



**HAL**  
open science

## Innate immune responses to *Listeria in vivo*

Claire Maudet, Sylvain Levallois, Olivier Disson, Marc Lecuit

► **To cite this version:**

Claire Maudet, Sylvain Levallois, Olivier Disson, Marc Lecuit. Innate immune responses to *Listeria in vivo*. *Current Opinion in Microbiology*, 2021, 59, pp.95-101. 10.1016/j.mib.2020.11.006 . pasteur-03276950

**HAL Id: pasteur-03276950**

**<https://pasteur.hal.science/pasteur-03276950>**

Submitted on 9 Jul 2021

**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

# Innate immune responses to *Listeria in vivo*

Claire Maudet<sup>1,2</sup>, Sylvain Levallois<sup>1,2,3</sup>, Olivier Disson<sup>1,2</sup>, Marc Lecuit<sup>1,2,3,4,5,\*</sup>

<sup>1</sup> Institut Pasteur, Biology of Infection Unit, Inserm U1117, 75015, Paris, France

<sup>2</sup> Inserm U1117, 75015, Paris, France

<sup>3</sup> Université de Paris, 75006, Paris, France

<sup>4</sup> National Reference Centre and WHO Collaborating Centre *Listeria*, Institut Pasteur, 75015, Paris, France

<sup>5</sup> Necker-Enfants Malades University Hospital, Division of Infectious Diseases and Tropical Medicine, APHP, Institut Imagine, 75006, Paris, France

\* Correspondence to: [marc.lecuit@pasteur.fr](mailto:marc.lecuit@pasteur.fr)

## Abstract

*Listeria monocytogenes* (*Lm*) is a foodborne bacterial pathogen that causes listeriosis, a severe infection that manifests as bacteremia and meningo-encephalitis mostly in immunocompromised individuals, and maternal-fetal infection. A critical pathogenic determinant of *Lm* relies on its ability to actively cross the intestinal barrier, disseminate systemically and cross the blood-brain and placental barriers. Here we illustrate how *Lm* both evades innate immunity, favoring its dissemination in host tissues, and triggers innate immune defenses that participate to its control.

## Highlights

- *Lm* has evolved a propensity to evade innate immune defenses.
- The intestinal phase of listeriosis is mostly silent.
- *Lm* placental infection triggers innate immune responses that can alter the immune balance needed for placental fetal survival and development.
- Little is known regarding *Lm* innate immune responses in the CNS and their impact on infection and its control.

## Introduction

*Listeria monocytogenes* (*Lm*) is a Gram-positive facultative intracellular bacterial pathogen. It causes listeriosis, a severe foodborne infection leading to bacteremia and meningo-encephalitis, particularly in immunocompromised individuals, and mother-to-child infections [1-4]. Upon ingestion of contaminated food, *Lm* crosses the intestinal barrier. This process is clinically silent or manifests as mild gastroenteritis. *Lm* can then disseminate systemically and can actively cross the blood-brain and placental barriers, thereby infecting the central nervous system (CNS) and foetal-placental unit, respectively [2,3].

*Lm* crossing of the intestinal barrier requires the expression of internalin (InIA) on *Lm* surface, which mediates, upon the interaction with its receptor E-cadherin (Ecad) [5-7], its translocation across mucus-secreting goblet cells (GCs) of intestinal villi [8,9]. The conjugated action of InIA and InIB, another *Lm* surface protein whose receptor is the hepatocyte growth factor receptor Met [10], is required for *Lm* crossing of the placental barrier [11,12]. The interaction of InIA and InIB with their respective receptors are species-specific: InIA can interact with human, guinea pig and gerbil Ecad but not with mouse or rat Ecad [7,13], while InIB can interact with human, mouse and gerbil Met receptor but not with guinea pig or rabbit Met [10,14].

Because of the species-specificity of InIA-Ecad interaction, most studies aimed at deciphering innate immune responses to *Lm* in mice have been performed upon intravenous inoculation and thus focused on listeriosis systemic phase [15-17]. To circumvent InIA-Ecad species-specificity, our lab developed humanized mouse lines expressing human Ecad or a humanized E16P mouse Ecad, allowing the study of human listeriosis in mouse models permissive to InIA [9,11]. Wollert et al. also “murinized” InIA (InIA<sup>m</sup>) so that it can interact with mouse Ecad, providing an alternative tool to study mouse *Lm* infection at the gut and placenta levels [18,19]. However, InIA<sup>m</sup> also interacts with mouse N-cadherin, and this alters *Lm* cell tropism and host responses [18,19].

*Lm* is a prototypic inducer of the cellular adaptive responses, whose antigen-specific effectors are cytotoxic CD8<sup>+</sup> T cells [15,20]. Innate immune responses also play a role in modulating the efficiency of adaptive cellular immune responses [21]. Deciphering innate immune responses to *Lm*, and their impact on its dissemination and persistence in host tissues is important to fully decrypt the pathophysiology of listeriosis.

## Innate immune responses at the gut level

In contrast to other enteropathogens such as *Shigella* or *Salmonella* [22,23], and consistent with the paucity of intestinal symptoms in patients with listeriosis, *Lm* does not induce overt inflammation in the gut [1,24]. Moreover, oral infection with *Lm* leads to little if any barrier damages [9,18,24].

On top of the antibacterial activity of stomach acidity and biliary salts, *Lm* is faced upon ingestion to the gut microbiota which exerts a colonization resistance effect through competition for space, food and by producing bacteriocins that act as antimicrobial peptides [25]. Paneth cells and intestinal epithelial cells (IECs) also produce antimicrobial peptides such as the bactericidal lectin RegIII $\gamma$ , in a MyD88 dependent manner [26-28], and some alpha-defensins like cryptidins, in a NOD2-dependent manner [29]. These peptides accumulate in the mucus layer, killing *Lm* before it can reach the intestinal villus surface. Mucus also constitutes a physical barrier that prevents *Lm* from reaching the intestine cell wall and its thickness is controlled by innate immune pathways. Indeed, upon infection, type 3 innate lymphoid cells (ILC3) signal via lymphotoxin- $\beta$  to GCs, leading to mucus secretion that protects epithelial cells [30].

*Lm* has two intestinal portals of entry: one is specific and relies on active InIA-dependent cell targeting of GCs cells, which express lumenally-accessible Ecad [8], and one is non-specific and relies on the phagocytic activity of M cells in Peyer's patches (PPs) (Figure 1). Crossing of GCs by *Lm* has been shown to occur *via* transcytosis, and to be rapid [8]. That *Lm* does not seem to exit the vacuole in these cells may be due to a lack of time for LLO to lyse the vacuole, a too low level of LLO expression and/or activity, as the gamma-interferon-inducible lysosomal thiol reductase GILT necessary to activate LLO is not expressed fast enough [31] and/or at a sufficient level in those cells [32]. This is expected to account for the almost complete absence of InIA-dependent intestinal tissue response, considering the limited capacity of *Lm* to activate intracytosolic PRRs during intravacuolar transport [8,24]. Moreover, *Lm* peptidoglycan N-deacetylation by *pgdA* and O-acetylation by *oatA* also mediates *Lm* resistance and evasion from innate immune defenses [33,34] together with InIC and InIH, which dampen NF- $\kappa$ B signaling and IL-6 production, respectively [35,36]. Accordingly, neutrophils are only very modestly recruited in the intestinal villus *lamina propria* upon oral infection with *Lm* [18]. Indeed, host responses to *Lm* in the gut are

fully dependent on the infection of PPs, in an LLO-dependent and InlA-independent manner [24]. These conclusions have been drawn from experiments involving reference laboratory strains, and further studies with clinically-relevant strains are therefore needed to determine their relevance to human listeriosis [37].

Once translocated across PPs' M cells, *Lm* infects professional phagocytes, in particular CX3CR1<sup>+</sup> macrophages, and reaches their cytoplasm through the action of the pore-forming toxin LLO [38]. In response to *Lm* infection of PPs, CX3CR1<sup>+</sup> cells express IL-12, leading to the production of IFN $\gamma$  by small intestine NK cells and ILC1, in a STAT4-dependent manner [39], inducing a local inflammatory response and the recruitment of neutrophils and monocytes that will control the infection [40]. IFN $\gamma$  is a critical cytokine involved in host response to *Lm*, most likely by enhancing bactericidal activities of myeloid cells [41,42]. Inhibiting its action, by a blocking antibody or gene knock-out, renders mice highly susceptible to orally acquired listeriosis in mice non permissive to InlA, in which *Lm* enters host tissues exclusively through PP [38,40]. Infected PPs' CX3CR1<sup>+</sup> cells also express IL-23, triggering to the production of IL-22 by ILC3s [38-40] and IL-11 by GP38<sup>+</sup> stromal cells, which were recently identified as participating in innate immune responses in the gut [38]. The conjugated activation of STAT1 by IFN $\gamma$  and STAT3 by IL-22 and IL-11 in the intestinal epithelium leads to an accelerated IEC renewal and a consequent decrease in the number of mature GCs, thus limiting *Lm* InlA-dependent translocation across these cells and the resulting systemic dissemination [38] (Figure 1). This reveals an unsuspected functional link between the sensing of *Lm* infection at the PPs and the inhibition of *Lm* entry at the villus level. This innate immune response towards *Lm* has a cost for the host, since IL-22 and IL-11 synthesis in the colon tissue upon *Lm* infection [38,39] leads to a decrease in mucus thickness, and a corresponding increase in host susceptibility to colitis [38]. IFN $\gamma$  has been shown to control mucus secretion upon infection by other pathogens such as *Salmonella* [43-45] and *Citrobacter rodentium* [46]. However, since *Lm* crosses the intestinal barrier through GCs, IFN $\gamma$  also has a specific effect on *Lm* entry, by locking its portal of entry [38]. Once *Lm* has reached the *lamina propria*, it can disseminate to the liver and spleen, and in the pregnant host to the placenta.

## Innate immune responses at the placenta level

Maternal-neonatal listeriosis has very severe consequences on pregnancy outcome, as 95% result in fetal/neonatal adverse effects [1]. It occurs mostly sporadically [1,47], yet large outbreaks linked to a single contaminating source can occur in countries where listeriosis surveillance is not as strict as in Western countries. The largest outbreak reported so far occurred in South Africa in 2017, where almost 500 cases of maternal-neonatal listeriosis were reported (50% of total cases) [48]. Infection is thought to occur at any time during pregnancy but is most often diagnosed in its second and third trimesters [49]. Depending on pregnancy stage, it can lead to abortion, stillbirth, preterm labor and/or fetal/neonatal infection [1,47]. Almost no maternal symptoms are present before fetal-placental infection manifests [1].

The placenta is made of fetal cells that organize a selective barrier that either blocks or actively transports the molecules needed for fetal growth and development. It blocks maternal and fetal cells from mixing and acts as an immune barrier to ensure immune tolerance towards the fetus. Maternal immune cells are found in the decidua, at the maternal-fetal interface. They consist mainly of NK cells (around 70%), macrophages (around 20%) and T cells [50].

During the second and third trimesters, a symbiotic balance is reached between the mother and the fetal-placental unit. Decidual immune cells shift from an inflammatory state during implantation and placentation to an anti-inflammatory ( $T_H2$ ) state along pregnancy. This  $T_H2$  environment is critical for healthy pregnancy as inflammation at this stage can result in miscarriage, stillbirth or preterm birth [50]. Upon infection, immune cells in the placenta will have to maintain fetal tolerance while also preventing infectious processes to reach the fetus.

As a facultative intracellular bacterium, *Lm* accesses the placenta free or in circulating myeloid cells. *Lm* is able to infect the syncytiotrophoblast, the most outer cells of the placenta (Figure 2) [11,51]. The syncytiotrophoblast is an epithelial syncytium that derives from the fusion of trophoblastic cells, is bathed in maternal blood and materializes the placental barrier. *Lm* crosses the placental barrier through the conjugated action of InlA and InlB *ex vivo* in human placental explants and *in vivo* in permissive rodent models such as gerbils and K1E16P mice [11,51]. This indicates that extracellular bacteria can interact with their host cell receptors Ecad and Met at the placental barrier level. InlA-mediated *Lm* internalization into cells requires PI3-kinase [52]. In trophoblast cells, PI3K basal activity is low, and InlB, acting as an

agonist of HGF on its receptor Met, activates PI3K, allowing InIA-mediated entry in the syncytiotrophoblast [12]. In contrast, at the intestinal level, GCs exhibit a constitutive PI3K activity, accounting for the absence of contribution of InIB in InIA-dependent translocation across GCs *in vivo* [12]. Upon infection, trophoblasts produce CSF-1 and MCP-1 leading to the recruitment of maternal neutrophils and macrophages [53,54]. What triggers expression of CSF-1 and MCP-1 in infected trophoblast is currently unknown. In the spleen, induction of MCP-1 by *Lm* requires its access to the cytosol (LLO-dependent) and is MyD88-independent [55]. Whether a similar process occurs in the placenta remains to be investigated. Macrophages, through TNF- $\alpha$  and IL-12, signal to decidual NK cells to produce IFN $\gamma$ , increasing their bactericidal activity against *Lm* [56] (Figure 2). In decidual macrophages, *Lm* infection induces the expression of Perforin-2, a membrane-attack-complex-perforin-containing factor, that mediates the killing of intracytoplasmic *Lm* [57]. However, Perforin-2 can also trigger miscarriage. Therefore, Perforin-2 contributes to protect both the mother and the fetus in case of mild infection, but can trigger fetal expulsion in case of an uncontrolled infection, resulting in maternal protection at the expense of fetal survival. Infected placental cells also produce IL1- $\beta$  and activate the inflammasome in recruited monocytes, helping clear *Lm* [58]. Infection of cultured trophoblast cells by *Lm* also leads to the induction of the type III interferons (IFN $\lambda$ ) [59]. *Ifn $\lambda$ 2* and *Ifn $\lambda$ 3* transcripts are expressed in placental homogenates from infected KIE16P mice, activating the transcription of interferon stimulated genes (ISG) [59]. IFITM is an ISG which has been shown to block syncytiotrophoblast formation, impair placental development and function, and favor fetal growth retardation and miscarriage [60]. Yet, the contribution of IFITM production in *Lm*-infected placenta to placental dysfunction and miscarriage remains to be established. Decidual NK cells can also selectively kill *Lm* directly in the infected trophoblast without killing infected cells [61]. Indeed, they can transfer granulysin, an antimicrobial peptide, via nanotubes directly into infected cells (Figure 2), and granulysin can kill cytosolic *Lm* present without damaging the infected cell. Here, innate immune responses are expected to allow controlling infection without altering the placental barrier. Indeed, transgenic mice expressing granulysin show a lower bacterial burden in the placenta compared to wild-type mice upon *Lm* infection and are resistant to *Lm*-induced abortion [61].

## **Innate immune responses at the blood brain barrier and in the CNS**

In elderly people or immunocompromised individuals, *Lm* can also cross the blood-brain barrier and induce neurolisterosis, characterized by meningo-encephalitis [1]. As for maternofetal infection, neurolisterosis is rare, yet its mortality rate is high, up to 30%, with almost 50% of surviving patients presenting with neurological sequelae [1], a frequency amongst the highest for CNS infections [62]. How *Lm* invades the CNS and the nature and impact of the resulting immune responses remain poorly understood. Experiments in mice treated with gentamicin suggest that bloodborne *Lm* reaching the blood-brain barrier are located intracellularly [63]. Leukocytes transfer experiments have shown that infected inflammatory monocytes can carry *Lm* to the CNS [64,65]. The targeting of *Lm*-infected monocytes to the CNS is IFN $\gamma$ -dependent but CCR2-independent [66]. Once at the endothelial barrier level, it remains unclear if *Lm* reaches the parenchyma by cell-to-cell spread in an ActA-dependent manner, or by transmigration of infected monocytes through the endothelial barrier [67]. In *ex vivo* organotypic slices and *in vitro* models of infection, *Lm* can infect microglial cells, the resident macrophages of the brain [68,69]. Infected microglial cells secrete inflammatory cytokines such as TNF- $\alpha$  and MCP-1 upon infection. The consequences of cytokines production by microglia as well as the impact of infection on the fate of these cells remain unknown. In the liver, resident macrophages known as Kupffer cells, actively phagocytose *Lm*, leading to their rapid death, triggering the recruitment of inflammatory monocytes. *Lm* infection of the liver is first controlled by an M1 pro-inflammatory response, followed by a M2 polarization of infiltrating monocytes allowing their proliferation and differentiation into macrophages [70]. Whether a similar process takes place in the CNS during neurolisterosis remains to be investigated. Pro-inflammatory signaling in the CNS might be deleterious and induce long-term neuronal damages [71] and the renewal of microglial cells may lead to altered immune functions in the CNS [72].

The fact that reference lab strains are poorly neuroinvasive have so far prevented detailed mechanistic *in vivo* studies [37]. CNS infection occurs with these strains only in immunocompromised animals or upon systemic injection of a very large inoculum. Conclusions obtained with these strains are therefore not necessarily transposable to clinical neuroinvasive and clinically relevant isolates, and the reasons for their enhanced neuroinvasiveness remains poorly understood. Characterization of CNS invasion by these neuroinvasive isolates and the resulting immune responses will



bring important insights into neurolisteriosis, a deadliest infection in human and a model infection [1].

## **Conclusions**

*Lm* is a model microorganism that played a critical role in the discovery and the characterization of the adaptive immune system [15]. From its ingestion with contaminated food up to its final target organs the CNS and the fetal-placental unit, it is exposed to innate immune defenses. Deciphering the impact of innate immune responses on *Lm* in the *in vivo* context is key to fully understand the biology of listeriosis. As illustrated in this non-exhaustive review, *Lm* has a propensity to evade innate immune responses, which favors its silent dissemination in host tissues. Yet, innate immune responses play a key role in orchestrating host defenses against *Lm*, both in a direct way by the action of antibacterial effectors, and indirectly as a trigger of anti-*Lm* sterilizing and protective adaptive cell-based immunity.

## **Acknowledgments**

Research in the Biology of Infection Unit is supported financially by Institut Pasteur, Inserm, ANR and ERC. Marc Lecuit is a senior member of Institut Universitaire de France. Figures were created using BioRender.com

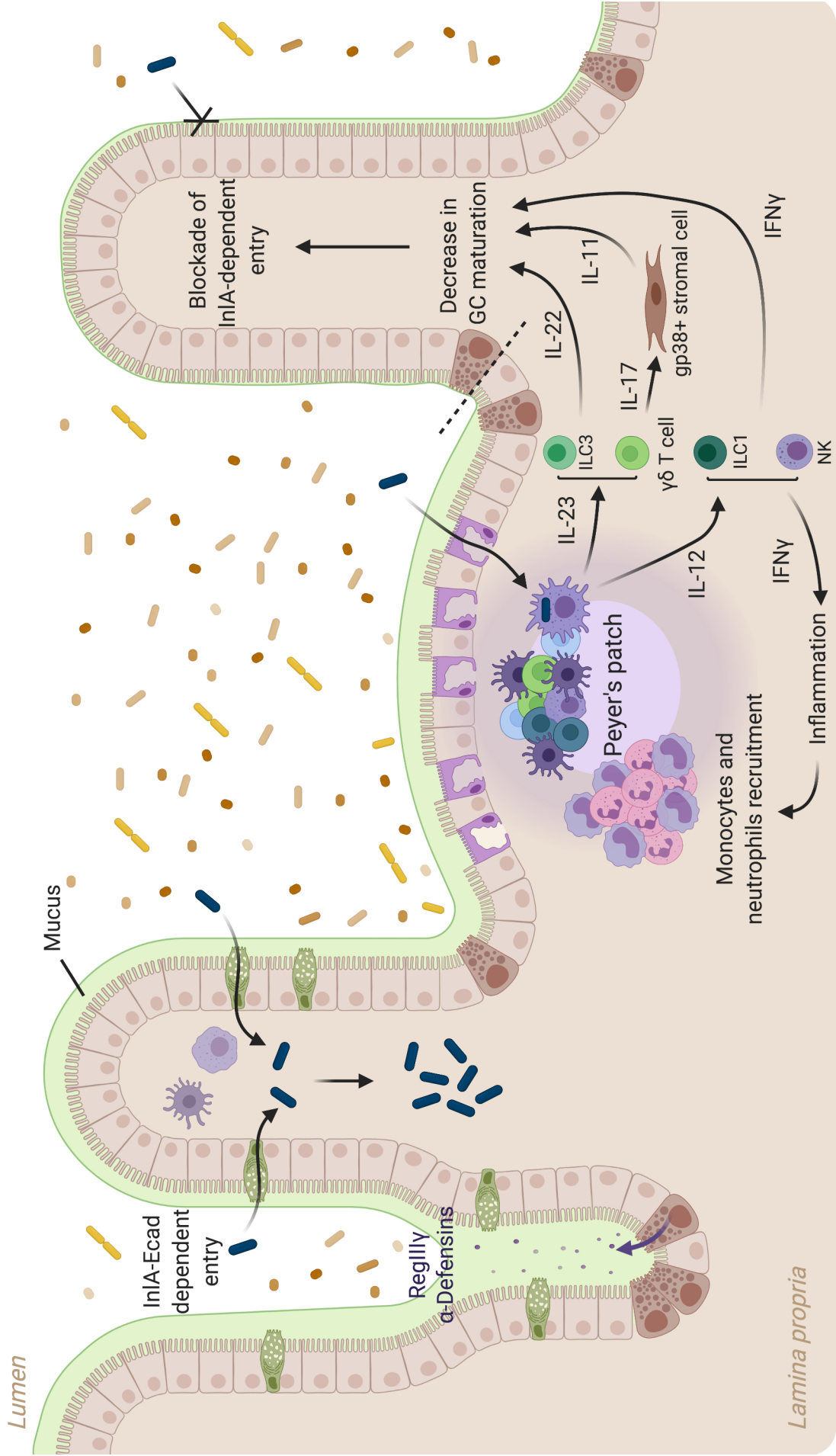
## Figure legends:














### Figure 1: Innate immune responses in the gut

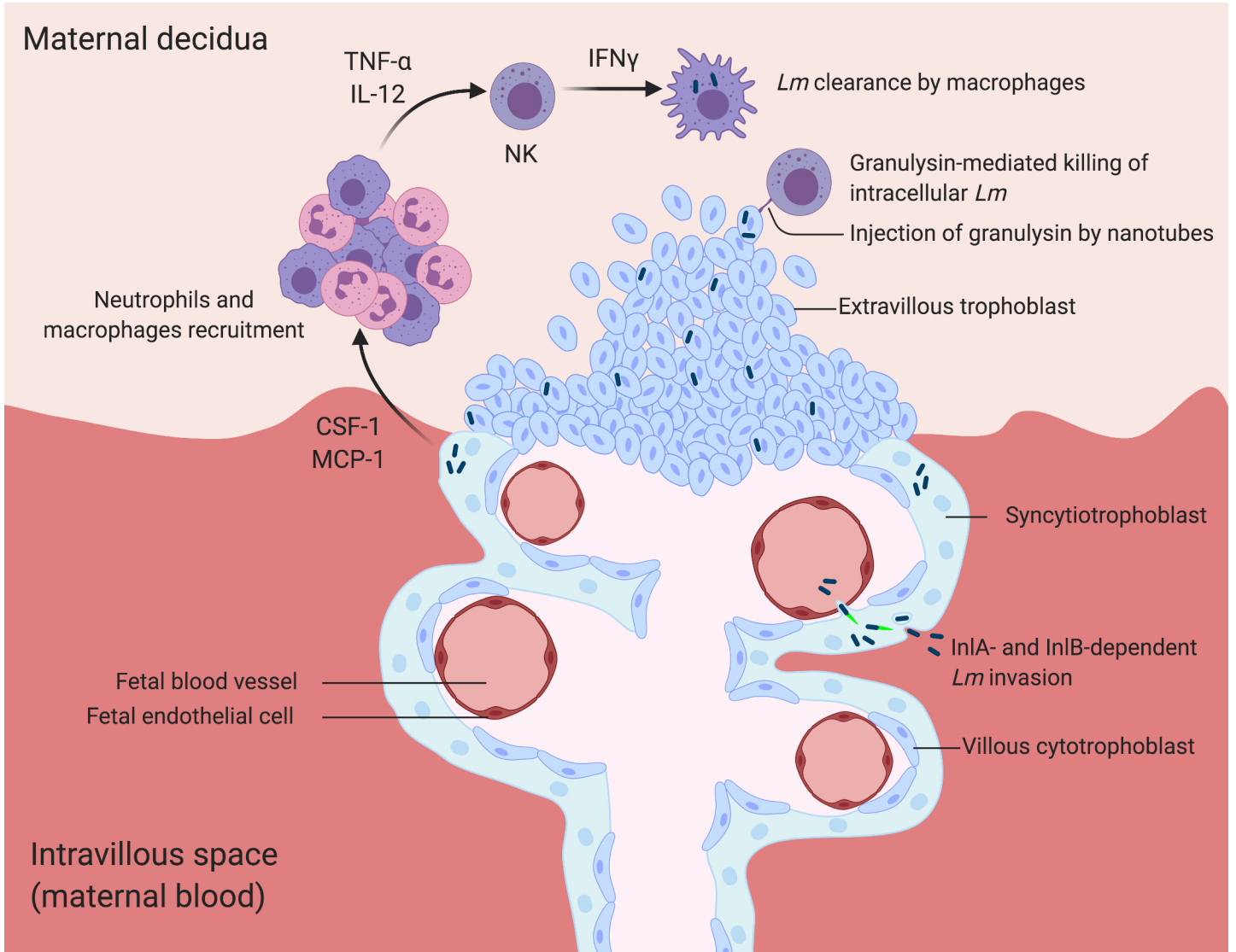
*Lm* can cross the intestinal barrier via two portals of entry. *Lm* crosses villi in an InIA-dependent manner, through mucus-secreting goblet cells, replicate in the *lamina propria* and disseminates into deeper organs. *Lm* can also be phagocytosed by M cells in PPs and infect CX3CR1<sup>+</sup> macrophages. This leads to the blocking of InIA-dependent entry of *Lm*. In addition, IFN $\gamma$  is involved in the recruitment of neutrophils and inflammatory monocytes in PPs.

### Figure 2: Innate immune responses at the placental level

Maternal blood-borne *Lm* infects the syncytiotrophoblast in an InIA- and InIB-dependent manner, allowing its crossing of the placental barrier and access to fetal circulation. Infected syncytiotrophoblast produces CSF-1 and MCP-1 which lead to the recruitment of neutrophils and macrophages. These cells, through TNF- $\alpha$  and IL-12 signaling, induce the production of IFN $\gamma$  by decidual NK cells, the major decidual innate immune effector cell. IFN $\gamma$  increases the bactericidal activity of decidual macrophages, and *Lm* killing. *Lm* can also infect extravillous trophoblast present in the decidua. NK cells can directly kill *Lm* without killing these infected extravillous trophoblast, via the delivery, through nanotubes, of granulysin, which acts as an antimicrobial peptide.



-  Enterocyte
-  M cell
-  Goblet cell
-  Paneth cell
-  Listeria
-  Microbiota
-  CX3CR1+ Macrophage
-  Activated Macrophage
-  DC
-  Neutrophil
-  Monocyte
-  B cell
-  T cell



1. Charlier C, Perrodeau E, Leclercq A: **Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study (vol 17, pg 510, 2017).** *Lancet Infectious Diseases* 2017, **17**:897-897.
2. Lecuit M: **Understanding how Listeria monocytogenes targets and crosses host barriers.** *Clin Microbiol Infect* 2005, **11**:430-436.
3. Lorber B: **Listeriosis.** *Clin Infect Dis* 1997, **24**:1-9; quiz 10-11.
4. Schlech WF, 3rd, Lavigne PM, Bortolussi RA, Allen AC, Haldane EV, Wort AJ, Hightower AW, Johnson SE, King SH, Nicholls ES, et al.: **Epidemic listeriosis--evidence for transmission by food.** *N Engl J Med* 1983, **308**:203-206.
5. Gaillard JL, Berche P, Frehel C, Gouin E, Cossart P: **Entry of L. monocytogenes into cells is mediated by internalin, a repeat protein reminiscent of surface antigens from gram-positive cocci.** *Cell* 1991, **65**:1127-1141.
6. Lebrun M, Mengaud J, Ohayon H, Nato F, Cossart P: **Internalin must be on the bacterial surface to mediate entry of Listeria monocytogenes into epithelial cells.** *Mol Microbiol* 1996, **21**:579-592.
7. Mengaud J, Ohayon H, Gounon P, Mege RM, Cossart P: **E-cadherin is the receptor for internalin, a surface protein required for entry of L. monocytogenes into epithelial cells.** *Cell* 1996, **84**:923-932.
8. Nikitas G, Deschamps C, Disson O, Niaux T, Cossart P, Lecuit M: **Transcytosis of Listeria monocytogenes across the intestinal barrier upon specific targeting of goblet cell accessible E-cadherin.** *J Exp Med* 2011, **208**:2263-2277.
9. Lecuit M, Vandormael-Pournin S, Lefort J, Huerre M, Gounon P, Dupuy C, Babinet C, Cossart P: **A transgenic model for listeriosis: role of internalin in crossing the intestinal barrier.** *Science* 2001, **292**:1722-1725.
10. Shen Y, Naujokas M, Park M, Ireton K: **InIB-dependent internalization of Listeria is mediated by the Met receptor tyrosine kinase.** *Cell* 2000, **103**:501-510.
11. Disson O, Grayo S, Huillet E, Nikitas G, Langa-Vives F, Dussurget O, Ragon M, Le Monnier A, Babinet C, Cossart P, et al.: **Conjugated action of two species-specific invasion proteins for fetoplacental listeriosis.** *Nature* 2008, **455**:1114-1118.
12. Gessain G, Tsai YH, Travier L, Bonazzi M, Grayo S, Cossart P, Charlier C, Disson O, Lecuit M: **PI3-kinase activation is critical for host barrier permissiveness to Listeria monocytogenes.** *J Exp Med* 2015, **212**:165-183.
13. Lecuit M, Dramsi S, Gottardi C, Fedor-Chaiken M, Gumbiner B, Cossart P: **A single amino acid in E-cadherin responsible for host specificity towards the human pathogen Listeria monocytogenes.** *EMBO J* 1999, **18**:3956-3963.
14. Khelef N, Lecuit M, Bierne H, Cossart P: **Species specificity of the Listeria monocytogenes InIB protein.** *Cell Microbiol* 2006, **8**:457-470.
15. Pamer EG: **Immune responses to Listeria monocytogenes.** *Nat Rev Immunol* 2004, **4**:812-823.
16. Regan T, MacSharry J, Brint E: **Tracing innate immune defences along the path of Listeria monocytogenes infection.** *Immunol Cell Biol* 2014, **92**:563-569.
17. Serbina NV, Shi C, Pamer EG: **Monocyte-mediated immune defense against murine Listeria monocytogenes infection.** *Adv Immunol* 2012, **113**:119-134.
18. Tsai YH, Disson O, Bierne H, Lecuit M: **Murinization of internalin extends its receptor repertoire, altering Listeria monocytogenes cell tropism and host responses.** *PLoS Pathog* 2013, **9**:e1003381.

19. Wollert T, Pasche B, Rochon M, Deppenmeier S, van den Heuvel J, Gruber AD, Heinz DW, Lengeling A, Schubert WD: **Extending the host range of *Listeria monocytogenes* by rational protein design.** *Cell* 2007, **129**:891-902.
20. Mackaness GB: **Cellular resistance to infection.** *J Exp Med* 1962, **116**:381-406.
21. Medzhitov R, Janeway CA, Jr.: **Innate immunity: impact on the adaptive immune response.** *Curr Opin Immunol* 1997, **9**:4-9.
22. Broz P, Ohlson MB, Monack DM: **Innate immune response to *Salmonella typhimurium*, a model enteric pathogen.** *Gut Microbes* 2012, **3**:62-70.
23. Liu G, Pilla G, Tang CM: **Shigella host: Pathogen interactions: Keeping bacteria in the loop.** *Cell Microbiol* 2019, **21**:e13062.
24. Lecuit M, Sonnenburg JL, Cossart P, Gordon JI: **Functional genomic studies of the intestinal response to a foodborne enteropathogen in a humanized gnotobiotic mouse model.** *J Biol Chem* 2007, **282**:15065-15072.
25. Becattini S, Littmann ER, Carter RA, Kim SG, Morjaria SM, Ling L, Gyaltsen Y, Fontana E, Taur Y, Leiner IM, et al.: **Commensal microbes provide first line defense against *Listeria monocytogenes* infection.** *J Exp Med* 2017, **214**:1973-1989.
26. Brandl K, Plitas G, Schnabl B, DeMatteo RP, Pamer EG: **MyD88-mediated signals induce the bactericidal lectin RegIII gamma and protect mice against intestinal *Listeria monocytogenes* infection.** *Journal of Experimental Medicine* 2007, **204**:1891-1900.
27. Cash HL, Whitham CV, Behrendt CL, Hooper LV: **Symbiotic bacteria direct expression of an intestinal bactericidal lectin.** *Science* 2006, **313**:1126-1130.
28. Loonen LMP, Stolte EH, Jaklofsky MTJ, Meijerink M, Dekker J, van Baarlen P, Wells JM: **REG3 gamma-deficient mice have altered mucus distribution and increased mucosal inflammatory responses to the microbiota and enteric pathogens in the ileum.** *Mucosal Immunology* 2014, **7**:939-947.
29. Kobayashi KS, Chamaillard M, Ogura Y, Henegariu O, Inohara N, Nunez G, Flavell RA: **Nod2-dependent regulation of innate and adaptive immunity in the intestinal tract.** *Science* 2005, **307**:731-734.
30. Pian YY, Chai Q, Ren BY, Wang Y, Lv MJ, Qiu J, Zhu MZ: **Type 3 Innate Lymphoid Cells Direct Goblet Cell Differentiation via the LT-LT beta R Pathway during *Listeria* Infection.** *Journal of Immunology* 2020, **205**:853-863.
31. Singh R, Jamieson A, Cresswell P: **GILT is a critical host factor for *Listeria monocytogenes* infection.** *Nature* 2008, **455**:1244-1247.
32. Luster AD, Weinshank RL, Feinman R, Ravetch JV: **Molecular and biochemical characterization of a novel gamma-interferon-inducible protein.** *J Biol Chem* 1988, **263**:12036-12043.
33. Aubry C, Goulard C, Nahori MA, Cayet N, Decalf J, Sachse M, Boneca IG, Cossart P, Dussurget O: **OatA, a peptidoglycan O-acetyltransferase involved in *Listeria monocytogenes* immune escape, is critical for virulence.** *J Infect Dis* 2011, **204**:731-740.
34. Boneca IG, Dussurget O, Cabanes D, Nahori MA, Sousa S, Lecuit M, Psylinakis E, Bouriotis V, Hugot JP, Giovannini M, et al.: **A critical role for peptidoglycan N-deacetylation in *Listeria* evasion from the host innate immune system.** *Proc Natl Acad Sci U S A* 2007, **104**:997-1002.
35. Gouin E, Adib-Conquy M, Balestrino D, Nahori MA, Villiers V, Colland F, Dramsi S, Dussurget O, Cossart P: **The *Listeria monocytogenes* InlC protein interferes with innate immune**

- responses by targeting the I{kappa}B kinase subunit IKK{alpha}**. *Proc Natl Acad Sci U S A* 2010, **107**:17333-17338.
36. Personnic N, Bruck S, Nahori MA, Toledo-Arana A, Nikitas G, Lecuit M, Dussurget O, Cossart P, Bierre H: **The stress-induced virulence protein InlH controls interleukin-6 production during murine listeriosis**. *Infect Immun* 2010, **78**:1979-1989.
  37. Maury MM, Tsai YH, Charlier C, Touchon M, Chenal-Francois V, Leclercq A, Criscuolo A, Gaultier C, Roussel S, Brisabois A, et al.: **Uncovering Listeria monocytogenes hypervirulence by harnessing its biodiversity**. *Nat Genet* 2016, **48**:308-313.
  38. Disson O, Bleriot C, Jacob JM, Serafini N, Dulauroy S, Jouvion G, Fevre C, Gessain G, Thouvenot P, Eberl G, et al.: **Peyer's patch myeloid cells infection by Listeria signals through gp38(+) stromal cells and locks intestinal villus invasion**. *Journal of Experimental Medicine* 2018, **215**:2936-2954.
  39. Dulson SJ, Watkins EE, Crossman DK, Harrington LE: **STAT4 Directs a Protective Innate Lymphoid Cell Response to Gastrointestinal Infection**. *Journal of Immunology* 2019, **203**:2472-2484.
  40. Reynders A, Yessaad N, Manh TPV, Dalod M, Fenis A, Aubry C, Nikitas G, Escaliere B, Renaud JC, Dussurget O, et al.: **Identity, regulation and in vivo function of gut NKp46(+)ROR gamma t(+) and NKp46(+)ROR gamma t(-) lymphoid cells**. *Embo Journal* 2011, **30**:2934-2947.
  41. Dai WJ, Bartens W, Kohler G, Hufnagel M, Kopf M, Brombacher F: **Impaired macrophage listericidal and cytokine activities are responsible for the rapid death of Listeria monocytogenes-infected IFN-gamma receptor-deficient mice**. *J Immunol* 1997, **158**:5297-5304.
  42. Harty JT, Bevan MJ: **Specific immunity to Listeria monocytogenes in the absence of IFN gamma**. *Immunity* 1995, **3**:109-117.
  43. Furter M, Sellin ME, Hansson GC, Hardt WD: **Mucus Architecture and Near-Surface Swimming Affect Distinct Salmonella Typhimurium Infection Patterns along the Murine Intestinal Tract**. *Cell Rep* 2019, **27**:2665-2678 e2663.
  44. Klose CS, Kiss EA, Schwierzeck V, Ebert K, Hoyler T, d'Hargues Y, Goppert N, Croxford AL, Waisman A, Tanriver Y, et al.: **A T-bet gradient controls the fate and function of CCR6-RORgammat+ innate lymphoid cells**. *Nature* 2013, **494**:261-265.
  45. Songhet P, Barthel M, Stecher B, Muller AJ, Kremer M, Hansson GC, Hardt WD: **Stromal IFN-gammaR-signaling modulates goblet cell function during Salmonella Typhimurium infection**. *PLoS One* 2011, **6**:e22459.
  46. Chan JM, Bhinder G, Sham HP, Ryz N, Huang T, Bergstrom KS, Vallance BA: **CD4+ T cells drive goblet cell depletion during Citrobacter rodentium infection**. *Infect Immun* 2013, **81**:4649-4658.
  47. Charlier C, Disson O, Lecuit M: **Maternal-neonatal listeriosis**. *Virulence* 2020, **11**:391-397.
  48. Thomas J, Govender N, McCarthy KM, Erasmus LK, Doyle TJ, Allam M, Ismail A, Ramalwa N, Sekwadi P, Ntshoe G, et al.: **Outbreak of Listeriosis in South Africa Associated with Processed Meat**. *N Engl J Med* 2020, **382**:632-643.
  49. Madjunkov M, Chaudhry S, Ito S: **Listeriosis during pregnancy**. *Arch Gynecol Obstet* 2017, **296**:143-152.
  50. Mor G, Aldo P, Alvero AB: **The unique immunological and microbial aspects of pregnancy**. *Nature Reviews Immunology* 2017, **17**:469-482.
  51. Lecuit M, Nelson DM, Smith SD, Khun H, Huerre M, Vacher-Lavenu MC, Gordon JI, Cossart P: **Targeting and crossing of the human maternofetal barrier by Listeria**

- monocytogenes: role of internalin interaction with trophoblast E-cadherin.** *Proc Natl Acad Sci U S A* 2004, **101**:6152-6157.
52. Ireton K, Payrastre B, Chap H, Ogawa W, Sakaue H, Kasuga M, Cossart P: **A role for phosphoinositide 3-kinase in bacterial invasion.** *Science* 1996, **274**:780-782.
  53. Guleria I, Pollard JW: **The trophoblast is a component of the innate immune system during pregnancy.** *Nat Med* 2000, **6**:589-593.
  54. Qiu X, Zhu L, Pollard JW: **Colony-stimulating factor-1-dependent macrophage functions regulate the maternal decidua immune responses against *Listeria monocytogenes* infections during early gestation in mice.** *Infect Immun* 2009, **77**:85-97.
  55. Serbina NV, Kuziel W, Flavell R, Akira S, Rollins B, Pamer EG: **Sequential MyD88-independent and -dependent activation of innate immune responses to intracellular bacterial infection.** *Immunity* 2003, **19**:891-901.
  56. Barber EM, Fazzari M, Pollard JW: **Th1 cytokines are essential for placental immunity to *Listeria monocytogenes*.** *Infect Immun* 2005, **73**:6322-6331.
  57. Gayle P, McGaughey V, Hernandez R, Wylie M, Colletti RC, Nguyen KL, Arons M, Padula L, Strbo N, Schesser K: **Maternal- and Fetal-Encoded Perforin-2 Limits Placental Infection by a Bloodborne Pathogen.** *J Immunol* 2020, **205**:1878-1885.
  58. Megli C, Morosky S, Rajasundaram D, Coyne CB: **Inflammasome signaling in human placental trophoblasts regulates immune defense against *Listeria monocytogenes* infection.** *J Exp Med* 2021, **218**.
  59. Bierne H, Travier L, Mahlakoiv T, Tailleux L, Subtil A, Lebreton A, Paliwal A, Gicquel B, Staeheli P, Lecuit M, et al.: **Activation of type III interferon genes by pathogenic bacteria in infected epithelial cells and mouse placenta.** *PLoS One* 2012, **7**:e39080.
  60. Buchrieser J, Degrelle SA, Couderc T, Nevers Q, Disson O, Manet C, Donahue DA, Porrot F, Hillion KH, Perthame E, et al.: **IFITM proteins inhibit placental syncytiotrophoblast formation and promote fetal demise.** *Science* 2019, **365**:176-180.
  61. Crespo AC, Mulik S, Dotiwala F, Ansara JA, Sen Santara S, Ingersoll K, Ovies C, Junqueira C, Tilburgs T, Strominger JL, et al.: **Decidual NK Cells Transfer Granulysin to Selectively Kill Bacteria in Trophoblasts.** *Cell* 2020, **182**:1125-1139 e1118.
  62. Mailles A, De Broucker T, Costanzo P, Martinez-Almoyna L, Vaillant V, Stahl JP, Grp SCI: **Long-term Outcome of Patients Presenting With Acute Infectious Encephalitis of Various Causes in France.** *Clinical Infectious Diseases* 2012, **54**:1455-1464.
  63. Drevets DA, Leenen PJ, Greenfield RA: **Invasion of the central nervous system by intracellular bacteria.** *Clin Microbiol Rev* 2004, **17**:323-347.
  64. Drevets DA, Dillon MJ, Schawang JS, Van Rooijen N, Ehrchen J, Sunderkotter C, Leenen PJ: **The Ly-6Chigh monocyte subpopulation transports *Listeria monocytogenes* into the brain during systemic infection of mice.** *J Immunol* 2004, **172**:4418-4424.
  65. Join-Lambert OF, Ezine S, Le Monnier A, Jaubert F, Okabe M, Berche P, Kayal S: ***Listeria monocytogenes*-infected bone marrow myeloid cells promote bacterial invasion of the central nervous system.** *Cell Microbiol* 2005, **7**:167-180.
  66. Drevets DA, Dillon MJ, Schawang JE, Stoner JA, Leenen PJ: **IFN-gamma triggers CCR2-independent monocyte entry into the brain during systemic infection by virulent *Listeria monocytogenes*.** *Brain Behav Immun* 2010, **24**:919-929.
  67. Disson O, Lecuit M: **Targeting of the central nervous system by *Listeria monocytogenes*.** *Virulence* 2012, **3**:213-221.



68. Frande-Cabanes E, Fernandez-Prieto L, Calderon-Gonzalez R, Rodriguez-Del Rio E, Yanez-Diaz S, Lopez-Fanarraga M, Alvarez-Dominguez C: **Dissociation of innate immune responses in microglia infected with *Listeria monocytogenes***. *Glia* 2014, **62**:233-246.
69. Guldemann C, Bartschi M, Frey J, Zurbriggen A, Seuberlich T, Oevermann A: **Increased spread and replication efficiency of *Listeria monocytogenes* in organotypic brain-slices is related to multilocus variable number of tandem repeat analysis (MLVA) complex (vol 15, pg 134, 2015)**. *Bmc Microbiology* 2015, **15**.
70. Bleriot C, Dupuis T, Jouvion G, Eberl G, Disson O, Lecuit M: **Liver-resident macrophage necroptosis orchestrates type 1 microbicidal inflammation and type-2-mediated tissue repair during bacterial infection**. *Immunity* 2015, **42**:145-158.
71. Forrester JV, McMenamin PG, Dando SJ: **CNS infection and immune privilege**. *Nature Reviews Neuroscience* 2018, **19**:655-671.
72. Bennett ML, Bennett FC: **The influence of environment and origin on brain resident macrophages and implications for therapy**. *Nature Neuroscience* 2020, **23**:157-166.