Antimicrobial Peptides Inhibit Lipopolysaccharide-Induced Inflammatory Response Postprint

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Abstract

Antimicrobial peptides are small-molecule polypeptides that exhibit specific antimicrobial mechanisms against multidrug-resistant strains. Additionally, antimicrobial peptides possess anti-inflammatory activity, capable of alleviating inflammatory responses by directly neutralizing lipopolysaccharide (LPS) and inhibiting the production of pro-inflammatory cytokines; they can also influence adaptive immunity through leukocyte chemotaxis and promotion of immune cell proliferation, thereby modulating the host immune system to exert protective effects. This article reviews recent advances in the mechanisms of LPS-induced inflammation and the mechanisms by which antimicrobial peptides inhibit LPS-induced inflammatory responses.

Full Text

Inhibitory Effects of Antimicrobial Peptides on Lipopolysaccharide-Induced Inflammation

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Abstract: Antimicrobial peptides (AMPs) are small molecular polypeptides that exhibit specific antibacterial mechanisms against multidrug-resistant strains. In addition to their antimicrobial properties, AMPs possess anti-inflammatory activity and can alleviate inflammatory responses by directly neutralizing lipopolysaccharide (LPS) and inhibiting the production of biological inflammatory factors. They also influence acquired immunity

by chemoattracting leukocytes and promoting immune cell proliferation, thereby regulating the host immune system to exert protective effects. This review summarizes recent advances in understanding the mechanisms of LPS-induced inflammation and the underlying mechanisms by which AMPs inhibit LPS-induced inflammatory responses.

Keywords: antimicrobial peptides; lipopolysaccharide; inflammatory factors; mechanism of inhibiting inflammation

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Lipopolysaccharide (LPS), also known as endotoxin, is a major component of the outer membrane of Gram-negative bacteria and is considered a key molecule in the pathogenesis of endotoxic shock associated with Gram-negative bacterial infections [1]. LPS is primarily released during bacterial cell division, death, or during antibiotic treatment of bacterial infections [2]. Essential for bacterial survival, LPS establishes an effective permeability barrier that prevents invasion by various antimicrobial compounds, including hydrophobic antibiotics and antimicrobial peptides [3].

Antimicrobial peptides are biologically active, positively charged small molecular polypeptides with hydrophobic and amphipathic properties. Research has confirmed that natural cationic antimicrobial peptides can prevent infections by bacteria, viruses, and parasites [4-5]. They can also directly neutralize LPS, control inflammatory responses by inhibiting excessive production and release of inflammatory cytokines, and reduce inflammatory damage through immunomodulation, playing an important role in inflammatory processes [6-7]. Recently, antimicrobial peptides have attracted considerable attention as potential alternative therapeutic agents for treating diseases in humans, animals, and plants due to their anti-infective properties [8].

1.1 Chemical Structure of LPS

LPS is a crucial structural and functional component of the cell wall of Gram-negative bacilli, composed of an O-specific polysaccharide chain, a core oligosaccharide, and lipid A. It is a hydrophobic long-chain fatty acid with negatively charged phosphate groups [Figure 1: see original paper]. Lipid A is the most conserved portion of the LPS structure and plays a primary regulatory role in LPS biological activity [9]. Both the core oligosaccharide and phosphate groups of LPS carry negative charges, indicating that LPS has extremely high affinity for cations [1].

1.2 Signaling Pathways of LPS-Induced Inflammatory Responses

Immune cells can recognize pathogen-associated molecular patterns (PAMPs), which play an important role in inflammatory responses [11]. During infection, LPS, one of the PAMPs, binds to CD14, one of the major receptors

on the surface of immune cells, and forms an LPS-LBP-CD14 triad complex through lipopolysaccharide binding protein (LBP), which then acts on Toll-like receptor 4 (TLR4) to initiate transmembrane signal transduction and exert pro-inflammatory effects [12]. LBP is a key carrier protein that mediates the binding of LPS to the CD14 receptor on target cells. The N-terminus of LBP contains the LPS binding site, particularly residues 109-133, which are rich in hydrophobic and basic amino acids that readily bind LPS, while the C-terminus serves as the binding site for CD14. Toll-like receptors (TLRs) are the first pattern recognition receptors (PRRs) to be discovered and characterized, with TLR4 identified as the receptor that recognizes LPS [13].

LPS participates in cell-mediated inflammatory responses through two distinct signal transduction pathways. The first is the myeloid differentiation factor 88 (MyD88)-dependent pathway, and the second is the Toll/IL-1 receptor (TIR) domain-containing adaptor inducing interferon-β (TRIF)-dependent pathway, both triggered by the association of LPS with TLR4 [14]. Experimental results from Sheng et al. [15] demonstrated that LPS can rapidly induce elevated expression levels of TLR4, reaching high levels within 20 minutes of LPS stimulation and maintaining these high levels throughout the experimental period.

Activation of the LPS/TLR4 signaling pathway is regulated by multiple signaling proteins or receptors [Figure 2: see original paper]. Myeloid differentiation protein-2 (MD-2) is a special secreted protein that assists TLR4 in recognizing LPS. First, MD-2 forms a TLR4-MD-2 complex with TLR4 on the surface of immune cells. When LPS enters the bloodstream, LBP acts as a carrier protein to transfer LPS to CD14, which further aggregates LPS and presents it to the TLR4-MD-2 complex. Finally, MD-2 recognizes and binds to LPS to form a TLR4-MD-2-LPS trimer, activating the TLR4 transmembrane signaling pathway. Activation of the MyD88-dependent signaling pathway leads to phosphorylation of mitogen-activated protein kinases (MAPKs), inhibitor of nuclear factor kappa-B kinase (IKK), and nuclear factor- B (NF- B), ultimately resulting in expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) [16]. The MAPKs pathway mainly includes p38, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK) [17]. Numerous studies have shown that inhibiting phosphorylation of these three pathways can achieve anti-inflammatory effects. Activation of p38 is a prerequisite for pro-inflammatory cytokine expression, and inhibition of the p38 pathway has been confirmed to exert anti-inflammatory effects in human endotoxemia [18].

2 Molecular Mechanisms of Antimicrobial Peptide Immunomodulatory Function

When PAMPs interact with PRRs, immune cells secrete chemokines and antimicrobial peptides such as defensin α and LL-37 [20]. Antimicrobial peptides can regulate host immunity by inducing mast cell degranulation to release his-

tamine and prostaglandin D2, causing vasodilation and leading to the release of immune cells into the bloodstream, thereby inducing macrophage apoptosis and lymphocyte activation. Additionally, antimicrobial peptides can enhance fibroblast chemotaxis, promote endothelial cell and lymphocyte proliferation, and accelerate wound healing. For example, the human antimicrobial peptide LL-37 can chemoattract monocytes, neutrophils, lymphocytes, and T lymphocytes by interacting with formyl peptide receptor 1 (FPR1) [21]. Studies have shown that activated FPR1 and LL-37 not only chemoattract leukocytes but also enhance leukocyte adhesion, phagocytic capacity, and promote reactive oxygen intermediate release, thereby enhancing bactericidal activity and immunity [22].

3 Relationship Between Structure and Activity of Antimicrobial Peptides in Interaction with LPS

Detailed studies on the structure-activity relationship of antimicrobial peptides have revealed that many AMPs possess LPS-neutralizing activity, though significant differences exist among peptides with different structures. Heinbockel et al. [23] investigated the effects of two antimicrobial peptides, Hbγ-35 and Pep19-2.5, on LPS aggregate structure. Hbγ-35 decomposed LPS into cubic structures and increased LPS-induced TNF-α secretion from human monocytes. In contrast, Pep19-2.5 transformed LPS from cubic to multilamellar structures, thereby inhibiting TNF-α secretion.

Kaconis et al. [24] studied the neutralizing effects of a series of synthetic peptides on LPS and demonstrated that the ability of LPS to form multilamellar structures directly correlates with the inhibition of LPS-stimulated cytokine production, and that binding of synthetic peptides to LPS plays an important role in both antimicrobial and anti-inflammatory activities of AMPs. rBPI21 is a fragment of the bactericidal/permeability-increasing protein (BPI) from neutrophil N-terminus that selectively inhibits Gram-negative bacteria and exhibits strong affinity for LPS. rBPI21 can cause leakage in Gram-negative bacterial membranes rich in phosphatidylcholine when interacting with LPS [25].

In fact, many naturally occurring antimicrobial peptides with suboptimal structures can have their activity improved through appropriate amino acid substitutions [26]. For example, Nan et al. [27] replaced phenylalanine residues at positions 5 and 15 with tryptophan in the LL-37 analog a4, significantly enhancing its LPS-neutralizing activity.

Singh et al. [28] used a series of antimicrobial peptides derived from S1 peptidase to investigate the role of electrostatic interactions in AMP-LPS binding, confirming that while peptide binding to phospholipid membranes largely depends on the amphipathic conformation of the peptide, binding to LPS depends on the net charge and hydrophobicity of the antimicrobial peptide. Similarly, Andrä et al. [29] reported that binding of LPS to the antimicrobial peptide NK-2 relies not only on electrostatic interactions but also critically on hydrophobic interactions. Lee et al. [30] synthesized an 18-amino-acid peptide based on bovine an-

timicrobial peptide BAMP-27, named BAMP-18 and its analogs (BAMP-18-W, BAMP-18-L, BAMP-18-I, and BAMP-18-F). The results confirmed that BAMP-18 and its analogs significantly inhibited TNF-α and nitric oxide (NO). Although BMAP-18-W was less hydrophobic than BMAP-18-L, its LPS-neutralizing capacity was stronger, indicating that LPS-neutralizing activity of antimicrobial peptides depends not only on positive charge and hydrophobicity but also on other factors.

4 Mechanism of Direct LPS Neutralization by Antimicrobial Peptides

Antimicrobial peptides originate from diverse sources, including the insect-derived hybrid antimicrobial peptide CEMA from cecropin and melittin, human antimicrobial peptide LL-37, bovine antimicrobial peptide BAMP-27, and synthetic small-molecule cationic antimicrobial peptides, most of which have been confirmed to significantly inhibit LPS-induced inflammatory responses and prevent endotoxemia [31].

Fang et al. [32] demonstrated that mature U937 cells activate the NF- B pathway and release TNF-α upon LPS stimulation. When U937 cells were co-treated with LBP and LPS, the degree of NF- B activation and TNF-α expression increased significantly, confirming that LBP can exacerbate LPS-induced inflammatory responses. However, peptides P1 and MP12 significantly inhibited LPS-LBP complex-induced NF- B activation and TNF-α expression, both of which were lower than with LPS treatment alone, confirming that peptides P1 and MP12 can bind to the binding sites of CD14 and LBP, preventing LPS from binding to CD14 through LBP and thereby inhibiting LPS-induced inflammatory factor release.

Nagaoka et al. [33] showed that antimicrobial peptides CAP18, CAP11, and LL-37 can inhibit LPS binding to CD14 and thus suppress LPS-induced TNF-α expression in macrophages, demonstrating that antimicrobial peptides can bind not only to LPS but also to the immune cell membrane receptor CD14 to inhibit LPS-induced inflammation. Recently, the same group demonstrated that LL-37 prevents LPS-induced endothelial cell apoptosis by inhibiting assembly of the LPS receptor complex and blocking CD14, TLR4, and phosphorylated JNK [34]. It should be noted that the regulatory mechanism of LL-37 on TNF-α expression requires further investigation. On one hand, LL-37 demonstrates strong ability to prevent TNF-α synthesis in mouse models of endotoxic shock; on the other hand, Bąbolewska et al. [35] recently showed that LL-37 can induce degranulation and migration of mature mast cells in rat connective tissue and stimulate these cells to synthesize various cytokines, including TNF-α.

Liu et al. [36] reported that CLP-19 inhibits LPS-induced inflammatory signaling pathways and significantly reduces cytokine TNF-α release by competing with LPS for binding to LBP. When antimicrobial peptides, LPS, and LBP coexist, the antimicrobial peptide can successfully prevent LPS from binding to LBP but rarely dissociates the LPS-LBP complex. Monisha [37] found that

when antimicrobial peptide MBI-28 was pre-incubated with phagocytes for 1 hour, followed by removal of the supernatant and addition of LPS in fresh medium, MBI-28 still inhibited TNF-α expression in macrophages, suggesting that antimicrobial peptides may have an additional mechanism for inhibiting LPS-induced inflammation that requires further investigation.

Recent studies have shown that LL-37 possesses remarkable ability to inhibit cell apoptosis. Another characteristic of septic shock is that LPS and ATP cause cell death through promoting overexpression of cysteine aspartate-specific proteases 1 (caspase-1), leading to extracellular release of large amounts of pro-inflammatory cytokines including IL-1β, which is a major factor causing systemic shock and tissue damage. Hu et al. [38] confirmed that LL-37 can not only inhibit LPS binding to CD14 and TLR4 but also suppress ATP-driven P2X7 receptor activation and caspase-1 activation. Swangchan et al. [39] demonstrated that when bovine endometrial cells are stimulated by LPS, the mRNA levels of lingual antimicrobial peptide (LAP), tracheal antimicrobial peptide (TAP), S100A8, S100A9, and S100A12 increase, indicating that antimicrobial peptide gene expression is upregulated during inflammation. They also confirmed that some antimicrobial peptide genes (such as TAP and S100A9) can serve as diagnostic markers for uterine inflammation.

Kim et al. [40] synthesized three synthetic antimicrobial peptides—Lf-GNU7, BPI-GNU7, and Syn-GNU7—by adding several rationally designed LPS-targeting peptides to the original antimicrobial peptide GNU7, including amino acids 28-34 of lactoferrin (Lf28~34), amino acids 84-99 of BPI (BPI84~99), and a de novo synthetic peptide (Syn). The results demonstrated that compared with GNU7, the synthetic peptides exhibited 8-32 times enhanced antimicrobial activity, with SYN-GNU7 showing the strongest LPS-neutralizing and anti-inflammatory activity. This indicates that adding small amounts of LPS-targeting peptides to existing antimicrobial peptides can significantly enhance their anti-inflammatory activity.

The anti-inflammatory modes of action of antimicrobial peptides are complex and involve multiple molecular mechanisms. The three most important mechanisms are: 1) preventing LPS binding to LBP and thus avoiding NF- B pathway activation by blocking the antigenic epitope of lipid A; 2) accumulating positive charges on macrophage and monocyte membranes through adsorption of antimicrobial peptides, which in turn facilitates membrane binding to LPS; and 3) phagocytosis induced by antimicrobial peptides, charge neutralization, and disruption of LPS aggregates [41].

Recent studies have confirmed that antimicrobial peptides possess excellent potential for inhibiting inflammation and treating septic shock caused by LPS. Additionally, antimicrobial peptides can exert anti-inflammatory effects by regulating inflammation-related signaling pathways and transcription factors, modulating immune activity-related molecules, and regulating immune function. Although antimicrobial peptides show broad application prospects, large-scale application is not yet feasible. Issues such as the cytotoxicity of some cationic an-

timicrobial peptides [42] and their instability [43-44] require urgent resolution. With continued in-depth research on antimicrobial peptides and the development of appropriate formulations, these peptides will bring broader prospects for clinical treatment of inflammation and are expected to be applied as novel anti-inflammatory drugs for various inflammatory diseases.

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