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Microbe Profile: *Listeria monocytogenes*: a paradigm among intracellular bacterial pathogens

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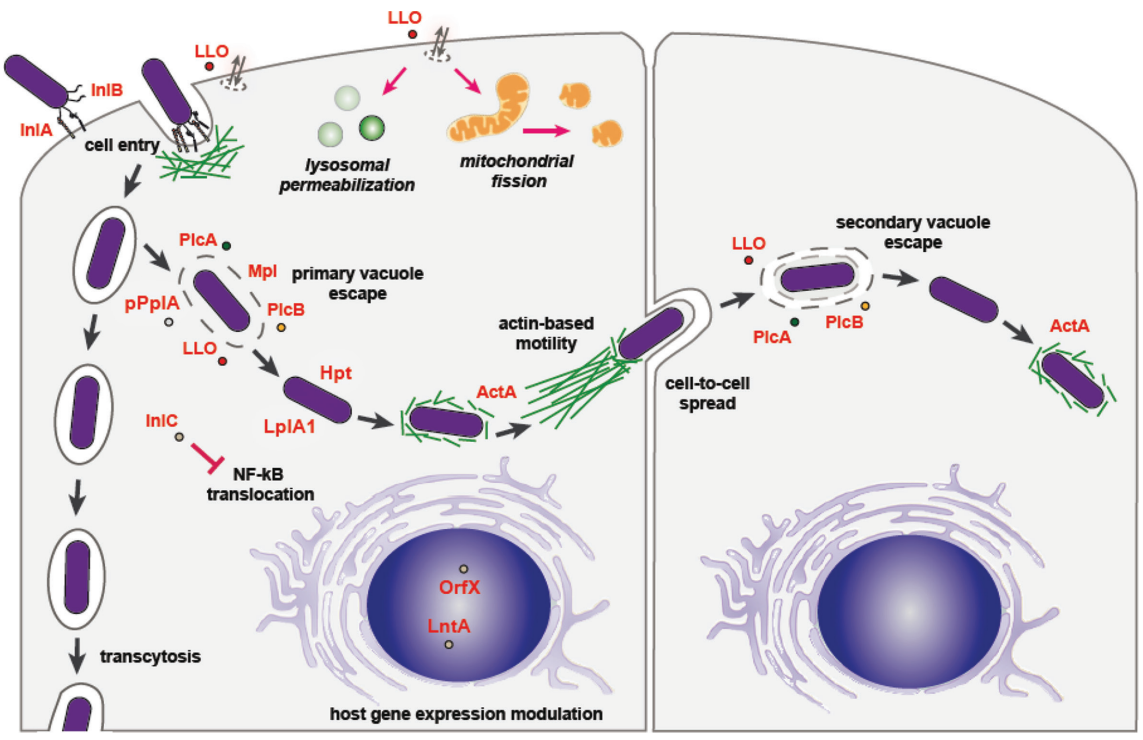

Graphical abstract

The cell infectious process. *Listeria monocytogenes* induces entry into non-phagocytic cells via the activity of the bacterial surface and secreted effectors that promote remodelling of the plasma membrane and bacterial engulfment. Secreted molecules allow vacuolar disruption and bacterial translocation to the host cell cytoplasmic, where host metabolites are catabolized and the actin cytoskeleton is hijacked to favour cell-to-cell spread. For survival, *L. monocytogenes* manipulates organelles such as mitochondria and lysosomes, as well as host gene expression. Major bacterial effectors are mentioned for each intracellular step. (From Pizarro-Cerdá J, Cossart P *Microbiology Spectrum* 2018;6:GPP3-0013-2018)

Abstract

Listeria monocytogenes is a food-borne bacterial pathogen that is responsible for listeriosis, a disease characterized by occasional febrile gastroenteritis in immunocompetent individuals, abortions in pregnant women, meningitis in the newborn and fatal bacteraemia in immunocompromised individuals or the elderly. The ability of *L. monocytogenes* to produce disease is intimately associated with its potential to traverse several human barriers (including the intestinal, placental and blood/brain barriers), to promote its internalization within diverse populations of epithelial cells and to proliferate in the intra-ic environment while escaping host immune responses. *L. monocytogenes* is often regarded as a paradigm for intracellular parasitism.

TAXONOMY

Domain *Bacteria*, phylum *Firmicutes*, class *Bacilli*, order *Bacillales*, family *Listeriaceae*, genus *Listeria*, species *L. monocytogenes*.

PROPERTIES

L. monocytogenes are Gram-positive bacilli that are non-spore-forming, facultatively anaerobic, catalase-positive, rod-shaped and circa 0.5×2–3 µm. At 20–25 °C, *L. monocytogenes* behaves as a flagellated environmental saprophyte; at 37 °C flagellar expression is repressed and *L. monocytogenes* activates a genetic program that allows bacterial life as a facultative intracellular pathogen.

GENOME

L. monocytogenes EGDe was the first strain to be sequenced [1], with a genome of 2 944 528 base pairs, an average G+C content of 38 %, 2853 protein coding sequences and 89.2 % of coding regions. No plasmids are present in *L. monocytogenes* EGDe and one to three prophage regions have been described in different sequenced strains. Six rRNA operons (16S-23S-5S) and 67 tRNA genes have been reported. *Listeria* pathogenicity island 1 (LIPI-1) encodes key factors required for bacterial growth and survival, while the inlA-inlB locus codes for surface proteins driving bacterial cell internalization.

PHYLOGENY AND GENOMIC POPULATION STRUCTURE

Four major evolutionary phylogenetic lineages (lineages I, II, III and IV) have been described for the species *L. monocytogenes*, comprising 13 different serotypes: 1/2b, 3b, 4b, 4d, 4e and 7 (lineage I) 1/2a, 3a, 3c and 1/2c (lineage II); 4a, 4c and 4b (lineages III and IV). Traditionally, serotype 4b (lineage I) has been associated most frequently with human listeriosis cases. Using a multi-locus sequence typing scheme based on the sequence analysis of seven housekeeping genes, different clonal complexes (CCs) have been identified within each evolutionary lineage: CC1, CC2, CC4 and CC6 (serotype 4b, lineage I) are significantly associated to human clinical isolates, while CC121 and CC9 (serotypes 1/2a and 1/2c, respectively, lineage II) are associated with food isolates [2].

KEY FEATURES AND DISCOVERIES

L. monocytogenes was first identified in 1926 in the United Kingdom by E. G. D. Murray as a pathogen causing a large mononuclear leucocytosis in rabbits. Soon afterwards, in 1927, *L. monocytogenes* was described by J. H. H. Pirie as a pathogen causing liver and spleen necrosis in gerbils in South Africa. In 1962, G. B. Mackaness used *L. monocytogenes* for the first time as a model to understand immune responses against intracellular pathogens, discovering that recovery from primary infection and protection against a secondary infection are cell-mediated, with antibodies playing no role in these processes. In 1983, *L. monocytogenes* was identified as being responsible for human food-borne infections after a major listeriosis outbreak in Canada, originating from contaminated coleslaw. In 1989, L. G. Tilney and D. A. Portnoy described the intracellular lifestyle of *L. monocytogenes*, revealing that after bacterial internalization and release in the host cell cytoplasmic, the bacteria polymerize actin structures that trigger intracellular motility and cell-to-cell spread (Fig. 1) [3]. In the 1990s, P. Cossart and co-workers identified internalins InlA and InlB as bacterial surface molecules required for *L. monocytogenes* host cell invasion. The interactions between InlA and InlB and their cellular receptors, E-cadherin and c-Met, respectively, are species-specific, and both are required for human placental infection. In contrast, a transgenic mouse model expressing human E-cadherin allowed researchers to demonstrate that only the InlA/E-cadherin interaction is required for intestinal barrier translocation through goblet cells [4]. Upon internalization in goblet cells, *L. monocytogenes* resides in a vacuole and transcytosis leads to bacterial translocation to the lamina propria. In other cells, the combined activity of the pore-forming toxin listeriolysin O (LLO), the metalloprotease Mpl, the phospholipases PlcA and PlcB, as well as the pheromone pPplA, favour disruption of the vacuole. Cytosolic *L. monocytogenes* imports host metabolites via the phosphate transporter Hpt and the lipate protein ligase LplA, and the bacterial surface protein ActA promotes actin-based cytoplasmic movement and cell-to-cell spread. The secreted effectors InlC, OfrX and LntA influence host gene expression, while extracellular LLO mediates entry and remodelling of mitochondria and lysosomes during the infectious process. A subset of *L. monocytogenes* strains from lineage I that are frequently associated with human listeriosis outbreaks encode a bacteriocin called listeriolysin S that modulates the host intestinal microbiota, thereby favouring intestinal infection. An attenuated *L. monocytogenes* strain has recently been proposed as a vector for cancer immunotherapy. Overall, *L. monocytogenes* is currently one of the best studied intracellular pathogens [5].

OPEN QUESTIONS

- Which mechanisms trigger *L. monocytogenes* tropism and traversal of the central nervous system?

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Keywords: listeriolysin S; actin cytoskeleton.
Abbreviations: CC, clonal complex.

- Which bacterial species are specifically targeted by listeriolysin S in the human intestinal tract?
- Are there additional bacterial factors responsible for the increased virulence associated with lineage I *L. monocytogenes* strains?
- Is there a special niche in the environment for *Listeria* species?

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Conflicts of interest
The authors declare that there are no conflicts of interest.

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