Regulatory Effects of Gut Microbiota on Poultry Intestinal Immune Function and Its Mechanisms

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Abstract

A large number of microorganisms colonize the poultry gut, and these microorganisms along with their metabolites actively participate in poultry digestive and immune response processes, exerting important regulatory effects on poultry health. With the global restriction or ban of antibiotics, poultry gut problems have become increasingly prominent, causing substantial economic losses to producers. However, research on poultry gut microbiota remains at a relatively preliminary stage. This paper first reviews the composition of poultry gut microbiota and the current research status of nutritional regulation measures for poultry gut health, and further explores in depth the regulatory effects of gut microbial genomes and their metabolites on animal intestinal immune function, as well as the potential mechanisms by which the intestinal mucosal immune system regulates gut microbiota, aiming to provide references for further research on nutritional measures to improve poultry gut health.

Full Text

Regulation and Mechanisms of Gut Microbiota on Poultry Intestinal Immune Function

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Abstract

The avian gastrointestinal tract harbors a vast and diverse microbial community that actively participates in digestion and immune responses, playing a crucial regulatory role in poultry health. As antibiotics face global restrictions or complete bans, intestinal disorders in poultry have become increasingly prominent,

causing substantial economic losses to producers. However, research on poultry gut microbiota remains relatively nascent. This review first summarizes the composition of poultry gut microbiota and current nutritional strategies for modulating intestinal health, then delves into how microbial genomes and their metabolites regulate intestinal immune function. We further explore potential mechanisms through which the intestinal mucosal immune system modulates gut microbiota, aiming to provide a foundation for developing nutritional interventions to improve poultry intestinal health.

Keywords: poultry; gut microbiota; intestinal immunity; gut health

The intestine serves not only as a digestive organ but also as the body' s largest immune organ, playing vital roles in maintaining normal nutrient metabolism and immune defense. The animal gut harbors a massive and complex microbial community composed primarily of bacteria, along with fungi, yeasts, viruses, and archaea. These microorganisms have co-evolved with their hosts in a mutually dependent relationship, forming a microecosystem. This microecosystem contains approximately 100 times more genes than the host' s own genome, conferring metabolic and immune functions that the host lacks. In humans, for example, the normal adult gut contains up to 10^{14} microbial cells comprising approximately 4,000 bacterial strains that constitute the important intestinal microbiota [**?**]. With advances in molecular biology, researchers have gradually recognized that gut microbiota, as a complex microbial community, plays a critical regulatory role in host health and disease. Poultry serve as important animal models in biological research and represent a significant component of the global protein industry with substantial economic value. In poultry production, maintaining intestinal health is essential for improving production efficiency. On one hand, the intestine regulates nutrient digestion and absorption to provide necessary nutrition for growth; on the other hand, it serves as a critical barrier against environmental pathogens, effectively defending against invasive disease agents [**?**]. As antibiotics become restricted or banned, poultry intestinal health problems have become increasingly prominent, particularly in the layer industry. In recent years, intestinal health has garnered growing attention from animal scientists and poultry producers. This review focuses on the potential regulatory mechanisms between gut microbiota and the intestinal immune system and the impact of gut microbiota on poultry immune regulation.

1 Composition of Poultry Gut Microbiota

Poultry gastrointestinal tissues harbor over one million microbial genes, equivalent to 40-50 times the chicken' s entire genome. Among these, 90-95% of cecal microorganisms cannot be cultured in laboratories and can only be identified through molecular biological methods. Nevertheless, these microbes play crucial roles in dietary nutrient digestion, absorption, and poultry immune metabolism. Gut microbiota diversity correlates with diet, sex, age, and individual conditions, and microbial distribution varies across different intestinal segments. However, numerous studies have shown that Lactobacillaceae, Streptococcaceae, Clostridi-

aceae, and Enterobacteriaceae constitute the main components of gastrointestinal microbiota across different sites in poultry. These microbial communities colonize the intestine in a regular pattern, maintaining an "ecological balance" with poultry immune metabolism [**?**].

The crop, the first organ for feed storage in poultry, harbors a large microbial population dominated by lactic acid bacteria that produce substantial amounts of lactic acid and short-chain fatty acids (SCFAs). Microbial fermentation in the crop represents the first stage of feed digestion, and the formation of organic acids provides effective protection against invading pathogens. The proventriculus has relatively low pH and serves as an important site for nutrient digestion, particularly protein hydrolysis, containing high concentrations of lactobacilli, enterococci, and lactose-negative-regulating enterobacteria. Whether these bacteria originally colonize the intestine or originate from feed remains unclear. Additionally, microbial density in the small intestine fluctuates considerably, primarily comprising lactic acid bacteria, enterococci, *E. coli*, and *Clostridium*. The relatively low microbial density in the small intestine facilitates nutrient digestion and absorption by reducing competition between host and microbes. Low pH in the duodenum, along with substantial bile and pancreatic secretions, serves as an important regulatory factor reducing intestinal microbial density. Studies have shown that in distal small intestine contents, total bacterial counts reach 7-9 log(CFU/g), dominated by lactobacilli, enterobacteria, and enterococci [**?**]. The cecum represents the main colonization site for gut microbiota and the primary region for anaerobic fermentation, with anaerobe density significantly higher than in the upper digestive tract. Consequently, feed fermentation capacity in the cecum substantially exceeds that of the small intestine [**?**]. SCFA concentrations are highest in the cecum, primarily acetate, propionate, and butyrate, with relatively low lactate levels [**?**]. This regular distribution of intestinal microorganisms constitutes the poultry gastrointestinal digestive and immune system, maintaining intestinal health.

2 Factors Affecting Poultry Gut Health and Regulatory Measures

Despite extensive research on gut health by medical and veterinary scientists over the past decade, our understanding remains limited. In livestock and poultry research, gut health represents a major challenge, with necrotic enteritis and bacterial enteritis characterized by intestinal dysbiosis being the most significant clinical manifestations. Necrotic enteritis, primarily caused by *Clostridium perfringens*, *Eimeria*, and *Salmonella enteritidis*, induces intestinal inflammation and necrosis, leading to poultry mortality. Intestinal dysbiosis results from imbalance between commensal and pathogenic bacteria, typically without obvious clinical symptoms, and its etiology remains unclear. As antibiotic growth promoters face global restrictions or bans, intestinal problems in livestock and poultry have become increasingly prominent. Particularly under current conditions of suboptimal poultry production environments and inadequate feed nutri-

tional and raw material processing practices in China, the incidence of intestinal diseases remains high, causing substantial economic losses.

2.1 Influencing Factors

Factors causing poultry intestinal problems are numerous and complex, primarily including environmental stress (high temperature and humidity, rodents), feed mold (mycotoxins), bacterial contamination of drinking water, feed nutrition (feed viscosity), bacterial infections (*Campylobacter*, *Clostridium perfringens*, *Salmonella*), coccidiosis, and viral infections (avian influenza, bronchitis, respiratory diseases). Studies have shown that heat stress reduces feed intake, increases intestinal mucosal permeability, and induces intestinal inflammation and decreased growth performance [**?**]. Moldy feed damages the liver and immune system, affects intestinal mucosal integrity and permeability, impairs intestinal barrier function, and reduces growth performance [**?**]. Infection with *Clostridium perfringens*, *Eimeria*, and *Salmonella enteritidis* alters cecal microbiota structure and modulates expression of interleukin-8 (IL-8) and interleukin-17 (IL-17) [**?**]. Furthermore, feed nutritional composition affects intestinal health; increased digesta viscosity often correlates with increased populations of *Clostridium perfringens*, *Campylobacter*, and spirochetes [**?**]. Replacing corn with viscous wheat increases disease risk in poultry, and viscous feed also increases susceptibility to parasitic infections. Recent research shows that antibiotic administration to chicks significantly alters gut microbiota composition, with fecal microbiota dominated by Proteobacteria, particularly *E. coli*, whereas untreated chicks harbor primarily Firmicutes, including lactobacilli and clostridia. Moreover, early-life gut microbiota disturbance affects adaptive immunity in later rearing and laying phases [**?**]. Thus, poultry intestinal health represents a complex issue requiring comprehensive technical solutions.

2.2 Regulatory Technologies

Gut microbiota serves as an important health regulator in poultry, participating in maintenance of intestinal mucosal structure integrity and functional performance. The intestinal mucosal immune system specifically distinguishes commensal microbiota from pathogens, defending against pathogen invasion and protecting intestinal health. Therefore, modulating gut microbiota to maximize beneficial bacterial populations represents a crucial measure for maintaining poultry intestinal health.

Current research on poultry gut health modulation focuses primarily on nutritional strategies, including prebiotics [**?**], probiotics [**?**] (*Lactobacillus*, *Bifidobacterium*, *Bacillus licheniformis*, yeasts), enzymes (xylanase, glucanase, mannanase) [**?**], microbial metabolites (butyrate, etc.) [**?**], and vitamins and minerals [**?**]. These nutritional additives can modulate gut microbiota, increase colonization of beneficial bacteria (lactobacilli and bifidobacteria), promote intestinal villus growth, reduce pathogen colonization on intestinal epithelial cells, enhance immune capacity, and improve intestinal health. Additionally, studies

show that dietary supplementation with mycotoxin binders, zeolite, and aluminosilicates [**?**] can improve growth performance and disease resistance, alter gut microbiota, and promote intestinal health. In practical production, besides nutritional modulation, attention must be paid to poultry rearing environment and management practices, with establishment of robust biosecurity systems to reduce disease risk.

3 Impact of Microbial Flora on Intestinal Immunity

To maximize the regulatory role of microbial flora in poultry intestinal health, understanding the underlying mechanisms between gut microbiota and the intestinal immune system is essential. Similar to mammals, the avian intestinal immune system is relatively complex, comprising intestinal mucosal layers, epithelial cells, commensal microorganisms, and immune cells that collectively form the intestinal immune defense system [**?**]. Gut microbiota serves as a critical initiator and regulator of both innate and adaptive immunity in poultry. When encountering pathogens, the host activates its innate immune system, which relies primarily on pattern recognition receptors including Toll-like receptors (TLRs) and NOD-like receptors (NLRs). TLRs specifically recognize pathogen-associated molecular patterns, initiate inflammatory responses, and ultimately clear pathogens [**?**]. The mechanism involves the fact that commensal and pathogenic microorganisms share similar pattern recognition molecular structures, raising the question of how the host immune system distinguishes commensal from pathogenic bacteria on the intestinal mucosal surface during long-term microbial exposure. The specific mechanisms remain unclear, and research on molecular mechanisms of poultry immune modulation by gut microbiota is limited. The following discussion primarily references human studies on gut microbiota immune regulation.

3.1 Gut Microbe-Derived Nucleic Acids

Host cells initiate innate immunity primarily by recognizing pathogen-associated molecular patterns, specifically conserved nucleic acid structures from pathogenic microorganisms. These nucleic acid domains can be recognized by host TLR receptors (TLR3, TLR7, TLR8, and TLR9) and intracellular DNA sensors [**?**]. TLR3 is activated by double-stranded RNA, TLR7 and TLR8 by single-stranded RNA, and TLR9 by CpG motifs in single-stranded DNA. When host-derived TLR3 and TLR7-9 detect pathogens, they activate the innate immune system to clear pathogens automatically. When TLRs encounter host-derived nucleic acids, they can bypass or modify self-nucleic acids to provide immune protection [**?**].

Furthermore, gut microbiota DNA contains abundant unmethylated CpG dinucleotides that can be recognized by TLR9, regulating gastrointestinal T cell function and demonstrating that gut microbiota DNA can serve as an immunomodulator [**?**]. The mechanisms by which gut microbiota modulates host cellular

immunity require further investigation. It is generally accepted that unmethylated CpG in microorganisms can bypass antigen-presenting cells to stimulate T cell differentiation. Studies have confirmed that bacterial DNA and synthetic oligonucleotides (rich in unmethylated CpG) can effectively modulate innate and adaptive immunity by regulating dendritic cell and macrophage functions [**?**].

Additionally, research shows that commensal bacterial DNA contains suppressive DNA oligonucleotide fragments that participate in promoting intestinal immune homeostasis. These DNA oligonucleotide fragments regulate host immune responses in a species-specific manner, correlating with the frequency of immunosuppressive DNA sequences in gut microbiota [**?**]. For example, *Lactobacillus* DNA is rich in suppressive oligonucleotide fragments that can effectively maintain regulatory T cell conversion under inflammatory conditions, suppress pathogen-induced inflammatory responses, preserve immunosuppression in the microbiota, promote balanced microbial DNA structure, and thereby effectively regulate intestinal immune homeostasis [**?**].

3.2 Gut Microbial Metabolites

Mammalian studies have revealed that specific gut microorganisms play crucial roles in the proliferation and differentiation of certain intestinal immune cells. For instance, *Bacteroides fragilis* can promote IL-17 production and subsequent T helper (Th) cell generation [**?**]. *Lactobacillus* can effectively stimulate production of low-molecular-weight peptides that activate the intestinal immune system and enhance disease defense [**?**]. Gut microbiota also produces large amounts of SCFAs that directly or indirectly lower intestinal pH, produce bacteriocins capable of killing cells, and alter pathogen colonization receptors to eliminate certain bacteria and defend against pathogen invasion [**?**]. Recent studies have confirmed that microbial metabolites (primarily small molecules) such as SCFAs (acetate, propionate, and butyrate) and quorum-sensing signal molecules play important roles as chemical signals in microbe-host interactions (Figure 1 [Figure 1: see original paper]).

Figure 1 Relationship between intestinal microbial metabolites and intestinal mucosal immunity [**?**]. (Gut microbiota: gut microbiota; SCFA: short-chain fatty acid; Acetate: acetate; Propionate: propionate; Butyrate: butyrate; GPR41: G protein-coupled receptor 41; GPR43: G protein-coupled receptor 43; Epithelial cell: epithelial cell; Energy: energy; Neutrophils chemotaxis: neutrophil chemotaxis; NF- B: nuclear factor- B; IL-12: interleukin-12; TNF-α: tumor necrosis factor α; IL-18: interleukin-18; Inflammasome activation: inflammasome activation; MAPK signaling: mitogen-activated protein kinase signaling; IL-10: interleukin-10; GPR109A: G protein-coupled receptor 109A; Dendritic cell: dendritic cell; QS signal molecules: quorum sensing signal molecules; AI-2: autoinducer 2; γ-PGA: poly-γ-glutamic acid; AHL: N-acylhomoserine lactones; PQS: pseudomonas quinolone signal; TLRs: Toll-like receptors; IL-8: interleukin-8; Inflammatory gene expression: inflammatory gene expression;

NF- B signaling: nuclear factor- B signaling; Inhibit innate immunity: inhibit innate immunity; Naïve CD4+ T cell: naïve CD4+ T cell; Treg differentiation: Treg differentiation; IL-17: interleukin-17; IL-22: interleukin-22.)

3.2.1 Short-Chain Fatty Acids Acetate is primarily metabolized and absorbed by the liver, while propionate is released into peripheral tissues. In the intestine, acetate and propionate are mainly produced by Bacteroidetes metabolism, whereas butyrate is produced by Firmicutes metabolism [**?**]. Studies have found that butyrate can effectively modulate intestinal macrophage immune responses by inhibiting histone deacetylase expression, thereby weakening macrophage reactions to cecal microbiota [**?**]. Currently, butyrate is recognized as an important regulator of host immune responses, acting as both a histone deacetylase inhibitor and G protein-coupled receptor agonist [**?**]. Furthermore, butyrate can inhibit nuclear factor- B (NF- B) expression [**?**], induce mucin synthesis [**?**], alter mucosal layer composition, inhibit release of interleukin-12 (IL-12) and tumor necrosis factor-α (TNF-α) [**?**], and exert anti-inflammatory effects. Under stress conditions, butyrate can reduce bacterial translocation and enhance intestinal barrier function by strengthening tight junction assembly [**?**]. Additionally, both butyrate and propionate can induce differentiation of regulatory T cells in colonic mucosa and improve colitis symptoms [**?**].

Other studies have confirmed that SCFAs produced by gut microbiota can bind G protein-coupled receptor 43 (GPR43) on neutrophils to inhibit inflammatory responses [**?**], while also regulating glucagon-like peptide synthesis in enteroendocrine cells [**?**]. SCFAs activate GPR41 and GPR43 expression in intestinal epithelial cells, further activating mitogen-activated protein kinase (MAPK) signaling pathways and promoting release of inflammatory cytokines [**?**]. Butyrate and propionate can also promote gluconeogenesis and regulate host carbohydrate and energy metabolism balance [**?**].

3.2.2 Quorum Sensing Signal Molecules Gut microbiota also metabolically produce quorum-sensing signal molecules such as autoinducers and poly-γ-glutamic acid (γ-PGA) that participate in regulating host immune responses (Figure 1). Quorum sensing is an important bacterial regulatory mechanism whereby bacteria perceive surrounding population density through self-produced autoinducers. When bacterial density reaches a certain threshold, a series of genes are activated to regulate collective bacterial behavior [**?**]. This bacterial communication plays crucial roles in various bacterial processes, including bioluminescence, symbiosis, biofilm formation, antibiotic production, swarming motility, sporulation, gene exchange, and pathogenesis.

Bacterial quorum-sensing autoinducers can be classified into four categories: (1) Gram-negative bacterial signals, primarily N-acylhomoserine lactones (AHL), also called autoinducer-1 (AI-1). These water-soluble, membrane-permeable molecules can freely enter and exit cells, maintaining equal intra- and extracellular concentrations. AHL is synthesized by LuxI-type enzymes that catalyze

binding of acyl side chains from acyl-carrier proteins to homoserine moieties from S-adenosylmethionine, followed by lactonization [**?**], regulating processes such as bioluminescence, sporulation, conjugation, nutrient acquisition, biofilm formation, biocorrosion, and antibiosis [**?**]; (2) Gram-positive bacterial signals, primarily amino acids and short peptides; (3) Furanone boric acid diesters, also called autoinducer-2 (AI-2), which together with the key biosynthetic enzyme LuxS form the AI-2/LuxS system mediating intra- and interspecies communication in both Gram-positive and Gram-negative bacteria [**?**]; and (4) Diffusible signal factors (DSF), such as quinolone and phenazine signals found in *Pseudomonas aeruginosa* [**?**] and indole from *Escherichia coli* [**?**].

Pathogens can utilize quorum-sensing autoinducers to activate virulence factor expression and promote biofilm formation, facilitating invasion and colonization in hosts. For example, the opportunistic pathogen *P. aeruginosa*, which causes cystic fibrosis, produces multiple quorum-sensing molecules such as AHL and quinolone autoinducers to assist its pathogenic process [**?**, **?**]. *P. aeruginosa* AHL signal molecules can selectively reduce NF- B function, particularly inhibiting NF- B-induced inflammatory cytokines and immune-related gene expression, thereby facilitating bacterial colonization and infection [**?**]. Additionally, the *P. aeruginosa* quorum-sensing signal molecule 4-hydroxy-2-alkylquinoline, a derivative of the pseudomonas quinolone signal (PQS), can inhibit NF- B binding to its receptors, downregulate NF- B target genes, delay degradation of NF- B inhibitors (I B), and thereby activate NF- B signaling pathways to suppress host innate immunity [**?**]. Furthermore, *E. coli* in the gut also produces the quorum-sensing autoinducer AI-2, which can promote release of the inflammatory cytokine IL-8, stimulate transcription of immune-related pathways in intestinal epithelial cells, upregulate negative regulatory factors, and thereby suppress host inflammatory responses [**?**].

Gut microbiota can also produce γ-PGA, which exists primarily in *Bacillus subtilis* but not in mammalian intestines, though it is produced during soybean fermentation [**?**]. Studies have confirmed that *B. subtilis*-derived γ-PGA can regulate Th1/Th2 cell development, particularly favoring stimulation of dendritic cells to develop into Th1-type naïve CD4+ T cells, inducing release of IL-12 and interleukin-6 (IL-6) [**?**], and stimulating natural killer cell anti-tumor immune effects [**?**]. Additionally, γ-PGA can promote selective differentiation of regulatory T cells and inhibit Th17 cell differentiation [**?**]. Dietary γ-PGA supplementation can increase intestinal lactobacilli populations, reduce *Fusobacterium* numbers [**?**], inhibit release of Th2-type cytokines in atopic dermatitis mouse serum, and exert anti-inflammatory effects [**?**].

4 Regulation of Microbial Flora by Intestinal Mucosal Immune System

The intestinal immune system comprises numerous immune cells and molecules scattered throughout the intestinal mucosal epithelium and lamina propria, as well as gut-associated lymphoid tissue. The intestinal mucosal epithelium

forms the first line of defense against invading pathogens, consisting of at least seven different cell types including enterocytes, goblet cells, endocrine cells, and Paneth cells that constitute physical and chemical barriers. The physical barrier comprises the mucosal layer, mucins, and cellular tight junctions, while the chemical barrier consists of defensins secreted by intestinal epithelial cells, particularly Paneth cells, such as antimicrobial peptides, lysozyme, α-defensins, and β-defensins. These defensins are encoded by homologous genes in the jejunum and ileum, recognizing microbial-associated molecular patterns to identify bacterial colonization. Once abnormal colonization by pathogens or commensals is detected, the intestinal mucosa secretes defensins to resist bacterial invasion [**?**]. Simultaneously, the host secretes immunoglobulins that can cross the intestinal barrier to coat microbial surfaces, participating in regulation of bacterial translocation and stimulating phagocytosis by intestinal immune cells [**?**]. Studies show that mice with reduced immunoglobulin secretion exhibit impaired intestinal barrier function, while polyphenol-rich foods can stimulate immunoglobulin A (IgA) secretion, defend against high-fat diet-induced gut microbiota imbalance, and restore intestinal function [**?**].

Immune cells in the intestinal mucosa (macrophages, dendritic cells, neutrophils) are extremely sensitive to changes in gut microbiota. When intestinal microorganisms translocate from the mucosal layer to Peyer' s patches, these immune cells can rapidly capture and phagocytose abnormal bacterial fragments or microbes [**?**]. Recent research shows that lymphocytes play important roles in initiating inflammatory responses at the intestinal barrier surface, particularly at the epithelial fence. Lymphocytes can stimulate secretion of intestinal mucosal defensins to respond to pathogen infection and tissue damage [**?**], thereby inducing release of inflammatory cytokines IL-6, IL-17, interleukin-22 (IL-22), macrophage-stimulating factors, and TNF-α. Among these, IL-22 is a direct regulator of non-specific intestinal mucosal defense in metabolic diseases, inducing secretion of intestinal mucosal defensins [**?**]. The nuclear hormone receptor retinoic acid-related orphan receptor γ can induce pro-inflammatory processes in lymphocytes, promoting differentiation into type I, II, and III lymphocytes. Type III lymphocytes are most abundant in the intestine and show the most pronounced bacterial responses, primarily preventing translocation of commensal bacteria. IL-22 and IL-17 secreted by type III lymphocytes act directly on intestinal epithelial cells to stimulate antimicrobial peptide secretion, thereby non-specifically targeting commensal bacteria. Lymphocytes can also regulate Treg cells and exert anti-inflammatory effects by inducing interleukin-10 (IL-10) production [**?**].

5 Summary

Compared with mammalian gut health research, studies on poultry intestinal health are relatively limited, particularly in laying hens. Current research on modulating poultry gut health through nutritional additives has made some progress, but different additives affect different categories of gut microbiota.

Moreover, due to variations in poultry physiology (short intestine), health status, and rearing environment, the expected effects of additives are often inconsistent, resulting in variable practical outcomes. Given the significance of gut health for poultry well-being, elucidating the specific types and regulatory mechanisms of different gut microorganisms, particularly the regulatory mechanisms between gut microbiota and intestinal mucosal immunity, and investigating how to modulate specific bacterial populations to maximize innate immune function are crucial for maintaining livestock health, improving growth performance, and ensuring product safety.

References

[1] LEY R E, PETERSON D A, GORDON J I. Ecological and evolutionary forces shaping microbial diversity in the human intestine[J]. Cell, 2006, 124(4): 837-848.
[2] ATARASHI K, HONDA K. Microbiota in autoimmunity and tolerance[J]. Current Opinion in Immunology, 2011, 23(6): 761-768.
[3] YEGANI M, KORVER D R. Factors affecting intestinal health in poultry[J]. Poultry Science, 2008, 87(10): 2052-2063.
[4] CHOCT M. Managing gut health through nutrition[J]. British Poultry Science, 2009, 50(1): 9-
[5] REHMAN H U, VAHJEN W, AWAD W A, et al. Indigenous bacteria and bacterial metabolic chickens[J]. Archives of Animal in the gastrointestinal tract of broiler products Nutrition, 2007, 61(5): 319-335.
[6] CHOI J H, KIM G B, CHA C J. Spatial heterogeneity and stability of bacterial community in the gastrointestinal tracts of broiler chickens[J]. Poultry Science, 2014, 93(8): 1942-1950.
[7] QUINTEIRO-FILHO W M, RIBERIO A, FERRAZ-DE-PAULA V, et al. Heat stress impairs injury, and decreases macrophage activity in performance parameters, induces intestinal broiler chickens[J]. Poultry Science, 2010, 89(9): 1905-1914.
[8] FRITZ J C, MISLIVEC P B, PLA G W, et al. Toxicogenicity of moldy feed for young chicks[J]. Poultry Science, 1973, 52(4): 1523-1530.
[9] VAN IMMERSEEL F, DE BUCK J, PASMANS F, et al. Clostridium perfringens in poultry: an emerging threat for animal and public health[J]. Avian Pathology, 2004, 33(6): 537-549.
[10] CRHANOVA M, HRADECKA H, FALDYNOVA M, et al. Immune response of chicken gut to natural colonization by gut microflora and to Salmonella enterica serovar enteritidis infection[J]. Infection and Immunity, 2011, 79(7): 2755-2763.
[11] BRANTON S L, LOTT B D, DEATON J W, et al. The effect of added complex carbohydrates in broiler chickens[J]. Poultry lesions or added dietary fiber on necrotic enteritis Science, 1997, 76(1): 24-28.
[12] FERNANDEZ F, SHARMA R, HINTON M, et al. Diet influences the colonisation of Campylobacter jejuni and distribution of mucin carbohydrates in the chick intestinal tract[J]. Cellular and Molecular Life Sciences, 2000,

57(12): 1793-17801.
[13] PHILLIPS N D, LA T, PLUSKE J R, et al. A wheat-based diet enhances colonization with the intestinal spirochaete Brachyspira intermedia in experimentally infected laying hens[J]. Avian Pathology, 2004, 33(4): 451-457.
[14] SIMON K, VERWOOLDE M B, ZHANG J, et al. Long-term effects of early life microbiota disturbance on adaptive immunity in laying hens[J]. Poultry Science, 2016, 95(7): 1543-1554.
[15] KIM G B, Seo Y M, KIM C H, et al. Effect of dietary prebiotic supplementation on the performance, intestinal Science, 2011, 90(1): 75-82. microflora, and immune response broilers[J]. Poultry
[16] PENDER C M, KIM S, POTTER T D, et al. In ovo supplementation of probiotics and its effects chicks[J]. Poultry and immune-related gene expression in broiler on performance Science, 2017, 96(5): 1052-1062.
[17] KAREEM K Y, LOH T C, FOO H L, et al. Effects of dietary postbiotic and inulin on growth performance, IGF1 and GHR mRNA expression, faecal microbiota and volatile fatty acids in broilers[J]. BMC Veterinary Research, 2016, 12: 163.
[18] KIARIE E, ROMERO L F, NYACHOTI C M. The role of added feed enzymes in promoting gut health in swine and poultry[J]. Nutrition Research Reviews, 2013, 26(1): 71-88.
[19] ZHANG W H, JIANG Y, ZHU Q F, et al. Sodium butyrate maintains growth performance by Poultry chickens[J]. British response broiler regulating immune Science, 2011, 52(3): 292-301.
[20] 吳于明, 刘丹, 张炳坤. 家禽肠道屏障功能及其营养调控 [J]. 动物营养学报, 2014, 26(10): 3091-3100.
[21] RINTTILÄ T, APAJALAHTI J. Intestinal microbiota and metabolites-implications for broiler Poultry performance[J]. The Applied Journal health chicken Research, 2013, 22(3): 647-658.
[22] O' NEILL L A. The interleukin-1 receptor/toll-like receptor superfamily: 10 years of progress[J]. Immunological Reviews, 2008, 226(1): 10-18.
[23] KAWASAKI T, KAWAI T, AKIRA S. Recognition of nucleic acids by pattern-recognition receptors and its relevance in autoimmunity[J]. Immunological Reviews, 2011, 243(1): 61-73.
[24] KRIEG A M, VOLLMER J. Toll-like receptors 7, 8, and 9: linking innate immunity to autoimmunity[J]. Immunological Reviews, 2007, 220(1): 251-269.
[25] HALL J A, BOULADOUX N, SUN C M, et al. Commensal DNA limits regulatory T cell immune intestinal adjuvant natural conversion responses[J]. Immunity, 2008, 29(4): 637-649.
[26] LAMPHIER M S, SIROIS C M, VERMA A, et al. TLR9 and the recognition of self and non-self nucleic acids[J]. Annals of the New York Academy of Sciences, 2006, 1082: 31-43.
[27] BOULADOUX N, HALL J A, GRAINGER J R, et al. Regulatory role of suppressive motifs from commensal DNA[J]. Mucosal Immunology, 2012, 5(6): 623-634.
[28] TROY E B, KASPER D L. Beneficial effects of Bacteroides fragilis polysaccharides on the immune system[J]. Frontiers in Bioscience, 2010, 15(1):

25-34.
[29] HORAI R, SEN H N, CASPI R R. Commensal microbiota as a potential trigger of autoimmune uveitis[J]. Expert Review of Clinical Immunology, 2017, 13(4): 291-293.
[30] DEN BESTEN G, VAN EUNRN K, GROEN A K, et al. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism[J]. Journal of Lipid Research, 2013, 54(9): 2325-2340.
[31] MACFARLANE S, MACFARLANE G T. Regulation short-chain fatty production[J]. Proceedings of the Nutrition Society, 2003, 62(1): 67-72.
[32] CHANG P V, HAO L M, OFFERMANNS S, et al. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition[J]. Proceedings of the National Academy of Sciences of the United States of America, 2014, 111(6): 2247-2252.
[33] KOH A, DE VADDER F, KOVATCHEVA-DATCHARY P, et al. From dietary fiber to host bacterial acids fatty physiology: short-chain metabolites[J]. Cell, 2016, 165(6): 1332-1345.
[34] SEGAIN J P, DE LA BLÉTIÈRE D R, BOURREILLE A, et al. Butyrate inhibits inflammatory Crohn' s inhibition: implications through NF- B responses disease[J]. Gut, 2000, 47(3): 397-403.
[35] BROWN C T, DAVIS-RICHARDSON A G, GIONGO A, et al. Gut microbiome metagenomics analysis suggests a functional model for the development of autoimmunity for type 1 diabetes[J]. PLoS One, 2011, 6(10): e25792.
[36] ARTIS D. Epithelial-cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut[J]. Nature Reviews Immunology, 2008, 8(6): 411-420.
[37] LEWIS K, LUTGENDORFF F, PHAN V, et al. Enhanced translocation of bacteria across butyrate[J]. Inflammatory Bowel epithelia reduced metabolically Diseases, 2010, 16(7): 1138-1148.
[38] RAQIB R, SARKER P, MILY A, et al. Efficacy of sodium butyrate adjunct shigellosis: a randomized, double-blind, placebo-controlled clinical Diseases, 2012, 12(1): 111. therapy in trial[J]. BMC Infectious
[39] ARPAIA N, CAMPBELL C, FAN X Y, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation[J]. Nature, 2013, 504(7480): 451-455.
[40] BROWN A J, GOLDSWORTHY S M, BARNES A A, et al. The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids[J]. The Journal of Biological Chemistry, 2003, 278(13): 11312-11319.
[41] TOLHUSRT G, HEFFRON H, LAM Y S, et al. Short-chain fatty acids stimulate glucagon-like receptor G-protein-coupled peptide-1 FFAR2[J]. Diabetes, 2012, 61(2): 364-371. secretion
[42] KIM M H, KANG S G, PARK J H, et al. Short-chain fatty acids activate GPR41 and GPR43 on inflammatory responses promote intestinal mice[J]. Gastroenterology, 2013, 145(2): 396-406.e10. epithelial cells
[43] DE VADDER F, KOVATCHEVA-DATCHARY P, GONCALVES D, et al. Microbiota-generated neural metabolic gut-brain benefits metabolites

circuits[J]. Cell, 2014, 156(1/2): 84-96. promote
[44] MILLER M B, BASSLER B L. Quorum sensing in bacteria[J]. Annual Review of Microbiology, 2001, 55(1): 165-199.
[45] WATERS C M, BASSLER B L. Quorum sensing: cell-to-cell communication bacteria[J]. Annual Review of Cell and Developmental Biology, 2005, 21(1): 319-346.
[46] DIGGLE S P, WINZER K, LAZDUNSKI A, et al. Advancing the quorum in Pseudomonas aeruginosa: MvaT and the regulation of N-acylhomoserine lactone production and virulence gene expression[J]. Journal of Bacteriology, 2002, 184(10): 2576-2586.
[47] KIMURA N. Metagenomic approaches to understanding phylogenetic diversity in quorum sensing[J]. Virulence, 2014, 5(3): 433-442.
[48] XAVIER K B, BASSLER B L. LuxS quorum sensing: more than just a numbers game[J]. Current Opinion in Microbiology, 2003, 6(2): 191-197.
[49] DIGGLE S P, MATTHIJS S, WRIGHT V J, et al. The Pseudomonas aeruginosa 4-quinolone signal molecules HHQ and PQS play multifunctional roles in quorum sensing and iron entrapment[J]. Chemistry & Biology, 2007, 14(1): 87-96.
[50] PIÑERO-FERNANDERZ S, CHIMEREL C, KEYSER U F, et al. Indole transport across Escherichia coli membranes[J]. Journal of Bacteriology, 2011, 193(8): 1793-1798.
[51] KIM K, KIM Y U, KOH B H, et al. HHQ and PQS, two Pseudomonas aeruginosa quorum-sensing molecules, down-regulate the innate immune responses through the nuclear factor-kappaB pathway[J]. Immunology, 2010, 129(4): 578-588.
[52] BLACHER E, LEVY M, TATIROVSK E, et al. Microbiome-Modulated Metabolites at Interface of Host Immunity[J]. The Journal of Immunology, 2017, 198(2): 572-580.
[53] KRAVCHENKO V V, ULEVITCH R J, KAUFMANN G F. Modulation of mammalian cell quorum sensing molecules[C]//RUMBAUGH K. Quorum processes Sensing. Methods in Molecular Biology. New York: Humana Press, 2011, 692: 133-145. bacterial
[54] ZARGAR A, QUAN D N, CARTER K K, et al. Bacterial secretions of nonpathogenic interkingdom inflammatory pathways: a closer investigation of Escherichia coli elicit signaling[J]. mBio, 2015, 6(2): e00025-15.
[55] SHIH I L, VAN Y T. The production of poly-(γ-glutamic acid) from microorganisms and its various applications[J]. Bioresource Technology, 2001, 79(3): 207-225.
[56] UTO T, WANG X, SATO K, et al. Targeting of antigen to dendritic cells with poly(γ-glutamic acid) nanoparticles induces antigen-specific humoral and cellular immunity[J]. Journal of Immunology, 2007, 178(5): 2979-2986.
[57] LEE S W, PARK H J, PARK S H, et al. Immunomodulatory effect of poly-gamma-glutamic acid derived from Bacillus subtilis on natural killer dendritic cells[J]. Biochemical and Biophysical Research Communications, 2014, 443(2): 413-421.
[58] LEE K, HWANG S, PAIK D J, et al. Bacillus-derived poly-γ-glutamic acid

reciprocally regulates the differentiation of T helper 17 and regulatory T cells and attenuates experimental Experimental autoimmune Immunology, 2012, 170(1): 66–76. encephalomyelitis[J]. Clinical
[59] JIN H E, CHOI J C, LIM Y T, et al. Prebiotic effects of poly-gamma-glutamate on bacterial flora in murine gut[J]. Journal of Microbiology and Biotechnology, 2017, 27(1): 412–415.
[60] LEE T Y, KIM D J, WON J N, et al. Oral administration of poly-gamma-glutamate ameliorates atopic dermatitis in Nc/Nga mice by suppressing Th2-biased immune response and production of IL-17A[J]. The Journal of Investigative Dermatology, 2014, 134(1): 704–711.
[61] VORA P, YOUDIM A, THOMAS L S, et al. β-defensin-2 expression is regulated by TLR signaling in intestinal epithelial cells[J]. Journal of Immunology, 2004, 173(9): 5398–5405.
[62] PABST O, CERVOIC V, HORNEF M. Secretory IgA in the coordination of establishment and maintenance of the microbiota[J]. Trends in Immunology, 2016, 37(5): 287–296.
[63] TAIRA T, YAMAGUCHI S, TARKAHASHI A, et al. Dietary polyphenols increase fecal mucin and immunoglobulin A and ameliorate the disturbance in gut microbiota caused by a high fat diet[J]. Journal of Clinical Biochemistry and Nutrition, 2015, 57(3): 212–216.
[64] GARIDOU L, POMIÉ C, KLOPP P, et al. The gut microbiota regulates intestinal CD4 T cells expressing RORγt and controls metabolic disease[J]. Cell Metabolism, 2015, 22(1): 100–112.
[65] BOSTIC J W, ZHOU L. Innate immunity cells intestinal inflammation[J]. Cellular and Molecular Life Sciences, 2016, 73(2): 237–252.
[66] WANG X T, OTA N, MANZANILLO P, et al. Interleukin-22 alleviates metabolic disorders and restores mucosal immunity in diabetes[J]. Nature, 2014, 514: 237–241.
[67] QIU J, ZHOU L. Aryl hydrocarbon receptor promotes RORγt+ group 3 ILCs and controls intestinal immunity and inflammation[J]. Seminars in Immunopathology, 2013, 35(6): 657–670.

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