

Review

Impact of maternal dietary gut microbial metabolites on an offspring's systemic immune response in mouse models

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The gut microbiota has a great impact on the host immune systems. Recent evidence suggests that the maternal gut microbiota affects the immune systems of offspring. Metabolites produced by the gut microbiota play crucial roles in the immune system. Previous studies have also revealed that metabolites such as short-chain fatty acids (SCFAs) and the aryl hydrocarbon receptor (AhR) ligands are involved in host health and diseases. Great progress has been made in understanding the roles of diet-derived SCFAs in the offspring's immune system. The findings to date raise the possibility that maternal dietary soluble fiber intake may play a role in the development of the offspring's systemic immune response. In this review, we summarize the present knowledge and discuss future therapeutic possibilities for using dietary soluble fiber intake against inflammatory diseases.

Key words: maternal diet, gut microbiota, offspring's immune systems, metabolites, short-chain fatty acids, aryl hydrocarbon receptor ligands, early-life critical window

INTRODUCTION

Hundreds of bacterial species and trillions of commensal bacteria make up the gut microbiota of the intestinal tract. The gut microbiota and its metabolites are involved in host homeostasis and the developing immune system in the host's intestinal tract [1, 2]. Recent studies have shown that the maternal gut microbiota strongly affects the offspring's immune system development [3, 4]. However, the detailed mechanisms of this process remain unclear.

The components of the gut microbiota are closely linked to the host's diet. Cross-talk between the diet and the gut microbiota impacts the development of the immune system and the development of many diseases [5–7]. The diet shapes the gut microbiota's composition and function. As part of the diet, dietary fat and dietary fibers are important nutrients that affect the gut immune system. Dietary fiber can be either soluble or insoluble [8, 9]. Soluble dietary fiber is fermented into short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, by specific microbes in the gut [10]. SCFAs are end-products of microbial fermentation and influence the host's physiology [10]. Previous studies have shown that consuming soluble dietary fiber increases SCFA levels in the gut [11, 12], while low-fiber diets

and high-fat diets decrease these levels [13]. SCFAs provide energy to intestinal epithelial cells and affect the gut immune system by inducing regulatory T (T_{reg}) cells in the gut [14, 15].

The aryl hydrocarbon receptor (AhR) is a transcriptional factor that regulates the host immune system. AhR signals regulate the number of intraepithelial lymphocytes (IELs) and innate lymphoid cells (ILCs) [16, 17]. AhR activity is essential for the anti-inflammatory response that induces production of IL-22 in ILCs.

Endogenous ligands of AhR are contained in dietary components such as broccoli, cauliflower, Brussel sprouts, and cabbage [18]. These dietary components are converted into AhR ligands such as indole and indole derivatives by the gut microbiota in the gut.

The metabolism of tryptophan (Trp) is also a physiological source of AhR ligands. Trp is an essential amino acid absorbed by dietary protein, and Trp is converted into AhR ligands [19].

Recently, some studies demonstrated that metabolites derived from the maternal gut microbiota, including SCFAs and AhR ligands, can benefit the immune responses of the offspring [11, 20–22]. Increased maternal SCFAs affect the immune systems of their offspring; however, how the maternal gut microbiota impacts the offspring's immune system remains uncertain [20].

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Based on these reports, this review examines recent evidence regarding the maternal diet's effect on the offspring's immune system and the possible therapeutic effects of the maternal diet and gut microbiota against allergic diseases.

METABOLITES DERIVED FROM GUT MICROBIOTA

Maternal metabolites during pregnancy

SCFAs, such as acetate, propionate, and butyrate, in the gut content and in the plasma can be measured by gas chromatography-mass spectrometry (GC-MS), ¹H-nuclear magnetic resonance (NMR) spectroscopy, and liquid chromatography-mass spectrometry (LC-MS), and capillary electrophoresis [23]. The SCFA levels in the gut and plasma depend largely on the dietary fiber intake and the gut microbiota components. For example, De Fillipo *et al.* showed that African people living in a Burkina Faso village, the diets of which contain a lot of high-fiber components, had increased fecal SCFAs levels [13]. There are not so many reports about plasma SCFAs, but Vetrani *et al.* showed that 12 weeks of consumption of a diet rich in whole-grain products (mainly wheat) increases fasting propionate plasma levels in humans [24]. Physiologically, SCFAs are increased by the consumption of a soluble high-fiber diet (sHFD) and decreased by consuming a no-fiber diet (NFD) or a high-fat diet [11, 12, 22]. At the phylum level, the relative abundance of *Bacteroidetes* in the gut is decreased after NFD intake compared with that after sHFD intake. Consuming an sHFD increases the *Bacteroidetes* population and reduces *Firmicutes* at the phylum level, thus increasing SCFA levels under normal conditions [12].

The gut microbiota composition is altered during pregnancy [4, 25, 26]. Although the detailed mechanisms of the microbiota alterations are unclear, many factors, such as metabolic changes and increased hormone secretion, may be involved [4, 27]. Additionally, SCFA levels in the gut and plasma tend to be elevated in pregnant mice compared with those in nonpregnant mice. Acetate and propionate levels in cecum metabolites are also increased in pregnant mice compared with those in nonpregnant mice [28]. At the plasma level, SCFA levels are similar between pregnant and nonpregnant mice at the beginning of pregnancy; however, acetate and butyrate levels are significantly increased during the late stage of pregnancy [11, 29]. Further studies are warranted to clarify the mechanism underlying how SCFAs are increased during pregnancy.

Gut metabolite levels in offspring

Importantly, whether increased SCFAs in maternal plasma are transferred to offspring during pregnancy and lactation remains unclear. An embryo in utero during pregnancy resides in a nearly sterile environment. Neonates are exposed to maternal commensal bacteria during delivery. Coprophagy is the eating of feces and is believed to be important for development of the microbiota and the gut immune system in mice [30, 31]. Coprophagy might be one of the possible mechanisms of maternal transfer of the gut microbiota and metabolites from mother to offspring.

The ratio of the relative abundance of bacterial species in feces in neonates at 1 day after birth is relatively small. Additionally, 16S rRNA sequencing revealed that the gut microbiota compositions of neonate mice differed greatly from those of adult mice [11]. The neonatal intestine at birth is an

aerobic environment in which Enterobacteriaceae can grow [32]. Furthermore, the *Bacteroidetes*-to-*Firmicutes* ratio is minimal at 1 day after birth [11]. Despite the SCFA sources in neonatal mice being limited, SCFAs can be detected in the plasma by GC-MS at embryonic day 18 and at day 1 after birth [11, 12, 33]. Prentice *et al.* demonstrated that SCFAs such as butyrate, acetate, and formic acid can be detected in human milk by NMR and GC-MS [34]. In their study, they suggested that SCFAs in human milk play beneficial roles with respect to weight gain and adiposity during infancy [34]. Based on the evidence that SCFAs are largely produced from the gut microbiota, SCFAs detected in maternal milk might be derived from the maternal gut microbiota. This evidence suggests that SCFAs are transferred from mother to offspring during pregnancy and lactation.

The abovementioned findings regarding SCFA levels in offspring just after birth provide evidence that the maternal diet during pregnancy and lactation influences the gut microbiota composition. Thus, plasma SCFA levels in the offspring might reflect the maternal SCFA levels.

FUNCTIONS OF SCFAS IN THE IMMUNE SYSTEMS OF OFFSPRING

SCFAs derived from the gut microbiota have emerged as major contributors to the host immune response. Many studies have been performed on SCFAs to understand the mechanisms underlying how the microbiota modulates the host immune system [35]. Two SCFA properties may modulate the host immune system. The first property is that SCFA signals are transmitted through G protein-coupled receptors (GPCRs) [36]. GPCRs, such as GPR41, GPR43, and GPR109A, are SCFA receptors that modulate the gut homeostasis and regulate inflammatory responses [37]. GPR41, also known as free fatty acid receptor (FFAR)3, and GPR43, also known as FFAR2, have been identified as SCFA receptors. Both GPR41 and GPR43 recognize acetate, propionate, and butyrate, but with different affinities. For example, GPR43 has higher affinity for acetate than GPR41 [38]. Both are expressed in tissue-specific cells such as colon epithelial cells, adipocytes, and peripheral blood mononuclear cells and are activated by SCFAs [39]. GPCRs mediate the interaction of host cells and the gut microbiota and are associated with chronic inflammatory diseases such as colitis, asthma, and arthritis.

The second property is that SCFAs inhibit histone deacetylase (HDAC) [40, 41], which affects the expression of genes such as Forkhead box p3 (Foxp3). The expression of Foxp3 in T_{reg} cells is involved in the development and functions of T_{reg} cells as described below.

Recent evidence indicating that colonic T_{reg} cells are induced by SCFAs in the gut has greatly impacted our understanding of the mechanism by which SCFAs promote anti-inflammatory responses [14, 15, 42]. T_{reg} cells are a specific T cell subset with potential roles in inhibiting inflammation and maintaining homeostasis [43]. Butyrate inhibits HDACs to enhance histone H3 acetylation on the Foxp3 gene locus and induce T_{reg} cells in the gut [14, 15]. Propionate is involved in GPR43 dependently inducing colonic T_{reg} cells, which promotes gut homeostasis and prevents gut inflammation [42]. In addition to colonic T_{reg} cells, thymic T_{reg} (tT_{reg}) cells are influenced by fiber diets and gut SCFAs. One study found that the tT_{reg} cells were increased in offspring born to sHFD-fed mother [11] and decreased

in offspring born to NFD-fed mothers [11]. The thymus is a lymphoid organ that begins developing in the neonatal stage and generates T cells, including T_{reg} cells. T_{reg} cells may have roles in preventing autoimmune reactions against self-components that induce allergies and autoimmune diseases. Previous studies found that autoimmune regulator (Aire) expression in medullary thymic epithelial cells (mTECs) is essential for inducing T_{reg} cells in the thymus [44, 45]. Because maternal sHFD intake might increase the plasma SCFA levels in offspring during pregnancy and lactation, increased SCFAs in offspring born to sHFD-fed mothers yielded increased numbers of tT_{reg} cells in the offspring. Butyrate increases tT_{reg} cells through GPR41-mediated Aire induction in mTECs [11]. Notably, recent evidence suggested that Aire-dependent tT_{reg} cells in neonates can provide long-term protection against autoimmune diseases [46]. Consistent with this finding, maternal sHFD or acetate intake attenuates allergic airway diseases (AADs) in offspring in the long term because acetate inhibits HDACs, which results in enhancement of Foxp3 gene expression and production of T_{reg} cells in the lungs [22].

Collectively, these findings suggest that SCFAs promote T_{reg} induction in the thymus and peripheral organs through different mechanisms and pathways, including GPCRs and HDAC inhibitors, and thereby provide protection against allergies and inflammation.

AHR LIGANDS AND THE OTHER METABOLITES THAT MAY AFFECT OFFSPRING IMMUNE RESPONSES

The gut microbiota has crucial roles with respect to the production of many AhR ligands. Tryptophan is an essential amino acid that can be converted to AhR ligands such as indole and indole derivatives by certain gut microbiota. Indole and indole derivatives such as tryptamine and indole-3-acetic acid (IAA) activate AhR signaling that is involved in immune responses [47]. The agonists of AhR may play a role in increasing the number of NKp46⁺ ILC3 cells, which are ILCs [20]. NKp46⁺ ILC3 cells contribute to the mucosal barrier and play crucial roles in protecting against infections by producing IL-22 [48]. Maternal AhR ligands may be transferred from mother to offspring, thus increasing ILC3 in the offspring [20]. Additionally, ILC3 cells in utero are regulated by retinoic acid signaling, and maternal dietary retinoic acids control the size of secondary lymphoid organs and the abundance of ILC3 [21]. This evidence suggests that the maternal diet influences the number and function of ILC3 cells in offspring via retinoic acid and AhR ligands.

Several other gut microbiota-derived metabolites are reported to modulate the immune response. Polysaccharide A (PSA) and peptidoglycan (PGN) are also possible candidates for host immune modulators [1]. PSA is derived from *Bacteroides fragilis* and contributes to maintaining Th1/Th2 balance. It stimulates toll-like receptor (TLR) 2 signaling and IL-12 production by dendritic cells [49]. PGN is a component of the bacterial outer membrane and is a ligand of nucleotide oligomerization domains (NODs) 1 and 2 [50]. PGN derived from the gut microbiota contributes to immune responses via NOD1 and NOD2 signaling [50]. Notably, circulating PGN regulates the immune system systemically, thereby influencing expression of the Aire gene in mTECs via NOD1 signaling [51, 52]. Although the effects of maternal PSA or PGN on offspring are unclear, these metabolites

may affect immune system development in offspring in the same manner as SCFAs and AhR ligands.

Most vitamins must be supplied by the diet and the gut microbiota. Vitamin D deficiency is reported to be associated with asthma and allergic airway diseases [53, 54]. A recent study demonstrated that maternal vitamin C is required for proper DNA methylation in female fetal germ cells in a mouse model [55]. Thus, maternal vitamins are crucial for development and preventing allergic and inflammatory diseases in offspring [56, 57].

OFFSPRING IMMUNE DEVELOPMENT DURING THE EARLY-LIFE CRITICAL WINDOW

The gut microbiota affects the host's immune system as well as immune system development in the offspring. The early-life microbiome is critical for developing the host's immune system and maintaining future health. In humans, recent studies proposed that the early-life critical window is within 100 days after birth and is crucial to preventing allergic and metabolic diseases in the long term [58]. Maternal nutrition influences development of multiple organs in offspring, such as the gastrointestinal tract, lungs, and central nervous system, in addition to tT_{reg} cells in the thymus during the early-life critical window [11, 20–22].

One study found that maternal microbiota exposure increased the number of ILCs in the early-life critical window [20]. In mice, the microbiota shapes the number of NKp46⁺ ILC3s and F/480⁺CD11c⁺ intestinal mononuclear cells (iMNCs) in offspring born to mothers under gestation-only colonization conditions [20]. These cells promote production of IL-22, a cytokine that enhances epithelial intensity and infection resistance. The number of NKp46⁺ ILC3s and F/480⁺CD11c⁺ iMNCs was maximized between postnatal days 14 and 21 and persisted until 8 weeks of age in mice. This evidence suggests that NKp46⁺ ILC3s and F/480⁺CD11c⁺ iMNCs increase during the early-life critical window and may play roles in preventing future infections.

Recent studies have shown that the maternal microbiota affects brain and behavioral development in the offspring. Autism spectrum disorder (ASD) is a neurodevelopment disorder, and a maternal high-fat diet induces ASD via dysbiosis of maternal microbiota; this effect is referred to as the gut-brain axis [59]. The gut microbiota also modulates respiratory immune responses. Maternal intake of sHFDs and treatment of SCFAs attenuated AADs such as asthma in offspring. This modulation is referred to as the gut-lung axis [12, 22]. Recent evidence suggests that the maternal microbiome during pregnancy and lactation influences tT_{reg} cell differentiation in offspring in a GPR41-mediated Aire-dependent manner [11]. As described above, Aire gene expression during the prenatal stage is crucial for T_{reg} cell production in the thymus [11, 46], and tT_{reg} cells produced in the early-life critical window are indispensable for long-term prevention of autoimmune diseases [46]. Thus, the correlation of Aire gene expression in the thymus suggests that the gut-thymus axis emerges to develop the immune system early in life. This suggests that bacterial metabolic effects might be observed in multiple other organs. Metabolites such as SCFAs mediate interactions between the gut microbiota and the organs. The axis between the gut microbiota and other organs provides a clue to understanding the mechanism by which the gut microbiota affects the host immune system.

THERAPEUTIC POSSIBILITIES OF MATERNAL METABOLITES

Dysbiosis of the maternal microbiota increased the risk of allergic and metabolic diseases, such as asthma, obesity, and type 2 diabetes mellitus (T2DM), in offspring [60]. The maternal diet during pregnancy and lactation affects allergic diseases and asthma in offspring [61, 62]. Thus, nutrition during pregnancy and lactation represents a potential therapeutic target for improving the offspring's long-term health [63].

Consumption of Western-type diets during pregnancy induces dysbiosis and decreases SCFA production in offspring. Conversely, consumption of high-fiber diets improves glucose control via SCFA production in patients with T2DM [64]. Metabolites derived from the gut microbiota, such as SCFAs and AhR ligands, are potential candidates for preventing metabolic diseases and allergies. Recent studies suggested that maternal SCFA supplementation prevents type 1 diabetes mellitus [65]. Maternal sHFD intake during pregnancy prevented allergic airway inflammation in a mouse model [22]. AhR activation through dietary elements promotes T_{reg} responses and protects against AADs [66]. Treatment with SCFAs and AhR ligands during pregnancy and the early-life critical window might play a potential role in preventing allergic and metabolic diseases in offspring in the long-term because SCFAs and AhR ligands may modulate T_{reg} and ILC biology as described above [11, 20–22]. In addition, probiotics are also effective materials. Maternal supplementation with probiotics during pregnancy prevents allergic diseases and metabolic diseases such as asthma, diabetes mellitus, and obesity. Supplementation of short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides in pregnant mice reduced allergic asthma [67]. Maternal supplementation with probiotics can be widely applied for preventing or ameliorating diseases in offspring later in life. Recent studies suggested that maternal probiotic supplementation during pregnancy and lactation effectively prevents obesity, hypertension, and allergic diseases

in offspring [68–73].

In summary, evidence suggests that improving maternal nutrition during pregnancy and lactation affects the immune system development and prevents allergic and metabolic diseases in offspring (Table 1). Although several clinical studies have been performed, further studies are needed to clarify the significant association between probiotic supplementation during pregnancy and allergic diseases such as asthma in human offspring (Table 2).

CONCLUSION

The gut microbiota is a unique group of organisms that benefit the host's immune system. Cross-talk between gut microbiota metabolites and the host immune system greatly affects host homeostasis. Moreover, accumulating evidence suggests that maternal-host gut interactions during pregnancy and lactation play crucial roles in the offspring's immune system development.

In this review, we described the effects of maternal gut metabolites on the offspring's immune system development and the therapeutic possibilities for preventing allergic and metabolic diseases in a mouse model (Fig. 1). SCFAs may play roles in the development of the immune system by mediating various pathways. Future research should clarify SCFA signaling in GPCR pathways and HDAC inhibitors.

The numbers of allergic and metabolic patients are increasing in developed countries. Consumption of sHFDs that include vegetables, mushrooms, and seaweed during pregnancy and lactation may be a long-term and effective means of preventing allergies and metabolic diseases in offspring.

AUTHOR CONTRIBUTIONS

A. Nakajima conceived the project and wrote the draft of the protocol. A. Nakajima and S. Habu wrote the manuscript. All authors interpreted and discussed the results.

Table 1. The relationship between maternal gut metabolites and effects of the immune system in offspring

| Maternal gut metabolites derived from gut microbiota | Effect of immune system in offspring | References |
|--|--|------------|
| Short-chain fatty acids (SCFAs) | Ameliorate allergic airway diseases | [22] |
| | Ameliorate type 1 diabetes | [65] |
| | Increase the number of tT_{reg} | [11] |
| Aryl hydrocarbon receptor (AhR) ligands | Increase the number of NKp46 ILC3 cells | [20] |
| Vitamin C | DNA methylation of female fetal germ cells | [55] |
| Vitamin D and E | Decrease risk of childhood asthma | [56, 57] |
| Retinoic acid | Increase the number of ILC3 cells | [21] |

Table 2. Effects of probiotics during pregnancy to the immune system in offspring

| Probiotics | Effect | References |
|--|--|------------|
| Oligosaccharides | Reduce allergic asthma | [67] |
| Fructose | Prevent hypertension | [68] |
| Oligofructose | Prevent obesity | [69] |
| Fructo-oligosaccharide | Attenuate acute allergic skin response | [70] |
| Fructo-oligosaccharide | Intestinal immune function | [71] |
| <i>L. rhamnosus</i> , <i>B. animalis</i> , <i>L. acidophilus</i> | Decrease risk of atopic dermatitis | [72] |

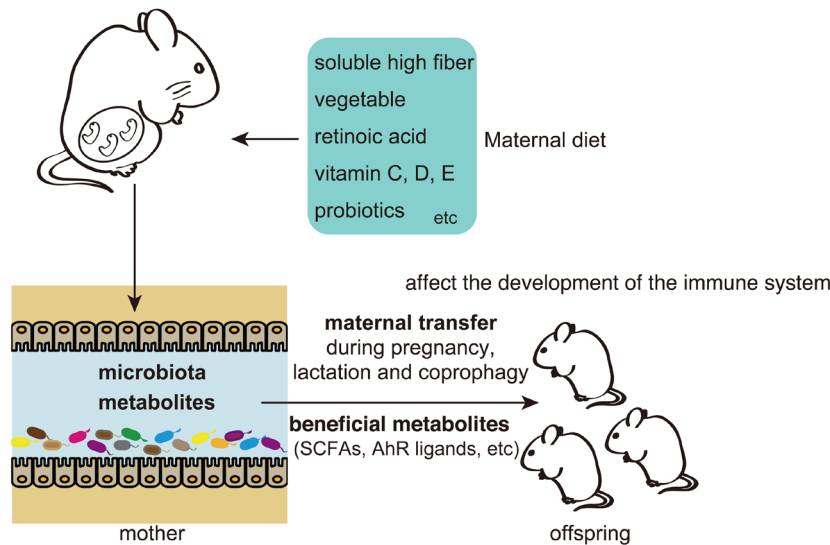


Fig. 1. Short-chain fatty acids (SCFAs) and other metabolites derived from the maternal gut microbiota affect offspring immune system development, thus preventing allergies and metabolic diseases. Maternal intake of a soluble high fiber that includes vegetable, retinoic acid, vitamins, and probiotics promotes the production of beneficial metabolites in the maternal gut and affects offspring immune system development in a mouse model. Maternal milk and coprophagy are the possible mechanisms underlying the involvement of maternal transfer and affect the composition of the microbiota and the immune system of offspring in mice. Effects of the maternal gut microbiota on offspring during the early-life critical window may impact the future health of the offspring.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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