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Review

The role of colonic microbiota amino acid metabolism in gut health regulation

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ABSTRACT

The human gut microbiota plays a critical role in maintaining host homeostasis through metabolic activities. Among these, amino acid (AA) metabolism by the microbiota in the large intestine is highly heterogeneous and relevant to host health. Despite increasing interest, microbial AA metabolism remains relatively unexplored. This review highlights recent advances in colonic microbial AA metabolism, including auxotrophies, AA synthesis, and dissimilatory AA metabolites, and their implications in gut health, focusing on major gastrointestinal diseases including colorectal cancer, inflammatory bowel disease, and irritable bowel syndrome.

1. Introduction

The human gut microbiota, a rich ecosystem, plays a pivotal role in maintaining host homeostasis through its metabolic activities. The large intestine, characterized by slow transit time, a relatively high pH, and limited host absorption, provides an enabling environment for extensive microbial metabolism (Davila et al., 2013; Diether and Willing, 2019). Amino acid (AA) metabolism by the gut microbiota is highly heterogeneous and compartmentalized. Amino acids (AAs) exhibit diverse utilization patterns in the colon, where they are primarily involved in catabolic processes (Li et al., 2024), while in the small intestine, AAs are primarily used for bacterial protein synthesis (Ma and Ma, 2019). The digestibility of proteins by the host is far more variable than that of carbohydrates and fats (Dai et al., 2022), resulting in distinct AA compositions available to gut microbiota and the production of diverse bioactive metabolites.

Despite emerging interest in recent years, microbial AA metabolism remains less investigated compared to the well-studied metabolism of carbohydrates. Moreover, the current literature lacks an updated, focused synthesis on the relationship between microbial AA metabolism and gut health and diseases (Lin et al., 2017; Ma and Ma, 2019; Neis et al., 2015; Portune et al., 2016; Wu et al., 2021; Yao et al., 2016). This review addresses these gaps by first introducing AA-based auxotrophies within colonic microbiota populations and their influence on microbial activities. Then, we briefly examine the biosynthesis of AAs by gut microbes and their contributions to maintaining gut health. This review further delves into specific microbial AA catabolism pathways and metabolites, and their mechanistic roles in gastrointestinal (GI) health and disease. We aim to integrate recent advances to offer an updated perspective on the interplay between microbial AA metabolism in the colon and gut health and diseases, highlighting potential therapeutic opportunities amidst emerging challenges.

2. AA auxotrophies and prototrophies in colon microbiota

The gut microbiota displays significant idiosyncrasies regarding AA metabolism. Auxotrophy in microbiota refers to the inability of certain microbial species to synthesize specific nutrients, such as AAs or vitamins, which they must obtain from their environment or other microbes. Prototrophy, in contrast, describes the capability of microbiota to produce these essential compounds *de novo*. These traits shape the metabolic interactions and dependencies within microbial communities, as auxotrophs often rely on prototrophs for survival in nutrient-limited environments (Zengler and Zaramela, 2018), while in the human gut with ample access to protein and AAs, there is little direct *in vivo* evidence for AA cross-feeding (Culp and Goodman, 2023). Rather, only in AA-restrcited circumstances, as modeled in gnotobiotic mice harboring a four-species consortium of engineered amino acid auxotrophs fed with

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low-protein diet, cross-feeding interactions were pronounced (Ziesack et al., 2019).

Several *in silico* studies have investigated the bacterial genome, suggesting that AA auxotrophies are ubiquitous in the human colon microbiota. Over half of the bacteria auxotrophic for at least one AA, with auxotrophy frequencies higher for AAs that are also essential to the human host (Ashniev et al., 2022; Ramoneda et al., 2023; Starke et al., 2023). Starke and colleagues found that higher overall AA auxotrophy frequencies were associated with greater microbiome diversity and stability (Starke et al., 2023). AAs were also found to be indispensable for gut microbiota survival, adaptation, and communication, mediating environmental stressors and microbial enzyme activities (MA & MA, 2019). This suggests that AA auxotrophies should be considered in both research and clinical settings. To date, microbiota-targeted diets have largely overlooked the potential prebiotic effect of AAs (Beaumont et al., 2022; GENTILE & WEIR, 2018; Wastyk et al., 2021). Understanding the gut microbial AA-based auxotrophies could aid in designing strategies, such as modulating diet components, to manipulate AA-obligate gut microbiota for promoting the host gut and overall health (Zeng et al., 2022).

3. Microbial AA biosynthesis and gut health

It is estimated that microbiota-synthesized AAs contribute to approximately 0.1%–10% of the circulating AA pool based on the SCAPIS study (Bergström et al., 2015; Dekkers et al., 2022). Perturbations in microbial AA biosynthesis are associated with various extraintestinal diseases. For example, the biosynthesis of branched-chain AAs (BCAAs) and aromatic AAs (AAAs) has been implicated in Parkinson's disease (Zhang et al., 2022) and insulin resistance (Gojda and Cahova, 2021; Li et al., 2023), and histidine production by *Lactobacillus reuteri* may affect the pathogenesis and treatment of ischemic stroke (Hu et al., 2024).

Coker and colleagues performed metabolomics and metagenomics profiling on fecal samples and found that colorectal cancer (CRC)-associated metabolites were enriched in BCAA and AAA biosynthesis pathways, which showed significant associations with bacteria abundances (Coker et al., 2022). Using an azoxymethane and dextran sulfate sodium-induced CRC mouse model, Yang and colleagues suggested an escalating difference in microbial isoleucine, valine, and tryptophan biosynthesis with disease progression (Yang et al., 2024).

The dysfunction of gut microbial AA synthesis in inflammatory bowel disease (IBD) remains controversial. While a series of studies corroborated the finding that genes for biosynthesis for nearly all AAs decrease in abundance in IBD (Gevers et al., 2014; Morgan et al., 2012; Vich Vila et al., 2018), other studies based on a pediatric Crohn's disease cohort suggest differently. These studies reported increased proteobacterial utilization of nitrogen for AA biosynthesis, which was positively associated with disease severity (Heinken et al., 2021; Ni et al., 2017).

Alterations in microbial AA biosynthesis in IBS are symptom-related, which displayed a decrease in arginine (irritable bowel syndrome with diarrhea, IBS-D) (Vich Vila et al., 2018), glutamine (irritable bowel syndrome with constipation, IBS-C) (Meydan et al., 2020), methionine, and isoleucine (IBS-C and IBS-D) biosynthesis (Phan et al., 2021). A recent study further identified significant enrichment of microbial genes involved in the biosynthesis of tryptophan, threonine, and histidine in pathogenic-like IBS, compared with health-like subtype (Vervier et al., 2022). In a recent study investigating alcohol-related liver disease, phenylalanine produced by *Lactobacillus acidophilus* was found to enhance intestinal barrier function (Chen et al., 2023). However, most of the above studies presented only preliminary empirical data to support the contribution of bacteria-derived AAs in human gut physiology, which warrants future experimental investigations to test for causal hypotheses.

4. Microbial AA catabolism and gut health

It is estimated that around 6–18 g of protein could reach the large intestine daily, where it becomes available for bacterial proteolysis and subsequent fermentation (Smith and Macfarlane, 1998; Wang et al., 2023a). Under typical conditions, AA-fermenting microbes constitute only a minor subset of coliform bacteria, accounting for less than 1% of the total population (Dai et al., 2011). Despite their small numbers, these microbes exhibit considerable diversity. *Clostridia* and *Peptostreptococci* are the most commonly isolated bacteria in media that use AAs as sources of energy and carbon. Additionally, other bacteria, including species from *Fusobacterium, Bacteroides, Propionibacterium, Actinomyces, Enterobacteria*, *Eubacterium* spp., *Lachnospiraceae*, and *Ruminococcaceae*, are frequently observed (Amaretti et al., 2019; Dai et al., 2011; Davila et al., 2013; Russell et al., 2013; Smith and Macfarlane, 1997, 1998).

The mechanism of microbial AA fermentation can be roughly categorized into Stickland reaction and non-Stickland fermentation (Smith and Macfarlane, 1998), with the former involving simultaneous oxidation and reduction of an AA pair, generating energy in the form of ATP (Dai et al., 2015). In contrast, the non-Stickland pathway produces a wide variety of products depending on the specific AAs metabolized (Oliphant and Allen-Vercoe, 2019). (Fig. 1)

Briefly, AAAs (phenylalanine, tryptophan, and tyrosine), through miscellaneous reactions of fission, deamination, decarboxylation, oxidation, and reduction, could produce indoles and phenols. Indole and its derivatives, including indole-3-aldehyde, indole-3-lactic acid (ILA), indole-3-acetic-acid (IAA), and indole-3-propionic acid (IPA), exert their biological effects primarily through the activation of the two critical nuclear receptors, aryl hydrocarbon receptor (AHR) and pregnane X receptor (PXR) (Agus et al., 2018). Notably, there is an 88% overlap in the activators of AhR and PXR. In the gut, AhR is expressed in epithelial cells and immune cells, while PXR is predominantly expressed in colonic epithelial cells (Li et al., 2021b). Indole and its derivatives are important signaling molecules that protect the intestinal barrier through promoting epithelial cell proliferation, goblet cell differentiation, and mucus secretion, and maintaining the integrity of the apical junctional complex (Zhou et al., 2023). Indoles modulate functions of macrophages, dendritic cells, intraepithelial lymphocytes (IELs), and innate lymphoid cells (ILCs) in an AhR-dependent manner. Indole derivatives have been reported to drive an anti-inflammatory phenotypic shift in macrophages, promoting IL-10 expression, and inhibiting TNF-α and IL-1β secretion (Lamorte et al., 2021). Similarly, in dendritic cells, AhR activation regulates cytokine secretion and suppresses antigen presentation, fostering a tolerogenic immune environment. IELs, ILCs, Th17, and Th22 cells contribute to gut immune homeostasis via the AhR/IL-22 axis (Shinde and McGaha, 2018).

Desulfurization of the sulfur-containing AAs, cysteine and methionine, results in the production of hydrogen sulfide (H_2S) and methanethiol, respectively, and could be further detoxified through methylation or oxidation. Microbiota-derived H_2S may exert dual effects on colonocyte metabolism and physiology regarding energy metabolism, redox balance, and DNA integrity (Blachier et al., 2021; Xiao et al., 2021). At low concentrations, H_2S contributes to maintaining gut epithelium homeostasis. Colonic epithelial cells are particularly efficient in oxidizing H_2S to support their own metabolism through stimulation of mitochondrial electron transport and ATP synthesis (Blachier et al., 2019). Exogenous H_2S has been well recognized for its anti-oxidative properties as a chemical reductant and could scavenge ROS directly. It could also influence the oxidant-antioxidant balance through the inhibition of oxidative enzymes (i.e., NADPH oxidase) (Wallace and Wang, 2015), and regulate gene expressions relevant to redox balance, such as enhancing Nrf2 activity, which upregulates its downstream antioxidant genes (Li et al., 2021a). However, when the luminal H_2S rises to levels that start to overwhelm the detoxification systems of the colon epithelium, the local H_2S becomes cytotoxic, genotoxic, and pro-inflammatory. This excess H_2S disrupts the protective mucus layer by reducing its disulfide bonds, inhibits colonic cell mitochondrial respiration, and triggers local inflammation, compromising barrier integrity and gut health (Buret et al., 2022). However, there is limited evidence that

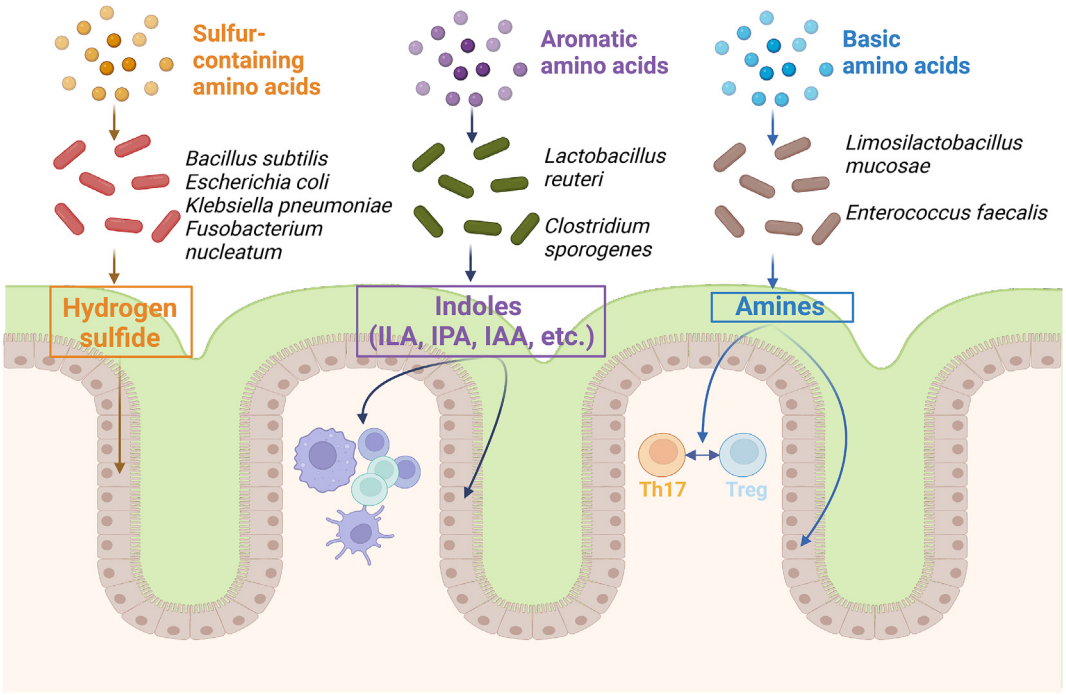

Fig. 1. Overview of Dissimilatory Microbial Amino Acid Metabolism in Colon
The schematic illustrates the roles of gut microbiota in metabolizing sulfur-containing, aromatic, and basic amino acids into bioactive compounds such as hydrogen sulfide (H_2S), indoles (e.g., ILA, IPA, IAA), and amines, separately. Several bacterial species involved in these processes were given. These metabolites influence epithelium physiology and immune responses, contributing to gut barrier integrity and immune homeostasis.

microbiota-derived luminal H_2S directly affects immune cells in the gut; rather, it indirectly influences the immune responses in the gut by regulating epithelial barrier integrity and subsequent cytokine signaling (Dilek et al., 2020).

Decarboxylation of basic AAs (arginine, histidine, and lysine) results in the formation of amine by-products. Arginine serves as a precursor of polyamine synthesis in the lower intestinal tract, including the production of putrescine, spermidine, and spermine. Microbiota-derived polyamines in the gut lumen are being increasingly recognized for their direct impact on epithelial cells and immune cells in the lamina propria, actively contributing to intracellular polyamine homeostasis via distinct uptake mechanisms (Milovic, 2001). These low-molecular-weight organic cations readily interact with anionic biomacromolecules, such as DNA, RNA, and proteins. A key role of polyamines is activating the eukaryotic translation initiation factor 5 A (eIF5A) via post-translational hypusination, a process that regulates gene transcription involved in cell proliferation, differentiation, and autophagy (Bekebrede et al., 2020a). These activities are required for gut epithelial renewal and stability. Moreover, polyamines have been found to be essential for the expression of tight junctions and adherens junctions, which enhance the barrier function, partly by regulating intracellular calcium levels (Rao et al., 2020). Although polyamines have long been associated with immune-metabolism (Mahalingam and Pandiyan, 2024), and are known to instruct $CD4^+$ helper T cell differentiation and function (Puleston et al., 2021), direct evidence of exogenous polyamines' effects on gut-resident immune cells remains scarce. Recent findings suggest that microbiota-transformed spermidine could induce the Th17/Treg balance towards the Treg cell population, likely through decreasing mTOR signaling and activating autophagic pathways; however, the specific molecular mechanism is still elusive (Carriche et al., 2021). Another study revealed that microbiota-derived polyamines could rewire macrophage metabolism via the hyp-eIF5A-OXPHOS axis, facilitating an anti-inflammatory polarization (Nakamura et al., 2021). Regarding the role of histidine metabolism in the gut, comprehensive literature reviews on histamine-producing bacteria and related gastrointestinal (GI) disorders mediated by the pleiotropic effects of histamine receptors (H1R, H2R, H3R, H4R) have been published (Fiorani et al., 2023; Smolinska et al., 2022).

Microbial AA catabolism also produce ammonia, organic acids, and gaseous compounds, with the most abundant end products being SCFAs. SCFAs account for over 30% of protein broken down in the colon (Frolova et al., 2022; Macfarlane et al., 1992; Van den Abbeele et al., 2022).

With evolving multi-omics approaches and emphasis on reliable models for causation inference (Lv et al., 2021), evidence linking microbiota AA metabolism and host health is rapidly accumulating. The impact of microbiota-derived SCFAs on intestinal physiology and response to related therapies is among the most prominent research topics in clinical microbiology, as reflected in a wide array of recent reviews (Deleu et al., 2021; Gomes et al., 2023; Hays et al., 2024; Jiang et al., 2022; Li and Martin, 2016; Mann et al., 2024; Rangan and Mondino, 2022; Shin et al., 2023). Thus, the present review will focus on the dissimilatory microbial metabolism of AAs.

4.1. *Sulfur-containing AAs*

Approximately 50% of fecal H_2S is derived from gut bacteria (Flannigan et al., 2011). There are mainly two pathways for microbial production of H_2S: sulfate reduction and degradation of sulfur-containing AAs. Methionine could be converted to cysteine, whose catabolized end product is H_2S.

Using bacterial genome analysis, researchers found that the H_2S production via cysteine degradation was ubiquitous in the human gut microbiota and that the abundance of the putative primary cysteine degraders was significantly higher than SRB. The same study found an increased abundance of primary cysteine-degrading bacteria (harboring genes such as *cysD*) and a simultaneous relative depletion of secondary cysteine-degrading bacteria (harboring genes such as *metC*) in CRC and IBD patients, compared with healthy controls (Braccia et al., 2021). Another interesting study found that methionine restriction-induced intestinal H_2S deficiency impaired anti-CRC immunity partially mediated

by the gut microbiota. However, oral supplementation with cysteine in methionine-sufficient mice promoted CRC progression, suggesting excessive microbial H_2S production could be detrimental to anti-tumor immunity (Ji et al., 2023). These new findings were in line with previous evidence summarized in excellent reviews that stated low levels of H_2S in the intestinal mucosa may participate in the resolution of mucosal inflammation, while high levels of H_2S may be implicated in IBD etiologies and symptomatic flairs (Portune et al., 2016; Walker and Schmitt-Kopplin, 2021). Additionally, a preliminary study reported that H_2S levels detected via breath testing were associated with gut microbial signatures and were more characteristic of IBS-D than IBS-C (Villanueva-Millan et al., 2022).

Analogous to H_2S, the majority of methanethiol biosynthesis in humans likely originates from the methionine-degrading gut microbiota, including *Fusobacterium nucleatum, Citrobacter freundii, Morganella morganii*, and several *Proteus* species (Philipp et al., 2023). This metabolite represents a novel and intriguing microbe-host interface in CRC: in healthy individuals, methanethiol could be rapidly detoxified by SELENBP1 highly expressed by the colon epithelium (Li et al., 2008), whereas, in CRC patients, downregulation of this gene was correlated with poor chemotherapy and immunotherapy response (Zhu et al., 2022). In contrast, methanethiol levels were significantly higher in healthy controls compared to IBD patients in studies exploring the fecal metabolomic characteristics of IBD (Walker and Schmitt-Kopplin, 2021).

4.2. Basic AAs

Recently, researchers have begun to uncover the gut-health-promoting effects of polyamines (Bekebrede et al., 2020b; Lu, 2006; Nakamura et al., 2019; Nüse et al., 2023). Intestinal microorganisms including *Bacteroides, Escherichia, Prevotella*, and *Lactobacillus* were recently demonstrated to produce polyamines, with *Lactobacillus* as the predominant bacterium (Kitada et al., 2018; Levy et al., 2015; Qi et al., 2019). Interestingly, an isolated study found that oral gavage of pasteurized *Akkermansia muciniphila* elevated intestinal concentrations of polyamines, possibly by altering the composition of the above-mentioned polyamine-producers (Grajeda-Iglesias et al., 2021). Conversely, polyamines in the gut lumen could also modulate microbiota composition (Holbert et al., 2022). Microbiota-derived polyamines have been proposed to ameliorate colitis in mouse models by increasing anti-inflammatory macrophages and accelerating epithelial renewal (Nakamura et al., 2021). The latest research also indicated the intersection between dietary fiber and microbial arginine metabolism. A fiber-modulated, mucin-rich luminal environment has been shown to enhance spermidine production by *Limosilactobacillus mucosae*, which subsequently improved intestinal barrier function (Zhou et al., 2024). Although polyamines have long been implicated in carcinogenesis (Novita Sari et al., 2021), currently, there is little evidence for the effect of polyamines synthesized by bacteria on CRC. Preliminary findings suggest that acetylated polyamines as a microbiota component were linked with age-related CRC progression and biofilm formation in CRC (Holbert et al., 2022). Conversely, the direct decarboxylated product of arginine, agmatine, has been proposed as an anti-cancer agent (Wei et al., 2023). A recent study found that inhibition of microbial agmatinases, which lead to agmatine accumulation by metformin augmented its therapeutic effects for type-2 diabetes (Tassoulas and Wackett, 2024). Another study illustrated that *Bacteroides vulgatus*-derived agmatine could act as a farnesoid X receptor agonist, which subsequently inhibited GLP-1 secretion (Pryor et al., 2019; Yun et al., 2024). These findings suggest that gut microbiota-derived agmatine could serve as a potential target for the prevention and treatment of CRC.

Histidine in the large intestine could be converted into histamine by microbial histidine decarboxylase enzyme, possessed by many Gram-negative and Gram-positive bacteria. *Lactobacillus reuteri*, one of the most studied histamine producers, has been shown to ameliorate gut inflammation by activating H2R and restricting pro-inflammatory H1R (Yu et al., 2023). This activity is often associated with suppression of colitis and inflammation-associated CRC (Shi et al., 2019). The role of microbiota-derived histamine in CRC of other etiologies remains under debate. In IBS patients, histamine production by enriched *Klebsiella aerogenes* has been shown to target H4R *in vivo*, inducing visceral hypersensitivity and mast cell accumulation (De Palma et al., 2022). The latest randomized, double-blind, placebo-controlled trial found that using an H1R antogonist effectively relieved symptoms of non-constipated IBS (Decraecker et al., 2024). These findings implicate that targeting histamine-producing microbes could be a promising approach for managing IBS.

A less investigated microbial metabolite of histidine is imidazole propionate. Previously linked with diabetes and cardiovascular diseases, imidazole propionate has been found to damage intestinal barrier integrity by disrupting the homeostasis of intestinal goblet cells and increasing the expressions of inflammatory cytokines, thereby inducing intestinal inflammation (Wu et al., 2022). A retrospective case-control study revealed a consistent elevation of urinary imidazole propionate in IBS patients compared with healthy controls (Yamamoto et al., 2019).

4.3. Aromatic AAs

Tryptophan metabolism has been proposed as an important link between the microbiota and GI disorders in recent years, operating through microbiota-tryptophan-immune (Gupta et al., 2023; Hou et al., 2023b; Seo and Kwon, 2023) and microbiota-tryptophan-brain axes (Gao et al., 2020; O'Mahony et al., 2015). Commensal microbes have been reported to transform tryptophan into indole (Dong et al., 2020) and its derivatives.

Many probiotic strains, such as *Lactiplanatibaillus plantarum, Clostridium butyricum,* and *Lactobacillus reuteri*, have been reported to produce indole-related substances at high levels (Liu et al., 2023). Liu and colleagues have elucidated the relationship between indole metabolites and CRC in a timely review (Liu et al., 2023). Additionally, Han and colleagues found that increased production of ILA by *L. reuteri* and subsequent downregulation of the IL-17 signaling pathway was likely the mechanism underlying the use of statins for CRC chemoprevention (Han et al., 2023). Present studies have mostly focused on the microbial indoles-AhR axis in IBD (Hou et al., 2023a), leaving other mechanisms of action understudied.

Cross-feeding interactions are another promising area of study with translational significance for applying single probiotic strains or probiotic consortia in clinical settings. For example, IPA produced by joint efforts of *Lactobacillus johnsonii* and *Clostridium sporogenes* improved CRC and pan-cancer immune checkpoint blockade responsiveness by modulating T cell stemness (Jia et al., 2024). ILA-mediated cross-feeding initiated by *L. reuteri* was found to alleviate intestinal inflammation in IBD (Wang et al., 2024). Conversely, fibre degradation might affect sequential microbial tryptophan metabolism. β-glucan degradation product nicotinamide by *Bacteroides uniformis* has been found to promote *L. johnsonii* ILA production in colitis (Zhang et al., 2024). In a three-species community, *Escherichia coli* and *Clostridium sporogenes* have been reported to compete for tryptophan. Fibre-degrading *Bacteroides thetaiotaomicron* cross-fed monosaccharides to *E. coli*, inhibiting indole production through catabolite repression and increasing tryptophan availability for *C. sporogenes*, hence boosting ILA and IPA production (Sinha et al., 2024).

Although evidence on the role of indole-related substances in IBS is limited, a double-blind, placebo-controlled, three-way crossover study in Sweden found that elevated plasma IPA levels were associated with FODMAP intervention, with only modest improvement in symptoms (Nordin et al., 2023). Recent studies have begun to uncover the potential role of tryptamine, previously known as a neurotransmitter, in GI physiology. Several strains of microbiota, including *Enterocloster asparagiformis, Blautia hansenii, Clostridium nexile, Clostridium sporogenes,* and *Ruminococcus gnavus DSM 108212*, are capable of producing tryptamine.

This metabolite has been implicated in regulating gut microbial communities (Otaru et al., 2024) and increasing colonic secretion by activating GPCR serotonin receptor-4 (5-HT_4R) (Bhattarai et al., 2018).

Latest studies also confirmed that certain gut microbiota could directly synthesize serotonin from tryptophan (Koopman et al., 2021; Nunzi et al., 2025; Potter et al., 2024; Sanidad et al., 2024; Wang et al., 2023b). This finding renewed the former recognition that they contribute to the serotonin pool by promoting serotonin synthesis of enterochromaffin cells (Yano et al., 2015). Elevated serotonin levels act on 5-HT_3R and 5-HT_4R, the most abundant serotonin receptors in the GI tract, stimulating GI motility, secretion, and visceral nociception—all of which prominently implicated in IBS-D (Bruta et al., 2021; Crowell, 2004). Integrating clinical markers, fecal metabolomics, and metagenomics, a recent study identified associations between *Bifidobacteriaceae, Bacteroidaceae,* and *Oscillospiraceae* with plasma serotonin levels (Mujagic et al., 2022). However, whether microbiota-derived serotonin contributes to extraintestinal symptoms of IBS remains unclear (Hanna-Jairala and Drossman, 2024). An intriguing intersectionality between AAA metabolism and serotonin production was found in IBS, where microbial degradation products of phenylalanine and tryptophan, phenylethylamine, and tyramine respectively, stimulated serotonin production in enterochromaffin cells (Zhai et al., 2023a, 2023b). The role of serotonin in IBD is still under investigation, with conflicting evidence regarding alterations in the serotonergic systemin GI inflammation, in both Crohn's disease and ulcerative colitis (Grondin and Khan, 2024; Pergolizzi et al., 2022). In CRC initiation, development, and treatment, serotonin plays dual roles through receptor-dependent signaling and serotonylation (Chen et al., 2024a; Kannen et al., 2020; Ling et al., 2024). While serotonin activity in CRC initiation is debated (Jia et al., 2022), it is widely considered to promote CRC progression by affecting tumor cells, immune cells, and angiogenesis, ultimately creating an immunosuppressive tumor microenvironment. However, the partitioning and contributions of microbial and host serotonin systems require further investigation.

Altered microbial phenylalanine and tyrosine metabolism has been associated with IBD pathology in cohort-based integrated metabolomics and metagenomics studies (Liu et al., 2020). However, experimental evidence supporting these associations is still lacking. A recent preprint study reported that tyramine metabolized from tyrosine promoted CRC progression by inducing CRC cell DNA damage, intestinal barrier dysfunction, and a suppressive immune TME in $Apc^{Min/+}$ mice model (Glymenaki et al., 2023). In functional GI disorders, tyramine has been reported to be associated with prostaglandin E2 hypersecretion, which could be alleviated with a novel nutraceutical agent, *Aspalathus linearis* (Pretorius and Smith, 2022).

5. Translational significance of microbial AA metabolism properties

Recent advancements underscore the potential of targeting gut microbial AA metabolism in clinical settings, representing promising avenues for therapeutic interventions.

Tailored dietary interventions, such as amino acid modulation, can influence microbial composition and metabolic pathways to alleviate disease symptoms and promote gut health. One illustration of this is dietary restriction of L-serine, which has been demonstrated to reduce the competitive fitness and gut colonization of the pathogenic *Escherichia coli LF82* and *Citrobacter rodentium*, thereby attenuating Crohn's disease microbiota-induced colitis in a mouse model (Kitamoto et al., 2020). However, whether these findings are applicable to human patients warrants further investigation. Battaglioli et al. reported that a subset of patients with diarrhea show increased availability of gut AA, especially proline, due to dysbiosis. This increased patients' risk of infection with *Clostridioides difficile*, a pathogen auxotrophic for proline. Thus, proline-deficient diet effectively prevented *C. difficile* colonization (Battaglioli et al., 2018). Methionine-restriction diet is arguably the most studied AA-based diet intervention. It has been investigated in clinical trials and is widely accepted for its anti-tumor and anti-inflammatory properties for GI health (Wu et al., 2023). However, Ji and colleagues found that sufficient levels of methionine-derived H_2S were indispensable for anti-CRC immunity (Ji et al., 2023). Thus, methionine content and intervention duration need to be titrated according to specific conditions to avoid complications as well as achieve maximal efficacy. Other AA-based diets are rarely studied, yet they hold significant potential for therapeutic applications.

Additionally, common foodstuffs could be assessed for their prebiotic properties in regulating microbiota AA metabolism and incorporated into daily diets. For example, the MD Anderson Cancer Center conducted a 16-week dietary intervention trial with beans (*Phaseolus vulgaris*) and found that its health-promoting effects were partly mediated by reductions in sulfur-containing AA biosynthesis and transsulfuration, and BCAA biosynthesis (Zhang et al., 2023c). Furthermore, microbial AA metabolites are starting to be proposed as dietary supplements (NCT06674018) (Frederiksen, 2024).

Probiotic formulations also show promise in managing GI diseases by producing beneficial metabolites. *Bifidobacterium* and *Lactobacillus* strains are the dominant probiotics investigated for effectively managing IBS symptoms, and improving overall quality of life. A systemic review also pointed out that that administration of combinations of probiotics outperformed single strains (Wu et al., 2024). Similarly, probiotic blends containing 2 to 3 strains of *Bifidobacterium* and *Lactobacillus* showed benefits for reducing ulcerative colitis activity. A *Faecalibacterium prausnitzii* strain is currently being evaluated for its therapeutic efficacy for remission maintenance in patients with ileal CD (Ananthakrishnan et al., 2024). Several up-to-date review articles summarized the rapidly growing strategies of probiotics intervention in CRC (Feizi et al., 2024; Ha et al., 2024; Han et al., 2024). Deciphering AA metabolizing properties of the gut microbiota could significantly accelerate the development of engineered probiotic strains designed to produce desired metabolites in greater quantities (Murali and Mansell, 2024). For example, *E. coli* Nissle 1917 has been successfully engineered to produce increased levels of ILA (Dimopoulou et al., 2023) and spermidine (Caffaratti et al., 2022) in the gut. Future clinical trials are urgently needed to focus on next-generation probiotics and effective consortia of symbiotic probiotic strains.

It is worthwhile to acknowledge that the gut microbial AA metabolism is sensitive to various stressors. For instance, the COVID-19 pandemic has emerged as a critical global event that has reshaped research in gut microbiota, revealing how infection, treatments, and lifestyle changes can alter microbial metabolism and interactions. Pandemic control measures, including social distancing, heightened hygiene practices, and travel restrictions, have been suggested to cause substantial, uneven, and potentially lasting impacts on the human microbiome. Infants, in particular, are vulnerable to these changes, as early life stages are critical for microbiome development, which can influence the future risk of immunogenic diseases, including those with GI involvement (Zhang et al., 2023b). Post-COVID-19 shifts in gut microbiota have been linked to metabolic dysfunctions in microbial AA pathways. Deep phenotyping of COVID-19 patients in a single-center study revealed a loss of beneficial GI flora and severe disturbance of microbiota-dependent indole metabolic pathway. This disruption was linked to enhanced production of inflammatory cytokines during the disease course (Essex et al., 2024). Additionally, impaired microbial isoleucine biosynthesis was strongly correlated with disease severity and elevated plasma inflammatory markers, persisting even after disease resolution (Zhang et al., 2021). “Long-COVID” patients, whose symptoms lingered long after recovery, demonstrated incomplete restoration of gut microbiota for up to a year (Chen et al., 2022; Liu et al., 2022; Zhang et al., 2023a). How overall loss of diversity and functional disturbances of gut microbiota affect human health in the longer term need to be monitored.

In light of recent developments, there is a growing need to investigate how the current exposome, such as air pollutants, greenspace, urbanicity,

pets, and smoking (Gacesa et al., 2022), shapes host-microbiota interactions through AA metabolism. This understanding is crucial for formulating rational, personalized, microbiota-targeted interventions aimed at improving gut health. For example, microplastic exposure has been shown to induce gut microbiota dysbiosis, alter AA availability and metabolism, and subsequently cause intestinal barrier dysfunction and metabolic disorders in mice (Jin et al., 2019; Sun et al., 2021). Moreover, the latest study by Chen and colleagues found that intervention with cyanidin-3-O-glucoside, a natural anthocyanin derived from red bayberry, could potentially mitigate microplastic-induced colonic inflammation by promoting microbial tryptophan metabolism. This intervention upregulated metabolites such as tryptophan, ILA, and N-acetylserotonin (Chen et al., 2024b). Additionally, mounting evidence suggests that air pollution—specifically particulate matter (PM2.5), nitrogen dioxide, ozone, and nitrogen oxides—can disrupt AA metabolic functions within the human gut microbiota (Filardo et al., 2022; Fouladi et al., 2020). Thus, it is essential to consider preserving the resilience of microbial ecosystems when designing microbiota-targeted regimens to promote gut health amidst these emerging environmental stressors.

6. Conclusions

The intricate interplay between gut microbiota and AA metabolism represents a critical axis in human health and disease. Emerging evidence highlights the importance of AA-based microbial auxotrophies and prototrophies in driving the establishment of complex consortia, affecting microbial survival and also mediating host health by producing bioactive metabolites with both localized and systemic effects. Biosynthesis and catabolism of AAs by gut microbes contribute to a diverse array of metabolites, including SCFAs, indoles, amines, and sulfides, many of which have significant implications for gastrointestinal health and beyond. Dysregulation in microbial AA metabolism has been implicated in various gastrointestinal conditions, while this review specifically focused on IBS, IBD, and CRC. Despite these associations, the causal links between microbial AA metabolism and host pathophysiology remain largely speculative. This warrants more robust experimental studies aimed at dicovering specific molecular and mechanistic pathways underlying the microbiota-host interactions through AA metabolism, and translational research directly assessing the clinical applicability of these findings. Furthermore, a deeper exploration of microbial interspecies interactions could unveil reliable targets.

Therapeutic strategies, such as probiotics, prebiotics, and dietary interventions, hold promise in modulating microbial composition and AA metabolic functions to improve gut health and manage disease. However, significant challenges remain, particularly in identifying specific microbial targets, developing precise dietary strategies, and overcoming the variability in host-microbiota interactions. In conclusion, advancing the field will require interdisciplinary collaboration across microbiology, immunology, and precision medicine. By addressing these gaps, we can better harness the therapeutic potential of the microbiota to promote gut health.

CRediT authorship contribution statement

Youli Chen: Writing – original draft, Validation, Investigation, Conceptualization. **Jing-Yuan Fang:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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