Journal of Asthma and Allergy

Dovepress
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REVIEW

Innovative Therapeutic Strategies for Asthma: The Role of Gut Microbiome in Airway Immunity

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Abstract: There is a growing acknowledgment of the gut microbiome's impact on widespread immune responses, which holds considerable importance for comprehending and addressing asthma. Recent research has clarified the complex interactions between gut microbiota and airway immune systems, demonstrating that microbial diversity and composition can affect both the initiation and advancement of asthma. Gut microbial species and metabolites primarily short-chain fatty acids (SCFAs) may either worsen or reduce airway inflammation by regulating the balance of helper T cell 1 (Th1) / helper T cell 2 (Th2) and other immune mediators. This interaction presents innovative therapeutic possibilities, including modulation of gut microbiome during early life through breastfeeding and control of antibiotic use, particularly with prebiotics, which could selectively stimulate the growth of beneficial bacteria, promote immune maturation, reducing susceptibility to asthma and allergic airway inflammation. Besides, investigating the gut-lung axis reveals new opportunities for personalized medicine in asthma treatment, emphasizing the necessity for integrated strategies that take individual microbiome profiles into account. This paper examines the latest developments in comprehending the mechanisms by which gut microbiota affect airway inflammation and hypersensitivity, especially focusing on treatment strategies.

Keywords: asthma, gut microbiota, immune response, metabolites, dietary, prebiotics, antibiotics

Introduction

The human gut microbiome is a complex ecosystem consisting of over a trillion microorganisms. It has become an essential factor in the regulation of our immune system and overall physiological health. This detailed community of bacteria, archaea, viruses, and fungi not only carries out essential functions in the gastrointestinal tract but also considerably affects widespread processes throughout the body.[1,2] The gut microbiome plays a critical role in various biochemical and metabolic pathways, improving nutrient absorption, assisting digestion, and enhancing metabolic activities.[3] Also, these microorganisms are essential for immune regulation, serving as mediators that help calibrate the host's immune response to environmental stimuli. Recent research has simplified the energetic interactions between the gut microbiome and widespread inflammatory responses. It has been shown that gut flora can activate and modulate these responses, which may have important repercussions on peripheral tissues.[2,4] Meanwhile, host immune response can also affect the homeostasis of gut microbiota. Previous studies show that exposure mouse lungs to lipopolysaccharide (LPS) can trigger inflammation, leading to a substantial augmentation of gut microbiome.[2] These findings imply that disruptions in gut microbiota may arise as a consequence of widespread inflammation, further complicating our understanding of host-microbe interactions.

Received: 4 November 2024
Accepted: 13 February 2025
Published: 20 February 2025

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Asthma is a prevalent chronic respiratory condition marked by limitations in airflow, increased bronchial responsiveness, excessive mucus production, and inflammation in the airways.[5] It is estimated that approximately 334 million individuals are currently affected by this disease.[6] A important portion of asthma attacks is attributed to an overabundance of Type 2 inflammation, and the contributions of immunoglobulin E (IgE) antibodies and T helper (Th) 2 cells have been investigated regarding their roles in the inflammatory processes.[7] However, research into the interactions between the gut microbiome and airway immune responses has not received the same level of attention as the study of inflammatory mechanisms in asthma. Recently, there have been promising clinical outcomes related to using orally administered probiotics for repairing bronchial epithelium, which indicates potential adjunctive therapeutic benefits in asthma management.[8] In addition, some experimental treatments designed to influence the interactions between the gut microbiome and airway immune responses have become potential options for asthma therapy. Evidence demonstrates that providing short-chain fatty acids (SCFAs), such as propionate, to neonatal mice lacking plasmacytoid dendritic cells (pDCs) can enhance the migration of monocyte-derived dendritic cells (moDCs) to the lungs, improve Sema4a signaling, and restore the response of Nrp-1^{+} regulatory T cells (Tregs), eventually leading to protection against severe viral bronchiolitis and subsequent asthma development.[9] Thus, the modulation of the interaction between gut microbiota and airway immune responses may represent a critical area for future asthma treatment research. In this review, we will simplify the crosstalk between the gut microbiome and airway immune responses, along with their therapeutic implications for asthma.

Crosstalk Between Gut Microbiome and Airway Immune Responses

Gut Microbiome Distribution and Airway Immune Responses

In the gastrointestinal tract (GIT), basic composition of GIT microbiota is mainly composed of bacteria from the phyla Firmicutes (64%, mainly Gram-positive Clostridium, Bacillus, Lactobacillus, and Enterococcus species), and Bacteroidetes (23%, mostly Gram-negative Bacteroides and Prevotella species.[10] Other microbial species include viruses, fungi, and even archaea.[2] Studies indicate that the gut microbiome is a critical component of physiological balance, offering numerous benefits from the digestion of complex carbohydrates to the regulation of immune responses.[11] Within this ecosystem, the composition and distribution of gut microbiota greatly impact host immune functions, suggesting that variations in these microbial populations may be associated with the pathophysiology of asthma and other allergic conditions. Among the various species present in the gut, *Bacteroides fragilis* is notable for its unique capacity to produce Polysaccharide A (PSA), which is essential for the differentiation of cluster of differentiation 4-positive (CD4+) T cells and the regulation of T helper cell responses. This interaction is essential in shaping the immune environment, as it encourages a balanced response between Th1 and Th2 cells.[12–14] At the same time, the colonization of segmented filamentous bacteria (SFB) activates the ILC3/IL-22/SAA1/2 signaling pathway, which subsequently boosts the production of IL-17A by RORγt Th17 cells.[14] Increased levels of IL-17A have been linked to a severe, neutrophilic inflammatory profile characteristic of certain asthma types.[15] In addition, fungi within the gut microbiota may also impact asthma-related immune responses by supporting the generation of immune cells in the gastrointestinal tract.[7] Mouse models have shown that fungal overgrowth can worsen Th2 cell-mediated airway inflammation after an airway challenge.[2] Collectively, these studies propose that there exist interactions between different gut microbiota species and airway immune responses and play an indispensable role in asthma development and exacerbation.

Gut Microbiome Dysbiosis in Early-Life and Airway Immune Responses

According to the "hygiene hypothesis", appropriate exposure to particular microbiome constituents early in life is essential to stimulate the immune development and maturation, while their absence could heighten the risk of developing asthma and allergic diseases.[16] Research indicates that the early microbial environment, influenced by commensal microbiota, plays a critical role in promoting immune maturation and establishing tolerance to environmental antigens.[17] Early-life dysbiosis, often triggered by factors such as antibiotic use, can disrupt immune development and raise the likelihood of asthma and allergies.[18] For example, research shows that administering antibiotics during the first six months of life is associated with a higher risk of developing allergic diseases.[19,20] The period between infancy and early childhood is essential for the

development of the immune system and the microbiome due to crosstalk at various levels.[14] A major decline in the relative abundance of beneficial microbiota, including genera such as *Lachnospira, Veillonella, Faecalibacterium*, and *Rothia*, has been documented in children with a tendency toward asthma.[21,22] One of the key factors is delivery through a Caesarean section (CS), which postpones the colonization of bacteria in the intestines. This method notably decreases the presence of beneficial bacteria, including *Dolosigranulum* and *Corynebacterium*, which are linked to health.[23] And the presence of *Clostridium* in the neonatal gut shortly after a cesarean section is greatly associated with the development of recurrent wheeze (OR = 1.75; 95% CI 1.09 to 2.80) and allergic sensitization (OR = 1.54; 95% CI 1.02 to 2.31), suggesting a potential increase in asthma risk later in life.[24,25]

Short-Chain Fatty Acids and Airway Immune Responses

Metabolites derived from microbes play an important role in asthma by influencing immune responses in the airways. The gut microbiota possesses an important metabolic capacity to change components derived from the host and dietary elements, such as lipids, carbohydrates, and proteins, into various metabolites that can either promote or hinder the development of the host's mucosal immunity.[26] Some of these metabolites, including SCFAs and secondary bile acids, exhibit antimicrobial properties, thereby providing protection against pathogenic bacteria and promoting immune homeostasis.[27] SCFAs are primarily produced by *Firmicutes* in the gastrointestinal tract from dietary fibers or through the fermentation of nondigestible carbohydrates.[28] As metabolites, SCFAs have been shown to modify cellular functions by influencing gene expression, chemotaxis, differentiation, proliferation, and apoptosis.[29] The SCFA-sensing G-protein-coupled receptor GPR109A, which is activated by SCFAs in intestinal epithelial cells, colonic macrophages, and dendritic cells, can induce anti-inflammatory effects, promote the differentiation of regulatory T cells and IL-10-producing T cells, and support epithelial homeostasis.[17,30,31] Therefore, it is likely that SCFAs have an impact on airway immune responses through these various mechanisms (Figure 1).

Three primary SCFAs, acetate, propionate, and butyrate, are produced by gut bacteria in a molar ratio of 60:20:20, contingent upon the fiber content of the diet.[22] Other SCFAs present in the gut, such as valerate, caproate, and isovalerate, are found in smaller quantities.[32] Research has shown that the antimicrobial effect induced by SCFA butyrate is the strongest when compared to propionate, while such an effect has not been observed with acetate.[33] Besides, the study conducted by Schulthess et al demonstrated that oral butyrate supplementation effectively limits the spread of pathogenic bacteria. Evidence indicates that children with the highest levels of propionate and butyrate (≥95th percentile) in their feces at one year of age exhibited considerably lower instances of atopic sensitization and reduced odds of developing asthma between the ages of 3 and 6 years.[34] Similarly, propionate intake can diminish the effectiveness of newly recruited dendritic cells (DCs) and enhance the responses of effector Th2 cells, thereby providing protection against allergic airway inflammation in mice, which is associated with decreased levels of serum total IgE.[35,36] When dietary supplementation containing butyrate, propionate, and acetate was administered, the physiological function of DCs in vancomycin-treated mice was modulated, correlating with weakened allergic immune responses in the lungs.[35] The introduction of SCFAs in microbiota-gut-lung communication emphasizes the influence of metabolites mediated by changes in gut microbiota, which may contribute to health by regulating immune tolerance and inflammation.

Implications for Asthma Treatment Strategies

Dietary Structure and Eating Habits

Diet is a fundamental necessity for our lives and is essential not only for enhancing health and supporting growth but also for influencing the diverse microbial communities within GIT. The sources, types, and quality of food can shape the gut microbiome by altering its composition and function, which in turn affects interactions between hosts and microbes.[37] Our focus is on the role of fiber intake and healthy dietary patterns, which contribute to the prevention and treatment of asthma generation and development. Chronic inflammation of the airways is a prominent characteristic of asthma, and emerging evidence indicates that diet can influence this inflammatory process.[38,39] Notably, previous studies have demonstrated a major correlation between the prevalence of asthma and the adoption of westernized dietary patterns.[40] The Western diet is typically characterized by a higher consumption of animal products, with inadequate intake of fruits,

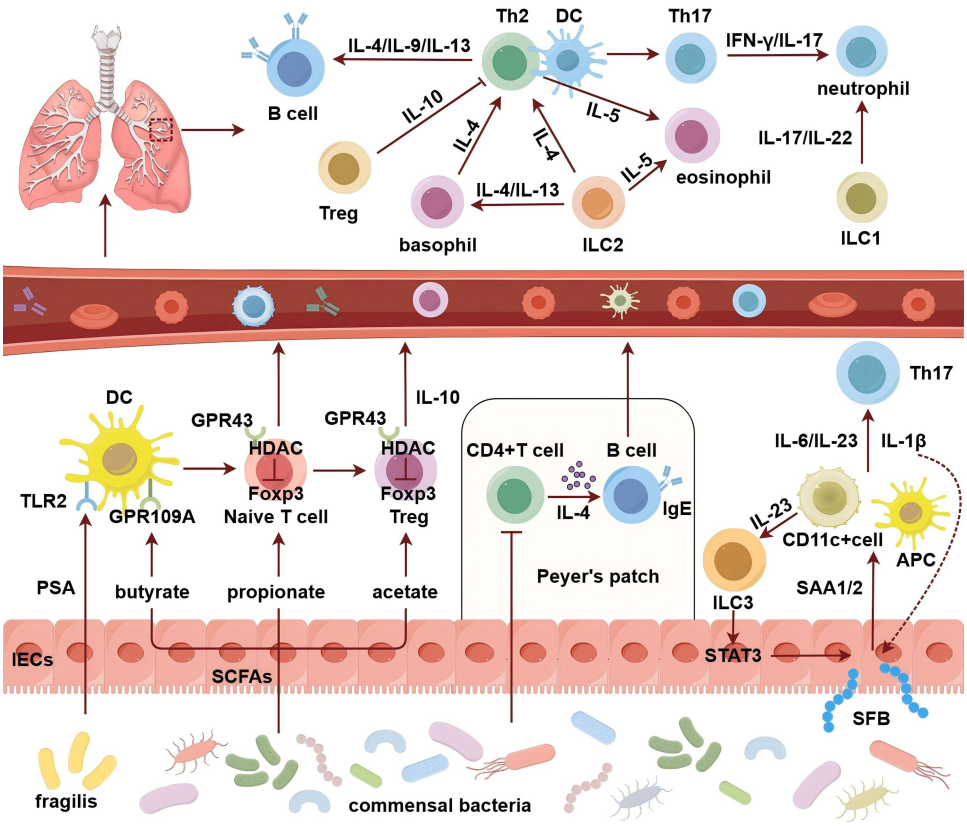

Figure 1 Molecular mechanism of gut microbiota and its metabolites in airway immunity of asthma (drawn by Figdraw, ID: TWAOO5cdc2). Short-chain fatty acid (SCFAs), including acetate, propionate, and butyrate, mainly produced by bacterial metabolism in the human gut after dietary fiber intake, inhibits HDAC function and enhances FOXP3 expression, thereby promoting Treg differentiation and IL-10 production via GPR43 and other pathways. Polysaccharide A (PSA) derived from Bacteroides fragilis, can also act on Tregs through TLR2 to promote Treg function by enhancing expression of IL-10. Adhesion of segmented filamentous bacteria (SFB) prompts intestinal epithelial cells (IECs) to release serum amyloid A (SAA), establishing a feedback loop with antigen-presenting cells (APCs) and type 3 innate lymphoid cells (ILC3) that facilitates interleukin-mediated differentiation of naive CD4+ T cells into Th17 cells. In Peyer's patch, B cells generated increased immunoglobulin E (IgE) via a CD4 T-cell / IL-4-dependent mechanism. Immune-related cells and cytokines produced by these pathways travel through blood circulation to the lungs, affecting Th2-mediated responses in asthma. Th2 cells release IL-4, IL-13, and IL-5 in response to allergen stimulation, facilitating inflammation and tissue remodeling by encouraging the infiltration and activation of eosinophils and basophils, enhancing IgE production by B cells, and causing excessive mucus secretion.

vegetables, whole grains, and legumes. This dietary pattern has been shown to exacerbate airway inflammation by increasing the production of cytokines, which subsequently affects the development and manifestation of asthma.[41,42] In contrast, a high intake of fruits and vegetables is associated with a reduction in pro-inflammatory cytokines and an increase in anti-inflammatory markers, thereby decreasing the risk of asthma exacerbation.[41,43] Besides, another study indicated that a higher consumption of vegetables, legumes, fruits, nuts, cereals, and fish, along with a reduced intake of meat and poultry, is linked to lower odds of asthma attacks.[44] Conversely, it has been demonstrated that a diet high in fat and low in fiber can influence the incidence of allergic diseases.[45] This may contribute to the rising prevalence of allergic diseases, including asthma, allergic rhinitis, and other allergic conditions over recent decades.[46]

Dietary fiber, defined as edible carbohydrate polymers that resist digestion by endogenous enzymes, plays a critical role in regulating intestinal bacteria and maintaining immune homeostasis.[37,46] Recent research has confirmed that the supplementation of dietary fiber enhances the proliferation of beneficial bacteria, such as Bifidobacterium and Lactobacillus, in healthy adults.[45] As a result, certain types of dietary fibers can be categorized as prebiotics.[47] The gut microbiota can effectively metabolize and use these fibers, leading to an increase in the concentration of circulating SCFAs.[36] Some studies have indicated that dietary fiber may positively influence the balance of Th1/Th2 immunity, considerably inhibit inflammatory responses in allergic rhinitis and concurrent asthma and reduce airway inflammation by suppressing DC function.[46,48] Both animal studies and clinical trials involving humans have demonstrated that early intake of dietary oligosaccharides can help prevent the onset of allergic asthma and other allergic conditions.[48,49]

Conversely, a long-term dietary pattern characterized by insufficient dietary fiber intake is strongly associated with an enhanced risk of airway allergic diseases, including asthma, due to a decrease in butyrate- and SCFA-producing bacteria.[14,46] Consequently, appropriate amounts of dietary fiber can regulate intestinal bacteria, preserve immune homeostasis, and thus may be regarded as an effective therapeutic strategy for the treatment and prevention of asthma. Although it presents challenges, this healthy dietary approach should be advocated for the majority of asthma patients.

Prebiotics and Probiotics Use

Prebiotics are characterized as specialized substrates that are selectively fermented by host microorganisms. They offer numerous health benefits, which include defense against pathogens, immune modulation, improved bowel function, positive metabolic effects, and enhanced satiety. Also, they play an essential role in maintaining the stability of microbiota[48,50–53]. Importantly, certain dietary fibers such as fructooligosaccharides, galactooligosaccharides, and inulin have been recognized as key prebiotic agents. These agents can notably influence the composition and functional capacities of probiotics while also favorably modifying the gut microbiota towards a more beneficial state.[26,54] At the same time, the interactions between probiotics and prebiotics indicate a complex relationship in which probiotics exert their beneficial effects through well-documented molecular and cellular mechanisms. These mechanisms include the enhancement of innate immunity, reduction of inflammation induced by pathogens, and promotion of the maturation of the mucosal immune system. Probiotics achieve these beneficial effects by secreting various antimicrobial compounds, which include organic acids and SCFAs.[55,56] A important study indicated that a four-week supplementation with synbiotics, which consisted of 90% short-chain galacto-oligosaccharides and 10% long-chain fructo-oligosaccharides, resulted in a notable decrease in Th2 cytokine production and an improvement in peak expiratory flow (PEF) among patients with allergic asthma.[57] Therefore, it can be inferred that the strategic incorporation of prebiotics and probiotics could represent a feasible therapeutic approach for managing conditions marked by airway inflammation, thus necessitating further investigation into their synergistic effects within clinical environments.

Several studies have indicated that probiotics might are an alternative form of medication for asthma or as an adjunct to asthma therapy.[58] Probiotics can greatly reduce disease severity primarily by modulating immune responses that are involved in allergic inflammation.[59] Conversely, a lack of pathogen exposure during early childhood heightens the risk of developing allergic asthma, resulting in a shift in the immune response from a Th1 to a Th2 response pattern.[54] Prior research has demonstrated that probiotics can affect respiratory immunity by influencing the production of interferons (IFNs), diminishing the synthesis of IL-4, IL-13, and IgE, redirecting the Th2 response toward a Th1 type, and collectively contributing to the mitigation of allergic predisposition and reactions.[50,60] Also, both prebiotics and probiotics may hinder the activation of genes related to asthma through the PI3K/Akt and TLR4/NF-κB pathways, thereby decelerating the progression of asthma.[54] Recently, some beneficial bacteria, including *Lactobacillus, Bifidobacterium, Lachnospira*, and *Akkermansia*, have demonstrated anti-asthmatic effects.[61] *Lactobacillus* and *Bifidobacterium*, considered traditional probiotics, are of particular interest.[62] For instance, *Lactobacillus* exhibits strong immunomodulatory capabilities and improves gastrointestinal disorders.[63] Meanwhile, the administration of *Lactobacillus* has been shown to alleviate asthma symptoms.[64] It has also been established that treatment with plantarum 06CC2 in ovalbumin-sensitized mice leads to a reduction in the levels of histamine, total IgE, and ovalbumin-specific IgE in the serum, thereby greatly easing allergic symptoms.[65] In a separate study, *L. reuteri*, a member of the *Lactobacillus* genus, modifies specific gut microbes and enhances butyrate production, which encourages regulatory T-cell proliferation and mitigates allergy-associated Th2 immune responses.[66,67] *Bifidobacterium*, another major probiotic, has been shown to alleviate respiratory symptoms and enhance quality of life.[68,69] It was demonstrated that *MRx0004*, an important type of *Bifidobacterium*, can reduce the infiltration of neutrophils, eosinophils in mice with severe asthma.[70] And *Bifidobacterium* infantis CGMCC313-2 has been found to greatly lower serum levels of IgE, IgG1, IL-4, and IL-13 in mice exhibiting allergic asthma.[71] Comprehensively, prebiotics and probiotics may be a therapeutic strategy for allergic asthma, warranting further investigation into their mechanisms of action, optimal dosing, and safety, all of which could contribute to more rational treatment approaches for asthma.

Antibiotics Use

The introduction of antibiotics marks one of the most important developments in modern medicine, fundamentally changing the field of infectious disease management and leading to a major decrease in both morbidity and mortality related to bacterial infections, thereby protecting countless lives and improving overall public health outcomes.[72,73] Nevertheless, new studies have started to reveal possible unintended consequences associated with antibiotic use, especially when administered during critical periods of early-life development, increased risk of developing early persistent asthma.[74,75] Besides, the disruption of the gut microbiome caused by antibiotics is linked to various infectious and autoimmune diseases affecting the gastrointestinal system.[76]

Currently, the primary mechanisms through which antibiotics influence the occurrence of allergic diseases, including asthma, are as follows.[77] To begin with, antibiotics may direct the immune system towards an allergic pathway by diminishing the severity and duration of infections.[19] The treatment with antibiotics can result in a reduction of phylogenetic diversity, which may lead to the displacement of potential pathogens and a delay in the maturation of both the microbiome and the immune system, eventually impacting immune homeostasis.[78] A recent investigation conducted by the STEPS study has shown that exposure to antibiotics before the age of one is linked to an increased vulnerability to asthma by the age of seven years.[79] Secondly, it has been demonstrated that the Th2-skewed response induced by antibiotics may play an important role in the etiology of allergies.[19] Evidence indicates that the administration of oral antibiotics can lead to enhanced serum IgE concentrations, exacerbating basophil-mediated Th2 inflammation by increasing the basophil population during asthma attacks in older children.[80] Lastly, antibiotics may exert their effects by disturbing the gut microbiota.[81] The perturbation of the gut microbiome induced by antibiotics may result in the depletion of SCFAs, which in turn can lead to hyperactivation of intestinal macrophages and expansion of pro-inflammatory Th cells, consequently increasing susceptibility to airway inflammation and infections.[14] In addition, it has been demonstrated that exposure to antibiotics in early life can alter the composition and function of the microbiome in the lungs, leading to dysregulation of innate and adaptive immunity, thus assisting the development of asthma.[77,79] A study conducted in Sweden, involving 493,785 children, has suggested a strong positive association between antibiotic use and the incidence and progression of asthma, particularly during the first six months of life.[82] This evidence indicates that reducing the excessive consumption of antibiotics is highly advisable for the prevention of asthma in childhood.[83]

While there are no definitive guidelines for the early use of antibiotics, it is worthwhile to explore methods of managing early antibiotic administration to reduce the risk of asthma as an emerging research focus. What's more, another study has shown that supplementation with SCFA butyrate may reverse the hypo-responsiveness of intestinal macrophages induced by antibiotics, support appropriate T cell functions, and avert immune dysfunction linked to antibiotics.[84] Accordingly, aiming to restore macrophage homeostasis following antibiotic treatment could represent a novel and effective approach to preventing enduring immune dysfunction in patients with asthma.[84]

Breast Feeding

Environmental exposures have gained increasing recognition as important factors contributing to the onset of allergic diseases, particularly through their interactions with various human host factors.[85] Specifically, breastfeeding is recognized as one of the earliest environmental exposures associated with respiratory health, with numerous studies demonstrating its protective effects against the development of asthma during childhood.[86,87] Research conducted by Dogaru et al indicates that exclusive breastfeeding for the initial six months of life considerably lowers the likelihood of developing asthma and other allergic conditions in later years.[88] Besides, a systematic review by reinforces this claim, emphasizing the critical role of breastfeeding influencing the infant's immune system and decreasing asthma incidence.[89]

The composition of human breast milk is detailed, comprising various factors that engage with the infant's immune system and intestinal environment, including allergens, cytokines, immunoglobulins, polyunsaturated fatty acids, and chemokines.[90] These factors have the potential to modify the gut microbiome and subsequent immune development in children, thereby affecting the risk of various respiratory infections.[91] Besides, multiple studies indicate that weaning is

linked to strong immune responses directed at the developing intestinal microbiota, thereby protecting against pathological imprinting through the induction of RORγt Tregs.[92] The mucosal immune system around the time of weaning undergoes a major transformation from the neonatal to the adult state, which is considered an important phase in the maturation of the immune system following birth.[93,94] In addition, another study has revealed that infants who ceased breastfeeding and began consuming solid foods within the first three months of life are more vulnerable to allergies, and respiratory and gastrointestinal infections.[95] This raises important questions regarding the appropriate timing and manner in which the breastfeeding process should conclude. It has been suggested that an extended duration of breastfeeding can reduce the risk of developing allergic asthma across all age groups.[96] Exclusive breastfeeding for a minimum of six months and partial breastfeeding for up to one year is highly recommended, as this may alleviate the incidence of respiratory infections during infancy.[97,98] Based on these findings, breastfeeding is deemed to possess properties that may prevent asthma throughout an individual's life.[99] Nevertheless, other factors may partially influence the relationship between breastfeeding and allergic diseases, including the diets of both the mother and the infant, maternal microbiota, and exposure to exogenous allergens.[90] Thus, further research into breastfeeding is essential to determine the optimal breastfeeding strategies for the prevention and treatment of asthma.

Conclusion

To summarize, the complex interaction between the host immune system and the gut microbiome stands out as an essential factor in maintaining immune homeostasis. This review has thoroughly examined a considerable amount of evidence that associates the gut microbiome with the development and regulation of airway immunity. It emphasizes the diverse mechanisms through which various gut microbial species and their metabolites influence immune responses within the airways. Importantly, SCFAs have been recognized as key contributors to the modulation of host immunity, playing an essential role in decreasing allergic reactions and alleviating airway inflammation.[100] The therapeutic implications of this relationship are major, particularly considering asthma management. The findings indicate that dietary modifications and the encouragement of early breastfeeding practices may function as protective strategies against the emergence of asthma and other related conditions. Besides, the timing and administration of probiotics and antibiotics in early life have been correlated with the development of asthma, emphasizing the necessity for a careful approach to these interventions. Despite the encouraging insights provided by current research, a critical gap exists concerning the establishment of specific protocols for using probiotics and antibiotics during early childhood. The available literature lacks thorough clinical trials that define optimal strategies for these interventions, suggesting an urgent need for further studies.[79,101] Future research should focus on clarifying the mechanisms that support the gut-lung axis and on creating evidence-based guidelines for microbiome-targeted interventions. Eventually, incorporating these findings into clinical practice could lead to innovative strategies for preventing and treating asthma and related respiratory conditions. By concentrating on the modulation of the microbiome during early life, it may be feasible to bolster immune resilience and lessen the impact of asthma, thereby enhancing public health outcomes. The ongoing investigation into the gut microbiome's role in airway immunity offers substantial potential for advancing our comprehension of asthma pathogenesis and for formulating effective preventive measures.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements.

Acknowledgments

We thank all the institutions affiliated with the authors for supporting this review.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Joint Foundation Established by Enterprises and the Basic and Applied Basic Research Foundation of Guangdong Province, China (Project Number:2022A1515220169), Natural Science Foundation of China (Project Number:81300012), and Appropriate Health Technology Promotion Project of Guangdong Province (Project Number:202006181142034974).

Disclosure

The authors have no conflicts of interest to declare.

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