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RECEIVED 24 April 2025

ACCEPTED 21 July 2025

PUBLISHED 31 July 2025

## CITATION

Lv J, Zhang Y, Liu S, Wang R and Zhao J (2025) Gut-lung axis in allergic asthma: microbiota-driven immune dysregulation and therapeutic strategies. *Front. Pharmacol.* 16:1617546. doi: 10.3389/fphar.2025.1617546

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# Gut-lung axis in allergic asthma: microbiota-driven immune dysregulation and therapeutic strategies

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**Background:** Allergic asthma, a chronic respiratory disorder, is intricately linked to gut microbiota dysbiosis and metabolite perturbations through the gut-lung axis.

**Objective:** This review the relationship between microbial immune crosstalk and the onset of asthma, with the aim of determining the mechanism by which gut microbiota drives the onset of asthma and providing evidence for therapeutic interventions.

**Methods:** Literature search was conducted on PubMed using keywords ("gut microbiota" or "gut microbiota" or "gut microbiota metabolites" or "lung gut axis"), ("allergic asthma" or "asthma"), and ("immune regulation"), without date restrictions. Including peer-reviewed studies on human/animal models, articles that do not meet the requirements are excluded.

**Result:** Microbial imbalance in asthma patients—marked by reduced  $\alpha$ -diversity, depletion of immunomodulatory taxa (e.g., *Bifidobacterium*, *Faecalibacterium*), and enrichment of pathobionts—disrupts short-chain fatty acid (SCFA) and tryptophan metabolism, skewing Th17/Treg balance toward Th2-dominated inflammation and airway hyperresponsiveness. SCFAs, particularly butyrate, activate GPR41/43 receptors and inhibit histone deacetylases (HDACs), enhancing Treg differentiation while suppressing Th2/Th17 responses. Tryptophan metabolites, such as indole derivatives, alleviate pulmonary inflammation via aryl hydrocarbon receptor (AhR)-dependent IL-22 production. Clinically, diminished SCFA levels correlate with impaired immune tolerance and airway remodeling, while probiotics (*Lactobacillus*, *Bifidobacterium*), prebiotics, and high-fiber diets restore microbial equilibrium, attenuating asthma severity.

**Conclusion:** Future research must integrate multi-omics data to delineate strain-specific functions, host-microbe interactions, and individualized responses influenced by genetics, diet, and environmental factors. This review

underscores the gut microbiota's dual role as a biomarker and therapeutic target, advocating for microbiota-directed strategies in asthma prevention and precision medicine.

#### KEYWORDS

gut microbiota, SCFAs, allergic asthma, gut-lung axis, immune regulation, probiotics

## 1 Introduction

Allergic asthma, a prevalent chronic respiratory disorder, imposes a substantial global health burden. Epidemiological data reveal that 60%–80% of asthma cases exhibit allergic phenotypes, constituting the predominant disease subtype (Zhang et al., 2025). Notably, geographic disparities exist in prevalence trends: high-income countries demonstrate plateauing incidence rates of allergic disorders, whereas low- and middle-income nations face escalating trends, potentially reflecting environmental and socioeconomic determinants (Genuneit and Standl, 2022). Clinically, this condition manifests through characteristic airway hyperresponsiveness, episodic dyspnea, nonproductive cough, and chest constriction, with symptom severity correlating with allergen exposure levels (Shah and Newcomb, 2018). Importantly, 40%–60% of patients present with allergic multimorbidity, particularly concurrent allergic rhinitis and atopic dermatitis, which synergistically exacerbate disease progression and substantially impair quality of life metrics (Humbert et al., 2019).

The gut microbiota, comprising a complex ecosystem of commensal microorganisms, exerts systemic immunomodulatory effects through bidirectional gut-lung axis communication. With estimated microbial densities exceeding  $10^{14}$  organisms and compositionally diverse taxonomy, this microbial consortium critically regulates host physiological homeostasis, including nutrient assimilation, xenobiotic metabolism, and intestinal epithelial barrier fortification (Yang and Chun, 2021). Mounting evidence from multi-omics studies implicates microbial imbalance in the pathogenesis of diverse disease states, spanning metabolic syndrome, autoimmune disorders, and neuropsychiatric conditions (Ding et al., 2024). Mechanistically, microbial-derived metabolites such as short-chain fatty acids (SCFAs) serve as key immunoregulatory mediators, modulating T-cell differentiation pathways and attenuating systemic inflammation through G protein-coupled receptor interactions (Li et al., 2022a). We hypothesize that gut microbiota modulation can recalibrate Th2/Th17-Treg imbalances in allergic asthma.

Emerging evidence has elucidated critical cross-talk between gut microbial communities and pulmonary pathophysiology through the gut-lung axis—a bidirectional immunoregulatory network involving microbial metabolites and immune cell trafficking. Contemporary research demonstrates that taxonomic alterations and functional perturbations in gut microbiota (microbial imbalance) significantly impact respiratory disease trajectories, particularly in COPD and allergic asthma exacerbations, as evidenced by longitudinal clinical cohort studies (Shi et al., 2021). Mechanistic investigations reveal that depleted microbial diversity compromises pulmonary immune homeostasis, predisposing hosts to enhanced type 2 inflammation and impaired antiviral defense mechanisms, as substantiated by

preclinical models of allergic airway disease (Neag et al., 2022). Microbial-derived metabolites, including but not limited to SCFAs, exert distal immunomodulatory effects through systemic circulation and vagus nerve signaling—notably regulating Treg cell differentiation and suppressing neutrophilic infiltration in bronchial tissues via G protein-coupled receptor (GPCR) signaling pathways (Alswat, 2024). These mechanistic insights are revolutionizing our understanding of asthma pathogenesis, positioning microbiota-targeted interventions (e.g., probiotics, postbiotics) as promising disease-modifying approaches in precision allergology.

## 2 Methods

### 2.1 Search strategy

To identify published studies, we conducted a comprehensive search of PubMed and Embase databases, covering records up to January 2025. Our search strategy includes the following keyword sets: (“gut microbiota” or “gut microbiota” or “gut microbiota metabolites” or “lung gut axis”), (“allergic asthma” or “asthma”), (“immune regulation”). We only search for English publications. Preliminary screening is conducted using search engines provided by various databases.

### 2.2 Data extraction and synthesis

Before reading the full text of a given paper, we manually select references related to the topic using Excel software. Finally, all included are peer-reviewed articles related to the topic. During the process of writing the paper, one author is responsible for data extraction. Subsequently, other authors conducted cross checks on the extracted data to maintain its integrity and reliability.

## 3 Gut microbiota composition in allergic asthma

The gut microbiota in healthy individuals forms a phylogenetically complex ecosystem comprising bacteria, archaea, fungi, and viruses, with bacterial dominance primarily observed in four phyla: Firmicutes, Bacteroidetes (including genera like *Prevotella*), Actinobacteria (exemplified by *Bifidobacterium* species), and Clostridia (particularly the butyrate-producing species *Faecalibacterium prausnitzii*). This microbial consortium demonstrates substantial  $\alpha$ -diversity (intra-individual species richness) and functional redundancy, enabling robust ecosystem stability that facilitates immune tolerance, epithelial barrier

maintenance, and metabolic homeostasis through mechanisms including short-chain fatty acid (SCFA) biosynthesis (notably butyrate) and essential vitamin production (Liu et al., 2024; Mirmohammadali and Rosenkranz, 2023). Bidirectional communication with the central nervous system further establishes the microbiota's role in regulating mood and cognitive functions through neuroendocrine, immune, and neural pathways, a relationship termed the gut-brain axis (Alves et al., 2024; Salami, 2021). These multifunctional interactions underscore the necessity of preserving microbial compositional integrity for systemic health maintenance.

Microbial diversity serves as a key biomarker for health status and pathological susceptibility. Epidemiological evidence associates reduced gut microbiota diversity with increased incidence of metabolic disorders (obesity, diabetes), cardiovascular pathologies, and immune-mediated conditions including allergic diseases (Guo et al., 2020; Shi et al., 2024). The diversity-immune function nexus manifests through microbial regulation of immune cell differentiation and inflammatory responses, where high diversity correlates with enhanced immune homeostasis and reduced chronic inflammation risks (Liu et al., 2024; Sottas et al., 2021). This immunological modulation, coupled with direct metabolic contributions, positions microbiota diversity preservation as a critical factor not merely for gastrointestinal health, but for comprehensive disease prevention strategies spanning multiple physiological systems.

Emerging evidence highlights significant compositional disparities between the gut microbiota of allergic asthma patients and healthy populations. Ke et al. demonstrated an inverse correlation between childhood gut microbiota diversity and susceptibility to asthma/allergic conditions, implicating depauperate microbiota as a potential risk amplifier (Ke et al., 2021). Asthma patients characteristically exhibit diminished  $\alpha$ -diversity, a feature mechanistically linked to dysregulated immune homeostasis (Heinrich et al., 2023; Hsu et al., 2021). Concurrently, these individuals display depletion of immunomodulatory taxa like *Bifidobacterium* and *Lactobacillus*, alongside pathobiont enrichment such as *Escherichia coli*—a microbial signature that may perpetuate inflammatory cascades (Heinrich et al., 2023; Li et al., 2022b). Mechanistically, early-life microbial colonization patterns exert long-term immunological consequences, exemplified by *Clostridium difficile* establishment at 1 month predicting asthma development by age 6–7 years (van Nimwegen et al., 2011). Parallel microbial imbalance extends to respiratory ecosystems, where asthma severity correlates positively with reduced bacterial diversity and elevated proteobacterial abundance in the airway microbiome (Carr et al., 2019). Age-stratified analyses further reveal distinct microbiota configurations between asthmatic and non-asthmatic cohorts across developmental stages (Lee et al., 2019). Exogenous modifiers including antibiotic exposure and dietary patterns potentially exacerbate these ecological perturbations, creating feedforward loops that may intensify symptomatology. Therapeutic modulation through targeted probiotics or precision nutrition emerges as a promising strategy to restore microbial equilibrium, with clinical studies suggesting concomitant improvements in both immunological parameters and quality-of-life metrics (Liao et al., 2022; Ozerskaia et al., 2021). This review

systematically delineates gut microbiota alterations in allergic asthma (summarized in Table 1), providing a framework to understand their pathogenic contributions and therapeutic potential.

## 4 Biological activity of gut microbial metabolites

The gut microbiota-derived metabolites exhibit significant biological activities through intricate biosynthetic pathways and host-microbe interactions. Short-chain fatty acids (SCFAs), principal microbial fermentation products of dietary fibers, are synthesized via carbohydrate-active enzymes expressed by commensal bacteria. These  $\leq 6$ -carbon molecules—predominantly acetate, propionate, and butyrate—exist in strictly regulated colonic ratios (Fernandes et al., 2014). Acetate production predominates through the Wood-Ljungdahl pathway in acetogenic bacteria, demonstrating superior metabolic efficiency compared to other SCFAs (Miller and Wolin, 1996). Propionate biosynthesis occurs via three distinct routes: Bacteroidetes species preferentially employ the succinate pathway (Reichardt et al., 2014), while Firmicutes utilize acrylate and propanediol pathways, particularly when metabolizing pentoses/hexoses (Macfarlane and Macfarlane, 2003). Butyrogenesis is specialized to select Firmicutes taxa expressing butyryl-CoA:acetate CoA-transferase, with *Faecalibacterium prausnitzii* being a key producer (Louis et al., 2010). SCFAs are key factors linking gut microbial imbalance with allergic airway diseases. Clinically relevant SCFA deficiencies are observed in allergic rhinitis patients and infants predisposed to later asthma/wheezing development (Zhou et al., 2021), establishing these metabolites as critical mediators in allergic airway pathogenesis (Cheng et al., 2022; Roduit et al., 2019). Some scholars speculate that low levels of butyrate may be associated with increased severity in asthma patients.

Tryptophan metabolism represents another pivotal microbial-host interaction axis. While dietary tryptophan is primarily absorbed intestinally for protein synthesis, colonic microbiota extensively catabolize residual tryptophan through multiple pathways. Direct bacterial conversion yields immunomodulatory indole derivatives (indole, IE, IPA, ILA) via tryptophanase-expressing species like *Escherichia coli* and *Proteus vulgaris* (Lee and Lee, 2010; Palusiak, 2013; Smith, 1897). Concurrently, microbial regulation of host tryptophan metabolism occurs through serotonin synthesis and kynurenine pathway modulation (Roager and Licht, 2018). These metabolites demonstrate dual neuroimmune regulatory capacity: indole derivatives activate aryl hydrocarbon receptor (AhR) signaling to promote anti-inflammatory cytokine production (Brown et al., 2022; Zhao et al., 2024), while kynurenine accumulation correlates with chronic inflammatory and neuropsychiatric disorders (Basnet et al., 2023; Diether et al., 2023).

The gut-lung axis operationalizes these metabolites through systemic immunomodulation. SCFAs mitigate allergic airway inflammation via GPR41/43-mediated suppression of Th2 responses and HDAC inhibition-induced Treg cell expansion, as evidenced by their therapeutic efficacy in murine asthma models (Bloor and Mitchell, 2021; Zhang et al., 2025). Clinical translation potential is suggested by probiotic

**TABLE 1** The correlation between gut microbiota and allergic asthma.

| Reference                  | Bacterial genus                                                                                                 | Type of study  | Material studied/model | Results of allergic compared with non-allergic subjects                                                                                                                                                                                                   |
|----------------------------|-----------------------------------------------------------------------------------------------------------------|----------------|------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| van Nimwegen et al. (2011) | <i>Clostridium difficile</i>                                                                                    | Clinical       | Fecal samples          | Colonisation with <i>C.difficile</i> at 1 month of age was associated with increased risk of asthma (OR: 2.06; 1.16–3.64) at 6 years of age                                                                                                               |
| Sagar et al. (2014)        | <i>Bifidobacterium breve</i> M-16 V, <i>Lactobacillus rhamnosus</i> NutRes1                                     | <i>In-vivo</i> | Mouse model            | <i>Bifidobacterium brevis</i> M-16 V and <i>Lactobacillus rhamnosus</i> NutRes1 have strong anti-inflammatory effects and alleviate asthma by regulating T cell responses                                                                                 |
| Stiemsma et al. (2016)     | <i>Lachnospira</i> , <i>Clostridium neonatale</i>                                                               | Clinical       | Fecal samples          | <i>Lachnospira</i> decreases and <i>Clostridium neonatale</i> increases in asthmatic children 3 months after birth                                                                                                                                        |
| Fujimura et al. (2016)     | <i>Bifidobacterium</i> , <i>Akkermansia</i> and <i>Faecalibacterium</i> , <i>Candida</i> and <i>Rhodotorula</i> | Clinical       | Fecal samples          | Children at high risk of asthma have lower relative abundance of <i>Bifidobacterium</i> , <i>Akkermansia</i> , and <i>Faecalibacterium</i> , while specific fungi such as <i>Candida</i> and <i>Rhodotorula cerevisiae</i> have higher relative abundance |
| Hevia et al. (2016)        | <i>Bifidobacterium</i>                                                                                          | Clinical       | Fecal samples          | Long term asthma patients have lower levels of bifidobacteria                                                                                                                                                                                             |
| Demirci et al. (2019)      | <i>Akkermansia muciniphila</i> , <i>Faecalibacterium prausnitzii</i>                                            | Clinical       | Fecal samples          | Compared with the healthy control group, <i>A. muciniphila</i> ( $5.45 \pm 0.004$ vs. $6.74 \pm 0.01$ ) and <i>F. prausnitzii</i> ( $5.71 \pm 0.002$ vs. $7.28 \pm 0.009$ ) were both reduced in the allergic asthma group                                |
| Hu et al. (2021b)          | <i>Faecalibacterium prausnitzii</i>                                                                             | <i>In-vivo</i> | Mouse model            | <i>Faecalibacterium prausnitzii</i> alleviates symptoms of allergic asthma in mice by improving gut microbiota dysbiosis                                                                                                                                  |
| Gao et al. (2021)          | <i>Prevotella bacteria</i>                                                                                      | Clinical       | Fecal samples          | Maternal carriage of <i>Prevotella copri</i> during pregnancy decreases the offspring's risk of asthma via production of succinate                                                                                                                        |
| Versi et al. (2023)        | <i>Haemophilus influenzae</i>                                                                                   | Clinical       | sputum                 | In neutrophilic asthma, there was greater abundance of <i>Haemophilus influenzae</i> and <i>Moraxella catarrhalis</i>                                                                                                                                     |
| Mousavian et al. (2024)    | <i>Bifidobacterium</i> , <i>Lachnospira</i> , <i>Roseburia</i> and <i>Flavonifractor</i>                        | Clinical       | Fecal samples          | Lower levels of bifidobacteria and <i>Lachnospira</i> are associated with a higher risk of allergies. In contrast, higher levels of <i>Roseburia</i> and <i>Flavonifractor</i> are associated with lower allergy risk                                     |

interventions restoring SCFA levels and improving respiratory outcomes (Hu et al., 2021b; Thorburn et al., 2015). Similarly, tryptophan metabolites regulate pulmonary immunity through AhR-dependent IL-22 production and Th17/ILC3 modulation, with microbial imbalance-induced kynurenine/SCFA imbalances exacerbating airway hyperreactivity (Basnet et al., 2023; Padhi et al., 2024). These mechanistic insights position microbial metabolite modulation as a promising therapeutic strategy for allergic asthma and related airway pathologies, bridging microbial ecology with clinical immunology through targeted microbiome engineering approaches.

## 5 The interaction between gut microbiota and immune system

The dynamic interplay between gut microbiota and the host immune system represents a fundamental axis in maintaining physiological homeostasis (Chen et al., 2022). Through multifaceted mechanisms—including immune cell modulation, metabolite production, and intestinal barrier maintenance—the microbiota directly shapes systemic immune competence. Microbial imbalance is increasingly implicated in immune-mediated pathologies such as autoimmune disorders, allergies, and inflammatory bowel diseases (Al-Rashidi, 2022; Yoo et al.,

2020). Key findings from investigations into these interactions are systematically summarized in Table 2 and Figure 1.

### 5.1 T cell regulation

Gut microbiota critically influences T cell ontogeny and polarization. Microbial-derived short-chain fatty acids (SCFAs), generated through dietary fiber fermentation, drive the differentiation of regulatory T cells (Tregs), a process essential for immune tolerance and prevention of autoimmunity (Wang et al., 2024; Yoo et al., 2020). SCFAs bind to G protein-coupled receptors (e.g., GPR41, GPR43) on intestinal epithelial and immune cells, enhancing barrier integrity, suppressing inflammation, and modulating T cell subsets. Butyrate, for instance, serves dual roles as a primary energy source for colonocytes and an anti-inflammatory mediator via inhibition of pro-inflammatory cytokine production, as demonstrated by Chen et al. (2018). Importantly, SCFAs promote Treg expansion while suppressing pro-inflammatory Th17 cell activation, thereby exerting protective effects in allergic and autoimmune contexts (Gong et al., 2023; Yang and Cong, 2021). Furthermore, specific microbial taxa enhance CD8<sup>+</sup> T cell cytotoxicity, as evidenced by Baruch et al. Research by Baruch et al. (2021), who reported improved anti-tumor immunity through microbiota-driven CD8<sup>+</sup> T cell priming. These findings

TABLE 2 The characteristics and functions of metabolites in the main gut microbiota.

| Metabolites of gut microbiota | Examples                                                         | Receptors                                                                                  | Effector cell | Cytokine                                                                                                        | Specific function                                                                                                                                                                             | Reference                                                                                                                                                                                                                                                                                                                                                                  |
|-------------------------------|------------------------------------------------------------------|--------------------------------------------------------------------------------------------|---------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| SCFAs                         | Formic acid<br>Acetate<br>Propionate<br>Butyrate<br>Valeric acid | GPR41 (Yang et al., 2020)<br>GPR43 (Sun et al., 2018)<br>GPR109a (Thangaraju et al., 2009) | T cell        | IL-10, GPCRs, STAT3, mTOR, HDAC, Foxp3, IL-6/STAT3/IL-17, acetyl CoA/mTOR, ROR $\gamma$ t, mitoROS/Foxp3, NR4A1 | Inducing differentiation of CD4 <sup>+</sup> T cells<br><br>Enhanced memory transfer of CD8 <sup>+</sup> T cells                                                                              | Arpaia et al. (2013), Balmer et al. (2016), Chen et al. (2019), Dupraz et al. (2021), Furusawa et al. (2013), Hang et al. (2019), Kespohl et al. (2017), Kibbie et al. (2021), Li et al. (2021), Luu et al. (2018), Park et al. (2015), Rangan and Mondino (2022), Shiratori et al. (2023), Smith et al. (2013), Song et al. (2023), Sun et al. (2018), Zhou et al. (2018) |
|                               |                                                                  |                                                                                            | B cell        | BCR, TLRs, IL-10                                                                                                | Increase acetyl CoA to promote energy and antibody production                                                                                                                                 | Föh et al., 2022; Kim (2016), Kim et al. (2021)                                                                                                                                                                                                                                                                                                                            |
|                               |                                                                  |                                                                                            | DCs           | IL-6, IL-12 p40, IL-10, GPR109A, NF- $\kappa$ B, cAMP-PKA, TGR5, HDAC, TGF- $\beta$                             | Affect the differentiation of DCs generated from human monocytes and can inhibit T cell proliferation                                                                                         | Hu et al. (2021a), Hu et al. (2022), Isobe et al. (2020), Kaiser et al. (2017), Nastasi et al. (2015), Wu et al. (2017)                                                                                                                                                                                                                                                    |
|                               |                                                                  |                                                                                            | Macrophages   | HDAC3, mTOR, PhoP K102, NO,WNT/ERK, NF- $\kappa$ B, IFN- $\beta$                                                | Modulate the function of intestinal macrophages                                                                                                                                               | Chang et al. (2014), Liang et al. (2022), Park et al. (2007), Park et al. (2019), Schulthess et al. (2019), Tang et al. (2023)                                                                                                                                                                                                                                             |
| Tryptophan metabolites        | Indole<br>IPA<br>IAA                                             | PXR (Venkatesh et al., 2014)<br>AhR (Hubbard et al., 2015)                                 | T cell        | IL-17                                                                                                           | Promote the production of T-regs cells while inhibiting the development of Th-17<br><br>Activated the aryl-hydrocarbon receptor in CD4 <sup>+</sup> T cells, and differentiation into DP IELs | Cervantes-Barragan et al. (2017), Rouse et al. (2013), Singh et al. (2016), Wilck et al. (2017)                                                                                                                                                                                                                                                                            |
|                               |                                                                  |                                                                                            | DCs           | IL-10, IFN- $\gamma$ , STAT3                                                                                    | Regulating cell differentiation and exerting anti-inflammatory effects                                                                                                                        | Aoki et al. (2018), Hwang et al. (2018)                                                                                                                                                                                                                                                                                                                                    |
|                               |                                                                  |                                                                                            | Macrophages   | IL-10, IL-12, TGF- $\beta$ 1, TNF $\alpha$ , IL-23, IL-6, IFN- $\gamma$                                         | Activate macrophages and downregulate pro-inflammatory cytokines                                                                                                                              | Huang et al. (2022b), Mohammadi et al. (2018)                                                                                                                                                                                                                                                                                                                              |
|                               |                                                                  |                                                                                            | B cell        | IL-35 <sup>+</sup> , TLR4                                                                                       | IAA promotes the production of IL-35+B cells                                                                                                                                                  | Su et al. (2022)                                                                                                                                                                                                                                                                                                                                                           |
|                               |                                                                  |                                                                                            |               |                                                                                                                 |                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                            |

Abbreviations: AhR, aryl hydrocarbon receptor; PXR, Retinoid X receptor; IPA, indolepropionic acid; IAA, 3-idoleacetic acid; HDAC3,histone deacetylase 3; NMDA, N-methyl-D-aspartate receptors; PXR, pregnane X receptor; SCFAs, short-chain fatty acids; DCs: Dendritic Cells.

underscore the microbiota’s role as a rheostat for T cell homeostasis, where microbial imbalance may disrupt effector-regulatory balances, predisposing to immune dysregulation (Wang and Gong, 2022).

5.2 Cytokine-mediated crosstalk

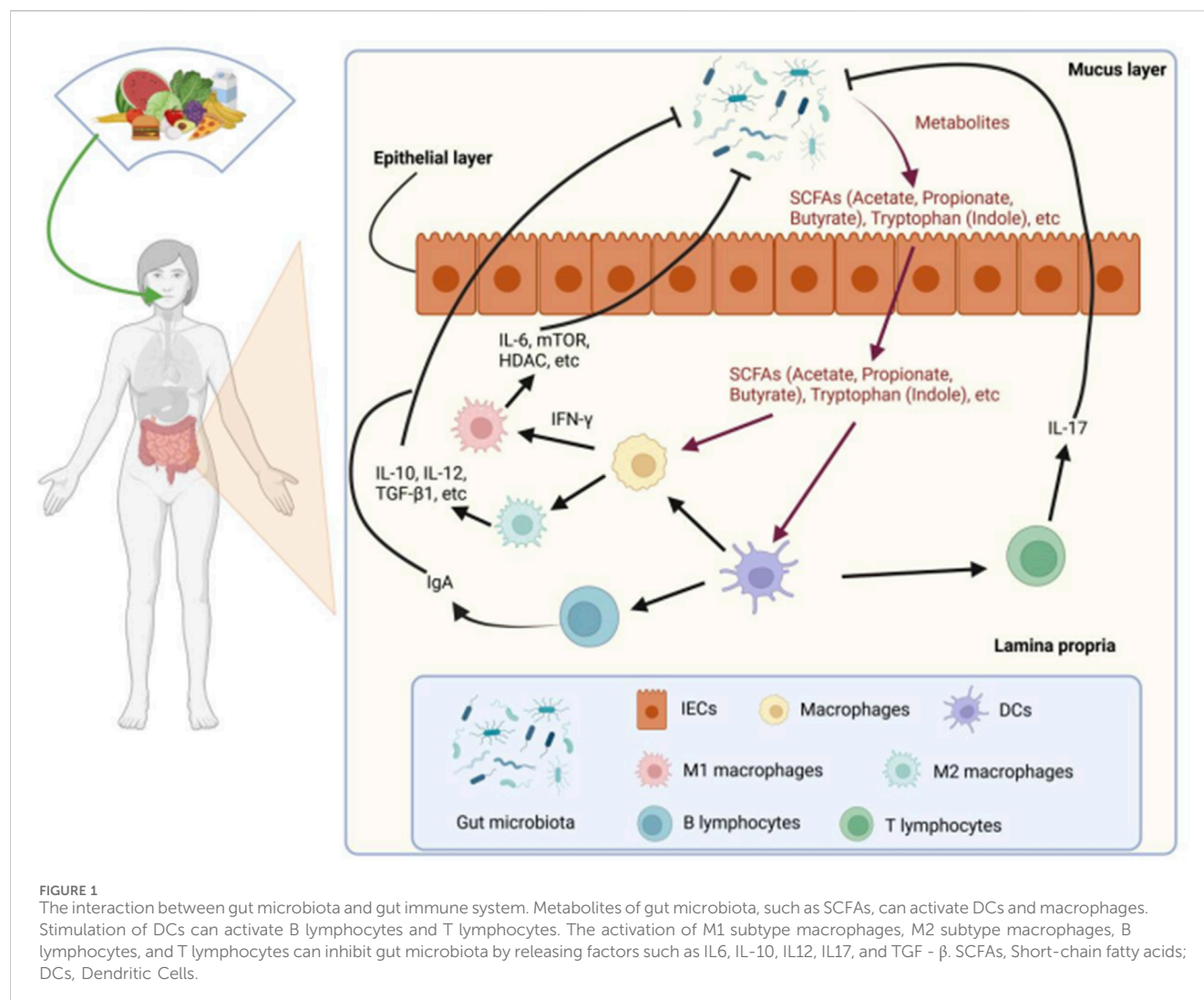
Microbial-immune crosstalk is further mediated through cytokine networks. Gut commensals stimulate epithelial and immune cells to secrete cytokines that orchestrate local and systemic immunity. For example, select taxa induce anti-inflammatory IL-10 production, counteracting inflammation,

while others trigger pro-inflammatory cytokines like TNF- $\alpha$  and IFN- $\gamma$ , exacerbating conditions such as inflammatory bowel disease (Saini et al., 2022). Microbial imbalance disrupts this cytokine equilibrium, skewing responses toward pathogenic inflammation or immunosuppression (Guo et al., 2021; Hou et al., 2022). This regulatory nexus highlights the microbiota’s capacity to calibrate immune activation thresholds through cytokine signaling.

5.3 Barrier-immune interactions

The intestinal barrier—comprising mucus layers, epithelial tight junctions, and mucosal immune cells—acts as a frontline defense





against luminal pathogens (Ulluwishewa et al., 2022). Gut microbiota fortify this barrier by stimulating epithelial cell proliferation, mucus secretion, and tight junction protein expression (e.g., occludin, claudins) (Huang et al., 2022a; Yoo et al., 2020). Conversely, microbial imbalance impairs barrier function, precipitating “leaky gut” syndrome, wherein bacterial translocation incites systemic inflammation and immune activation (Stepanova and Aherne, 2024; Terciolo et al., 2019). Thus, microbiota-barrier interactions are pivotal not only for intestinal health but also for preventing extra-intestinal immune pathologies. Collectively, these mechanisms illustrate the microbiota’s indispensable role in immune system education and regulation, positioning microbial modulation as a strategic target for immune-related disease management.

## 5.4 Other immune components

Short-chain fatty acids (SCFAs) enhance acetyl-CoA production, promoting antibody synthesis and IL-10 secretion (Luu et al., 2019). Tryptophan metabolites (e.g., indole-3-acetic acid) induce IL-35<sup>+</sup> B cells via TLR4 signaling (Tomii et al.,

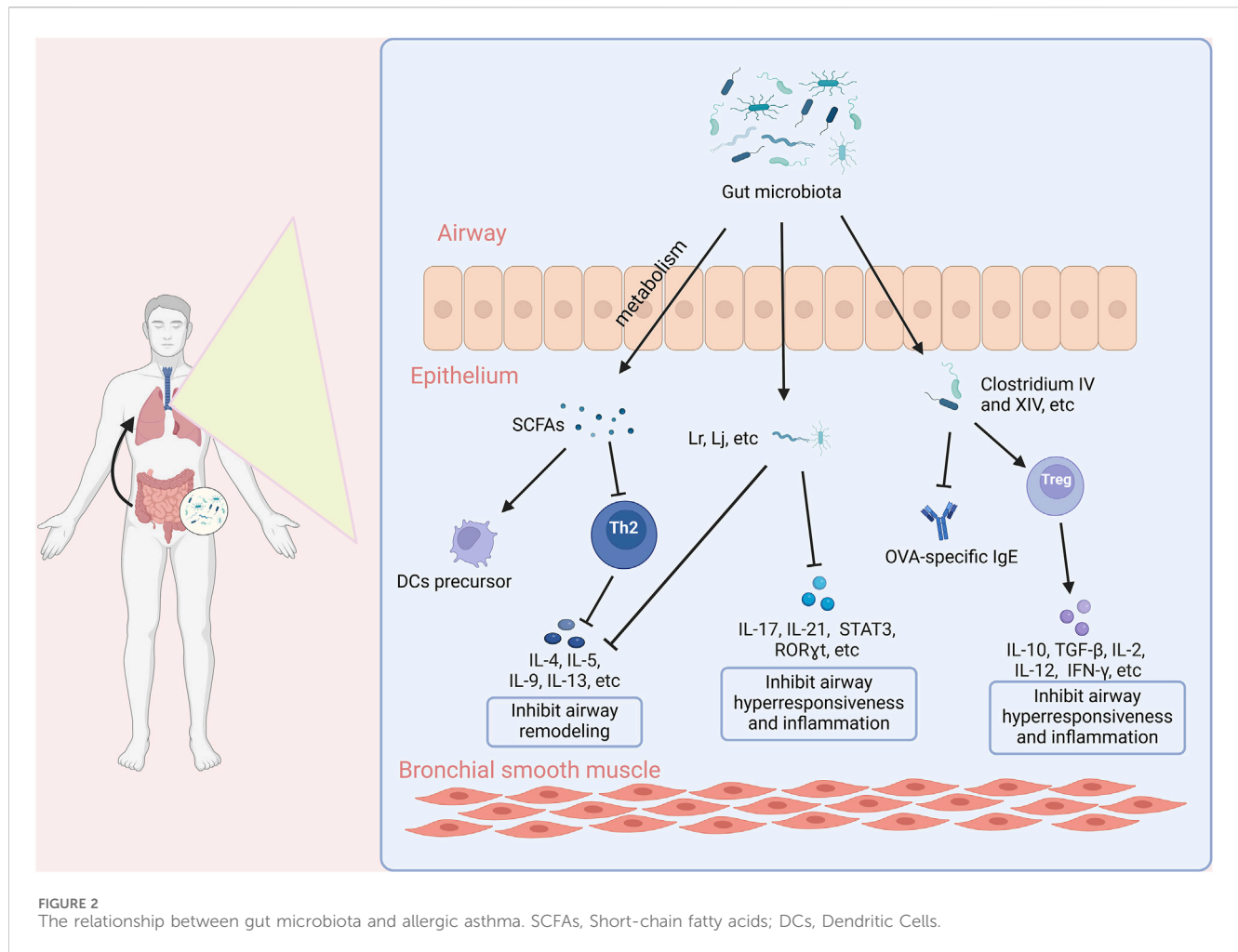
2023). SCFAs inhibit pro-inflammatory cytokine (IL-6, IL-12) release from DCs via GPR109A and HDAC suppression, skewing T cell differentiation toward tolerance (Kleuskens et al., 2022). Gut microbial metabolites (e.g., propionate) modulate macrophage phagocytosis and anti-inflammatory function via WNT/ERK pathways and HDAC inhibition (Liang et al., 2022).

## 6 Gut microbiota mechanisms in allergic asthma

We delineate the multifaceted role of gut microbiota in allergic asthma pathophysiology, highlighting microbial-immune interactions as a therapeutic frontier for airway hyperreactivity, remodeling, and allergenic sensitization as shown in Figure 2.

### 6.1 Airway hyperresponsiveness and microbial regulation

The nexus between gut microbiota imbalance and airway hyperresponsiveness (AHR) has emerged as a pivotal focus in



asthma pathogenesis. AHR, a hallmark of allergic asthma, is intricately linked to gut microbial composition and diversity through immune crosstalk. Gut microbiota modulate airway inflammation via systemic immune regulation, with microbial metabolites like short-chain fatty acids (SCFAs) playing central roles. Liu et al. demonstrated that SCFAs suppress inflammatory cytokine release, directly attenuating AHR severity (Liu et al., 2023). Patients with AHR exhibit marked reductions in gut microbial diversity, particularly depletion of immunomodulatory taxa such as *Bifidobacterium* and *Lactobacillus*, which may compromise immune tolerance and exacerbate allergic sensitization (Chen et al., 2024). Intervention studies highlight therapeutic potential: *Lactobacillus johnsonii* supplementation reduces immune cell activation in lungs and Th2 cytokine expression (IL-4, IL-5, IL-13, IL-17), suggesting microbiota-targeted strategies for AHR modulation (Aagaard et al., 2012).

## 6.2 Gut microbiota and airway remodeling

Airway remodeling—characterized by structural alterations like smooth muscle hypertrophy and subepithelial fibrosis—is mechanistically influenced by gut microbiota via systemic inflammatory pathways. Chen et al. identified that specific gut

microbes inhibit remodeling-associated cytokines (IL-4, IL-5, IL-9, IL-13) through SCFA production, mitigating airway wall thickening (Chen et al., 2024). Microbial imbalance may potentiate smooth muscle hyperplasia by enhancing pro-fibrotic signaling, as evidenced in murine models where *Lactobacillus rhamnosus* (Lr) administration reduced leukocyte infiltration, bronchial hyperreactivity, and remodeling markers (IL-4, IL-5, IL-13, STAT6, GATA3, IL-17, IL-21, IL-22, STAT3, RORγt) in asthma-COPD overlap syndrome (Vasconcelos et al., 2023). These findings position microbiota modulation as a viable approach to attenuate or reverse remodeling processes, potentially improving long-term asthma outcomes.

## 6.3 Microbial modulation of allergic sensitization

Gut microbiota critically shapes immune responses to allergens through T cell polarization and cytokine regulation. Pantazi et al. revealed that select commensals enhance regulatory T cell (Treg) differentiation, suppressing allergic effector responses (Pantazi et al., 2023). Murine studies demonstrate that *Clostridia* clusters IV/XIV supplementation elevates colonic Tregs and IL-10 production, correlating with reduced ovalbumin-specific IgE and IL-4 levels

in allergic models (Atarashi et al., 2011). In allergic asthma patients, microbial imbalance disrupts this immunoregulatory balance, amplifying hypersensitivity to aeroallergens (e.g., dust mites, pollen) and triggering exacerbations (Han et al., 2024). Microbial metabolites, particularly SCFAs, further mitigate allergic sensitization by modulating DC function and Th2 cytokine production. These mechanistic insights underscore the potential of microbiota-targeted interventions—probiotic supplementation, dietary modulation, or metabolite administration—as novel strategies for asthma prevention and management (Du et al., 2022; Zheng et al., 2023).

## 6.4 Gut-lung axis in asthma pathogenesis

SCFAs (e.g., butyrate) circulate to the lung, activating GPR43 on Tregs to suppress Th2-mediated eosinophilia (Yao et al., 2022). Tryptophan metabolites (e.g., IPA) activate pulmonary AhR, inducing IL-22 production by ILC3s (Zhang et al., 2024). Gut-primed DCs migrate to the lung via lymphatics, regulating local Th17/Treg balance (Zhang et al., 2022). Microbial imbalance reduces vagal tone, impairing acetylcholine-dependent suppression of airway mast cell degranulation (de Haan et al., 2013). Clinical evidence linking depleted *Faecalibacterium prausnitzii* (and reduced SCFAs) to airway hyperresponsiveness, reversible via probiotics, is also included (Hu et al., 2021b).

## 7 Intervention strategy based on gut microbiota

Probiotics, defined as live microorganisms conferring host health benefits, modulate gut microbial equilibrium by enhancing colonization resistance, immunomodulation, and epithelial barrier reinforcement. Clinical applications span gastrointestinal disorders (diarrhea, constipation, inflammatory bowel disease) through mechanisms involving pathogen exclusion, bacteriocin production, and immune cell priming (Li et al., 2024). Prebiotics—non-digestible substrates selectively fermented by commensals—stimulate beneficial taxa proliferation (e.g., *Bifidobacterium*, *Lactobacillus*) while increasing short-chain fatty acid (SCFA) production, thereby improving intestinal homeostasis (You et al., 2022). Synbiotic formulations combining probiotics with prebiotics demonstrate synergistic effects, enhancing microbial diversity and metabolic functions more effectively than individual components (Du et al., 2024). Despite therapeutic promise, clinical translation requires rigorous validation through randomized controlled trials to establish strain-specific mechanisms, dosing protocols, and long-term safety profiles (Raghani et al., 2024). Special attention should be paid to leveraging strain-specific effects, such as lactobacilli competing with pathogenic bacteria for nutrients and adhesion sites by occupying space on the surface of the intestinal mucosa, thereby inhibiting the overgrowth of harmful bacteria.

Dietary patterns exert profound effects on gut microbiota composition and functionality (Leeming et al., 2019). High-fiber diets increase SCFA producers by ~40% (*Faecalibacterium*, *Roseburia*) and improving metabolic parameters through GLP-1

secretion and hepatic gluconeogenesis suppression (Fu et al., 2022). Conversely, Western-style diets high in saturated fats and refined sugars drive microbial imbalance, characterized by *Bacteroides* enrichment and reduced microbial diversity, correlating with chronic inflammation and metabolic syndrome (Mehmood et al., 2021). Temporal dynamics further influence intervention efficacy: transient dietary changes induce reversible microbial shifts, whereas sustained dietary habits remodel enterotypes, suggesting long-term adherence is critical for durable ecological benefits (Li et al., 2024). Precision nutrition strategies, integrating host genetics, microbiota profiling, and lifestyle factors, represent emerging paradigms for personalized microbiota engineering.

Advancements in microbiota research are driving the development of multidimensional intervention frameworks. Combinatorial approaches—integrating probiotics, prebiotics, dietary modifications, and phage therapy—show enhanced efficacy in restoring microbial networks disrupted in conditions like obesity and diabetes (Sumida et al., 2023). Elucidating cross-system interactions (e.g., microbiota-immune-nervous axis crosstalk) will uncover novel therapeutic targets, as evidenced by SCFA-mediated neuroimmune regulation in allergic airway diseases [54]. Clinically, microbiota-targeted therapies are being incorporated into disease-specific protocols, including fecal microbiota transplantation for *C. difficile* infection and engineered probiotics for inflammatory bowel disease (Xu et al., 2024). However, challenges persist in standardizing microbial products, optimizing personalized dosing, and establishing long-term safety monitoring systems. Moreover, the optimal dosage and long-term safety of probiotics have not yet been determined. Addressing these barriers will be pivotal for translating microbiota science into mainstream clinical practice, ultimately enabling precision medicine approaches for complex chronic diseases.

## 8 Conclusion

New evidence highlights the key role of gut microbiota and their metabolites in allergic asthma development. Microbial imbalance—altered diversity, changes in key taxa (e.g., bifidobacteria) and metabolites (e.g., SCFAs, tryptophan derivatives)—may link to immune dysfunction. These microbe-immune interactions improve our understanding of asthma and reveal new microbial-targeted therapies. Probiotics, prebiotics, and dietary changes show potential to reset immune responses and reduce asthma severity. Yet, while microbial shifts correlate with disease, causal links are poorly defined, requiring more mechanistic research using gnotobiotic models and long-term human studies.

Future research should focus on clarifying strain-specific microbial functions, host-microbe interaction pathways (e.g., gut-lung axis signaling), and individual responses influenced by genetics, environment, and diet. Validating strain-specific probiotics through human trials is crucial. Large-scale multi-omics cohorts combined with randomized controlled trials of targeted microbiota interventions are needed to confirm therapeutic effects and improve precision medicine approaches. In short, the gut microbiota is both a biomarker and a modifiable driver of



allergic asthma. Unraveling its complex interactions with host immunity and physiology will advance microbiome-based strategies for asthma prevention, personalized treatment, and long-term control.

## Author contributions

JL: Data curation, Writing – review and editing, Writing – original draft. YZ: Writing – review and editing, Investigation. SL: Conceptualization, Writing – review and editing, Methodology. RW: Supervision, Writing – original draft, Project administration, Methodology, Validation. JZ: Investigation, Project administration, Formal Analysis, Data curation, Writing – original draft.

## Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

## References

- Aagaard, K., Riehle, K., Ma, J., Segata, N., Mistretta, T. A., Coarfa, C., et al. (2012). A metagenomic approach to characterization of the vaginal microbiome signature in pregnancy. *PLoS One* 7 (6), e36466. doi:10.1371/journal.pone.0036466
- Al-Rashidi, H. E. (2022). Gut microbiota and immunity relevance in eubiosis and dysbiosis. *Saudi J. Biol. Sci.* 29 (3), 1628–1643. doi:10.1016/j.sjbs.2021.10.068
- Alswat, A. S. (2024). The influence of the gut microbiota on host health: a focus on the gut-lung axis and therapeutic approaches. *Life (Basel)* 14 (10), 1279. doi:10.3390/life14101279
- Alves, J. L. B., Costa, P., Sales, L. C. S., Silva Luis, C. C., Bezerra, T. P. T., Souza, M. L. A., et al. (2024). Shedding light on the impacts of *Spirulina platensis* on gut microbiota and related health benefits. *Crit. Rev. Food Sci. Nutr.* 65, 2062–2075. doi:10.1080/10408398.2024.2323112
- Aoki, R., Aoki-Yoshida, A., Suzuki, C., and Takayama, Y. (2018). Indole-3-pyruvic acid, an Aryl hydrocarbon receptor activator, suppresses experimental colitis in mice. *J. Immunol.* 201 (12), 3683–3693. doi:10.4049/jimmunol.1701734
- Arpaia, N., Campbell, C., Fan, X., Dikiy, S., van der Veeken, J., deRoos, P., et al. (2013). Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* 504 (7480), 451–455. doi:10.1038/nature12726
- Atarashi, K., Tanoue, T., Shima, T., Imaoka, A., Kuwahara, T., Momose, Y., et al. (2011). Induction of colonic regulatory T cells by indigenous *Clostridium* species. *Science* 331 (6015), 337–341. doi:10.1126/science.1198469
- Balmer, M. L., Ma, E. H., Bantug, G. R., Grählert, J., Pfister, S., Glatzer, T., et al. (2016). Memory CD8(+) T cells require increased concentrations of acetate induced by stress for optimal function. *Immunity* 44 (6), 1312–1324. doi:10.1016/j.immuni.2016.03.016
- Baruch, E. N., Wang, J., and Wargo, J. A. (2021). Gut microbiota and antitumor immunity: potential mechanisms for clinical effect. *Cancer Immunol. Res.* 9 (4), 365–370. doi:10.1158/2326-6066.CIR-20-0877
- Basnet, T. B., Gc, S., Basnet, R., Fatima, S., Safdar, M., Sehar, B., et al. (2023). Interaction between gut microbiota metabolites and dietary components in lipid metabolism and metabolic diseases. *Access Microbiol.* 5 (6), acmi000403. doi:10.1099/acmi.0.000403
- Bloor, S. J., and Mitchell, K. A. (2021). Metabolic products of European-type propolis. Synthesis and analysis of glucuronides and sulfates. *J. Ethnopharmacol.* 274, 114035. doi:10.1016/j.jep.2021.114035
- Brown, J., Abboud, G., Ma, L., Choi, S. C., Kanda, N., Zeumer-Spataro, L., et al. (2022). Microbiota-mediated skewing of tryptophan catabolism modulates CD4(+) T cells in lupus-prone mice. *iScience* 25 (5), 104241. doi:10.1016/j.isci.2022.104241
- Carr, T. F., Alkatib, R., and Kraft, M. (2019). Microbiome in mechanisms of asthma. *Clin. Chest Med.* 40 (1), 87–96. doi:10.1016/j.ccm.2018.10.006
- Cervantes-Barragan, L., Chai, J. N., Tianero, M. D., Di Luccia, B., Ahern, P. P., Merriman, J., et al. (2017). *Lactobacillus reuteri* induces gut intraepithelial CD4(+) CD8α(+) T cells. *Science* 357 (6353), 806–810. doi:10.1126/science.aah5825
- Chang, P. V., Hao, L., Offermanns, S., and Medzhitov, R. (2014). The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. *Proc. Natl. Acad. Sci. U. S. A.* 111 (6), 2247–2252. doi:10.1073/pnas.1322269111
- Chen, G., Ran, X., Li, B., Li, Y., He, D., Huang, B., et al. (2018). Sodium butyrate inhibits inflammation and maintains epithelial barrier integrity in a TNBS-induced inflammatory bowel disease mice model. *EBioMedicine* 30, 317–325. doi:10.1016/j.ebiom.2018.03.030
- Chen, L., Sun, M., Wu, W., Yang, W., Huang, X., Xiao, Y., et al. (2019). Microbiota metabolite butyrate differentially regulates Th1 and Th17 cells' differentiation and function in induction of colitis. *Inflamm. Bowel Dis.* 25 (9), 1450–1461. doi:10.1093/ibd/izz046
- Chen, X., Yong, S. B., Yui, C. Y., Feng, B., Hsieh, K. S., and Li, Q. (2024). Intestinal microbiota and probiotic intervention in children with bronchial asthma. *Heliyon* 10 (15), e34916. doi:10.1016/j.heliyon.2024.e34916
- Chen, Z., Xu, Q., Liu, Y., Wei, Y., He, S., Lin, W., et al. (2022). Vancomycin-induced gut microbiota dysbiosis aggravates allergic rhinitis in mice by altered short-chain fatty acids. *Front. Microbiol.* 13, 1002084. doi:10.3389/fmicb.2022.1002084
- Cheng, H. Y., Chan, J. C. Y., Yap, G. C., Huang, C. H., Kioh, D. Y. Q., Tham, E. H., et al. (2022). Evaluation of stool short chain fatty acids profiles in the first year of life with childhood atopy-related outcomes. *Front. Allergy* 3, 873168. doi:10.3389/falgy.2022.873168
- de Haan, J. J., Hadfoune, M., Lubbers, T., Hodin, C., Lenaerts, K., Ito, A., et al. (2013). Lipid-rich enteral nutrition regulates mucosal mast cell activation via the vagal anti-inflammatory reflex. *Am. J. Physiol. Gastrointest. Liver Physiol.* 305 (5), G383–G391. doi:10.1152/ajpgi.00333.2012
- Demirci, M., Tokman, H. B., Uysal, H. K., Demiryas, S., Karakullukcu, A., Saribas, S., et al. (2019). Reduced *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* levels in the gut microbiota of children with allergic asthma. *Allergol. Immunopathol. (Madr)* 47 (4), 365–371. doi:10.1016/j.aller.2018.12.009
- Diether, N. E., Hulshof, T. G., Willing, B. P., and van Kempen, T. (2023). A blend of medium-chain fatty acids, butyrate, organic acids, and a phenolic compound accelerates microbial maturation in newly weaned piglets. *PLoS One* 18 (7), e0289214. doi:10.1371/journal.pone.0289214
- Ding, G., Yang, X., Li, Y., Wang, Y., Du, Y., Wang, M., et al. (2024). Gut microbiota regulates gut homeostasis, mucosal immunity and influences immune-related diseases. *Mol. Cell Biochem.* 480, 1969–1981. doi:10.1007/s11010-024-05077-y
- Du, Q., Li, Q., Liu, C., Liao, G., Li, J., Yang, J., et al. (2024). Probiotics/prebiotics/synbiotics and human neuropsychiatric outcomes: an umbrella review. *Benef. Microbes* 15 (6), 589–608. doi:10.1163/18762891-bja00035
- Du, T., Lei, A., Zhang, N., and Zhu, C. (2022). The beneficial role of probiotic *Lactobacillus* in respiratory diseases. *Front. Immunol.* 13, 908010. doi:10.3389/fimmu.2022.908010

## Conflict of interest

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.

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- Dupraz, L., Magniez, A., Rolhion, N., Richard, M. L., Da Costa, G., Touch, S., et al. (2021). Gut microbiota-derived short-chain fatty acids regulate IL-17 production by mouse and human intestinal  $\gamma\delta$  T cells. *Cell Rep.* 36 (1), 109332. doi:10.1016/j.celrep.2021.109332
- Fernandes, J., Su, W., Rahat-Rozenbloom, S., Wolever, T. M., and Comelli, E. M. (2014). Adiposity, gut microbiota and faecal short chain fatty acids are linked in adult humans. *Nutr. Diabetes* 4 (6), e121. doi:10.1038/nutd.2014.23
- Föh, B., Buhre, J. S., Lunding, H. B., Moreno-Fernandez, M. E., König, P., Sina, C., et al. (2022). Microbial metabolite butyrate promotes induction of IL-10+IgM+ plasma cells. *PLoS One* 17 (3), e0266071. doi:10.1371/journal.pone.0266071
- Fu, J., Zheng, Y., Gao, Y., and Xu, W. (2022). Dietary fiber intake and gut microbiota in human health. *Microorganisms* 10 (12), 2507. doi:10.3390/microorganisms10122507
- Fujimura, K. E., Sitarik, A. R., Havstad, S., Lin, D. L., Levan, S., Fadrosch, D., et al. (2016). Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nat. Med.* 22 (10), 1187–1191. doi:10.1038/nm.4176
- Furusawa, Y., Obata, Y., Fukuda, S., Endo, T. A., Nakato, G., Takahashi, D., et al. (2013). Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* 504 (7480), 446–450. doi:10.1038/nature12721
- Gao, Y., Nanan, R., Macia, L., Tan, J., Sominsky, L., Quinn, T. P., et al. (2021). The maternal gut microbiome during pregnancy and offspring allergy and asthma. *J. Allergy Clin. Immunol.* 148 (3), 669–678. doi:10.1016/j.jaci.2021.07.011
- Genuneit, J., and Standl, M. (2022). Epidemiology of allergy: natural course and risk factors of allergic diseases. *Handb. Exp. Pharmacol.* 268, 21–27. doi:10.1007/164\_2021\_507
- Gong, Y., Chen, A., Zhang, G., Shen, Q., Zou, L., Li, J., et al. (2023). Cracking brain diseases from gut microbes-mediated metabolites for precise treatment. *Int. J. Biol. Sci.* 19 (10), 2974–2998. doi:10.7150/ijbs.85259
- Guo, W., Chen, Y., Wang, C., Ning, R., Zeng, B., Tang, J., et al. (2020). The carnivorous digestive system and bamboo diet of giant pandas may shape their low gut bacterial diversity. *Conserv. Physiol.* 8 (1), coz104. doi:10.1093/conphys/coz104
- Guo, W., Zhou, X., Li, X., Zhu, Q., Peng, J., Zhu, B., et al. (2021). Depletion of gut microbiota impairs gut barrier function and antiviral immune defense in the liver. *Front. Immunol.* 12, 636803. doi:10.3389/fimmu.2021.636803
- Han, K., Xie, F., Animasahun, O., Newwani, M., Kitamoto, S., Kim, Y., et al. (2024). Inulin-gel-based oral immunotherapy remodels the small intestinal microbiome and suppresses food allergy. *Nat. Mater.* 23 (10), 1444–1455. doi:10.1038/s41563-024-01909-w
- Hang, S., Paik, D., Yao, L., Kim, E., Trinath, J., Lu, J., et al. (2019). Bile acid metabolites control T(H)17 and T(reg) cell differentiation. *Nature* 576 (7785), 143–148. doi:10.1038/s41586-019-1785-z
- Heinrich, V. A., Uvalle, C., Manni, M. L., Li, K., Mullett, S. J., Donepudi, S. R., et al. (2023). Meta-omics profiling of the gut-lung axis illuminates metabolic networks and host-microbial interactions associated with elevated lung elastance in a murine model of obese allergic asthma. *Front. Microbiomes* 2, 1153691. doi:10.3389/fmmbi.2023.1153691
- Hevia, A., Milani, C., López, P., Donado, C. D., Cuervo, A., González, S., et al. (2016). Allergic patients with long-term asthma display low levels of Bifidobacterium adolescentis. *PLoS One* 11 (2), e0147809. doi:10.1371/journal.pone.0147809
- Hou, X., Zheng, Z., Wei, J., and Zhao, L. (2022). Effects of gut microbiota on immune responses and immunotherapy in colorectal cancer. *Front. Immunol.* 13, 1030745. doi:10.3389/fimmu.2022.1030745
- Hsu, W. H., Lin, L. J., Lu, C. K., Kao, S. T., and Lin, Y. L. (2021). Effect of you-gui-wan on house dust mite-induced mouse allergic asthma via regulating amino acid metabolic disorder and gut dysbiosis. *Biomolecules* 11 (6), 812. doi:10.3390/biom11060812
- Hu, J., Wang, C., Huang, X., Yi, S., Pan, S., Zhang, Y., et al. (2021a). Gut microbiota-mediated secondary bile acids regulate dendritic cells to attenuate autoimmune uveitis through TGR5 signaling. *Cell Rep.* 36 (12), 109726. doi:10.1016/j.celrep.2021.109726
- Hu, J., Zhang, Y., Yi, S., Wang, C., Huang, X., Pan, S., et al. (2022). Lithocholic acid inhibits dendritic cell activation by reducing intracellular glutathione via TGR5 signaling. *Int. J. Biol. Sci.* 18 (11), 4545–4559. doi:10.7150/ijbs.71287
- Hu, W., Lu, W., Li, L., Zhang, H., Lee, Y. K., Chen, W., et al. (2021b). Both living and dead Faecalibacterium prausnitzii alleviate house dust mite-induced allergic asthma through the modulation of gut microbiota and short-chain fatty acid production. *J. Sci. Food Agric.* 101 (13), 5563–5573. doi:10.1002/jsfa.11207
- Huang, T., Che, Q., Chen, X., Chen, D., Yu, B., He, J., et al. (2022a). Apple polyphenols improve intestinal antioxidant capacity and barrier function by activating the Nrf2/Keap1 signaling pathway in a pig model. *J. Agric. Food Chem.* 70 (24), 7576–7585. doi:10.1021/acs.jafc.2c02495
- Huang, Z. B., Hu, Z., Lu, C. X., Luo, S. D., Chen, Y., Zhou, Z. P., et al. (2022b). Gut microbiota-derived indole 3-propionic acid partially activates aryl hydrocarbon receptor to promote macrophage phagocytosis and attenuate septic injury. *Front. Cell Infect. Microbiol.* 12, 1015386. doi:10.3389/fcimb.2022.1015386
- Hubbard, T. D., Murray, I. A., Bisson, W. H., Lahoti, T. S., Gowda, K., Amin, S. G., et al. (2015). Adaptation of the human aryl hydrocarbon receptor to sense microbiota-derived indoles. *Sci. Rep.* 5, 12689. doi:10.1038/srep12689
- Humbert, M., Bousquet, J., Bachert, C., Palomares, O., Pfister, P., Kottakis, I., et al. (2019). IgE-Mediated multimorbidities in allergic asthma and the potential for omalizumab therapy. *J. Allergy Clin. Immunol. Pract.* 7 (5), 1418–1429. doi:10.1016/j.jaip.2019.02.030
- Hwang, W. B., Kim, D. J., Oh, G. S., and Park, J. H. (2018). Aryl hydrocarbon receptor ligands indoxyl 3-sulfate and Indole-3-carbinol inhibit FMS-like tyrosine kinase 3 ligand-induced bone marrow-derived plasmacytoid dendritic cell differentiation. *Immune Netw.* 18 (5), e35. doi:10.4110/in.2018.18.e35
- Isobe, J., Maeda, S., Obata, Y., Iizuka, K., Nakamura, Y., Fujimura, Y., et al. (2020). Commensal-bacteria-derived butyrate promotes the T-cell-independent IgA response in the colon. *Int. Immunol.* 32 (4), 243–258. doi:10.1093/intimm/dx2078
- Kaisar, M. M. M., Pelgrom, L. R., van der Ham, A. J., Yazdanbakhsh, M., and Everts, B. (2017). Butyrate conditions human dendritic cells to prime type 1 regulatory T cells via both histone deacetylase inhibition and G protein-coupled receptor 109A signaling. *Front. Immunol.* 8, 1429. doi:10.3389/fimmu.2017.01429
- Ke, S., Yu, Y., Xu, Q., Zhang, B., Wang, S., Jin, W., et al. (2021). Composition-activity relationships of polysaccharides from Saccharina japonica in regulating gut microbiota in short-term high-fat diet-fed mice. *J. Agric. Food Chem.* 69 (37), 11121–11130. doi:10.1021/acs.jafc.1c04490
- Kespohl, M., Vachharajani, N., Luu, M., Harb, H., Pautz, S., Wolff, S., et al. (2017). The microbial metabolite butyrate induces expression of Th1-Associated factors in CD4(+) T cells. *Front. Immunol.* 8, 1036. doi:10.3389/fimmu.2017.01036
- Kibbie, J. J., Dillon, S. M., Thompson, T. A., Purba, C. M., McCarter, M. D., and Wilson, C. C. (2021). Butyrate directly decreases human gut lamina propria CD4 T cell function through histone deacetylase (HDAC) inhibition and GPR43 signaling. *Immunobiology* 226 (5), 152126. doi:10.1016/j.imbio.2021.152126
- Kim, C. H. (2016). B cell-helping functions of gut microbial metabolites. *Microb. Cell* 3 (10), 529–531. doi:10.15698/mic2016.10.536
- Kim, D. S., Woo, J. S., Min, H. K., Choi, J. W., Moon, J. H., Park, M. J., et al. (2021). Short-chain fatty acid butyrate induces IL-10-producing B cells by regulating circadian-clock-related genes to ameliorate Sjögren's syndrome. *J. Autoimmun.* 119, 102611. doi:10.1016/j.jaut.2021.102611
- Kleuskens, M. T. A., Haasnoot, M. L., Herpers, B. M., Ampting, M., Bredenoord, A. J., Garssen, J., et al. (2022). Butyrate and propionate restore interleukin 13-compromised esophageal epithelial barrier function. *Allergy* 77 (5), 1510–1521. doi:10.1111/all.15069
- Lee, J. H., and Lee, J. (2010). Indole as an intercellular signal in microbial communities. *FEMS Microbiol. Rev.* 34 (4), 426–444. doi:10.1111/j.1574-6976.2009.00204.x
- Lee, J. J., Kim, S. H., Lee, M. J., Kim, B. K., Song, W. J., Park, H. W., et al. (2019). Different upper airway microbiome and their functional genes associated with asthma in young adults and elderly individuals. *Allergy* 74 (4), 709–719. doi:10.1111/all.13608
- Leeming, E. R., Johnson, A. J., Spector, T. D., and Le Roy, C. I. (2019). Effect of diet on the gut Microbiota: rethinking intervention duration. *Nutrients* 11 (12), 2862. doi:10.3390/nu11122862
- Li, C., Liang, Y., and Qiao, Y. (2022a). Messengers from the gut: gut microbiota-derived metabolites on host regulation. *Front. Microbiol.* 13, 863407. doi:10.3389/fmicb.2022.863407
- Li, L., Liang, T., Jiang, T., Li, Y., Yang, L., Wu, L., et al. (2024). Gut microbiota: candidates for a novel strategy for ameliorating sleep disorders. *Crit. Rev. Food Sci. Nutr.* 64 (29), 10772–10788. doi:10.1080/10408398.2023.2228409
- Li, N., Chen, J., Xie, S., Zhang, M., Shi, T., He, Y., et al. (2022b). Oral antibiotics relieve allergic asthma in post-weaning mice via reducing iNKT cells and function of ADRB2. *Front. Immunol.* 13, 1024235. doi:10.3389/fimmu.2022.1024235
- Li, W., Hang, S., Fang, Y., Bae, S., Zhang, Y., Zhang, M., et al. (2021). A bacterial bile acid metabolite modulates T(reg) activity through the nuclear hormone receptor NR4A1. *Cell Host Microbe* 29 (9), 1366–1377.e9. doi:10.1016/j.chom.2021.07.013
- Liang, L., Liu, L., Zhou, W., Yang, C., Mai, G., Li, H., et al. (2022). Gut microbiota-derived butyrate regulates gut mucus barrier repair by activating the macrophage/WNT/ERK signaling pathway. *Clin. Sci. (Lond)* 136 (4), 291–307. doi:10.1042/CS20210778
- Liao, W., Liu, W., Yan, Y., Li, L., Tong, J., Huang, Y., et al. (2022). Hylocereus undatus flower extract suppresses OVA-induced allergic asthma in BALB/c mice by reducing airway inflammation and modulating gut microbiota. *Biomed. Pharmacother.* 153, 113476. doi:10.1016/j.biopha.2022.113476
- Liu, Y., Liu, J., Du, M., Yang, H., Shi, R., Shi, Y., et al. (2023). Short-chain fatty acid - a critical interfering factor for allergic diseases. *Chem. Biol. Interact.* 385, 110739. doi:10.1016/j.cbi.2023.110739
- Liu, Z., Chen, H., Ning, X., Li, J., and Pan, L. (2024). Oxymatrine and gut microbiota modulation: a potential therapeutic strategy for bone cancer pain management. *J. Pain* 25 (10), 104588. doi:10.1016/j.jpain.2024.104588
- Louis, P., Young, P., Holtrop, G., and Flint, H. J. (2010). Diversity of human colonic butyrate-producing bacteria revealed by analysis of the butyryl-CoA:acetate CoA-transferase gene. *Environ. Microbiol.* 12 (2), 304–314. doi:10.1111/j.1462-2920.2009.02066.x

- Luu, M., Pautz, S., Kohl, V., Singh, R., Romero, R., Lucas, S., et al. (2019). The short-chain fatty acid pentanoate suppresses autoimmunity by modulating the metabolic-epigenetic crosstalk in lymphocytes. *Nat. Commun.* 10 (1), 760. doi:10.1038/s41467-019-08711-2
- Luu, M., Weigand, K., Wedi, F., Breidenbend, C., Leister, H., Pautz, S., et al. (2018). Regulation of the effector function of CD8(+) T cells by gut microbiota-derived metabolite butyrate. *Sci. Rep.* 8 (1), 14430. doi:10.1038/s41598-018-32860-x
- Macfarlane, S., and Macfarlane, G. T. (2003). Regulation of short-chain fatty acid production. *Proc. Nutr. Soc.* 62 (1), 67–72. doi:10.1079/PNS2002207
- Mehmood, K., Moin, A., Hussain, T., Rizvi, S. M. D., Gowda, D. V., Shakil, S., et al. (2021). Can manipulation of gut microbiota really be transformed into an intervention strategy for cardiovascular disease management? *Folia Microbiol. (Praha)* 66 (6), 897–916. doi:10.1007/s12223-021-00926-5
- Miller, T. L., and Wolin, M. J. (1996). Pathways of acetate, propionate, and butyrate formation by the human fecal microbial flora. *Appl. Environ. Microbiol.* 62 (5), 1589–1592. doi:10.1128/aem.62.5.1589-1592.1996
- Mirmohammadi, S. N., and Rosenkranz, S. K. (2023). Dietary phytochemicals, gut microbiota composition, and health outcomes in human and animal models. *Biosci. Microbiota Food Health* 42 (3), 152–171. doi:10.12938/bmfh.2022-078
- Mohammadi, S., Memarian, A., Sedighi, S., Behnampour, N., and Yazdani, Y. (2018). Immunoregulatory effects of indole-3-carbinol on monocyte-derived macrophages in systemic lupus erythematosus: a crucial role for aryl hydrocarbon receptor. *Autoimmunity* 51 (5), 199–209. doi:10.1080/08916934.2018.1494161
- Mousavian, A. H., Zare Garizi, F., Ghoreschi, B., Ketabi, S., Eslami, S., Ejtahed, H. S., et al. (2024). The association of infant and mother gut microbiomes with development of allergic diseases in children: a systematic review. *J. Asthma* 61 (10), 1121–1135. doi:10.1080/02770903.2024.2332921
- Nastasi, C., Candela, M., Bonefeld, C. M., Geisler, C., Hansen, M., Krejsgaard, T., et al. (2015). The effect of short-chain fatty acids on human monocyte-derived dendritic cells. *Sci. Rep.* 5, 16148. doi:10.1038/srep16148
- Neag, M. A., Vultur, D. M., Gherman, D., Burlacu, C. C., Todea, D. A., and Buzoianu, A. D. (2022). Gastrointestinal microbiota: a predictor of COVID-19 severity? *World J. Gastroenterol.* 28 (45), 6328–6344. doi:10.3748/wjg.v28.i45.6328
- Ozerskaia, I. V., Geppe, N. A., Romantseva, E. V., and Yablokova, E. A. (2021). Prospects for the correction of intestinal microbiota in the prevention and treatment of asthma in children. *Vopr. Pitan.* 90 (4), 74–83. doi:10.33029/0042-8833-2021-90-4-74-83
- Padhi, S., Sarkar, P., Sahoo, D., and Rai, A. K. (2024). Potential of fermented foods and their metabolites in improving gut microbiota function and lowering gastrointestinal inflammation. *J. Sci. Food Agric.* 105, 4058–4069. doi:10.1002/jsfa.13313
- Palusiak, A. (2013). Immunochemical properties of *Proteus penneri* lipopolysaccharides—one of the major proteus sp. virulence factors. *Carbohydr. Res.* 380, 16–22. doi:10.1016/j.carres.2013.06.025
- Pantazi, A. C., Mihai, C. M., Balasa, A. L., Chisnoiu, T., Lupu, A., Frecus, C. E., et al. (2023). Relationship between gut microbiota and allergies in children: a literature review. *Nutrients* 15 (11), 2529. doi:10.3390/nu15112529
- Park, J., Kim, M., Kang, S. G., Jannasch, A. H., Cooper, B., Patterson, J., et al. (2015). Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway. *Mucosal Immunol.* 8 (1), 80–93. doi:10.1038/mi.2014.44
- Park, J. S., Lee, E. J., Lee, J. C., Kim, W. K., and Kim, H. S. (2007). Anti-inflammatory effects of short chain fatty acids in IFN- $\gamma$ -stimulated RAW 264.7 murine macrophage cells: involvement of NF- $\kappa$ B and ERK signaling pathways. *Int. Immunopharmacol.* 7 (1), 70–77. doi:10.1016/j.intimp.2006.08.015
- Park, J. W., Kim, H. Y., Kim, M. G., Jeong, S., Yun, C. H., and Han, S. H. (2019). Short-chain fatty acids inhibit staphylococcal lipoprotein-induced nitric oxide production in murine macrophages. *Immune Netw.* 19 (2), e9. doi:10.4110/in.2019.19.e9
- Raghani, N., Postwala, H., Shah, Y., Chorawala, M., and Parekh, P. (2024). From gut to brain: unraveling the intricate link between microbiome and stroke. *Probiotics Antimicrob. Proteins* 16 (6), 2039–2053. doi:10.1007/s12602-024-10295-3
- Rangan, P., and Mondino, A. (2022). Microbial short-chain fatty acids: a strategy to tune adoptive T cell therapy. *J. Immunother. Cancer* 10 (7), e004147. doi:10.1136/jitc-2021-004147
- Reichardt, N., Duncan, S. H., Young, P., Belenguer, A., McWilliam Leitch, C., Scott, K. P., et al. (2014). Phylogenetic distribution of three pathways for propionate production within the human gut microbiota. *ISME J.* 8 (6), 1323–1335. doi:10.1038/ismej.2014.14
- Roager, H. M., and Licht, T. R. (2018). Microbial tryptophan catabolites in health and disease. *Nat. Commun.* 9 (1), 3294. doi:10.1038/s41467-018-05470-4
- Roduit, C., Frei, R., Ferstl, R., Loeliger, S., Westermann, P., Rhyner, C., et al. (2019). High levels of butyrate and propionate in early life are associated with protection against atopy. *Allergy* 74 (4), 799–809. doi:10.1111/all.13660
- Rouse, M., Singh, N. P., Nagarkatti, P. S., and Nagarkatti, M. (2013). Indoles mitigate the development of experimental autoimmune encephalomyelitis by induction of reciprocal differentiation of regulatory T cells and Th17 cells. *Br. J. Pharmacol.* 169 (6), 1305–1321. doi:10.1111/bph.12205
- Sagar, S., Morgan, M. E., Chen, S., Vos, A. P., Garssen, J., van Bergenhenegouwen, J., et al. (2014). *Bifidobacterium breve* and *Lactobacillus rhamnosus* treatment is as effective as budesonide at reducing inflammation in a murine model for chronic asthma. *Respir. Res.* 15 (1), 46. doi:10.1186/1465-9921-15-46
- Saini, A., Dalal, P., and Sharma, D. (2022). Deciphering the interdependent labyrinth between gut microbiota and the immune system. *Lett. Appl. Microbiol.* 75 (5), 1122–1135. doi:10.1111/lam.13775
- Salami, M. (2021). Interplay of good bacteria and central nervous system: cognitive aspects and mechanistic considerations. *Front. Neurosci.* 15, 613120. doi:10.3389/fnins.2021.613120
- Schulthess, J., Pandey, S., Capitani, M., Rue-Albrecht, K. C., Arnold, I., Franchini, F., et al. (2019). The short chain fatty acid butyrate imprints an antimicrobial program in macrophages. *Immunity* 50 (2), 432–445.e7. doi:10.1016/j.immuni.2018.12.018
- Shah, R., and Newcomb, D. C. (2018). Sex bias in asthma prevalence and pathogenesis. *Front. Immunol.* 9, 2997. doi:10.3389/fimmu.2018.02997
- Shi, C. Y., Yu, C. H., Yu, W. Y., and Ying, H. Z. (2021). Gut-lung microbiota in chronic pulmonary diseases: Evolution, pathogenesis, and therapeutics. *Can. J. Infect. Dis. Med. Microbiol.* 2021, 9278441. doi:10.1155/2021/9278441
- Shi, Z., Yao, F., Chen, Q., Chen, Y., Zhang, J., Guo, J., et al. (2024). More deterministic assembly constrains the diversity of gut microbiota in freshwater snails. *Front. Microbiol.* 15, 1394463. doi:10.3389/fmicb.2024.1394463
- Shiratori, H., Oguchi, H., Isobe, Y., Han, K. H., Sen, A., Yakebe, K., et al. (2023). Gut microbiota-derived lipid metabolites facilitate regulatory T cell differentiation. *Sci. Rep.* 13 (1), 8903. doi:10.1038/s41598-023-35097-5
- Singh, N. P., Singh, U. P., Rouse, M., Zhang, J., Chatterjee, S., Nagarkatti, P. S., et al. (2016). Dietary indoles suppress delayed-type hypersensitivity by inducing a switch from proinflammatory Th17 cells to anti-inflammatory regulatory T cells through regulation of MicroRNA. *J. Immunol.* 196 (3), 1108–1122. doi:10.4049/jimmunol.1501727
- Smith, P. M., Howitt, M. R., Panikov, N., Michaud, M., Gallini, C. A., Bohlooly, Y. M., et al. (2013). The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* 341 (6145), 569–573. doi:10.1126/science.1241165
- Smith, T. (1897). A modification of the method for determining the production of indol by bacteria. *J. Exp. Med.* 2 (5), 543–547. doi:10.1084/jem.2.5.543
- Song, X., Zhang, H., Zhang, Y., Goh, B., Bao, B., Mello, S. S., et al. (2023). Gut microbiota fatty acid isomerization modulates intraepithelial T cells. *Nature* 619 (7971), 837–843. doi:10.1038/s41586-023-06265-4
- Sottas, C., Schmiedová, L., Kreisinger, J., Albrecht, T., Reif, J., Osiejuk, T. S., et al. (2021). Gut microbiota in two recently diverged passerine species: evaluating the effects of species identity, habitat use and geographic distance. *BMC Ecol. Evol.* 21 (1), 41. doi:10.1186/s12862-021-01773-1
- Stepanova, M., and Aherne, C. M. (2024). Adenosine in intestinal epithelial barrier function. *Cells* 13 (5), 381. doi:10.3390/cells13050381
- Stiemsma, L. T., Arrieta, M. C., Dimitriu, P. A., Cheng, J., Thorson, L., Lefebvre, D. L., et al. (2016). Shifts in *Lachnospira* and *Clostridium* sp. in the 3-month stool microbiome are associated with preschool age asthma. *Clin. Sci. (Lond)* 130 (23), 2199–2207. doi:10.1042/CS20160349
- Su, X., Zhang, M., Qi, H., Gao, Y., Yang, Y., Yun, H., et al. (2022). Gut microbiota-derived metabolite 3-idoleacetic acid together with LPS induces IL-35(+) B cell generation. *Microbiome* 10 (1), 13. doi:10.1186/s40168-021-01205-8
- Sumida, K., Pierre, J. F., Yuzefpolskaya, M., Colombo, P. C., Demmer, R. T., and Kovacs, C. P. (2023). Gut microbiota-targeted interventions in the management of chronic kidney disease. *Semin. Nephrol.* 43 (2), 151408. doi:10.1016/j.semnephrol.2023.151408
- Sun, M., Wu, W., Chen, L., Yang, W., Huang, X., Ma, C., et al. (2018). Microbiota-derived short-chain fatty acids promote Th1 cell IL-10 production to maintain intestinal homeostasis. *Nat. Commun.* 9 (1), 3555. doi:10.1038/s41467-018-05901-2
- Tang, H., Zhan, Z., Liu, X., Zhang, Y., Huang, X., and Xu, M. (2023). Propionate reduces the viability of *Salmonella enterica* Serovar Typhi in macrophages by propionylation of PhoP K102. *Microb. Pathog.* 178, 106078. doi:10.1016/j.micpath.2023.106078
- Terciolo, C., Dapigny, M., and Andre, F. (2019). Beneficial effects of *Saccharomyces boulardii* CNCM I-745 on clinical disorders associated with intestinal barrier disruption. *Clin. Exp. Gastroenterol.* 12, 67–82. doi:10.2147/CEG.S181590
- Thangaraju, M., Cresci, G. A., Liu, K., Ananth, S., Gnanaprakasam, J. P., Browning, D. D., et al. (2009). GPR109A is a G-protein-coupled receptor for the bacterial fermentation product butyrate and functions as a tumor suppressor in colon. *Cancer Res.* 69 (7), 2826–2832. doi:10.1158/0008-5472.CAN-08-4466
- Thorburn, A. N., McKenzie, C. I., Shen, S., Stanley, D., Macia, L., Mason, L. J., et al. (2015). Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. *Nat. Commun.* 6, 7320. doi:10.1038/ncomms8320
- Tomii, A., Higa, M., Naito, K., Kurata, K., Kobayashi, J., Takei, C., et al. (2023). Activation of the TLR4-JNK but not the TLR4-ERK pathway induced by indole-3-acetic acid exerts anti-proliferative effects on Caco-2 cells. *Biosci. Biotechnol. Biochem.* 87 (8), 839–849. doi:10.1093/bbb/zbad055



- Ulluwishewa, D., Mullaney, J., Adam, K., Claycomb, R., and Anderson, R. C. (2022). A bioactive bovine whey protein extract improves intestinal barrier function in vitro. *JDS Commun.* 3 (6), 387–392. doi:10.3168/jdsc.2022-0245
- van Nimwegen, F. A., Penders, J., Stobberingh, E. E., Postma, D. S., Koppelman, G. H., Kerkhof, M., et al. (2011). Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. *J. Allergy Clin. Immunol.* 128 (5), 948–55.e553. doi:10.1016/j.jaci.2011.07.027
- Vasconcelos, J. A., Mota, A. S., Olímpio, F., Rosa, P. C., Damaceno-Rodrigues, N., de Paula Vieira, R., et al. (2023). Lactobacillus rhamnosus modulates lung inflammation and mitigates gut dysbiosis in a murine model of Asthma-COPD overlap syndrome. *Probiotics Antimicrob. Proteins* 17, 588–605. doi:10.1007/s12602-023-10167-2
- Venkatesh, M., Mukherjee, S., Wang, H., Li, H., Sun, K., Benechet, A. P., et al. (2014). Symbiotic bacterial metabolites regulate gastrointestinal barrier function via the xenobiotic sensor PXR and toll-like receptor 4. *Immunity* 41 (2), 296–310. doi:10.1016/j.immuni.2014.06.014
- Versi, A., Ivan, F. X., Abdel-Aziz, M. I., Bates, S., Riley, J., Baribaud, F., et al. (2023). Haemophilus influenzae and Moraxella catarrhalis in sputum of severe asthma with inflammasome and neutrophil activation. *Allergy* 78 (11), 2906–2920. doi:10.1111/all.15776
- Wang, J., He, M., Yang, M., and Ai, X. (2024). Gut microbiota as a key regulator of intestinal mucosal immunity. *Life Sci.* 345, 122612. doi:10.1016/j.lfs.2024.122612
- Wang, Z. Y., and Gong, J. F. (2022). Gut microbiota and immune-related diseases. *Zhonghua Wei Chang. Wai Ke Za Zhi* 25 (9), 777–783. doi:10.3760/cma.j.cn441530-20211130-00480
- Wilck, N., Matus, M. G., Kearney, S. M., Olesen, S. W., Forslund, K., Bartolomaeus, H., et al. (2017). Salt-responsive gut commensal modulates T(H)17 axis and disease. *Nature* 551 (7682), 585–589. doi:10.1038/nature24628
- Wu, W., Sun, M., Chen, F., Cao, A. T., Liu, H., Zhao, Y., et al. (2017). Microbiota metabolite short-chain fatty acid acetate promotes intestinal IgA response to microbiota which is mediated by GPR43. *Mucosal Immunol.* 10 (4), 946–956. doi:10.1038/mi.2016.114
- Xu, Y., He, C., Xi, Y., Zhang, Y., and Bai, Y. (2024). Gut microbiota and immunosenescence in cancer. *Semin. Cancer Biol.* 104–105, 32–45. doi:10.1016/j.semcancer.2024.07.004
- Yang, J., and Chun, J. (2021). Taxonomic composition and variation in the gut microbiota of laboratory mice. *Mamm. Genome* 32 (4), 297–310. doi:10.1007/s00335-021-09871-7
- Yang, W., and Cong, Y. (2021). Gut microbiota-derived metabolites in the regulation of host immune responses and immune-related inflammatory diseases. *Cell Mol. Immunol.* 18 (4), 866–877. doi:10.1038/s41423-021-00661-4
- Yang, W., Yu, T., Huang, X., Bilotta, A. J., Xu, L., Lu, Y., et al. (2020). Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity. *Nat. Commun.* 11 (1), 4457. doi:10.1038/s41467-020-18262-6
- Yao, Y., Cai, X., Zheng, Y., Zhang, M., Fei, W., Sun, D., et al. (2022). Short-chain fatty acids regulate B cells differentiation via the FFA2 receptor to alleviate rheumatoid arthritis. *Br. J. Pharmacol.* 179 (17), 4315–4329. doi:10.1111/bph.15852
- Yoo, J. Y., Groer, M., Dutra, S. V. O., Sarkar, A., and McSkimming, D. I. (2020). Gut microbiota and immune system interactions. *Microorganisms* 8 (10), 1587. doi:10.3390/microorganisms8101587
- You, S., Ma, Y., Yan, B., Pei, W., Wu, Q., Ding, C., et al. (2022). The promotion mechanism of prebiotics for probiotics: a review. *Front. Nutr.* 9, 1000517. doi:10.3389/fnut.2022.1000517
- Zhang, B., Zeng, M., Zhang, Q., Wang, R., Jia, J., Cao, B., et al. (2022). Ephedrae Herba polysaccharides inhibit the inflammation of ovalbumin induced asthma by regulating Th1/Th2 and Th17/Treg cell immune imbalance. *Mol. Immunol.* 152, 14–26. doi:10.1016/j.molimm.2022.09.009
- Zhang, M., Qin, Z., Huang, C., Liang, B., Zhang, X., and Sun, W. (2025). The gut microbiota modulates airway inflammation in allergic asthma through the gut-lung axis related immune modulation: a review. *Biomol. Biomed.* 25 (4), 727–738. doi:10.17305/bb.2024.11280
- Zhang, Y., Han, L., Dong, J., Yuan, Z., Yao, W., Ji, P., et al. (2024). Shaoyao decoction improves damp-heat colitis by activating the AHR/IL-22/STAT3 pathway through tryptophan metabolism driven by gut microbiota. *J. Ethnopharmacol.* 326, 117874. doi:10.1016/j.jep.2024.117874
- Zhao, F., Huang, Y., Ji, J., Liu, X., Li, X., Zou, L., et al. (2024). IDO1 promotes CSFV replication by mediating tryptophan metabolism to inhibit NF- $\kappa$ B signaling. *J. Virol.* 98 (7), e0045824. doi:10.1128/jvi.00458-24
- Zheng, Y., Zhang, Z., Tang, P., Wu, Y., Zhang, A., Li, D., et al. (2023). Probiotics fortify intestinal barrier function: a systematic review and meta-analysis of randomized trials. *Front. Immunol.* 14, 1143548. doi:10.3389/fimmu.2023.1143548
- Zhou, L., Zhang, M., Wang, Y., Dorfman, R. G., Liu, H., Yu, T., et al. (2018). Faecalibacterium prausnitzii produces butyrate to maintain Th17/Treg balance and to ameliorate colorectal colitis by inhibiting histone deacetylase 1. *Inflamm. Bowel Dis.* 24 (9), 1926–1940. doi:10.1093/ibd/izy182
- Zhou, M. S., Zhang, B., Gao, Z. L., Zheng, R. P., Marcellin, D., Saro, A., et al. (2021). Altered diversity and composition of gut microbiota in patients with allergic rhinitis. *Microb. Pathog.* 161, 105272. doi:10.1016/j.micpath.2021.105272