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LC3-associated phagocytosis: host defense and microbial response

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The innate immune system has evolved to recognize diverse microbes and destroy them. At the same time, microbial pathogens undermine immunity to cause disease. Here, we highlight recent advances in understanding an antimicrobial pathway called LC3-associated phagocytosis (LAP), which combines features of autophagy with phagocytosis. Upon phagocytosis, many microbes, including bacteria, fungi, and parasites, are sequestered in an LC3-positive, single-membrane bound compartment, a hallmark of LAP. LAP depends upon NADPH oxidase activity at the incipient phagosome and culminates in lysosomal trafficking and microbial degradation. Most often LAP is an effective host defense, but some pathogens evade LAP or replicate successfully in this microenvironment. Here, we review how LAP targets microbial pathogens and strategies pathogens employ to circumvent LAP.

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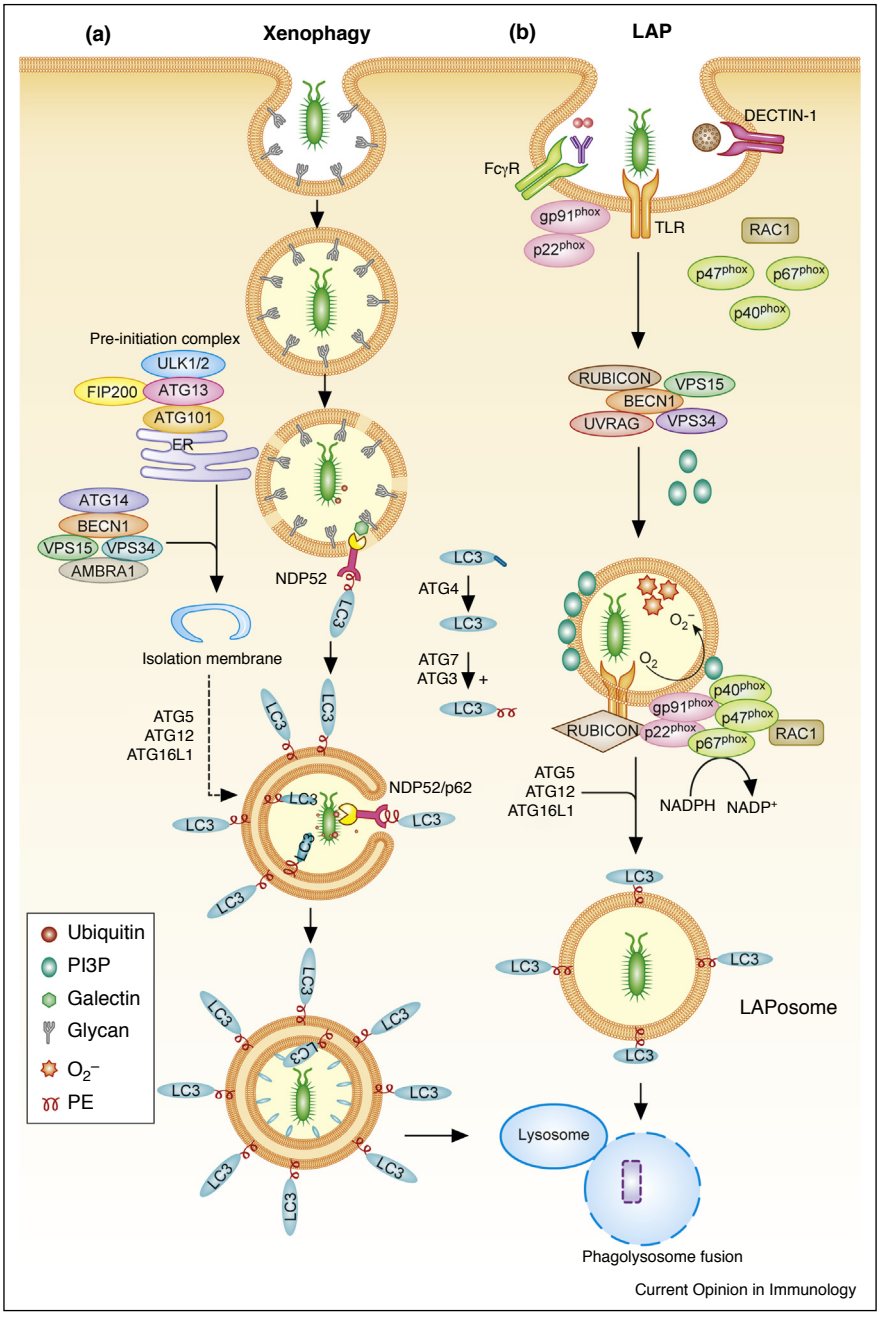
Introduction

In the arms war with microbial pathogens, innate immune phagocytes deploy two autophagy-related pathways to promote microbial degradation in lysosomes: LC3-associated phagocytosis (LAP) and xenophagy. When microbes activate certain pathogen recognition receptors, the LAP pathway utilizes autophagy proteins for a non-canonical function following phagocytosis to promote phagosome maturation. To evade phagolysosomal destruction, some pathogens escape into the cytosol, while others damage the phagosome and inject microbial effectors into the cytosol to disrupt lysosomal trafficking. In the face of damaged phagosomes, host cells employ xenophagy, a form of canonical autophagy that selectively sequesters invading microbes in a double membrane compartment so they can be routed to lysosomes. While LAP and xenophagy make use of shared components, such as certain ATG (autophagy related) proteins, they also have many unique requirements. For example, RUBCN/RUBICON promotes LAP, whereas it interferes with xenophagy. Since xenophagy and LAP are critical for clearing microbes, it is not surprising that a number of medically important pathogens interfere with these related processes. Given that there are already many excellent reviews on the role of canonical autophagy in infection and immunity [2–4], here we highlight recent work on the LAP pathway and the mechanisms by which pathogens undermine LAP.

Differences between LAP and xenophagy

The molecular distinctions between canonical autophagy and LAP have recently been reviewed in detail [1], and key differences are illustrated in Figure 1. LAP occurs during phagocytosis when the engulfed cargo activates cellular receptors that drive the recruitment of the NADPH oxidase and subsequent LC3-delivery to the phagosome. Both LAP and xenophagy are characterized by the association of lipidated LC3 (LC3-II) with microbe-containing compartments. The conversion of LC3 to its phosphatidylethanolamine (PE)-conjugated form is orchestrated by ATG proteins, including ATG5, ATG7, and ATG16L1 that are part of two ubiquitin-like ATG conjugation systems. A major distinction between LAP and xenophagy is the source of the membrane in which LC3-II is incorporated. LAP begins with phagocytosis, whereas autophagy commences with the formation of a phagophore at the endoplasmic reticulum, a process that is under control of the autophagic initiating complex. The initiation complex is composed of the serine threonine kinase ULK1, and non-catalytic subunits FIP200, ATG13, and ATG101. LAP does not rely on the formation of a double membrane phagophore or this machinery. Correspondingly, mTORC1 and AMPK, which regulate autophagy initiation, do not appear to influence LAP. Instead, during LAP, activation of the ATG conjugation systems depends upon the NADPH oxidase, which is dispensable for xenophagy [5••,6••]. In some cases, as shown during *Listeria* and *Salmonella* infection, both LAP and xenophagy occur at the same time [7••,8], and they can be difficult to distinguish since both are defined by membrane-associated LC3. LAP is established by nature of the LC3-containing membrane (single, not double) and genetic requirements (NADPH oxidase and RUBICON versus the autophagy initiation complex).

Figure 1



Xenophagy and LC3-associated phagocytosis.
(a) Xenophagy is a form of canonical autophagy, in which microbes are selectively captured into a double membrane autophagosome. When microbes disrupt the phagosomal membrane and gain access to the cytosol, damaged membrane remnants and bacterial surface proteins are ubiquitinated by host E3 ubiquitin ligases. Autophagy adaptors such as p62 and NDP52 bind ubiquitinated cargo and also LC3, thereby linking cargo to the emerging autophagosomal membrane. Damaged phagosomes also expose luminal glycans to the cytosol, which are recognized by cytosolic galectins, which also bind NDP52. Thus, autophagy adaptors target microbes and damaged phagosomes to the LC3-decorated double membrane compartment. Formation of this compartment requires the ULK1 pre-initiation complex (ULK1/2, FIP200, ATG13 and ATG101), which translocates from the cytoplasm to the endoplasmic reticulum. The ULK1 complex and the PI3K complex (ATG14L, BECLN1, VPS15, and VPS34) promote autophagy initiation during xenophagy. The autophagosome fuses with lysosomes to degrade sequestered microbes.
(b) LAP is initiated on host phagocytes by engagement of surface receptors such as TLR2, DECTIN-1, FcγR, and TIM4 by bacteria, fungi, immune complexes, and dead cells, respectively. The signaling cascade initiated upon receptor engagement results in recruitment and assembly of NADPH oxidase complex on incipient phagosomes, which is stabilized by RUBICON. RUBICON is also a component of the PI3K complex (RUBICON, BECLN1, VPS15, and VPS34), which generates PI3P. PI3P binds the $p40^{phox}$ subunit of the NADPH oxidase and is required for LAP.

LAP initiation

LAP serves as an innate defense against invading microbes, including a variety of bacteria, fungi, and parasites (Table 1). LAP is activated by pathogen recognition receptors (Toll-like receptors (TLRs), CLEC7/DECTIN1, CLEC6A/DECTIN2, SLAM), as well as receptors that detect phosphatidylserine (TIM4) and antibodies (FcγR2a). Hence, apoptotic bodies, fungi, bacteria, outer membrane vesicles released by bacteria, and antibody-opsonized cargo trigger LAP [9••,10•,11•,12,13]. Signaling from these receptors through SYK kinase and protein kinase C (PKC) activates NADPH oxidase and LAPosome formation [7••,14,15]. Likely other receptors can activate LAP, and recently *Listeria* was shown to stimulate LAP through the ß2 integrin Mac-1 receptor (ITGAM–ITGB2/Mac-1) [16••]. A process that resembles LAP, with some unconventional features, targets apicomplexan parasites, *Plasmodium* and *Toxoplasma gondii*, although the triggering events are not well defined [17,18]. The induction of LAP can also be influenced by cytokines, as an IFN-γ effector DAPK1, a Ca^{+2}/calmodulin-regulated kinase, promotes the formation of *Aspergillus* LAPosomes [19].

LAP orchestration

LAP depends upon the phosphatidylinositol 3-kinase (PI3K) complex and the NADPH oxidase, which generate phosphatidylinositol 3-phosphate (PI3P) and reactive oxygen species (ROS), respectively, at the microbe-containing phagosome. The PI3K complex is composed of BECN1, VPS15, and the kinase, VPS34, which are found in distinct sub complexes in LAP and xenophagy. RUBICON serves as a molecular switch that promotes LAP and interferes with xenophagy by associating with the UVRAG-containing PI3K complex at the phagosome and inhibiting autophagy-initiating, ATG14L1-containing complexes [20••]. The NADPH oxidase produces ROS when membrane-bound subunits ($p22^{phox}$ and $gp91^{phox}$) assemble with cytosolic subunits ($p40^{phox}$, $p47^{phox}$, $p67^{phox}$) and GTP-bound RAC [21]. RUBICON stabilizes the $p22^{phox}$ subunit, while PI3P recruits the $p40^{phox}$ subunit [5••,21,22•,23]. ROS is toxic to invading microbes and is essential for activating the ATG-conjugation systems during LAP [5••,6••,9••].

Exactly how ROS activates the ATG-conjugation systems at the LAPosome is not well understood. During xenophagy, bacteria damage the phagosome, and damaged membrane remnants and bacterial surface proteins are ubiquitinated by cytosolic E3 ubiquitin ligases. Ubiquitinated bacteria are linked to LC3 by autophagy adaptors, such as p62 and NDP52. Although ROS can damage membranes [24], ubiquitination and autophagy adaptors do not appear to be involved in LAP [7••,25,26]. For example during *Salmonella typhimurium* infection, some bacilli associate with autophagy adaptors, while the other population is associated with diacylglycerol (DAG) [6••,7••]. Inhibition of p62 and DAG has an additive effect on LC3 trafficking, suggesting that these markers identify distinct pathways [7••]. How ATG16L1 is recruited to the microbial compartment is also different between the two processes, as the C-terminal domain of ATG16L1 is essential during LAP but not canonical autophagy [27].

Studies on *Aspergillus*, *Salmonella*, and *Listeria* demonstrate that calcium and lipid signaling act upstream of NADPH oxidase recruitment during LAP (Figure 2). Kyrmizi *et al.* showed the importance of calcium–calmodulin signaling in regulating PI3K and NADPH oxidase during *Aspergillus* infection (discussed below in LAP evasion) [28••]. Recent work on *Listeria* points to the importance of ceramide. *Listeria*, through its interaction with Mac-1, activates acid sphingomyelinase (ASMase), which cleaves membrane sphingomyelin into phosphorylcholine and ceramide [16••]. Ceramide-enriched membrane platforms serve as a scaffold for the NADPH oxidase. The resulting phosphorylcholine may also serve as a substrate for host phospholipase D (PLD). During *S. typhimurium* infection, the sequential action of host PLD and phosphatidic acid phosphatase (PAP) generates DAG [7••]. DAG regulates PKCδ activity, which can activate the NADPH oxidase [21]. Bacterial phospholipases from *Listeria* can also contribute to DAG production [26]. Combined, these studies convincingly place calcium–CaM, ASMase–ceramide, and DAG–PKC in the LAP pathway, although it is not clear whether they are universally involved or whether they are cargo-specific.

Consequences of LAP

The full impact of LC3 recruitment to phagosomes remains to be fully elucidated and may depend upon the cargo and host cell physiology. Although ATG proteins are not universally required for phagolysosomal trafficking [29•], in some cases recruitment of LC3 has been shown to enhance phagosome maturation and microbial killing [6••,9••,10•,15,30]. However, in dendritic cells LAP impairs phagosome maturation, thereby prolonging MHCII antigen presentation [11•,31]. LAP influences the immune response triggered by the cargo, and again, the outcome depends upon the nature of the cargo and host cell. In plasmacytoid dendritic cells (pDCs), the ability of DNA-containing immune complexes to activate IFN-α signaling is LAP-dependent [12]. During uptake of dying cells, the inefficient degradation of corpses in the context of LAP-deficiency leads

(Figure 1 Legend Continued) NADPH oxidase generates ROS, which is required for recruitment of the LC3 conjugation machinery to the phagosome. LC3 becomes lipidated and decorates the single-membrane structure referred as a LAPosome, which undergoes fusion with lysosomes to degrade phagocytosed cargo.

Table 1

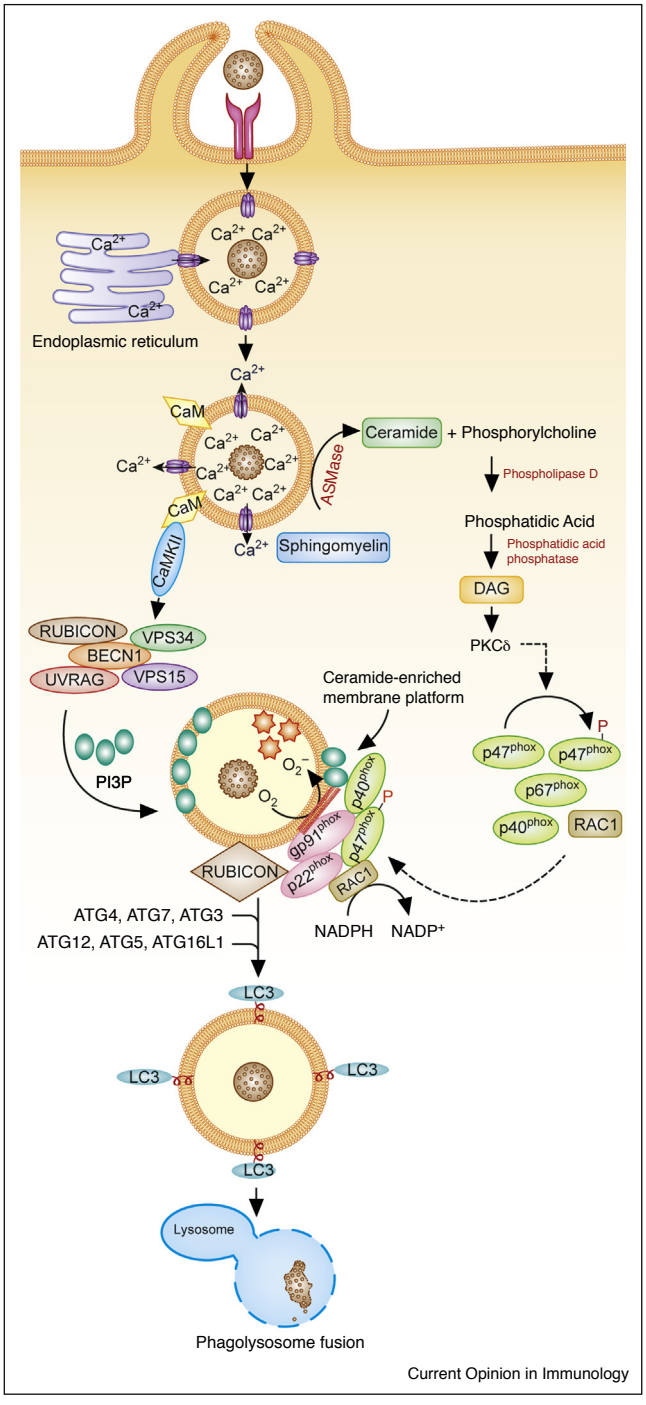
The role of LAP in microbial pathogenesis

Microbe	Antimicrobial role of LAP	Activating receptor	Microbial factors that impact LAP	LAP-specific evasion mechanisms	Notable findings	References
Bacteria						
Burkholderia pseudomallei	LAP restricts growth in macrophages			BopA promotes phagosome escape, thereby evading LAP		Gong *et al.* [40]
Legionella dumoffi	LAP restricts bacterial growth	TLR2	T4SS			Hubber *et al.* [25]
Listeria monocytogenes	LAP contributes to control of *Listeria* infection in peritoneal macrophages and mice; LAP has also been shown to create a permissive niche (SLAPs) in RAW264.7 macrophages	Mac-1 and evidence for a second pathway	*In vivo*, LAP is independent of LLO and *prfA*		Role of host ASMase and DAG demonstrated	Huang *et al.* [6••], Shahnazari *et al.* [7••], Lam *et al.* [26], Mitchell *et al.* [8], Gluschko *et al.* [16••]
Mycobacterium tuberculosis	LAP has little to no impact on wild type Mtb. In the *cpsA* mutant, LAP restricts bacterial growth in macrophages and in mice		In the *cpsA* mutant, there is a partial dependence on the ESX-1 secretion system	Secreted bacterial effector, CpsA, inhibits NADPH oxidase recruitment to phagosome		Köster *et al.* [47••], Köster *et al.* [54]
Mycobacterium marinium	*M. marinum* resides in an LC3-positive single membrane compartment in macrophages, which is non-degradative		Depends upon ESX-1 secretion system			Lerena and Colombo [37]
Salmonella typhimerium	*Salmonella* are subject to both LAP and xenophagy. LAP serves as a host protective mechanism of macrophages for restricting *Salmonella* during systemic infection					Masud et al. [57]
Shigella flexneri	In human colonic epithelial cells, *S. flexneri* is found in a LC3 single-membrane compartment		LAP correlates with activity of T3SS effectors	Effectors IcsA, IcsB and VirA allow bacilli to evade LC3-positive vacuoles		Campbell-Valois *et al.* [35], Baxt and Goldberg [36]
Yersinia pseudotuberculosis	LAP provides a non-acidified, permissive niche in epithelial cells				VAMP3 and VAMP7 consecutively colocalize with *Yersinia* containing vacuoles and regulate the ratio of single to double membrane compartments	Ligeon *et al.* [52]
Fungi						
Aspergillus fumigatis	Conidia resist LAP by virtue of melanin; upon swelling, melanin is lost and LAP is host protective	Dectin-1		Melanin	DAPK1 involved in linking LAP to reduced inflammatory responses	Akoumianaki *et al.* [43•], Kyrmizi *et al.* [28••], Oikonomou *et al.* [19]

Table 1 (*Continued*)

Microbe	Antimicrobial role of LAP	Activating receptor	Microbial factors that impact LAP	LAP-specific evasion mechanisms	Notable findings	References
Rhizopus oryzae	Fungal melanin inhibits LAP, promoting persistence	Dectin-1		Melanin		Andrianaki *et al.* [44]
Candida albicans	LAP is fungicidal in macrophages; LAP promotes antigen presentation in dendritic cells	Dectin-1				Ma *et al.* [11•], Tam *et al.* [15], Ma *et al.* [55], Additional studies reviewed in (Tam *et al.* [56]
Histoplasma capsulatum	LAPosome is non-acidified	Dectin-1 and evidence for an additional receptor			NLRX1 facilitates LAP; LAP does not depend upon RUBICON.	Huang *et al.* [51]
Saccharyomces cerevisiae, Kazachstania unispora	S. *cerevisiae* and *K. unispora trigger LAPosome* formation and induced TNF-α and IL-1β in bone marrow- derived dendritic cells	Dectin-2			LAP is required for inflammatory cytokine production from BMDCs in response to gut commensal yeast	Lamprinaki *et al.* [13]
Protozoa						
Leishmania major	Viable *L. major* promastigotes escape LAPosomes, whereas apoptotic phosphatidylserine-expressing promastigotes are degraded by LAP			GP63 cleaves VAMP8, which inhibits NADPH oxidase recruitment, thereby blocking LAP		Matte *et al.* [46••], Matheoud *et al.* [45]
Plasmodium	*P. vivax* and *P. berghei* reside within a single-membrane LC3-positive vacuole, targeted by LAP in an IFN-γ-dependent and IFN-γ independent manner, respectively. *P. vivax* infection gets cleared by LAP, whereas *P. berghei* evades LAP by unknown mechanism					Boonhok *et al.* [18], Wacker *et al.* [58], Prado *et al.* [59]
Toxoplasma gondii	*T. gondii* resides in a single membrane LC3-bound parasitophorous vacuole (PV)				LC3/GABARAPs facilitate targeting of IRGs and GBPs to PVs, leading to vacuolar disruption and subsequent death of *T. gondii*	Howard *et al.* [60], Zhao *et al.* [61]

Figure 2



Role of calcium signaling and lipid second messengers in LAP. Studies of LAP in the context of *Aspergillus*, *Salmonella*, and *Listeria* infection have revealed the importance of calcium signaling and lipid second messengers. Melanin in the cell wall of *A. fumigatus* dormant conidia sequesters intra-phagosomal calcium. Upon germination, melanin is shed from the conidial cell surface, leading to calcium flux from the lumen to the cytosol, which activates CaM/CAMKII signaling that regulates recruitment of the downstream PI3K complex and NADPH oxidase assembly. *Listeria* engagement of the Mac-1 receptor activates acid sphingomyelinase (ASMase), which converts sphingomyelin into ceramide and phosphorylcholine. Ceramide-enriched membrane platforms promote NADPH oxidase assembly and activation, resulting in ROS generation. Phosphorylcholine can be converted to DAG by the sequential action of Phospholipase D and Phosphatidic acid phosphatase. DAG activates PKCδ, which promotes activation of NADPH oxidase via phosphorylation of p47 ^{phox} subunit.

to increased levels of the pro-inflammatory cytokines IL-1β and IL-6. In mice, defects in LAP in the myeloid compartment lead to systemic lupus erythematosus-like autoimmune disease [32•]. LAP is also involved in both tumor and mucosal tolerance. Outer membrane vesicles released from the gut microbe *Bacteriodes fragilis* trigger LAP in DCs, which helps to induce regulatory T cells in the intestine to protect from inflammatory bowel disease [33]. Tumor-associated macrophages that are deficient in LAP exhibit enhanced type I IFN responses after uptake of dying cells, which promotes the activity of tumor-infiltrating T cells [34]. Taken together, LAP contributes to immune regulation and can be protective against autoimmunity in mice and detrimental in the tumor microenvironment.

Specialized secretion systems and LAP

Although LAP occurs if relevant receptors are activated during the uptake of non-viable cargo, including apoptotic corpses, zymosan, and opsonized beads, in a number of cases, LAP depends upon bacterial virulence systems. For example, the *Legionella dumoffii* vacuole has all the hallmarks of LAP: its formation requires TLR2, RUBICON, DAG signaling, and the NADPH oxidase, while ULK1 is dispensable. Yet, LAPosome formation also depends on the bacterial Type IV Secretion System (T4SS) [25]. Similarly, *Shigella flexneri*'s presence in a single membrane LC3-positive compartment early after infection of human colonic epithelial cells correlates with Type III secretion apparatus secretion (T3SA) [35,36], and for *Mycobacterium marinum*, LC3-recruitment depends upon bacterial viability and a Type VII secretion system that damages the phagosome [37]. Why there is a requirement for bacterial secretion systems in these cases is not well understood. One possibility is that in some cases LC3-recruitment reflects a non-canonical autophagy pathway that is different than LAP. For example, chloroquine and osmotic imbalance can also induce LAP-like LC3 lipidation on phagosomes in a PI3K-independent manner [38]. The VacA toxin of *Helicobacter pylori*, which forms a selective anion channel in endosomes, activates this LAP-like pathway [38]. Alternatively, in some cases a bacterial effector or phagosomal damage may enhance LAP. For example, although dead *Listeria* can activate LAP in peritoneal macrophages [16••], *Listeria*'s phospholipases (PI-PLC and PC-PLC) promote NADPH oxidase activity through DAG production in RAW264.7 macrophages [26,39]. Thus, while there is a well-demonstrated relationship between phagosomal damage and xenophagy, phagosomal damage is not an absolute requirement for LAP and the relationship

between LAP, phagosome perturbations, and bacterial secretion systems remains incompletely characterized.

LAP evasion

How pathogens evade LAP is an active area of research. One effective strategy to avoid LAP is to escape the phagosome, as shown for *Burkholderia pseudomallei*, the cause of melioidosis [40]. In general, microbes that take this approach impair their subsequent clearance by xenophagy. The ability of pathogens to avoid the NADPH oxidase has been an area of investigation for a long time [41], and doing so is predicted to undermine LAP. Indeed, this is how *Aspergillus fumigatus*, *Leishmania major*, and *Mycobacterium tuberculosis*, avoid LAP, as discussed in more detail below. Microbes also target the ATG machinery, which could undermine both LAP and xenophagy [4]. For example, the T4SS effector RavZ from *Legionella pneumophila* delipidates LC3 [42•]. Lastly, microbes interfere with the antimicrobial capacity of LAPosomes, for example, by impairing acidification of the compartment, as discussed below. In these cases, LAP provides a replicative niche.

Aspergillus is a saprophytic fungus that makes spore-forms called conidia. Melanin in the cell wall of the conidia sequesters calcium, which prevents the activation of calmodulin (CaM), a necessary signal for RUBICON recruitment, PI3P generation, NADPH oxidase activation, and LAPosome formation [43•]. However, when the conidia swell during germination, the melanin is shed, and the phagosome releases luminal Ca^{2+}. The periphagosmal Ca^{2+} flux then activates CaM and calmodulin-dependent protein kinase II (CaMKII) and triggers LAPosome formation. Thus, although conidia can evade LAP initially, once they germinate, LAP is host protective, consistent with *Aspergillus* being a particular problem in individuals with defects in NADPH oxidase activity (the cause of chronic granulomatous disease). Other fungi that contain cell wall melanin, such as *Rhizopus oryzae*, also interfere with LAP [44].

L. major is a vector born parasite that causes cutaneous infection. *L. major* expresses a glycosylphosphatidylinositol (GPI)-anchored metalloprotease, GP63, which cleaves host factors that regulate membrane fusion events. GP63 cleaves vesicle associated membrane protein 8 (VAMP8), which is involved in delivery of $gp91^{phox}$, a membrane component of NADPH oxidase, to phagosomes [45]. As anticipated, by preventing NADPH oxidase recruitment, GP63 also blocks LAP [46••].

M. tuberculosis (*Mtb*) is one of the world's most successful pathogens. Although *Mtb* activates a variety of pathogen recognition receptors, it very effectively avoids LAP. Recently, we identified CpsA as an *Mtb* virulence factor that blocks NADPH oxidase recruitment and LAPosome formation in macrophages [47••]. The *cpsA* mutant is attenuated in mice, a phenotype that is partially reversed in mice lacking the NADPH oxidase or deficient in LAP (*Atg7* $^{Myel\ KO}$ or *Atg5* $^{Myel\ KO}$) but not xenophagy (*Atg14* $^{Myel\ KO}$). Thus, LAP has the potential to be an antimycobacterial pathway, but CpsA protects *Mtb* from LAP by impairing the NADPH oxidase. *Mtb* likely impairs LAP by a number of additional mechanisms, such as impairing gene expression of MORN2, which is important in LAP [48], as well as other ATG proteins [49]. In addition, *Mtb* inhibits RAC1, calcium–CaM/CAMKII signaling, and PI3P production on the phagosome, all of which are predicted to impair LAP [50], although this remains to be demonstrated.

In some cases, LAPosomes are permissive for microbial survival. In *Histoplasma capsulatum*, the LAPosome fails to acidify in response to living fungi, although it does acidify when dead *H. capsulatum* are ingested, pointing to LAPosome manipulation by the pathogen. Interestingly, although *H. capsulatum*-induced LAP depends upon ROS and SYK, it is RUBICON independent [51]. Furthermore, NLRX1 was shown to enhance LAP of *H. capsulatum* [51]. NLRX1 is a mitochondrial Nod-like receptor that complexes with mitochondrial Tu translational elongation factor (TUFM), which interacts with ATG5–ATG12 and ATG16L1 during canonical autophagy. Thus, this recent study suggests that the NLRX1–TUFM pathway can also collaborate in LAP. In epithelial cells, *Yersinia pseudotuberculosis* replicates within a non-acidic, LC3-positive single-membrane vacuole. Vesicle-associated membrane proteins, VAMP3 and VAMP7 are sequentially recruited to these single membrane vacuoles (YCVs) [52]. Knockdown of VAMP3 in epithelial cells reduced the number of single-membrane LC3-bound vacuoles and increased double membrane LC3-positive autophagosomes. Thus, the fate of *Y. pseudotuberculosis* to either canonical autophagy or LAP depends on VAMP3 expression [52]. Finally, although recent *in vivo* data suggest that LAP is critical for antilisterial immunity *in vivo* [16••], there may be certain contexts where single-membrane, LC3-positive compartments, termed spacious *Listeria*-containing phagosomes (SLAPs), can serve as a replicative niche [53].

Conclusions and future directions

The importance of LAP in immune defense is underscored by the diverse mechanisms pathogens have evolved to subvert LAP (Table 1). In addition to the strategies described here, there are undoubtedly additional mechanisms that will be become apparent as LAP is further investigated in the context of these and other pathogens. Since LAP is one of several emerging non-canonical functions ascribed to autophagy proteins, it seems likely, even within the context of phagocytosis that there will be variations on the pathway described here, based upon differences in host cell type and the nature of the microbial challenge. Even in the

best-described examples of LAP, there are many molecular details that remain to be elucidated. How ROS regulates the ATG-conjugation systems and the other signals that control LC3 recruitment to the phagosome remain major questions. In addition, how the deposition of LC3 modulates phagosome functions is not well understood. Moreover, while there is an emerging appreciation of the role of LAP in inflammation and autoimmunity, the inflammatory consequences have not been extensively evaluated in the context of microbial challenge. To conclude, while there is a growing appreciation for the importance of LAP in microbial defense, there are many unanswered questions. Understanding the pathway in more detail and the molecular mechanisms employed by pathogens to evade LAP is important for a better understanding of innate immunity, and may lead to novel therapeutics to promote microbial clearance and modulate the inflammatory response.

Conflict of interest statement

Nothing declared.

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