



HAL
open science

Listeriosis, a model infection to study host-pathogen interactions in vivo

Hana Kammoun, Minhee Kim, Lukas Hafner, Julien Gaillard, Olivier Disson,
Marc Lecuit

► **To cite this version:**

Hana Kammoun, Minhee Kim, Lukas Hafner, Julien Gaillard, Olivier Disson, et al.. Listeriosis, a model infection to study host-pathogen interactions in vivo. *Current Opinion in Microbiology*, 2022, 66, pp.11-20. 10.1016/j.mib.2021.11.015 . hal-04609211

HAL Id: hal-04609211

<https://hal.science/hal-04609211>

Submitted on 12 Jun 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **Listeriosis, a model infection to study host-pathogen interactions *in vivo***

2
3 Hana Kammoun^{1,2}, Minhee Kim^{1,2}, Lukas Hafner^{1,2,3}, Julien Gaillard^{1,2,3},
4 Olivier Disson^{1,2}, Marc Lecuit^{1,2,3,4,5,*}

5
6
7 ¹ Institut Pasteur, Biology of Infection Unit, Paris, France

8 ² Inserm U1117, 75015, Paris, France

9 ³ Université de Paris, 75006, Paris, France

10 ⁴ National Reference Centre and WHO Collaborating Centre *Listeria*, Institut Pasteur, 75015,
11 Paris, France

12 ⁵ Necker-Enfants Malades University Hospital, Division of Infectious Diseases and Tropical
13 Medicine, APHP, Institut Imagine, 75006, Paris, France

14
15 * Correspondence to: marc.lecuit@pasteur.fr

16 17 **Highlights**

- 18 • Humanized animal models allow deciphering *L. monocytogenes* interactions with host
19 tissues.
- 20 • *L. monocytogenes* adapts to challenging environments inside and outside the host.
- 21 • Sequence-tagged *L. monocytogenes* are instrumental to study infection within-host
22 dynamics.
- 23 • *L. monocytogenes* evades immune responses, favoring its systemic dissemination.

24 25 **Key future questions**

- 26 - What are the mechanism(s) of *L. monocytogenes* immune escape at the mucosal
27 level?
- 28 - What are the respective roles of microbiota, host and *Listeria* factors involved in *L.*
29 *monocytogenes* fecal carriage and shedding in the environment?
- 30 - What are the mechanism(s) underlying *L. monocytogenes* hypervirulence?

31
32

33 **Abstract**

34 *Listeria monocytogenes* (*Lm*) is a foodborne pathogen and the etiological agent of listeriosis.
35 This facultative intracellular Gram-positive bacterium has the ability to colonize the intestinal
36 lumen, cross the intestinal, blood-brain and placental barriers, leading to bacteremia,
37 neurolisteriosis and maternal-fetal listeriosis. *Lm* is a model microorganism for the study of the
38 interplay between a pathogenic microbe, host tissues and microbiota *in vivo*. Here we review
39 how animal models permissive to *Lm*-host interactions allow deciphering some of the key
40 steps of the infectious process, from the intestinal lumen to the crossing of host barriers and
41 dissemination within the host. We also highlight recent investigations using tagged *Lm* and
42 clinically relevant strains that have shed light on within-host dynamics and the purifying
43 selection of *Lm* virulence factors. Studying *Lm* infection *in vivo* is a way forward to explore
44 host biology and unveil the mechanisms that have selected its capacity to closely associate
45 with its vertebrate hosts.

46 **Introduction**

47 *Listeria monocytogenes* (*Lm*) is a Gram-positive bacterium and the etiological agent of
48 listeriosis, one of the deadliest foodborne infections. Listeriosis manifests as bacteremia and
49 neurolisteriosis in elderly and immunocompromised patients, with a high fatality rate of 20 to
50 30% even with appropriate antibiotic treatment, and maternal-fetal infection in pregnant
51 women [1]. *Lm* is a highly diverse species that can be classified into clonal complexes (CCs)
52 of uneven virulence [2,3] (reviewed in [4]). The CCs most prevalent in food samples and under-
53 represented in clinical cases tend to be hypovirulent compared to reference strains, invading
54 less efficiently host tissues in a mouse model of infection, while they form more biofilm on
55 food-processing environments [2,5]. In contrast, CCs over-represented in clinical cases tend
56 to be hypervirulent compared to reference strains, colonize better the gut lumen, invade more
57 efficiently host tissues and lead to higher fecal shedding [2,5,6].

58

59 *Lm* is widespread in the environment where it can thrive as a saprophyte, and is able to infect
60 a wide range of hosts including vertebrates, from birds to mammals [7]. Importantly, *Lm* is
61 frequently isolated from domestic ruminants, in which it can lead to rhombencephalitis and
62 abortion, and be a source of contamination of dairy products [5,8-10]. Even though *Lm* host
63 range is wide, murine laboratory animals are not permissive to orally-acquired listeriosis, due
64 to the species specificities of *Lm* interactions with mammalian cells. Indeed, the *Lm* surface
65 protein internalin (InIA), which mediates *Lm* internalization in epithelial cells [11], interacts with
66 its receptor E-cadherin (Ecad) [12] in a species-specific manner that relies on the nature of its
67 16th amino-acid [13]. It is a proline in permissive species and a glutamic acid in non-permissive
68 species [13]. Mouse and rat Ecad exhibit a glutamic in position 16 and are therefore not able
69 to serve as a receptor for InIA, in contrast to human, guinea pig, rabbit and gerbil [13,14]. InIB,
70 another virulence factor of *Lm*, interacts with c-Met, the hepatocyte growth factor receptor [15],
71 in human, gerbils and mice but not guinea pigs and rabbits [16]. Ideally, human listeriosis
72 should therefore be studied in animals that are naturally permissive to both InIA and InIB, such
73 as ruminants, gerbils, or non-human primates [14,17,18]. However, ethical considerations and
74 the relative unavailability of molecular tools limits the use of these models. To circumvent
75 these limitations, two genetically modified mouse models have been generated: iFABP-hEcad
76 transgenic mice, which express human Ecad under the control of the enterocyte specific
77 promoter iFABP [19], and the KIE16P knock-in mouse line in which mouse Ecad is specifically
78 modified and harbors a proline at position 16 in place of a glutamic acid [14]. A "murinized"
79 *Lm* expressing a modified version of InIA (InIA^m) so that it interacts with mouse Ecad has also
80 been generated [20] to overcome InIA-Ecad species specificity. However, InIA^m happens to
81 interact with both mouse E-cad and N-cadherin, which modifies *Lm* cell tropism at the intestinal
82 level, leading to gut inflammation that delays and decreases *Lm* systemic dissemination [21].

83 Upon ingestion of contaminated food, *Lm* colonizes the gut lumen and can cross the intestinal
84 barrier. *Lm* has the ability to spread systemically to the spleen and liver, and breach the blood-
85 brain and placental barriers, leading to neurolisteriosis and maternal-fetal listeriosis,
86 respectively [22]. Recent studies have shown that *Lm* is shed back from infected tissues to
87 the gut lumen, in particular via the bile duct, favoring its release in the feces and the
88 environment [23,24]. Investigating how *Lm* crosses host barriers, amplifies in host tissues and
89 is shed back to the environment is critical to understand the pathophysiology of listeriosis and
90 the forces that have shaped its genome and selected its virulence factors.

91

92 ***Lm* adaptation to the host environment**

93 ***Sensing and adapting to the host*** — Once in the intestinal lumen, *Lm* has to adapt to the
94 physical and chemical conditions of the gut. Sensing its environment is key for *Lm* to switch
95 from saprophytism to a host-adapted phenotype [25]. The alternative sigma factor B (SigB) is
96 the major *Lm* transcriptional factor of the general stress response and is activated through the
97 stressosome, a multi-protein complex linked to the membrane by Prli42, a small protein
98 essential for stress sensing by the stressosome [26] (reviewed in [27]). SigB has been shown
99 to be required for *Lm* adaptation to the gut lumen [25]. It activates *bsh* transcription, which
100 gene product allows bacteria to hydrolyze bile salts [28], and *inlA* and *inlB* transcription [29].
101 These genes, as well as the major virulence genes *hly* (encoding Listeriolysin O, LLO)
102 and *actA* from *Listeria* pathogenicity island 1 (LIPI-1), are also under the control of the
103 transcriptional factor PrfA, which is itself regulated by SigB, and is key to allow *Lm* transition
104 from an extracellular to an intracellular environment (reviewed in [30]). *prfA* translation is
105 activated at 37°C via an RNA thermosensor in its 5'UTR [31]. Activation of PrfA also requires
106 the presence of its co-factor glutathione (GSH) synthesized by the host or the *Lm* glutathione
107 synthase GshF [32,33]. GSH synthesis by GshF requires sensing the intracellular
108 environment and host metabolites, as *Lm* is auxotrophic for cysteine, a precursor of GSH. It
109 has been recently shown that methylglyoxal, a toxic byproduct of metabolism produced by the
110 host and *Lm*, induces the expression of *gshF* [34]. The Opp *Lm* transporter imports peptides
111 from the host cell cytosol that provides cysteine for GSH synthesis [35]. Another ABC
112 transporter, TcyKLMN, is a cystine/cysteine importer also involved in GSH synthesis and
113 activation of PrfA in infected cells [36]. *Lm* can also adapt to the redox state of its
114 environment [37]. The transcriptional regulator Rex senses the ratio of reduced and oxidized
115 nicotinamide adenine dinucleotides (NADH/and NAD⁺). It represses the fermentative
116 metabolism and allows *Lm* to adapt to an intracellular oxygen-rich environment. Rex is
117 dispensable for gut lumen colonization but is involved in spleen, liver and gallbladder
118 infection [38].

119

120 **Interaction with the host microbiota** — The gut microbiota, which is constituted of >100
121 bacterial species and >10¹³ bacterial cells per individual [39], exerts a protective role against
122 orally acquired pathogens, a process called colonization resistance (reviewed in [40]).
123 Conditions associated with an immature or disbalanced microbiota (e.g. young age or after
124 antibiotic treatment) can increase host susceptibility to incoming pathogens such as group B
125 streptococcus [41], *Enterococcus faecium* [42], *Salmonella* [43] or *Clostridium difficile* [44,45].
126 The microbiota can act directly through competition for nutrients, the production of
127 bacteriocins, contact-dependent killing [46-48], or indirectly through stimulation of the host
128 immune system [49,50].

129 The gut microbiota also plays a protective role against *Lm* infection in mice [23,51]: microbiota
130 depletion by antibiotics increases susceptibility to *Lm*, but this effect can be rescued by a group
131 of four *Clostridia* species, potentially by directly inhibiting or killing *Lm* [51]. Depleting the
132 microbiota with antimicrobials can however also increase host protection against a second
133 infectious challenge. Indeed, it leads to an increase in tissue resident memory CD8+ T cells,
134 which protects the host against a second encounter with *Lm* [52]. It has also been shown that
135 antibiotic-resistant commensal *E. coli* can indirectly protect sensitive *Lm* from anti-bacterial
136 treatment, by favoring antibiotic degradation in the intestine [53]. The impact of microbiota
137 composition on listeriosis has also been observed in aged mice, in which age-related dysbiosis
138 favors *Lm* inflammation and infection [54].

139 Some *Lm* isolates, mostly belonging to Lineage I, also express bacteriocins which are active
140 on the host microbiota and potentially decrease colonization resistance. Two *Lm* bacteriocins
141 have been described so far: the bacteriocin LLS (encoded by LIPI-3), synthesized by strains
142 from hypervirulent CCs [55,56], which induces membrane permeabilization of Gram-positive
143 bacteria by direct contact [57] and Lmo2776, which targets *Prevotella* species, and is, for
144 reasons which are not fully understood, associated to a decrease in *Lm* intestinal colonization
145 [58] (Figure1).

146 *Lm* might also compete with the microbiota when it is shed back into the intestinal lumen from
147 host tissues after infection. Indeed, recent results show that *Lm*, but not its non-pathogenic
148 related species can establish asymptomatic carriage in humans and other animals, being
149 present in up to 10% of asymptomatic human stool samples. This process depends on the
150 composition of the microbiota: *Lm* abundance in feces positively correlates with the ratio of
151 abundance of (i) Firmicutes and (ii) Actinobacteria to Bacteroidetes phyla [59].

152 Considering the wide range of interactions between this model microorganism and the host
153 microbiota, *Lm* stands as a powerful model to further investigate the tripartite interplay
154 between foodborne pathogens, their host and microbiota.

155

156 **Intestinal barrier crossing**

157 **Transcytosis across goblet cells at the intestinal villus level** — *In vitro* studies have
158 demonstrated that *Lm* enters epithelial cells upon the interaction of InIA with its receptor E-
159 cadherin (Ecad) [11]. The critical role of InIA in crossing the intestinal barrier was shown *in*
160 *vivo* in animal models naturally permissive to InIA-Ecad interaction (guinea pig, gerbils) and in
161 genetically modified iFabp-hEcad and KIE16P mice [14,19]. However, Ecad forms *adherens*
162 junctions, which are located below tight junctions on polarized epithelia, and is therefore
163 inaccessible from the intestinal lumen. This apparent paradox was addressed by whole mount
164 tissue imaging, which showed that Ecad can be lumenally accessible around mucus-expelling
165 goblet cells [60]. Upon inoculation of *Lm* into the intestinal lumen, *Lm* specifically associates
166 with goblet cells and is transferred across these cells within vacuoles and is released in the
167 *lamina propria*. This translocation is solely dependent on InIA, and is in particular independent
168 of LLO and ActA, involved respectively in escape from the vacuole and intracytosolic
169 movement (Figure1). Moreover, the translocation of *Lm*-containing vacuole also requires host
170 microtubule dynamics and the exocytic machinery [60]. These results collectively indicate that
171 *Lm* breaches the intestinal epithelium by transcytosis through goblet cells [60]. The molecular
172 mechanism of *Lm* transcytosis has been studied in intestinal organoids in which *Lm* can be
173 microinjected. The advantage of intestinal organoids also referred to as “minigut” is that it
174 allows the differentiation in an *in vitro* context of goblet cells surrounded by classical
175 enterocytes, and that they are easily genetically amenable [61]. In this experimental setting,
176 *Lm* translocation across the intestinal epithelium can be imaged in real-time, and has been
177 shown to last less than 12 minutes [62]. *Lm*-containing vesicle remains associated with the
178 cell apex when endocytosis is inhibited, while transcytosis towards the cell basal pole requires
179 functional host microtubules, in line with *in vivo* studies [60,62]. Finally, in organoids
180 expressing a dominant-negative version of Rab11 (Rab11DN), *Lm* is stuck at the basal pole
181 of goblet cells, enwrapped with mucus material, and fails to finalize its translocation [62].
182 These results collectively indicate that *Lm* hijacks the recycling of its receptor Ecad to cross
183 the intestinal barrier through goblet cells [62] (Figure 1).

184

185 **Crossing of the intestinal barrier via M cells** — The gut-associated lymphoid tissue (GALT)
186 is distributed along the gastrointestinal tract. It consists of Peyer’s patches (PP) in the small
187 intestine, cecal and colonic patches, and isolated lymphoid follicles. These immune structures
188 sample luminal antigens and orchestrate the induction of mucosal immune responses.
189 Microfold cells (M cells) are specialized epithelial cells that overlay the GALT, which
190 phagocytic activity allows sampling luminal antigens.

191 *Lm* can cross PP through M cells in InIA-independent manner, and this has been shown to be
192 sufficient to trigger *Lm* intestinal tissue response to infection [63-65] (Figure 1). An *in vitro*
193 study has reported that M cell infection by *Lm* may also propagate to neighboring enterocytes

194 [66]. Once translocated *via* M-cells, *Lm* infects CX3CR1⁺ myeloid cells in PP, leading to the
195 expression of IL-12 and IL-23 and subsequent decrease in the number of mature goblet cells.
196 As a consequence, it locks InIA-dependent entry, while sensitizing the host to colitis [67].
197 Adaptive immune response to *Lm* at the PP level has been recently shown to be complement-
198 dependent. Indeed, lysozyme-expressing dendritic cells close to M cells in PPs express the
199 complement C5a receptor (C5aR), and induce *Lm*-specific CD8⁺ T cells response in a C5a-
200 dependent manner [68].

201 As indicated above, *Lm* expressing a murinized version of InIA (InIA^m) interacts not only with
202 mouse Ecad [20], but also with lumenally accessible N-cadherin expressed by villus M cells
203 [21,64]. This artefactual entry elicits host immune responses at the villus level and epithelial
204 damage, which are not observed with wild-type *Lm* infection [21]. This indicates a role for villus
205 M cells in the induction of immune responses, in contrast to goblet cells [21,65]. Comparison
206 of the mechanisms by which *Lm*-InIA^m- and wt-*Lm*-dependent host responses are either
207 triggered or prevented is therefore a way forward to investigate how host responses are
208 differentially induced by M cells and goblet cells.

209

210 **Systemic dissemination**

211 ***Within-host dynamics of *Lm* infection*** — Once *Lm* has crossed the intestinal barrier, it
212 spreads to inner organs (Figure 2). The standard method to follow a bacterial infection is to
213 dissect animals at sequential time points post inoculation and count CFUs, and also to image
214 bacteria in host tissues [69]. Use of bioluminescent bacteria allows following qualitatively and
215 over time *Lm* infection within individual animals [14,70,71]. In order to follow and model the
216 spatiotemporal dynamics of infection within the host, several methods based on tagged clones
217 have been developed (reviewed in [72]).

218 *Lm* within-host dynamics has been studied based on sequence tag-based analysis of
219 microbial populations (STAMP), a methodology initially set up to study *Vibrio cholerae*
220 intestinal phase of infection [73]. This technique makes use of hundreds of individually tagged
221 bacterial clones, whose numbers and relative proportions are measured over time in various
222 anatomical locations by high throughput DNA sequencing. This, combined to mathematical
223 modelling allows evaluating the barrier exerted by each organ (bottleneck effect), by analyzing
224 the clonality and the number of bacteria from the inoculum that reach the organs (founding
225 population). It also allows comparing clones retrieved from various host organs and retrace
226 their dissemination routes along the infectious process.

227 The modelling of *Lm* infection was performed using STAMP with the 10403S reference strain
228 modified so that it expressed InIA^m, upon oral and intravenous (iv) inoculation. The founding
229 populations in liver and spleen were relatively high, but decreased drastically in the
230 gallbladder, which collects the bile produced by the liver to release it in the duodenum, the

231 proximal part of the intestine. Comparison of the tags between the gallbladder and the gut
232 upon iv inoculation indicates that the gallbladder is a reservoir fueling *Lm* fecal shedding in
233 this model [24], a phenomenon which is dependent on both LLO and ActA, two core virulence
234 genes of *Lm* [3,23]. The observation of the low number of tags and the implication of LLO and
235 ActA in gallbladder-mediated shedding of *Lm* in the gut suggests that *Lm* release by the biliary
236 tract is involved in the purifying selection of virulence genes [3,23].

237

238 ***Infection of mesenteric lymph nodes and spleen*** — The mesenteric lymph nodes (MLN)
239 are lymphoid organs that drain lymph irrigating the intestinal mucosa. As such, they become
240 rapidly infected upon oral inoculation of *Lm* [19] (Figure 2). A recent study using *Lm* InIA^m
241 suggests that migration to and bacterial accumulation into MLN occurs in a dendritic cell- (DC)
242 dependent manner and triggers a robust CD8⁺ T cell response [74]. However, it remains to be
243 determined where *Lm* mostly disseminates from (intestinal villi vs. PPs vs. cecum vs. colon),
244 and if the infection route plays a role in host responses.

245 The spleen is the major lymphoid organ filtering the systemic circulation and plays a critical
246 role in controlling bloodborne infections (reviewed in [75]). The histological structure of the
247 spleen includes the red and white pulps and marginal zone (MZ), which contain different
248 populations of immune cells. Upon crossing the intestinal barrier, *Lm* disseminates rapidly
249 from the bloodstream to the spleen (Figure 2). It is taken up mainly by MZ macrophages.
250 Depletion of MZ macrophages leads to the spread of *Lm* to the red pulp and exacerbation of
251 the infection [76]. These cells are therefore crucial for early bacterial control and represent a
252 critical line of defense against *Lm*, in line with their strategic location in the spleen [77]. MZ
253 macrophages closely interact with MZ CD8 α^+ DCs to initiate *Lm* transfer to T cell zones and
254 induce effective adaptive immune responses, while the mechanism of *Lm* transmission from
255 MZ macrophages to DCs remains to be elucidated [77]. In infected phagocytes, *Lm* escape
256 from the vacuole induces the production of prostaglandin E₂ (PGE₂), which is necessary for
257 an effective T-cell priming [78]. Splenic DCs can also initiate innate immune responses by
258 inducing TNF and iNOS to clear bacteria through CCR2-dependent signaling [79].

259 While the spleen plays a major role in inducing protective immunity to *Lm*, splenectomized
260 mice are actually more resistant to infection and have less bacteria in the liver compared to
261 non-splenectomized controls [80]. This paradoxical phenotype reflects the fact that *Lm* takes
262 advantage of the splenic environment to increase its survival and replication and promote
263 infection. Indeed, *Lm* can grow exponentially in MZ CD8 α^+ DCs during the first 18 hours of
264 infection, and the lack of these cells leads to a rapid bacterial clearance in MZ [81]. This growth
265 is at least partly due to the release of the regulatory cytokine IL-10 upon *Lm* infection by MZ
266 B cells in the spleen. IL-10 exerts multiple suppressive effects on myeloid and T cells [82]. In

267 *Lm* infected spleen, IL-10 inhibits iNOS production and favors the bacterial burden in MZ
268 macrophages, which in turn transfer *Lm* to CD8 α^+ DCs, as described above. This leads to two
269 opposite effects: a high bacterial load in the spleen, but also a strong CD8 T⁺ cell response
270 induced by infected CD8 α^+ DCs [83]. In addition, *Lm* can also take advantage of IL-10
271 produced by regulatory NK cells to promote host susceptibility, by blocking the accumulation
272 and activation of inflammatory myeloid cells [84] [85].

273

274 **Liver invasion** — In the liver, *Lm* is rapidly taken up by tissue-resident macrophages called
275 Kupffer cells, leading to their rapid death [86]. This triggers monocyte recruitment and induces
276 a type-1 antimicrobial inflammatory response that controls the infection. In addition, Kupffer
277 cell death also induces secretion of IL-33 by hepatocytes, which induce IL-4 expression in
278 basophils that orchestrates the switch from an inflammatory type-1 to a type-2 response that
279 dampens inflammation, allowing the replacement of embryo derived Kupffer cells by myeloid-
280 derived macrophages and return to homeostasis [86].

281 As for the spleen, *Lm* may benefit from the immune response elicited in the liver to promote
282 infection. Indeed, it has been observed that mice lacking type I interferon receptor are
283 paradoxically more resistant to *Lm* infection, highlighting its role in promoting *Lm* pathogenesis
284 [87]. Further studies reviewed in [88] have investigated the mechanisms involved in this
285 atypical facilitating effect of type I IFN on infection. Recently, it has been shown that type-I IFN
286 expressed by myeloid cells impairs the degradation of *Lm* virulence factors (ActA and LLO) in
287 phagosomes, which promotes intracellular bacterial growth and cell-to-cell spread in the liver
288 [89,90]. It also inhibits proinflammatory cytokine signaling and immune cell recruitment *via* the
289 IFN-induced transmembrane protein 3 (IFITM3) [90].

290 Liver, as the producer of bile, also fuels the bile duct with *Lm* [23,24,70], even though *Lm*
291 clinically patent bile infection in human is extremely rare [91].

292

293 **Brain and placenta infection**

294 Neurolisteriosis and maternal-fetal listeriosis are the two most severe presentations of human
295 listeriosis [1,92,93].

296 **Brain infection** — Crossing of the blood-brain barrier is considered as the way by which *Lm*
297 enters the CNS in human, while retrograde nervous infection is likely to be at play in ruminants
298 [9]. The blood-brain barrier is actually highly efficient to prevent brain infection [24] and several
299 mechanisms of neuroinvasion have been proposed, using rodents as animal models. Infection
300 of monocytes by *Lm* is involved in brain infection with reference strains in mice non-permissive
301 to InlA-Ecad interaction [94,95]. Extracellular bacteria have also been proposed to cross the
302 blood-brain barrier, and InlF, expressed by some but not all *Lm* strains, has been reported to

303 be involved in brain infection in mice, by interacting with Vimentin present on the surface of
304 endothelial cells [96,97] (Figure 2).

305 Seminal studies on *Lm* pathogenesis have been performed with commonly used laboratory
306 reference strains EGD, 10403S, EGDe or L028. However, strains from the CCs most
307 associated to neurolisteriosis and maternal-fetal listeriosis (CC1, 4 and 6) are hypervirulent
308 compared to these reference *Lm*, which are actually very poorly neuroinvasive [2]. In contrast,
309 hypervirulent strains infect the brain and fetal-placental unit to a high level in humanized mice,
310 suggesting that factors specific to these strains are involved in neuro- and placental invasion
311 [2]. A comparative genomic analysis has shown that the LIPI-4 locus coding for a putative
312 cellobiose-family phosphotransferase system (PTS) is involved in hypervirulence and
313 neuroinvasiveness of CC4 [2] (Figure2). However, the mechanism by which LIPI-4 mediates
314 hypervirulence remains unknown and ongoing studies are under way to decipher the
315 neuroinvasion of *Lm*.

316

317 **Placenta infection** — The maternal-fetal interface is constituted by the syncytiotrophoblast,
318 a tight syncytial epithelial barrier of fetal origin in direct contact with the maternal blood
319 (reviewed in [98]). As for the intestine, InIA is involved in the crossing of this barrier by
320 interacting with Ecad apically accessible at the surface of the syncytiotrophoblast [99].
321 However, in contrast to the intestine, InIA acts in a conjugated manner with InIB for placental
322 invasion [14]. Indeed, InIA-dependent entry requires phosphoinositide 3-kinase (PI3-K)
323 activity, which is induced by InIB-c-Met interaction [64]. Goblet cells targeted by *Lm* exhibit a
324 detectable basal level of PI3-K activity (PI3K is involved in mucus production), which makes
325 InIB-c-Met interaction dispensable for intestinal barrier crossing [64]. In contrast, PI3-K activity
326 is low at the syncytiotrophoblast level, and InIB stimulates, *via* c-Met, PI3-K activation and
327 therefore allows InIA-dependent entry, leading to placental and fetus invasion [64]. InIP is
328 another *Lm* factor reported as involved in *Lm* crossing of the placental barrier, through its
329 interaction with Afadin and is also involved in other steps of listeriosis, including spleen and
330 liver infection [100,101]. As for the CNS infection, the LIPI-4 locus, which is associated with
331 CC4 hypervirulence, is also involved in placental invasion [2] (Figure 2).

332

333 **Concluding remarks**

334 As illustrated in this review, many steps of listeriosis, from ingestion of contaminated food,
335 intestinal barrier crossing to brain and placenta infection, have been thoroughly investigated
336 and deciphered *in vivo*. This allowed to deepen knowledge in infection biology, and also
337 revealed unexpected properties of host tissues (as previously reviewed in [4,22,102,103]).
338 However, many questions remain unanswered, for which animal models of listeriosis will be
339 instrumental, especially regarding the natural history of *Lm* association with its hosts and the

340 forces that have shaped and select its core and accessory genes. *Ex vivo* models such as
341 organoids will also help to further study the cell biology of the successive steps of *Lm* infection
342 of mammalian cells.

343 **Figure legends:**

344

345 **Figure 1: Interaction of *Lm* with the intestine**

346 *Lm* competes with the microbiota for survival by producing bacteriocins.

347 *Lm* crosses the intestinal barrier via mucus-producing goblet cells in villi and M cells in Peyer's
348 patches.

349

350 **Figure 2: *Lm* dissemination within the host**

351 *Lm* crosses the intestinal barrier, spreads systemically and crosses the placental and blood-
352 brain barriers to induce maternal-fetal listeriosis and neurolisteriosis, respectively. It is
353 released via the biliary tract back into the intestinal lumen.

354 *Lm* virulence factors are indicated in red, followed by their host receptor in black.

355 **Acknowledgements**

356 Research in the Biology of Infection Unit is supported by Institut Pasteur, Inserm, ANR, ERC,
357 LabEx IBEID and the Inception program. Marc Lecuit is a senior member of Institut
358 Universitaire de France. BioRender.com was used to create figures.

359

360 **References**

361 • **Annotated references:**

362 ** Maury MM, Bracq-Dieye H, Huang L, Vales G, Lavina M, Thouvenot P, Disson O,
363 Leclercq A, Brisse S, Lecuit M: **Hypervirulent *Listeria monocytogenes* clones'**
364 **adaption to mammalian gut accounts for their association with dairy products.** *Nat*
365 *Commun* 2019, **10**:2488.

366 This study demonstrates that hypervirulent *Lm* clones, which are most prevalent in dairy
367 products, are better adapted to the host gut than hypovirulent clones. In contrast,
368 hypovirulent clones are adapted to food industry environment, and more frequently found
369 in processed food.

370 * Moura A, Lefrancq N, Wirth T, Leclercq A, Borges V, Gilpin B, Dallman TJ, Frey J,
371 Franz E, Nielsen EM, et al.: **Emergence and global spread of *Listeria***
372 ***monocytogenes* main clinical clonal complex.** *Science Advances* 2021, **In press**
373 (under embargo).

374 This study analyses the phylogeography of the hypervirulent *Lm* clonal complex 1 (CC1).
375 It shows that the emergence and world spread of CC1 is linked to transatlantic livestock
376 and growth of cattle population in North America and Europe.

377 * Louie A, Zhang T, Becattini S, Waldor MK, Portnoy DA: **A multiorgan trafficking**
378 **circuit provides purifying selection of *Listeria monocytogenes* virulence genes.**
379 *mBio* 2019, **10**.

380 The study of *Lm* clonality *in vivo* shows that the biliary tract releases *Lm* in the gut, and
381 that LLO is involved in this process.

382 * Dorey A, Marinho C, Piveteau P, O'Byrne C: **Role and regulation of the stress**
383 **activated sigma factor sigma B (sigma(B)) in the saprophytic and host-associated**
384 **life stages of *Listeria monocytogenes*.** *Adv Appl Microbiol* 2019, **106**:1-48.

385 An extensive review on SigmaB

386 * Anaya-Sanchez A, Feng Y, Berude JC, Portnoy DA: **Detoxification of methylglyoxal**
387 **by the glyoxalase system is required for glutathione availability and virulence**
388 **activation in *Listeria monocytogenes*.** *PLoS Pathog* 2021, **17**:e1009819.

389 This study shows that methylglyoxal, a toxic byproduct of host and bacteria metabolisms,
390 can induce virulence factors *via* PrfA.

391 * Halsey CR, Glover RC, Thomason MK, Reniere ML: **The redox-responsive**
392 **transcriptional regulator Rex represses fermentative metabolism and is required**
393 **for *Listeria monocytogenes* pathogenesis.** *PLoS Pathog* 2021, **17**:e1009379.

394 This study illustrates the ability of *L. monocytogenes* to sense the redox state of the
395 infected cell and adapt to the intracellular environment.

396 ** Hafner L, Pichon M, Burucoa C, Nusser S, Moura A, Garcia-Garcera M, Lecuit M:
397 ***Listeria monocytogenes* faecal carriage is common and driven by microbiota.** *Nat*
398 *Commun* 2021, **In press** (under embargo).

399 This work reveals that 10% of humans are asymptomatic carriers of *Lm*, and that a
400 specific microbiota signature is involved in long-term colonization of the gut by *Lm*.

401 * Kim SH, Cho BH, Kim KS, Jang YS: **Complement C5a promotes antigen cross-**
402 **presentation by Peyer's patch monocyte-derived dendritic cells and drives a**
403 **protective CD8(+) T cell response.** *Cell Rep* 2021, **35**:108995.

404 This study demonstrates the role of the complement in inducing adaptive immune
405 response in Peyer's patches.

406 ** Liu D, Yin X, Olyha SJ, Nascimento MSL, Chen P, White T, Gowthaman U, Zhang T,
407 Gertie JA, Zhang B, et al.: **IL-10-dependent crosstalk between murine marginal zone**
408 **B cells, macrophages, and CD8alpha(+) dendritic cells promotes *Listeria***
409 ***monocytogenes* infection.** *Immunity* 2019, **51**:64-76 e67.

410 This study unveils the IL-10 dependent mechanism, by which CD8alpha(+) dendritic cells
411 paradoxically lead to T cell activation, while also favoring *L. monocytogenes* proliferation
412 in the spleen.

413 * McDougal CE, Morrow ZT, Christopher T, Kim S, Carter D, Stevenson DM, Amador-
414 Noguez D, Miller MJ, Sauer JD: **Phagocytes produce prostaglandin E2 in response**
415 **to cytosolic *Listeria monocytogenes*.** *PLoS Pathog* 2021, **17**:e1009493.

416 This study elucidates the link between vacuolar escape and induction on an adaptive
417 immune response.

418 * Tan JMJ, Garner ME, Regeimbal JM, Greene CJ, Marquez JDR, Ammendolia DA,
419 McCluggage ARR, Li T, Wu KJ, Cemina M, et al.: ***Listeria* exploits IFITM3 to suppress**
420 **antibacterial activity in phagocytes.** *Nat Commun* 2021, **12**:4999.

421 This study shows that the interferon-induced transmembrane protein 3 (IFITM3) is
422 required for phagosome escape and cell-to-cell spread, and plays a role in the type-I
423 Interferon-dependent enhanced susceptibility to *Lm*.

424 * Charlier C, Kermorvant-Duchemin E, Perrodeau E, Moura A, Maury MM, Bracq-Dieye
425 H, Thouvenot P, Vales G, Leclercq A, Ravaut P, et al.: **Neonatal listeriosis**
426 **presentation and outcome: a prospective study of 189 cases.** *Clin Infect Dis* 2021.

427 This prospective cohort study reports on the detailed clinical features of neonatal
428 listeriosis.

429

430

431 1. Charlier C, Perrodeau E, Leclercq A, Cazenave B, Pilmis B, Henry B, Lopes A, Maury MM,
432 Moura A, Goffinet F, et al.: **Clinical features and prognostic factors of listeriosis:**
433 **the MONALISA national prospective cohort study.** *Lancet Infect Dis* 2017, **17**:510-
434 519.

435 2. Maury MM, Tsai YH, Charlier C, Touchon M, Chenal-Francisque V, Leclercq A, Criscuolo
436 A, Gaultier C, Roussel S, Brisabois A, et al.: **Uncovering Listeria monocytogenes**
437 **hypervirulence by harnessing its biodiversity.** *Nat Genet* 2016, **48**:308-313.

438 3. Moura A, Criscuolo A, Pouseele H, Maury MM, Leclercq A, Tarr C, Bjorkman JT, Dallman
439 T, Reimer A, Enouf V, et al.: **Whole genome-based population biology and**
440 **epidemiological surveillance of Listeria monocytogenes.** *Nat Microbiol* 2016,
441 **2**:16185.

442 4. Disson O, Moura A, Lecuit M: **Making Sense of the Biodiversity and Virulence of Listeria**
443 **monocytogenes.** *Trends Microbiol* 2021, **29**:811-822.

444 5. Maury MM, Bracq-Dieye H, Huang L, Vales G, Lavina M, Thouvenot P, Disson O, Leclercq
445 A, Brisse S, Lecuit M: **Hypervirulent Listeria monocytogenes clones' adaption to**
446 **mammalian gut accounts for their association with dairy products.** *Nat Commun*
447 2019, **10**:2488.

448 6. Moura A, Lefrancq N, Wirth T, Leclercq A, Borges V, Gilpin B, Dallman TJ, Frey J, Franz E,
449 Nielsen EM, et al.: **Emergence and global spread of Listeria monocytogenes main**
450 **clinical clonal complex.** *Science Advances* 2021, **In press** (under embargo).

451 7. Yoshida T, Sugimoto T, Sato M, Hirai K: **Incidence of Listeria monocytogenes in wild**
452 **animals in Japan.** *J Vet Med Sci* 2000, **62**:673-675.

453 8. Dreyer M, Aguilar-Bultet L, Rupp S, Guldemann C, Stephan R, Schock A, Otter A,
454 Schupbach G, Brisse S, Lecuit M, et al.: **Listeria monocytogenes sequence type 1**
455 **is predominant in ruminant rhombencephalitis.** *Scientific reports* 2016, **6**:36419.

456 9. Oevermann A, Zurbriggen A, Vandeveld M: **Rhombencephalitis Caused by Listeria**
457 **monocytogenes in Humans and Ruminants: A Zoonosis on the Rise?** *Interdiscip*
458 *Perspect Infect Dis* 2010, **2010**:632513.

459 10. Palacios-Gorba C, Moura A, Leclercq A, Gomez-Martin A, Gomis J, Jimenez-Trigos E,
460 Moce ML, Lecuit M, Quereda JJ: **Listeria spp. Isolated from Tonsils of Wild Deer**
461 **and Boars: Genomic Characterization.** *Appl Environ Microbiol* 2021, **87**.

462 11. Gaillard JL, Berche P, Frehel C, Gouin E, Cossart P: **Entry of L. monocytogenes into**
463 **cells is mediated by internalin, a repeat protein reminiscent of surface antigens**
464 **from gram-positive cocci.** *Cell* 1991, **65**:1127-1141.

465 12. Mengaud J, Ohayon H, Gounon P, Mege RM, Cossart P: **E-cadherin is the receptor for**
466 **internalin, a surface protein required for entry of L. monocytogenes into**
467 **epithelial cells.** *Cell* 1996, **84**:923-932.

468 13. Lecuit M, Dramsi S, Gottardi C, Fedor-Chaiken M, Gumbiner B, Cossart P: **A single amino**
469 **acid in E-cadherin responsible for host specificity towards the human pathogen**
470 **Listeria monocytogenes.** *EMBO J* 1999, **18**:3956-3963.

471 14. Disson O, Grayo S, Huillet E, Nikitas G, Langa-Vives F, Dussurget O, Ragon M, Le
472 Monnier A, Babinet C, Cossart P, et al.: **Conjugated action of two species-specific**
473 **invasion proteins for fetoplacental listeriosis.** *Nature* 2008, **455**:1114-1118.

474 15. Shen Y, Naujokas M, Park M, Ireton K: **InIB-dependent internalization of Listeria is**
475 **mediated by the Met receptor tyrosine kinase.** *Cell* 2000, **103**:501-510.

476 16. Khelef N, Lecuit M, Bierne H, Cossart P: **Species specificity of the Listeria**
477 **monocytogenes InIB protein.** *Cell Microbiol* 2006, **8**:457-470.

478 17. Gitter M, Richardson C, Boughton E: **Experimental infection of pregnant ewes with**
479 **Listeria monocytogenes.** *Vet Rec* 1986, **118**:575-578.

480 18. Smith MA, Takeuchi K, Brackett RE, McClure HM, Raybourne RB, Williams KM, Babu US,
481 Ware GO, Broderson JR, Doyle MP: **Nonhuman primate model for Listeria**
482 **monocytogenes-induced stillbirths.** *Infect Immun* 2003, **71**:1574-1579.

- 483 19. Lecuit M, Vandormael-Pournin S, Lefort J, Huerre M, Gounon P, Dupuy C, Babinet C,
484 Cossart P: **A transgenic model for listeriosis: role of internalin in crossing the**
485 **intestinal barrier**. *Science* 2001, **292**:1722-1725.
- 486 20. Wollert T, Pasche B, Rochon M, Deppenmeier S, van den Heuvel J, Gruber AD, Heinz
487 DW, Lengeling A, Schubert WD: **Extending the host range of Listeria**
488 **monocytogenes by rational protein design**. *Cell* 2007, **129**:891-902.
- 489 21. Tsai YH, Disson O, Bierne H, Lecuit M: **Murinization of internalin extends its receptor**
490 **repertoire, altering Listeria monocytogenes cell tropism and host responses**.
491 *PLoS Pathog* 2013, **9**:e1003381.
- 492 22. Lecuit M: **Listeria monocytogenes, a model in infection biology**. *Cellular microbiology*
493 2020, **22**:e13186.
- 494 23. Louie A, Zhang T, Becattini S, Waldor MK, Portnoy DA: **A Multiorgan Trafficking Circuit**
495 **Provides Purifying Selection of Listeria monocytogenes Virulence Genes**. *mBio*
496 2019, **10**.
- 497 24. Zhang T, Abel S, Abel Zur Wiesch P, Sasabe J, Davis BM, Higgins DE, Waldor MK:
498 **Deciphering the landscape of host barriers to Listeria monocytogenes infection**.
499 *Proc Natl Acad Sci U S A* 2017, **114**:6334-6339.
- 500 25. Toledo-Arana A, Dussurget O, Nikitas G, Sesto N, Guet-Revillet H, Balestrino D, Loh E,
501 Gripenland J, Tiensuu T, Vaitkevicius K, et al.: **The Listeria transcriptional**
502 **landscape from saprophytism to virulence**. *Nature* 2009, **459**:950-956.
- 503 26. Impens F, Rolhion N, Radoshevich L, Becavin C, Duval M, Mellin J, Garcia Del Portillo F,
504 Pucciarelli MG, Williams AH, Cossart P: **N-terminomics identifies Prli42 as a**
505 **membrane miniprotein conserved in Firmicutes and critical for stressosome**
506 **activation in Listeria monocytogenes**. *Nat Microbiol* 2017, **2**:17005.
- 507 27. Dorey A, Marinho C, Piveteau P, O'Byrne C: **Role and regulation of the stress activated**
508 **sigma factor sigma B (sigma(B)) in the saprophytic and host-associated life**
509 **stages of Listeria monocytogenes**. *Adv Appl Microbiol* 2019, **106**:1-48.
- 510 28. Dussurget O, Cabanes D, Dehoux P, Lecuit M, Buchrieser C, Glaser P, Cossart P,
511 European Listeria Genome C: **Listeria monocytogenes bile salt hydrolase is a**
512 **PrfA-regulated virulence factor involved in the intestinal and hepatic phases of**
513 **listeriosis**. *Mol Microbiol* 2002, **45**:1095-1106.
- 514 29. Kim H, Marquis H, Boor KJ: **SigmaB contributes to Listeria monocytogenes invasion**
515 **by controlling expression of inlA and inlB**. *Microbiology (Reading)* 2005, **151**:3215-
516 3222.
- 517 30. Gaballa A, Guariglia-Oropeza V, Wiedmann M, Boor KJ: **Cross Talk between SigB and**
518 **PrfA in Listeria monocytogenes Facilitates Transitions between Extra- and**
519 **Intracellular Environments**. *Microbiol Mol Biol Rev* 2019, **83**.
- 520 31. Johansson J, Mandin P, Renzoni A, Chiaruttini C, Springer M, Cossart P: **An RNA**
521 **thermosensor controls expression of virulence genes in Listeria**
522 **monocytogenes**. *Cell* 2002, **110**:551-561.
- 523 32. Hall M, Grundstrom C, Begum A, Lindberg MJ, Sauer UH, Almqvist F, Johansson J, Sauer-
524 Eriksson AE: **Structural basis for glutathione-mediated activation of the virulence**
525 **regulatory protein PrfA in Listeria**. *Proc Natl Acad Sci U S A* 2016, **113**:14733-
526 14738.
- 527 33. Reniere ML, Whiteley AT, Hamilton KL, John SM, Lauer P, Brennan RG, Portnoy DA:
528 **Glutathione activates virulence gene expression of an intracellular pathogen**.
529 *Nature* 2015, **517**:170-173.
- 530 34. Anaya-Sanchez A, Feng Y, Berude JC, Portnoy DA: **Detoxification of methylglyoxal by**
531 **the glyoxalase system is required for glutathione availability and virulence**
532 **activation in Listeria monocytogenes**. *PLoS Pathog* 2021, **17**:e1009819.
- 533 35. Kryptou E, Scotti M, Grundstrom C, Oelker M, Luisi BF, Sauer-Eriksson AE, Vazquez-
534 Boland J: **Control of Bacterial Virulence through the Peptide Signature of the**
535 **Habitat**. *Cell Rep* 2019, **26**:1815-1827 e1815.

- 536 36. Brenner M, Friedman S, Haber A, Borovok I, Sigal N, Lewinson O, Herskovits AA: **Listeria**
537 **monocytogenes TcyKLMN cystine/cysteine transporter facilitates glutathione**
538 **synthesis and virulence gene expression.** *bioRxiv* 2021.
- 539 37. Ruhland BR, Reniere ML: **Sense and sensor ability: redox-responsive regulators in**
540 **Listeria monocytogenes.** *Curr Opin Microbiol* 2019, **47**:20-25.
- 541 38. Halsey CR, Glover RC, Thomason MK, Reniere ML: **The redox-responsive**
542 **transcriptional regulator Rex represses fermentative metabolism and is required**
543 **for Listeria monocytogenes pathogenesis.** *PLoS Pathog* 2021, **17**:e1009379.
- 544 39. Sender R, Fuchs S, Milo R: **Are We Really Vastly Outnumbered? Revisiting the Ratio**
545 **of Bacterial to Host Cells in Humans.** *Cell* 2016, **164**:337-340.
- 546 40. Buffie CG, Pamer EG: **Microbiota-mediated colonization resistance against intestinal**
547 **pathogens.** *Nat Rev Immunol* 2013, **13**:790-801.
- 548 41. Travier L, Alonso M, Andronico A, Hafner L, Disson O, Lledo PM, Cauchemez S, Lecuit
549 **M: Neonatal susceptibility to meningitis results from the immaturity of epithelial**
550 **barriers and gut microbiota.** *Cell Rep* 2021, **35**:109319.
- 551 42. Ubeda C, Bucci V, Caballero S, Djukovic A, Toussaint NC, Equinda M, Lipuma L, Ling L,
552 **Gobourne A, No D, et al.: Intestinal microbiota containing Barnesiella species**
553 **cures vancomycin-resistant Enterococcus faecium colonization.** *Infect Immun*
554 **2013, 81:965-973.**
- 555 43. Bohnhoff M, Miller CP: **Enhanced susceptibility to Salmonella infection in**
556 **streptomycin-treated mice.** *J Infect Dis* 1962, **111**:117-127.
- 557 44. Buffie CG, Jarchum I, Equinda M, Lipuma L, Gobourne A, Viale A, Ubeda C, Xavier J,
558 **Pamer EG: Profound alterations of intestinal microbiota following a single dose**
559 **of clindamycin results in sustained susceptibility to Clostridium difficile-**
560 **induced colitis.** *Infect Immun* 2012, **80**:62-73.
- 561 45. Hasegawa M, Kamada N, Jiao Y, Liu MZ, Nunez G, Inohara N: **Protective role of**
562 **commensals against Clostridium difficile infection via an IL-1beta-mediated**
563 **positive-feedback loop.** *J Immunol* 2012, **189**:3085-3091.
- 564 46. Basler M, Ho BT, Mekalanos JJ: **Tit-for-tat: type VI secretion system counterattack**
565 **during bacterial cell-cell interactions.** *Cell* 2013, **152**:884-894.
- 566 47. Kommineni S, Bretl DJ, Lam V, Chakraborty R, Hayward M, Simpson P, Cao Y, Bousounis
567 **P, Kristich CJ, Salzman NH: Bacteriocin production augments niche competition**
568 **by enterococci in the mammalian gastrointestinal tract.** *Nature* 2015, **526**:719-
569 **722.**
- 570 48. Rea MC, Sit CS, Clayton E, O'Connor PM, Whittal RM, Zheng J, Vederas JC, Ross RP,
571 **Hill C: Thuricin CD, a posttranslationally modified bacteriocin with a narrow**
572 **spectrum of activity against Clostridium difficile.** *Proc Natl Acad Sci U S A* 2010,
573 **107**:9352-9357.
- 574 49. Atarashi K, Honda K: **Microbiota in autoimmunity and tolerance.** *Curr Opin Immunol*
575 **2011, 23:761-768.**
- 576 50. Ivanov, II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, Wei D, Goldfarb KC, Santee
577 **CA, Lynch SV, et al.: Induction of intestinal Th17 cells by segmented filamentous**
578 **bacteria.** *Cell* 2009, **139**:485-498.
- 579 51. Becattini S, Littmann ER, Carter RA, Kim SG, Morjaria SM, Ling L, Gyaltsen Y, Fontana
580 **E, Taur Y, Leiner IM, et al.: Commensal microbes provide first line defense against**
581 **Listeria monocytogenes infection.** *J Exp Med* 2017, **214**:1973-1989.
- 582 52. Becattini S, Littmann ER, Seok R, Amoretti L, Fontana E, Wright R, Gjonbalaj M, Leiner
583 **IM, Plitas G, Hohl TM, et al.: Enhancing mucosal immunity by transient microbiota**
584 **depletion.** *Nat Commun* 2020, **11**:4475.
- 585 53. Gjonbalaj M, Keith JW, Do MH, Hohl TM, Pamer EG, Becattini S: **Antibiotic Degradation**
586 **by Commensal Microbes Shields Pathogens.** *Infect Immun* 2020, **88**.
- 587 54. Alam MS, Gangiredla J, Hasan NA, Barnaba T, Tartera C: **Aging-Induced Dysbiosis of**
588 **Gut Microbiota as a Risk Factor for Increased Listeria monocytogenes Infection.**
589 *Front Immunol* 2021, **12**:672353.

- 590 55. Quereda JJ, Dussurget O, Nahori MA, Ghozlane A, Volant S, Dillies MA, Regnault B,
591 Kennedy S, Mondot S, Villoing B, et al.: **Bacteriocin from epidemic *Listeria* strains**
592 **alters the host intestinal microbiota to favor infection.** *Proc Natl Acad Sci U S A*
593 2016, **113**:5706-5711.
- 594 56. Quereda JJ, Meza-Torres J, Cossart P, Pizarro-Cerda J: **Listeriolysin S: A bacteriocin**
595 **from epidemic *Listeria monocytogenes* strains that targets the gut microbiota.**
596 *Gut Microbes* 2017, **8**:384-391.
- 597 57. Meza-Torres J, Lelek M, Quereda JJ, Sachse M, Manina G, Ershov D, Tinevez JY,
598 Radoshevich L, Maudet C, Chaze T, et al.: **Listeriolysin S: A bacteriocin from**
599 ***Listeria monocytogenes* that induces membrane permeabilization in a contact-**
600 **dependent manner.** *Proc Natl Acad Sci U S A* 2021, **118**.
- 601 58. Rolhion N, Chassaing B, Nahori MA, de Bodt J, Moura A, Lecuit M, Dussurget O, Berard
602 M, Marzorati M, Fehlner-Peach H, et al.: **A *Listeria monocytogenes* Bacteriocin Can**
603 **Target the Commensal *Prevotella copri* and Modulate Intestinal Infection.** *Cell*
604 *Host Microbe* 2019, **26**:691-701 e695.
- 605 59. Hafner L, Pichon M, Burucoa C, Nusser S, Moura A, Garcia-Garcera M, Lecuit M: ***Listeria***
606 ***monocytogenes* faecal carriage is common and driven by microbiota.** *Nat*
607 *Commun* 2021, **In press** (under embargo).
- 608 60. Nikitas G, Deschamps C, Disson O, Niault T, Cossart P, Lecuit M: **Transcytosis of**
609 ***Listeria monocytogenes* across the intestinal barrier upon specific targeting of**
610 **goblet cell accessible E-cadherin.** *J Exp Med* 2011, **208**:2263-2277.
- 611 61. Nigro G, Hanson M, Fevre C, Lecuit M, Sansonetti PJ: **Intestinal Organoids as a Novel**
612 **Tool to Study Microbes-Epithelium Interactions.** *Methods Mol Biol* 2019, **1576**:183-
613 194.
- 614 62. Kim M, Fevre C, Lavina M, Disson O, Lecuit M: **Live Imaging Reveals *Listeria* Hijacking**
615 **of E-Cadherin Recycling as It Crosses the Intestinal Barrier.** *Curr Biol* 2021,
616 **31**:1037-1047 e1034.
- 617 63. Bregenholt S, Berche P, Brombacher F, Di Santo JP: **Conventional alpha beta T cells**
618 **are sufficient for innate and adaptive immunity against enteric *Listeria***
619 ***monocytogenes*.** *J Immunol* 2001, **166**:1871-1876.
- 620 64. Gessain G, Tsai YH, Travier L, Bonazzi M, Grayo S, Cossart P, Charlier C, Disson O,
621 Lecuit M: **PI3-kinase activation is critical for host barrier permissiveness to**
622 ***Listeria monocytogenes*.** *J Exp Med* 2015, **212**:165-183.
- 623 65. Lecuit M, Sonnenburg JL, Cossart P, Gordon JI: **Functional genomic studies of the**
624 **intestinal response to a foodborne enteropathogen in a humanized gnotobiotic**
625 **mouse model.** *J Biol Chem* 2007, **282**:15065-15072.
- 626 66. Rey C, Chang YY, Latour-Lambert P, Varet H, Proux C, Legendre R, Coppee JY, Enninga
627 J: **Transcytosis subversion by M cell-to-enterocyte spread promotes *Shigella***
628 ***flexneri* and *Listeria monocytogenes* intracellular bacterial dissemination.** *PLoS*
629 *Pathog* 2020, **16**:e1008446.
- 630 67. Disson O, Bleriot C, Jacob JM, Serafini N, Dulauroy S, Jouvion G, Fevre C, Gessain G,
631 Thouvenot P, Eberl G, et al.: **Peyer's patch myeloid cells infection by *Listeria***
632 **signals through gp38(+) stromal cells and locks intestinal villus invasion.** *J Exp*
633 *Med* 2018, **215**:2936-2954.
- 634 68. Kim SH, Cho BH, Kim KS, Jang YS: **Complement C5a promotes antigen cross-**
635 **presentation by Peyer's patch monocyte-derived dendritic cells and drives a**
636 **protective CD8(+) T cell response.** *Cell Rep* 2021, **35**:108995.
- 637 69. Disson O, Nikitas G, Grayo S, Dussurget O, Cossart P, Lecuit M: **Modeling human**
638 **listeriosis in natural and genetically engineered animals.** *Nat Protoc* 2009, **4**:799-
639 810.
- 640 70. Hardy J, Francis KP, DeBoer M, Chu P, Gibbs K, Contag CH: **Extracellular replication**
641 **of *Listeria monocytogenes* in the murine gall bladder.** *Science* 2004, **303**:851-853.
- 642 71. Ur Rahman S, Stanton M, Casey PG, Spagnuolo A, Bensi G, Hill C, Francis KP, Tangney
643 M, Gahan CGM: **Development of a Click Beetle Luciferase Reporter System for**

- 644 **Enhanced Bioluminescence Imaging of *Listeria monocytogenes*: Analysis in**
645 **Cell Culture and Murine Infection Models.** *Front Microbiol* 2017, **8**:1797.
- 646 72. Hausmann A, Hardt WD: **Elucidating host-microbe interactions in vivo by studying**
647 **population dynamics using neutral genetic tags.** *Immunology* 2021, **162**:341-356.
- 648 73. Abel S, Abel zur Wiesch P, Chang HH, Davis BM, Lipsitch M, Waldor MK: **Sequence tag-**
649 **based analysis of microbial population dynamics.** *Nat Methods* 2015, **12**:223-226,
650 223 p following 226.
- 651 74. Imperato JN, Xu D, Romagnoli PA, Qiu Z, Perez P, Khairallah C, Pham QM, Andrusaite
652 A, Bravo-Blas A, Milling SWF, et al.: **Mucosal CD8 T Cell Responses Are Shaped**
653 **by Batf3-DC After Foodborne *Listeria monocytogenes* Infection.** *Front Immunol*
654 2020, **11**:575967.
- 655 75. Lewis SM, Williams A, Eisenbarth SC: **Structure and function of the immune system**
656 **in the spleen.** *Sci Immunol* 2019, **4**.
- 657 76. Aichele P, Zinke J, Grode L, Schwendener RA, Kaufmann SH, Seiler P: **Macrophages of**
658 **the splenic marginal zone are essential for trapping of blood-borne particulate**
659 **antigen but dispensable for induction of specific T cell responses.** *J Immunol*
660 2003, **171**:1148-1155.
- 661 77. Perez OA, Yeung ST, Vera-Licona P, Romagnoli PA, Samji T, Ural BB, Maher L, Tanaka
662 M, Khanna KM: **CD169(+) macrophages orchestrate innate immune responses by**
663 **regulating bacterial localization in the spleen.** *Sci Immunol* 2017, **2**.
- 664 78. McDougal CE, Morrow ZT, Christopher T, Kim S, Carter D, Stevenson DM, Amador-
665 Noguez D, Miller MJ, Sauer JD: **Phagocytes produce prostaglandin E2 in response**
666 **to cytosolic *Listeria monocytogenes*.** *PLoS Pathog* 2021, **17**:e1009493.
- 667 79. Serbina NV, Salazar-Mather TP, Biron CA, Kuziel WA, Pamer EG: **TNF/iNOS-producing**
668 **dendritic cells mediate innate immune defense against bacterial infection.**
669 *Immunity* 2003, **19**:59-70.
- 670 80. Skamene E, Chayasirisobhon W: **Enhanced resistance to *Listeria monocytogenes* in**
671 **splenectomized mice.** *Immunology* 1977, **33**:851-858.
- 672 81. Edelson BT, Bradstreet TR, Hildner K, Carrero JA, Frederick KE, Kc W, Belizaire R, Aoshi
673 T, Schreiber RD, Miller MJ, et al.: **CD8alpha(+) dendritic cells are an obligate**
674 **cellular entry point for productive infection by *Listeria monocytogenes*.** *Immunity*
675 2011, **35**:236-248.
- 676 82. Ouyang W, O'Garra A: **IL-10 Family Cytokines IL-10 and IL-22: from Basic Science to**
677 **Clinical Translation.** *Immunity* 2019, **50**:871-891.
- 678 83. Liu D, Yin X, Olyha SJ, Nascimento MSL, Chen P, White T, Gowthaman U, Zhang T,
679 Gertie JA, Zhang B, et al.: **IL-10-Dependent Crosstalk between Murine Marginal**
680 **Zone B Cells, Macrophages, and CD8alpha(+) Dendritic Cells Promotes *Listeria***
681 ***monocytogenes* Infection.** *Immunity* 2019, **51**:64-76 e67.
- 682 84. Clark SE, Schmidt RL, McDermott DS, Lenz LL: **A Batf3/Nlrp3/IL-18 Axis Promotes**
683 **Natural Killer Cell IL-10 Production during *Listeria monocytogenes* Infection.**
684 *Cell Rep* 2018, **23**:2582-2594.
- 685 85. Clark SE, Filak HC, Guthrie BS, Schmidt RL, Jamieson A, Merkel P, Knight V, Cole CM,
686 Raulet DH, Lenz LL: **Bacterial Manipulation of NK Cell Regulatory Activity**
687 **Increases Susceptibility to *Listeria monocytogenes* Infection.** *PLoS Pathog* 2016,
688 **12**:e1005708.
- 689 86. Bleriot C, Dupuis T, Jouvion G, Eberl G, Disson O, Lecuit M: **Liver-resident macrophage**
690 **necroptosis orchestrates type 1 microbicidal inflammation and type-2-mediated**
691 **tissue repair during bacterial infection.** *Immunity* 2015, **42**:145-158.
- 692 87. Auerbuch V, Brockstedt DG, Meyer-Morse N, O'Riordan M, Portnoy DA: **Mice lacking the**
693 **type I interferon receptor are resistant to *Listeria monocytogenes*.** *J Exp Med*
694 2004, **200**:527-533.
- 695 88. Dussurget O, Bierne H, Cossart P: **The bacterial pathogen *Listeria monocytogenes***
696 **and the interferon family: type I, type II and type III interferons.** *Front Cell Infect*
697 *Microbiol* 2014, **4**:50.

- 698 89. Osborne SE, Sit B, Shaker A, Currie E, Tan JM, van Rijn J, Higgins DE, Brumell JH: **Type**
699 **I interferon promotes cell-to-cell spread of Listeria monocytogenes.** *Cell*
700 *Microbiol* 2017, **19**.
- 701 90. Tan JMJ, Garner ME, Regeimbal JM, Greene CJ, Marquez JDR, Ammendolia DA,
702 McCluggage ARR, Li T, Wu KJ, Cemma M, et al.: **Listeria exploits IFITM3 to**
703 **suppress antibacterial activity in phagocytes.** *Nat Commun* 2021, **12**:4999.
- 704 91. Charlier C, Fevre C, Travier L, Cazenave B, Bracq-Dieye H, Podevin J, Assomany D,
705 Guilbert L, Bossard C, Carpentier F, et al.: **Listeria monocytogenes-associated**
706 **biliary tract infections: a study of 12 consecutive cases and review.** *Medicine*
707 2014, **93**:e105.
- 708 92. Charlier C, Kermorvant-Duchemin E, Perrodeau E, Moura A, Maury MM, Bracq-Dieye H,
709 Thouvenot P, Vales G, Leclercq A, Ravaud P, et al.: **Neonatal listeriosis**
710 **presentation and outcome: a prospective study of 189 cases.** *Clin Infect Dis* 2021.
- 711 93. Charlier C, Poiree S, Delavaud C, Khoury G, Richaud C, Leclercq A, Helenon O, Lecuit
712 M, Group MS: **Imaging of Human Neurolisteriosis: A Prospective Study of 71**
713 **Cases.** *Clin Infect Dis* 2018, **67**:1419-1426.
- 714 94. Drevets DA, Jelinek TA, Freitag NE: **Listeria monocytogenes-infected phagocytes can**
715 **initiate central nervous system infection in mice.** *Infect Immun* 2001, **69**:1344-
716 1350.
- 717 95. Join-Lambert OF, Ezine S, Le Monnier A, Jaubert F, Okabe M, Berche P, Kayal S: **Listeria**
718 **monocytogenes-infected bone marrow myeloid cells promote bacterial invasion**
719 **of the central nervous system.** *Cell Microbiol* 2005, **7**:167-180.
- 720 96. Ghosh P, Halvorsen EM, Ammendolia DA, Mor-Vaknin N, O'Riordan MXD, Brumell JH,
721 Markovitz DM, Higgins DE: **Invasion of the Brain by Listeria monocytogenes Is**
722 **Mediated by InlF and Host Cell Vimentin.** *mBio* 2018, **9**.
- 723 97. Bastounis EE, Yeh YT, Theriot JA: **Matrix stiffness modulates infection of endothelial**
724 **cells by Listeria monocytogenes via expression of cell surface vimentin.** *Mol Biol*
725 *Cell* 2018, **29**:1571-1589.
- 726 98. Charlier C, Disson O, Lecuit M: **Maternal-neonatal listeriosis.** *Virulence* 2020, **11**:391-
727 397.
- 728 99. Lecuit M, Nelson DM, Smith SD, Khun H, Huerre M, Vacher-Lavenu MC, Gordon JI,
729 Cossart P: **Targeting and crossing of the human maternofetal barrier by Listeria**
730 **monocytogenes: role of internalin interaction with trophoblast E-cadherin.** *Proc*
731 *Natl Acad Sci U S A* 2004, **101**:6152-6157.
- 732 100. Faralla C, Bastounis EE, Ortega FE, Light SH, Rizzuto G, Gao L, Marciano DK, Nocadello
733 S, Anderson WF, Robbins JR, et al.: **Listeria monocytogenes InlP interacts with**
734 **afadin and facilitates basement membrane crossing.** *PLoS Pathog* 2018,
735 **14**:e1007094.
- 736 101. Faralla C, Rizzuto GA, Lowe DE, Kim B, Cooke C, Shioh LR, Bakardjiev AI: **InlP, a New**
737 **Virulence Factor with Strong Placental Tropism.** *Infect Immun* 2016, **84**:3584-3596.
- 738 102. Maudet C, Levallois S, Disson O, Lecuit M: **Innate immune responses to Listeria in**
739 **vivo.** *Curr Opin Microbiol* 2021, **59**:95-101.
- 740 103. Radoshevich L, Cossart P: **Listeria monocytogenes: towards a complete picture of**
741 **its physiology and pathogenesis.** *Nature reviews. Microbiology* 2018, **16**:32-46.
- 742



