Glutamine-Induced Secretion of Intestinal Secretory Immunoglobulin A: A Mechanistic Perspective

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Secretory immunoglobulin A (SIgA) is one important line of defense in the intestinal mucosal surface to protect the intestinal epithelium from enteric toxins and pathogenic microorganisms. Multiple factors, such as intestinal microbiota, intestinal cytokines, and nutrients are highly involved in production of SIgA in the intestine. Recently, glutamine has been shown to affect intestinal SIgA production; however, the underlying mechanism by which glutamine stimulates secretion of intestinal SIgA is unknown. Here, we review current knowledge regarding glutamine in intestinal immunity and show that glutamine-enhanced secretion of SIgA in the intestine may involve intestinal microbiota, intestinal antigen sampling and presentation, induction pathways for SIgA production by plasma cells (both T-dependent and T-independent pathway), and even transport of SIgA. Altogether, the glutamine-intestinal SIgA axis has broad therapeutic implications for intestinal SIgA-associated diseases, such as celiac disease, allergies, and inflammatory bowel disease.

Keywords: glutamine, intestinal microbiota, secretory IgA, T cells

INTRODUCTION

The mammalian intestine is home to large numbers of bacteria, many of which invade the intestinal epithelium to enter the systemic circulation. In addition to bacteria, the intestine is challenged by viruses, parasites, food and environmental antigens, and bacterial metabolites. In order to maintain homeostasis, the intestinal mucosal surfaces have multiple layers of defense, including

Abbreviations: APCs, antigen-presenting cells; APRIL, a proliferation-inducing ligand; BAFF, B cell-activating factor of the tumor necrosis factor family; CLP, cecal ligation and puncture; DCs, dendritic cells; FAE, follicle-associated epithelium; FcRs, neonatal Fc receptor; FISH, fluorescence in situ hybridization; GABA, gamma-aminobutyric acid; GALT, gut-associated lymphoid tissue; IFN, interferon; IGBP, IgA-inducing protein; IL, interleukin; iNOS, inducible nitric oxide synthase; JAK, Janus kinase; LP, lamina propria; MAPK, mitogen-activated protein kinase; M cells, microfold cells; MHC-II, major histocompatibility class II molecule; MLN, mesenteric lymph nodes; NO, nitric oxide; plgR, polymeric immunoglobulin receptor; RANKL, receptor activator of NF-κB ligand; SC, secretory component; SIgA, secretory IgA; STAT, signal transduction and activator of transcription; TEDs, extending transepithelial dendrites; TGF, transforming growth factor; TLRs, toll-like receptors; VE, villus epithelium; VIP, vasoactive intestinal peptide.
innate defenses and adaptive defenses. Innate defenses include mucus, antimicrobial substances (e.g., lysozyme and defensins), and tight junctions (1). Secretory immunoglobulin A (SIgA) is the principal regulator of adaptive defenses on the intestinal mucosal surface of humans and many other mammals, such as mice, pigs, and rats. SIgA has critical roles in intestinal homeostasis by regulating immune responses via multiple mechanisms (2, 3). The characterized functions of SIgA in the intestine include: (1) immune exclusion via interacting with environmental antigens (e.g., bacteria, viruses, and toxins); (2) anti-inflammation by sampling intestinal antigens to induce Th2 or regulatory T cell-biased mucosal immune responses; (3) homeostasis of commensals by enhancing the cross talk between the probiotic bacteria and the intestinal mucosa (2, 3). Thus, the lack of SIgA in the intestine is associated with various intestinal diseases, such as necrotizing enterocolitis and gastrointestinal mucositis (3). Targets to increase secretion of intestinal SIgA are promising and directed at mitigating pathogenesis of diseases. Compelling evidence from well-designed investigations have shown that glutamine supplementation increases the abundance of SIgA in the intestine in various hosts, including rats (4, 5), mice (6, 7), Chinese Holstein calves (8), pigs (9), humans (10), and even broiler chickens (11). Similarly, we found that glutamine supplementation increases SIgA in the luminal contents of the jejunum and ileum, and the number of IgA+ plasma cells in the ileum in mice (12). However, underlying mechanisms by which glutamine promotes the production of intestinal SIgA are unknown. In our recent study, we found that dietary glutamine-mediated secretion of intestinal SIgA through effects on the intestinal microbiota, and T cell-dependent and T cell-independent pathways (12). In this review, we discuss the current evidence about underlying mechanisms whereby glutamine enhances production of intestinal SIgA.

**GENERATION OF INTESTINAL SIgA**

**M Cells and SIgA Production**

Intestinal epithelia can be classified as villus epithelium (VE), which is mainly involved in digestion and absorption of nutrients, and follicle-associated epithelium (FAE), which promotes contact with luminal antigens to induce mucosal immune responses. VE contains primarily of enterocytes, scattered goblet cells, and, occasionally, enteroendocrine cells. Compared to the VE, FAE has fewer goblet cells, a thinner mucus layer, lack of expression of polymeric immunoglobulin receptor (pIgR) in enterocytes, and an absence of antimicrobial peptide-producing Paneth cells (13–15), which results in easier access of luminal antigens to FAE. Besides the above differences, FAE harbors a unique subset of epithelial cells, called microfold cells (M cells) (15, 16). M cells continuously sample and transport luminal antigens to the underlying gut-associated lymphoid tissue (GALT), where antigen-presenting cells (APCs), mainly immature DCs, capture the antigens and undergo maturation. After maturation, DCs migrate to the T-cell area of GALT to present antigens to T cells, which help in activation of antigen-specific B cells and ultimately production of slgA by lamina propria IgA+ B cells (17).

The development of M cells in mice depends on the receptor activator of NF-κB ligand (RANKL) secreted by a subepithelial network of reticular cells and B cells. The binding of RANKL to its receptor, RANK (TNFRSF11a), promotes activation of the non-canonical (RelB) NF-κB signaling pathway, and expression of Spi-B that drives M cell fate determination and maturation (18, 19). Mice with Tnfrsf11a deletion lack intestinal M cells and have profound delays in emergence of lamina propria IgA+ plasma cells (20). The diminished amounts of fecal SIgA persist into adulthood, which suggests that antigen sampling by intestinal M cells is the principal pathway initiating mucosal SIgA production (20).

**Induction of Intestinal SIgA**

For the induction of intestinal SIgA, both T cell-dependent and T cell-independent modes are proposed (3, 21–23). In the T cell-dependent model, M cells and intraepithelial dendritic cells (DCs) sample and deliver antigens from the intestinal lumen to APCs (like DCs and macrophages) in the underlying subepithelial dome region. Antigens are processed by APCs to peptide-derived antigens and then expressed with the major histocompatibility class II molecule (MHC-II). CD40 and the peptide-MHC-II complex on APCs bind to CD40L and T cell receptor (TCR) on T cells, respectively, to activate T cells in the interfollicular region. The activated T cells can promote B cell activation with signaling through the B cell receptor (BCR) and CD40 on B cells. Meanwhile, Th2 cytokines, such as transforming growth factor (TGF)-β1, interleukins (IL)-4,-5,-6,-10, and -13, are necessary for differentiation of immature B cells into IgA-secreting plasma cells. TGF-β1 is essential for activation and class switching recombination of IgM-positive B cells to IgA-positive B cells. Other Th2-derived ILs, including IL-4,-5,-6,-10, and -13, promote proliferation of IgA+ B cells and their differentiation into IgA-secreting plasma cells.

The production of most intestinal IgA in extrafollicular structures, such as isolated lymphoid follicles and lamina propria (LP), depends on the T cell-independent pathway. The B cells are activated by signaling through BCR and toll-like receptors (TLRs) recognizing microbial signatures. The release of the B cell-activating factor (BAFF), a member of the tumor necrosis factor family, a proliferation-inducing ligand (APRIL), the peptide hormone vasoactive intestinal peptide (VIP), IgA-inducing protein (IGIP), and nitric oxide (NO) from other cells (e.g., DCs), also promote T cell-independent mucosal IgA responses.

**TRANSPORTATION OF INTESTINAL SIgA**

The process for transport of SIgA has also been well established (3, 22, 23). Briefly, most IgA-secreting plasma cells secrete IgA in the lamina propria as polymeric IgA (dimer or polymer), which is covalently linked to the joining (J) chain. The uptake of dIgA or pIgA is mediated by pIgR. pIgR is a 120 kDa transmembrane protein consisting of five extracellular immunoglobulin (Ig) homology domains, a transmembrane region and a cytoplasmic domain, and is expressed on the basolateral surface of epithelial cells. pIgR binds dIgA or pIgA at the basolateral side of epithelial cells, then the dIgA-pIgR or pIgA-pIgR complex is shuttled to the...
apical membrane of epithelial cells by vesicles. Upon reaching the apical side, plgR is cleaved to release SlgA into the lumen of the intestine as a hybrid molecule including pIgA and secretory component (SC) from plgR.

**GLUTAMINE AND GENERATION OF INTESTINAL SlgA**

Available evidence suggests that glutamine increases the abundance of intestinal SlgA, probably through the intestinal microbiota, induction pathway (T-dependent and T-independent), IgA-secreting plasma cells, and even transport of intestinal SlgA.

**Glutamine and Intestinal Microbiota**

The first step in generation of SlgA from plasma cells is induction by intestinal antigens, mostly bacterial antigens from the lumen of the gut (24, 25). Germ-free mice have fewer IgA-expressing cells in the Peyer's patches and lamina propria, and the colonization of germ-free mice with a microbiota quickly triggers production of IgA (26). Even a single strain of bacteria can effectively promote the secretion of intestinal SlgA. For example, not only *Streptococcus thermophilus* (27), but most *Bifidobacterium*, such as *Bifidobacterium adolescentis* BBMN23 (28), *Bifidobacterium longum* BBMN68 (28), and *Bifidobacterium animalis* (29), induce the production of intestinal SlgA. However, some members of the microbiota (e.g., species of *Sutterella*) degrade both IgA and SC, thus they negatively influence the amount of intestinal SlgA (30). In a previous study, we found that glutamine modulates the intestinal microbial community in mice (31). At the phyla level, the content of Firmicutes in the jejunum and ileum of glutamine-supplemented mice is lower than for the control group, resulting in a shift in the Firmicutes-to-Bacteroidetes ratio to favor Bacteroidetes in the ileum (31). Meanwhile, glutamine supplementation increases the abundance of *Streptococcus* and *Bifidobacterium* in the jejunum, compared to the controls (31). As we discussed in a previous study (31), one possible mechanism is that glutamine supplementation changes the intestinal microenvironment, thereby altering the composition of intestinal microbiota (32). For instance, glutamine supplementation regulates utilization and metabolism of amino acids in bacteria in the small intestine in a niche-specific manner (33, 34), which may in turn affect the activity and number of certain microorganisms (31). Whether the decrease in Firmicutes-to-Bacteroidetes ratio promotes the production of intestinal SlgA is unknown, but we also found that arginine promotes the production of intestinal SlgA, coinciding with shifting the Firmicutes-to-Bacteroidetes ratio to favor Bacteroidetes in the jejunum and ileum (35).

Indeed, monoclonization of the intestine of rats with *Bacteroides thetaiotaomicron* (belonging to Bacteroidetes) induces production of intestinal SlgA 6 days after colonization (36). Collectively, glutamine regulation of production of intestinal SlgA may be mediated by the intestinal microbiota. Indeed, our recent study using fluorescence in situ hybridization (FISH) analysis revealed that glutamine supplementation increases intestinal microbiota invasion into the wall of the ileum (12). Interestingly, disruption of the mouse intestinal microbiota with an antibiotic cocktail (37, 38) during glutamine supplementation abrogates the influence of glutamine supplementation on secretion of SlgA (12). Similarly, in antibiotic cocktail-treated mice, dietary glutamine supplementation for 7 days fails to enhance intestinal SlgA production (12).

Paradoxically, it is widely known that glutamine decreases the translocation of bacteria from the gastrointestinal lumen to Peyer's patches or mesenteric lymph nodes (MLNs) in rats (39, 40) and mice (7, 41). One possible reason for this conclusion is that it comes from the use of animal models with an impaired intestinal mucosal barrier (42, 43), thereby affecting the function of glutamine in intestinal bacteria. Indeed, although glutamine significantly decreases the translocation of bacteria across the gut in rats with chronic portal hypertension and common bile duct ligation, glutamine has little effect on bacterial translocation in rats subjected to a sham laparotomy (44). However, we found that dietary glutamine supplementation decreases bacterial translocation based on the lower bacterial load in the MLN of healthy mice (12). Another possible explanation is based on functions of SlgA to prevent the translocation of intestinal bacteria across the intestinal epithelium (2, 3, 22). Glutamine induces production of intestinal IgA, which inhibits the translocation of intestinal bacteria across the intestinal epithelium and reduces intestinal bacterial translocation after glutamine supplementation (40, 45). This finding is supported by evidence that glutamine decreases bacterial translocation in most models after a long period of usage (at least 8 days) (40, 41), while glutamine has little effect on bacterial translocation when supplemented for shorter periods of time (40, 46). It is possible that short periods of supplementation are insufficient to induce functional levels of SlgA. Thus, we propose the following model as to how glutamine supplementation promotes intestinal production of SlgA by influencing the intestinal microbiota. Glutamine supplementation affects the intestinal microbiota (31, 47) by increasing bacterial stimulation of the intestinal wall (12), which promotes intestinal secretion of SlgA, and the SlgA intercepts the invading bacteria and neutralizes them in the lamina propria (2, 3, 22, 48–50), which decreases the bacterial load in MLN after glutamine supplementation.

In conclusion, glutamine may modulate intestinal bacteria to effect production of intestinal SlgA and increases in SlgA inhibit the translocation of intestinal bacteria.

**Glutamine, Antigen Sampling, and Antigen Presentation**

**Glutamine and Mononuclear Phagocytes**

Although M cells have critical roles in intestinal SlgA production, there are not publications that describe effects of glutamine on M cell maturation and function. This may be due to the scarcity of M cells available for research on their amino acid requirements and metabolism. Besides M cells, mononuclear phagocytes in VE can sample and deliver antigens from the intestinal lumen to Peyer's patches or mesenteric lymph nodes (MLNs) in rats (51). LP contains CD11c+ mononuclear phagocytes: CD11c+CD103+ CD11b+ CX3CR1+ cells (CD103+ DCs) and CD11c−CD103− CD11b+ CX3CR1+ cells (CX3CR1− macrophages), which capture antigen from the intestinal lumen by extending transepithelial dendrites (TEDs) from the LP into the lumen of the gut by penetrating tight junctions (52, 53). Unlike
CX3CR1+ macrophages, CD103+ DCs migrate from the LP into the epithelium and crawl laterally while sending dendrites into the intestinal lumen to actively sample intestinal antigen (53). Indeed, activated B cells can move to the subepithelial dome of PPs, where they interact with DCs, which enhances IgA production by integrin αvβ8-mediated activation of TGF-β (54). The uptake of Bacillus amyloliquefaciens SQ9 by DCs induces the maturation and expression of CD80, CD86, CD40, MHCI, and cytokines in DCs, and secretion of SlgA (55). Also, lung CD103+ DCs and CD24+DC1b+ DCs have been shown to activate B cells through T cell-dependent or -independent pathways (56). Besides DCs, recent investigations have also shown that macrophages promote IgA production by B-1 cells in the intestine via TGF-β2-dependent manner (57, 58). Some amino acids affect migration and function of DCs. For example, DCs of mice with Toxoplasma gondii infection increase gamma-aminobutyric acid (GABA) secretion and exhibit a hyper-migratory phenotype because the increase in GABA activates GABAA receptor-mediated currents in T. gondii-infected DCs (59). Inhibition of GABA synthesis and signaling in T. gondii-infected DCs or blockade of GABAA receptor impairs function of DCs in vitro, including their transmigration capacity, motility, and chemotactic response to CCL19 (59). Glutamine increases the migration of T. gondii-infected bone marrow-derived DCs, while 2-(methylamino)-isobutyrate (MeAIB; inhibitor of glutamine transport by SNAT2), or methionine sulfoximine (MSO, a glutamine synthetase inhibitor) blocks glutamine-enhanced migration of T. gondii-infected bone marrow-derived DCs (60). Lower concentrations of glutamine diminish the function of monocyte-derived macrophages, such as cytokine synthesis, phagocytosis, and antigen presentation (61–63). Glutamine affects the expression of HLA-DR, intercellular adhesion molecule-1 (ICAM-1/CD54), Fc receptor for IgG (Fc gamma RI/CD64), complement receptors type 3 (CR3; CD11b/CD18) and type 4 (CR4; CD11c/CD18), and tetanus toxoid-induced antigen presentation on human monocyte-derived macrophages (61). Thus, glutamine may regulate intestinal SlgA production through its influence on intestinal antigen sampling and presentation by macrophages and DCs.

Glutamine, Epithelial Cells, and Goblet Cells
Villous epithelial cells expressing neonatal Fc receptor (FcRn) and goblet cells play a role in intestinal antigen sampling (51, 64). FcRn contributes to the uptake of intestinal antigens by VE cells because it functions as IgG secretion across the intestinal epithelium into the lumen and also IgG-dependent sampling of luminal antigens (65, 66). Although details of the process are unknown, goblet cells from the small intestine of mice deliver low molecular weight soluble antigens from the intestinal lumen to underlying CD103+ LP-DCs (64). The beneficial effects of glutamine on intestinal epithelial cells and goblet cells are well known (31, 67). For example, glutamine supplementation enhances expression of goblet cell-specific-mucin 4 in the mouse jejunum (31). However, it remains to be determined if glutamine affects intestinal antigen sampling by VE cells and goblet cells.

In conclusion, glutamine may influence sampling of intestinal antigens and presentation by APCs in intestine through M cells, macrophages, DCs, epithelial cells, and goblet cells.

Glutamine and Th2 Lymphocytes
The activation of Th2 lymphocytes plays a critical role in the generation of intestinal SlgA by activating B cells (22, 23). Glutamine is known to affect the number and function of T lymphocytes, and their subgroups (helper T lymphocytes, cytotoxic T lymphocytes) in humans (68), mice (69), and rats (70). Unfortunately, there has been no further investigation into the effects of glutamine on subgroups of helper T lymphocytes, including Th1, Th2, Th17, and Tregs. However, in dextran sulfate sodium-induced colitis in mice, glutamine suppressed Th1/Th17 and expression of their associated cytokine expressions, but promoted Treg responses (71–73). Indeed, total parenteral nutrition decreases SlgA in the intestine and the abundance of Th2 cytokines, like IL-4 and IL-10, which are known to stimulate SlgA production in vivo (74). However, glutamine supplementation in such situations enhances expression of IL-4 and IL-10 and the abundance of SlgA in the intestine (74). We demonstrated that glutamine promotes Th2 responses in mice infected with bacteria or viruses (75, 76). In mice infected with porcine circovirus type 2 or Pasteurella multocida, glutamine supplementation increases expression of Th2 cytokines, like IL-6 and IL-10 (75, 76). However, others have reported that glutamine has little or even inhibitory effects on Th2 responses in some animal models (71, 77, 78). The discrepancy may be related to the animal model, dosage, route of administration, and/or duration of glutamine supplementation, as well as time of analyses and methodologies. We also found that the function of glutamine varies due to those variables (31, 75, 76, 78).

In our recent study, 7 days of dietary 1.0% glutamine supplementation had little effect on expression of IL-4 and IL-10 mRNAs in the ileum, but increased expression of IL-5, -6, and -13 mRNAs in the ileum (12). Meanwhile, glutamine supplementation increased TGF-β signaling based on greater expression of TGF-β1, -β2, and -β3 and TGF-β receptor 2 in the ileum of glutamine-supplemented mice, compared to control mice (12). Although dietary 1.0% glutamine supplementation for 7 days had little effect on the abundance of IL-5 protein in the ileum, glutamine supplementation enhances the abundance of IL-13 protein in the ileum (12). Glutamine supplementation also increased the abundance of TGF-β1 protein in the ileum (12). Interestingly, interference of IL-13 signaling during glutamine supplementation by intraperitoneal injection of the IL-13 antibody decreased expression of J-chain mRNA in the ileum (12). Collectively, glutamine promotes the secretion of SlgA in the intestine, and this may be mediated by Th2 cytokines, such as TGF-β and IL-13.

Glutamine and T Cell-Independent Pathway
In LP, the production of most intestinal SlgA depends mainly on T cell-independent pathways associated with TLRs on B cells, and BAFF, APRIL, VIP, IGIP, and NO from other cells. Although effects of glutamine on expression of TLRs on B cells is not known, glutamine is an important energetic and biosynthetic nutrient for B lymphocytes (79) that may affect the expression of TLRs on B cells. In a mouse model with P. multocida infection, we found that glutamine supplementation affects the expression...
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Possible mechanisms whereby glutamine promotes secretion of intestinal secretory immunoglobulin A (SIgA). intestinal secretory immunoglobulin A (SIgA) production requires stimulation via a T cell-dependent or a T cell-independent pathway. In the T cell-dependent pathway (left), M cells sample and deliver antigens from the intestinal lumen to dendritic cells (DCs) in the underlying subepithelial dome region. DCs activate T cells in the interfollicular region and stimulate production of Th2 cytokines necessary for the differentiation of immature B cells into IgA-secreting plasma cells. In the T cell-independent pathway (right), release of the B cell-activating factor of the tumor necrosis factor family (BAFF) and a proliferation-inducing ligand (APRIL) from DCs promote T cell-independent mucosal IgA responses. Other factors, such as vasoactive intestinal peptide (VIP), IgA-inducing protein (IGIP), and nitric oxide (NO) also play important roles (not shown) in T-cell-independent pathways. SIgA is transported across the epithelium after binding to the polymeric immunoglobulin receptor (pIgR). In the intestinal lumen, SIgA binds intestinal antigens from microbes and diet. Glutamine may affect intestinal production of SIgA through intestinal microbiota (A), antigen sampling and presentation (B), induction pathways for SIgA production by plasma cells via either a T cell-dependent and T cell-independent pathway (C), activation and homing of IgA+ plasma cells (D), and transport of SIgA (E).

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Glutamine and IgA-Secreting Plasma Cells

Glutamine is an important energetic and biosynthetic nutrient for proliferation, survival, and function of B cells (68, 79, 80). Notably, glutamine significantly increases IgA-positive plasma cells in the jejunal LP in rats with proximal colonic resection (81). Although the septic rats with cecal ligation and puncture (CLP) have a lower number of intestinal LP IgA-positive plasma cells, compared with the sham CLP controls, parenteral glutamine supplementation increases the number of IgA-positive plasma cells in intestinal LP (82). Similarly, 7 days of 1.0% glutamine supplementation increased IgA-positive plasma cells in the ileum of mice compared with control mice without glutamine supplementation (12). The underlying mechanisms by which glutamine increases the number of the IgA-positive plasma cells are unknown. It is well known that retinoic acid released by DCs is involved to imprint gut-homing receptors, such as α4β7 integrin, CCR9, and CCR10 on IgA-positive B cells, resulting in the migration of IgA-positive B cells from Peyer’s patches to the LP (83, 84). However, it will be of interest to determine whether glutamine metabolism in DCs or intestine also affects homing of IgA-positive B cells.

GLUTAMINE AND TRANSPORT OF INTESTINAL SIgA

The expression of plgR is critical for transport of intestinal SIgA. Various intracellular signaling pathways are associated with the expression of plgR, such as Janus kinase-signal transduction and activator of transcription (JAK-STAT), NF-κB, and mitogen-activated protein kinase (MAPK) (48, 85). Multiple cytokines produced by innate and adaptive immune cells in the
host, including interferons (IFNs)-γ, IL-1, IL-4, IL-17, TNF, and lymphotoxin (LT)-β, are reported to regulate the expression of plgR through intracellular signaling pathways (48, 85). For example, binding of IL-17 to its receptor activates the classical NF-κB pathway through MyD88-independent signaling, which results in nuclear translocation of an NF-κB dimer comprising p65/RelA and p50 subunits, and expression of plgR because this NF-κB dimer may bind to a cognate element in intron 1 of the gene of plgR (86). Indeed, inhibition of the classical NF-κB activation pathway by Bay11-7082 blocks the induction of plgR expression by IL-17 in HT-29 cells (86). Mice deficient in the IL-17 receptor (II17r−/−) have less SIgA in fecal content and lower expression of plgR in both the small and large intestines, compared to wild-type mice (86). Similarly, intestinal microbes, especially segmented filamentous bacteria (SFB), which induce Th17 responses (87) and have a critical role in the production of intestinal SIgA (88) perhaps by affecting expression of plgR. Indeed, intestinal microbiota can regulate the expression of plgR (85). For example, in an in vitro study with HT-29 cells, the expression of plgR was induced by co-culture with different strains of intestinal bacteria, such as E. coli and Salmonella typhimurium (89). An in vivo study with germ-free mice revealed that those mice have lower expression of plgR, compared with mice with a normal microbiota. Further, monoclonization of commensal bacterium B. thetaiotaomicron to germ-free mice restored intestinal expression of plgR to levels comparable to those in mice with a normal microbiota (90). The regulation of plgR expression by intestinal microbiota may largely depend on the microbial products as most commensal bacteria are spatially segregated from the epithelial surface because of mucus, SIgA, and other antibacterial products. For example, some bacterial products, like butyrate and lipopolysaccharide, upregulate expression of plgR (85, 89, 91, 92). Besides bacterial products, nutrients such as arginine (35) and retinoic acid (93, 94) can regulate the expression of plgR. In our recent study, we found that glutamine supplementation affected expression of plgR mRNA in our mouse model (12). Glutamine may affect plgR expression through its effects on the intestinal microbiota, cytokines, and intracellular signaling pathways. The influence of glutamine on intestinal microbiota was discussed previously. Our research with various animal models revealed that glutamine influences production of multiple cytokines, such as IFN-γ (75), IL-1β (31, 76, 95), and IL-17 (31, 95). Furthermore, glutamine regulated the activation of intracellular signaling pathways, such as STAT, NF-kB, and MAPK (31, 95, 96). For example, glutamine affects the activation of NF-kB signaling by regulating the expression of NF-kB protein, the translocation of the dimer (p65 and p50) from the cytoplasm to nucleus, the degradation of p65 and IkB, and the expression of IkB kinase (31, 95, 96). Thus, glutamine may affect SlgA transport by affecting the expression of plgR.

CONCLUSION

It is well known that glutamine affects intestinal production of SlgA; however, the underlying mechanism by which glutamine promotes intestinal secretion of SlgA is unknown. The increase in knowledge of functions of glutamine in intestinal immunity suggests that glutamine affects intestinal production of SlgA through effects on intestinal microbiota, antigen sampling and presentation, induction pathways for SlgA production by plasma cells, including T-dependent and T-independent pathway, and even expression of plgR (Figure 1). However, more well-designed experiments are required to provide convincing evidence to validate this hypothesis regarding relationships between glutamine and intestinal SlgA. New molecules affecting SlgA production are being found, such as Th17 cells (97) and innate lymphoid cells (98). It will be of interest to study the influence of glutamine on signaling by those cells. The amount of SlgA in the intestine has been associated with the pathogenesis of various intestinal diseases, such as inflammatory bowel disease (99, 100), food allergies (49, 101), and Celiac disease (102). Thus, manipulation of the glutamine-intestinal SlgA axis has a broad therapeutic potential for treating diseases associated with altered production of intestinal SlgA. As a functional amino acid, glutamine holds promise for improving the intestinal health of animals and humans (103–106).

AUTHOR CONTRIBUTIONS

WR, BT, and YY conceived this study. WR wrote the manuscript. KW, JY, SC, and GL provided critical discussion in manuscript preparation. FB, GW, and YP revised the manuscript.

ACKNOWLEDGMENTS

Our profound admiration and respect go to researchers in this field and in our laboratories, for their dedication and hard work. We apologize to scientists who work in this field if their papers are not cited owing to space limitations. This study was supported by Key Programs of frontier scientific research of the Chinese Academy of Sciences (QYZDY-SSW-SMC008), the National Key Basic Research Program of China (2013CB127302, 2013CB127301), the National Science and Technology Ministry (2014BAD08B11), Changsha City Science and Technology Program of China (k1508008-21), the National Natural Science Foundation of China (31330075, 31372326, 31672433, 31301989, 31560640), the earmarked fund for China Agriculture Research System (Beef/Yak, CARS-38), International Partnership Program of Chinese Academy of Sciences (161343KYSB20160008), National Key Research and Development Program of China (2016YFD0500504) and Texas A&M AgriLife Research (H-8200).

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer NS and handling Editor declared their shared affiliation, and the handling Editor states that the process nevertheless met the standards of a fair and objective review.

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