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Listeria monocytogenes: cell biology of invasion and intracellular growth

JAVIER PIZARRO-CERDÁ[1,2,3] and PASCALE COSSART[1,2,3]

[1]Unité Interactions Bactéries-Cellules, Institut Pasteur, Paris F-75015, FRANCE; [2]INSERM U604, Paris F-75015, FRANCE; [3]INRA USC2020, Paris F-75015, FRANCE

ABSTRACT The Gram-positive pathogen *Listeria monocytogenes* is able to promote its entry into a diverse range of mammalian host cells by triggering plasma membrane remodeling, leading to bacterial engulfment. Upon cell invasion, *L. monocytogenes* disrupts its internalization vacuole and translocates to the cytoplasm, where bacterial replication takes place. Subsequently, *L. monocytogenes* uses an actin-based motility system that allows bacterial cytoplasmic movement and cell-to-cell spread. *L. monocytogenes* therefore subverts host cell receptors, organelles and the cytoskeleton at different infection steps, manipulating diverse cellular functions that include ion transport, membrane trafficking, post-translational modifications, phosphoinositide production, innate immune responses as well as gene expression and DNA stability.

Listeria monocytogenes is a facultative intracellular pathogen that has the capacity to actively invade and multiply within mammalian cells. Intracellular replication of *L. monocytogenes* within mononuclear cells was noted in the 1926 publication by Murray and colleagues reporting on this bacterial pathogen for the first time (1). In the 1960s, the seminal work of Mackaness that identified the main actors of cellular immunity against bacterial intracellular pathogens took advantage of the *L. monocytogenes* intracellular lifestyle as a model (2). In the late 1980s and early 1990s, major *L. monocytogenes* virulence factors involved in bacterial adaptation to intracellular life were molecularly characterized (3–7) and the precise stages of the *L. monocytogenes* intracellular life-cycle were morphologically identified (8, 9). Since then, cellular effectors involved in the infection process have been also identified and characterized (10–12). In this article, we review the molecular mechanisms driving *L. monocytogenes* adaptation to the mammalian host cell intracellular environment.

ADAPTATION TO INTRACELLULAR LIFE: GENERALITIES

L. monocytogenes is able to invade and proliferate within macrophages and epithelial nonphagocytic cells. For entry into the latter, bacterial surface molecules (InlA, InlB) interact with cellular ligands, activating signaling cascades that lead to internalization of the pathogen within a membrane-bound compartment (Fig. 1).

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Correspondence: Javier Pizarro-Cerdá, pizarroj@pasteur.fr and Pascale Cossart, pcossart@pasteur.fr

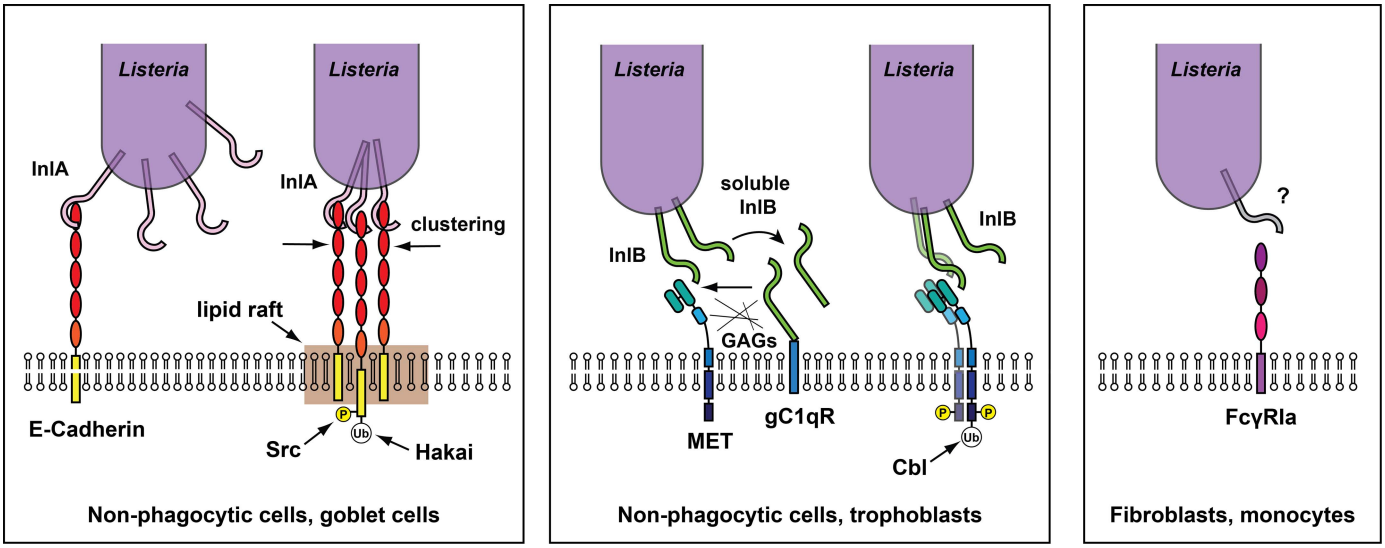

FIGURE 1 Cellular receptors for *L. monocytogenes* in host cells. The receptor for InlA in nonphagocytic polarized cells (including goblet cells) is the transmembrane molecule E-cadherin. Interaction takes place between the InlA leucine-rich repeats (LRRs) and the first extracellular domain of E-cadherin, leading to phosphorylation and ubiquitylation of the cytoplasmic domain of E-cadherin by the kinase Src and the ubiquitin ligase Hakai, respectively. Clustering of E-cadherin requires the presence of lipid rafts (left panel). Via its C-terminal glycine-tryptophan (GW) repeats, InlB interacts with the receptor for the globular part of the C1q complement component (gC1qR) and glycosaminoglycans, which enable interaction of the N-terminal LRRs of InlB with the tyrosine receptor kinase Met in nonphagocytic cells (including trophoblasts). Met dimerization upon interaction with InlB leads to autophosphorylation and recruitment of the ubiquitin ligase Cbl, which ubiquitylates the cytoplasmic tail of Met (center panel). In fibroblasts and monocytes, a function for the FcγRIA receptor has been described for *L. monocytogenes* internalization, via interaction with a still unidentified *L. monocytogenes* surface molecule (right panel). Modified from reference 12.

Residency in the internalization vacuole is prevented by secretion of a pore-forming toxin (listeriolysin O [LLO]) and two phospholipases (PlcA, PlcB) that disrupt the vacuolar membrane, promoting *L. monocytogenes* translocation to the host cell cytoplasm. In this intracellular location, *L. monocytogenes* activates several bacterial metabolic pathways that favor the uptake of cellular resources sustaining bacterial proliferation. The pathogen also displays several strategies to escape cytoplasmic innate immune responses, which include the polymerization of actin by a bacterial surface protein (ActA), allowing *L. monocytogenes* to spread to neighboring cells. In secondary infected cells, *L. monocytogenes* is located in a double-membrane compartment that is disrupted by the same set of secreted enzymes that favor lysis of the primary internalization vacuole. *L. monocytogenes* translocation to the cytoplasm of secondary infected cells leads to a new bacterial replication cycle and further spread to other cells in infected tissues. The intracellular lifestyle is therefore critical for *L. monocytogenes* virulence: it allows escape from extracellular host defense mechanisms, including the complement or antibodies, and hinders detection by patrolling cell populations, e.g., neutrophils; in macrophages, cytoplasmic translocation allows escape from degradative components of the phagocytic cascade, while it provides access to a "Trojan horse" host cell population that can safely transport bacteria to distant locations within the infected organism.

THE CELLULAR INVASION PROCESS

Upon *L. monocytogenes* contact with host target tissues, cellular invasion is morphologically characterized by a localized extension of the plasma membrane around invading bacteria, triggering bacterial internalization within a tight vacuolar compartment. Mechanistically, bacterial surface proteins interact with host cell receptors that are posttranslationally modified (phosphorylation, ubiquitylation), favoring the recruitment of

protein adaptors and enzymes that contribute to actin polymerization, the key molecular event required for plasma membrane reorganization. Depending on the invaded cell type, bacterial modulation of the phosphoinositide (PI) metabolism is also critical to trigger cortical actin polymerization.

InlA is the archetypal member of a family of *L. monocytogenes* surface proteins named internalins, which are characterized by the presence of N-terminal leucine-rich repeats (LRR) which mediate interaction with host cell ligands (6, 13). The internalins InlA and InlB, encoded within a single locus in the *L. monocytogenes* genome, are the two major surface molecules driving bacterial entry into host cells. More than 20 other internalins have been identified, but they do not necessarily participate in the cell invasion process, contributing instead to diverse functions including cell-to-cell spread and escape from innate immune responses (i.e., InlC [14, 15]) and escape from autophagy (i.e., InlK [16]). The pore-forming toxin LLO, the actin polymerizing factor ActA, and other bacterial surface proteins have been described as supporting bacterial entry independently of the InlA and InlB invasion pathways (see below).

InlA/E-Cadherin-Mediated Entry

InlA displays a C-terminal LPXTG domain that favors covalent binding to the *L. monocytogenes* cell wall (6). The LRR domain of InlA interacts with the cellular receptor E-cadherin (17, 18), a transmembrane glycoprotein present in the adherens junctions of polarized tissues (e.g., the intestine and the placenta). E-cadherin normally plays a key role in the maintenance of tissue stability, and while the ectodomain participates in most cases in homotypic interactions (E-cadherin/E-cadherin intercellular binding), the cytoplasmic domain interacts with the actin cytoskeleton machinery. By subverting the E-cadherin physiological function, *L. monocytogenes* promotes cortical actin polymerization and plasma membrane rearrangements, favoring cellular invasion and traversal of the intestinal and the feto-maternal barriers (19, 20). InlA access to intestinal E-cadherin mostly occurs at the level of goblet cells, which expose this cellular receptor to bacteria during mucus secretion (21). Exposure of E-cadherin to *L. monocytogenes* during apoptotic cell extrusion at the tip of intestinal villi has also been documented (22). The interaction between InlA and E-cadherin is species-specific (23). A proline at position 16 allows interaction between InlA and human E-cadherin, while a glutamic acid at the same position, as observed in the mouse E-cadherin, does not allow InlA binding. A transgenic mouse model specifically expressing the human E-cadherin in the murine intestine allows a more efficient animal infection through the oral route, demonstrating the pivotal role of InlA in the crossing of the intestinal barrier (19).

In *in vitro* polarized cellular systems, lipid rafts are critical for InlA-dependent E-cadherin clustering (24). InlA binding promotes two successive posttranslational modifications in the cytoplasmic tail of E-cadherin: phosphorylation by the host kinase Src, followed by ubiquitylation by the ubiquitin ligase Hakai (25). These events are critical for the recruitment of a clathrin coat via the adaptor Dab2; the coat is stabilized by tyrosine phosphorylation of the clathrin heavy chain, followed by sequential recruitment of the protein adaptor Hip1R, which in turn coordinates recruitment of actin; myosin VI and unconventional myosin VIIa provide the pulling force that finally leads to bacterial internalization (26, 27). Interestingly, the nonmuscle myosin heavy chain IIA is specifically phosphorylated by Src upon *L. monocytogenes* infection and restricts bacterial entry (28). Several other molecules modulate actin association to the E-cadherin cytoplasmic site during *L. monocytogenes* InlA-dependent invasion: β- and α-catenins provide a physical link between E-cadherin and actin filaments during bacterial entry (29, 30), while cortactin and Src participate in the activation of the Arp2/3 complex, a major actin nucleator (31), highlighting the exploitation of adheren junctions and classical E-cadherin endocytosis components by *L. monocytogenes* during invasion of polarized tissues (32, 33). In the intestinal barrier, the constitutive PI 3-kinase activity is required for promoting actin polymerization during *L. monocytogenes* cell entry; in the placenta, PI 3-kinase activity is not constitutive, and InlB is required for PI 3-kinase activation and InlA-mediated cell invasion (34, 35).

InlB/Met-Mediated Entry

InlB was identified as a second *L. monocytogenes* invasion protein (6, 36). InlB allows *L. monocytogenes* entry into nonpolarized epithelial cells *in vitro* (37), and it cooperates with InlA during placental invasion *in vivo* (34, 35). In nonpregnant animals, InlB expression is associated with an increase of necrotic foci in the liver and spleen (38). The C-terminal region of InlB is characterized by the presence of glycine-tryptophan (GW) repeats that favor loose binding to bacterial membrane-tethered lipoteichoic acids (39, 40) and pedptidoglycan-bound wall teichoic acids (41). At the surface of host cells, the GW repeats mediate binding to the receptor of

the globular part of the complement component C1q (42) and to glycosaminoglycans (43). The N-terminal region displays LRRs that are critical for cell invasion (44, 45) and bind the hepatocyte growth factor receptor Met (46) in a species-specific manner (47). Met expression is modulated by epithelial keratins, which promote InlB-mediated *L. monocytogenes* infection of epithelial cells (48). Met is a tyrosine kinase receptor, and its interaction with InlB leads to Met autophosphorylation and recruitment of the protein adaptors Gab1, Shc, Cbl, and CrkII (49–51), which play key roles in the activation of PI 3-kinase (52–54). Production of PI(3,4,5)P_3 and its accumulation in lipid rafts leads to Rac1 activation (24, 55) and recruitment of Ena/VASP, WAVE, and N-WASP, which activate the Arp2/3 complex promoting actin polymerization in a tightly regulated manner (56, 57). The serine/threonine kinases mTOR and protein kinase C-α also control actin polymerization downstream of the InlB/Met interaction (58). The host 5′-phosphatase OCRL restricts *L. monocytogenes* entry by reducing PI(3,4,5)P_3 levels and actin polymerization at bacterial entry foci (59). Production of PI 4P by type II PI 4-kinases, downstream of the tetraspanin CD81, is also critical for *L. monocytogenes* entry into host cells (60, 61). The PI 3-kinase adaptor Cbl also displays ubiquitin ligase activity and promotes ubiquitylation of Met upon InlB binding, leading to modulation of actin polymerization via clathrin recruitment (62–64). InlB also modulates exocytosis and favors the delivery of the endocytic GTPase dynamin 2 to bacterial entry sites (65). Finally, the septin cytoskeleton is recruited during cell invasion by *L. monocytogenes* in an InlB-dependent manner (66), and it controls the anchorage of Met to the cortical actin cytoskeleton (67–69).

Additional Adhesion/Entry Effectors

L. monocytogenes displays other surface and secreted molecules that can modulate adhesion and entry into host cells by indirectly affecting the surface exposure of InlA or InlB, by behaving as adhesins, by directly binding putative cellular receptors, and/or by activating cellular pathways that lead to actin rearrangements and bacterial engulfment. For example, the internalins InlE, InlG, and InlH support the InlA-dependent-invasion pathway in Caco-2 cells and might modulate the bacterial cell wall organization, consequently affecting InlA exposure (70). On the other hand, InlJ favors bacterial adhesion but not invasion in a specific subset of polarized epithelial cells (71, 72). A role for InlF in cell adhesion and invasion has been detected only upon inhibition of the RhoA/Rho kinase pathway (73, 74).

Several *L. monocytogenes* autolysins modulate cell adhesion and/or entry processes: Ami is involved in cell adhesion (75, 76), and Auto has been implicated in entry (77), while IspC is required for adhesion and/or invasion in a cell line-dependent manner (78). The lipoteichoic acid modifiers GtcA and DltA (79, 80), the lipoprotein LpeA (81), the prolipoprotein transferase Lgt (82), and the lysylphosphatidylglycerol modifier MprF (83) play roles in host cell adhesion or invasion probably by modulating the bacterial surface charge and/or by altering the organization of bacterial surface proteins. The surface protein ActA, involved in cytoplasmic actin-based motility (see below), has been proposed to favor host cell invasion through interaction with heparan sulfate (84, 85). Additional *L. monocytogenes* surface adhesins or invasins include Vip (86, 87), Lap (88), LapB (89), and FbpA (90).

LLO, a secreted cholesterol-dependent pore-forming toxin that is required for *L. monocytogenes* vacuolar escape (see below), is also secreted by extracellular bacteria and induces a transient influx of extracellular calcium within host cells that correlates with increased cell invasion (91). Mitochondrial fragmentation also correlates with the LLO-dependent calcium influx, and it has been proposed that *L. monocytogenes* modulates the bioenergetic state of resting cells to trigger cell invasion (92). LLO has been recently proposed to mediate *L. monocytogenes* entry into epithelial cells in a $Ca2^+$/K^+-, cholesterol-, dynamin-, tyrosine kinase- and actin-dependent but InlA/InlB- and clathrin-independent manner (93, 94). A broad-range phospholipase C of *L. monocytogenes*, PlcB (see below), has been reported to induce a calcium influx required for efficient bacterial internalization in macrophages (95).

THE VACUOLAR STAGE

The modulation of the actin cytoskeleton and the rearrangements of the plasma membrane upon *L. monocytogenes* interaction with its host cell receptors lead to bacterial engulfment and internalization in a membrane-bound vacuole (Fig. 2). In the intestinal epithelium, and particularly in the goblet cells, *L. monocytogenes* does not escape from this compartment and is directly transcytosed to the lamina propria, where the bacteria disseminate systemically (21). In other cell types, *L. monocytogenes* is able to disrupt its containing compartment and translocates to the host cell cytoplasm. The cholesterol-dependent pore-forming toxin LLO, together with two bacterial phospholipases, are the major bacterial effectors controlling *L. monocytogenes*

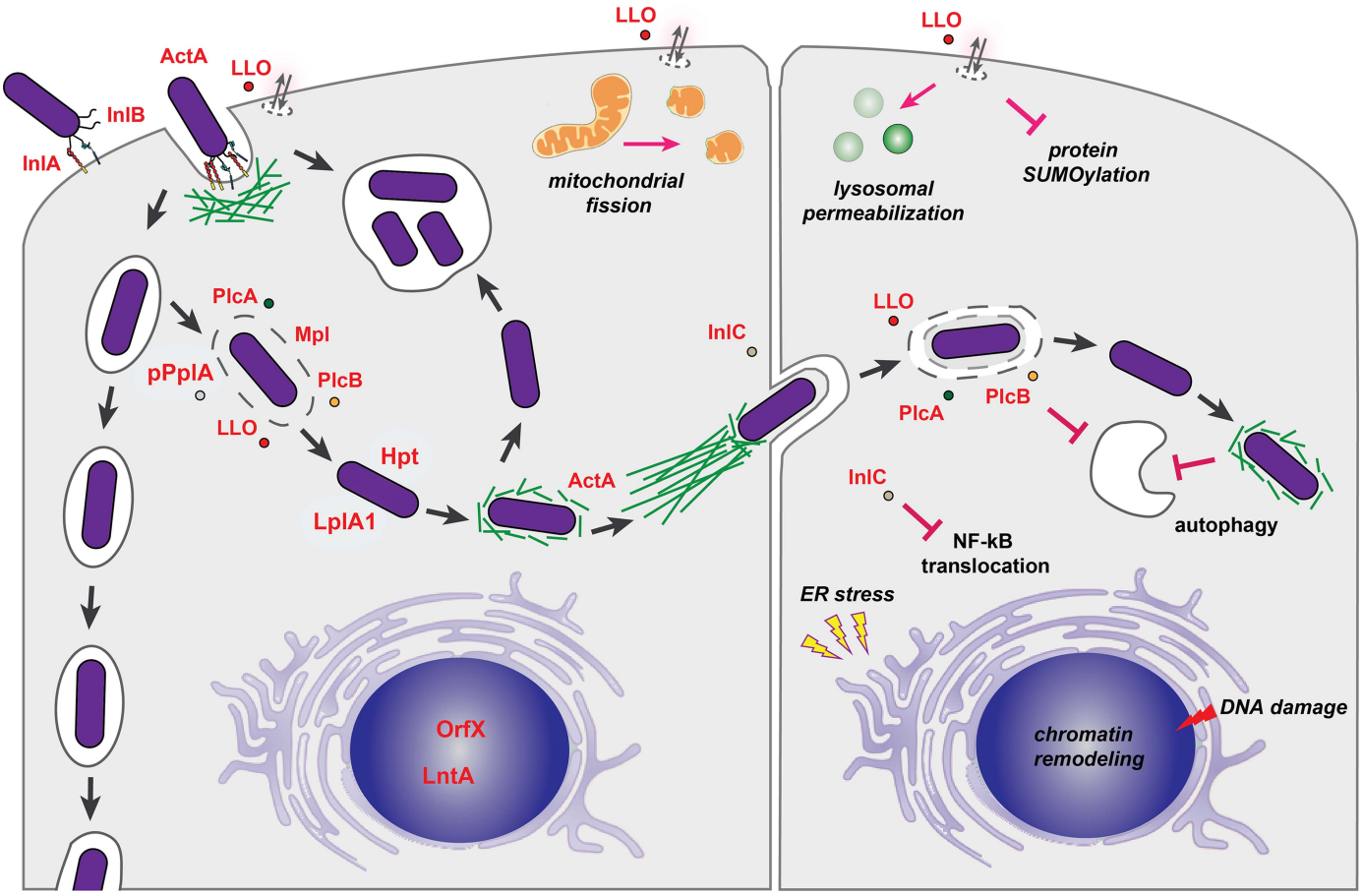

FIGURE 2 *L. monocytogenes* intracellular stages. *L. monocytogenes* is able to induce its entry into nonphagocytic cells mainly via the interaction of InlA and InlB with host cells receptors that promote actin recruitment, remodeling of the plasma membrane, and bacterial engulfment. The surface molecule ActA and the secreted pore-forming toxin LLO have also been implicated in the early *L. monocytogenes* entry steps (left cell, upper left). In goblet cells, upon internalization, *L. monocytogenes* is localized in a vacuole, and through transcytosis the bacterium is translocated to the lamina propria (left cell, left). In other cells, the combined activity of diverse virulence factors, including the pore-forming LLO, the metalloprotease Mpl, the phospholipases PlcA and PlcB, and the pheromone pPplA, favor disruption of the vacuole and *L. monocytogenes* release in the cytosol, where the bacteria takes advantage of host metabolites via the phosphate transporter Hpt and the lipoate protein ligase LplA. The surface protein ActA promotes actin-based motility, and the secreted protein InlC favors reduction of plasma membrane cortical tension, allowing *L. monocytogenes* to form protrusions and to invade neighboring cells. LLO and the phospholipases PlcA and PlcB contribute to the disruption of the double-membrane vacuole (right cell). *L. monocytogenes* has been observed in large spacious compartments that may arise rapidly after internalization of bacteria or upon decrease of ActA expression in already cytoplasmic bacteria (left cell, upper center). Extracellular LLO is able to modulate different cellular functions, including mitochondrial fission, lysosomal permeabilization, protein SUMOylation, ER stress, DNA damage, and chromatin remodeling. The phospholipases PlcA and PlcB, together with actin polymerization by ActA, have been implicated in the resistance to autophagy (195). The secreted molecule InlC prevents NF-κB translocation to the nucleus. Modified from reference 12.

vacuolar escape. *L. monocytogenes* residency and persistence in vacuolar compartments have also been described (96, 97) (see below).

LLO and Vacuolar Disruption

LLO is able to induce hemolysis *in vitro*, and early on, this activity was correlated with *L. monocytogenes* virulence (98). This toxin is encoded by the *hly* gene, located within a pathogenicity island that also encodes other important virulence factors, including two phospholipases, a metalloprotease, the actin polymerizing factor ActA, and the transcriptional activator PrfA (99). Inactivation of the *hly* gene coupled with electron microscopic observations subsequently demonstrated that LLO is required for bacterial escape from internalization vacuoles (100). LLO belongs to the family of cholesterol-dependent cytolysins which also includes perfringolysin O from *Clostridium perfringens* and streptolysin O from *Streptococcus pyogenes* (101). Perfringolysin O studies indicate that a conserved undecapeptide provides a structural conformation for a threonine-leucine pair at the C-terminal region of cholesterol-dependent cytolysins responsible for cholesterol binding (102, 103). Theoretically predicted to form large pores (20 to 80 monomers), based on initial perfringolysin O studies (104), electron microscopy and atomic force microscopy analyses indicate that LLO oligomers actually form arc-like structures that assemble into lineactants, and these heterogenous structures are responsible for membrane disruption and vacuolar rupture (105, 106). Membrane perforation by LLO not only facilitates *L. monocytogenes* translocation to the cytoplasm, but it also controls the vacuolar pH and calcium concentration, delaying the maturation of the bacteria-containing compartment and inhibiting lysosomal fusion (107, 108).

Several physical parameters and host molecules modulate the activity of LLO. Removal of LLO pores from the host cell plasma membrane is mediated by an LLO PEST-like sequence recognized by the clathrin adaptor Ap2a2, favoring pore endocytosis and protection of plasma membrane integrity (109). At 37°C and neutral pH, LLO undergoes denaturation, but it is in a stable conformation at acidic conditions (105). Consequently, within mammalian hosts, the LLO pore-forming activity is compartmentalized to slightly acidified bacteria-containing compartments (110, 111). Cytoplasmic LLO activity, which is cytotoxic to host cells and detrimental to intracellular *L. monocytogenes* (112), is limited by translational regulation of LLO synthesis (113) and by cytoplasmic LLO degradation by the ubiquitin system (114). LLO is activated by reducing agents (115), and within the vacuole of macrophages, the γ-interferon-inducible lysosomal thiol reductase is responsible for reducing and activating LLO (116). The increase in vacuolar chloride concentration mediated by the cystic fibrosis transmembrane conductance regulator has been proposed to enhance LLO oligomerization and *L. monocytogenes* cytoplasmic escape (117). LLO-disrupted vacuoles trigger the recruitment of the protein kinase C (PKC) ε, suggesting that this enzyme is involved in the recognition of damaged membrane organelles (118).

Phospholipases PlcA/PlcB and Vacuolar Disruption

L. monocytogenes secretes two phospholipases, a phosphatidylinositol-specific phospholipase C named PlcA (119) and a broad-range phospholipase C/sphingomyelinase named PlcB (120, 121), which is activated by the metalloprotease Mpl (122–124). Both enzymes have been shown to contribute to *L. monocytogenes* escape from primary vacuoles and from secondary vacuoles during bacterial cell-to-cell spread (4, 125–128).

PlcA from *L. monocytogenes* is the only bacterial-phosphatidylinositol-specific phospholipase C that lacks a Vb β-strand that increases activity toward glycosylphosphatidylinositol-anchored proteins (129); interestingly, expression of this β-strand in PlcA impairs bacterial escape from vacuoles and cell-to-cell spread (130), suggesting that an *L. monocytogenes* adaptation to the intracellular environment requires reduced activity against glycosylphosphatidylinositol-anchored proteins. It has been proposed that PlcA translocating via LLO pores reaches the host cell cytoplasm, and in this compartment PlcA cleaves intracellular phosphatidylinositol into inositol phosphate and diacylglycerol (131); production of diacylglycerol, which might also take place through activation of host phospholipases C and D in an LLO-dependent signaling pathway (132), leads to activation of PKC βI and βII, which are required for vacuolar disruption (133). Because both PKC βI and βII are recruited to the *L. monocytogenes* internalization vacuole (134), it is speculated that the phosphorylation of PKC βI and βII targets at the surface of the bacteria-containing compartment is critical for a still unidentified signaling cascade leading to vacuolar rupture (133).

PlcB maturation and activation by the metalloprotease Mpl requires acidification of the vacuole (135, 136), and as has been observed for LLO, compartmentalization of this phospholipase C activity is critical for intracellular survival of *L. monocytogenes* (137). Both PlcA and PlcB have been found to activate NADPH

oxidase during *L. monocytogenes* infection, which might be harmful to internalized bacteria via the production of reactive oxygen species; however, modulation of vacuolar maturation by LLO restricts NADPH oxidase localization to the *L. monocytogenes*-containing compartments (138).

Additional Mechanisms Regulating Vacuolar Disruption

Several other bacteria- and host-related mechanisms have been proposed to modulate the *L. monocytogenes* vacuolar stage. A recent study indicates that *L. monocytogenes* secretes a pheromone, pPplA, that triggers the production of an unknown factor that cooperates with LLO in facilitating vacuolar disruption (139): pPplA is processed from the N-terminal secretion signal sequence of the lipoprotein PplA; pPplA is secreted, accumulates in the space of the *L. monocytogenes* vacuole, and is then exported by the CtaP peptide transporter; cytoplasmic pPplA induces the production of a factor that accelerates vacuolar disruption mediated by LLO in a still unidentified manner (139).

Modulation of bacterial gene expression by "reversible lysogeny" has also been proposed to modulate *L. monocytogenes* vacuolar escape (140). The prophage A118 is inserted within the coding region of the gene *comK*, a master regulator of competence genes that are normally not expressed by *L. monocytogenes*; interestingly, during the bacterial vacuolar stage, A118 is excised, and this event allows reactivation of *comK* and expression of the competence machinery by *L. monocytogenes*; by a still unknown mechanism, the competence system promotes efficient bacterial translocation to the host cell cytoplasm. In this environment, the phage reinserts into *comK* (140).

Additional host factors have been reported to control *L. monocytogenes* vacuolar residency. Rab5a was shown to control the accelerated maturation of *L. monocytogenes*-containing vacuoles (141, 142); the product of the gene *Lmo*2459 was subsequently shown to induce the specific ADP ribosylation of Rab5a, inhibiting its activation and reverting its bactericidal functions (143). The activity of the cytosolic cysteine protease calpain has been shown to be required for efficient *L. monocytogenes* vacuolar escape, but the targets of this protease remain to be identified (144).

THE CYTOPLASMIC STAGE

By translocating from the vacuolar stage toward the cytoplasm, *L. monocytogenes* escapes cellular degradative mechanisms associated with phagosomal pathways. On the other hand, *L. monocytogenes* must adapt its metabolism to nutrients and metabolites found in this novel intracellular compartment and must also escape from additional innate immunity defenses including autophagy. The hexose phosphate transporter Hpt and the actin-polymerizing surface protein ActA play key roles in the survival of *L. monocytogenes* in the host cell cytoplasm.

Utilization of Host Metabolites

Glucose-1-phosphate is the primary degradation product of glycogen and is broadly available within mammalian cells. The observation that *L. monocytogenes* uses glucose-1-phosphate as a carbon source in a PrfA-dependent manner suggested that related hexose phosphates could be important growth substrates for intracellular bacteria (145). *In silico* analysis of the *L. monocytogenes* genome identified the gene *hpt* as encoding a hexose phosphate transporter responsible for the uptake of glucose-6-phosphate in the cytoplasm of host cells, playing a key role in *L. monocytogenes in vivo* virulence (146). A subsequent screen for identification of additional genes required for bacterial intracellular replication recognized lplA1 as a lipoate protein ligase that could potentially use host-derived lipoic acid to modify bacterial substrates (147). LplA1 was later confirmed to be essential for intracellular growth of *L. monocytogenes* under limiting concentrations of available small mammalian lipoylated peptides (148). A genetic screen led to the discovery that the menaquinone synthesis intermediate 1,4-dihydroxy-2-naphtoate is required for *L. monocytogenes* cytosolic survival, but full-length menaquinone is not (149).

Cytoplasmic Innate Immune Responses

Autophagy is a cellular mechanism responsible for protein turnover and removal of abnormal or superfluous subcellular components. The pioneering work of Rich et al. (150) demonstrated that cytoplasmic and metabolically arrested *L. monocytogenes* can be targeted for destruction by the autophagic machinery. Different mechanisms have been proposed to participate in the active escape of cytoplasmic *L. monocytogenes* from autophagy: polymerization of actin by the surface protein ActA favors cytoplasmic motility and avoidance of autophagosomes (151); polymerized actin or Arp2/3 sequestering by ActA may also act as a protective physical barrier preventing the accumulation of signaling molecules (i.e., ubiquitin) that are required for autophagy activation (152, 153). PlcA and PlcB have

also been implicated in autophagosomal avoidance (151, 154, 155), and recent studies suggest that these PLCs decrease cytoplasmic levels of PI 3P, causing stalling of preautophagosomal structures and preventing efficient targeting of cytosolic bacteria (156). The surface internalin InlK has also been proposed to recruit the major vault protein and to protect cytoplasmic *L. monocytogenes* from autophagic recognition (16), but these results have been recently challenged using a different *L. monocytogenes* strain (157).

Cytoplasmic *L. monocytogenes* secretes small molecules leading to activation of an IRF3-dependent cytosolic pathway, resulting in type I interferon activation (158). One of these small molecules, cyclic-di-AMP, is sufficient to activate production of interferon β in macrophages (159). Sensing of tri-phosphorylated RNA via RIG-I and a MAVS-dependent pathway triggers type I interferon production in epithelial cells (160, 161). *L. monocytogenes* cytoplasmic DNA is recognized through STING, TBK1, IRF3, and IRF7, leading to the upregulation of the di-ubiquitin-like protein ISG15 and ISGylation of endoplasmic reticulum (ER) and Golgi proteins, which correlate with increased secretion of cytokines that counteract infection (162). *L. monocytogenes* also activates the type III interferon pathway (163).

Persistence

It is increasingly recognized that bacterial pathogens may persist within host tissues in a dormant state that allows resistance to antibiotics and subsequent reinfection. In macrophages of severe combined immunodeficient (SCID) mice, *L. monocytogenes* can persist in large compartments termed spacious *Listeria*-containing phagosomes (SLAPS), which are formed in an LLO-dependent manner (96). LC3-associated phagocytosis has been proposed to precede the formation of SLAPS (164). A recent study indicates that in epithelial cells, cytoplasmic *L. monocytogenes* bacteria in which ActA production is halted are trapped in acidic vacuoles that are not associated with classical autophagosomal markers and in which bacteria enter a viable but nonculturable state (97). These studies indicate that *L. monocytogenes* may persist in different host cellular populations, favoring the asymptomatic carriage of this pathogen.

CELL-TO-CELL SPREAD

Actin-based motility allows *L. monocytogenes* not only to escape autophagy but also to reach neighboring cells within infected tissues, favoring cell-to-cell spread and bacterial dissemination in organs, avoiding exposure to humoral immunity. Motile *L. monocytogenes* first induces the formation of a membrane protrusion in the primary infected cell that is accompanied by membrane internalization in the neighboring bystander cell, leading to bacterial entrapment in a double-membrane vacuole that is then disrupted (9). Several bacterial virulence factors, including ActA, the internalin InlC, the pore-forming toxin LLO, and the phospholipases PlcA and PlcB, participate at different stages of *L. monocytogenes* cell-to-cell spread.

Cytoplasmic Actin-Based Motility

The surface protein ActA is sufficient to trigger actin polymerization at the surface of *L. monocytogenes* (7). The central region of ActA contains four short proline-rich repeats that bind members of the enabled/vasodilator-stimulated phosphoprotein (Ena/VASP) family; these molecules contribute to the persistence of speed/directionality of bacterial movement by recruiting profilin, which provides polymerization-competent actin monomers (165). The N-terminal region of ActA recruits the Arp2/3 complex which drives actin nucleation (166, 167). The Arp2/3 complex is formed of seven subunits, and it has been traditionally considered a single molecular entity (168). A genome-wide small interfering RNA screen demonstrated that different Arp2/3 complexes are required to control *L. monocytogenes* cell invasion and actin-based motility: the Arp2, Arp3, ARPC2, and ARPC3 subunits are conserved, but the ARPC1B subunit is only involved in cell invasion, while the ARPC1A subunit is required for actin-based motility, and the ARPC4 subunit is dispensable for cell invasion, while the ARPC5 subunit is dispensable both for cell invasion and actin-based motility (169). Multiple actin cross-linking proteins, actin filament-capping or -severing proteins, and protein scaffolds are recruited to the *L. monocytogenes* actin tail (170). Cryo-electron tomography of actin tails has demonstrated that actin bundling is critical for ensuing actin-based motility (171).

Cortical Actin Rearrangements and Protrusion Formation

In mammalian tissues, cortical membrane tension represents a physical barrier for motile *L. monocytogenes*, inhibiting the deformation of the plasma membrane into protrusions. InlC, a secreted member of the internalin family devoid of a cell wall anchoring motif (13), perturbs apical cell junctions by interacting with the protein adaptor Tuba, inhibiting the recruitment of the actin

regulatory protein N-WASP and COPII proteins and therefore relieving cortical membrane tension favoring *L. monocytogenes* protrusion formation (14, 172, 173). The downregulation by *L. monocytogenes* of the small GTPase Cdc42, another Tuba interactor, is also required for efficient protrusion formation (174). Within the protrusion, the membrane-cystoskeletal linker ezrin has been proposed to support the formation and stabilization of protrusions (175). Arp2/3 drives actin polymerization at the proximal *L. monocytogenes* rear-end within protrusions, but at distal locations the recruitment of Rho GTPases activate diaphanous-related formins which promote the formation of unbranched actin filaments (176). Inhibition of actin polymerization by components of the AIP1-dependent actin disassembly machinery (177) and ActA processing by the metalloprotease Mpl (178) are proposed mechanisms for the resolution of membrane protrusions into double membrane vacuoles. Efficient cell-to-cell spread can be facilitated by the exofacial exposure of phosphatidylserine at the tip of protrusions promoted by the pore-forming activity of LLO, which leads to phosphatidylserine binding by the TIM-4 receptor in macrophages and protrusion internalization (179).

Lysis of Secondary Vacuoles

Internalization of *L. monocytogenes*-induced protrusions into neighboring bystander cells leads to bacterial localization within a double-membrane compartment (9). Initial studies suggested that phospholipases PlcA and PlcB, together with LLO, contributed to cell-to-cell spread (4, 125, 127), and a more specific contribution of PlcB to double-membrane vacuolar rupture was suggested (128). A current model proposes that PlcA and PlcB contribute to the disruption of the inner membrane of the spreading vacuole, while LLO participates more precisely in the disruption of the outer membrane of this vacuole (180). Bacterial translocation to the cytoplasmic space of neighboring cells allows *L. monocytogenes* to start a new infection process.

MODULATION OF CELLULAR, ORGANELLAR, AND NUCLEAR FUNCTIONS

L. monocytogenes is able to modulate a broad range of cellular functions, even before being internalized within host cells. The pore-forming toxin LLO, which plays a major role in vacuolar escape (see above) is able to modulate from the extracellular space the function of mitochondria, the ER, lysosomes, protein posttranslational modifications, and DNA stability. Several bacterial nucleomodulins have been identified which directly affect the transcription of host genes involved in the control of immune responses.

LLO Influence on Mitochondria

Mitochondria are critical organelles involved in the generation of chemical energy in eukaryotic cells. As mentioned above, extracellular LLO triggers the influx of calcium, which leads to transient fission of mitochondria, triggering a bioenergetic change of host cells that is beneficial for *L. monocytogenes* host cell invasion (92). Interestingly, atypical mitochondrial fission through a Drp1-independent fragmentation process has been associated with *L. monocytogenes* cellular infection (181).

LLO Influence on the ER

The unfolded protein response is a signaling cascade that maintains the function of the ER under stress conditions. *L. monocytogenes* activates the unfolded protein response in an LLO-dependent manner prior to bacterial entry into host cells (182). The induction of ER stress by drugs such as thapsigargin or tunicamycin leads to a decrease in bacterial intracellular numbers, suggesting that the unfolded protein response represents an innate immune response to bacterial infection (182).

LLO Influence on Lysosomes

The integrity of lysosomes has been shown to be compromised by extracellular LLO, which induces permeabilization and release of lysosome content, including cathepsins, which remain transiently active in the cytoplasm (183). The functional significance of this finding for *L. monocytogenes* infection and survival remains to be identified.

LLO Influence on Protein Posttranslational Modifications

Posttranslational modifications allow the rapid modification of the activity of cellular proteins. Sumoylation is an essential posttranslational modification that is impaired by *L. monocytogenes* through the proteasome-independent degradation of the E2 enzyme Ubc9 following calcium influx mediated by extracellular LLO (184). The downregulation of cellular protein sumoylation, together with the proteasome-dependent degradation of some sumoylated proteins, favors bacterial infection *in vitro* and *in vivo* (184). Histone modifications are also associated with the *L. monocytogenes* infection process (185) (see below).

LLO Influence on DNA Stability

L. monocytogenes modulates general DNA stability in host cells in different manners. *L. monocytogenes* induces DNA strand breaks and simultaneously blocks the DNA damage response through degradation of the sensor Mre11 in an extracellular LLO-dependent manner (186), promoting a cell cycle delay that favors bacterial intracellular replication (187). Interestingly, it has been also reported that LLO-induced calcium influx leads to the proteasomal degradation of the human telomerase reverse transcriptase, an event that is detrimental to bacterial replication (188).

Bacterial Influence on Gene Expression

LntA is the first nucleomodulin discovered in *L. monocytogenes* (189): it targets the chromatin repressor BAHD1 and fine-tunes transcription of interferon-stimulated genes, which is required for efficient *in vivo* infection (190, 191). More recently, the nucleomodulin OrfX has been shown to interact and decrease the levels of the regulatory protein RybP, dampening the oxidative response in macrophages probably through modulation of host transcriptional responses (192). The secreted internalin InlC interferes with innate immune responses by targeting the IκB kinase subunit IKKα, inhibiting NF-κB translocation to the nucleus (15). LLO modulates gene transcription with opposite effects for infection: LLO induces a dramatic dephosphorylation of histone H3 and deacetylation of histone H4 that leads to reduced transcriptional activity of key immunity host genes (185); LLO has also been shown to modulate the functionality of the promyelocytic leukemia protein nuclear bodies, activating a signaling response that decreases *L. monocytogenes* infection (193). Finally, an InlB/PI 3-kinase pathway is required for the SIRT2-dependent deacetylation of histone H3 on lysine 18, which is involved in efficient bacterial infection *in vitro* and *in vivo* (194).

CONCLUSIONS

The study of the interactions of *L. monocytogenes* with eukaryotic host cells during bacterial invasion, intracellular growth, and cell-to-cell spread has proven to be fundamental to better understanding the exquisite adaptation of this bacterial pathogen to mammalian hosts. Indeed, *L. monocytogenes* is able to hijack multiple cellular functions including receptor signaling, membrane trafficking, cytoskeletal rearrangements, organellar dynamics, DNA stability, and gene transcription. The work reviewed in this article also highlights that *L. monocytogenes* is an extraordinary tool to manipulate and to unravel host cell signaling cascades, in particular, innate immune responses that allow us to expand our understanding of the control of bacterial intracellular infections.

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