Interactions Between Gut Microbiota and Host Intestinal Immune System in Monogastric Animals and Potential Mechanisms: Postprint

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Abstract

A vast and complex microbiota resides in the intestinal tract of monogastric animals, co-evolving with the host immune system. Microorganisms and their metabolites play a crucial role in maintaining intestinal homeostasis. The normal gut microbiota promotes immune system development, participates in maintaining host immune function, and synergistically antagonizes the proliferation and invasion of pathogenic bacteria. Conversely, the host immune system also exerts regulatory control over the gut microbiota, manifesting as immune tolerance toward normal commensal bacteria and immune rejection toward pathogenic bacteria. Once this dynamic equilibrium is disrupted, it leads to disease development. This article reviews the interrelationship between gut microbiota and host intestinal immune system in monogastric animals, and based on existing research findings, provides a systematic summary of their potential interaction mechanisms.

Full Text

Interaction between Gut Microflora and Intestinal Immune System of Host and Its Underlying Mechanisms in Monogastric Animals

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Abstract: The gastrointestinal tract of monogastric animals harbors a vast and complex microbial community that coevolves with the host immune system. These microorganisms and their metabolites play crucial roles in maintaining intestinal homeostasis. Normal gut microbiota promotes immune system development, participates in maintaining host immune function, and collaboratively resists pathogen proliferation and invasion. Conversely, the host immune system exerts restrictive and regulatory effects on gut microbiota, demonstrating immune tolerance toward commensal bacteria while mounting immune rejection against pathogens. Disruption of this dynamic equilibrium leads to disease development. This review summarizes the interactions between gut microbiota and the host intestinal immune system in monogastric animals and systematically outlines the potential underlying mechanisms based on existing research findings.

Keywords: monogastric animals; gut microflora; intestinal immune system; immune cells; underlying mechanisms

The microbial community in animals includes bacteria (the most abundant), archaea, fungi, viruses, and others, with total numbers reaching 10^{13}-10^{1} — approximately ten times the number of host cells themselves—most of which colonize the gastrointestinal tract [1]. In monogastric animals, gut microbiota distribution exhibits spatial specificity, with bacterial quantities increasing progressively from proximal to distal digestive tract, reaching the highest levels in the colon (10^{11}-10^{12} cells) [2]. From intestinal epithelial cells to the lumen, both the quantity and diversity of bacteria increase incrementally, and the microbial communities in the lumen differ markedly from those attached to the mucus layer and epithelial crypts [3]. These commensal microorganisms play vital roles in promoting gut-associated lymphoid tissue (GALT) development and resisting pathogen invasion [4]. The structure and distribution of animal gut microbiota can be influenced by genetics [5], diet [6], environment [7], antibiotic usage [8], and other factors, directly resulting in altered microbial composition. When the dynamic balance among microbial communities is disturbed, metagenomic functions inevitably change. The animal intestine serves not only as a site for nutrient digestion and absorption but also as the first line of defense and a critical immune organ. The intestinal mucosa contains numerous immune-related receptors and signaling molecules, and since bacteria represent one of the most important targets for immune recognition, changes in microbiota structure inevitably trigger rapid responses from the host intestinal immune system, which in turn regulates microbial composition and distribution [9]. Therefore, complex interactions likely exist between gut microbiota and host immunity, though most current research remains superficial, with limited understanding of which specific bacteria affect the proliferation and differentiation of particular immune cells and the underlying mechanisms. This article synthesizes recent domestic and international findings to systematically review the interactions between gut microbiota and host intestinal immune function in monogastric animals and their potential mechanisms.

1. Regulation of Host Intestinal Immune System by Gut Microbiota

The intestinal immune system of monogastric animals comprises three major barriers: the mechanical barrier formed by intestinal epithelial cells and goblet cells, the immune barrier composed of intestinal immune cells and their secreted factors, and the biological barrier constituted by normal gut microbiota [10]. Mounting evidence demonstrates that gut microbiota can regulate the differentiation and function of various immune cells, and the presence of commensal bacteria is essential for the development of intestinal and tissue lymphoid structures.

1.1 Mediating GALT Development

GALTs include Peyer' s patches (PP), isolated lymphoid follicles (ILF), and mesenteric lymph nodes (MLN) [11]. Studies show that GALT development in germ-free mice is significantly impaired, particularly PP and ILF [12]. During fetal development, lymphoid tissue inducer (LTi) cells can induce PP development under sterile conditions [13], whereas ILF development requires microbial mediation [14]. Research on germ-free rabbits (GF-APX) found that injecting a mixed suspension of six bacterial species (1×10 CFU each of *Bacillus subtilis*, *B. licheniformis*, *B. pumilus*, *Bacteroides fragilis*, *Staphylococcus epidermidis*, and *Clostridium subterminale*) into the intestinal lumen promoted GALT development by inducing B cell proliferation. To identify which specific bacteria could induce GALT development, researchers inoculated these strains individually or in pairs into GF-APX intestines. Only *B. subtilis* and *B. fragilis*, either alone or in combination, could induce GALT development, while the other four strains failed to do so individually or in pairs, suggesting that a single bacterial species may be insufficient for complete GALT development and that bacterial diversity is necessary for full development of the intestinal immune system [15].

1.2 Mediating Proliferation and Differentiation of Intestinal Helper T (Th) Cells

Th17 cells are a unique CD4 Th cell subset critical for host defense, which contribute to autoimmune disease development by producing pro-inflammatory cytokines interleukin-17A (IL-17A), IL-17F, and IL-22 [16]. Studies show that Th17 cells are substantially reduced in the colon of antibiotic-treated or germ-free animals [17,18], indicating that microbes are essential for Th17 cell development. Subsequently, Gaboriau-Routhiau et al. [19] identified segmented filamentous bacteria (SFB), a commensal clostridial species, as crucial for Th17 cell development. They found that adult C57BL/6 mice lacking SFB had low Th17 cell numbers in small intestinal lamina propria, which increased significantly two weeks after SFB colonization, demonstrating that SFB can induce Th17 cell generation in mouse small intestine. Additionally, colonizing germ-free mice with altered Schaedler flora (ASF)—a defined consortium of eight bacterial species—also significantly increased Th17 cell numbers in colonic lamina propria,

though the effect was weaker than that of SFB [20]. Other studies found that gavaging 3–4-week-old germ-free mice with 200 L of adult human fecal suspension similarly induced Th17 cell proliferation [21]. Since adult human intestines generally lack SFB colonization [22], this suggests that numerous other commensal species in the animal gut can specifically induce Th17 cell proliferation and differentiation.

1.3 Mediating Proliferation and Differentiation of Regulatory T (Treg) Cells

Forkhead box P3-positive (FOXP3) Treg cells, another CD4 Th cell subset, play important roles in maintaining intestinal homeostasis. Although Treg cells can still be detected in antibiotic-treated or germ-free mouse intestines, their numbers are significantly reduced in small intestinal lamina propria, indicating that microbes help maintain Treg cell numbers or promote their differentiation [23]. Several commensal species have been shown to possess Treg cell-inducing activity. Gavaging germ-free mice with a suspension of 46 *Clostridium* strains significantly increased colonic lamina propria Treg cell numbers, and these bacteria were identified as belonging to two *Clostridium* clusters—clusters IV and XIVa [23]. ASF colonization also induced Treg cell proliferation in germ-free mouse colonic lamina propria, notably containing three strains from *Clostridium* cluster XIVa [20]. Atarashi et al. [24] further identified 17 human gut bacterial strains (belonging to *Clostridium* clusters IV, XIVa, and XVIII) that could induce intestinal Treg cell generation. Additionally, the human commensal *Bacteroides fragilis* could promote Treg cell proliferation and IL-10 production in mouse colon [25].

1.4 Mediating Proliferation and Differentiation of Intestinal Mucosal B Cells

Early B cell development occurs not only in fetal liver and bone marrow but also in intestinal mucosa [26]. A close relationship exists between microbes and gut-specific B cells: B cells prevent microbial infection by producing immunoglobulin A (IgA) [27], while microbes can induce extracellular signal-regulated receptors on intestinal B cells [26]. In germ-free mice, the lack of microbial signals leads to immature germinal center development in PP, reducing B cell generation [28]. Therefore, B cells mature in PP through stimulation by commensal microbiota in the digestive tract, though the specific mechanisms remain unknown. Additionally, in mouse colonic lamina propria dendritic cells (DCs), commensal bacterial flagellin can induce differentiation of various B cells by promoting retinoic acid synthesis [29].

1.5 Mediating Proliferation and Differentiation of Innate Lymphoid Cells (ILCs)

ILCs are innate immune cells gaining increasing attention due to their functional similarity to T cells [30]. Lymphoid precursors can differentiate into three

ILC subtypes: T-bet ILCs (ILC1s), GATA-binding protein 3 (GATA3) ILCs (ILC2s), and retinoic acid receptor-related orphan receptor- t (ROR t) ILCs (ILC3s) [31]. The role of microbes in ILC development and function remains controversial. Studies show that germ-free mice have significantly reduced numbers of ROR t NKp46 CD127 NK1.1 ILCs or ROR t NKp46 CD127 NK1.1 ILCs, indicating that microbes are required for ILC3 differentiation [32]. IL-22 secretion by ILCs is also significantly reduced in the absence of gut microbiota, suggesting that commensal bacteria regulate ILC immune function [33]. Conversely, other studies found that gut microbiota had no significant effect on ILC3 differentiation and could inhibit IL-22 secretion [34].

2. Mechanisms of Microbiota-Mediated Regulation

2.1 Regulating GALT Development

Gut microbiota stimulates GALT development primarily through DC recognition of bacteria and their metabolites, which activate various pattern recognition receptors (PRRs) on DCs [35]. Common PRRs include Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs). Upon recognizing bacteria or their metabolites, TLRs activate the myeloid differentiation factor 88 (MYD88) adaptor-like protein (MAL)-MYD88 and Toll/interleukin-1 receptor (TIR) domain-containing adaptor-inducing interferon- (TRIF)-related adaptor molecule (TRAM)-TRIF signaling pathways to activate DCs [36]. Activated DCs can induce T cell proliferation in PP germinal centers, promote IgA secretion by B cells, and travel via lymphatic vessels to MLN to induce effector T cell proliferation, enabling cryptopatches to develop into mature ILFs. Bouskra et al. [12] also found that ILFs could develop and mature through NOD1 binding to peptidoglycan in bacterial cell walls.

2.2 Regulating Th17 Cell Proliferation and Differentiation

Increasing evidence demonstrates that gut microbiota promotes intestinal Th17 cell development through lamina propria mononuclear phagocytes, including DCs and macrophages. As mentioned, SFB specifically induces Th17 cell differentiation through a mechanism where SFB stimulates intestinal epithelial cells to secrete serum amyloid A (SAA), which promotes IL-6 and IL-23 secretion by ileal lamina propria CD11c DCs—key cytokines for Th17 cell differentiation [37]. Another critical cytokine for Th17 cell differentiation is IL-1 . Shaw et al. [38] found that IL-1 secretion by lamina propria macrophages was reduced in germ-free mice, and mice lacking IL-1 receptors showed significantly decreased intestinal Th17 cell numbers, suggesting that commensal bacteria promote Th17 cell development by inducing IL-1 production. Further studies revealed that both IL-1 and Th17 cell contents were significantly reduced in MYD88-knockout mice [38], leading to the hypothesis that commensal bacteria induce IL-1 production in intestinal lamina propria macrophages via the TLR-MYD88 signaling pathway to promote Th17 cell differentiation.

2.3 Regulating Treg Cell Proliferation and Differentiation

Due to limited research, the mechanisms by which specific gut microbiota induce Treg cell development remain unclear. Available studies suggest that transforming growth factor- (TGF-) participates in microbiota-induced Treg cell differentiation. *Clostridium* clusters IV and XIVa can induce Treg cell differentiation by stimulating TGF- production from colonic epithelial cells [23]. Beyond epithelial cells, certain lamina propria DC subsets also participate in Treg cell induction: CD103 CD11b CD11c and CD103 CD11b CD11c lamina propria DCs preferentially induce CD4 T cell differentiation into Treg cells [39]. CD103 lamina propria DCs express factors that drive Treg cell differentiation, such as TGF- and retinoic acid dehydrogenase (RALDH), as retinoic acid (RA) can effectively induce Treg cell differentiation [40]. Additionally, in the presence of TGF- , lamina propria CD11b CD11c macrophages can induce intestinal Treg cell differentiation by producing RA [41]. Polysaccharide A (PSA) from *Bacteroides fragilis* can also stimulate Treg cell differentiation and IL-10 secretion by activating the TLR2-MYD88 signaling pathway [42].

2.4 Regulating B Cell Proliferation and Differentiation

Intestinal commensal bacteria regulate B cell differentiation through multiple pathways. MYD88-deficient mice show significantly decreased numbers of CD11b IgA B cells [43], indicating that commensal bacteria promote IgA B cell generation by activating MYD88 signaling on lamina propria DCs or follicular DCs. Upon bacterial stimulation, follicular DCs in PPs secrete TGF- , chemokine CXCL13, and B-cell activating factor (BAFF) to promote B cell differentiation and IgA generation [44]. Lamina propria DCs can promote IgA B cell generation by secreting TGF- , RA, tumor necrosis factor- (TNF-), BAFF, inducible nitric oxide synthase (iNOS), and a proliferation-inducing ligand (APRIL) [45].

2.5 Regulating ILC Function

As mentioned, gut microbiota exerts both positive and negative effects on ILC development and function. On one hand, commensal bacteria promote IL-22 secretion by ROR t ILCs to generate corresponding immune functions [46]. On the other hand, commensal bacteria can induce intestinal epithelial cells to secrete IL-25, which acts on lamina propria IL-17RB DCs to inhibit IL-22 secretion by ILC3s [47]. However, the specific mechanisms remain unclear.

Beyond direct regulation (Figure 1 [Figure 1: see original paper]), various microbial metabolites can indirectly regulate the host intestinal immune system. For example, butyrate—a metabolite of *Clostridium* clusters IV and XIVa—can induce CD4 T cell differentiation into Treg cells [48], while vitamin D, a metabolite of *Bifidobacterium*, can promote Th cell differentiation [49].

3. Influence of Host Intestinal Immune System on Commensal Microbiota Distribution and Function

3.1 Affecting Microbial Spatial Distribution

As described, commensal microbiota plays important roles in host intestinal immune system development, yet excessive microbial stimulation may lead to inappropriate immune cell activation and intestinal inflammation. The intestinal mucosal barrier—composed of the mucus layer on the epithelial surface, the epithelium itself with its tight junctions, and the underlying lamina propria—serves as a physical barrier and first line of defense against luminal microorganisms, reducing direct contact between microbes and small intestinal epithelium [50] and effectively preventing bacterial translocation across the mucosa. Additionally, regenerating islet-derived protein III (RegIII) serves as another barrier limiting bacterial penetration into the intestinal mucosa [51]. ILC3s secrete IL-22, which acts on epithelial cells to activate p38-mitogen-activated protein kinase (MAPK) or signal transducer and activator of transcription 3 (STAT3) signaling pathways, promoting RegIII production [52]. Zheng et al. [53] found that IL-22 could inhibit *Citrobacter rodentium* infection in mouse colon by inducing RegIII expression in small intestinal epithelial cells. Reduced ILC3 numbers increase opportunities for the commensal *Alcaligenes xylosoxidans* to enter the intestinal lumen, causing host intestinal damage and systemic inflammation [46]. Secretory IgA (SIgA) on the intestinal mucosal surface can also specifically bind to commensal bacteria (*Enterobacter cloacae* or wild-type *E. coli*), preventing their translocation across the epithelial barrier [54]. Thus, the host intestinal immune system exerts a restrictive effect on commensal bacteria, limiting their access to intestinal epithelial cells under normal conditions to avoid excessive microbial stimulation and maintain normal host-microbe symbiosis.

3.2 Affecting Commensal Microbiota Composition and Function

The immune factor IgA maintains host-microbe symbiosis by regulating gut microbiota composition and function. Studies show that deficiency or mutation of activation-induced cytidine deaminase (AICD) in mice leads to defective intestinal IgA responses, causing bacterial overgrowth (especially anaerobes) and altered gut microbiota composition [55]. Deficiency of the inhibitory co-receptor programmed death-1 reduces IgA binding capacity to bacteria, altering mouse gut microbiota structure: compared with wild-type mice, commensal populations such as *Bifidobacterium* and *Bacteroides* showed no significant changes, while Enterobacteriaceae increased nearly 400-fold [56], suggesting that such structural changes may promote proliferation of certain opportunistic pathogens, transforming low-abundance residents into harmful pathogens. Beyond altering bacterial community structure, a mouse study found that IgA binding to the commensal *Bacteroides thetaiotaomicron* affected its gene expression, significantly upregulating a nitrite reductase operon (BT1414–1418), genes involved in nitric oxide metabolism (BT0687), and a cytochrome D ubiquinol oxidase subunit operon (related to bacterial oxygen tolerance) [57]. When ILC3 func-

tion is defective, reduced IL-22 secretion leads to abnormal SFB expansion and increased intestinal Th17 cell immune responses [58].

Additionally, deficiency of certain immune genes may affect gut microbiota structure. For example, the transcription factor T-bet (encoded by *Tbx21*) regulates inflammatory responses in cells involved in innate and adaptive immunity. *Tbx21*-deficient mice accumulate potential pathogens (*Klebsiella pneumoniae*, *Proteus mirabilis*, and *Helicobacter typhlonius*) in the intestine and are susceptible to ulcerative colitis [59]. NLRP6 inflammasome-deficient mice show reduced production of the inflammatory cytokine IL-18 and altered microbiota structure, with substantially increased *Prevotellaceae* populations [60].

These studies demonstrate that the intestinal immune system regulates commensal microbiota distribution, composition, and function through various pathways. However, only preliminary investigations of a few immune cells and factors have been conducted, and the effects of additional immune cell factors on host gut microbiota and their specific mechanisms require further exploration.

Conclusion

Numerous studies have preliminarily revealed the complex interactions between gut microbiota and host intestinal immune system in monogastric animals, with these mechanisms ensuring intestinal environmental stability. However, research remains superficial, and many questions are still unclear. For instance, do other commensal microorganisms in the digestive tract (such as fungi and viruses) also interact with the intestinal immune system? What are the specific mechanisms? How do these compare with bacteria-host immune system interactions? Do gut microbiota-host immune system interactions follow the classic "gut-brain-gut" axis rule? From a nutritional perspective, investigating whether nutritional regulation can improve gut microbiota structure or even target specific microbial groups to enhance animal immunity represents a novel research field in animal nutrition. Related findings will provide fundamental data for enriching animal disease-resistance nutrition theory.

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Figure 1. Gut microbiota-mediated development of the intestinal immune system (summarized according to references [37-49]).

SFB: segmented filamentous bacteria; ASF: altered Schaedler flora; IgA : immunoglobulin A-positive; SAA: serum amyloid A; TGF- : transforming growth factor- ; PSA: polysaccharide A; DCs: dendritic cells; Th17 cell: T helper 17 cell; Treg: regulatory T cell; RA: retinoic acid; BAFF: B-cell activating factor; Foxp3 : forkhead/winged helix transcription factor 3-positive; TNF- : tumor necrosis factor- ; APRIL: a proliferation-inducing ligand; iNOS: inducible nitric oxide synthase; SIgA : secretory immunoglobulin A-positive; IL: interleukin; RegIII : regenerating islet-derived protein III .

Note: Figure translations are in progress. See original paper for figures.