Research Progress on the Regulatory Effects of Probiotics on the Toll-like Receptor-Nuclear Factor- B Signaling Pathway (Postprint)

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Abstract

Toll-like receptors (TLRs) constitute the primary pattern recognition receptors through which host cells detect various pathogenic microorganisms, while nuclear factor- B (NF- B) serves as a pivotal hub in TLR downstream signaling pathways. The TLR-NF- B signaling cascade is ubiquitously expressed in nearly all cell types. Upon cellular stimulation, this pathway becomes activated, thereby eliciting inflammatory, immune, and numerous pathological responses. Probiotics demonstrate capabilities in enhancing immune function, enriching beneficial intestinal microbiota, and suppressing the production of inflammatory factors associated with intestinal diseases. Certain specific probiotics can modulate the TLR-NF- B signaling pathway, consequently regulating inflammatory factor expression and ameliorating intestinal mucosal inflammation. This review primarily summarizes the principal structural and functional characteristics of TLRs and NF- B, the TLR-NF- B signaling pathway, and the regulatory effects of probiotics on this pathway, offering novel perspectives for further investigation into the mechanisms of probiotic action within host organisms.

Full Text

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Abstract

Toll-like receptors (TLRs) are the primary pattern recognition receptors through which host cells identify various pathogenic microorganisms. Nuclear factor- B (NF- B) serves as the central hub in the downstream signaling pathway of TLRs, and the TLR-NF- B signaling pathway is present in nearly all cell types. Cellular stimulation activates this pathway, triggering inflammatory, immune, and numerous pathological responses. Probiotics can enhance immunity, enrich beneficial intestinal bacteria, and inhibit the production of inflammatory factors in intestinal diseases. Certain specific probiotics can regulate the TLR-NF- B signaling pathway to modulate inflammatory factor expression and ameliorate intestinal mucosal inflammation. This review summarizes the primary structural and functional characteristics of TLRs and NF- B, the TLR-NF- B signaling pathway, and the regulatory mechanisms of probiotics on this pathway, providing new insights for further research on the role of probiotics in host organisms.

Keywords: Toll-like receptor; nuclear factor- B; Toll-like receptor-nuclear factor- B signaling pathway; probiotics; inflammatory factors
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Toll-like receptors (TLRs) are crucial pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) to initiate downstream pathways and regulate the transcriptional expression of cytokines and inflammatory factors [1]. Nuclear factor- B (NF- B) is ubiquitously present in all animal cells and serves as a bridge between innate and adaptive immunity [2]. In its inactive state, NF- B remains dormant through binding with its inhibitory protein (inhibitor kappa B, I B), but rapidly responds to upstream signals to initiate immune responses. Most research indicates that NF- B is overactivated in humans and animals with inflammatory diseases, exacerbating inflammatory responses and compromising health. Probiotics, known for their powerful beneficial effects, are widely used in humans and animals to enhance immunity, promote gastrointestinal digestion, and regulate intestinal flora balance. Recent studies have demonstrated that probiotics can also prevent and treat inflammatory diseases such as ulcerative colitis and colon cancer [3]. The primary signaling pathway involved in probiotic treatment of inflammatory diseases is the TLR-NF- B pathway, which probiotics modulate by downregulating TLR expression and inhibiting I B degradation to maintain NF- B in its dormant state, thereby alleviating inflammatory responses. Therefore, a thorough understanding of the TLR-NF- B signaling mechanism and its regulation by probiotics holds significant guiding importance for clinical disease prevention and treatment.

1.1 Structure and Classification

TLRs are cell surface pattern recognition receptors that specifically identify pathogenic microorganisms, with their structure determining their unique functions. As type I transmembrane proteins spanning the cell membrane, TLRs consist primarily of three domains: an extracellular region, a transmembrane region, and an intracellular region. The intracellular domain represents the core functional region that triggers downstream signaling cascades and activates other signaling pathways [4].

Multiple TLR types have been identified, including 11 in humans (TLR1–TLR11) and 13 in mice (TLR1–TLR13). Studies have reported 10 TLRs in chickens, among which chTLR1LA, chTLR1LB, and chTLR15 are chicken-specific [5]. Currently, TLR2, TLR4, TLR5, and TLR9 have been most extensively studied. TLRs play critical roles in the immune system and are expressed in dendritic cells, lymphocytes, macrophages, and epithelial cells.

1.2 TLR Ligands

TLRs specifically recognize pathogenic microorganisms and transmit signals into cells through their unique transmembrane structures, triggering cascades that lead to the activation of inducible factors such as NF- B and initiating both innate and adaptive immunity. TLRs recognize numerous ligands: TLR1 recognizes bacterial and fungal cell wall components; TLR2 and TLR6 recognize double-stranded RNA from damaged tissues, lipoproteins, lipopolysaccharides (LPS), and lipoteichoic acid; TLR3 recognizes viral double-stranded RNA; TLR4 recognizes LPS, defensins, and fibrinogen; TLR5 recognizes bacterial flagellin; TLR7 recognizes single-stranded RNA; and TLR9 recognizes unmethylated CpG motifs in DNA [6]. The ligands recognized by TLRs are illustrated in Figure 1 [Figure 1: see original paper].

2.1 Biological Characteristics

NF- B is a transcription factor present in nearly all cells, typically remaining dormant through binding with its inhibitory protein I B. In cancer and immunology, NF- B plays a pivotal role, particularly in immune regulation. The NF- B family comprises five related transcription factors: p50, p52, p65, RelB, and c-Rel, which can combine to form homodimers or heterodimers. All NF- B family members share an N-terminal DNA-binding domain known as the Rel homology domain (RHD), which interacts with multiple target genes to regulate their expression [7]. NF- B regulates the expression of over 400 genes, including interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)- , earning it the designation as a master switch controlling gene expression.

2.2 Role in the Immune System

In the immune system, NF- B influences immune organ formation by regulating adhesion molecules, cytokines, and organ chemokines. In RelB-knockout mice, spleen development is impaired, while mice lacking both RelB and p52 exhibit disorganized macrophages between white and red pulp regions [8]. NF- B also participates in hematopoietic cell proliferation, differentiation, and apoptosis. Studies have reported granulocytosis affecting cell proliferation in mice deficient in p50 and p65. NF- B plays an important role in adaptive immunity; in p65-knockout experiments, mouse B cell and T cell proliferation and activation were suppressed. Additionally, NF- B affects CD86 and CD80 activation, with CD8+ T cell involvement also requiring NF- B participation [9].

2.3 Mediated Inflammatory Responses

Inflammatory responses represent a self-protective mechanism triggered when normal physiological functions are threatened. These responses adversely affect health, causing conditions such as ulcerative colitis and cancer, with numerous studies linking these inflammatory reactions to NF- B. NF- B-mediated inflammatory responses proceed through three main stages: the latent phase, the induction phase, and the resolution phase.

1. **Latent Phase**: Before NF- B activation, genes related to inflammatory stimuli, cell proliferation and apoptosis, and certain viral genes are expressed at very low "basal levels." These latent-phase genes are rapidly induced upon NF- B activation. During this phase, all Rel family genes are expressed, with p50 forming heterodimers with p65 that bind to I B inhibitors. Additionally, p50 homodimers (p50-p50) circulate in the cell, interacting with other regulatory factors to maintain downstream gene silencing, while RelB and c-Rel are also expressed, albeit at very low levels due to their requirement for NF- B induction [10, 11].
2. **Induction Phase**: Inducers of NF- B activation include pro-inflammatory cytokines, tumor necrosis factors, and antigens, which bind to recognition receptors on the cell surface or within cells, triggering cascades that activate the I B kinase (IKK) complex. The IKK complex primarily exists as IKK , IKK , and IKK , with IKK phosphorylating I B, leading to its degradation by proteasomes. Normally, I B binds to the p65-p50 heterodimer; following I B degradation, the p65-p50 heterodimer enters the nucleus and binds to specific sites on downstream genes to regulate their transcription [12].
3. **Resolution Phase**: As inflammation persists, pro-inflammatory factor concentrations decrease, I B degradation slows, and NF- B expression gradually diminishes, thereby reducing the inflammatory response [13].

3.1 TLR-NF- B Signaling Pathway

As PRRs, TLRs recognize various foreign microorganisms and initiate complex intracellular signal transduction pathways. These signaling networks involve adaptor proteins and protein kinases including p38 mitogen-activated protein kinase, c-Jun N-terminal kinase, activator protein, and NF- B [14]. Due to extensive research on TLR2 and TLR4, the TLR-NF- B signaling pathway has been relatively well characterized. Numerous studies have confirmed that NF- B is the main component of TLR signal transduction, with the expression of many genes being regulated through TLR-induced NF- B pathway activation.

In cells, the RHD of NF- B typically binds to its inhibitor I B, maintaining a dormant state. When PAMPs stimulate the TIR domain of TLRs, TLRs respond and transmit signals to the NF- B pathway, causing NF- B to rapidly dissociate from I B and enter the nucleus, where it binds to relevant DNA sequences to regulate downstream cytokines or target genes. Interestingly, different TLRs activate the TLR-NF- B signaling pathway through distinct routes, with two major pathways currently recognized: the myeloid differentiation factor 88 (MyD88)-dependent pathway and the MyD88-independent pathway [15]. The TLR-NF- B signaling pathway is illustrated in Figure 2 [Figure 2: see original paper].

MyD88-Dependent Pathway: In the extracellular space, inflammatory factors such as LPS, IL-1, and TNF bind to TLR4, which transmits signals into the cell. The TIR domain of TLR4 binds to the carboxyl terminus of MyD88, while the amino terminus of MyD88 binds to the amino terminus of IL-1 receptor-associated kinase (IRAK), thereby activating IRAK autophosphorylation. The resulting IRAK1, IRAK2, IRAK4, and IRAK6 activate downstream pathways, with IRAK1, IRAK2, and IRAK4 activating tumor necrosis factor receptors and IRAK6 activating the inhibitor of NF- B kinase (IKK) complex. The IKK complex phosphorylates I B, which is then ubiquitinated by ubiquitin ligase and degraded, activating NF- B from its dormant state and allowing it to enter the nucleus to regulate gene transcription.

MyD88-Independent Pathway: This pathway bypasses MyD88 and instead activates interferon regulatory factors through Toll-like receptor adapter molecules (TICAM) 1 and TICAM2. Upon activation, these interferon regulatory factors enter the nucleus to initiate type I interferon gene expression. Toll-interacting protein (TOLLIP) can inhibit TLR signal transduction by preventing protein kinase phosphorylation, thereby blocking the MyD88-dependent signaling pathway [16]. Fu et al. [17] stimulated bovine endometrial epithelial cells with LPS and found significant upregulation of TLR4, transcription factors, and cytokines, along with increased TOLLIP mRNA levels, indicating that LPS activates both MyD88-dependent and MyD88-independent pathways. Hou et al. [18] demonstrated that LPS could stimulate interferon-inducible gene transcription in MyD88-knockout cells, acting directly through interferon regulatory factor 3 binding to NF- B without requiring the MyD88-dependent pathway.

Abbreviations: LPS: lipopolysaccharides; IL-1: interleukin-1; TNF: tumor necrosis factor; TLR: Toll-like receptor; MyD88: myeloid differentiation primary response protein 88; IRAK6: interleukin-6 receptor-associated kinase; IKK: inhibitor of nuclear factor- B kinase; I B: inhibitor of nuclear factor- B; NF- B: nuclear factor- B; TRIF: TIR-domain-containing adaptor inducing interferon- ; TBK1: tank-binding kinase 1; IRF3: interferon regulatory factor-3.

3.2 Regulatory Mechanisms of Probiotics on the TLR-NF- B Signaling Pathway

Probiotics are widely used as feed additives in animal husbandry. Dietary supplementation with probiotics enables colonization of beneficial bacteria in the gastrointestinal tract, promotes intestinal mucosal and immune system development, maintains intestinal mucosal structural integrity, enhances intestinal flora abundance, and maintains intestinal immune balance through multiple mechanisms, all of which positively impact animal health and production. Furthermore, numerous studies have shown that probiotics can ameliorate intestinal mucosal inflammation by inhibiting TLR-NF- B signaling pathway activation, thereby controlling diseases.

Under unstimulated conditions, NF- B remains dormant in the cytoplasm through binding with I B. When inflammatory factors stimulate TLRs, the MyD88-dependent pathway activates NF- B signaling, leading to I B phosphorylation by kinases and subsequent ubiquitination and degradation. Upon dissociation from I B, NF- B rapidly enters the nucleus, binds to specific DNA sites, and initiates transcription of inflammation-related genes, ultimately causing inflammatory responses that harm animal health. Research has demonstrated that certain live probiotic cells, dead cells, and their extracellular metabolites can improve inflammatory responses in animals [19]. When ingested, probiotics can intervene in the TLR-NF- B signaling pathway by inhibiting TLR expression, regulating I B phosphorylation and ubiquitination, preventing I B degradation, and blocking NF- B nuclear translocation, thereby preventing NF- B from regulating downstream factors. Probiotics can also export NF- B subunit p65 from the nucleus through peroxisome proliferator-activated receptor (PPAR)-dependent signaling pathways, limiting NF- B pathway activity and effectively preventing enteritis while improving the gastrointestinal immune environment [20]. However, the specific regulatory mechanisms of probiotics on the TLR-NF- B signaling pathway remain unclear, and further investigation of these mechanisms is crucial for probiotic applications in humans and animals.

4.1 Effects on the TLR-NF- B Signaling Pathway in Macrophages

Macrophages are antigen-presenting cells that play vital roles in immune regulation. Soluble factors secreted by some probiotics can modulate inflamma-

tory responses by regulating the TLR-NF- B signaling pathway in macrophages, thereby preventing tissue damage. Jang et al. [21] induced macrophages with LPS and found that treatment with *Lactobacillus brevis* G-101 reduced secretion of TNF- , IL-6, and IL-1 , thereby alleviating inflammation. Matsumoto et al. [22] reported that *Lactobacillus casei* downregulated NF- B activity and inhibited IL-6 secretion from inflamed macrophages. However, some studies have shown that certain probiotics can stimulate inflammatory responses in macrophages; for example, *Enterococcus faecium* can stimulate macrophages to produce IL-6 and IL-10, while *Lactobacillus casei* can induce IL-12 production [23].

4.2 Effects on the TLR-NF- B Signaling Pathway in Epithelial Cells

The TLR-NF- B signaling pathway is central to probiotic interactions with various epithelial cells. Probiotics or their secretions can regulate inflammatory responses in epithelial cells by reducing NF- B activity or inhibiting I B degradation. Wang et al. [24] reported that *Lactobacillus plantarum* inhibited I B degradation to alleviate TNF-induced inflammatory responses. Sokol et al. [25] found that *Faecalibacterium prausnitzii* DSM17677 could inhibit NF- B activity induced by IL-1 , while *Streptococcus salivarius* could also inhibit TLR-NF- B signaling and downregulate IL-8 secretion to prevent inflammation. Liu [26] demonstrated that infecting bovine endometrial epithelial cells with *E. coli* upregulated total protein expression of NF- B2 and p65, while pretreatment with *Lactobacillus rhamnosus* GR-1 inhibited expression of these proteins, indicating that GR-1 can attenuate both MyD88-dependent and -independent signaling pathways, enhance interactions between NOD-like receptors (NLRs) and TLRs, and reduce release of inflammatory cytokines including IL-1, IL-18, TNF- , and IL-6, thereby inhibiting *E. coli*-induced inflammation in bovine endometrial epithelial cells. Mihai et al. [27] treated porcine intestinal epithelial cells with lactobacilli and found lower IL-6 and IL-8 expression compared to untreated cells. Since IL-6 and IL-8 are inflammatory cytokines produced through the TLR4-mediated TLR-NF- B signaling pathway, this indicates that lactobacilli can inhibit TLR-NF- B signal transduction. Xu et al. [28] established a colitis mouse model to study the effects of three probiotic strains on ulcerative colitis and found that NF- B p65 protein expression was relatively high in colonic tissue of model mice, confirming colitis induction. Following probiotic treatment, NF- B p65 protein expression decreased significantly while I B expression increased, further demonstrating that probiotics can reduce inflammation by inhibiting the TLR-NF- B signaling pathway. Zhang et al. [29] found that *Lactobacillus rhamnosus* LGG could inhibit the TLR-NF- B signaling pathway by reducing I B degradation rate, decreasing NF- B nuclear translocation and consequently lowering IL-8 expression levels. Lee et al. [30] used dextran sulfate sodium (DSS) to induce inflammatory responses in mice and demonstrated that *Lactobacillus plantarum* HY115 and *Lactobacillus brevis* HY7401 exerted anti-inflammatory effects. In mouse tissues, DSS stimulated the IKK complex, causing I B degradation and dissociation from NF- B, which then rapidly entered the nucleus

to regulate inflammatory factor mRNA expression and induce inflammation. The study proved that HY115 and HY7401 could inhibit NF- B activation by suppressing I B phosphorylation, thereby inhibiting mRNA expression of IL-1 , TNF- , and other factors to reduce inflammation. However, not all probiotics inhibit NF- B activation; Matsuguchi et al. [31] found that some probiotics such as *Lactobacillus* YIT9029 and *Lactobacillus fermentum* YIT0159 not only fail to suppress NF- B activation but actually stimulate it, leading to TNF- secretion that exacerbates inflammation.

5 Conclusions

Research on TLRs, NF- B, and the TLR-NF- B signaling pathway has become increasingly comprehensive in recent years. The TLR-NF- B signaling pathway plays a crucial role in inflammation development in animal organisms, and strategies for blocking this pathway have attracted significant attention from life science and medical researchers. Although many NF- B inhibitors are commercially available, they often have unclear side effects and poor specificity, limiting their therapeutic efficacy. Probiotics have numerous applications as feed additives, and beyond their roles in increasing intestinal flora abundance, improving intestinal health, and enhancing immunity, substantial evidence indicates that specific probiotics can serve as TLR-NF- B signaling pathway inhibitors to effectively treat inflammatory diseases. However, the specific inhibitory mechanisms of probiotics on the TLR-NF- B signaling pathway remain unclear, and probiotic effects exhibit specificity. Future research should focus on elucidating the inhibitory mechanisms of probiotics on the TLR-NF- B signaling pathway and comparing the inhibitory effects of different probiotic strains.

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