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Porphyromonas gingivalis and the autophagic pathway: an innate immune interaction?

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TABLE OF CONTENTS

1. ABSTRACT

Autophagy is a mechanism used to maintain several intracellular functions essential to eukaryotic cells. Recently, a role for autophagy in innate and adaptive immunity has also been established including the elimination of invading bacteria. Although some intracellular pathogens are killed by autophagy, several others subvert autophagy to the pathogen's benefit for survival and replication. *Porphyromonas gingivalis*, an important periodontal pathogen, has been shown to stimulate autophagy in endothelial cells and to use the autophagic pathway to its advantage. In human coronary artery endothelial cells (HCAEC), *P. gingivalis* localizes within autophagosomes. After intracellular uptake, *P. gingivalis* transits from early autophagosomes to late autophagosomes and prevents the formation of autolysosomes, either by delaying the autophagosome-lysosome fusion or by redirecting the normal autophagic trafficking. In addition, *P. gingivalis* was also found to stimulate autophagy in human aortic endothelial cells (HAEC) since co-localization of LC3-II, an autophagosome marker, with *P. gingivalis* was observed. The trafficking of *P. gingivalis* into the autophagic pathway appears to be dependent upon the host cell type. Survival of *P. gingivalis* through the subversion of the host autophagic pathway can be considered a bacterial strategy to evade the innate immune system and persist in the host.

2. INTRODUCTION

Pathogenic bacteria have developed a collection of surface appendices and secreted proteins/toxins that allow them to colonize many different niches in the host. In order to cause disease, some of these pathogens invade non-phagocytic host cells such as epithelial and endothelial cells. To limit this type of bacterial infection, host cells have developed innate immune mechanisms that serve as critical barriers to the invading bacteria. These innate antimicrobial mechanisms are activated to eradicate the intracellular bacteria while the adaptive immune response is progressing as a more specific immune response against the bacteria. While a number of innate immune mechanisms have been described, it has been relatively recent that autophagy has been recognized as an innate immune mechanism against invading intracellular pathogens. Autophagy is a conserved process by which eukaryotic cells recycle cytoplasmic constituents and organelles, thus maintaining cellular homeostasis. Autophagy can also be stimulated by the entry of intracellular bacteria (1).

There are a considerable number of publications describing innate immune responses to *P. gingivalis* invasion of macrophages as well as endothelial and epithelial cells. Although, *P. gingivalis* has been shown to invade several different cell types, both *in vivo* and *in vitro*

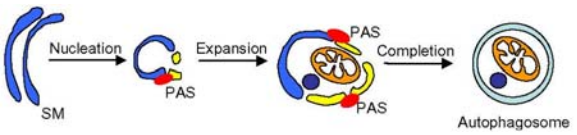

Figure 1. Formation of the autophagosome. The induction of autophagosome formation is influenced by Tor, which regulates the activity of a protein complex containing Atg1 and Atg13. Upon induction, membrane nucleation proceeds whereby the sequestering membranes (SM) begin to take shape and surround those organelles destined for degradation. This event requires a phosphatidylinositol 3-kinase complex and proceeds at the preautophagosome structure (PAS), which also acts as a site of membrane recruitment for the expansion of the sequestering membranes. The expansion (yellow) of the sequestering membranes to engulf large organelles or intracellular pathogens and eventual completion of the autophagosome requires two protein conjugation pathways. The first is the conjugation of Atg12 to Atg5 requiring Atg7 and Atg10. The second is the conjugation of Atg8 to the lipid, phosphatidylethanolamine, requiring Atg4, Atg7, and Atg3.

(2-8); to date, there are only two reports describing the interactions of *P. gingivalis* and the autophagic pathway (9, 10). Since both of these studies have been done using human cardiovascular endothelial cells and interactions between *P. gingivalis* and epithelial cells do not appear to involve autophagy, there may be a relationship to cardiovascular disease.

During the past 10-15 years, a substantial number of epidemiological studies have suggested a link between oral health and cardiovascular diseases. Subsequently, several studies have been published demonstrating that *P. gingivalis* can be detected in atheromas and can accelerate atherosclerosis in animal models (11-15). Additionally, Kozarov *et al.* (2005) showed that viable *P. gingivalis* could be recovered from atherosclerotic lesions (16). *In vitro* studies have shown that *P. gingivalis* induces the expression of cytokines and Toll-like receptors (TLR), causes angiogenesis and procoagulant effects in cardiovascular endothelial cells and increases mononuclear cell adhesion to these cells (6, 17-23). In addition, studies have shown that in *P. gingivalis*-infected animal models used for the study of atherosclerosis, there is an increased expression of innate immune receptors in aortic tissues of these animals (24). Therefore, there is an innate immune response to *P. gingivalis* challenge in cardiovascular endothelial cells *in vitro* and likely *in vivo*.

To date, however, there are no reports discussing autophagy as an innate immune effector against *P. gingivalis*. Thus, the purpose of this review is to summarize the role of autophagy in innate immunity, the interactions between autophagy and other intracellular pathogens, and to discuss the interactions of *P. gingivalis* with the autophagic pathway including the possible role of this pathway as an innate immune response against this bacterium.

3. AUTOPHAGY

3.1. Recycling of cytoplasmic content and organelles

The primary function of autophagy is the degradation of damaged or surplus organelles, such as leaky mitochondria, excess peroxisomes and endoplasmic reticulum, especially during starvation conditions in order to maintain the intracellular substrate pool of amino acids for cell survival (25). It has been shown that the absence of growth factors, which are signals to the cell for nutrient uptake, can also induce autophagy (26). In addition, autophagy has also been shown to be involved in tissue differentiation and remodeling as well as in cell development (27). Autophagy contributes to the routine turnover of cytoplasmic components and is also involved in a number of human diseases, such as cancer, muscular disorders, neuropathies and infectious diseases (28).

Cellular homeostasis by autophagy is achieved primarily using two distinct proteolytic structures; proteasomes and lysosomes (29, 30). Proteasomes degrade short lived, aged- and misfolded proteins (31). Lysosomes are vacuoles in which the degradation of substrates is accomplished by either endocytosis or by autophagy (32, 33).

Three forms of autophagy have been described: chaperone-mediated autophagy, microautophagy, and macroautophagy. In chaperone-mediated autophagy, proteins, assisted by heat-shock protein 70 cognate (Hsc70) family members, are to be transported into lysosomes via the protein transporter LAMP-2 (32-38). Microautophagy is characterized by the formation of invaginations in the lysosomal membrane whereby the sequestered cytoplasm is degraded (39). Macroautophagy (here referred to as autophagy) is mediated by the formation of an autophagosome (Figure 1), a double- or multiple-membrane structure, in which sequestered cytosol or intracellular organelles are enveloped and delivered to lysosomes for subsequent degradation (40). Autophagy is a process, conserved from yeast to mammalian cells, strictly regulated by multiple Atg (**Au**toph**ag**y-related genes) genes. It has been extensively studied, mostly in yeasts, in which the Atg genes were discovered (many have counterparts in other organisms) (41). This process is induced and regulated by a mechanism that involves the protein kinase Tor, Atg1 and Atg13 (42, 43). Proteins Atg1 and Atg13 are part of a not yet completely described complex. Following the induction, sequestering membranes nucleate and begin to take shape. Next, membrane recruitment expands these membranes to allow engulfment of large organelles and intracellular pathogens. The nucleation and expansion events proceed from the preautophagosome structure (PAS). Membrane recruitment to the forming autophagosome is influenced by two ubiquitin-like conjugation systems requiring Atg7. The conjugation of Atg12 with Atg5 and its interaction with Atg16 appears to be the trigger mechanism for this event. At the nascent structure, a second ubiquitin-like molecule, Atg8/LC3, linked to phosphatidylethanolamine, is acquired, which then recruits membranes and increases the size of the autophagosomes (Figure 1). Once the autophagosome is completed, the Atg5, Atg12 and Atg16 complex is

dissociated from it, but Atg8/LC3 remains in the autophagosome until its fusion with the lysosome. It is still unknown which factor senses completion of the double-membrane vesicle and triggers this disassembly mechanism (reviewed in (40, 41)).

3.2. Role in innate immunity

More recently, it has been shown that autophagy also has a role(s) in innate immunity since there is an accumulating amount of evidence indicating that autophagy also targets intracellular pathogens for degradation as part of the innate immune response (1, 44, 45). For example, certain intracellular bacteria have been shown to be degraded by autophagosomes (46, 47). Interestingly, cytokine IFN-γ has been shown to increase the elimination of *Mycobacterium tuberculosis* in infected macrophages by modulating autophagy (48). In addition, degradation of intracellular pathogens by autophagy enables their processing for major histocompatibility complex class II presentation (49-51), therefore, there may be a connection between autophagy, innate and adaptive immunity.

Bacterial invasion of eukaryotic cells may occur by cellular phagocytosis or by assisting their own uptake. During these processes, innate immune sensors including the TLR and Nod-like receptors may be triggered by bacterial components, usually leading to expression and activation of proinflammatory cytokines such as IL-1ß. These receptor networks play a critical role in innate resistance to intracellular bacteria by allowing infected cells to communicate with other members of the innate and adaptive immunity as well as by having specialized functions within infected cells to mediate resistance to intracellular bacteria (52, 53). Nevertheless, a number of bacterial species are able to enter and survive within host cells, even within phagosomes and endosomes (54-56).

Thus, autophagy may kill intracellular bacteria and may also enhance immune recognition of infected cells via the generation of antigenic bacterial peptides. Notably, some bacteria have developed mechanisms to escape lysosomal degradation by modulating the autophagy pathway, indicating that this process may play a role in host defense as an important mechanism of the innate immune response.

4. INTRACELLULAR PATHOGENS AND AUTOPHAGY

4.1. Elimination of pathogens by autophagy

Streptococcus pyogenes, a Group A *Streptococcus* (GAS) and an important human pathogen, invades non-phagocytic cells via endocytosis and escapes from the early endosome by secreting streptolysin O (57). Then, *S. pyogenes* is enveloped in unusually large autophagosomes which later fuse with lysosomes, ultimately resulting in the degradation of the bacterium (47). These autophagosomes appear to be morphologically distinct from those of the non-selective canonical pathway as they selectively target the GAS. The GAS-induced autophagic vacuoles also persist longer in the host cell when compared to the classical autophagosomes (47, 58). The obligate intracellular pathogen, *Rickettsia conorii*, is also likely eliminated by autophagy. An ultrastructural study of murine endothelial cells infected by *R. conorii* demonstrated that double-membrane autophagosome-like structures were surrounding the bacteria. In addition, phagolysosomes were observed destroying the *Rickettsia* (59). Therefore, autophagy can efficiently kill a number of intracellular pathogens upon their entry into the host cell. In addition, some intracellular pathogens appear to survive autophagy under certain conditions and are susceptible to autophagic killing under other conditions. It is likely that additional bacteria that are killed by autophagic mechanisms will be identified in the future as more studies that focus on intracellular pathogens and autophagy are completed.

4.2. Survival of pathogens via autophagy

Intracellular pathogens have evolved multiple pathways and mechanisms to traffick and survive within eukaryotic cells (55, 60-62). To avoid lysosomal killing, some bacterial species escape into the cytoplasm (63, 64) (Figure 2). A second group of intracellular pathogens are able to remain inside the phagosome, inhibiting its maturation into lysosomes, indicating that pathogens can control the biogenesis of their compartments (62). A third strategy is to traffick from early phagosomes into the autophagic pathway and subvert this cellular defense pathway to the pathogen's benefit for survival and replication (Figure 2).

One such organism is *Staphylococcus aureus*. Upon the induction of autophagy, it replicates and escapes the autophagosomes to become free in the host cytoplasm. Host cell death is then induced via caspase-independent pathways (65). The ability to induce autophagy is a requirement for survival of *S. aureus* since an accessory gene regulator (*agr*) system-deficient *S. aureus*, that is unable to induce autophagy, is degraded following maturation of the phagosome and lysosomal fusion.

Another intracellular pathogen, *L. monocytogenes*, enters macrophages via endocytosis and has developed a strategy to escape from the endosomes by lysing the endosome vesicle using its listeriolysin O protein and subsequently replicating in the cytosol. Inhibition of *de novo* protein synthesis of cytoplasmic *L. monocytogenes* leads to their sequestration into the autophagic pathway, suggesting that *L. monocytogenes* actively avoids the autophagy vacuoles (66, 67). More recently, Py *et al.* demonstrated that following *L. monocytogenes* escape from the endosomes, the bacteria are found in autophagic vacuoles (68). The authors suggested that bacterial phospholipases are necessary for this "second" evasion of autophagy and, then, bacteria can ultimately be found free in the cytosol (68). Similarly, *Shigella flexneri* lyses its entry phagosome via IpaB and escapes to the cytosol where it may replicate. Once in the cytosol, *S. flexneri* is sequestered by autophagic vesicles. However, *Shigella* prevents its degradation via autophagy by secreting another gene product, IcsB. The *Shigella* IcsB protein does not directly inhibit autophagy. Instead, IcsB competitively inhibits the complex formation between VirG, a protein

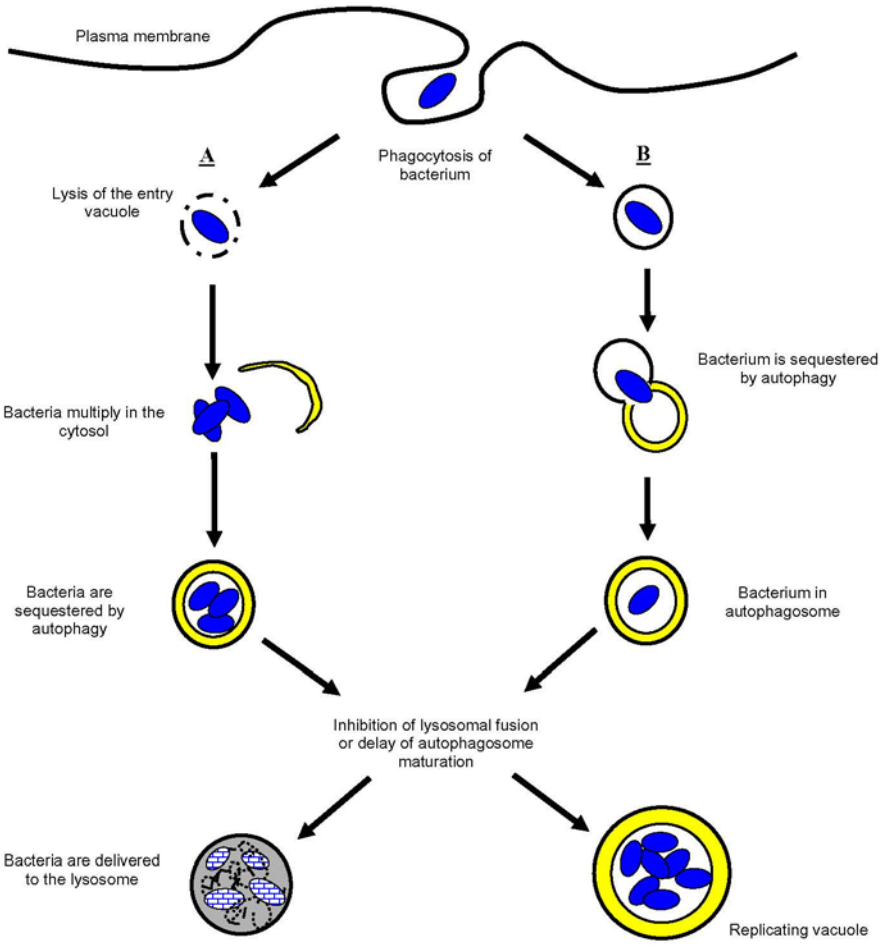

Figure 2. Subversion of the autophagy pathway during bacterial infection. (A) Some pathogens can lyse the entry vacuole and multiply in the cytosol. Eventually, bacteria still can be targeted by autophagy. (B) For some pathogens, the bacteria-containing vacuole is sequestered by autophagy. Later in the autophagic pathway, bacteria can avoid the maturation of the autophagosome or delay the autophagosome-lysosome fusion. Eventually, the bacteria can either replicate inside these specialized vacuoles or be degraded in the lysosome.

required for *S. flexneri* intracellular actin-based motility, and Atg5, a protein required for the formation of autophagosomes, consequently allowing *S. flexneri* to escape autophagy (69).

In addition to *Shigella* and *Listeria*, a number of other pathogenic bacterial species are able to avoid degradation by autophagy and redirect normal vesicular trafficking. For example, upon infection of macrophages, *M. tuberculosis* trafficks into autophagosomes. However, *M. tuberculosis* prevents fusion of the autophagosomes with lysosomes because of its mycobacterial lipids. The latter mimic cellular phosphatidylinositols, therefore interfering with phosphatidylinositol 3-kinase mechanisms that prepare phagosomes for fusion with other organelles (70). Another pathogen, *Salmonella enterica* serovar *Typhimurium*, when invading dendritic cells, resides within membrane-bound vesicles also referred to as *Salmonella*-containing vacuoles (SCV). However, the fusion of such compartments with lysosomes is prevented by the secretion of effector proteins encoded within the *Salmonella* pathogenicity island 2, an important element of *Salmonella* pathogenesis (71). In addition, the delivery of the nicotinamide adenine dinucleotide phosphate oxidase and inducible nitric oxide synthase to the SCV is blocked (72). However after invading HeLa cells, a subpopulation of *S. enterica* escape from the SCV into the cytosol and is targeted by the autophagy pathway which restricts their intracellular growth (73).

Legionella pneumophila requires the secretion of effector molecules to become established inside the autophagosome-like vesicles in macrophages, therefore evading transport to lysosomes. These effectors are secreted into the host cytosol by a type IV secretion system encoded by the *icm*/*dot* genes (74, 75). These bacterial proteins may facilitate the formation of the sequestering vesicles or may delay their maturation to allow bacteria to remain within these normally transient compartments, thus supporting their multiplication (76). Also, in HeLa cells, *B.*

Table 1. Examples of microorganisms that interact with autophagy in the host cell

Mechanism of escape	Bacteria	Autophagic killing	Reference
Avoid/delay maturation of autophagosomes	*Brucella abortus*	No	99
	Coxiella burnetii	No	100, 101
	Legionella pneumophila	No	102
	Mycobacterium spp.	No	103
Lyses phagosomes/autophagosomes	*Listeria monocytogenes*	No	68, 104
	Shigella flexneri	No	69
	Staphylococcus aureus	Yes	65
	Rickettsiae spp.	Yes/No	59, 105
Unknown	*Porphyromonas gingivalis*	No	9
None	*Streptococcus pyogenes*	Yes	47
Avoid phagosome-lysosome fusion	*Salmonella enterica* serovar *Typhimurium*	No	106
Avoid maturation of the endocytic compartment/suppress acidification of the phagolysosomes	*Rhodococcus equi*	No	107, 108

abortus was shown to be internalized into phagosomes that fuse with autophagosomes where it replicates (77). These and other examples of bacteria that interact with the autophagic pathway are listed in Table 1.

5. *PORPHYROMONAS GINGIVALIS* AND AUTOPHAGY

5.1. *P. gingivalis* and invasion of host cells

P. gingivalis possesses multiple virulence factors (78, 79). Among these is the ability to invade multiple types of eukaryotic cells including KB cells (a human epidermoid carcinoma) (2, 80), primary human coronary artery endothelial cells (HCAEC) and coronary artery smooth muscle cells (3), primary gingival epithelial cells (GEC) (4, 81), bovine aortic endothelial cells (BAEC), fetal bovine heart endothelial cells (FBHEC), human umbilical vein endothelial cells (HUVEC) (5), human aortic endothelia cells (HAEC) (6) and dendritic cells (7). It is likely that cell invasion is significant with regard to *P. gingivalis* pathogenicity since it was found to be internalized *in vivo* (8). The discussion for this review will focus on *P. gingivalis* invasion of human cardiovascular endothelial cells.

The initial step required for bacterial invasion is the adhesion of the bacterium to the host cell. It has been shown that the major fimbria of *P. gingivalis*, FimA, is a key adhesin involved in adherence to different host cells, including endothelial cells (78). In addition, we have demonstrated that hemagglutinin B is important in the adherence of *P. gingivalis* to HCAEC (82). However, our knowledge of the initial events of *P. gingivalis* adhesion/internalization is limited, especially with regards to HCAEC. Bacterial pathogens that traffick through the autophagy pathway, such as *Mycobacterium* spp. (83, 84), *Brucella* spp. (85) and *Salmonella* spp. (86) interact during entry with lipid rafts. These specialized cholesterol-rich regions of the cell membrane have many functions such as polarized secretion, membrane transport, signal transduction and transcytosis across epithelial monolayers (87). Amer *et al.*, reported that *L. pneumophila* interaction with lipid rafts is necessary for the localization of the bacterium with autophagic vesicles (88). There is also evidence that *P. gingivalis* uses lipid rafts as a gateway to enter host cell since *P. gingivalis* adheres to lipid rafts in HCAEC (89), as well as KB cells (90), HeLa cells (91), and macrophages (92). In KB and HCAEC, *P. gingivalis* was shown to colocalize with caveolin-1, a marker of caveolae. Also, methyl-β-cyclodextrin, a cholesterol-binding agent and a disruptor of caveolae, reduced invasion of *P. gingivalis* (90, 93). However, it is not yet known if entry of *P. gingivalis* through lipid rafts is necessary for its interactions with the autophagic pathway.

Once inside the cells, *P. gingivalis* shows a predilection for specific regions in different cell types. In contrast to KB and human GEC in which *P. gingivalis* is found free in the cytoplasm, and the peri-nuclear area (2, 94-97), internalized *P. gingivalis* are found within multimembrane vacuoles in FBHEC and BAEC (5). Furthermore, *P. gingivalis* localizes within autophagosomes in HCAEC (9). Thus, trafficking of *P. gingivalis* into the autophagic pathway appears to be dependent upon the host cell type and occurs in at least some endothelial cells.

5.2. Autophagy in human cardiovascular endothelial cells

In previously reported studies, we have shown that *P. gingivalis* strain 381 trafficks from early phagosomes to autophagosomes in HCAEC (3, 9). We demonstrated that at 25-35 min of invasion, *P. gingivalis* localizes within vesicles containing Rab5, a protein marker for phagosomes. Our ultrastructural data shows that profiles of rough endoplasmic reticulum (RER) were routinely observed in close association with *P. gingivalis* containing vacuoles, suggesting that these vacuoles have been derived from the RER. At 30 to 90 min, *P. gingivalis* was found in BiP-positive compartments, an RER luminal protein and marker for the early steps of autophagy. Our study also showed that *P. gingivalis* co-localized with vesicles containing Atg7, another early stage marker of autophagosomes. As the invasion progresses, we demonstrated that most of the internalized *P. gingivalis* localized in vesicles containing LAMP1, a late autophagosome membrane protein also found in autolysosomes, whereas few of the bacteria localized with cathepsin L, an phagolysosome/autolysosome proteinase. This suggests that *P. gingivalis* predominantly trafficks to the late autophagosomes (LAMP1) and, at least initially, avoids degradation by the autolysosome (cathepsin L). Overall, our data demonstrate that, after intracellular uptake, *P. gingivalis* is engulfed in phagosomes, transits from early autophagosomes to late autophagosomes and prevents the formation of autolysosomes, either by delaying

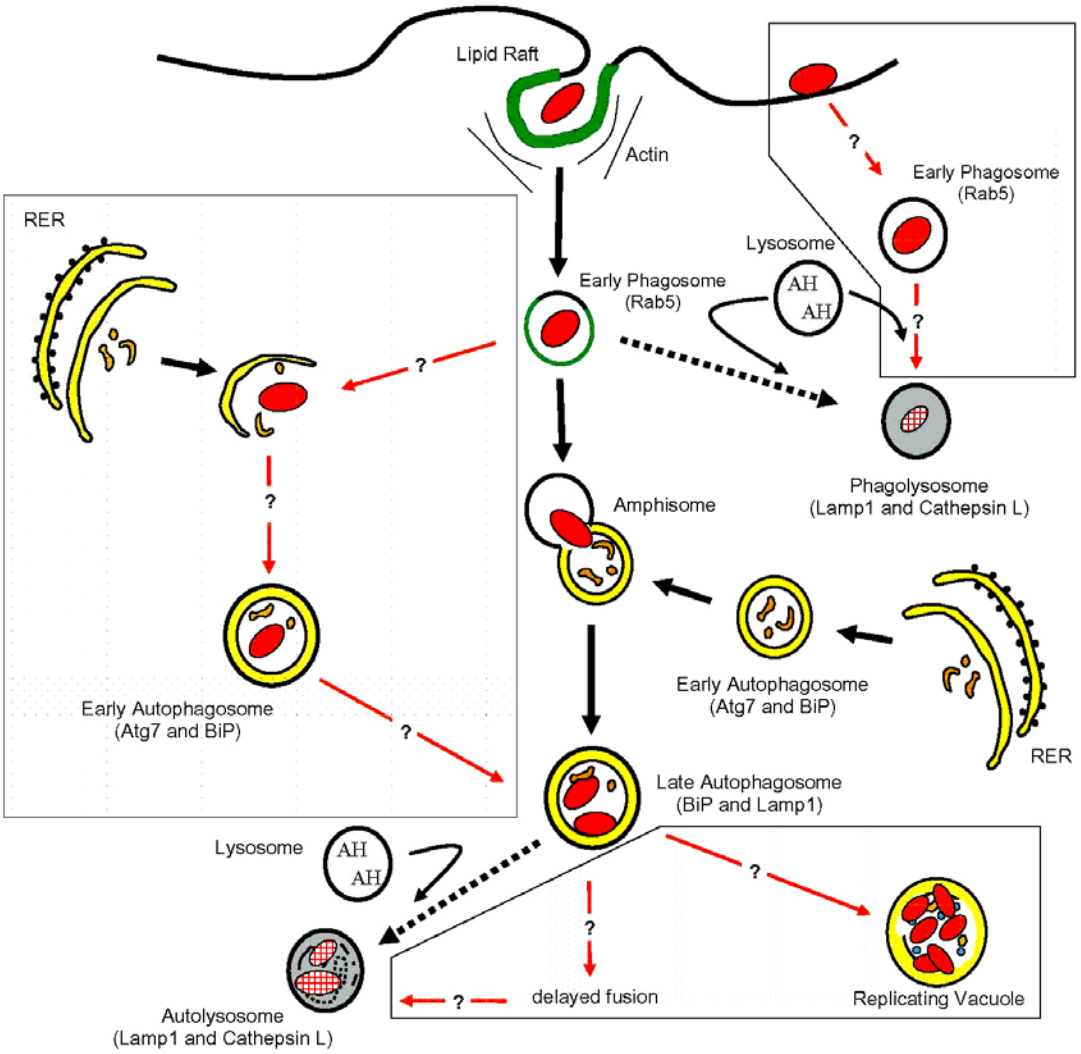

Figure 3. Model of *P. gingivalis* invasion of HCAEC. The solid black arrows represent the predominant trafficking pathway of the internalized *P. gingivalis* in HCAEC. The dotted black arrows represent possible degradative fates of internalized *P. gingivalis* in HCAEC. The red arrows and the shaded boxes represent trafficking pathways that are possible but not established for *P. gingivalis*.

the autophagosome-lysosome fusion or by redirecting the normal autophagic trafficking (Figure 3). However, the molecular mechanisms by which *P. gingivalis* directs its intracellular trafficking has not yet been described. Current studies in our laboratory are being conducted to address such phenomena.

A recent article by Yamatake *et al.* (10) reported that *P. gingivalis* also stimulates autophagy in human aortic endothelial cells (HAEC). Colocalization of LC3-II, an autophagosome marker, with *P. gingivalis* was observed at 30 min, 2 h, and 4 hours of infection. These data were confirmed by immunogold electron microscopy. However, the data also indicated that at 30 min to 4.0 h of invasion, more than 90% of the internalized bacteria localized in vesicles containing cathepsin B, a lysosomal marker, although there was also colocalization with LC3-II, depending on the strain tested. Thus, these results would seem to differ from our previously reported data. However, there are multiple explanations for these differences. First, Yamatake *et al.* (10) used a multiplicity of infection (MOI) ten to 100 times higher than the MOI of 1:100 used in our studies. We suggest that the high internalization of *P. gingivalis* inside the cells would saturate the autophagic pathway, shunting *P. gingivalis* to the phagocytic pathway. Therefore, only those *P. gingivalis* that escape into the autophagic pathway would be able to survive in the host cell. Interestingly, Gibson *et al.* reported that varying the MOI of *P. gingivalis* invasion of HAEC altered the expression of cytokines IL-8 and MCP-1 (98). In fact, after 24 h of invasion, lower amounts of IL-8 and MCP-1 could be detected in cells infected with an MOI of 1:500 than in cells infected with an MOI of 1:100. Other possibilities included differences in strains and host cells. Therefore, differences in experimental designs, including variances in the MOI as well as strains used in these studies likely

explain the inconsistencies in data observed between the two groups (3, 9, 10).

6. CONCLUSION

Autophagy is an important innate immune mechanism which can be used to ensure the survival of infected host cells but that can also be subverted by certain bacteria. *P. gingivalis* has been shown to stimulate autophagy in endothelial cells and to use the autophagic pathway to its advantage. In HCAEC, *P. gingivalis* localizes within autophagosomes. After intracellular uptake, *P. gingivalis* is located in early phagosomes, transits from early autophagosomes to late autophagosomes and prevents the formation of autolysosomes, either by delaying the autophagosome-lysosome fusion or by redirecting the normal autophagic trafficking. In addition, *P. gingivalis* was also found to stimulate autophagy in HAEC since colocalization of LC3-II, an autophagosome marker, with *P. gingivalis* was observed. The trafficking of *P. gingivalis* into the autophagic pathway appears to be dependent upon the host cell type since such trafficking does not occur in epithelial cells. This trafficking may also be strain dependent. Survival of *P. gingivalis* through the subversion of the host autophagic pathway can be considered a bacterial strategy to evade the innate immune system and persist in the host. Several questions arise from work done with *P. gingivalis* as well as with other bacteria. For example, what are the bacterial proteins or signals used to stimulate/inhibit autophagy? It is likely that these factors interact directly or indirectly with innate immune effectors. Studies performed with defined mutants will be needed to answer this question. A gingipain deficient triple mutant of *P. gingivalis* was used to demonstrate that gingipains promote resistance to phagolysosomal destruction within infected hosts. However, the exact mechanism by which this occurs remains to be elucidated. Finally, the level of autophagy in response to bacterial invasion or stimulation might ultimately determine the survival fate of both the bacterium and the host cell.

7. ACKNOWLEDGMENTS

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Abbreviations: Atg: **Au**toph**ag**y-related genes, agr: accessory gene regulator system, BAEC: bovine aortic endothelial cells, CVD: cardiovascular diseases, FBHEC: fetal bovine heart endothelial cells, GAS: Group A *Streptococcus*, GEC: gingival epithelial cells, HAEC: human aortic endothelia cells, HCAEC: human coronary endothelial cells, Hsc70: heat-shock protein 70 cognate, HUVEC: human umbilical vein endothelial cells**,** IFN: interferon, IL: interleukin, LAMP: lysosome-associated-membrane protein, LC3: microtubule associated protein 1 light chain 3, LC3-II: microtubule associated protein 1 light chain 3 linked to phosphatidylethanolamine, MCP-1: monocyte chemoattractant protein-1, MOI: multiplicity of infection, PAS: preautophagosome structure, RER: rough endoplasmic reticulum, SCV: *Salmonella*-containing vacuoles, TLR: toll-like receptors.

Key Words: Autophagy, *Porphyromonas gingivalis*, Intracellular Pathogens, Innate Immunity, Endothelial Cells, Pathogenicity, Periodontal Diseases, Review

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