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REVIEW

Recent Advances in Host Immune Mechanisms Against *Listeria monocytogenes* Infection

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Abstract: *Listeria monocytogenes* (*Lm*) is a foodborne Gram-positive pathogenic bacterium that primarily causes clinical manifestations such as sepsis, meningitis, and monocytosis. The main susceptible populations include newborns, pregnant women, adults over 40 years old, and immunocompromised individuals. Currently, antibiotic therapy remains the primary clinical treatment, but in recent years the issue of antibiotic resistance has become increasingly prominent. This review summarizes recent advances in host immune mechanisms against *Lm* infection, focusing on: (1) the defensive roles of host barrier systems (intestinal, blood-brain, and placental barriers); (2) innate immune responses, including pathogen recognition via TLRs/NLRs signaling pathways, macrophage phagocytosis, and NK cell immune surveillance; and (3) adaptive immunity, particularly CD4$^+$/CD8$^+$ T cell-mediated specific immune responses and the long-term protective effects of memory T cells. By systematically elucidating the molecular mechanisms of these immune processes, this review aims to provide novel therapeutic strategies through enhancement of host immune functions for clinical management of *Lm* infection.

Keywords: *listeria monocytogenes*, infection, host, immunity

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Introduction

Listeria monocytogenes (*Lm*) is a Gram-positive facultative anaerobic bacterium, which is also a facultative intracellular pathogen. It is widely distributed in the natural environment and can replicate at low temperatures and a wide range of pH values.[1] Currently, there are 10 recognized strains of *Listeria* internationally, among which *Lm* is the only species that can cause human diseases, leading to human *Listeriosis* with a high mortality rate.[2] Among those recognized *Listeria* serovars, serotype 4b strains (Lineage I) exhibit heightened epidemic potential due to virulence factors, contrasting historical assumptions of uniform pathogenicity across serovars.[2,3]

Lm is a typical foodborne pathogenic bacterium that is mainly transmitted through contaminated food.[4] It is also present in most foods such as unpasteurized cheeses or meat products, pre-packaged sandwiches, cold-smoked fish, salads, fruits, etc.[5] Other food sources such as caramel apples or mung bean sprouts are also associated with *Listeriosis* (Figure 1). [6]

Listeriosis is usually divided into invasive and non-invasive forms. Non-invasive *Listeriosis* mainly occurs in people with low immunity. Infected individuals may experience fever, muscle aches, and gastrointestinal symptoms. Invasive *Listeriosis* mainly occurs in certain elderly individuals, pregnant women, newborns, and those with weak immunity, increasing the likelihood of serious symptoms such as meningitis, endocarditis, sepsis, septicemia, miscarriage or stillbirth (Figure 1). [7,8]

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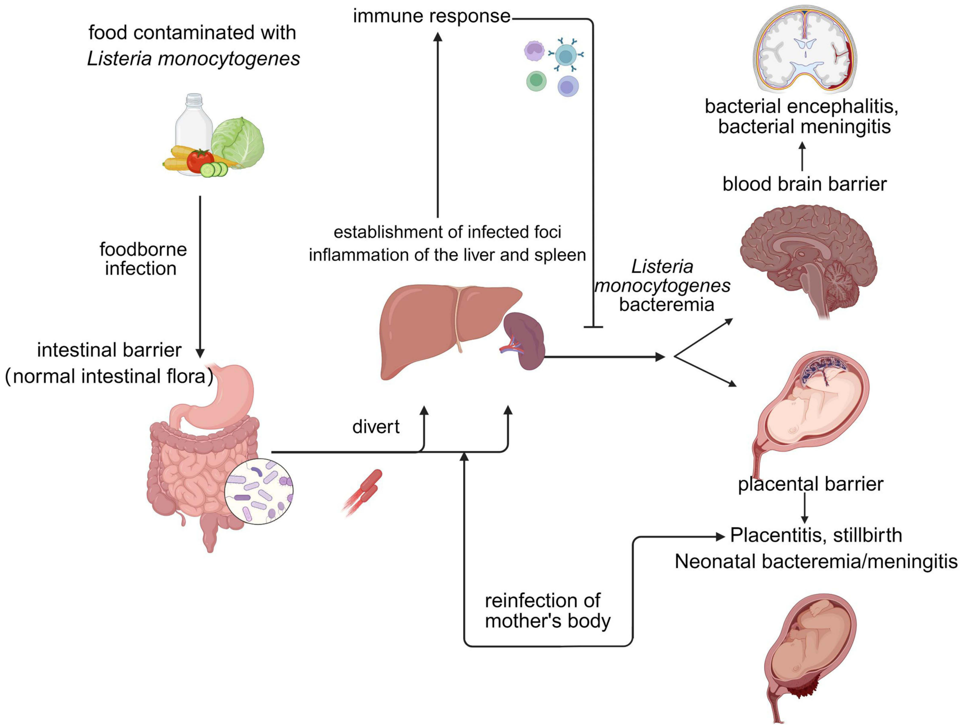

Figure 1 Schematic diagram of the pathogenic mechanism of *Lm* infection of the host. When foodborne infection with *Lm* occurs, *Lm* invades the intestinal epithelial cells through its virulence factors, crosses the host's intestinal mucosal barrier, and reaches the intestine, and can be transferred through the intestinal tract to the liver and spleen, where foci of infection are established. Immunocompromised individuals are unable to generate an effective T-cell immune response, leading to the development of bacteremia. Parasitized within monocytes, *Lm* mediated brain invasion through its virulence factors, crossing the blood-brain barrier without difficulty. It leads to *Listeria monocytogenes* bacterial encephalitis and meningitis. *Lm* in infected pregnant women can also crosses the blood-fetal barrier and colonizes the uterus, leading to placentitis, stillbirth, and neonatal meningitis. Created in BioRender. Xiang, W. (2025) https://BioRender.com/f6ha632.

Currently, antibiotics such as ampicillin, penicillin, and amoxicillin are commonly used in clinical practice to treat *Lm* disease. The most commonly used treatment for invasive *Listeria* infection is combination therapy with ampicillin and gentamicin, and the effectiveness of gentamicin combination therapy has also been preliminarily confirmed in recent clinical studies.[9,10] Although *Lm* is susceptible to most antibiotics, it also exhibits intrinsic resistance to certain antimicrobial drugs. Additionally, *Lm* can increase its tolerance to antibiotics through stress responses such as reducing cell membrane permeability, increasing efflux pump activity, altering antibiotic structure, or changing cell components that serve as antibiotic targets[11]—diverging from earlier "uniform susceptibility" models. This complexity, stemming from *Lm*'s facultative intracellular lifestyle and barrier-transgressing capabilities (eg, blood-brain/placental penetration), complicates antibiotic efficacy and necessitates immune-focused strategies.

It is now clear that the cephalosporin antibiotics have been shown to have no activity against *Lm*. Nevertheless, cephalosporins are still frequently used as empirical treatment for infections that have not been definitively diagnosed.[6] With the increasing resistance of *Lm* to antibiotics and the rare and sporadic cases of *Listeriosis*, it is challenging to conduct clinical trials, leading to increased difficulty in treating *Listeriosis*.[9] Finding effective methods to combat *Lm* remains a significant challenge. Thus, this review synthesizes advances in host-barrier defenses, innate/adaptive immunity, and emerging immunomodulatory approaches against *Lm*, aiming to bridge mechanistic insights and clinical innovation for high-risk populations.

Immune Response to Lm

When *Lm* invades the body, the innate immune response serves as the first line of defense against foreign pathogens, mainly by combating *Lm* infection through three aspects: immune barriers, innate immune cells, and innate immune molecules.

Barrier System

Intestinal Barrier

According to research, gut microbiota acts as the first line of defense against pathogenic *Lm* infection, playing a role in maintaining host nutrition, immunity, metabolism, and resistance to pathogens.[12] During *Lm* infection, there are complex interactions between gut microbiota and the normal bacterial community.

The gut microbiota can bind to receptors on the intestinal epithelial cells to block the interaction between pathogens and epithelial cells, or inhibit intestinal pathogens directly or indirectly by producing antimicrobial peptides or competing for nutrients.[13] *Lactobacillus* and *Bifidobacterium* secrete antimicrobial peptides to inhibit the growth of *Lm*,[14] while *Clostridium* achieves anti-infection purposes by reducing the ability of *Lm* to colonize the gastrointestinal tract. Recently, Tong Jin et al found that *Akkermansia muciniphila* can play an anti-infection role by enhancing the intestinal barrier function and increasing the level of arachidonic acid.

Short-chain fatty acids (SCFAs) are metabolic products produced by the gut microbiota, mainly including acetic acid, propionic acid, and butyric acid. Due to the ability of SCFAs to protect intestinal barrier integrity by promoting the formation of tight junctions (TJ),[15] they play an important role in resisting colonization and dissemination of *Lm*, as well as regulating inflammation. SCFAs can directly inhibit bacterial growth by disrupting cell metabolism and regulating intracellular pH.[16] They also regulate the reactions of multiple Toll-like receptors (TLRs) and Tumor necrosis factor-α (TNF-α) by inhibiting histone deacetylase (HDAC) to promote proliferation of intestinal epithelial cells and enhance the expression of antimicrobial peptides in the gut microbiota to weaken pathogen colonization.[17] Additionally, SCFAs can inhibit protein kinase B (PKB) and nuclear factor kappa-B (NF-κB) by binding to G protein-coupled receptors (GPCR) on the cell surface, reducing inflammation and improving intestinal epithelial barrier function.[18] The breakdown metabolites of tryptophan and butyric acid can stimulate group 3 innate lymphoid cells (ILC3) in intestinal epithelial cells to produce interleukin 22 (IL-22),[19] which is capable of maintaining intestinal homeostasis and facilitating recovery during intestinal infections.[20] In addition, intestinal epithelial cells (IECs) can secrete a bactericidal protein - small proline-rich protein 2A (SPRR2A) rich in proline, which selectively kills *Lm* by disrupting cell membranes.[21]

From the above, it can be seen that the intestinal flora and its metabolites are essential in combating *Lm* infection and inflammation response, however, their mechanism of action is complex and requires further research.

Blood-Brain Barrier

Bacterial meningitis has a high incidence and mortality rate, among which *Lm* is one of the main causes of adult bacterial meningitis.[22] Studies have shown that *Lm* can pass through the intestinal barrier via the surface virulence factor internalin,[23] enter the bloodstream, and then transfer to the brain tissue. The central nervous system (CNS) has a specific protective barrier – the blood-brain barrier (BBB), which is composed of endothelial cells of capillary walls, astrocyte end-feet, and pericytes,[24] preventing harmful substances like toxins and pathogens from entering the brain to maintain brain homeostasis.[25]

Studies have shown that *Lm* secretes listeriolysin-O (LLO) which can activate the NF-κB pathway in endothelial cells, promote the transcription of inflammatory factors such as IL-1β and TNF-α, thereby disrupting the integrity of BBB. At the same time, LLO can also induce the production of cell surface adhesion molecules P-selectin, E-selectin, intercellular cell adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), while the expression of inflammatory factors such as IL-1β and TNF-α can enhance LLO-induced ICAM-1 expression, further mediating cell adhesion and promoting the entry of white blood cells into the CNS.[26] The surface protein InlB of *Lm* also upregulates the expression of caspase-8 inhibitory protein FLIP (FADD-like IL-1β-converting enzyme) through the InlB/c-Met/PI3Kα-dependent cell pathway, thereby mediating the inactivation of the Fas cell death pathway in infected monocytes, extending the lifespan of infected cells, and providing opportunities for central invasion by crossing BBB.[27]

Lm infection can cause a series of inflammatory reactions, leading to infiltration of inflammatory cells and increased release of inflammatory factors, thus disrupting the integrity of BBB and ultimately leading to bacterial meningitis. Therefore, we can protect the integrity of BBB and enhance the body's ability to resist *Lm* infection by regulating inflammatory factors.

Placental Barrier

Pregnant women, as is well known, experience an increase in progesterone levels, which suppresses individuals' immune function, making pregnant women highly susceptible to *Lm* infection. The placental barrier (PB) is composed of cells at the maternal-fetal interface, primarily including chorionic trophoblast cells, syncytiotrophoblast cells, extrachorionic trophoblast cells, and metamyelocytes, which can separate maternal blood from fetal blood.[28]

According to reports, when *Lm* infects decidual macrophages, it induces macrophages to express Perforin-2, thereby inhibiting *Lm* colonization on the placenta and killing *Lm*.[29] Infected placental cells can also produce IL-1β, activating monocytes' inflammasome to prevent *Lm* infection.[30] It is worth mentioning that decidual natural killer cells (dNK cells) can selectively transfer their highly expressed antimicrobial peptide granulysin (GNLY) to extracellular trophoblast cells through nanotubes, targeting and killing *Lm*.[31]

In addition, a small number of *Lm* can also invade the human body through damaged skin and corneal epithelium. Therefore, the skin mucosal barrier and corneal epithelium also play a certain role in resisting *Lm* infection.

Innate Immune Cells

Macrophages

Macrophages are an important component of the innate immune system, with functions such as phagocytosis and antigen presentation. Upon stimulation by *Lm*, macrophages undergo polarization into M1 (Classically activated macrophages, M1) and M2 (Alternatively activated macrophages, M2) subtypes. M1 cells secrete pro-inflammatory cytokines, such as IL-1 and IL-6 mediating inflammatory responses,[32] while M2 cells secrete anti-inflammatory cytokines like IL-10 mediating tissue repair.[33] In response to *Lm* infection, macrophages first polarize towards the M1 type, triggering an inflammatory response to kill *Lm*.

After ingestion of *Lm* by macrophages, Myeloid differentiation factor 88 (MyD88)-dependent response genes are activated through TLRs, thereby activating the NF-κB signaling pathway, exerting an anti-infection effect.[34] The NF-κB signaling pathway is the main signaling pathway through which the body produces pro-inflammatory factors to combat *Lm*. Recent studies have found that GTP-binding protein 2 (DRG2) in macrophages can regulate the expression of IL-6 during the early stage of *Lm* infection. Lack of DRG2 reduces the transcriptional activity of NF-κB, increases host susceptibility to *Lm*, indicating the crucial role of DRG2 in combating *Lm* infection during early inflammatory response.[35] Research has also shown that macrophages regulate the production of inducible nitric oxide synthase (iNOS) through the NF-κB and JAK-STAT1 signaling pathways, inhibiting *Lm* proliferation. Meanwhile, studies have shown that inhibiting lipid droplet formation can reduce the intracellular survival rate of *Lm*.[36]

After *Lm* infection, pro-inflammatory factors activate calcium homeostasis modulator family member 6 (CALHM6) in macrophages, and CALHM6 relocates from intracellular compartments to macrophage-NK cell synapses, promoting ATP release and controlling NK cell activation.[37] Joel et al found that type I Interferon (IFN) can inhibit macrophages' bactericidal activity against *Lm*, and mice lacking the type I interferon receptor are resistant to *Lm* infection. The specific mechanism involves IFN-induced transmembrane protein 3 (IFITM3) which can inhibit the proteolytic activity in macrophages, thus facilitating the spread of *Lm* between cells.[38]

Current studies have shown that macrophages in the innate immune system mainly rely on the M1 subtype NF-κB signaling pathway to induce the production of inflammatory factors, playing a role in anti-infection and anti-proliferation and spread of *Lm*. Subsequently, the M2 subtype of macrophages limits tissue damage and repairs injuries.[39] The specific mechanism of macrophages in response to *Lm* and targeted therapies still require further research.

Dendritic Cells

Dendritic cells (DCs), as professional antigen presenting cells (APCs), play important roles in activating and initiating T cell immune responses in both innate and adaptive immunity. *Lm*, as an intracellular bacterium, primarily induces cell-mediated immunity mediated by $CD8^+$ T lymphocytes. Post-synaptic dendritic cells (psDCs) helps $CD8^+$ T cell responses with the assistance of $CD4^+$ T cells. Diego et al report that immune synapse formation facilitates lipid peroxidation and MHC-I upregulation in licensed dendritic cells for efficient priming of $CD8^+$ T cells.[40] The immunological synapse can induce MHC I and lipid peroxidation both in vivo and in vitro. Lack of lysine-specific demethylase 5C in DCs increases inflammatory cell expression and decreases antigen presentation ability of conventional type 1 dendritic cells (cDC1s). CD8$^+$ T cell responses are reduced in Lysine Demethylase 5C (KDM5C)-deficient mice. Therefore, KDM5C is a key regulatory factor in DCs.[41] Wang et al recently report that mice lacking Zeb1 in cDC1s exhibit stronger resistance to *Lm*, suggesting Zeb1 as a potential target to enhance antibacterial functions of cDC1s.[42]

Neutrophils

Neutrophils play various roles in combating infection after being infected by *Lm*, including degranulation and releasing reactive oxygen species (ROS) as well as chemotaxis, activation, and phagocytosis. The response of neutrophils to *Lm* mostly requires the activation of Ca^{2+} channels. Current studies have shown that Stromal-interaction molecule 1 (STIM1) calcium sensor is an effective target for activating neutrophils against *Lm*. Recently, Ning Wu discovered that Transmembrane Protein 16F (TMEM16F) repaired *Lm* toxin Listeriolysin O (LLO) which induced plasma membrane damage in T cells in vitro.[43] Most research on neutrophil antibacterial activity is related to extracellular bacteria, while the mechanism of action of neutrophils against *Lm* is still under further exploration.

Innate Immune Molecules

TLRs

TLRs are the most important innate immune molecules against *Lm*. TLRs are a type I transmembrane protein, mainly composed of extracellular domain, transmembrane domain, and cytoplasmic domain. The extracellular domain of TLRs is rich in leucine-rich repeat sequences (LRRs), which are mainly responsible for ligand recognition and binding. The cytoplasmic domain of TLRs and the cytoplasmic domain of members of the IL-1 receptor (IL-1R) family are highly homologous, thus referred to as the Toll-IL-1 receptor domain (TIR) (Figure 2A).[44]

In the human body, there are ten confirmed members of the TLR family, namely TLR1-TLR10. Among the innate immune mechanisms against *Lm*, TLR2 is particularly important. TLR2 is expressed on various cell types such as intestinal epithelial cells, CD8$^+$ T cells, but is most abundant in bone marrow-derived macrophages (BMMs). TLR2 mainly exerts its effects by forming heterodimers with other TLRs (such as TLR1, TLR6), which then bind to their

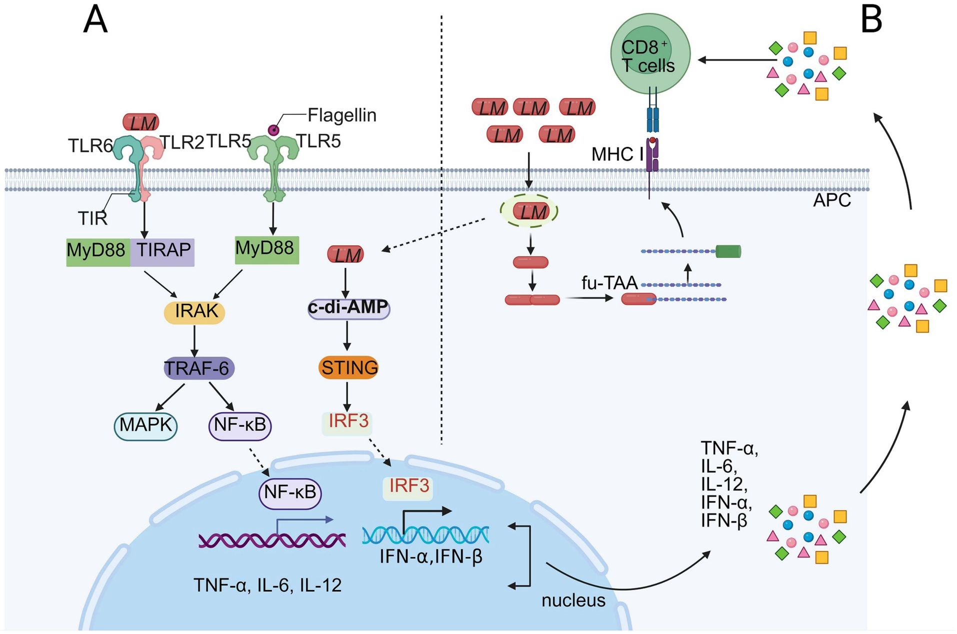

Figure 2 Schematic diagram of the host immune mechanism against *Lm* infection. (**A**) Inherent host immune response: APC recognizes *Lm* surface antigens via TLR2/TLR6 heterodimer or TLR5 homodimer, which interacts with MyD88. MyD88 attracts interleukin-1 receptor associated kinase (IRAK), which is phosphorylated and interacts with tumor necrosis factor receptor-associated factor 6 (TRAF-6), leading to activation of NF-κB; secondly, *Lm* is internalized by APC and enters cytoplasmic replication and secretes cyclicdeadenylate (c-di-AMP). c-di-AMP transmits infection signals to the stimulator of interferon genes (STING), triggering type I interferon (IFN) production. (**B**) Adaptive host immune response: APCs phagocytose *Lm*, process its antigens, and present them to CD8$^+$ T cells, priming an adaptive response. Cytokines further stimulate CD8$^+$ T cells, enabling them to execute cell-mediated immunity against *Lm*. Created in BioRender. Qu, S. (2025) https://BioRender.com/48n3dbj.

respective ligands.[45] Several studies have shown that wild-type mice have significantly increased levels of IL-10 in the serum 3–4 days after *Lm* infection. However, mice lacking IL-10 have a stronger ability to clear bacteria after *Lm* infection compared to wild-type mice.[46] A comparison of the two can illustrate that IL-10 partially inhibits the innate immune response to *Lm* in mice. Recent studies have indicated that TLR2, along with the endosomal TLR-mediated signaling pathway, can increase the expression of IL-10, thereby inhibiting the innate immune response.[47] Recent research have showed that *Lm* activates multiple signaling pathways in mast cells, mainly modulating cytokine production. TLR2 mediates IL-6 and IL-13 synthesis and p38 activation. In contrast, TNF-α, IL-1β, and MCP-1 production, ROS release, mast cell degranulation, endocytic/bactericidal functions, and ERK/NF-κB activation are TLR2-independent, indicating the crucial role of TLR2 in regulating the synthesis of IL-6 and IL-13 during *Lm* infection in mast cells.[48]

TLRs, as the most important innate immune molecules, play a role in resisting *Lm* invasion by activating downstream signaling pathways. Therefore, enhancing the ability of Toll-like receptors to resist *Lm* invasion can be used as a therapeutic approach.

C-Type Lectin Receptors

The structure domain of classical C-type lectin receptors (CLRs), C-type lectin-like domain CTLDs, consists of conserved amino acid sequences and Ca^{2+}, where Ca^{2+} mainly assists CTLDs in recognizing carbohydrates. Recent studies by Chen et al have shown that C-type lectin domain containing 5A (CLEC5A) plays a crucial role in the innate immune response to *Lm*. Mice deficient in Clec5a$^{-/-}$ show reduced production of IL-1β. Furthermore, *Lm* interacts with both TLR2 and CLEC5A on the cell surface, jointly activating TLR2 and CLEC5A to enhance pro-inflammatory responses.[49]

On the surface of natural killer cells (NK cells), there exists a non-classical C-type lectin receptor, which recognizes ligands (mainly non-carbohydrates) that are independent of Ca^{2+}. Hamid mentioned in the article that the killer cell lectin-like receptors (KIRs) located on the surface of NK cells can activate NK cells to release IFN-γ for indirect killing or directly kill *Lm* by binding with the corresponding ligands.[50]

The C-type lectin receptor plays an important role in the host immune response against *Lm*, but its specific mechanism of action still needs further research.

Nucleotide-Binding Oligomerization Domain-Like Receptors

Nucleotide-binding oligomerization domain-like receptors (NLRs) are a type of pattern recognition receptor (PRR) located in the cytoplasm. They act as receptor proteins involved in the formation of inflammasome. The inflammasome is a multiprotein complex assembled in the cytoplasm, mainly composed of PRR, apoptosis-associated speck-like protein containing a CARD (ASC), and pro-caspase-1. It serves as a platform for the activation of caspase-1, secretion of pro-inflammatory cytokines IL-1β, IL-18, and caspase-1-dependent pyroptosis.[51] Previous studies have shown that NOD-like receptor family, pyrin domain-containing protein 4 (NLRC4), NOD-like receptor family, pyrin domain-containing protein 3 (NLRP3), and absent in melanoma 2 (AIM2) inflammasomes in macrophages contribute to caspase-1 activation, exacerbating inflammation and inducing cell pyroptosis.[52] Hideki Hara et al report that lipoteichoic acid (LTA) produced after *Lm* infection can bind and activate NOD-like receptor family, pyrin domain-containing protein 6 (NLRP6), recruit and activate caspase-11 through ASC, thus promoting caspase-1 activation, IL-8 secretion, and worsening *Lm* infection.[53]

Adaptive Immune Response to Lm

Cellular Immunity

CD8$^+$ T Cells

Lm is a facultative intracellular bacterium, therefore, identifying the cells it infects is crucial for controlling infection. *Lm* antigens can be presented in multiple ways, depending on the type of infected cells.[54] Mayer et al identified 206 peptides among 79 *Lm* antigens, with 116 peptides presented on major histocompatibility complex I (MHC I) molecules,[55] elucidating that the antigen presentation of *Lm* is mainly through the MHC class I cytosolic antigen presentation pathway (Figure 2B). However, some studies have also shown the existence of MHC class II antigen presentation pathway for *Lm*, with the antigen processing and presentation depending on the type of infected cells and the compartmentalization of antigens.[45,56–58]

After entering the cell membrane, *Lm* can induce the production of IFN-γ, induce the maturation of DCs in a MyD88-independent manner, thereby stimulating and activating T cells. CD8$^+$ T cells are the most effective specific anti-*Lm* immune effector, playing an important role in clearing *Lm* infection and inducing the host to acquire lifelong protective immunity.[56,59] The primary immune response against *Lm* infection is mediated by two CD8$^+$ T cell subsets: one is MHC Ia class-restricted CD8$^+$ T cells, and the other is MHC Ib class H2-M3-restricted CD8$^+$ T cells (Figure 3). Recent studies have found that there are subgroups of cells within the memory T cell population that exhibit effector-like characteristics, which highly express Killer Cell Lectin-like Receptor G1 (KLRG1) and lowly express CD27, belonging to a subgroup of CD27^{lo}CD43^{lo} memory cells. Marie Louise Jahn et al confirm through adoptive transfer studies that these memory CD8 T cells expressing KLRG1 are core in protecting individuals from systemic *Lm* infection.[45] Therefore, the application of KLRG1$^+$ memory T cells provides a new approach for clinical anti-*Lm*.

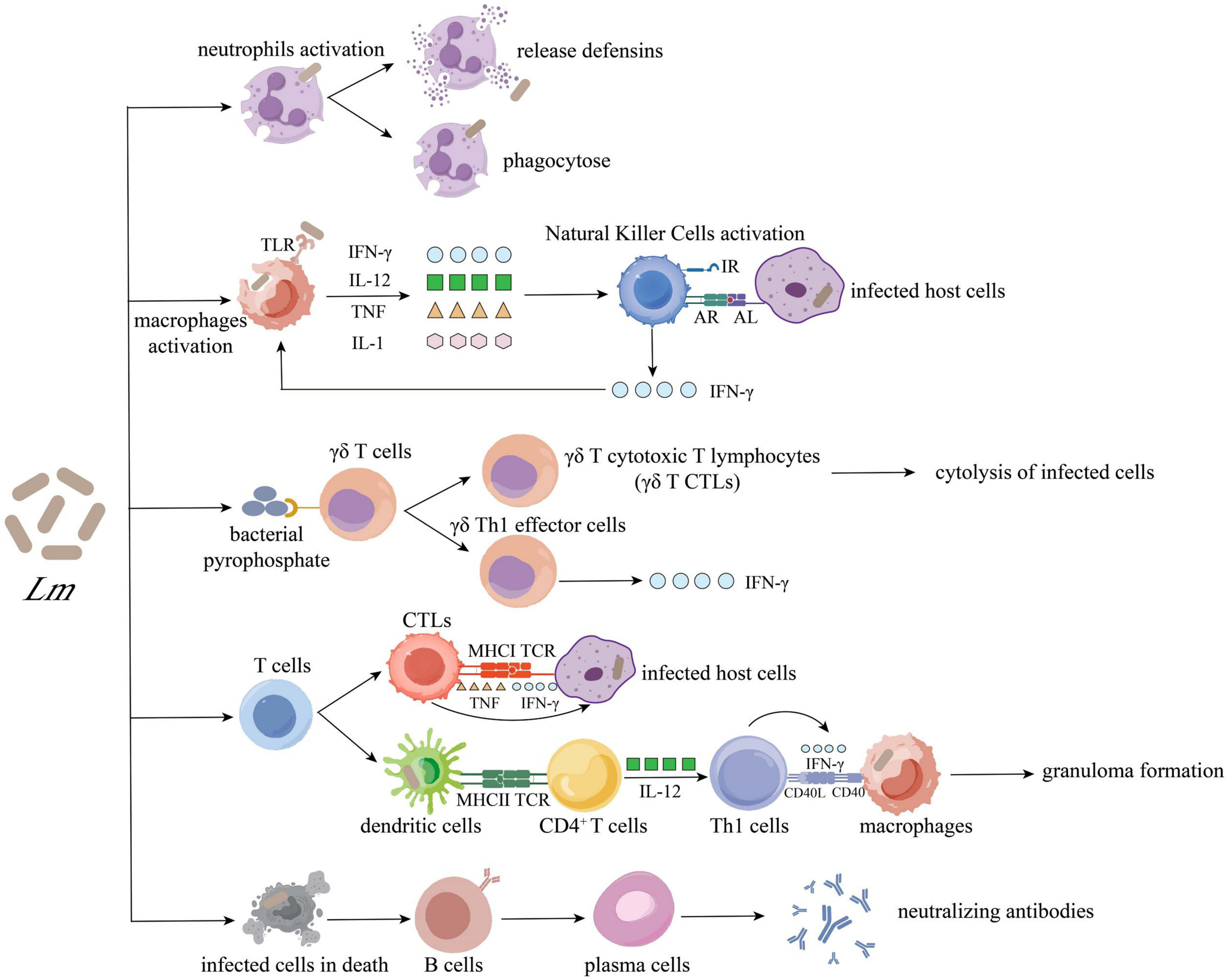

Figure 3 Main mechanisms of host immune defense against *Lm*.Neutrophils secrete defensins and phagocytose *Lm*. Macrophages activated via TLRs produce IFN-γ/IL-12, enhancing NK/Th1 responses. NK cells kill infected cells and secrete IFN-γ. γδT cells respond to pyrophosphates via cytolysis/IFN-γ. CTLs (MHCI) and Th1 cells (MHCII+IL-12) clear infection via TNF/IFN-γ, inducing macrophage ROI/RNI production and granulomas. B cells produce neutralizing antibodies against released antigens. (Created with Adobe Illustrator).

CD4$^+$ T Cells

CD4$^+$ T cells not only play an assisting role in helping CD8$^+$ T cells establish a lifelong protective memory response to *Lm*, but also assist in the clearance of *Lm* by inducing dendritic cells to produce a large amount of T helper 1 (Th1) type cytokines.[46,60] The product of the *Lm arpJ* gene can upregulate the expression of tumor necrosis factor superfamily/tumor necrosis factor receptor superfamily (Tnfsf/Tnfrsf) molecules on APC cells, thereby inhibiting the differentiation of T helper 2 type (Th2) cell subset during *Lm* infection.[61]

The CD4$^+$ T cell subpopulations of T helper 1 Cells (Th1), T helper 17 Cells (Th17), and regulatory cells (Tregs), all play certain roles in the host's response to *Lm* infection (Figure 3). D'Orazio et al found that Th17 cells can produce the pro-inflammatory cytokine IL-17A, which helps in clearing *Lm*.[45] In adaptive immunity, Tregs act as dynamic "brakes" to amplify or suppress CD8$^+$ effector T cell responses in a way most beneficial to the host. The regulation mediated by Tregs is dynamic and diverse.[62] Dolina et al revealed the dynamic changes of Tregs and their different effects mechanism at various stages:[62] on the first day of acute *Lm* infection, Tregs increase, rapidly activating the inhibitory mechanism mediated by CD73 to generate adenosine, which fine-tunes the activation of CD8$^+$ T cells through cell contact-independent suppression, thus preventing immunopathological reactions.[49,63,64] This Treg-mediated inhibition is short-lived. Subsequently, on the third day of *Lm* infection, Tregs decrease, leading to the primary expansion of *Lm*-specific CD8$^+$ T cells. By the seventh day of *Lm* infection, as *Lm*-specific antigens are cleared and CD8$^+$ T cell accumulation reaches its peak, a specific group of Tregs appears, depending on cell contact-dependent cyclic AMP transfer, mediating T cell contraction and restoring internal balance. Mischo Kursar et al found that during secondary *Lm* infection, Treg cells can limit the expansion of memory CD8$^+$ T cells.[65] Additionally, NK T cells can provide early protection by producing systemic IFN-γ, preventing intestinal *Lm* infection.[66]

The α-Galactosyl ceramide (α-GalCer) can promote the presentation of *Lm* antigen on MHC class I molecules, activate invariant NK T cells (iNKT cells) and CD8$^+$ T cells, promote a burst of cytokines and chemokines, and facilitate and regulate immune responses led by iNKT cells.[67]

In recent years, there has been no major progress in the study of cellular immune responses against *Lm*, with more research focusing on *Lm*'s evasion mechanisms of cellular immunity and the development of bacterial tumor immunotherapy using *Lm*'s adaptive immune features. For example, Selvanesan et al found that vaccines using *Lm* as a vector can activate CD4$^+$ T cells in mice for the treatment of pancreatic ductal adenocarcinoma.[68] Flickinger et al discovered that the immunodominant epitopes of *Lm* vectors can tightly bind to host MHC molecules, competitively inhibiting the presentation of cancer antigens.[3] Clinical trials are also ongoing with *Lm* that can secrete tumor-associated antigens (TAAs) effectively treating tumor-related mice in vivo.

These studies all demonstrate the key role of cellular immunity in the resistance to *Lm*. Activation of iNKT cells and CD8$^+$ T cells by glycolipid α-GC enhances host adaptive immune responses and regulates the expression of *Lm* surface protein InlB, providing new strategies for clinical defense against *Lm* infection.

Deng et al suggested that combining *Lm*-induced lifelong immune protection with newly developed therapies such as checkpoint blockade to develop live vaccines will have promising prospects,[69] suggesting that vaccine development using *Lm* as a vector may have huge potential in the future of anti-tumor field.

Humoral Immunity

As known, *Lm* is a typical intracellular bacterium, which can spread directly between cells without relying on extracellular humoral immunity, so the role of humoral immunity in resisting *Lm* infection is relatively small, and its mechanism is not clear. However, research has found that during the infection of *Lm* in mice, the host itself does not induce a strong antibody response, but the presence of certain antibodies can inhibit bacterial growth (Figure 3). [45] In addition, the vaccine of *Lm* is related to humoral immunity of the host, and results have shown that the mRNA vaccine of some adjuvants such as α-GC, ISA61 VG, etc., has a synergistic protective effect against *Listeriosis*, and can also inhibit bacterial growth by activating or enhancing the cell-mediated immune pathways.[70,71]

Despite the limited direct role of antibodies in clearing intracellular *Lm*, emerging studies highlight their synergistic potential in vaccine design. Recent work by Mayer et al (2022) identified that antibodies targeting *Lm* surface antigens can opsonize extracellular bacteria, enhancing phagocytosis by macrophages and DCs. This process indirectly promotes antigen presentation and CD8$^+$ T cell priming, bridging humoral and cellular immunity.[72]

Critically, conflicting evidence exists regarding the functional efficacy of anti-*Lm* antibodies. While some studies report antibody-mediated inhibition of bacterial adhesion to host cells, others suggest *Lm* evades neutralization through rapid intracellular translocation. This gap underscores the need to dissect antibody specificity (eg, anti-LLO vs anti-InlB) and their spatial-temporal roles in different infection stages.

Therapeutic implications are particularly promising in vaccine development. Memory T cell-based vaccines can be enhanced by incorporating humoral components. For instance, Selvanesan et al demonstrate that *Lm*-vectored vaccines expressing tumor antigens (eg, for pancreatic cancer) not only activate CD8$^+$T cells but also elicit antigen-specific IgG responses, which reduce bacterial dissemination and prolong host survival.[68]

Further, novel adjuvant technologies synergize B cell activation with iNKT cell-mediated immunity, as shown in recent mRNA-LNP vaccines. Meulewaeter et al (2024) reported that such formulations significantly boosted anti-*Lm* IgG2c and Th1-skewed memory responses, highlighting the potential of combinatorial approaches.[73]

However, major knowledge gaps persist in clinical translation. For example, Flickinger et al revealed that immunodominant *Lm* epitopes may competitively inhibit tumor antigen presentation in cancer vaccines—a challenge requiring epitope engineering to optimize humoral-cellular crosstalk.[3]

Summary and Outlook

Listeria infection in human body can manifest in three different forms, including bacteremia, neuroinvasive Listeriosis, and maternal-neonatal infection.[9] After infecting the human body, it triggers a series of immune responses and mechanisms, including innate immune response and adaptive immune response (Table 1). Various immune barriers, immune factors, and cells are activated in the process of combating *Listeria* infection (Table 1). Since *Lm* is a typical intracellular bacterium, cellular immunity plays an especially important role in resisting *Listeria* infection, while humoral immunity plays an important role in *Listeria* vaccine.

As a conditional pathogen, *Lm* infection does not have a serious impact on most normal populations, but it can cause serious harm and even death to immunocompromised groups, especially pregnant women and newborns.[7] Pregnant

Table 1 Host Defense Effects and Mechanisms of Lm

		Mechanism	Effect	References
Innate immune response	Intestinal barrier	Intestinal flora secretes antimicrobial peptides; reduces *Lm* colonization ability; increases levels of linoleic acid	Enhances intestinal barrier function and inhibits *Lm* growth	(EWIDA R M.et al,2022; JIN Tet al,2024)
		SCFA promotes TJ formation; regulates intracellular pH; inhibits HDAC; inhibits PKB and NF-κB; stimulates ILC3 to produce IL-22	Protects intestinal barrier integrity; inhibits *Lm* growth; promotes intestinal epithelial cell proliferation and weakens *Lm* colonization; reduces inflammation occurrence	(OLOFSSON L E. et al,2022;LIU X F. et al,2023;ZHANG D. et al,2023;FACHI J L. et al,2024)
	Blood-brain barrier	LLO activates NF-κB pathway in endothelial cells; induces expression of cell surface adhesion molecules P, E-selectin, ICAM-1 and VCAM-1	Promotes transcription of pro-inflammatory cytokines such as IL-1β and TNF-α; mediates cell adhesion and facilitates leukocyte entry into CNS	(SHAHID A D.et al,2021)
		InlB upregulates FLIP expression via InlB/c-Met/PI3Kα-dependent cell pathway	Mediates inactivation of Fas cell death pathway in infected monocytes	(MAUDET C.et al,2022)

(*Continued*)

Table 1 (Continued).

		Mechanism	Effect	References
	Placental barrier	Induces perforin-2 expression	Inhibits *Lm* colonization	(GAYLE P.et al,2020)
		Placental cells produce IL-1β	Activates monocyte inflammatory inducer, prevents *Lm* infection	(MEGLI C.et al,2021)
		dNK cells selectively transfer GNLY to extracellular trophoblast cells	Targets killing of *Lm*	(CRESPO Â C.et al,2020)
	Macrophages	TLRs activate TLR/MyD88/NF-κB signaling pathway	Induces DC maturation, presents *Lm* antigens	(LIU M.et al,2023)
	Dendritic cells	Immunological synapse induces MHC I and lipid peroxidation	Promotes psDC activation of CD8^{+}T cells	(GUAK H.et al,2024)
	Neutrophils	TMEM16F resists cell lysis by *Lm* by perturbing lipid	Alleviates inflammation and tissue damage	(TANG J.et al,2024)
	TLRs	TLR2 activation downstream signaling pathways increase release of IL-10, induce IL-6, IL-13 production, activate mast cells	Activates signaling pathways, releases inflammatory factors, prevents *Lm* invasion	(NGUYEN B N., C; SORIA-CASTRO R. et al,2021)
	C-type lectin receptors	Classic CLR reduces IL-1β production, interacts with TLR2; non-classical CLR activates NK cells	Activates signaling pathways, enhances host innate immune response to *Lm*; non-specifically clears *Lm*	(SHEGARFI H.,2023)
Adaptive immune response	Cellular immunity	*Lm*-induced IFN-γ production promotes DC maturation, activates CD8^{+}T cells	Clears *Lm*, induces lifelong protective immunity	(MACKANESS G B.,1962; CHáVEZ-ARROYO A. et al,2020)
		KLRG^{+} memory T cells	Protection against systemic *Lm* infection	(D'ORAZIO S E F.,2019)
		CD4^{+}T cells induce DC, produce Th1	Assists in clearing *Lm*, assists in establishing lifelong protective immunity	(LI T.et al,2021)
		iNKT-mediated innate and adaptive immune response	Explosive release of cytokines and chemokines, promote and regulate immunity	(BRENNAN P J. et al,2013)
		Th17 cells produce pro-inflammatory cytokine IL-17A	Clears *Lm*	(D'ORAZIO S E F.,2019)
		Treg cells limit expansion of memory CD8^{+}T cells	Secondary *Lm* infection	(MAYER R L.et al,2022)
		NKT cells produce systemic IFN-γ	Provides early protection, prevents *Lm* infection	(RANSON T.et al,2005)
	Humoral immunity	Antigen-antibody response	Inhibits bacterial growth	(D'ORAZIO S E F.,2019)

women can transmit *Lm* to their fetuses through the placenta,[74] increasing the risk of miscarriage, premature birth, and death.[75] Furthermore, the probability of postpartum infants developing neurological complications such as sepsis and meningitis will also significantly increase. Notably, *Lm*'s unique ability to induce potent CD8^{+}T cell responses positions it as a promising vector for bacterial tumor immunotherapy. Clinical trials using *Lm*-secreting tumor antigens demonstrate its potential to remodel the tumor microenvironment via CD8^{+} T cell-dependent mechanisms.[69] Combining *Lm*-based vaccines with checkpoint blockade or metabolic modulators may unlock synergistic antitumor efficacy. In conclusion, deepening our understanding of *Lm*-host immune interactions will accelerate the development of targeted immunotherapies and next-generation vaccines, ultimately reducing the burden of *Listeriosis* in vulnerable populations. With the continuous in-depth research on *Lm*, targeted inhibitors are also continuously being developed, such as amentoflavone can effectively inhibit LLO pore formation etc.[76] Hopefully, these new targets can help in the development of immunotherapeutics, thus prolonging the survival period of immune cells during infection and enhancing the host's ability to fight against bacteria. It is believed that the treatment methods for *Lm* will continue to be updated and improved in the future.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, conceptualization of the theoretical framework, execution and interpretation, or in all these areas. And all authors took part in drafting, revising or critically reviewing the article, gave final approval of the version to be published and agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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