 5-kinase PIKfyve, thereby enriching PI3P on CCVs membranes which promote the recruitment of autophagosomal machinery to mediate homotypic fusion of CCVs (Table 1, Figure 1).[42] Furthermore, autophagy can repair damaged membranes of CCVs to maintain the membrane integrity therefore promote bacteria replication.[43]

Chlamydia trachomatis

C. trachnomatis is an obligate intracellular bacterial pathogen which is associated with several human diseases, such as trachoma, pneumonia, and atherosclerosis.[44] *C. trachnomatis* replicates within a membrane-bound compartment (the inclusion) which is not associated with autophagosomes. However, after inhibition of autophagy, the chlamydial inclusion size and progeny infectivity were decreased,

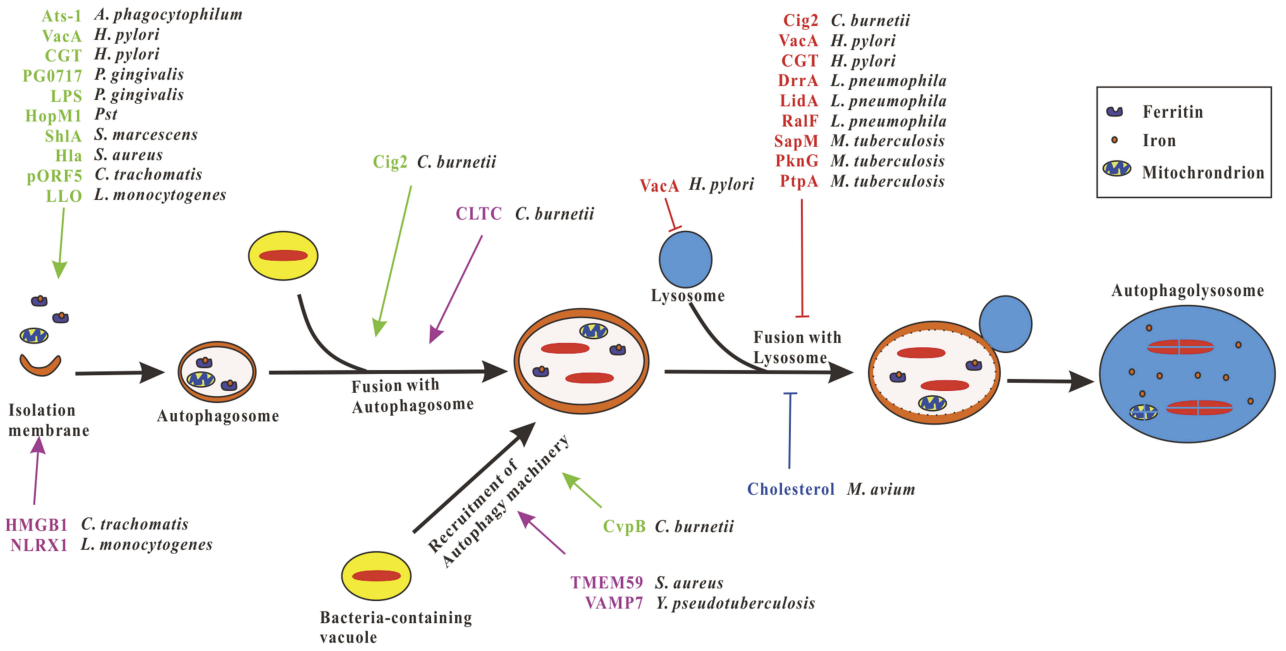

Figure 1 Exploitation of autophagy pathway by bacterial pathogens. After the invasion of the host cell, vacuoles containing intracellular bacteria fuse with autophagosomes or recruit autophagy machinery to form autophagic vacuoles favor the bacteria replication. Several bacteria have evolved different effector proteins that induce autophagy to form autophagosomes or promote bacteria-containing vacuoles fuse with autophagosomes or facilitate the recruitment of autophagy machinery to bacteria-containing vacuoles (green), thereby promoting the replication of bacteria. Some bacteria secrete effector proteins that impair the functions of lysosomes or inhibit bacteria-containing autophagosomes fuse with lysosomes (red) to block the lysosomal degradation of the bacteria. Furthermore, cholesterol of host cells prevents *M. avium*-containing autophagosomes fusion with lysosomes (blue), CLTC promotes *C. burnetii*-containing vacuoles fusion with autophagosomes, HMGB1 and NLRX1 induce mitophagy thus promote survival of *C. trachomatis* and *L. monocytogenes* respectively, TMEM59 and VAMP7 facilitate the recruitment of autophagy proteins to the *S. aureus* and *Y. pseudotuberculosis*-containing vacuoles, respectively (violet), and UPEC benefits from ferritinophagy.

morphology of chlamydial forms was aberrant suggest a potential supportive role of host autophagy in the pathogenesis of *Chlamydia*.[44] In autophagy-deficient ATG5(-/-) fibroblasts, the growth of *C. trachnomatis* was increased, but in the presence of Bafilomycin A1, an inhibitor of vacuolar ATPase (vATPase), the growth was inhibited indicates that there should be at least two types of vATPase-bearing organelles that one defends against chlamydiae, while the other supports chlamydial growth.[45] It was also showed that lysosomal degradation products were transferred to chlamydiae suggest that products generated within lysosomes contribute to the intracellular survival of *C. trachnomatis*.[46] Moreover, Lei et al demonstrated that *C. trachnomatis* plasmid-encoded protein pORF5 up-regulated the expression of high mobility group box 1 (HMGB1) which induces mitophagy and inhibits apoptosis of host cells (Table 1, Figure 1).[47] These findings suggest that *C. trachnomatis* could manipulate host cell death to usurp enough nutrients generated via autophagy for their survival and replication.

Francisella tularensis

F. tularensis is a Gram-negative, highly infectious, facultative intracellular pathogen that causes tularemia.[48] After phagocytosed by host cells, *Francisella* escaped from the phagosome and underwent replication in *Francisella*-containing vacuoles (FCVs). FCV is a large, juxtanuclear, LC3- and LAMP1-positive vacuole whose formation is dependent on autophagy.[49] Optimal intracellular bacterial growth requires autophagy that induces autophagic degradation of cellular proteins, thereby generating a surplus of amino acids to support intracellular growth of *F. tularensis* in macrophages as well as mouse embryo fibroblast (MEFs), but this process is independent of ATG5.[50]

Helicobacter pylori

H. pylori infection is associated with the development of chronic gastritis, peptic ulcer and gastric cancer. After internalization of human macrophage and gastric epithelial cells, autophagy was induced and *H. pylori* replicates in a double-layer vesicle which is characteristic of autophagosome.[51,52] The secreted effector protein, vacuolating cytotoxin (VacA) can induce autophagy through binding to the low-density lipoprotein receptor-related protein-1 (LRP1) or through inhibition of mTORC1, but prevent autophagosome-lysosome fusion and decrease the level of cathepsin D thus impair the catalytic activity of lysosome (Table 1, Figure 1).[53–56]

The cholesterol-α-glucosyltransferase (CGT) of *H. pylori* also could trigger autophagy, and restrain autophagosome fusion with lysosomes to impair macrophage clearance of the bacteria (Table 1, Figure 1).[57] Zhang et al demonstrated that gastric epithelial cells infected with *H. pylori* resulted in impaired lysosomal acidification and retrograde trafficking of mannose-6-phosphate receptors (MPRs). Inhibition of autophagosome formation and lysosomal functions promote intracellular survival of *H. pylori*.[58] However, the induction of autophagy in turn limits the multiplication of *H. pylori* thereby conferring protection to host cells against *H. pylori* infection.[51] In the early stage of infection of murine bone marrow derived-dendritic cells (BMDCs), *H. pylori* transiently replicates in autophagosomes, but in the late stage, *H. pylori* was degraded by autophagolysosomes.[59]

Legionella pneumophila

L. pneumophila, a Gram-negative bacterium, is an intracellular bacterial pathogen responsible for an acute form of pneumonia called Legionnaire's disease. *L. pneumophila* could activate the autophagy pathway by a mechanism that does not require phagocytosis of the bacteria.[60] After invasion, *L. pneumophila* resides within vacuoles whose biogenesis resembles autophagy, escapes the toxic phagosome-lysosome pathway,[61] and perturb and delay the maturation of autophagosomes into autophagolysosomes.[60,62] It has been demonstrated that the effector proteins such as DrrA/SidM, LidA and RalF prolong the association time of the *Legionella*-containing vacuoles with the ER and inhibit the immediate delivery to lysosomes (Table 1, Figure 1).[62] Remarkably, *Legionella* continues to replicate within acidic lysosomal vacuoles.[63] The replication of *Legionella* was inhibited when autophagosome formation is impaired, or vacuoles acidification and fusion with lysosomes is blocked.[63,64] Thus, it seems that *L. pneumophila* persist in immature autophagosomal vacuoles for a period that is suitable for them to differentiate into an acid-resistant, replicative form. Subsequently, the adapted progeny continues to replicate within autophagolysosomes.[62]

Listeria monocytogenes

L. monocytogenes is Gram-positive bacterium causes enteritis, occasionally causes listeriosis. After infection of host cells, *L. monocytogenes* could secrete several effector proteins such as internalins, listeriolysin O (LLO), ActA and so on to evade killing by autophagy.[10] Recently, Zhang and colleagues found that the bacterial effector LLO and host factor nucleotide-binding leucine-rich repeat-containing family member X1 (NLRX1) could induce mitophagy. Increased mitophagy decreased the production of mitochondrial reactive oxygen species (ROS) which controls *L. monocytogenes* infection, thereby facilitating its survival (Table 1, Figure 1).[65]

Mycobacterium

Mycobacterium tuberculosis causes tuberculosis which is one of the major causes of death from an infectious disease worldwide. In human lymphatic endothelial cells (LECs), *M. tuberculosis* was observed within autophagosomes, and autophagy promotes the growth of the bacterium in resting LECs.[66] In human alveolar epithelial cells, *M. tuberculosis*-containing compartments surrounded by double membranes and labelled with autophagy marker LC3, inhibition of the autophagy impaired intracellular bacteria replication and improved host cell viability, and the bacteria-containing compartment fusion with lysosomes appears to be inhibited, suggesting that autophagy is involved in trafficking of *M. tuberculosis* bacilli and is required for its survival.[67] It has already demonstrated that the secreted effector proteins, acid phosphatase M (SapM), the *M. tuberculosis* eukaryotic-like serine/threonine-protein kinase G (PknG) and the protein tyrosine phosphatase (PtpA) could prevent mycobacteria-containing phagosomes fusion with lysosomes (Table 1, Figure 1).[68–70] The cholesterol, a component of host cell plasma membrane, could prevent *M. avium*-containing phagosomes maturation and fusion with lysosomes in mouse bone marrow-derived macrophages (BMDMs) (Table 1, Figure 1).[71] Similar phenotypes were observed in mouse macrophages cell line Raw 264.7 infected with closely relative to *M. tuberculosis, M. marinum*.[72] Furthermore, in the model organism *Dictyostelium discoideum*, autophagy is required for nonlytic ejection of *M. marinum*. Autophagic machinery was recruited at the distal pole of ejecting bacteria, disruption of autophagy causes the host cells to become leaky and die during ejection suggest that autophagy maintains the integrity of plasma membrane and promotes cell-to-cell transmission of *M. marinum*.[73]

Porphyromonas gingivalis

P. gingivalis is a Gram-negative bacterium causes periodontitis. It is also linked to several systemic chronic diseases such as rheumatoid arthritis, diabetes, and cancer.[74] After internalization by host cells, the lipoprotein PG0717 of *P. gingivalis* activates autophagy (Table 1, Figure 1), then the bacterium evades the endocytic pathway to lysosomes and instead traffics to autophagosome, thereby

establishing a replicative niche in an ATG7-dependent manner.[75–77] When autophagy is inhibited in HCAEC and human gingival epithelial cells (GECs), the bacterium enter the endocytic pathway to lysosomes thus the viability of intracellular *P. gingivalis* is reduced.[77,78] Recently, studies showed that lipopolysaccharide (LPS) from *P. gingivalis* can induce autophagy by suppressing PI3K/Akt/mTOR signaling pathway in human gingival fibroblasts (HGFs) (Table 1, Figure 1) and enhance the co-localization of bacterium with autophagosomes in human-cultured keratinocyte cells (HaCaT).[79,80] Remarkably, *P. gingivalis* is an asaccharolytic pathogen, thus the bacterium traffic through the autophagic pathway can acquire essential nutrients from the autophagosomes, and also evade cell defense.[60]

Pseudomonas syringae pv. *tomato* DC3000

Autophagy plays an important role in maintaining a functional immune system in plants.[81,82] Recently, Hofius and coworkers demonstrated that autophagy has both pro- and antibacterial functions upon infection of *Arabidopsis thaliana* with *Pseudomonas syringae* pv. *tomato* DC3000 (*Pst*).[83] Autophagy was activated after infection with *Pst* and NEIGHBOR of BRCA1 (NBR1), a cargo receptor-mediated autophagic degradation limited the growth of *Pst*.[84] In turn, as proteasome acts as a hub for plant immunity,[85] *Pst* employs the effector protein Hrp outer protein M1 (HopM1) to suppress proteasomal activity and activate autophagic degradation of proteasomes (proteaphagy), thereby enhancing its pathogenicity (Table 1, Figure 1).[83,85]

Salmonellaenterica Serovar Typhimurium

It has been demonstrated that the ATG16L1 knock-out or T300A variant confers protection from cellular invasion by *S. typhimuriunm* in HCT116 cells, re-expression of wild-type ATG16L1 not T300A variant in ATG16L1 knock-out cells facilitates *Salmonella* invasion into the cells.[86] Since ATG16L1 was recruited to the entry sites of *Shigella flexneri*, the ATG16L1 T300A variant may be less efficiently recruited to the plasma membrane, therefore reduce *Salmonella* invasion.[87] Interestingly, Yu and colleagues found that depletion of autophagy components such as ATG5, LC3 and/or p62 inhibits the replication of cytosolic *Salmonella* but not affect the *Salmonella* invasion ability in HeLa cells suggest that autophagy facilitates *Salmonella* replication.[88] Later, Kreibich et al demonstrated that, similar to *Coxiella*, autophagy proteins promote repair of *Salmonella*-containing vacuole (SCV) membrane damaged by the *Salmonella* type three secretion system 1 (T3SS-1) in an unknown mechanism, thereby allowing compartment maturation and subsequent expression of type three secretion system 2 (T3SS-2), which together promote intracellular survival.[89–91] These findings suggest that *Salmonella* uses the autophagic process to its advantage and survives in cells.

Serratia marcescens

S. marcescens is a Gram-negative bacterium which is commonly involved in hospital-acquired infections (HAIs). After internalized by epithelial cells, *Serratia* replicates inside a large membrane-bound compartment which displays autophagic-like characteristics.[92] However, the autophagic-like vacuoles are non-acidic and have no degradative properties suggest that *Serratia* utilizes autophagosomes for survival and proliferation by preventing the vacuoles fusion with lysosomes.[92] Interestingly, the pore-forming toxin ShlA secreted by *Serratia* can induce autophagy prior to bacterial internalization which may pave the way for subsequent proliferation inside the autophagosomes (Table 1, Figure 1).[93]

Staphylococcus aureus

S. aureus can invade epithelial cells and then transit to an autophagosome-like vacuole which is characterized by double membrane and colocalization with LC3.[94] In this process, human transmembrane protein TMEM59 which mainly localized in late endosomes/lysosomes may perform an in situ autophagic function that facilitates the recruitment of ATG16L1 and then promotes LC3 labelling of *S. aureus*-containing phagosomes.[95] After the invasion of epithelial cells, *S. aureus* inhibits the bacteria-containing autophagosome maturation and fusion with lysosomes dependent on accessory gene regulator (Agr) system. Activation of autophagy by the inducer rapamycin significantly increases the intracellular load of *S. aureus*. In contrast, the growth of intracellular *S. aureus* was drastically impaired upon treatment with the autophagy inhibitor wortmannin. Similar results were obtained using *atg5*-deficient MEFs suggest that autophagy is indispensable for *S. aureus* replication.[94] The virulence factor pore-forming toxin α-hemolysin (Hla) can trigger autophagy hence promote bacterial replication (Table 1, Figure 1).[96] After replication, *S. aureus* eventually escape from autophagosomes into the cytoplasm and induce apoptosis-like cell death.[94] Therefore, the autophagy machinery is essential for *S. aureus* replication and host cell killing.

Uropathogenic *Escherichia coli* (UPEC)

UPEC causes a frequent and important disease in humans, urinary tract infection (UTI). UPEC colonize the bladder and persist within the bladder epithelium as membrane-enclosed quiescent intracellular reservoirs (QIRs) that can seed recurrent UTI.[97] The autophagy gene *ATG16L1* plays an important role in inflammatory disease and intestinal cell abnormalities, however, studies showed that ATG16L1 deficiency confers protection in vivo to the host against both acute and latent uropathogenic *E. coli* (UPEC) infection,[97–99] suggesting that UPEC can use autophagy to provide potential nutrient sources or a protected environment for their survival.[100] ATG16L1 deficient mice cleared UPEC more rapidly and thoroughly which is associated with increased recruitment of innate immune cells to the infected bladders and a robust proinflammatory response,[99] and this process is independent of the pathogen sensor nucleotide-binding oligomerization domain containing 2 (NOD2) but is dependent of IL-1β.[101,102] Recent studies have demonstrated that T300A variant in ATG16L1 increases the expression level of small secretory RAB GTPases, such as RAB11A, RAB27B and RAB33B that are important for UPEC expulsion, thereby limiting the UPEC persistence in urothelium.[103] Mechanistic studies revealed that UPEC shuttles with ferritin-bound iron into the autophagosomal and lysosomal compartments within the urothelium, autophagic degradation of iron-bound ferritin (ferritinophagy) led to increased iron availability for UPEC (Table 1, Figure 1), then triggered bacterial overproliferation and host cell death. Inhibition of autophagy or inhibition of iron-regulatory proteins, or chelation of iron reversed the bacterial overgrowth and promoted host cell survival suggests that UPEC exploit ferritinophagy for their own survival.[104]

Yersinia pestis

Y. pestis is a Gram-negative bacterium and causes plague.[105] *Y. pestis* can survive and replicate in phagosomes of murine macrophages.[106] It has been demonstrated that *Y. pestis*-containing vacuoles colocalized with autophagy protein LC3, further, the *Y. pestis*-containing vacuoles failed to acidity below pH 7 in mouse BMDMs. These findings suggest that *Y. pestis* could avoid xenophagy by preventing vacuole maturation to the autolysosome, thus promotes its survival in autophagosomes.[84] However, the replication of bacterium was not decreased in ATG5-deficient BMDMs suggest that autophagy is not required for *Y. pestis* survival in macrophages.[84] It is possible that the bacteria only recruits the membrane to enlarge the *Y. pestis*-containing vacuoles into a spacious compartment or interferes normal process of autophagy to promote cell death thus escape from the macrophage.[107] The connection between autophagy and *Y. pestis* still need to be addressed in future work.

Yersinia pseudotuberculosis

Y. pseudotuberculosis is a Gram-negative enteropathogenic bacterium that causes mesenteric lymphadenitis. After ingestion, the bacterium activates autophagy and replicates within autophagosomes in mouse BMDMs and HeLa cells.[108,109] The vesicle-associated membrane proteins (VAMPs) play pivotal roles in the membrane traffic during the internalization of *Y. pseudotuberculosis*. VAMP7 promotes LC3 recruitment to *Y. pseudotuberculosis*-containing autophagosomes (YCVs) (Table 1, Figure 1).[109] Like *Y. pestis, Y. pseudotuberculosis* also prevents YCVs mature to autophagolysosomes. However, different to *Y. pestis*, autophagy is required for *Y. pseudotuberculosis* survive, *Y. pseudotuberculosis* traffics to lysosomes for degradation upon autophagy inhibition.[108]

Conclusions

The role of autophagy in host defense against bacteria has investigated in depth. Generally, autophagy is antipathogenic, however, several bacterial pathogens have evolved countermeasures to hijack the autophagic pathway for their own profit. In most cases, these bacteria actively induce autophagy and/or block autophagosome fusion with the lysosome through secreted effector proteins, then use the autophagosome as a replicative niche for their growth (Figure 1). Interestingly, several bacteria could utilize the host components such as cholesterol, TMEM59 and VAMP7, thereby favoring the survival of some bacteria. The role of autophagy in enhancing replication of these pathogens is unknown, but nutrient acquisition and escape from cell defense are two likely explanations for these phenotypes. Remarkably, the role of autophagy in microbial infection may depend on the type of invading microbe and the cell type. In an era of increasing antibiotic resistance, understanding how pathogens interact with and manipulate the host autophagy pathway to achieve this will hopefully provide a basis for combating infection and increase our understanding of

the role and regulation of autophagy. Considering the variety of mechanisms that developed by different pathogens, we need to correctly use autophagy modulators in eliminating bacterial pathogens and it is necessary to determine an effective strategy in the clinical treatment.

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Disclosure

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