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Gut microbiota bridges dietary nutrients and host immunity

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Dietary nutrients and the gut microbiota are increasingly recognized to cross-regulate and entrain each other, and thus affect host health and immune-mediated diseases. Here, we systematically review the current understanding linking dietary nutrients to gut microbiota-host immune interactions, emphasizing how this axis might influence host immunity in health and diseases. Of relevance, we highlight that the implications of gut microbiota-targeted dietary intervention could be harnessed in orchestrating a spectrum of immune-associated diseases.

amino acid, carbohydrate, lipid, trace element, vitamin, gut microbiota, immunity

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Introduction

Human is facing the challenge that the prevalence of diet-related chronic diseases (e.g., obesity and type 2 diabetes) has been steadily growing (Jaacks et al., 2019; Panagiotakos et al., 2015). The consistent escalation of these diseases in nonindustrialized populations that transition to a Western-style diet has evidenced the crucial role of diet in host health (Armet et al., 2022). Therefore, it is of great importance to comprehensively understand whether and how diverse dietary nutrients manipulate host health.

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A considerable part of the dietary influences on human health and diseases are mediated or modified by gut microbiome (Hills et al., 2019; Paoli et al., 2019). Notably, the gut microbiota is composed of distinct microbial populations, affecting most aspects of host physiological processes, especially host metabolism and immunity (de Vos et al., 2022). The establishment of a healthy community structure of gut microbiota, such as early-life probiotic exposure, significantly contributes to modulate host immunity (Huang et al., 2022b). Intriguingly, diet-related chronic diseases, most of which are tightly associated with the gut microbiota as well as host immunity (Yamashiro, 2017), have well highlighted the crucial roles of host immunity-microbe interactions in orchestrating diet-mediated host health and diseases (Armet et al., 2022).

Herein, we systematically delineate the distinct roles of various types of dietary nutrients, including amino acids (AAs), carbohydrates, fat (lipids), trace elements, and vitamins in the modulation of gut microbiota. We then summarize the most recent insights regarding the metabolism of dietary nutrients by gut microbes and the effects of the interactions of dietary nutrients-gut microbiota on host health and diseases, with a focus on immune-related diseases. We also propose the manipulation of dietary nutrients and gut microbes for improving human health.

Gut microbiota bridges dietary AAs and host immunity

Dietary AAs determine the composition of gut microbiota, and reciprocally, gut microbiota modulates AA metabolism, both of which profoundly affect host immunity (Chen et al., 2020a; Fan et al., 2021; Ren et al., 2020). For instance, dietary tryptophan (Trp) converted into aryl hydrocarbon receptor (AHR) ligands by gut microbes (*Peptostreptococcus russellii*, *Lactobacillus* spp., and *Clostridium sporogenes*), which are also sensed by pregnane X receptor (PXR) (Venkatesh et al., 2014), 5-HT_4 receptor (5-HT_4R) (Bhattarai et al., 2018), and transient receptor potential ankyrin A1 (Trpa1) (Ye et al., 2021), could modulate intestinal function and immunity (Dodd et al., 2017; Wlodarska et al., 2017). Additionally, the loss of dietary Trp results in diminished abundance of *L. reuteri*, and promotes expansion of RORγt$^+$ regulatory T cells (Tregs) and the loss of Gata3$^+$ Tregs in a microbiota-dependent manner (Rankin et al., 2023).

A recent study has also revealed the precise molecular cascades of how branched-chain amino acids (BCAAs) affect the immune system via gut microbes (Figure 1). Specifically, BCAAs are absorbed by *B. fragilis* and converted into sphinganine chain branching of BfaGCs by the BCAA aminotransferase, and the presentation of BfaGC by CD1d to the natural killer T (NKT) cell dictates the corresponding anti-inflammatory character (Oh et al., 2021). It is worth considering that the molecules produced by gut microbes have enormous structural diversity, causing structure-specific immunomodulatory activity (Oh et al., 2021). Combining the above interactions between gut microbiota and AAs, gut microbiota bridges dietary AAs and host immunity and a shift of gut microbiota caused by dietary AAs widely affects host immunity and related diseases.

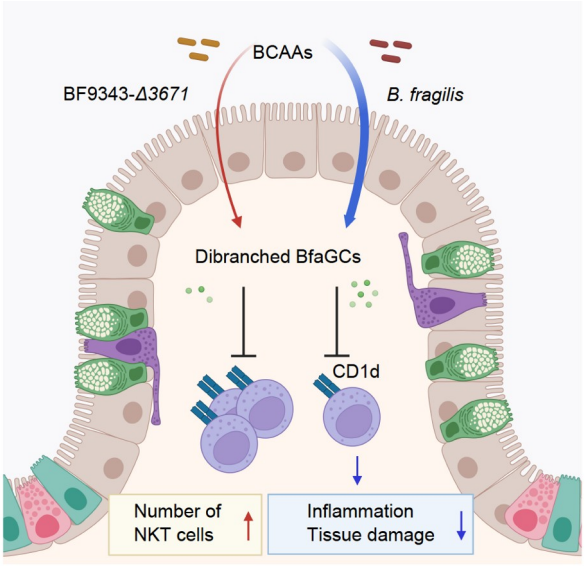

Figure 1 Dibranched BfaGCs converted from BCAAs by *Bacteroides fragilis* modulate gut NKT cells. BF9343-Δ*3671* monocolonization results in a significantly lower level of dibranched BfaGCs and increased NKT cells; dibranched BfaGCs perform immunomodulatory functions via the CD1d-NKT cell receptor axis. BfaGCs, α-galactosylceramides from the human symbiont *Bacteroides fragilis*; BF9343-3671, *B. fragilis* gene deaminating BCAAs to α-keto-carboxylic acids. This figure was created using BioRender.com.

Influences of AAs on gut microbiota

Dietary AAs have significant effects on the composition of gut microbiota (Table 1). In this section, we mainly summarize the effects of AA types and/or levels on distinct responses of intestinal microbes, which might be largely associated with the ecological niches of microbiota and species characteristics of the host.

Effect of AA type on gut microbiota

AAs have different degradation patterns by various microbes, suggesting that the modulation of dietary AAs might represent a feasible approach for regulating amino acid-fermenting bacterial species. For instance, a diet supplemented with 0.4% Trp enhances the abundance of Verrucomicrobia but decreases the abundance of Firmicutes and Actinobacteria in mice (Yin et al., 2021), and dietary leucine (Leu) supplementation (1.0%) causes a lower richness of gut

Table 1 Dietary AAs alter the composition of gut microbiota in human and animal models

Dietary AAs	Species	Bacteria[a)]	Samples
Branched-chain amino acids	Male BALB/c mice	↑*Akkermansia* and *Bifidobacterium*; ↓The ratio of *Enterobacteriaceae* (Yang et al., 2016)	Fecal samples
Branched-chain amino acids	Sprague-Dawley rats	↑*R. flavefaciens* (Iwao et al., 2020)	Fecal samples
Sulfur amino acid restriction	C57BL/6J mice	↑Firmicutes, *Clostridiaceae*, and *Turicibacteraceae*; ↓Verrucomicrobia (Nichenametla et al., 2021)	Fecal samples
L-Gln	Human	↑unclassified Clostridales (Org et al., 2017)	Fecal samples
L-Ile and L-Val	Human	↑*Blautia*; ↓Christensenellaceae (Org et al., 2017)	Fecal samples
L-Gln	Overweight and obese adults	↓The ratio of Firmicutes to Bacteroidetes; ↓*Dialister*, *Dorea*, *Pseudobutyrivibrio*, and *Veillonella* belonging to the Firmicutes phylum (de Souza et al., 2015)	Fecal samples
1.0% L-Gln	Mini sows	↑Bacteroidetes and Actinobacteria; ↓*Oscillospira* and *Treponema* (Zhang et al., 2017)	Fecal samples
0.4% L-Trp	Aging mice	↑*Akkermansia* (Yin et al., 2021)	Fecal samples
0.2% or 0.4% L-Trp for 4 weeks	Weaned piglets	↑*Prevotella*, *Roseburia*, and *Succinivibrio* in 0.2% L-Trp group; ↓*Clostridium sensu stricto*, *Clostridium XI* and *Lactobacillus* in 0.4% L-Trp (Liang et al., 2018)	Cecal
Monosodium L-Glu	Growing pigs	↑*Faecalibacterium prausnitzii* and *Roseburia* (Feng et al., 2015)	Contents of cecum, Colon
120 g d^{-1} Gln for 90 d	Male Qinghai plateau yaks	↑F/B ratio in the jejunum and ileum (Ma et al., 2021a)	Digesta sample
30% Lys limitation	Male piglets (Landrace×Large White)	↑Actinobacteria, Saccharibacteria, and Synergistetes (Yin et al., 2017)	Ileal digesta
L-Arg for 40 d	Yellow-feathered chickens	↑Firmicutes phylum, *Romboutsia* and *Candidatus Arthromitus* genera; ↓*Clostridium sensu stricto 1* (Ruan et al., 2020)	Ileal digesta
1.0% crystalline L-Leu	Female ICR mice (6-week-old)	↓Richness of microbiota and microbial diversity; ↑Firmicutes and down-regulation of the abundance of Bacteroidetes (Song et al., 2020)	Fecal samples
1% L-Gln for 14 d	Female ICR	↑*Streptococcus* and *Bifidobacterium* in the jejunum; ↓*Streptococcus* and *Lactobacillus* in the ileum (Ren et al., 2014)	Luminal content
300 mg kg^{-1} D-Met	Male Wistar rats (176–200 g, 6 weeks old)	↑*Lachnospiraceae* and *Lactobacillus* (Wu et al., 2019)	Cecum content
4 g kg^{-1} high-Trp diet	DBA/1 mice	↑The species richness and diversity and abundance of Proteobacteria and Actinobacteria (Yue et al., 2021)	Fecal samples
0.3% L-Thr for 12 weeks	Lohmann Brown hens	↑Genera *Bacteroides*, *Clostridium*, *Faecalibacterium*, *Bifidobacterium*, *Parabacteroides*, and *Eubacterium* (Dong et al., 2017)	Cecal contents
0.1% L-His	Piglets (Landrace×large white)	↑*Butyrivibrio* and *Bacteroides* (Kang et al., 2020)	Distal intestinal digesta samples
2% L-Gly for 7 d	Piglets (Yorkshire×Landrace)	↑Blautia, *Lachnospiraceae*, *Anaerostipes*, and *Prevotella*; ↓*Escherichia-Shigella*, *Clostridium*, and *Burkholderiales* (Ji et al., 2022)	Colonic contents
1% L-Asp for 35 d	Young pigs (Duroc×Landrace×Yorkshire)	↑Actinobacteria and Bacteroidetes; ↓Firmicutes (Li et al., 2019b)	Terminal ileum

a) Arrows on bacteria indicate that an increase or decrease in abundance is observed following consumption of the AAs.

microbiota and microbial diversity in mice, as evidenced by higher relative abundance of Firmicutes while lower relative abundance of Bacteroidetes (Song et al., 2020). Moreover, the abundance of *Akkermansia* and *Bifidobacterium* is increased while the ratio of Enterobacteriaceae is decreased upon BCAAs supplementation in middle-aged mice (Yang et al., 2016). The above studies show that the addition of Trp and Leu may have diametrically opposite effects on Firmicutes, one of the most abundant prokaryotic groups in human gut microbiota that is responsible for type 2 diabetes (T2D), obesity, and Alzheimer's disease (Larsen et al., 2010; Vogt et al., 2017). Collectively, different kinds of AAs seem to se-

lectively influence gut microbiota, which may be due to the alteration in the luminal environment for gut microbe colonization affected by a specific AA metabolism.

Effect of AA level on gut microbiota

The level of dietary AAs affects the metabolic function and composition of intestinal microbiota. High protein diet feeding promotes succinate production by the gut microbiota, driving the T cell-independent secretory immunoglobulin A (SIgA) response (Tan et al., 2022). Indeed, increased intestinal succinate is observed in inflammatory bowel disease (IBD) patients (Macias-Ceja et al., 2019), suggesting a potential pathway involved in IBD through the increased production of the bacterial metabolite succinate.

In addition, lower levels of dietary protein are recommended for livestock, contributing to the enrichment of beneficial bacteria. For instance, dietary supplementation with 0.2% Trp increases the relative abundance of *Prevotella*, *Roseburia*, and *Succinivibrio* in weaned piglets, while 0.4% Trp reduces the relative abundance of beneficial bacteria including the butyric acid-producing bacteria (*Clostridium sensu stricto*, *Clostridium XI*, and *Lactobacillus*) (Liang et al., 2018). These findings provide evidence that changes in AA level shape different microbial landscapes. In addition, high levels of AAs lead to reduction of beneficial bacteria, a possible explanation is that the residual protein and AAs that are not absorbed in the small intestine would be transferred to the distal gut and metabolized by the microbes in that location, resulting results in decreased organic acid production and a higher luminal pH that conducive to the colonization of AA-fermenting bacteria rather than the butyric acid-producing bacteria.

Effects of AAs on gut microbiota in different intestinal segments

The abundance and diversity of microorganisms throughout the gastrointestinal tract (GIT) increase from proximal to distal gut. Interestingly, the effects of AAs on gut microbiota differ over intestinal segments. For example, supplementation of glutamate markedly decreases the percentages of *Peptostreptococcus productus*, *Prevotella*, and *Clostridium coccoides* in the jejunum and the *Bacteroides thetaiotaomicron*, *Peptostreptococcus productus*, and *Methanobrevibacter smithii* in the colon, while increases the Firmicutes, Bacteroidetes, and *Prevotella* in the ileum and the *Roseburia* in the cecum (Feng et al., 2015). In addition, a higher Firmicutes-to-Bacteroidetes (F/B) ratio is observed in the jejunum and ileum of growth-retarded yaks with dietary glutamine (Gln) supplementation, whereas no difference is observed for F/B ratio in the rumen and cecum (Ma et al., 2021a).

Effects of AAs on gut microbiota among different species

Part of the factors that shape the composition of gut microbiota is performed on the genetic level (Grieneisen et al., 2021), which leads to variation in gut microbial structure across species. Therefore, it is necessary to investigate the effects of dietary AAs on gut microbes in different species. For instance, in obese individuals, Gln supplementation decreases the F/B ratio and reduces Actinobacteria (de Souza et al., 2015). In mini sows, Gln increases the abundance of Bacteroidetes and Actinobacteria and decreases that of the *Oscillospira* and *Treponema* (Zhang et al., 2017). As for mice model, Gln supplementation increases the abundance of *Streptococcus* and *Bifidobacterium* in the jejunum, and decreases the abundance of *Streptococcus* and *Lactobacillus* in the ileum (Ren et al., 2014). These aforementioned findings demonstrate that the changes in the gut microbiota mediated by dietary AAs are diverse in different animal models. Host genetic makeup and the environment to which it is exposed during early stages of life determine the composition of microbiota; thus, the responses of gut microbiota to dietary AAs in different animal models depend in part on their differing microbial backgrounds.

In sum, these results suggest that AAs have broad regulatory effects on gut microbes. Factors such as the AA type, level, the spatial location of the digestive tract, and the species-specificity of the gut microbiota are likely associated with the effects of AAs on the gut microbiota. This presents a challenge to accurately define the regulatory role of AAs on gut microbiota. The importance of the gut microbiota as a mediator of diet and host has been widely described. Future research should fully elucidate the interaction between AAs and gut microbiota under various conditions, and clarify the specific relationship between AAs and microbial species is conductive to understand the broad effects of dietary AAs on the host.

Gut microbes modulate AA metabolism of host

It is reported that germ-free (GF) mice possess an altered distribution of host AA metabolism in the GIT (Mardinoglu et al., 2015). In addition, we have compared the overall AA metabolism profile of GF pigs and fecal microbiota transplantation (FMT) pigs, showing that the histidine (His), methionine (Met), isoleucine (Ile), Leu, phenylalanine (Phe) (unpublished), and Trp (Liu et al., 2022a) are increased in the colon tissue of GF pigs. Studies based on GF animal models highlight that the resident species of the gut microbiota are crucial to the AA metabolism of the host.

Effects of different intestinal segments on AA metabolism

Small intestine allows dietary AAs into the bloodstream and sustains the supply of AAs to all tissues (Ryan et al., 2021). Indeed, the small intestine not only transports AAs into the portal circulation, but also catabolizes AAs originating from the diets, evidenced by a study carried out on piglets (Wu et

al., 2014). The enterocytes catabolize nearly all of the dietary Glu and aspartate (Asp) taken up from the intestinal lumen, along with roughly 35% of BCAAs, 30% to 40% of proline (Pro) (Mayneris-Perxachs et al., 2022). Among these AAs, Gln serves as the major source of *de novo* citrulline synthesis of enterocytes. Further, as much as 30%–50% of the arginine (Arg), Met, lysine (Lys), threonine (Thr), glycine (Gly), serine (Ser), Leu, Ile, and valine (Val) absorbed in the small intestine are catabolized and unavailable to extraintestinal tissues (Ma and Ma, 2019).

Despite efficient absorption and metabolism of AAs in the small intestine, a part of dietary AAs will transfer to the large intestine. However, these compounds are not substantially absorbed by the colon mucosa, except during a short period after birth. In the distal gut, AAs have 3 possible metabolic fates in general: (i) excretion in feces; (ii) used by the intestinal microbiota for its own protein synthesis; (iii) serving as the substrate for microbial dissimilatory metabolism that generates numerous metabolic end products. These microbial metabolites are key regulators in host-microbiota crosstalk. In fact, the degree to which the gut microbiota metabolizes AAs is largely dictated by substrate availability and the luminal environment. Specifically, higher rates of bacterial fermentation of protein occur in the context of low carbohydrate availability and higher colonic pH value. However, degradation of protein by the microbiota contributes a small amount to the total short-chain fatty acids (SCFAs) pool accounting for ~38% of distal gut (sigmoid colon or rectum) SCFA pools (Krautkramer et al., 2021), which is less than that of from carbohydrates fermentation.

Effects of gut microbiota on AA metabolism

The recently conducted research indicates substantial quantities of protein- and AAs-fermenting bacteria within the human colon (Lin et al., 2017). Bacteria of the genera *Fusobacterium*, *Bacteroides*, and *Veillonella* and the species *Megasphaera elsdenii* and *Selenomonas ruminantium* play prominent roles in AA metabolism in the large intestine. Particularly, bacteria of the *Clostridium* genus are the key driver of Lys or Pro utilization, whereas bacteria of the *Peptostreptococcus* genus are the key driver of Glu or Trp usage. In this perspective, we focus on the microbial metabolic pathways of AAs.

(1) Aromatic amino acids. Aromatic amino acids (AAAs) refer to AAs that have an aromatic ring in the side chain, including Trp, tyrosine (Tyr), and Phe. Evidence suggests that less than 1% of dietary Trp is utilized for protein synthesis, and a considerable amount of dietary Trp is therefore metabolized by 3 pathways: (i) kynurenine pathway; (ii) serotonin pathway; (iii) decarboxylation (to tryptamine) and transamination (to indol-3-ylpyruvic acid) pathway, which is mediated by the gut microbiota (Badawy, 2017). At present, the metabolism of AAAs in gut microbes mainly focuses on Bacteroidetes and Firmicutes, among which, *Clostridium sporogenes* (from the phylum Firmicutes) has been extensively studied on the metabolism of AAAs.

A shared pathway of the metabolism of AAAs by gut microbe involves in the aromatic amino acid decarboxylase (AADC) pathway to produce arylethylamine. For example, *Morganella morganii*, *Ruminococcus gnavus*, and *Staphylococcus pseudintermedius* are responsible for the phenethylamine (PEA), tyramine, and tryptamine production from Phe, Tyr, and Trp, respectively (Liu et al., 2020b). In addition to *C. sporogenes* and *Staphylococcus pseudintermedius*, intestinal bacteria such as *R. gnavus*, *Xenorhabdus nematophila*, *Bacillus subtilis*, and some *Staphylococcus* harbor decarboxylases that convert Trp to tryptamine (Williams et al., 2014). These results suggest a potential bacterial population that is endowed with the AADC pathway of Trp. Of note, 10% of the human population harbors at least one bacterium encoding a tryptophan decarboxylase in their gut community (Williams et al., 2014). Another common pattern is AAAs aminotransaminase (ArAT)-mediated transamination, where Phe, Tyr, and Trp are converted to phenylpyruvic acid (PPA), 4-hydroxyphenylpyruvic acid, and indole-3-pyruvate (IpyA), respectively. Following the aminotransferase reaction, the arylpyruvic acid products undergo reductive pathway and oxidative pathway to produce arylpropionic acid and arylacetic acid, respectively. For the reductive pathway in *C. sporogenes*, phenyllactate dehydrogenase (FldH) converts arylpyruvic acid to aryllactic acid, followed by converting to aryl acrylic acid via phenyllactate dehydratase (FldABC). Finally, the aryl acrylic acid is reduced to aryl propionic acid, which is the final metabolite. For example, indole propionic acid (IPA), the final metabolite of the microbial reduction pathway of Trp, has been demonstrated as an endogenous ligand for PXR, functions to strengthen the gut barrier through Toll-like receptor 4 (TLR4) signaling or epithelial IL-10 receptor 1 (Alexeev et al., 2018). In the oxidative branch, the transamination product of Phe, PPA, is converted to phenylacetyl-CoA by phenylpyruvate: ferredoxin 2-oxidoreductase, followed by the formation of corresponding phenylacetate (Dickert et al., 2000). Moreover, 4-hydroxyphenylpyruvic acid and IpyA are converted to 4-hydroxyphenyl acetic acid (4-HPAA) and indole-3-acetic acid (IAA). Overall, the deamination action appears to be the more common strategy of AA catabolism by the gut microbiota compared with the AADC pathway (Oliphant and Allen-Vercoe, 2019).

In addition to common decarboxylation and transamination pathways, gut microbes present other diverse and complex ways driving AA metabolism. Driven by tryptophan 2-monoxygenase (TMO), bacterial degradation of Trp into indole-3-acetamide (IAM) provides another metabolic

precursor to IAA. Then, IAA is metabolized to 3-methylindole (skatole) or indole-3-aldehyde (IAld), serving as the end product of microbial Trp metabolism. Tyrosine phenol-lyase (TPL) and tyrosine lyase (ThiH) metabolizes L-Tyr to phenol and p-cresol, respectively (Saito et al., 2018). In addition, gut microbes participate in the synthesis pathway of 4-ethylphenyl sulfate (4EPS). *Bacteroides ovatus* (*BACOVA_01194*) produces p-coumaric acid from Tyr depending on tyrosine ammonia lyase (AL). Then, *Lactobacillus plantarum* produce 4-ethylphenol (4EP) using p-coumaric acid as a substrate via phenolic acid decarboxylase (PAD) and vinyl phenol reductase (VPR) enzymes, and 4EP could subsequently sulfate to 4EPS by host sulfotransferase (SULT1A1) (Santamaria et al., 2018).

Collectively, the resident microbes in the gut have great potential for the metabolism of AAAs. Current researches have successfully revealed the metabolic pathways and genes involved at the strain level (Figure 2), suggesting that it is feasible to manipulate gene expression at the strain level to manipulate the metabolic pathway of AAAs.

(2) Sulfur-containing amino acids. The sulfur-containing AAs in mammals include Met and cysteine (Cys). Met is an essential amino acid, whereas Cys is non-essential and a metabolite of Met. There are two pathways currently that mediate the convertion of Met into methanethiol (MT) in micro-organisms (He and Slupsky, 2014): (i) the *Citrobacter freundii* which express methionine γ-lyase (MGL) can convert Met to MT (Manukhov et al., 2005); (ii) Met is first converted to α-keto-γ-methyl-thiobutyric acid (KMBA) via aminotransferase, followed by C-S lyase to convert KMBA to MT in *Lactococcus lactis* (He and Slupsky, 2014).

Moreover, the pathways that are responsible for bacterial degradation of Cys (Walker and Schmitt-Kopplin, 2021) are dependent on enzymatic reactions, including (i) cysteine desulfhydrase (CDS) and cystathionine γ-lyase (CSE), that catalyze the Cys to produce pyruvate, NH_3, and H_2S; (ii) 3-mercaptopyruvate sulfurtransferase (3-MST), that generates Ser and H_2S from Cys; (iii) cystathionine β-synthase (CBS) in catalyzing the reaction of Cys to produce pyruvate and H_2S; and (iv) Cys desulfurase (IscS) in converting Cys to H_2S in *Escherichia coli* (*E. coli*) under anaerobic condition (Figure 3).

(3) Branched-chain amino acids. BCAAs include Leu, Ile, and Val (White and Newgard, 2019). Bacterial fermentation of Val, Ile, and Leu produces isobutyrate, 2-methylbutyrate, and isovalerate, respectively. Degradation of BCAAs occurs in several steps. BCAAs are first transformed into branched-chain α-ketoacids (and $NH4^+$+H_2) through the removal of the amino group by a BCAA transferase enzyme, and branched-chain α-ketoacids (α-ketoisovalerate, α-keto-β-methylvalerate, and α-ketoisocaproate) are further decarboxylated by branched-chain-α-ketoacid dehydrogenase producing isobutyral-CoA, isovaleryl-CoA, and 2-methylbutyral-CoA (and CO_2+H_2), which are finally converted to the corresponding branched chain fatty acids (BCFAs) that are the main components of membrane lipids of gut bacteria (Taormina et al., 2020). Moreover, it is mentionable that the major source of BCFAs is from bacteria rather than from host cells.

(4) Basic amino acids. Basic amino acids include Arg, Lys, and His. Indeed, there exist arginine deiminase systems (ADIs) in gut microbes. Bacterial ADIs convert Arg to or-

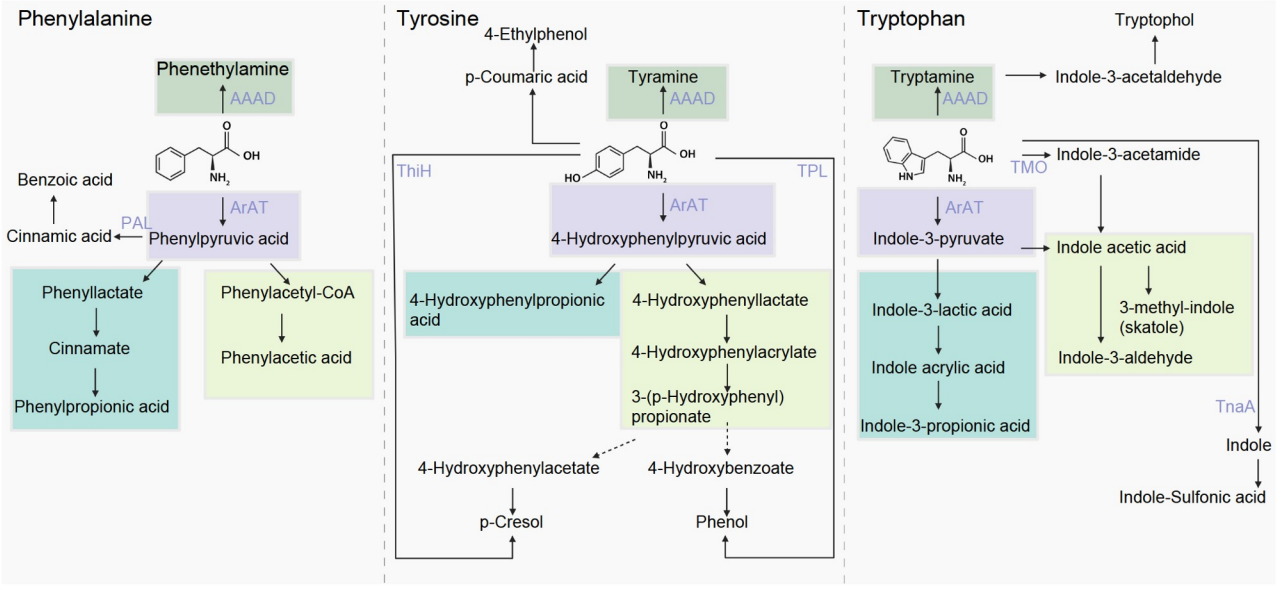

Figure 2 Phenylalanine, tyrosine and tryptophan metabolism by gut microbes. Overview of aromatic L-amino acid metabolism by gut microbes to major products. AAAD, aromatic L-amino acid decarboxylase; PAL, phenylalanine ammonia lyase; TnaA, tryptophanase. This figure was created using BioRender.com.

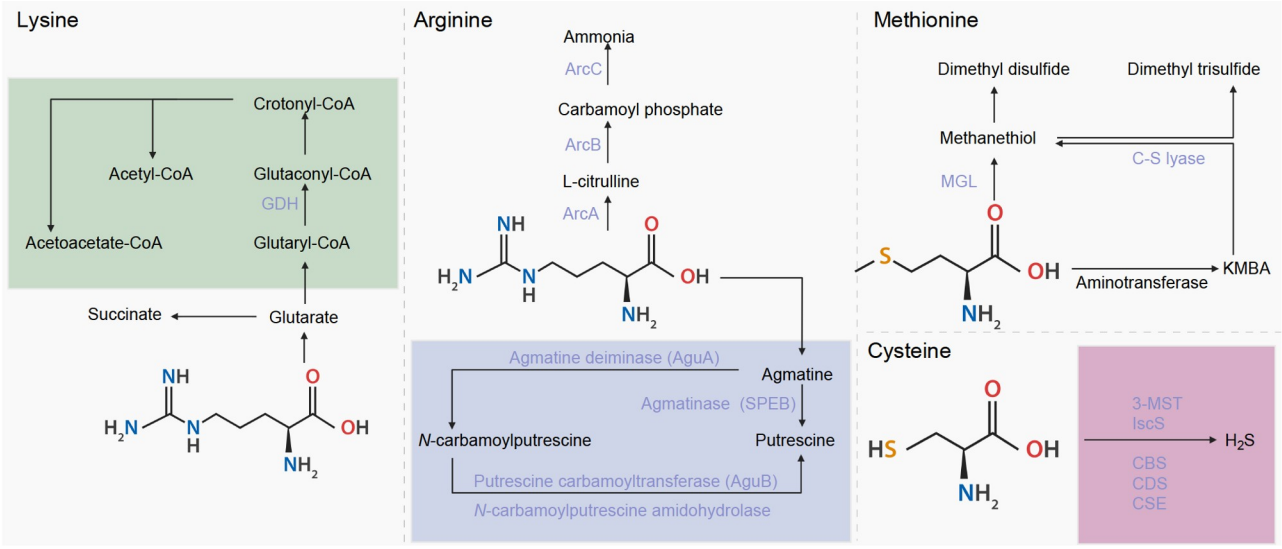

Figure 3 Lysine, arginine and methionine metabolism by gut microbes. Overview of lysine, arginine and methionine metabolism by gut microbes to major products. GDH, glutaryl-CoA dehydrogenase; ArcA, arginine deiminase; ArcB, ornithine transcarbamylase; ArcC, carbamate kinase. This figure was created using BioRender.com.

nithine, ammonia, carbon dioxide, and ATP. In addition, Arg converts to agmatine by the arginine decarboxylases SpeA and AdiA in bacteria, followed by biosynthesis of putrescine. There are two metabolic pathways for the conversion of agmatine to putrescine: (i) the agmatine ureohydrolase (SpeB) pathway, where agmatine is directly converted to putrescine (Chitrakar et al., 2021); (ii) the *N*-carbamoylputrescine pathway, which involves *N*-carbamoylputrescine production from agmatine mediated by agmatine deiminase, and its conversion to putrescine by *N*-carbamoylputrescine amidohydrolase (Landete et al., 2010). A novel putrescine production pathway is identified due to the intestinal acidification environmental caused by acid-producing bacteria, represented by *Bifidobacterium* spp., and there is a hybrid system for putrescine production composed of *Enterococcus faecalis* and *E. coli* in the mouse intestinal tract (Kitada et al., 2018). Interestingly, to survive and multiply within the GIT of the host, bacteria could adjust the expression and activity of polyamine biosynthetic enzymes in response to different environmental stresses and metabolic cues (Herrero del Valle et al., 2020).

Lys is originally thought to be degraded only via the pathway involving acetyl-CoA. Glutarate is an intermediate of Lys degradation in *P. putida* and is converted to acetyl-CoA to supply a C2 compound to the tricarboxylic acid (TCA) cycle. In accordance with that, Lys is traditionally viewed as a solely ketogenic AA. Recently, Zhang et al. (2018) have characterized a CoA-independent glutarate catabolism route that glutarate can be converted into succinate by CsiD and LhgO to supply a C4 compound to the TCA cycle, which could be confirmed by RB-TnSeq screening (Thompson et al., 2019). Moreover, recent work has shown that *E. coli K-12* also use CsiD to metabolize Lys into succinate, suggesting a possible conserved role for this pathway across bacteria (Knorr et al., 2018). Given the glutarate hydroxylation pathway provides a C4 compound for the TCA cycle more efficiently, it confers a competitive advantage over the pathway of acetyl-CoA. Based on the work results above, Lys could be viewed as a ketogenic and glucogenic amino acid in bacterial strains with both the glutaryl-CoA dehydrogenation pathway and the glutarate hydroxylation pathway.

His can be converted to histamine via histidine decarboxylase (HDC). Barcik et al. (2016) have detected the microbial-specific HDC from the fecal samples of 161 volunteers, and isolated histamine-secreting bacteria including *E. coli*, *M. morganii*, and *L. vaginalis* species. Also, Mou et al. (2021) annotated bacterial HDC in the Unified Human Gastrointestinal Genome (UHGG) and Genome Taxonomy Database (GTDB), and identified 117 putative histamine-secreting bacteria species including those in Fusobacteriota and Verrucomicrobiota where no histamine-secreting bacteria had been previously described. These findings provide an understanding of histamine-secreting bacteria in the human gut.

The role of AAs-gut microbe crosstalk in host immunity and related diseases

Studies suggest that AAs may regulate the development of osteoporosis (Ling et al., 2021), T2D (White and Newgard, 2019), and Parkinson's disease (Zhang et al., 2022b) through the alterations of gut microbes. In addition, Pro supplementation exacerbates depressive-like behavior in mice,

which is associated with microbial translocation (Mayneris-Perxachs et al., 2022). Leu supplementation markedly decreases microbiota richness and induces a shift in the F/B ratio, which is associated with the promoted SIgA secretion (Song et al., 2020). Glycine-based treatment ameliorates non-alcoholic fatty liver disease (NAFLD) by modulating the gut microbiome (Rom et al., 2020). The above studies show that the shift of gut microbiota caused by dietary AAs widely affects host immunity and related diseases.

In addition to affecting host physiology in a manner that alters gut bacterial diversity and abundance, microbial conversion of dietary substrates into small bioactive molecules represents an alternative regulatory mechanism. AAs catabolism by anaerobic bacteria yields numerous metabolites, including SCFAs, BCFAs, indoles, phenols, ammonia, and amines (O'Keefe, 2016). These bacterial metabolites have been demonstrated to influence various signaling pathways in epithelial cells and modulate immunity of host (Beaumont and Blachier, 2020).

SCFAs

SCFAs are derived mainly from the gut microbiota through the fermentation of dietary fiber and other complex carbohydrates. Indeed, they are also by-products of the bacterial metabolism of AAs as well. In anaerobic bacteria, Thr, Glu, Gly, Lys, ornithine, and Asp are converted to acetate, butyrate, and/or propionate (Neis et al., 2015). The immunomodulatory functions of SCFAs are summarized in the section of carbohydrate in modulating host immunity.

BCFAs

Compared with the extensive study of SCFAs, there is a paucity of published data about the impact of BCFAs on host health. It is worth noting that BCFAs are highly abundant in the cecum and colon (concentrations in the mmol L^{-1} range), and constitute approximately 5%–10% of the total SCFAs (Verbeke et al., 2015). Preliminary work has shown that isobutyric acid and isovaleric acid modulate glucose and lipid metabolism in primary adipocytes (Heimann et al., 2016). Recently, isovalerate is also reported to be a potent enterochromaffin (EC) cell stimulus that is detected by the olfactory receptor 558 (Olfr558). EC cell stimulation leads to voltage-gated Ca^{2+} channel-dependent serotonin release, and forms synaptic-like contacts with 5-HT_3R-expressing nerve fibers (Bellono et al., 2017). Therefore, isovalerate modulates 5-HT_3R-expressing primary afferent nerve fibers via synaptically-coupled endothelial cells. This finding clues an axis by which microbial-derived metabolites can be sensed by the enteric nervous system. To explore immune regulatory role of gut microbiota derived BCFAs, Guo et al. (2019) constructed a Δ*porA*/Δ*hadB* double mutant of *C. sporogenes*, eliminating the production of BCFAs (isobutyrate, 2-methylbutyrate, and isovalerate via Δ*porA* and isocaproate via Δ*hadB*) in the corresponding mice. Interestingly, the Δ*porA*/Δ*hadB*-colonized mice had an increased number of IgA-producing plasma cells and increased levels of IgA bound to the surface of a variety of innate immune cells, which uncover a role for the BCFAs in modulating IgA-related immune cells (Figure 4). In conclusion, the discovery of the regulatory role of BCFAs on primary afferent nerves and IgA-related immune cells indicates that BCFAs may play an important role in nerve communication and IgA-related diseases.

Moreover, it should be noted that the levels of BCFAs are tightly associated with BCAAs metabolism in bacteria (Li et al., 2017b). Therefore, the reduced BCAA uptake and/or BCAA catabolism in microbes (e.g., *Butyrivibrio crossotus* and *Eubacterium siraeum*) may lower concentrations of BCFAs. Given that the accumulated circulating BCAAs are a strong biomarker for insulin resistance and an increased risk of T2D, it is conceivable that the depletion of BCFAs may be involved in the process of insulin resistance and T2D. However, the understanding of the function of microbial-derived BCFAs is in its infancy, and the relevant mechanism still needs to be verified by further investigation.

Indole and indolic compounds

Indole is the most abundant tryptophan-derived microbial catabolite and presents at high amounts (250–1,100 μmol L^{-1}) in the gut. The commensal-secreted indole is crucial for the protective responses to gut pathogens. For instance, indole (secreted by commensal *E. coli*) lowers the chemotaxis, motility, and adherence of pathogenic *E. coli* to host intestine epithelial cells (IECs). In addition, indole attenuates inflammation (Bansal et al., 2010), and GF mice treated with indole display an enhanced resistance against dextran sulfate sodium (DSS)-induced colitis (Shimada et al., 2013).

Except for indole, microbial Trp metabolism produces large amounts of indole derivatives, for which the immunomodulatory activities have been extensively demonstrated (Figure 5). For example, *B. longum CCFM1029* converts Trp into indole-3-carbaldehyde (I3C) to suppress AhR-mediated aberrant T helper 2 type immune responses, alleviating atopic dermatitis symptoms (Fang et al., 2022). In addition, IAA promotes the expression of *Il10*, *Arg1*, and *Cyp1a1* in tumor-associated macrophages (TAM) and inhibits IFN-γ expression in $CD8^+$ T cells via AhR activation, and finally promotes pancreatic tumor growth (Hezaveh et al., 2022). This study warns patients with pancreatic ductal adenocarcinoma to limit their intake of foods high in Trp, and provides a new direction for more personalized pancreatic cancer treatment by reducing the proportion of indole-producing bacteria.

Edwardsiella tarda-derived IAld activates enteroendocrine cells (EECs) through transient receptor potential ankyrin A1

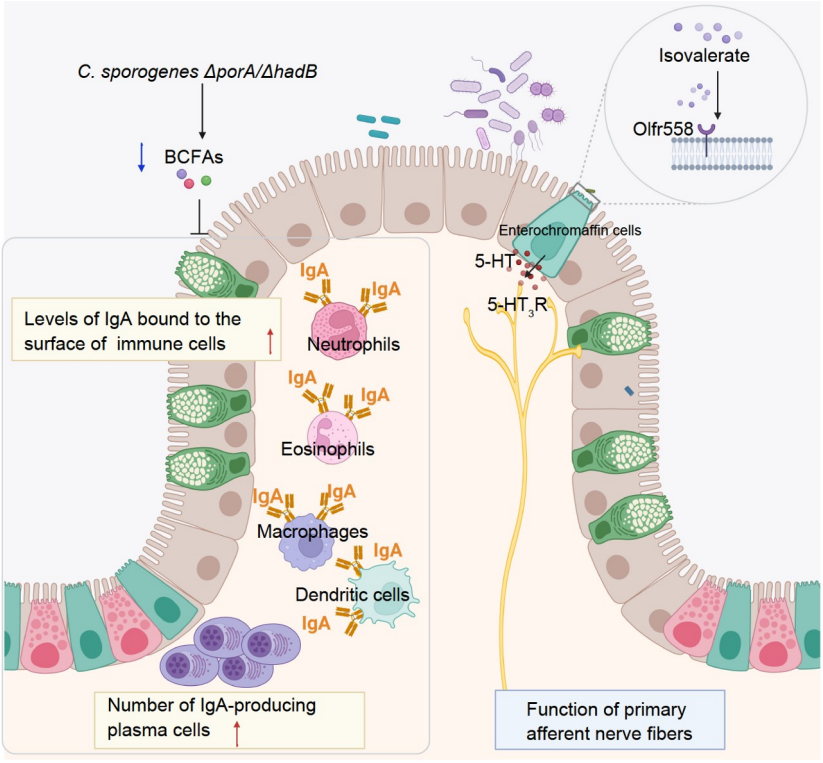

Figure 4 Immune modulatory properties of BCFAs converted from BCAAs by gut microbes. *C. sporogenes* Δ*porA*/Δ*hadB* colonization increases the number of immunoglobulin A-producing plasma cells and the levels of IgA bound to the surface of innate immune cells; isovalerate modulates the function of 5-HT_3R-expressing primary afferent nerve fibers via synaptically-coupled EC cells.; 5-HT, 5-hydroxytryptamine; 5-HT_3R, 5-hydroxytryptamine type 3 receptors. This figure was created using BioRender.com.

(Trpa1) and activates enteric cholinergic neurons by secreting the neurotransmitter 5-hydroxytryptamine (5-HT) to promote intestinal motility (Ye et al., 2021). The finding suggests that the intestinal epithelium senses microbial stimuli using epithelial sensory EECs, and EECs relay signals from intestinal microbes to the nervous system. Combined with the aforementioned studies that isovaleric acid is sensed by the enteric nervous system, it appears to be a greater diversity of EECs' functions than we have previously recognized. Given that specific host cells identify microbial metabolites of nutrients in the gut and transduce this information to the nervous system, future research should continue to elucidate microbial metabolites-enteroendocrine cell-nervous system-related mechanisms, which will facilitate endocrine cell-targeted therapy in the treatment of intestinal and nervous system-related diseases. In addition, IAld from *L. reuteri* contributes to AhR-dependent IL-22 transcription. The AhR-IL-22 axis provides colonization resistance to the fungus *Candida albicans* and mucosal protection from inflammation (Zelante et al., 2013). Thus, microbe-derived Trp metabolites may provide cues to the host that are crucial for resistance to colonization and for protection from mucosal inflammation (Zelante et al., 2021).

Indole-3-lactic acid (ILA) is also a product metabolized from Trp by *L. reuteri*, which actives the AhR in $CD4^+$ T cells, causing down-regulation of $CD4^+$ T cell transcriptional regulator ThPOK, and differentiation into $CD4^+CD8\alpha\alpha^+$ double-positive intraepithelial T lymphocytes (DP IELs) which take part in a variety of immune responses (Cervantes-Barragan et al., 2017). Data from IAld and ILA underscore that in the presence of Trp, *L. reuteri* is able to mediate the induction of a regulatory profile to control intestinal inflammation through AhR. These findings emphasize the important relationship among Trp, microbial metabolism, and gut immunity regulation.

C. sporogenes is reported to produce IPA from Trp. Dodd et al. (2017) found a significant increase in circulating *C. sporogenes*-specific IgG as well as secreted IgA levels in the caecum in mice colonized by the IPA-deficient fldC mutant compared with WT colonized-mice. These results show that the alterations of microbiota-derived metabolites initiate broad changes in host immune activation and pervasive changes in bacteria-specific humoral immunity.

Phenols

Tyr fermentation by intestinal bacteria generates p-cresol. In blood, p-cresol is circulated mainly as p-cresyl sulfate (pCS), a sulfate conjugate of p-cresol. *In vitro*, pCS down-regulates the percentage of Th1 cells and the production of IFN-γ (Shiba et al., 2014). *In vivo*, administration of pCS to mice

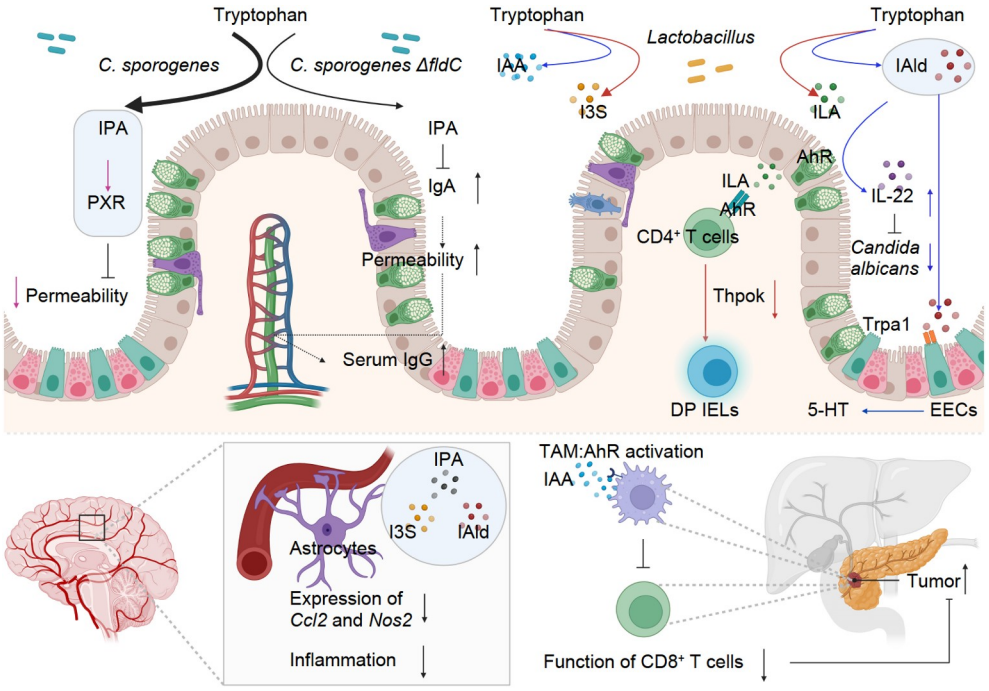

Figure 5 Immune modulatory properties of indole derivatives converted from L-tryptophan by gut microbes. IPA produced by *C. sporogenes* combines PXR to fortify the intestinal barrier; *C. sporogenes ΔfldC* increases the levels of lumen IgA and the circulating IgG, and the intestinal permeability; ILA actives the AhR in $CD4^+$ T cells and promotes the differentiation into DP IELs; IAld activates EECs and activates enteric cholinergic neurons by secreting 5-HT to promote intestinal motility; IAld contributes to AhR-IL-22 axis that provides colonization resistance to the fungus *Candida albicans*; IAA inhibits IFN-γ expression in $CD8^+$ T cells via the activation AhR of TAM, which finally promotes pancreatic tumor growth; IPA, IAld, and I3C suppress CNS inflammation. IgA, immunoglobulin A; IgG, immunoglobulin G; I3S, indoxyl 3-sulfate; ILA, indole-3-lactic acid; 3-IAld, indole-3-carboxaldehyde; AhR, aryl hydrocarbon receptor; DP IELs, $CD4^+CD8\alpha\alpha^+$ double-positive intraepithelial T lymphocytes; 5-HT, 5-hydroxytryptamine; EECs, enteroendocrine cells. This figure was created using BioRender.com.

with nephrectomy causes neurological disorders with increased oxidative stress and neuroinflammation (Sun et al., 2020), suggesting that pCS may be a therapeutic target for chronic kidney disease-associated CNS disorders. Clinical studies have showed that patients with chronic kidney disease (CKD) accumulate high concentrations of pCS in blood. Giving the high protein-binding properties of pCS, they could not be sufficiently removed by hemodialysis. Thus, the accumulation of pCS in the blood might be associated with mortality.

4EPS is a sulfate conjugate of 4EP, and enters brain to impair oligodendrocyte maturation in mice, and also decreases oligodendrocyte-neuron interactions in *ex vivo*. In addition, mice colonized with 4EP-producing bacteria exhibit reduced myelination of neuronal axons, and mice exposed to 4EPS display anxiety-like behaviors (Needham et al., 2022). These findings reveal that gut-derived 4EP influences complex behaviors in mice through affecting oligodendrocyte function and myelin patterning in the brain. pCS and 4EPS are the archetypical examples of the microbial molecules that impact brain activity and complex behaviors of animals. Therefore, it is not difficult to speculate that molecules with phenolic structures similar to pCS and 4EP (S) may have similar functions. However, the immunomodulatory functions of pCS and 4EP still need further investigations.

Amines

Polyamines (PAs), including putrescine and spermidine, are important metabolites of intestinal bacteria, which are present in mammalian cells in millimolar concentrations (putrescine is present in the intestinal lumen at 0.5 to 1 mmol L^{-1} concentrations in healthy humans).

Probiotic strain *lactis LKM512* is known to up-regulate the PA concentrations in intestinal lumen. Mice colonized with *LKM512* have a better colonic mucosal function with increased mucus secretion and better maintenance of tight junctions. Likewise, the expressions of aging- and inflammation-associated genes are downregulated in 21-month-old LKM512-treated mice, which resembles those in 10-month-old untreated mice (Matsumoto et al., 2011). Furthermore, intake of Arg with the probiotics *LKM512* long-term shows suppressed inflammation, improved longevity, and protection from age-induced memory impairment (Kibe et al., 2014). The above studies suggest that microbial-derived PAs are closely involved in alleviating inflammation and delaying aging-related physiological processes. Nakamura et al. (2021) concluded that the PAs derived from gut

microbes are absorbed by the host, which eventually increases intracellular PA levels. In mammalian cells, spermidine acts as a precursor of hypusine, a post-translational addition to eukaryotic initiation factor 5A isoform 1 (eIF5A) that is necessary to prevent ribosomal stalling in the translation of mRNAs encoding polyproline tracts and certain other amino acid combinations (Shin et al., 2017). In addition, the bacterial polyamines ameliorate symptoms of DSS-induced colitis in mice. This finding provides a potential therapeutic strategy for IBD, namely, manipulating microbial polyamine synthesis strains (e.g., *Bifidobacterium* spp.). Notably, PAs are essential for neoplastic cell function and replication as well. Dysregulation of PA metabolism is common in cancers. Recent data indicate that polyamines can establish a tumor-permissive microenvironment (Holbert et al., 2022). Moreover, bacteria-generated PAs in biofilms promote and potentiate cancer development (Johnson et al., 2015).

Tyramine is a trace amine that is reported to stimulate fast ileal contraction and neuropeptide Y release. A study *in vitro* demonstrated that tyramine induced by indigenous spore-forming bacteria elevates 5-HT biosynthesis, and increases *TPH1* expression in RIN14B cells subsequently (Yano et al., 2015). However, the physiological function of gut microbe-derived tyramine has not been extensively reported.

Ammonia

The colonic epithelium is constantly exposed to ammonia in millimolar concentrations (Verbeke et al., 2015). Research has shown that ammonia is involved in the down-regulation of monocarboxylate transporter 1 (MCT1) gene expression in the colon of pigs, wherein MCT1 plays a critical role in lactate shuttling, and is known to contribute to cancer development through multiple mechanisms (Kumagai et al., 2022). Accordingly, ammonia seems to have the beneficial potential to inhibit the development of cancer by inhibiting the expression of MCT1. Also, ammonia is transported into the portal vein, where it enters the liver and is then re-synthesized into urea. Urea enterohepatic circulation facilitates to maintain a low concentration of ammonia in human blood (Chen et al., 2020b). When enterohepatic circulation is cut off, the ammonia concentration in the blood is increased. It is demonstrated that ammonia accounts for cognitive disorders, and lower blood ammonia level is beneficial for recovering cognitive impairment (Balzano et al., 2020). Together, it is certain that high-protein diets might increase the concentration of ammonia in the intestinal lumen, and excess ammonia in the blood participates in the gut-brain axis dialogue to regulate the CNS homeostasis and the related inflammation.

In conclusion, dietary AAs and the gut microbiota are increasingly recognized to cross-regulate and entrain each other, and thus affect host health and immune-mediated diseases. However, we are still lacking a comprehensive understanding of how gut microbiota bridges dietary AAs and host immunity. For example, some certain AAs that are not involved in protein synthesis (e.g., γ-aminobutyric acid (GABA)) orchestrate immune cell fates (including macrophages, T cells, and B cells) (Liao et al., 2022; Ren et al., 2019; Xia et al., 2021b) and/or intestinal epithelial cell homeostasis (Xia et al., 2019), and there exists a crosstalk between GABA and intestinal microbiota (Strandwitz et al., 2019); nevertheless, whether and how gut microbiota mediates the roles of GABA in directing host immunity is unknown. Moreover, the main Trp-associating metabolite-melatonin is well demonstrated to affect immune cell functions (Du et al., 2022; Xia et al., 2022); however, only little attention has been paid to the interaction of melatonin and gut microbiota in dictating host immunity as well as the inflammatory diseases (Liu et al., 2020c; Xia et al., 2023; Zhai et al., 2021). Notably, given the complex interactions between the AAs and gut microbiota, multi-omics methods, for example, spatial-omics (transcriptomics, proteomics, and metabolomics), may be essential tools to improve our understanding of the AAs and gut microbiota in determining host health and immune-mediated diseases.

Gut microbiota bridges dietary carbohydrates and host immunity

There is a debate on the amount and type of dietary carbohydrates required for intestinal health (Chandel, 2021). Dietary carbohydrates in cereals contain a variety of different chemical compounds (Coker et al., 2021), and different dietary carbohydrate requires different metabolic processing/digestion, which elicits different metabolic responses (Chandel, 2021).

Polysaccharides with a degree of polymerization (DP)>9 units could either be digestible by amylolytic enzymes produced in mouth and small intestine (Ye et al., 2022). On the other end, there are many of complex polysaccharides that cannot be digested in the small intestine but partially fermented by the intestinal microbiota (Makki et al., 2018). The non-digestible fermentation polysaccharides are functionally known as microbiota-accessible carbohydrates (MACs) that could be classified into two categories, including structurally complex and utilized by a narrow group of gut bacteria, and structurally simple and utilized by many gut bacteria (O'Grady et al., 2019; Song et al., 2021).

Dietary MACs are the major substrates for the commensal bacteria in the GIT, particularly the colon (Cronin et al., 2021) and the capability to utilize and process MACs in the diet is responsible for the maintenance and survival of gut microbiota. The amount, chemical, and physical characteristics of the dietary MACs arriving in the lower gut are the

principal drivers of the composition/diversity of the gut microbiome (Cronin et al., 2021; Shang et al., 2018). Particularly, different types of MACs can regulate the composition of gut microbiota by increasing beneficial intestinal microbes (Cai et al., 2020b; Fernandez-Julia et al., 2021) and reducing harmful intestinal microbes that can affect pH and composition of digesta and have been linked to IBD outcomes. Interestingly, MACs are fermented by specific intestinal microorganisms that encode microbial hydrolytic enzymes, releasing bound compounds and nutrients that can be utilized by the body (Holscher, 2017; Shang et al., 2018). Fermentation of carbohydrates leads to the production of the final products such as SCFAs and secondary metabolites, which are metabolized and absorbed in the epithelial cells and are used by the host as energy substrates (Moscoviz et al., 2021; Porter and Martens, 2017). These MACs-induced microbial changes and fermentation products have attracted a lot of attention as they have been shown to have numerous benefits including providing the energy requirements of colonocytes, influencing gene expression, and modulating the immune system (Daïen et al., 2017; Porter and Martens, 2017). The present review will focus on how dietary MACs shape the structure and function of intestinal microbiota, which exerts a considerable effect on host metabolism and immune homeostasis, especially in the associated disease development.

Influence of dietary MACs on gut microbiota

Influence of dietary MACs on microbial ecology in the gut

Different intestinal microorganisms have great differences in degrading different types of MACs (Akkerman et al., 2019; York, 2019). Considering the diversity of bacteria and their widespread distribution in the environment, the research on the utilization of MACs has been attracting much attention. The intestinal bacterial species that have been reported to have the ability to utilize MACs include Bacteroidetes, Firmicutes, and Actinobacteria (Delzenne and Bindels, 2020). Specifically, Firmicutes and *Bacteroides* dominated in the human and animal intestine can easily utilize MACs as energy sources to produce specific metabolites that selectively stimulate the growth of the beneficial bacteria and inhibit the growth of some harmful bacteria (Seal et al., 2021). The main Bacteroides with polysaccharide utilization ability are *Bacteroides thetaiotaomicron*, *Bacteroides cellulosilyticus*, *Bacteroides ovatus*, *Prevotella ruminicola*, and *Prevotella bryantii* in human and bovine intestine. The main Firmicutes with polysaccharide utilization ability are *Roseburia intestinalis*, *Butyrivibrio fibrisolvens*, *Ruminococcus bromii*, and *Ruminococus flavefaciens* (Wardman et al., 2022). Therefore, the relative abundance, composition and diversity changes of gut microbiota are determined by the availability of MACs in a rapid and reversible manner.

Bacteroides multiforme is a group of bacteria that digest complex carbohydrates at the end of the human large intestine (Cantu-Jungles et al., 2021; Turroni et al., 2018). This group of bacteria encoded enzymes related to polysaccharide hydrolysis that can degrade more than a dozen different types of polysaccharides (Wardman et al., 2022). When the carbohydrate content in food decreases, *Bacteroides polymorphus* can use the endogenous polysaccharide in intestinal mucus, and increase the utilization rate of mucopolysaccharide by changing its different gene expression, to meet the energy requirements of the body (Schwalm and Groisman, 2017; Wang et al., 2021b). Dietary MACs with high intake result in a significant increase in the abundance of *Bacteroides* (especially *Prevotella* and Xylobacter) and the level of SCFAs in feces, which is related to the consumption of chlamydomycetes and lower fecal pathogen abundance, such as *Escherichia* and *Shigella*. In contrast, low intake of MACs reduces the proportion of butyrate-producing Firmicutes and Actinomycetes, while increases the proportion of *Bacteroides* spp. and the reduction of gene diversity of the whole microbiome, which might have harmful effects on human health (Koh et al., 2016; Oliver et al., 2021).

MACs-restricted diets lead to lower diversity and distinct community composition in the large intestine (Sonnenburg et al., 2016). Under low dietary MACs conditions, the abundance of mucin-degrading bacteria, including mucin-degrading specialists and generalists, rapidly increases (Desai et al., 2016). Specifically, dietary fiber deprivation induces the reduction of *Bacteroidetes S24-7 family*, *Bifidobacterium*, and the expansion of *Ruminococcaceae*. Importantly, xylan supplementation promotes the proliferation of *Bifidobacterium pseudoctenulatum* and increases SCFAs concentration in both ileum and feces. An elevated abundance of xylan degradation-related enzyme genes is also observed in the gut microbiome after xylan supplementation. *In vitro* growth assay further verifies the xylan utilization and SCFAs production capacity of *B. pseudocatenulatum* (Wang et al., 2021c). Xylo-oligosaccharide, considered as a potential prebiotic, modulated gut microbiota composition by significantly stimulating *Bifidobacterium animalis*, and reducing *Salmonella* counts (Pang et al., 2021). Dietary fiber intake can effectively compensate for the impact of high-fat diet (HFD), which is conducive to the maintenance of body health, and also contributes to the prevention and treatment of IBD (Fischer et al., 2020; Kim et al., 2020). These data show the plasticity of human intestinal microbiota to dietary MACs changes and the potential impact of these changes on human health.

Role of carbohydrate-active enzymes in the gut microbiome

MACs can be utilized by a variety of microorganisms, and their degradation mechanisms underlying MACs are different. Some members of the colonic microbial community

exhibit profound flexibility as they encode numerous enzymes that can contribute to the degradation of multiple MACs subtypes. Enzymes that act on various glycoconjugates, oligosaccharides, and polysaccharides are collectively referred to as carbohydrate active enzymes (CAZymes). According to the characteristics and functions of enzymes, CAZymes are divided into glycoside hydrolases (GHs), glycosyltransferases (GTs), polysaccharide lyases (PLs), carbohydrate esterases (CEs), auxiliary activities (AAs), and carbohydrate-binding modules (CBMs) (Lombard et al., 2014). Three common patterns of MACs utilization are free enzymes secreted and expressed extracellular, fibrosomes, and polysaccharide utilization sites, which mainly with CAZymes, supplemented by binding and transporters involved in various polysaccharide utilization patterns (Lombard et al., 2014). Polysaccharide utilization sites are a group of gene clusters that encode proteins related to polysaccharide metabolism. Polysaccharide utilization sites can be cascaded to achieve efficient degradation of polysaccharides. The cascade process begins with the recognition and binding of extracellular polysaccharides, and then is degraded into oligosaccharides and oligosaccharides or monosaccharides with smaller molecular weight, which are transported to the cytoplasm for storage or utilization (Wardman et al., 2022). A specific MACs type may require multiple steps of enzymatic catalysis in order to yield an SCFA product (Fu et al., 2019). Thus, numerous microbes may be required in order for the host to benefit fully from these reactions.

Ruminococcus flavefaciens can degrade cellulose in food by secreting cellulase and further assembling into cellulosomes (extracellular multienzyme complex) (Wardman et al., 2022). *B. animalis* subsp. *lactis* can use its own ABC transport system to transport xylooligosaccharides into cells, and further degrade xylooligosaccharides through the related enzymes (Sun et al., 2022). However, there are few studies on the specific mechanism of carbohydrate metabolism in intestinal microbiome. This problem can be solved by combining omics and bioinformatics in the future.

During the long-term evolution, intestinal flora will respond to the changes in food types and adapt to specific diets by adjusting the content of certain digestive enzymes (Ray, 2018). There is a high content of *Clostridium* in the intestines of giant pandas, with capable of degrading cellulose (Jin et al., 2021). Moreover, the data of metagenomics also find that compared with other herbivorous animals (kangaroos, termites, and cattle), the intestinal flora of giant pandas contains diminished levels of cellulase and hemicellulase, which reflects the low digestibility of cellulose and hemicellulose in the diet of giant pandas when eating bamboo. It shows that the gut of giant pandas is still a typical structure of carnivores. However, cellulose and hemicellulose degrading bacteria in the gut have adapted to the high fiber bamboo diet (Jin et al., 2021; Yang et al., 2018). The composition of intestinal microbes in wild mammals usually changes dynamically with the seasonal fluctuation of food, and such changes are often adapted to eating habits. The seasonal changes (winter, spring, and summer) of intestinal flora have been investigated in wild black howler monkeys (*Alouatta pigra*). It is found that the intestinal flora of black howler monkeys in spring is characterized by high content of *Prevotella*, which utilize polypeptides and iron elements as substrates. The content of protein bound tannic acid and iron in the leaves mainly fed in spring is higher than that in other seasons. Therefore, polypeptides and iron elements can be used by *Prevotella* when they arrive in the large intestine, indicating that this dynamic change of intestinal microbes in black howler monkeys is related to the seasonal change of their dietary habits (Amato et al., 2015). However, whether the seasonal changes of intestinal microbes in wild mammals are still affected by habitat changes, biological rhythms, and other factors need further exploration.

Microbial cross-feeding is beneficial for the fermentation of dietary MACs

MACs with complex structure can be degraded into SCFAs by specific degrading bacteria and reduce the pH of GIT (Figure 6). Most degrading bacteria are beneficial microorganisms and can inhibit the proliferation of pathogenic bacteria (Ho Do et al., 2021). However, due to the differences in the properties, structures and monosaccharide compositions, different types of MACs have different effects on intestinal microbial composition and diversity. Specific species of microbes in the gut possess the enzymatic machinery to degrade complex carbohydrates (Flint et al., 2012). An extensive range of microbial enzymes facilitates gut bacteria to extract carbon from MACs or endogenous mucus in the diet as an energy source (Wardman et al., 2022; Ye et al., 2022). Therefore, dietary MACs can have a profound impact on the composition, diversity, and abundance of the microbiome. A large number of microbial communities defined as MACs fermenters in the large intestine can decompose different types of dietary MACs. Among them, some bacteria can degrade MACs with high specificity, and are so-called primary degrading bacteria or key-stone species. Moreover, the primary degrading bacteria ferment dietary MACs to produce some secondary products that are used by other microorganisms, in a mechanism called cross-feeding (Hirmas et al., 2022; Lindstad et al., 2021). Cross-feeding is beneficial to the key-stone species themselves and other secondary fermenters from the catalytic labor carried out by the primary degraders (Fagundes et al., 2021). Further studies are required to establish these relationships in the process of cross-feeding by fully breaking down of dietary MACs types. *Bacteroides*, an important MAC-degrading

bacterium, degrades arabinoxylan into small molecules of nutrients in the anterior colon, which are then fermented and metabolized by *Bifidobacterium*, *Lactobacillus* and other microorganisms, via cross-feeding (Yasuma et al., 2021). Dietary β-glucan can also selectively promote the proliferation of *Bifidobacterium*, *Lactobacillus* and other butyric acid-producing bacteria, but inhibits the growth of *Lachnospiracea_XPB_1014_Group* and *Bacteroides* after fermentation *in vitro* (Bai et al., 2021b). Hence, dietary MACs will not only impact MAC-dependent bacteria but also the growth of such cross-fed bacteria.

The role of dietary MACs-gut microbe crosstalk in host immunity

Diet composition, as well as changes in gut microbiota, can profoundly impact immune function. Significant advances have been made in recent years to understand the impact of MACs on the immune system (Daïen et al., 2017); however, much of the focus has been on high-MAC diets with little insight on the impact of MAC deprivation on the immune system. A comprehensive survey of MAC enrichment *vs*. deprivation is essential for deciphering how specific immune pathways are regulated under varied dietary habits, and whether MACs play a preventative or corrective role in various diseases.

Epithelial cells in the intestine have been reported to take up SCFAs via both active and passive mechanisms with the help of monocarboxylate transporters, which are either sodium-dependent or -independent (Wu et al., 2017). These transporters transfer bacterial metabolites into the cytosol of the epithelial cells, and as a result, the majority of butyrate is metabolized, whereas propionate is taken up by the liver for the metabolism of cholesterol and other activities (Dalile et al., 2019). SCFAs increase the production of cytokines and chemokines, including TNF-α, IL-6, CXCL1 and CCL10, by colon epithelial cells (Kayama et al., 2020). SCFAs produced by bacteria alter neutrophils by regulating the production of inflammatory mediators such as TNF-α, and IL-17 and neutrophil chemoattractants such as CXCL1 and CXCL8, which are involved in the activation of endothelial cells (Abdalkareem Jasim et al., 2022). Neutrophils have been reported to exert an inhibitory effect on the production of TNF-α in the presence of TLR and SCFAs (Vinolo et al., 2011a). However, another study has shown that neutrophils increase the production of CXCL8 in the presence of TLR2 and SCFAs (Vinolo et al., 2011b). Moreover, SCFAs modulate neutrophil activity by suppressing their migratory behavior while shifting their microbial killing phenotype toward increased phagocytic activity with diminished proinflammatory cytokine production (Rodrigues et al., 2016).

As well as epithelial cells and neutrophils, SCFAs also regulate monocytes and macrophages (Corrêa-Oliveira et al., 2016). SCFAs have been reported to exert an anti-inflammatory effect by inducing the production of cytokines and prostaglandin E2 by human monocytes *in vitro*. Of note, SCFAs significantly reduce the production of lipopolysaccharide (LPS)-induced TNF-α, IL-1β, and IL-6 in the murine macrophage cell line RAW264.7 (Liu et al., 2012). Butyrate has exerted an inhibitory effect on the production of TNF-α by RAW264.7 cell lines and displayed an anti-inflammatory effect in bone marrow-derived macrophages (BMDMs) (Lee et al., 2017a). Therefore, it is not surprised that SCFAs could facilitate the polarization of macrophages toward an M2 phenotype (Wang et al., 2020c).

Dendritic cells treated with butyrate have been reported to exert a weaker stimulatory effect on T cells and reduce the production of IL-12 and IFN-γ (Nastasi et al., 2017). Moreover, butyrate could reduce the expression of surface markers (CD40, CD80, and CD86) on dendritic cells (Berndt et al., 2012). The butyrate-induced activation of GPR109 in macrophages and dendritic cells is helpful for maintaining the balance between pro- and anti-inflammatory $CD4^+$ T cells (Singh et al., 2014). Likewise, SCFAs promote the generation of Tregs from dendritic cells and T-lymphocytes. Propionate has been reported to modify hematopoiesis and increase the production of precursors of macrophages and dendritic cells with an increase in phagocytic activity and a decrease in the expression of MHC-II and CD40 (Trompette et al., 2014), and moderately ameliorates cardiac hypertrophy in hypoxic rats (Pan et al., 2022). In contrast, acetate largely bypasses colonic and liver metabolism and is metabolized by peripheral tissues (e.g., muscle). A high-fiber diet and the administration of acetate have been reported to protect against the development of allergic airway disease in mice (Arrieta et al., 2015). Acetate, propionate, and butyrate have been reported to enhance the polarization of naive T cells to Tregs (Abdalkareem Jasim et al., 2022) and also to promote the generation of Th17 and Th1 effector cells under *in vitro* conditions (Park et al., 2015).

Subpopulations of immunosuppressive Tregs play an essential role in both the maintenance of immunotolerance and, ultimately, the prevention of many associated disease development (Kim, 2021). Microbiota-derived SCFAs, particularly butyrate and propionate, have been demonstrated to encourage immunotolerance through expansion and differentiation of Tregs (Arpaia et al., 2013). This process has been shown to occur through GPR43-dependent signaling, as well as through the epigenetic regulation of the Foxp3 promoter through inhibition of histone deacetylase (Luu and Visekruna, 2019). This systemic immunoregulatory effect is thought to be determined largely by the immunologic context (Trapecar et al., 2020). For example, in a state of infection, SCFAs enhance the differentiation of pro-inflammatory T-helper cell subsets (e.g., Th1 and Th17 cells) instead of Tregs

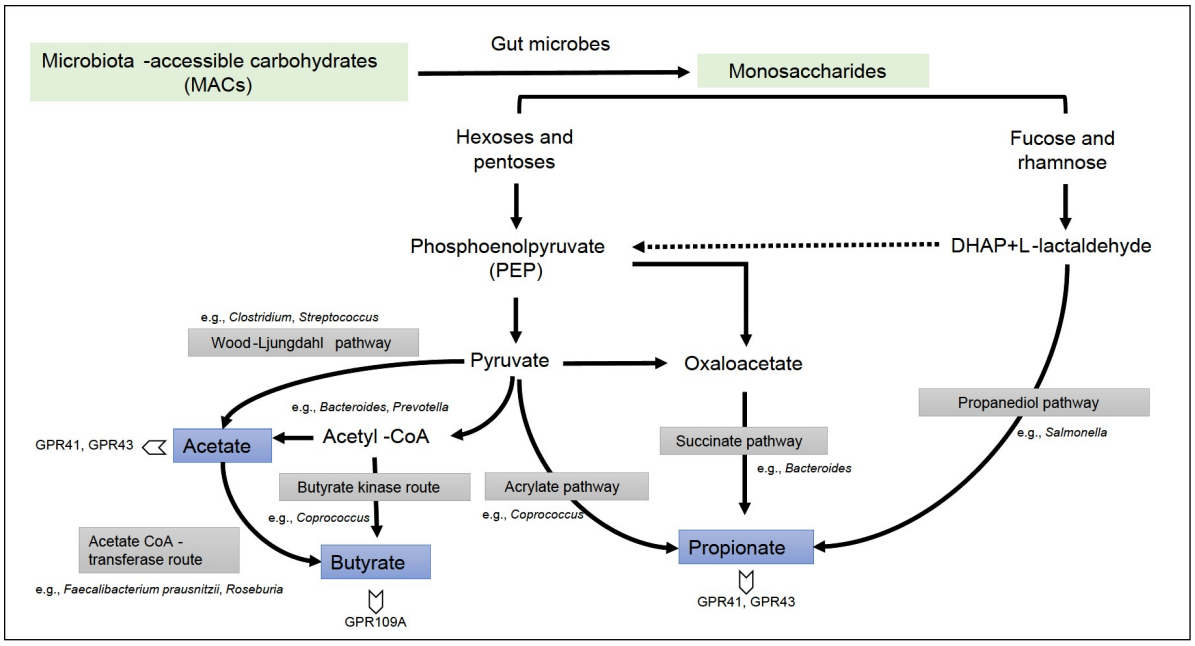

Figure 6 Interaction between fermentation products of dietary MACs and gut microbiota. MACs with complex structure can be degraded into metabolites by specific degrading bacteria in order to yield end products involved in host health.

(Park et al., 2015). This suggests that SCFA production from the fermentation of NDFCs may play an intricate role in host immune responses to infection. The immunoregulatory effect of SCFAs is, however, not solely reliant upon an expansion of Tregs and can occur in organ systems throughout the body (e.g., lungs and skin) (Sun et al., 2017). Furthermore, SCFAs act directly on plasma to enhance the production of IgA, both by acting as an energy source and by upregulating the expression of genes necessary for plasma cell differentiation (Wu et al., 2017). SCFAs can also act on nonimmune cells to stimulate the release of antimicrobial peptides. Within the pancreas, SCFAs act on pancreatic β-cells in a GPR-dependent manner to enhance the secretion of cathelicidin-related antimicrobial peptide, which ultimately induces Treg cell expansion and protects against the development of autoimmune diabetes. Although additional research is needed, these animal and *in vitro* models elegantly illustrate the central mechanisms by which microbiota-derived SCFAs reduce inflammation.

In conclusion, MACs consumption not only has beneficial impacts on gut microbiota in particular but also on the host as a whole (Daïen et al., 2017) (Figure 7). Although much work remains to be done to further understand dietary MACs-microbiome interactions, this remains the most promising and cost-effective method to reduce the burden of metabolic disease, and it is imperative that habitual MACs intakes are increased to current recommendations in Western societies. A greater understanding of what types of MACs are most efficient at diversifying the microbiota and promoting the production of SCFAs, how different types of dietary MACs influence gut microbiota composition and gut metabolome, as well as the biological mechanisms at play that influence host physiology, and how much MACs should be consumed to optimize maintenance of health, or to treat different types of inflammatory diseases, will be required to devise future recommendations regarding dietary fiber intervention as an adjunct therapy to treat metabolism and immune-related diseases.

Gut microbiota bridges dietary fat and host immunity

Dietary fat modulates the microbial composition and, in turn, gut microbiota affects fatty acid metabolism of host (Duan et al., 2022). Microbial metabolites derived from dietary fat are involved in modulating various physiological processes (Chadaideh and Carmody, 2021; Choi et al., 2021). Notably, studies have revealed that fat-induced alterations in gut microbiota are differential due to the amounts and types of dietary fat (Merra et al., 2021; Xu et al., 2022). Furthermore, dietary fat has been reported to be associated with the development of inflammation by altering gut microbiota and damaging intestinal barrier integrity (Fritsch et al., 2021; Zhang et al., 2021b).

Here, we provide an overview of the impacts of different amounts and types of dietary fat on gut microbiota. Next, we discuss the potential underlying mechanisms by which gut microbiota is involved in the dietary fat-mediated inflammation.

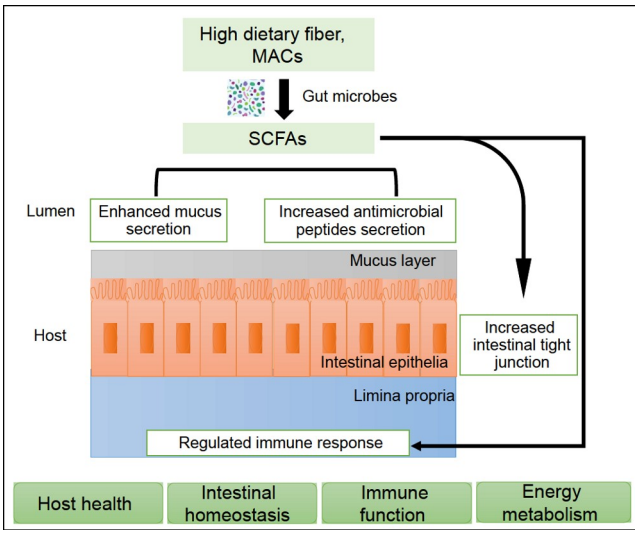

Figure 7 Impact of SCFAs on host metabolism, immune function, and inflammatory bowel disease. The fermentation of MACs generates SCFAs, mainly including acetic acid, propionic acid and butyric acid, under the action of anaerobic microorganisms in large intestine. SCFAs play an important role in maintaining host energy homeostasis, metabolism, immune function and inflammatory bowel disease.

Effects of dietary fat on gut microbiota

Interaction between dietary fat and gut microorganisms participates in various physiological processes (Daniel et al., 2014) (Figure 8). Recently, intestinal microecological disorders and chronic diseases caused by improper dietary fat intake have become a research hotspot. The following section elaborates on how dietary fat regulates the structure and function of intestinal microbiome, thus affecting host health.

Fat level

Dietary fat is the second primary source of dietary energy from 10% to 58% for modern humans (Chadaideh and Carmody, 2021). It has been reported that both short-term and long-term HFD treatment have the ability of altering microbial communities and thus resulting in metabolic disturbances in mice and humans (Frazier et al., 2022; Wan et al., 2019). In addition, animal and clinical studies have revealed the effects of different fat levels ranging from 5% to 70% energy on gut microbiota (Liu et al., 2016; Wan et al., 2019). Furthermore, HFD alters the production and transformation of gut microbiota-associated metabolites, such as SCFAs and bile acids (BAs) (Parséus et al., 2017; Wei et al., 2020), which in turn plays a key role in regulating lipid metabolism and absorption. GF mice have impaired small intestinal lipid digestion and absorption, which protects the mice against from HFD-induced obesity (Martinez-Guryn et al., 2018). Notably, GF mice received microbiota from HFD-fed mice have higher lipid absorption than those received microbiota from low-fat diet (LFD)-fed mice, regardless of whether they were fed with HFD or LFD (Martinez-Guryn et al., 2018). These data demonstrate that HFD-altered microbiota has the ability of enhancing lipid absorption.

However, the large intestine and feces are more frequently selected to investigate the taxonomical alterations in gut microbiota induced by HFD. HFD (45% and 60% energy) increases the F/B ratio in mice and rats (Li et al., 2021a; Yin et al., 2018). Furthermore, a study showed that Firmicutes can harvest higher energy from the diet than Bacteroidetes (Turnbaugh et al., 2006), which might explain the higher body weight gain induced by HFD. In contrary, others reported decreased F/B ratio in rats fed an HFD (35% energy) (Ortega-Hernández et al., 2020). Similarly, HFD (40% energy) decreases the F/B ratio in healthy young adults (Wan et al., 2019). The inconsistent results underscore that the effects of HFD on F/B ratio depend on fat level. At lower taxonomical levels, HFD is always associated with increased abundance of harmful bacteria, such as *Clostridium*, *Turicibacter*, and *Ruminococcaceae* (belong to Firmicutes phylum) in mice and rats (Bai et al., 2022; Wang et al., 2022b). Additionally, HFD is able to decrease the abundance of some beneficial bacteria, such as *Lactobacillus*, *Muribaculaceae*, *Alistipes*, and *Akkermansia* in mice and rats (Bai et al., 2022; Wang et al., 2020a; Wang et al., 2022b). Collectively, these data confirmed that the level of fat have complex influences on gut microbiota. Of note, some specific microbial changes at genus or species level might be more reliable than F/B ratio.

Fat type

Evidence from animal models and humans demonstrated that even if total fat intake is comparable, the saturation degree, as well as the location of carbon double bound of fat may influence the gut microbial diversity and composition. Identification of specific fatty acids and associated effects on gut microbiota is necessary to better understand the impacts of dietary fat on host health. The following section outlines this information.

(1) Saturated fatty acids. SCFAs are saturated fatty acids (SFAs) that contain 1–6 carbons. The most common SCFAs are acetate, propionate, and butyrate. It has been reported that some species from *Acetobacteraceae*, *Precottella*, *Ruminococcus*, *Bifidobacterium*, *Bacteroides*, *Clostriudium*, *Streptococcus* contribute to the synthesis of acetate; some species from *Akkermansia* and *Bacteroides* have the ability of producing propionate; *Faecelibacterium* and *Rumincoccus* species are responsible for the butyrate production (Nogal et al., 2021; van der Hee and Wells, 2021). Butyrate treatment increases the richness and diversity of gut microbiota, as evidenced by increasing the abundance of *Lactobacillus*, *Butyricicoccus*, and *Meganonas*, and decreasing the abundance of *Bacteroides*, *Klebsiella*, and *Haemophius* in mice with cerebral ischemic stroke (Chen et al., 2019). Moreover, sodium butyrate has been demonstrated

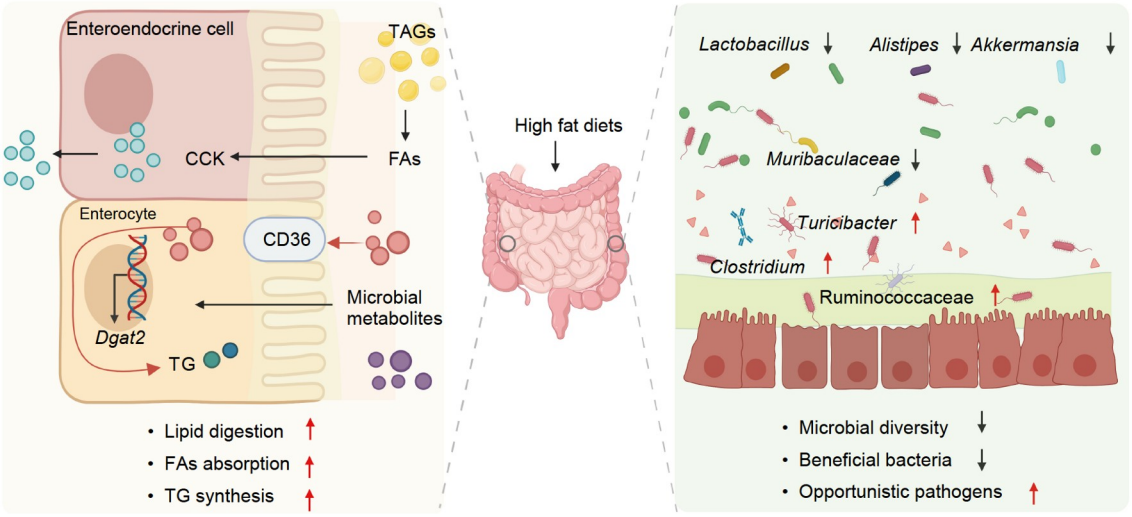

Figure 8 Schematic presentation of effects of HFD on gut microbiota. In the small intestine, HFD-altered gut microbiota increases fatty acid intake via three ways: (i) enhancing fatty acid absorption by upregulating the expression of fatty acid translocase CD36; (ii) increasing TG synthesis by upregulating the expression of diacylglycerol O-acyltransferase 2 (Dgat2); (iii) promoting lipid digestion through cholescystokinin (CCK)-related signaling. In the large intestine, HFD increases the abundance of opportunistic pathogens and decreases the abundance of beneficial bacteria. This figure was created using BioRender.com.

to increase the abundance of *Allobaculum* and *Desulfovibrio* while decrease the abundance of *Oscillospira*, *Helicobacter*, *Parabacteroides*, and *Mucispirillum* in mice with *Helicobacter pylori*-induced inflammation (Huang et al., 2021). A clinical study showed that butyrate intake could alter the proportion of *Lachnospiraceae* and *Bacteroides* in lean people, while change *Coriobacteriaceae* and *Clostridiales cluster XIVa* in patients with metabolic diseases (Bouter et al., 2018). Propionate could enhance the abundance of *Verrucomicrobia* in the small intestine, but fail to affect the gut microbiota in the large intestine in mice (Brütting et al., 2021). Although the studies revealing the effects of SCFAs on gut microbiota are too limited, the present data suggest that there is a bidirectional relationship between SCFAs and gut microbiota. Furthermore, given the potential protective effects of SCFAs on host metabolism and inflammation, therapies targeted on SCFAs modulation via dietary supplementation or regulation of SCFAs-producing microbiota have received increasing attention.

Medium-chain fatty acids (MCFAs) contain 7–12 saturated carbons. The most common MCFAs are caprylic (C8:0), capric (C10:0), and lauric (C12:0) acids. Dietary coconut, palm kernel, and human milk are major sources of MCFAs. MCFAs (caprylic and capric acid) could increase the jejunal *Escherichia-Hafnia-Shigella* and colonic *Clostridial cluster XIVa* in piglets (Zentek et al., 2013). Treatment with salts of MCFAs distilled from coconut oil is supposed to increase the abundance of Fibrobacteraceae and *Fibrobacter* while decrease the abundance of *Dialister*, *Lachnobacterium*, and *Butyrivibrio* in piglets with pathogenic infection (López-Colom et al., 2019). A study using *in vitro* gastro-intestinal digestive systems has shown that Coconut oil enriched with MCFAs increases the abundance of *Escherichia*, *Dialister*, and *Clostridium sensu stricto 1*, but decreases the abundance of *Muribaculaceae* and *Streptococcus* (Gu et al., 2020).

Long-chain fatty acids (LCFAs) contain 13–18 carbons. The most common dietary LCFAs are myristic (C14:0), palmitic (C16:0), and stearic (C18:0). Dietary coconut, palm olein, human milk, pumpkin, and sesame are major sources of LCFAs. Chen et al. (2015) suggested that LCFAs can be metabolized by *Lactobacillus* and thus can promote the growth of *Lactobacillus*. It has been reported that the combination of medium- and long-chain triacylglycerols decrease the F/B ratio and the proportion of Proteobacteria in mice with diet-induced obesity (Zhou et al., 2017). In an *in vitro* gastro-intestinal digestive system, beef tallow rich in LCFAs decreases the abundance of *Stretococcus* and *Allisonella*, but increases the abundance of *Acidaminococcus* and *Parasutterella* (Gu et al., 2020).

Overall, these findings suggest that dietary SFAs exert diverse impacts on microbial composition, which might contribute to protective effects on host metabolism and inflammation. However, future clinical researches are warranted to find out whether dietary supplementation with fat has similar positive effects on humans.

(2) Monounsaturated fatty acids. Monounsaturated fatty acids (MUFAs) consumption has been shown to have beneficial health effects by modulating gut microbiota. For example, MUFAs derived from fish oil decrease the F/B ratio while increase the abundance of *Akkermansia*, and thus improving metabolism in mice with atherosclerosis (Tsutsumi et al., 2021). Extra-virgin olive oil (EVOO) is enriched with MUFAs, especially oleic acids. Mediterranean diet rich in EVOO is a typically MUFA-rich diet. It has been reported

that the Mediterranean diet is able to increase the abundance of microbiota associated with short- and branch-chained fatty acid production, such as *Roseburia*, *Eubacterium*, *Bacteroides thetaiotaomicron*, *Prevotella copri*, and lactic acid bacteria, which might contribute to alleviating inflammation and metabolic syndrome in humans (Ghosh et al., 2020; Luisi et al., 2019). Both EVOO and high oleic peanut oil (HOPO) could increase the abundance of *Bifidobacterium*, which has the ability of improving lipid metabolism in HFD-fed mice (Zhao et al., 2019). Similarly, EVOO supplementation promotes the growth of beneficial microbiota (e.g., *Lactobacilli* and *Clostridia* XIVa) (De Filippis et al., 2016; Ghosh et al., 2020). However, in addition to oleic acids, some other compounds in EVOO, such as phenols, that also have the ability of altering gut microbiota. A randomized, controlled, double-blind, crossover human trial showed that the ingestion of EVOO containing a mixture of olive oil and thyme phenolic compounds for 3 weeks remarkably enhances the abundance of *Bifidobacteria* compared with participants who supplemented only phenolic compounds from EVOO (Martín-Peláez et al., 2017), suggesting that the beneficial effects of EVOO on gut microbiota can be, at least partly, due to oleic acid. Together, these data indicate that MUPAs have the ability of promoting the growth of beneficial microbiota, and thus contribute to improving metabolism and alleviating inflammation.

(3) Polyunsaturated fatty acids. Effects of a diet rich in n-3 polyunsaturated fatty acids (PUFAs) on gut microbiota are controversial. A recent study showed that dietary fish oil rich in n-3 PUFAs, especially DHA and EPA, elevates the abundance of Bacteroidetes and Prevotellaceae and decreases the abundance of butyrate-producing bacteria, which is associated with the protective effects of fish oil on depressive phenotype in maternally separated rats (Egerton et al., 2022). In contrast, supplementation with n-3 PUFAs (EPA and DHA) increases the abundance of butyrate-producing bacteria, such as *Bifidobacterium*, *Oscillospira*, *Roseburia*, and *Lachnospira* (Robertson et al., 2017; Watson et al., 2018). Similarly, fish oil rich in DHA can increase the abundance of SCFAs-producing bacteria, such as *Akkermansia* and *unclassified_Muribaculaceae*, but decrease the abundance of conditionally pathogenic bacteria, such as *unclassified_Lachnospiraceae*, which might have positive effects on metabolism in genetically obese mice (Al-Bulish et al., 2022). In patients with T2D, dietary sardines rich in abundant n-3 PUFAs and essential amino acids for 6 months could increase the PUFAs concentrations in erythrocyte membrane and decrease the F/B ratio and increase the abundance of *Bacteroides-Prevotella* (Balfegó et al., 2016). In line with this, another clinical study has shown that n-3 PUFAs supplementation decreases the F/B ratio and the abundance of *Phascolarctobacterium* and *Veillonella*, which might contribute to the beneficial effects of n-3 PUFAs on metabolism in subjects with hyperlipidemia (Liu et al., 2022b). However, in individuals with overweight, dietary n-3 PUFAs intervention for 4 weeks has no significant effects on gut microbiota (Kjølbæk et al., 2020), which might be due to the short intervention time. Thus, long-term intervention studies in humans are necessary to fully understand the impacts of dietary intervention with PUFAs on host metabolism. Contrarily, dietary n-3 PUFAs have negative effects on animal health by inducing gut dysbiosis. Compared with dietary lard (rich in SFAs), dietary fish oil increases the H_2S-producing bacteria, such as Desulfovibrionaceae and *Bilophila*, which might aggravate intestinal inflammation in rats (Li et al., 2017a). Collectively, these data suggest that dietary n-3 PUFAs are able to modulate the growth of gut microbiota associated with SCFAs and H_2S production. Although some studies have shown the beneficial health effects of n-3 PUFAs, there are still some inconsistent results about their effects on health (Shahidi and Ambigaipalan, 2018). Thus, further long-term clinical studies are essential to confirm whether n-3 PUFAs have beneficial effects on human metabolism and inflammation.

Similar to n-3 PUFAs, n-6 PUFAs also can influence the diversity and composition of gut microbiota. For instance, dietary supplementation with microalga rich in n-6 PUFAs (dihomo-gamma-linolenic acid (DGLA)) enhances the microbial diversity and increases the abundance of *Planctomycetes*, although had no significant effects on the gut microbiota at the genus level in zebrafish (Nayak et al., 2020). In addition, compared with a Western diet (WD, 27.8% E from fat, 11% palm oil) rich in SFA and MUFA, an HFD rich in linoleic acid (n-6 HFD) decreases the abundance of Firmicutes while increases the abundance of Bacteroidetes in mice (Selmin et al., 2021). Moreover, linoleic acid could induce increases in the proportion of *Mucispirillum scaedleri* and *Lactobacillus murinus*, which might lead to the incidence of inflammation in mice (Selmin et al., 2021). Moreover, arachidonic acid, a derivate of linoleic acid, is demonstrated to decrease microbial richness and exacerbates the HFD-induced gut dysbiosis, which is characterized by the further decreased F/B ratio in mice (Zhuang et al., 2017). These data show that n-6 PUFAs are able to cause or exacerbate gut dysbiosis and thus have negative effects. Contrarily, n-6 PUFAs and their derivatives also have been reported to have beneficial effects. Compared with low fat/low sucrose, high fat/high sucrose based on safflower oil (rich in n-6 PUFAs) increases the microbial diversity and elevates the abundance of *Blautia* (a butyrate-producing bacteria) in mice (Danneskiold-Samsøe et al., 2017). Additionally, 10-hydroxy-cis-12-octadecenoic acid (HYA, microbial metabolites from linolenic acid) supplementation could decrease the abundance of Firmicutes but increase the abundance of *Lactobacillus* (Miyamoto et al., 2019), which might be associated with an improved metabolic condition in

HFD-fed mice.

Besides, the ratio between unsaturated fatty acids (n-6/n-3 ratio) can also affect health status via altering gut microbiota. In a pig model, compared with a higher dietary n-6/n-3 PUFA ratio (8:1), a low n-6/n-3 PUFA ratio (5:1 and 3:1) increases abundance of Firmicutes and decreases that of Bacteroidetes (Wang et al., 2022a). Furthermore, at the genus level, a low n-6/n-3 PUFA ratio is able to decrease the abundance of microbiota related to fatty acid metabolism, including *Cellulosilyticum*, Bacteroidetes, and *Alloprevottella*, which might have protective effects on host metabolism and health (Wang et al., 2022a). Similarly, another study determined the effects of diets with normal (6.21), regular (6.39), low (3.02), and high (9.29) n-6/n-3 PUFA ratios on gut microbiota in rats with obesity and diabetes. The results show that mice fed with a diet with a low n-6/n-3 PUFA ratio exhibit lower microbial diversity than those fed with a normal diet. However, the low n-6/n-3 PUFA ratio is associated with increased abundance of *Allobaculum*, a SCFA-producing bacteria (Lee et al., 2019). These data indicate that a lower dietary n-6/n-3 PUFA ratio might regulate the microbiota, thereby benefitting host metabolism and health.

Taken together, although evidence that dietary n-3 PUFAs and lower n-6/n-3 PUFA ratio benefit health via altering gut microbiota has been found, other lines of evidence have shown the controversies about the effects of PUFAs. The potential molecular mechanisms underlying the effects of PUFAs on gut microbiota and health still need further investigation. Additionally, further clinical studies are necessary to understand the positive effects of n-3 PUFAs and low n-6/n-3 PUFA ratio and determine whether there are beside effects on human health.

Effects of gut microbiota on dietary fat absorption and metabolism

After food ingestion, dietary fat will be emulsified by bile acids in preparation for digestion and absorption. Most of the intestinal BAs can be re-absorbed in the distal ileum and recirculated to the liver. It is evident that gut microbiota plays a critical role in the enterohepatic circulation of BAs via mediating the deconjugation of BAs, which ultimately influences fat absorption (Schoeler and Caesar, 2019). Studies in gnotobiotic mice have further confirmed the role of gut microbiota in of dietary fat absorption. Comparisons between SPF and GF mice fed an HFD showed that the absence of gut microbiota impairs fat absorption and digestion (Martinez-Guryn et al., 2018). However, GF mice colonized with HFD-induced jejunal microbiota have increased fat absorption than those colonized with LFD-induced jejunal microbiota (Martinez-Guryn et al., 2018). Similarly, another study showed that reduced microbial profile via antibiotics treatment reduces intestinal fat absorption by inhibiting the formation of chylomicrons and apolipoproteins, but without influencing intestinal digestion in rats (Sato et al., 2016). Moreover, an *in vitro* study showed that *Lactobacillus paracasei* and *E. coli* decrease lipid secretion and increase lipid storage by producing L-lactate and acetate, respectively, in enterocyte (Araújo et al., 2020). Consistently, treatment with *L. paracasei*, L-lactate, *E. coli*, and acetate reduces intestinal secretion of lipids in mice (Araújo et al., 2020). As for the mechanism, the authors suggested that L-lactate-derived metabolites, malonyl-CoA, inhibit lipid oxidation which induces intestinal lipid storage (Araújo et al., 2020). Meanwhile, acetate-derived metabolites, acetyl-CoA and AMP, are able to promote lipid consumption via enhancing AMPK/PGC-1α/PPARα-mediated lipid oxidation (Araújo et al., 2020).

In addition to its role in fat absorption, gut microbiota also participates in metabolizing dietary fat to generate a variety of FAs. Intestinal bacteria that exhibit biohydrogenation capacity are able to mediate the saturation of PUFAs derived from dietary fat as a detoxifying process. Similarly, another study showed that some species from *Lactobacillus* promote the saturation of PUFA and generate *trans*-FAs, conjugation FAs, and hydroxy FAs (Hirata et al., 2015). Additionally, compared with GF mice, SPF mice have higher concentration of intestinal hydroxy FAs derived from linoleic acid and oleic acid, demonstrating the critical role of gut microbiota in modulating PUFA-saturation metabolism (Kishino et al., 2013). Furthermore, Miyamoto et al. (2019) reported that dietary PUFA (initial linoleic acid)-derived gut microbial metabolites have beneficial effects on HFD-induced metabolic dysfunction in mice. Another study showed that unsaturated FAs-derived microbial metabolites, saturated FAs, accumulate in the liver and induce liver inflammation, which alleviated by microbial depletion via antibiotics treatment in mice fed a steatohepatitis-inducing HFD (Yamada et al., 2017).

Overall, these studies provide convincing evidence that gut microbiota is crucial in mediating dietary fat absorption and metabolism. However, the precise role of specific bacterial species in fat metabolism requires further investigations.

The role of fat-gut microbe crosstalk in host immunity and related diseases

Studies have demonstrated the critical role of gut microbiota in dietary fat-induced disorders, including inflammation-related diseases, associated with the production of LPS or flagellin, at least partly (Figure 9).

High fat-diet

HFD could decrease the abundance of bacteria associated with improved intestinal barrier integrity, such as *Lactoba-*

cillus spp., *Bifidobacterium* spp., *Bacteroides-Prevotella* spp., *Clostridiales* spp., and *Akkermansia muciniphilia* (Rohr et al., 2020). In addition, HFD is capable of increasing the abundance of *Oscillibacter* spp., *Desulfovibrio* spp., and sulfate-reducing bacteria, which produces LPS (Rohr et al., 2020). Under normal conditions, the intestinal barrier is able to protect the host against toxic pathogens, such as LPS, from the gut lumen. However, LPS can be translocated into the systemic circulation via a paracellular manner, as well as a transcellular pathway mediated by a damaged intestinal barrier (Hersoug et al., 2016). In addition, LPS can be incorporated into chylomicron remnants and then be transported into the circulation via lymph (Hersoug et al., 2016), which might explain HFD-enhanced circulating LPS level. TLR4 is mainly expressed in endothelial and immune cells and can recognize pathogen-associated molecular pattern (PAMP), such as LPS (Ciesielska et al., 2021). The activation of TLR4 leads to the release of MyD88, which enhances the activation and translocation of NF-κB and AP-1 and eventually results in the production of pro-inflammatory cytokines, including IL-1β and TNF-α (Gnauck et al., 2016). The effects of LPS on HFD-induced inflammation are further confirmed by another study using mice without LPS receptor, CD14. The deficiency of CD14 could alleviate the HFD-induced inflammation in mice, which is characterized by decreased expression of TNF-α in the liver and adipose depot (Cani et al., 2007). Furthermore, it has been reported that lipid exposure induces the translocation of lumen LPS into portal vein via lipid raft and CD36-associated pathways (Akiba et al., 2020). These data suggest that HFD can cause damage to the gut barrier, increase the abundance of LPS-producing bacteria, and enhance the absorption of LPS, which collectively elevate the circulating LPS level and thus induce or aggravate inflammation. However, further studies should focus on the HFD-induced alterations in the LPS from specific microbiota, since the effects of LPS on gut barrier and inflammation response are dependent on the LPS type found in different microbiota (Anhê et al., 2021).

Apart from LPS, HFD is also associated with increased flagellin. Flagellin is mainly found in Gram-negative bacteria for locomotion and induces inflammation by activating its receptor, TLR5. TLR5 is expressed in various cells, including monocytes, macrophages, NK cells, and dendritic cells (Hajam et al., 2017). The activation of TLR5 is able to activate NF-κB and MAPK signaling in a MyD88-dependent manner, and thus promotes the transcription of pro-inflammatory cytokines (Hajam et al., 2017). HFD increases the abundance of flagellated bacteria (Yiu et al., 2020). Furthermore, transplantation of gut microbiota from mice fed with HFD increases the hepatic and fecal flagellin levels, which activates the TLR5/MyD88/NF-κB signaling pathway in mice fed with normal diet (Yiu et al., 2020), suggesting the casual role of gut microbiota in HFD-mediated inflammation.

In sum, gut microbiota-derived endotoxins, including LPS and flagellin are involved in HFD-mediated inflammation response, which highlights nutrition strategies as a promising area for future research on inflammation-associated diseases.

Saturated fatty acids

Besides the amounts of fat, the gut microbiota-inflammation

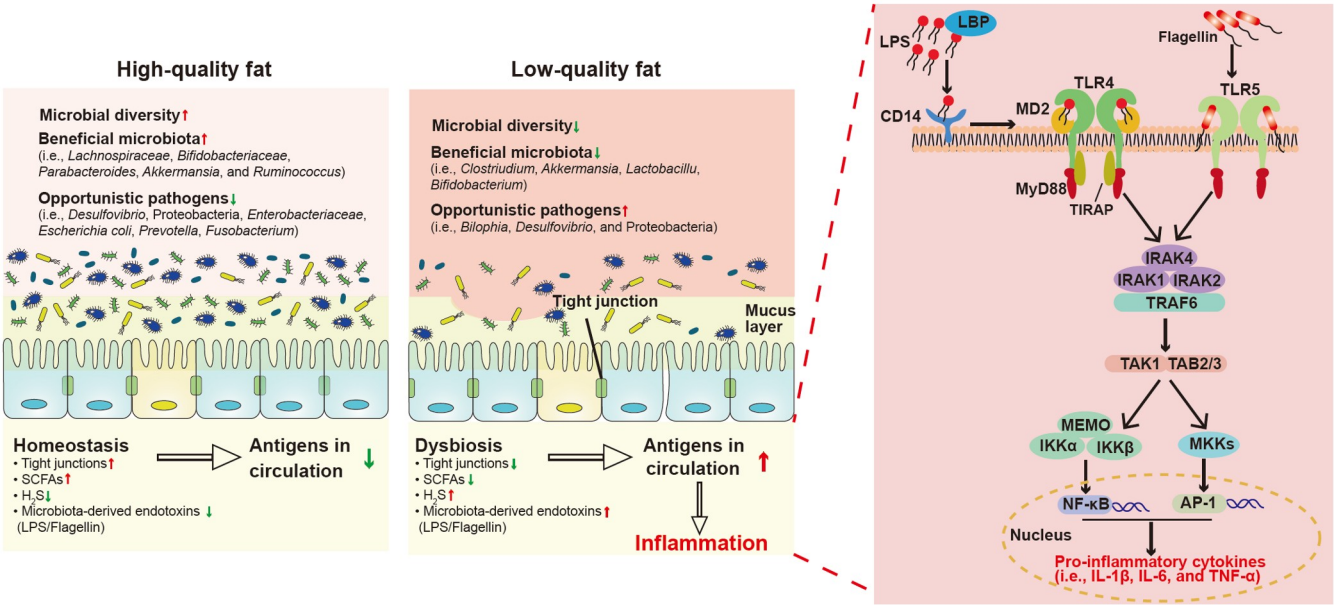

Figure 9 A proposed schema for the role of gut microbiota in dietary fat-mediated inflammation. High-quality fat increases the microbial diversity, promotes the growth of SCFA-producing bacteria, and inhibits the growth of opportunistic pathogens, which collectively improves intestinal barrier integrity and decreases the leakage of microbiota-derived endotoxins. On the contrary, low-quality fat induces gut dysbiosis, which increases the leakage of microbiota-derived endotoxins and thus induces inflammation.

processes induced by different types of dietary fat have also been reported. For example, when fed with lard (rich in SFAs), GF mice exhibited lower inflammation than WT mice, suggesting the casual role of gut microbiota in the SFA-mediated inflammation process (Caesar et al., 2015). Furthermore, the alterations in gut microbiota induced by lard could promote inflammation involving the TLR4 signaling pathway (Caesar et al., 2015). Moreover, a diet rich in SFAs, but not n-3 or n-6 PUFAs, can decrease the transepithelial electrical resistance and enhance the bacterial DNA levels in mesenteric fat compared with a control diet in mice, indicating that SFA is responsible for improved intestinal integrity (Lam et al., 2015). A diet rich in SFAs could also elevate the abundance of gram-negative bacteria and circulating LPS levels (Rocha et al., 2016). In addition, a diet rich in SFA increases the abundance of H_2S-producing bacteria (*Bilophia* and *Desulfovibrio*) (Lam et al., 2015). However, a diet rich in n-3 PUFAs, but not n-6 PUFAs, decreases the abundance of H_2S-producing bacteria (Lam et al., 2015). Sulfate-reducing bacteria (SRB), mainly belonging to *Desulfovibrio* genus, is able to produce H_2S, which can cause damage to the intestinal mucus barrier by decreasing disulfide bonds present in the mucus network (Figliuolo et al., 2017). Furthermore, the damaged mucus barrier allows the lumen toxic compounds and potential pathogens directly interact with the intestinal epithelial cells and thus contributing to the development of inflammation (Ijssennagger et al., 2016). Interestingly, supplementation with saturated palm oil can inhibit the expression of ZO-1 and adherence junction protein (E-cadherin) as well as promote the expression of IL-1β in mice (Ghezzal et al., 2020). Meanwhile, palm oil decreases the abundance of *Clostriudium leptum* and *Akkermansia mucinphila*, which might contribute to the incidence of inflammation (Ghezzal et al., 2020). Besides, palmitic acid causes damage to cell junctions and enhances the expression of IL-8 in human epithelial cells, suggesting that palm oil is able to damage intestinal barrier and initiate inflammation independently of gut microbiota (Ghezzal et al., 2020). These data demonstrate that SFAs are able to cause damage to intestinal integrity and aggravate the development of inflammation, which might at least partly be due to the increased abundance of H_2S-producing bacteria. Contrarily, SCFAs, the well-studied SFAs, have been shown to have protective effects on inflammation and health via modulating gut microbiota (Li et al., 2019a; Rosser et al., 2020). For instance, butyrate treatment increases the proportion of SCFAs-producing bacteria (*Erysipelotrichaceae*, *Lachnospiraceae*, and *Bifidobacteriaceae*) while decreases the abundance of potential pathogenic bacteria (Desulfovibrionaceae and Proteobacteria), which might contribute to the improved intestinal barrier function and alleviated inflammation in mice fed with HFD (Fang et al., 2019; Zhai et al., 2019).

Polyunsaturated fatty acids

Dietary fish oil (rich in PUFAs) decreases the body weight and lessens the inflammation in white adipose tissue of GF and WT mice compared with dietary lard (rich in SFAs) (Caesar et al., 2015). Indeed, dietary n-3 PUFAs (EPA and DHA) decrease circulating LPS levels in mice (Robertson et al., 2017). Moreover, algal oil rich in DHA (n-3 PUFAs) increase the abundance of *unclassified_Lachnos- piraceae*, a SCFA-producing bacteria, decrease the serum levels of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), and enhance the colonic expression of tight junction proteins, which might collectively contribute to the attenuated inflammation in mice with colitis (Xu et al., 2020). Also, in a pig model of infection-induced colitis, krill oil rich in n-3 PUFAs restores gut dysbiosis by increasing microbial richness and reducing the abundance of *Lactobacillus* to decrease the production of histamine, and ultimately inhibit intestinal inflammation via inhibiting MAPK signaling (Liu et al., 2020a).

n-3 PUFAs are generally associated with anti-inflammatory effect, while n-6 PUFAs are generally associated with pro-inflammatory efficacy. Lower dietary n-6/n-1 PUFA ratio (1:1) is associated with decreased levels of circulating pro-inflammatory cytokines, including TNF-α and IL-6, than dietary SFAs and higher n-6/n-3 PUFA ratio (4:1) in rats (Liu et al., 2013). Moreover, a lower dietary n-6/n-3 PUFA ratio decreases the expression of TLR4 in gastrocnemius muscle in comparison with dietary SFAs (Liu et al., 2013). *Fat-1* transgenic mice are able to encode an n-3 fatty acid desaturase, which promotes the conversion of n-6 to n-3 PUFAs and eliminates confounding factors of diet. Intriguingly, a study using fat-1 transgenic mouse model to investigate the effects of n-3 PUFAs on gut microbiota found that *Fat-1* transgenic mice have improved intestinal barrier and less plasma LPS levels than WT mice when fed with high-fat/high-sucrose (HFHS) diet (Bidu et al., 2018). In terms of the alterations in gut microbiota, *Fat-1* transgenic mice fed with HFHS diet exhibit higher microbial diversity than those in WT mice. In addition, *Fat-1* transgenic mice have higher abundance of *Akkermansia* and lower *Ruminococcus* than WT mice after fed with normal diet and HFHS, respectively (Bidu et al., 2018). However, transplantation with microbiota from *Fat-1* transgenic mice enhance the intestinal permeability of WT mice fed with HFHS, suggesting that gut microbiota altered by n-3 PUFAs is responsible for the increased intestinal permeability (Bidu et al., 2018). Similarly, after feeding with HFD, the offspring of *Fat-1* transgenic mice exhibit lower serum levels of LBP and intestinal permeability than those of WT mice, which might be associated with increased *Akkermansia* (Robertson et al., 2018). It has been reported that *Akkermansia* is able to enhance the mucin production and thus increase intestinal integrity (Si et al., 2022). Additionally, *Akkermansia* inhibits

the production of pro-inflammatory cytokines by enhancing the fraction of Tregs (Si et al., 2022). These data suggest that n-3 PUFAs are capable of improving intestinal barrier function and lessening inflammation by promoting the growth of *Akkermansia*. Additionally, another study using *Fat-1* transgenic mouse model showed that after supplementation with n-6 PUFAs, the serum LPS, LPB, and pro-inflammatory cytokines levels are lower in comparison with those in WT mice, which could be eliminated by gut microbiota depletion with antibiotics treatment (Kaliannan et al., 2015). In addition, *Fat-1* transgenic mice have decreased abundance of bacteria related to LPS production and pro-inflammation, such as *Enterobacteriaceae*, *E. coli*, and *Prevotella Fusobacterium* (Kaliannan et al., 2015). However, n-6 PUFA treatment increases the serum LPS and pro-inflammatory cytokines concentrations and elevates the abundance of intestinal LPS-producing bacteria in WT mice (Kaliannan et al., 2015). These data further demonstrate that n-3 PUFAs, rather than n-6 PUFAs, have the ability of alleviating inflammation, which might be due to the alterations in gut microbiota induced by n-3 PUFAs. However, other studies also show the anti-inflammatory effects of n-6 PUFAs (Bersch-Ferreira et al., 2017; Peppone et al., 2019). Taken together, these data suggest that n-3 and n-6 PUFAs exhibit different effects, which might be due to their different downstream lipid metabolites (Costantini et al., 2017). Further study is necessary to figure out the inconsistent results about the effects of PUFAs on host health. Additionally, more pre-clinical and clinical investigations are necessary to determine the effective dose and formulas of dietary PUFAs for specific inflammation-related diseases.

Gut microbiota bridges dietary trace elements and host immunity

In recent decades, there has been a focus on the modulating effects of trace elements on host immunity, and formulas of dietary trace elements for specific inflammation-related diseases. Appropriate levels of dietary trace elements are conducive to achieve intestinal homeostasis that enables the normal performance of related immune function. In this section, we focus on recent advances regarding interactions among trace elements (zinc, selenium, iron, and copper), gut microbes, and host immune response, as well as their role in immune-related diseases.

Effects of trace elements on gut microbiota

Trace elements have been demonstrated to participate in altering the intestinal microbiota composition, supporting the host immune system and reducing the risk of infections. Here, we discuss the recent advances regarding the effect of trace elements (zinc, selenium, iron, and copper) on gut microbiota.

Zinc

The association between zinc status and gut microbiota was reported more than 30 years ago. Zinc deficiency causes a reduction in the abundance of Firmicutes and Actinobacteria, and an increase in Proteobacteria and *Bacteroides* in chickens (Reed et al., 2015), while inconsistent results were observed in pregnant mice fed a zinc-deficient diet. Zinc deficiency increases the abundance of Firmicutes, *Bacteroides*, and Actinobacteria, and decreases Proteobacteria abundance (Sauer and Grabrucker, 2019). Inexplicably, the zinc-deficient associated microbiota is comparable to the well-nourished profile in another murine model (Mayneris-Perxachs et al., 2016). These contradictory results indicate that zinc deficiency-associated alterations in microbiota are dependent on the mode of treatment and the species, age, and physiological status of the animals (Skalny et al., 2021). The abundance of *Ruminococcus* could also be one of the crucial genera affected by zinc deficiency (Reed et al., 2018). In addition to significant alterations in composition of intestinal microbiota, zinc deficiency promotes prolonged infection outcomes by enteric pathogens (Q.S. Medeiros et al., 2019).

On the other hand, zinc oxide supplementation at the pharmacological level has been widely applied to prevent weanling-induced diarrhea in piglets, mostly through its influence on microbiome profiles, including reductions of coliforms and enterobacteria such as *E. coli* (Kociova et al., 2020). However, the effects of zinc on gut microbiota are dependent on factors such as zinc concentrations and forms, treatment periods and regimens, animal age, and physiological conditions (Pajarillo et al., 2021). For example, metagenomic sequencing of colon microbiota showed remarkable differences in composition at the species level, as well as the expression of functional genes and metabolite concentrations in response to different dietary zinc concentrations and forms (Pieper et al., 2020). In addition, the alteration of microbiota composition by zinc is also site-specific. Zinc oxide decreases microbiota abundance with decreased *Lactobacillus* abundance in the ileum, whereas it has contrasting effects in the cecum and colon (Skalny et al., 2021). Notably, excessive zinc supplementation can cause toxic effects on microbes by liberating redox-active metals. This creates advantages for the *Enterococci* genus, which is highly resistant to metal toxicity and thrives in the intestine (Zackular and Skaar, 2018). Excess zinc also alters diversity, disrupts structure, and increases the translocation of intestinal microbiota, thus exacerbating *Clostridium difficile*-associated diseases (Zackular et al., 2016). Prediction of microbiota function has indicated that pathways including carbohydrate metabolism, stress responses, and infectious diseases are also altered (Chen et al., 2021; Pieper et al., 2020). Decreased biodi-

versity and functional changes are accompanied by decreased total SCFA concentrations (Zhang et al., 2021a). Additionally, excessive zinc exposure induces the expression of antibiotic resistance genes and causes bacterial resistance (Pieper et al., 2020).

Selenium

(1) Selenium regulates gut microbes and their metabolites. Selenium helps maintain the overall diversity of existing intestinal microbiota, as well as the establishment of gastrointestinal microbiota (Gangadoo et al., 2018; Liu et al., 2022c), thus ensuring intestinal homeostasis. Low intake of selenium might result in a phenotype of the gut microbiota that is more susceptible to IBD, including colitis and infection by pathogens such as *Salmonella typhimurium* (Saulnier et al., 2011). Importantly, the abundance of *Dorea* spp., which is positively related to irritable bowel syndrome, increased in response to a selenium-deficient diet (Zhai et al., 2018).

Dietary selenium supplementation optimizes the gut microbiota by increasing health-promoting bacteria, including *Lactobacillus* and *Faecalibacterium*, and decreasing undesirable bacteria, including *Bacteroides* and *Clostridia* (Gangadoo et al., 2018). In addition, mice supplied with supra-nutritional selenium exhibit increased levels of *Turicibacter* and *Akkermansia*, which are critically involved in gut barrier protection, immune modulation, and metabolic regulation of the host (Derrien et al., 2017; Zhai et al., 2018). Dietary supplementation with selenium also increases the abundance of *Ruminococcaceae* and *Phascolarctobacterium*, two important producers of SCFAs (Li et al., 2021c). However, the microbes that are critical targets of selenium, and whether other pathways of microbial metabolism could also be affected by selenium, remain to be explored.

(2) Selenium bioavailability to gut microbes and the host. There is an intertwined relationship between host and gut microbes with respect to the use of selenium (Callejón-Leblic et al., 2021). The gastrointestinal microbiota affects selenium status and selenoprotein expression by sequestering selenium and restricting its availability in the host (Arias-Borrego et al., 2019). Bacteria may compete with the host for selenium under limited availability of selenium, while they may consume extra selenium when it is excessive or becomes toxic to host cells (Bielik and Kolisek, 2021; Ferreira et al., 2021). About 25% of bacteria express selenoproteins after sequestering selenium; therefore, they usually sequester selenium from the host for optimal growth. The use of selenium by gut microbes decreases its availability to the host for the formation of selenoproteins. Consequently, the host requirement for selenium increases under such conditions.

Notably, when the host requires extra selenium, gut microbes secrete selenoproteins into the intestinal lumen (Callejón-Leblic et al., 2021). Some gut microbes can transform various chemical forms of bioselenocompounds from diets to selenomethionine (SeMet), and then part of the SeMet is used by the microbes, and the remainder is absorbed by host cells and/or excreted (Takahashi et al., 2020). For instance, selenium-enriched *Bifidobacterium longum* can efficiently biotransform inorganic selenium into more bioactive forms of organic selenium, including SeMet (Zhu et al., 2019); several *Lactobacillus* species are able to transform intracellular sodium selenite into the form of selenocysteine (SeCys) and SeMet, thus providing a more bioavailable form of selenium (Ferreira et al., 2021).

Iron

In general, gut microbes secrete siderophores, low-molecular-weight secondary metabolites that capture iron from the environment and deliver iron to bacterial cells via binding to specific receptors, thereby competing for iron acquisition with the host (Kramer et al., 2020). Iron acquisition is critical for the colonization, growth, replication, and virulence of most enteric bacteria. Low-iron diets affect the gut microbiota composition in both humans and rats. Specifically, low-iron diets increase *Lactobacilli* and *Enterobacteriaceae* while decreasing *Roseburia* spp./*E. rectale* group (Dostal et al., 2012; Dostal et al., 2013). Iron fortification can be effective in providing additional dietary iron and reducing rates of anemia in iron-deficient populations, especially infants and children in developing countries. However, Jaeggi et al. (2015) reported that iron fortification by consuming iron-containing micronutrient powders increases intestinal pathogenic Enterobacteriaceae, especially *E.coli*/*Shigella*, *Enterobacter*/*Bifidobacterium* ratios, and *Clostridium* in 6-month-old Kenyan infants with iron deficiency; in addition, infants with iron supplementation have increased fecal calprotectin (a marker of intestinal inflammation) and elevate diarrhea incidence compared with non-supplemented individuals. A subsequent study of iron supplementation in healthy and non-anemic 6-month-old Swedish children similarly suggested that consumption of high-iron formula for 45 days might be associated with a significantly lower abundance of *Bifidobacteria* compared with consumption of low-iron formula. Furthermore, administration of iron as drops leads to a decreased relative abundance of *Lactobacilli* and potentially increases susceptibility to bacterial infection (Simonyté Sjödin et al., 2019). Similarly, a survey of micronutrients in the fecal microbiota of children aged 12–24 months in Pakistan showed that micronutrient supplements with iron significantly increase the carriage of six phylogenetically distinct protozoa and six fungi (Popovic et al., 2021). Overall, these results demonstrate that excessive iron supplementation promotes the growth of pathogenic bacteria and hampers the survival of protective microbes.

It remains debatable whether differences in the route of

administration of iron supplementation could differently modulate the composition of the gut microbiome. An open-labeled clinical trial with iron-deficient participants with or without IBD demonstrated that both oral and intravenous iron replacement therapy could almost equally restore iron levels, reduce disease activity, and improve the quality of life of patients with IBD. However, 16S rRNA sequencing and metabolomic analysis suggested that oral and intravenous iron replacement therapy differentially affect the bacterial communities and metabolic landscape, respectively. Specifically, *Collinsella aerofaciens*, *Faecalibacterium prausnitzii*, *Ruminococcus bromii*, and *Dorea* spp. are reduced in patients receiving oral iron supplementation (Lee et al., 2017b). Recently, this perspective has been challenged. La Carpia et al. (2019) reported that dietary iron, intravenous iron administration, and chronic transfusion in mice increase iron bioavailability. They found that these different routes for administration of iron have consistent and reproducible effects on murine gut microbiota. However, it is unclear whether different iron formulations could differentially modulate the composition of gut microbiota. Therefore, further systematic investigations are needed.

Copper

In animal production, feed supplementation with copper can promote animal growth, reduce the frequency of diarrhea, and improve gut health (Di Giancamillo et al., 2018; Villagómez-Estrada et al., 2020). Copper supplementation can decrease the relative abundance of potentially pathogenic bacteria, including *Streptococcus*, *Enterobacter*, and *Escherichia* in weanling pigs (Villagómez-Estrada et al., 2020). In growing pigs, Kim et al. (2021) reported that the inorganic and organic forms of copper modulate the composition of gut microbiota differently. In general, the relative abundances of *Prevotella*, *Lactobacillus*, *Megasphaera*, and SMB53 significantly increase after organic copper supplementation. In Sprague-Dawley rats, Dai et al. (2020) found that copper exposure during early life changes the diversity of microbiota in a dose-dependent manner. Specifically, the abundance of probiotics, the ratio of *Firmicutes* to *Bacteroidetes*, and bacteria associated with fat metabolism and intestinal inflammation are reduced. Additionally, copper exposure could increase the abundances of *Bacteroides* and *Alistipes*, whereas decreasing the abundances of *Ruminococcaceae_UCG014*, *Allobaculum*, *Mollicutes_RF9_norank*, *Rikenellaceae_RC9_gut_group*, *Ruminococcaceae_unclassified*, and *Turicibacter* in mice (Zhai et al., 2017). Wilson's disease is an autosomal recessive inherited disorder of chronic copper toxicosis with high mortality and disability. A recent study revealed that patients with Wilson's disease have significantly decreased phylum levels of Actinobacteria and Verrucomicrobia compared with a healthy population. Patients with Wilson's disease also present a unique richness of Gemellaceae, Pseudomonadaceae, and Spirochaetaceae at the family level, which are rarely detected in healthy individuals (Cai et al., 2020a). This compositional change in gut microbiota may act as a potential bacterial biomarker for Wilson's disease. Fecal microbiota transplantation and protective microbiota metabolite-associated therapy may hold promise as therapeutic designs for the clinical prevention of Wilson's disease.

Gut microbiota may regulate host copper uptake and metabolism. Using isotopic fractionation techniques, Miller et al. (2019) observed that both CTR1 and ATP7A, two major copper transport proteins, are significantly downregulated in the colon of mice treated with antibiotics. However, the mechanisms underlying the modulation of these two proteins by intestinal microbiota need to be further explored.

Gut microbes modulate iron metabolism

Studies based on GF animals have suggested that the absence of gut microbes reduces iron storage in several tissues compared with their conventional counterparts, while conventionalization of fecal bulk from conventional animals or mono-colonization of certain bacterial species improves the iron status in GF mice (Reddy et al., 1972). Certain gut microbes can facilitate iron bioavailability by increasing iron solubility or reducing ferric iron to its ferrous form by secreting diverse metabolites, thus leading to higher iron absorption (Bering et al., 2006; González et al., 2017). Recent studies have suggested that gut microbes may inhibit host iron absorption. Das et al. (2020) reported that gut microbiota, especially *Lactobacillus* species, suppress the major transcription factor responsible for intestinal iron absorption, hypoxia-inducible factor 2α (HIF-2α), which transcriptionally activates the expression of DcytB and DMT1. Specifically, microbiota-derived 1,3-diamino propane (DAP) and reuterin are considered critical metabolites for inhibiting HIF-2α via the inhibition of HIF-2α heterodimerization with HIF-1β. Therefore, the exact effect of gut microbiota on intestinal iron absorption is complex, which may be due to the different animal models used and different physiological status (e.g., iron deficiency *vs*. iron replete). Further identification of the critical microbiota facilitating or suppressing intestinal iron absorption could help to understand the symbiosis between the hosts and gut microbiota, as well as the therapeutic design of iron-related diseases by targeting corresponding gut microbes.

Hepcidin is a master regulator of systemic iron homeostasis. Specifically, hepcidin binds to FPN and leads to its degradation, resulting in iron retention in enterocytes and macrophages (Muckenthaler et al., 2017). Gut microbiota can modulate the expression of hepatic hepcidin in the context of DSS-induced intestinal inflammation (Shanmugam et al., 2014). In addition, hepcidin can be secreted by

myeloid cells, including neutrophils and macrophages (Peyssonnaux et al., 2006). Dendritic cell-derived hepcidin acts on FPN-expressing phagocytes, promotes local iron sequestration, and confines iron release. Thus, the iron-deficient microenvironment limits tissue infiltration by the microbiota and promotes mucosal healing. Additionally, the gut microbiota fine-tunes host iron recycling and modulates hematopoiesis. Gut microbiota-derived SCFAs facilitate BMDM-mediated erythrophagocytosis and expedite iron availability. This local iron supports stress-induced hematopoietic stem cell self-renewal, differentiation, and blood regeneration (Zhang et al., 2022a). Collectively, these studies highlight the hypothesis that gut microbiota can modulate host iron metabolism and iron homeostasis.

The role of trace elements-gut microbe crosstalk in host immunity and related diseases

Zinc

(1) Zinc and innate immune function. Sufficient supply of zinc guarantees the normal function of neutrophil granulocytes, monocytes, macrophages, and natural killer cells, whereas deficient or excessive zinc impairs their activity. Zinc homeostasis is crucial for ROS production in leukocytes, which helps granulocytes in their defense against and killing of pathogens (Maares and Haase, 2016). Zinc deficiency impairs granulocyte adhesion and chemotaxis and affects the release of chemokine IL-8 and anti-inflammatory IL-1 receptor antagonist, further resulting in reduced phagocytosis (Hasan et al., 2016).

(2) Zinc and adaptive immune function. Zinc supports the proliferation, differentiation, and activity of T cells and B cells, which form the basis of the adaptive immune system. The activities of cytotoxic $CD8^+$ T cells and $CD4^+$ Th cells are affected under zinc-deficient conditions. Zinc deficiency decreases the secretion of Th1 cytokines but has no effect on Th2 cytokines, leading to an imbalance of Th cells, which is critical for an effective immune response (Prasad, 2000). Zinc could suppress the allergic immune response by modulating the Th1/Th2 ratio and increasing the number and activity of Tregs (Maares and Haase, 2016). It is noteworthy that zinc supplementation also reduces the number of Th17 cells, thus alleviating experimental autoimmune encephalomyelitis (Rosenkranz et al., 2016). Although supplementation with a high dosage of zinc first increases the number of activated Th cells, it exhibits the opposite effect after 2 weeks of supplementation (Kreuzer-Redmer et al., 2018).

Zinc deficiency impairs lymphopoiesis and results in decreased pre-B cell numbers, which are important for humoral immunity. Notably, the zinc transporter ZIP10 may mediate the effects of zinc on B cell function. ZIP10 promotes B cell receptor signal strength and alleviates apoptosis during early B cell development (Hojyo et al., 2014). In addition, zinc treatment has been suggested to enhance antibody formation, although these effects and related mechanisms need to be further confirmed.

(3) Indirect effects of zinc on immune responses. Zinc can exert indirect effects on the immune system via host receptors and zinc transporters. Zinc ion concentration determines the activity of porcine aminopeptidase N (APN), which is a Zn^{2+}-dependent membrane-bound exopeptidase that further affects the adherence of *E. coli* F4 to epithelial cells (Chen et al., 2012). The regulatory effects of APN on MAPK/ERK1/2 in monocytes are also diminished by blocking its zinc-binding site (Melkebeek et al., 2012). Zinc reduces MUC4 expression, which acts as a receptor for enterotoxigenic *E. coli*, and thus decreasing the inflammatory responses (Sargeant et al., 2010). Zinc shortage can reduce Hodor signaling, which enhances antigen presentation in the intestinal epithelium and exacerbates the pathology of IBD (Fernández-Gallego et al., 2021). The expression of zinc transporters is regulated by zinc concentration, and zinc transporters modulate zinc homeostasis and *vice versa*. ZIP8 promotes zinc uptake by monocytes and macrophages, thus inhibiting inflammatory responses (Ohashi and Fukada, 2019). In early B cell development, activation of signaling through the B cell antigen receptor (BCR) requires zinc homeostasis regulated by the zinc transporter ZIP7 (Anzilotti et al., 2019). ZIP10 also plays a critical role in BCR signaling, which affects the proliferation of mature B cells (Hojyo et al., 2014). Although zinc could affect the expression of zinc transporters and the crosstalk between microbiota and epithelial cells, the detailed molecular mechanisms involving zinc transporters and the role of zinc in immune cell biology remain to be elucidated.

(4) Zinc and nutritional immunity. There is a well-known mechanism for mammalian hosts to prevent microbial growth, which is called nutritional immunity, referring to transition metals, including zinc, iron, copper, and manganese. For example, host cells maintain zinc homeostasis by regulating zinc transporters, including Zip and ZnT proteins, while sequestering zinc ions via zinc-binding proteins, including S100 proteins and metallothionein (MT). Calprotectin, as the major antibacterial protein in neutrophils, exerts high zinc-binding affinity and restricts zinc uptake of bacteria, further inhibiting the growth of pathogens, including *E. coli*, *Salmonella*, and *S. aureus* (Xia et al., 2021a). Concomitantly, bacterial cells compete for Zn via the Zn transport system and Zn uptake proteins. *Campylobacter jejuni*, the cause of campylobacteriosis in humans, cannot replicate in the GIT without a high-affinity ABC transporter for zinc uptake (Gielda and DiRita, 2012). *S. typhimurium* with the transporter ZnuABC can overcome metal sequestration by calprotectin and compete for zinc in hosts with IBD (Sheng et al., 2015). Fungi such as *Candida albicans* are equipped

with robust zinc sensory (Zap1), transporters (Zrt1), and scavengers (Sap6) to maximally exploit zinc sources from the host (Alamir et al., 2021). This competition for zinc makes "nutritional immunity" an effective strategy for the host to defend against pathogen infections.

(5) Interaction among zinc, gut microbe and gut immune system. Although zinc exerts a direct effect on the functioning of the immune system, regulation of gut microbiota also mediates the beneficial effects of zinc. Zinc alleviates the immune responses caused by pathogens and toxins by improving intestinal barrier integrity, thus preventing the translocation of bacteria and their metabolites. However, zinc over-expression also substantially alters gut microbiota composition, which may cause systemic inflammation. Dietary zinc affects the expression of microbial functional genes and the production of metabolites, including SCFAs. Specifically, both zinc deficiency and overexposure inhibit the abundance of SCFA-producing genera (Chen et al., 2021). SCFAs may play a mediating role in the microbiota-gut-brain axis crosstalk by activating hormonal and immune pathways (Dalile et al., 2019). Neurons that are abundant along the GIT can be activated by zinc and detect specific metabolites and toxins secreted by pathogens, thus playing critical roles in inflammatory responses (Ghaisas et al., 2016; Xia et al., 2021a). Exploration of the complex interactions among intestinal neurons, microorganisms, and immune cells, which could be mediated by the microbe-gut-brain axis in mammals, will further improve our knowledge of how zinc modulates immunity.

(6) Involvement of zinc in SARS-CoV-2 infection. Recently, therapeutic application of zinc in the worldwide COVID-19 pandemic has been reported. SARS-CoV-2 infection is associated with significant alterations in the fecal microbiome, which has potential therapeutic value in COVID-19 (Xia et al., 2021a). Zinc may directly block viral replication by affecting viral proteins, thereby helping the host against SARS-CoV-2 (Oyagbemi et al., 2021). However, whether microbes are involved in immune system activation by zinc needs to be further explored.

As discussed above, disturbance of zinc homeostasis plays a critical role in innate and adaptive immunity, and thus affects the immune response and host defense. Notably, the zinc status-related composition of microbiota and function mediate these effects (Figure 10). Although the role of zinc in immunity has been extensively explored, a detailed understanding of the gut microbes involved in the molecular effects of zinc and related mechanisms is required to improve its efficacy in the treatment of immune-related diseases.

Selenium and selenoproteins

Selenium is involved in the regulation of oxidation and inflammatory and immune responses by modulating the expression or activity of selenoproteins (Ferreira et al., 2021). Glutathione peroxidases (GPXs) and thioredoxin reductase (Txnrds) are two of the most important selenoproteins and improving selenium status could enhance their activities and decrease the concentrations of protein carbonyl, malonedialdehyde, hydrogen peroxide, and lipid hydroperoxides, thus modifying the inflammatory and immune responses in patients with cancer and other diseases (He et al., 2023; Santos et al., 2018).

Innate immune cells, such as macrophages, exhibit decreased expression of pro-inflammatory mediators in response to inflammatory stimuli only when selenoproteins are expressed (Wu et al., 2021b). The incorporation of SeCys into the selenoproteome is the key process by which selenium exerts its anti-inflammatory effects on macrophages and other immune cells (Nettleford and Prabhu, 2018). The underlying mechanism is that selenoproteins switch arachidonic acid metabolism from pro-inflammatory mediators to anti-inflammatory mediators. Selenium deficiency or lack of selenoproteins in mice results in higher mortality after enteric infection-induced inflammation, whereas dietary selenium protects these mice against inflammation by increasing innate lymphoid cells (ILC)-3 and Th17 cells (Nettleford et al., 2020). These effects of dietary selenium are blocked by the prevention of metabolic inactivation of prostaglandin E_2 (PGE_2), a major pro-inflammatory mediator involved in arachidonic acid metabolism (Nettleford et al., 2020). Deletion of selenoproteins in T cells via ablation of the Sec $tRNA^{[Ser]Sec}$ gene, which mediates the formation of selenoproteins, results in a decrease in mature T cell numbers and T cell-dependent antibody responses with increased oxidative stress in T cells (Shrimali et al., 2008). Thus, selenium also supports adaptive immune functions via the promotion of secreted selenoproteins. Selenoproteins also play antioxidant roles in immune regulation. Deletion of the *Selenop* gene in epithelial cells exacerbates oxidative status and tumor progression, indicating that selenoprotein P plays a critical role in the antioxidant capabilities of colonocytes. Thus, selenoprotein P could be a promising biomarker for IBD patients and patients predisposed to the development of colitis-associated cancer (Short et al., 2021). Selenium and selenoproteins alleviate diseases such as IBD by altering microbiota composition. These bacteria, including *Salmonella*, can utilize tetrathionate for growth, whereas Txnrd1 promotes the reduction of tetrathionate to thiosulfate, thus improving oxidative status and microbiota diversity during IBD (Narayan et al., 2015).

Selenium modulates immune function by affecting immune cells and regulating the production of inflammatory cytokines. Selenium increases the abundance of neutrophils and $CD4^+CD25^+$ T cells and decreases the abundance of γδT, $CD4^+$, $CD4^+CD44^+$, and $CD4^+CD69^+$ T cells. By increasing the number of $CD4^+CD25^+$ Tregs, selenium suppresses pro-inflammatory cytokine production in mice with DSS-in-

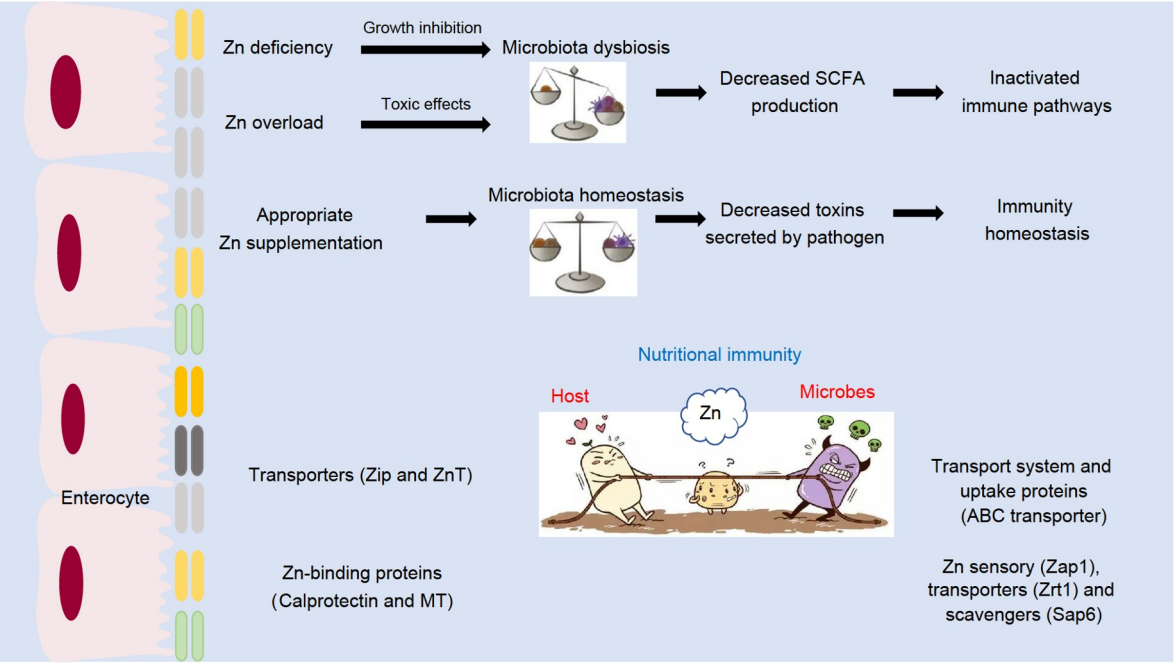

Figure 10 The interaction effects among zinc, gut microbes, and host immune response. Both Zn deficiency and overload could cause microbiota dysbiosis. Zn deficiency results in growth inhibition of microbes, while Zn overload causes toxic effects on microbes. The microbiota dysbiosis further leads to decreased SCFA production and then inactivates immune pathways. Appropriate Zn supplementation is beneficial to the ecological balance of microbiota with decreased toxins secreted by pathogens, and the maintenance of immunity homeostasis. Host and gut microbes compete for zinc which is called "nutritional immunity". Host cells maintain zinc homeostasis by regulating zinc transporters including Zip and ZnT proteins and sequestering zinc ions via zinc-binding proteins including MT and Calprotectin; bacterium and fungus compete for Zn via transporters (ZnuABC, Zrt1), sensory (Zap1) and scavengers (Sap6).

duced colitis (Sang et al., 2017). In addition, selenium promotes the transformation of M1 macrophages into M2 macrophages, thereby inhibiting the development of inflammation (Wu et al., 2021b). Selenium exerts its effects on immune functions by modulating the production of inflammatory factors, including IL-1β, IL-17, IFN-γ, TNF-α, and TGF-β (Li et al., 2021c; Wu et al., 2021b). However, whether these effects are mediated by selenoproteins requires further exploration.

NF-κB and peroxisome proliferator-activated receptor γ (PPARγ) are two of the most studied pathways that mediate the effects of selenium. Selenium can resolve such inflammatory conditions in the intestine by blocking NF-κB activation. Selenium can either directly inhibit the dissociation of IκB proteins from NF-κB or directly interact with cysteine thiols in NF-κB (Nettleford and Prabhu, 2018). In addition, by regulating the TLR4/MYD88 signaling pathway, selenium inhibits the expression of NF-κB, increases the expression of tight junction-related genes *Claudin-1*, *Occludin*, and *ZO-1* and antagonizes the intestinal barrier injury caused by oxidative stress (Yang et al., 2020). Selenium plays a crucial role in the activation of PPARγ by upregulating PGD_2, which is an agonist of PPARγ. Selenium activates PPARγ while inactivating NF-κB in intestinal epithelial cells and macrophages, thus decreasing the secretion of inflammatory cytokines and increasing the expression of $Foxp3^+$ Treg cells (Nettleford and Prabhu, 2018). As discussed above, selenium can mitigate inflammation through the NF-κB and PPARγ pathways; however, the intricate mechanisms between selenium and gut microbes that could regulate the activation or inactivation of NF-κB and PPARγ or other factors involved in the immune response need to be further explored.

Although selenium has direct effects on intestinal pathogens and probiotics, most of its biological impacts on gut microbiota and the immune system are exerted through selenoproteins (Figure 11). Like aforementioned, although there are 24–25 selenoproteins identified in mammals, not all selenoproteins have been shown to be essential for the immune system. Future studies revealing the roles of unexplored selenoproteins in the gut microbiota and immune function are urgently needed.

Iron

Crosstalk between iron and immune responses has been widely reported. In innate immunity, iron status and metabolism are involved in the regulation of macrophage polarization, neutrophil recruitment, and natural killer cell activity against virus infection (Xia et al., 2021c). For instance, hepcidin decelerates iron release by facilitating FPN degradation, which enhances the expression of CXCL1 chemokine for subsequent neutrophil recruitment to limit

infection (Malerba et al., 2020). In the adaptive immune response, iron modulates the differentiation, activation, and immune response of myeloid cells including Th1, Th2, Th17, Treg, and B cells. A homozygous Tyr20His mutation in TFR1, which disrupts the endocytosis of transferrin-bound iron, leads to combined immunodeficiency, characterized by impaired function, proliferation, and class switching of B and T cells (Jabara et al., 2016). Importantly, the increased expression of TFR1 and enhanced uptake of transferrin-bound iron kills Treg cells by boosting oxidative insults (Feng et al., 2021). Furthermore, iron sustains B cell proliferation and plasma cell formation by supporting cyclin E1 induction (Huang et al., 2019b).

Iron is essential for the growth and virulence of pathogenic bacteria. Iron fortification in infants and animals increases the risk of morbidity and mortality from infections. Therefore, the limitation of iron from pathogens holds promise for therapeutic design against infection. For instance, enhanced FPN1 expression in macrophages leads to iron export and limits the replication of intracellular pathogens *M. tuberculosis* and *S. typhimurium* (Nairz et al., 2015). Furthermore, iron deficiency in macrophages also activates the transcriptional factors HIF-1α and NF-IL6, which would sustain NOS2 transcription and thus promote NO-mediated antimicrobial potential.

Increasing evidence has emerged that dietary iron levels and host iron homeostasis can modulate host immunity and inflammatory responses by finely tuning the composition and metabolism of gut microbiota. Iron deficiency anemia is one of the most common complications of IBD (Ramos and Papadakis, 2019). Oral iron supplementation is a common treatment that has been shown to exacerbate intestinal inflammation (Mahalhal et al., 2018), while low iron supplementation would be beneficial in alleviating the inflammatory response in colitis. Mechanistically, Maharshak et al. (2015) found that a low iron condition would facilitate some intestinal bacteria, including *E. coli*, to express a heme oxygenase-like enzyme, chuS, which catalyzes heme to iron, biliverdin, and carbon monoxide. The metabolite carbon monoxide then reprograms macrophages, as manifested by decreased IL-12 p40 and increased IL-10 secretion. In contrast to oral iron supplementation, the appropriate dose of intraperitoneal iron supplementation could alleviate DSS-induced colitis (Liang et al., 2021). Mechanistically, the abundance of Bacteroidetes is significantly reduced in mice with colitis and significantly restored by intraperitoneal iron supplementation. In addition, intraperitoneal iron supplementation reduces colonic $CD4^+$ T cell infiltration and inhibits the expression of pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, and iNOS in mice with colitis, thereby exhibiting the effect of colitis relief. This also suggested that iron may be involved in the host gut immune response by influencing the abundance of Bacteroidetes.

Hereditary hemochromatosis is an autosomal recessive disorder associated with iron overload (Katsarou et al., 2019). Excessive iron can cause a variety of metabolic disorders throughout the body, and some studies have found that hereditary hemochromatosis can promote colitis and colon cancer by altering microbial composition (Sivaprakasam et al., 2020). The colon microbiome of hereditary hemochromatosis model ($Hfe^{-/-}$) mice shows a significant increase in

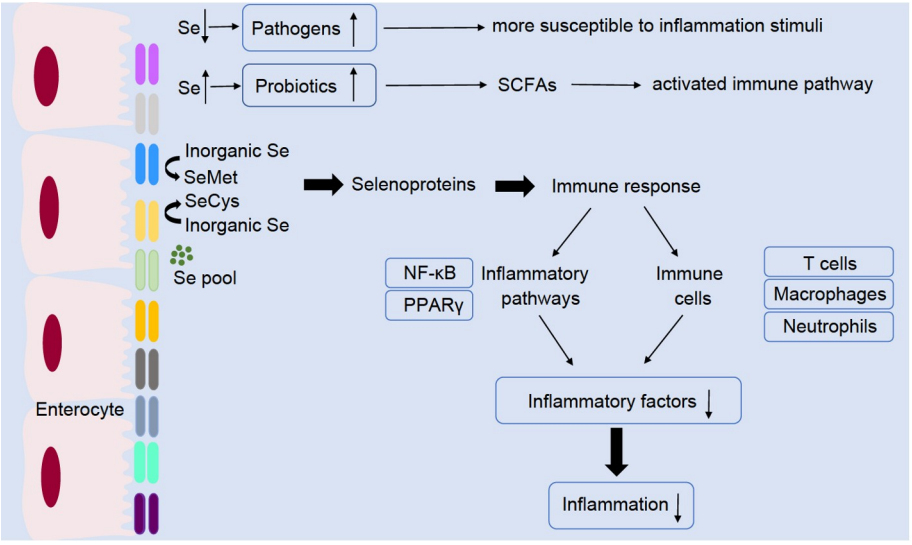

Figure 11 The interaction effects among selenium, gut microbes and host immune response. Se deficiency leads to the increase of pathogenic bacteria and the host is more susceptible to inflammation stimuli; Se supplementation leads to the increase of probiotics with increased SCFA production, which could activate immune pathway. Certain gut microbes could transform inorganic Se into the form of SeCys and SeMet, which then incorporate into selenoproteins. Selenoproteins improve immune response by inhibiting inflammatory pathway including NF-κB and PPARγ and improving immune cell function (T cells, macrophages and neutrophils), which further alleviate inflammatory response.

pathogenic bacteria of the *Aspergillus* phylum and TM7, as well as a significant increase in the release of pro-inflammatory cytokines (IL-1β and TNF-α) following inflammatory stimulation compared with wild-type mice. This suggests that excess iron may increase the expression of host pro-inflammatory factors by affecting the gut microbes, which in turn modulates the host immune response to exacerbate inflammation.

Although studies on the effects of iron status and metabolism on intestinal microbiota composition and host immunity have been reported (Figure 12), the understanding of the molecular mechanisms underlying this interaction remains unclear. In future, the mechanisms by which gut bacteria and their metabolites regulate host iron homeostasis and immunity, as well as iron status and iron metabolism, and modulate intestinal microbiota and immunity should be further explored. This would provide further understanding of the pathogenesis of intestinal flora-dependent inflammatory or infectious diseases and iron metabolism disorders.

Copper

Copper toxicity is always used by immune cells as an antimicrobial weapon against infection (Samanovic et al., 2012), whereas nutritional copper deficiency causes immunosuppression and increased susceptibility to bacterial infection (Djoko et al., 2015). Pathogens have evolved a range of means for copper resistance and escape from immune cells. Bacteria can be conferred copper resistance through multiple mechanisms, including reducing copper permeability, enhancing copper export, and facilitating copper chelation or detoxification (Arendsen et al., 2019). For example, the human fungal pathogen *Cryptococcus neoformans* expresses copper-detoxifying metallothionein proteins that have been identified as virulence factors. Deletion of these copper-detoxifying metallothionein proteins or mutations disturbing their copper binding capacity in *Cryptococcus neoformans* severely attenuates virulence and reduces pulmonary colonization (Ding et al., 2013). Similarly, *Mycobacterium tuberculosis* expresses copper transport proteins to facilitate efflux of excess copper and maintain a low-copper intracellular microenvironment for infection (Wolschendorf et al., 2011). Furthermore, it should be noted that chronic copper exposure can increase the copy number of heavy metal resistance genes, antibiotic resistance genes, and mobile genetic elements (Zhang et al., 2019). As the widespread dissemination of these antibiotic resistance genes from the environment to human pathogens potentially challenges human health, copper utilization should be minimized.

Copper modulates host immunity and inflammatory responses by finely tuning the composition and metabolism of

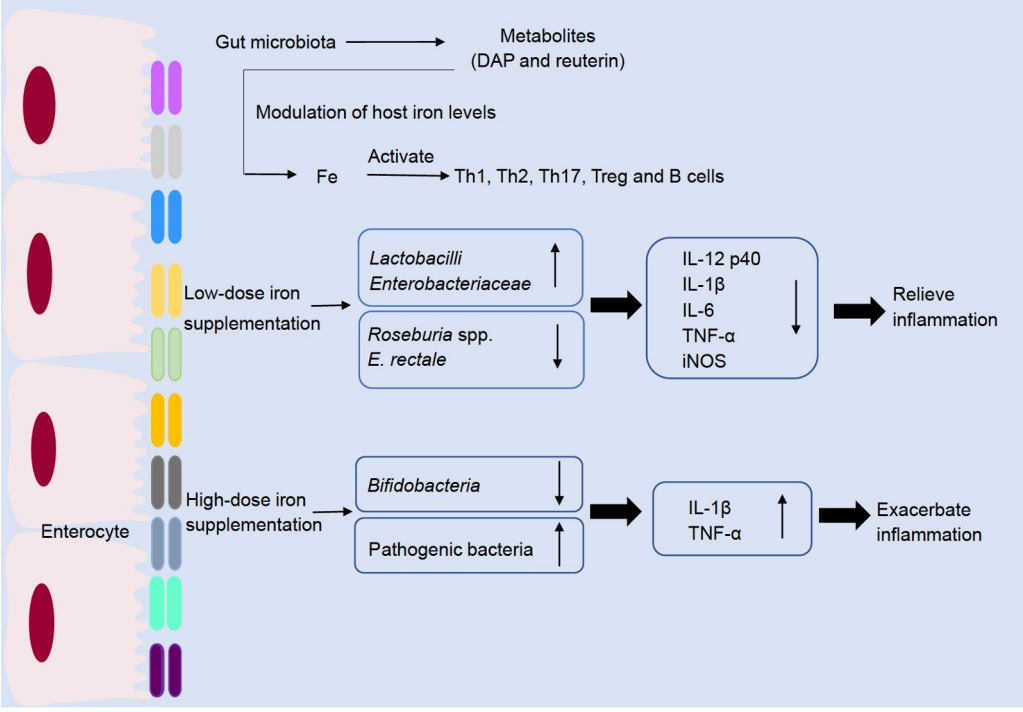

Figure 12 The interaction effects among iron, gut microbes and host immune response. The microbial metabolites DAP and reuterin could modulation host iron levels and further activate Th1, Th2, Th17, Treg and B cells. Low dose iron supplementation leads to increased abundance of *Lactobacilli* and *Enterobacteriaceae* and decreased abundance of *Roseburia* spp. and *E. rectale*. Low dose iron supplementation also leads to decreased expression of IL-12 p40, IL-1β, IL-6, TNF-α and iNOS, and relieves inflammation. High dose iron supplementation leads to a decreased abundance of *Bifidobacteria* and an increased abundance of pathogenic bacteria. Iron supplementation leads to increased levels of IL-1β and TNF-α, and exacerbates inflammation.

gut microbiota. A recent study showed that the pathogenesis of Wilson's disease is related to dysfunction of the gut microbiota in patients. The abundance of Bacteroidetes (*Bacteroides* and *Prevotella* genera) in patients with Wilson's disease is significantly higher than that in the control group, whereas the abundance of Firmicutes, Proteobacteria, and Fusobacteria is significantly lower than that in the control group (Geng et al., 2018). Bacteroidetes plays an important role in maintaining the homeostasis of mucosal T cells and establishing a symbiotic relationship with the host (Wu et al., 2011). Patients with Wilson's disease exhibit immune disorders; their T lymphocytes are lower, whereas B lymphocytes, NK cells, and circulating immune complex IgM are higher than those in healthy individuals (Zhirnova et al., 1998). This also suggests that copper may influence host immune cell production by modulating gut microbiota.

Taken together, both the gut microbiota and copper are important for maintaining a proper host immune response (Figure 13). Although an increasing number of studies have demonstrated that copper can modulate immunity, at least partially, by regulating the composition of gut microbiota, the underlying regulatory mechanism is still uncertain and worthy of further investigation.

Gut microbiota bridges dietary vitamins and host immunity

Unlike proteins, carbohydrates or lipids, which provide energy for the host, vitamins are neither energy sources nor compositions of body tissue. However, as micronutrients, vitamins are essential for host metabolism and health. Vitamins E and C are well known for their antioxidant properties. In addition, B vitamins serve as cofactors for enzymes in a myriad of metabolic processes including glycolysis, TCA, amino acid metabolism, DNA synthesis, methylation, and other critical reactions (Figure 14). Thus, vitamin deficiency alters metabolic homeostasis and is involved in the pathogenesis of many diseases.

Since vitamins can not be endogenously synthesized by the host, most vitamins need to be supplemented from diets. However, the gut microbes have the ability to generate vitamins due to encoding the enzymes of *de novo* synthesis or intermediates utilization, especially B vitamins (Putnam and Goodman, 2020); *vice versa*, vitamins play a key role in modulating intestinal microbiome via direct or indirect mechanisms (Pham et al., 2021a; Steinert et al., 2020), which affect host health (Chen et al., 2022; Huang et al., 2022a). In this part, we mainly outline the crosstalk of vitamin-gut microbiota in regulating host immunity.

Effect of vitamins on gut microbiota

Gut microbes sense and respond to the status/exposure of vitamins through cross-feeding on intermediary and endpoint metabolites (Steinert et al., 2020). The underlying mechanisms are involved indirectly in (i) changing of metabolic physiology of bacteria themselves: it has been re-

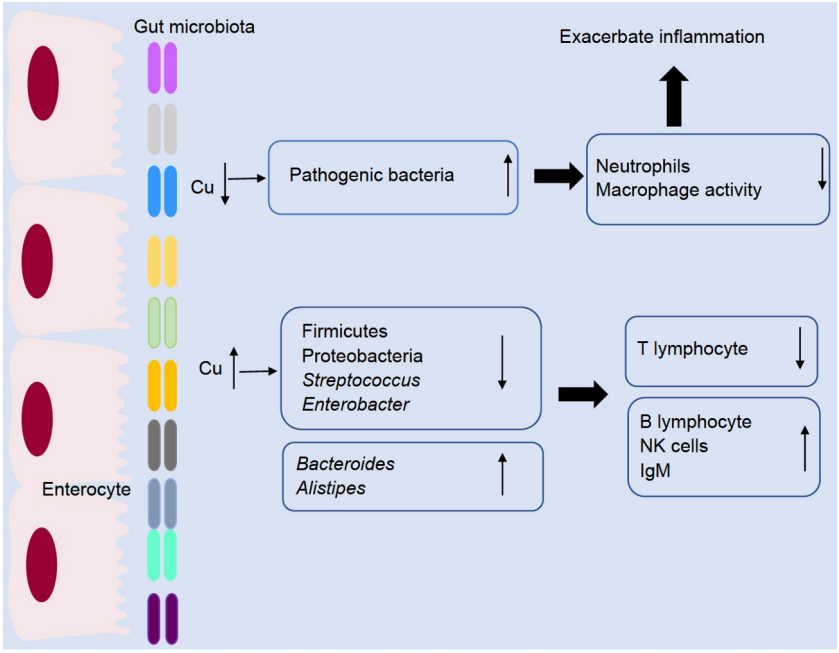

Figure 13 The interaction effects among copper, gut microbes, and host immune response. Copper deficiency leads to an increase in pathogenic bacteria abundance and decreases neutrophil number and macrophage activity, which worsens inflammation; copper supplementation leads to decreased abundance of Firmicutes, Proteobacteria, *Streptococcus* and *Enterobacter*, and increased abundance of *Bacteroides* and *Alistipes*, which leads to improved immune function. IgM, Immunoglobulin M.

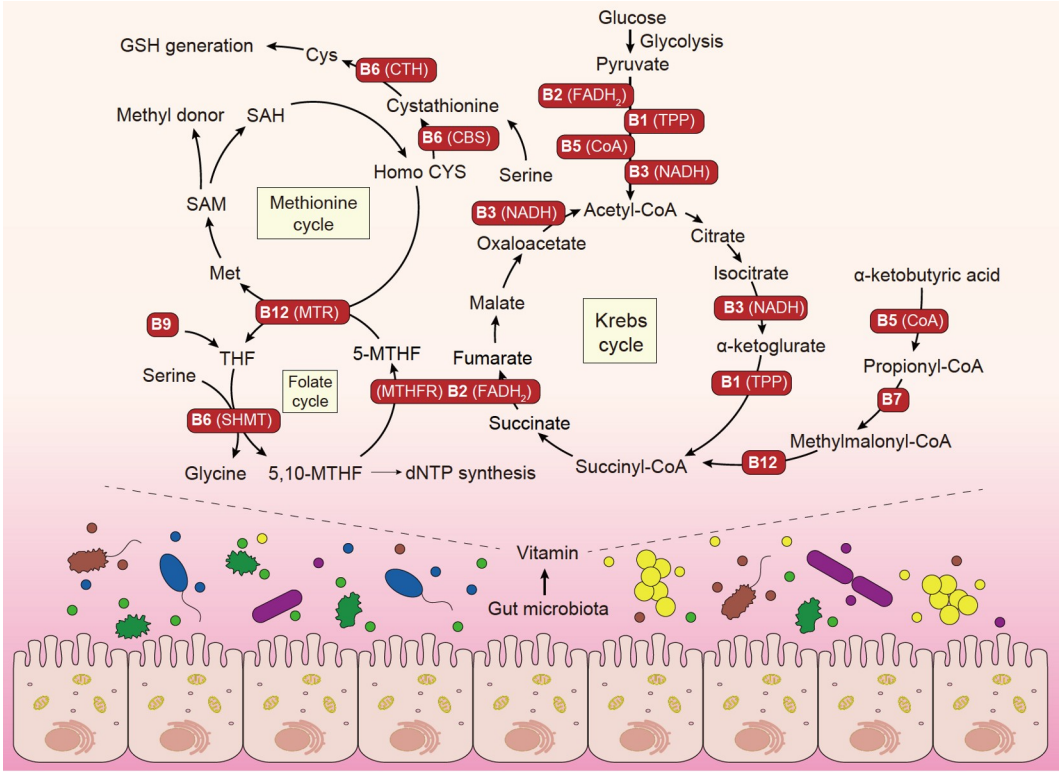

Figure 14 Model of interactions among B vitamins, nutrient metabolism and gut microbes. B vitamins could be produced by the microbiota and they are also involved in carbohydrate and amino acid metabolism. FADH2, flavine adenine dinucleotide; CoA, coenzyme A; NADH, nicotinamide adenine dinucleotide; TPP, thiamin pyrophosphate; SHMT, serine hydroxymethyltransferase, MTR, 5-methyltetrahydrofolate-homocysteine methyltransferase; MTHFR, methylene tetrahydrofolate reductase; CTH, cystathionine γ-lyase.

ported that most bacteria encoded genes were associated with vitamins absorption and transportation (Magnúsdóttir et al., 2015); (ii) maintaining physical barrier integrity in epithelial cells: such as vitamin A, D, and E exerted effects on the regeneration of mucosal epithelial cells, and then responded to intestinal bacterial colonization (Lee et al., 2021; Pham et al., 2021a); (iii) affecting the host immunity (Pham et al., 2021b): vitamin D deficiency causes the imbalance between Th17 and Treg cells in the intestine (Battistini et al., 2020); (iv) changing the gut redox potential, vitamin E and vitamin C are antioxidants in themselves. Vitamin B2 is phosphorylated intracellular to flavin mononucleotide (FMN) and further metabolized to flavin adenine dinucleotide (FAD), which are required in numerous oxidation and reduction reactions. In this section, we summarize the role of vitamins in relation to the gut microbiota.

Water soluble vitamins

Water soluble vitamins contain B vitamins and vitamins C. B vitamins include thiamin (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folic acid (B9) and cobalamin (B12), all of which act as a cofactor of enzymes involved in glycolysis, TCA, AA metabolism and so on. For example, most dehydrogenases require the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), suggesting vitamin B3 is involved in energy production due to redox reactions (Fontecha-Barriuso et al., 2021). Vitamin C, known as ascorbic acid, could be synthesized by mammal animals due to endogenous GULO gene expression, while GULO expression is low in human beings and chickens. Vitamin C functions as an important antioxidant, relying on its hydroxyl and carbonyl groups by donating electrons and hydrogen ions (Gropper and Smith, 2012), and the genetic variant in vitamin C transporter is identified to be related to ulcerative colitis (Amir Shaghaghi et al., 2014). Therefore, inadequate or excess water-soluble vitamins lead to perturbation in host physiology, further affecting gut microbiota stability.

(1) Effect of water-soluble vitamins on microbial growth *in vitro*. Experimental *in vitro* study has found that 0.5 mmol L^{-1} vitamin C and B2 alone or in combination enhances *Blautia coccoides* and *Roseburia intestinalis* growth under mild oxidative conditions, playing beneficial roles in the gut by producing SCFAs; whereas *E. coli* growth is not affected after incubation with these vitamins (da Silva Ferreira et al., 2021). In addition, vitamin C has been proved to have an antibacterial effect on *Mycobacterium tuberculosis*, *Pseudominas aeruginosa*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Helicobacter pylori*, and *Campylo-*

bacter jejuni (Mousavi et al., 2019). The possible antibacterial mechanism may be that vitamin C is known for the antioxidant hydroxyl and carbonyl groups against radicals and ROS due to its reversibly oxidized form. On the other hand, low pH of vitamin C might modify culture properties and further potently affect bacterial growth.

Vitamin B5 is reported to promote the phagocytosis of macrophages and limit *Mycobacteria* growth *in vitro* by promoting the maturity of macrophages and its pro-inflammatory effect (He et al., 2018). In addition, vitamin B5 and its derivatives are proved to own antimicrobial activities against *Staphylacoccus aureus* and *Plasmodiun falciparum* (Abidin et al., 2018). Additionally, methylcobalamin and cyanocobalamin increase the amount of butyrate and propionic acid in an *in vitro* colon simulation; while methylcobalamin promotes lipid, terpenoid, and polyketide metabolism by gut microbiota, which is considered as the first option of vitamin B12 (Xu et al., 2018).

(2) Effect of water-soluble vitamins on gut microbiota *in vivo*. There is evidence showing thiamine supplementation reduces N loss by decreasing *Thaumarchaeota* abundance (Xue et al., 2019). In addition, thiamine supplementation causes a strong shift in bacterial composition and structure including increasing cellulolytic bacteria contents to enhance fiber degradation in dairy cows (Pan et al., 2017) and goats (Ma et al., 2021b; Wen et al., 2021). Similarly, dietary riboflavin supplementation enhances rumen microbial growth about cellulolytic bacteria (Wu et al., 2021a). In models of methotrexate-induced mucositis and esophageal epithelial atrophy mediated by riboflavin deficiency, alpha diversity and gut microbiota composition disorders could be identified, while vitamin B2 replenishment is effective in curing these diseases via restoring gut microbiota (da Silva Ferreira et al., 2021; Pan et al., 2021).

Nicotinamide ribose has been shown to reverse disease status by reshaping intestinal flora (Jiang et al., 2020; Lozada-Fernandez et al., 2022). In contrast, it has recently been found that niacin exacerbated fatty liver disease in HFD fed rats due to impaired fatty acid oxidation and lower VLDL production and secretion (Fang et al., 2020), suggesting the role of vitamin B3 might be varied in different animal species.

Oral administration of vitamin B5 inhibits *Mycobacterial* growth in the lung of mice with *Mycobacterial* infection (He et al., 2018). Vitamin B6 deficiency leads to decreased abundance of *Bacteroides* and elevated abundance of *Lachnospiraceae*_NK4A136_group (Mayengbam et al., 2020). Biotin absorption depends on the sodium-dependent multivitamin transporter (Smvt) in the gut. Intestinal stem cell (ISC) with smvt silencing makes biotin unavailable to cells, resulting in gut dysbiosis and ISC apoptosis, which favors the growth of the pathogen *Providencia sneebia*; while biotin-producing *E. coli* manipulation rescue ISC mitosis (Neophytou and Pitsouli, 2022). Additionally, a study suggests that dietary biotin deprivation promotes the overgrowth of *Lactobacillus murinus* in the gut (Hayashi et al., 2017). These findings indicate that dietary vitamin B7 affects gut microbiota composition.

Vitamins B6 and B12 play key roles in the conversion of different coenzymes forms of folic acid. It is revealed that cecum *Fusobacterium*, *Campylobacter*, *Butyricicoccus*, *Faecalibacterium*, *Aeriscardovia*, and *Megamonas* are positively correlated with dietary folic acid level, while negative relationships could be found for *Alistipes*, *Akkermansia*, *Perlucidibaca*, *Barnesiella*, and *Blvii28* (Bai et al., 2021a). Similarly, gut microbiota and SCFAs alteration mediated by imbalanced folic acid diets lead to the obesogenic phenotypes in rats (Mjaaseth et al., 2021). It was found that vitamin B12 supports the metabolic interaction between *Akkermansia muciniphila* and butyrate-producing *Eubacterium hallii* through bidirectional cross-feeding (Belzer et al., 2017). Moreover, dietary 100 μg kg^{-1} vitamin B12 addition increases the abundance of *Faecalibacterium* and *Lactobacillus*, but decreases *Acinetobacter* content in cecum (Wang et al., 2021a). However, vitamin B12 in animals accounts for heterogeneous results about α or β diversity, microbiota composition and metabolism function (Guetterman et al., 2022).

Vitamin C and *Lactobacillus acidophilus* treatment together attenuates ethanol-induced intestinal and liver injury in mice by restoring gut microbiota homeostasis and reinstating the immune balance of colonic Treg cells (Lu and Wang, 2021). Notable results include positive effects that dietary vitamin C improves gut pathology and integrity and decreases inflammatory cytokines in gut epithelial cells in spontaneously hypertensive rats, suggesting that antihypertensive effects of vitamin C were involved in the reshaping of gut microbiota via gut-brain-axis (Li et al., 2021b). Clinical work has shown that colon-delivered vitamin C increases microbial alpha diversity and metabolic activity by improving fecal total SCFAs concentration (Pham et al., 2021b), and high-dose vitamin C increases the relative abundances of *Lachnospiraceae*, while decreases Bacteroidetes, *Enterococci* and *Gemmiger formicilis* in humans (Otten et al., 2021). The alteration of intestinal microbiota is supposed to improve liver health and glucose metabolism homeostasis in patients with NAFLD (He et al., 2021).

Fat soluble vitamins

Water soluble vitamins are usually non-toxic and have a relatively wide dosage range for the host. However, excess fat-soluble vitamins (including vitamins A, D, E, and K) intake cause hepatic metabolic stress and disturb the homeostasis of host.

Fat soluble vitamins are related to gut microbiota composition: at the phylum level, vitamin A is positively related

to the ratio of Proteobacteria/Actinobacteria and *P*roteobacteria/Firmicutes, but the opposite result is found for vitamin E; vitamin D increases Actinobacteria/Proteobacteria, Actinobacteria/Bacteroidetes, Proteobacteria/Firmicutes, and Other/Bacteroidetes; at the genus level, higher vitamin A or D intake increases the relative abundance of *Methanobrevibacter* and Staphyococcus, respectively; while vitamin E decreases *Sutterella* relative abundance (Mandal et al., 2016). It has been suggested that vitamin A deficiency reduces the abundance of filamentous bacteria, which in turn inhibited Th17 cell differentiation in the small intestine (Cha et al., 2010). A clinical trial also showed that lower diversity of gut microbiota is found in fecal samples of vitamin A-deficient children with persistent diarrhea, and *Enterococcus* is predominated when compared with the vitamin A-normal group (Lv et al., 2016). In mice, vitamin A deficiency reduces the relative abundance of Bacteroidetes in cecum (Tian et al., 2018). Furthermore, acute dietary vitamin A deficiency elicits alterations in the bacterial community and meta-transcriptome of feces, and significantly increases the proportion of *Bacteroides vulgatus*, which is correlated with colonitis (Hibberd et al., 2017), suggesting that vitamin A is related to intestinal inflammation.

Vitamin D, known as calciferol, is associated with bone growth and development. Vitamin D deficiency alters microbial composition and translocating ability across the epithelium, leading to host immune alterations (Yamamoto and Jørgensen, 2019). Specifically, vitamin D-free diets increase the abundance of *Escherichia*, *Candidatus blochmannia* and *Enterobacter* and reduce that of *Butyricimonas* in fecal samples of rats (Robles-Vera et al., 2019). There are also preliminary indications that vitamin D supplementation reduces trimethylamine-N-oxide level in plasma by increasing *Bacteroides* and *Akkermansia* relative contents in cecum, suggesting the potential role of vitamin D in cardiovascular diseases (Wang et al., 2020b). The contribution of vitamin D to radiation resistance in radiotherapy has been reported where the underlying mechanisms may be related to gut microbiota via vitamin D receptors (Huang et al., 2019a). In addition, there are some literatures about the effect of vitamin D on gut microbiota in the models of IBD and NASH, which will be discussed in detail in the following part about the role of vitamins-gut microbiota in host immunity or related diseases.

Vitamin E is reported to influence the F/B ratio in caecum of mice, and the relative percentage of Proteobacteria increased along with dietary vitamin E levels (Choi et al., 2020). Vitamin E addition in DSS-induced colitis mice could partly rescue the tight junction protein down-regulation and *Roseburia* reduction, which belongs to butyrate producing bacteria, suggesting the protective effect of vitamin E on intestinal barrier function and favorable recovery of gut microbiota imbalance (Liu et al., 2021). Studies about the effect of vitamin E on gut microbiota are relatively rare.

Vitamin K promotes the carboxylation of osteocalcin, thus serum high undercarboxylated osteocalcin is used an indicator of vitamin K deficiency (Castaneda et al., 2020). The diversity of the gut microbiota is found to be negatively associated with serum undercarboxylated osteocalcin level (Wagatsuma et al., 2019). It has been reported that vitamin K deficiency decreases *Lactobacillus* and increases *Bacteroides* and *Ruminococcus* abundances in mice (Ellis et al., 2021). Although considerable data have revealed the role of vitamin K in the gut microbiota, large gaps in our knowledge still remain because the responses of gut microbiota to dietary vitamin K levels are different with different diseases in animals (Lai et al., 2021).

The effect of gut microbiota on vitamin metabolism

Gut microbiota regulates vitamin metabolism via metabolites, enzymes, and receptors based on the relationship of cross-feeding among bacteria and completion with the hosts. We cover the contribution of microbiome to vitamin production and metabolism in this section.

Genomes of gut bacteria contain genes related to vitamins de novo biosynthesis

Gut microbiota is considered as an extension of human genome (Magnúsdóttir et al., 2015), the synthesis of vitamin B1 is prevalent in Bacteroidetes and Fusobacteria, but is less in Firmicutes. All Bacteroidetes and Fusobacteria, 92% Proteobacteria, and half of Firmicutes are predicted for vitamin B2 biosynthesis, and they all share the one preserved route. However, Actinobacteria is predicted to be non-producing organism for vitamin B2. For vitamin B3, its production is predicted in Actinobacteria, Fusobacteria, Proteobacteria, Firmicutes, and Bacteroidetes, but the ratios for the first two phyla are lower than the other three. In case of vitamin B5, all Bacteroidetes, 95% Proteobacteria, a few Actinobacteria and Firmicutes are predicted to possess the ability of pantothenate biosynthesis, which is a precursor for coenzyme A (CoA). For vitamin B6, most of Actinobacteria, Bacteroidetes, and Proteobacteria have the ability to produce vitamin B6 as well as a few Firmicutes and Fusobacteria, which are involved in two different routes. There are three different routes for vitamin B8 synthesis identified in human gut microbiota, although most of Bacteroidetes (96%), Fusobacteria (100%), and Proteobacteria (84%) are predicted to synthesize biotin, their biosynthesis routes are different. About 92% Bacteroidetes, 79% Fusobacteria, and 71% Proteobacteria have been predicted to synthesize folate, while Actinobacteria and Firmicutes genomes might be absence of folate biosynthesis. All Fusobacteria and about half of Bacteroidetes and Firmicutes genomes are predicted to be cobalamin (B12) producers, while the synthesis of cobalamin

is rare in Actinobacteria and Proteobacteria.

Except for the prediction from genome annotation, many experimental studies have also proved the fact that microorganisms are related to B vitamins production. *Helicobacter pylori*, *S. pneumonia*, and *Mycobacterium tuberculosis* are reported to be related to vitamin B6 biosynthesis and pathogenicity, suggesting that B6 could be a potential drug target to prevent bacteria or pathogens infection (Parra et al., 2018). Ruminal vitamin B12 concentration is positively related to the abundance of *Prevotella* but negatively to the abundance of Bacteroidetes, *Ruminiclostridium* and *Butyrivibrio* (Fakhoury et al., 2020). *Propionobacterium shermanii* and *Pseudomonas denitrificans* are mostly used as commercial strains to produce vitamin B12 because they code all enzymes involved in B12 *de novo* biosynthesis (Balabanova et al., 2021). Antibiotic-induced gut dysbiosis and dietary biotin deprivation promote the overgrowth of *Lactobacillus murinus*, reducing available biotin in the gut and led to the development of alopecia in a biotin-dependent manner (Hayashi et al., 2017). In addition, food-related lactic acid bacteria such as *Bifidobacteria*, *Lactobacilli*, *Bacillus subtilis* are widely used for fermented milk to increase the levels of B vitamins.

In sum, the percent for B vitamins biosynthesis in human gut microbiota is 40% for biotin, 42% for cobalamin, 43% for folate, 63% for niacin, 51% for CoA, 50% for vitamin B6, 65% for vitamin B2, and 56% for vitamin B1. These suggest that one vitamin could be produced by different bacteria, and one bacterial also could produce more than one vitamin. The contribution of microbiome produced vitamins to human requirements is different among B vitamins with 86% for B6, 37% for B9, 31% for B12, 27% for B3, only 3% for B12, 2.3% for B1, which has been concluded in a recent review (Pham et al., 2021a). From the perspective of gut microbiota, not all bacteria can simultaneously produce all B vitamins, indicating there exist symbiotic relationships for B vitamins utilization among gut microbiota. *Faecalibacterium prausniztii* is reported to use vitamin B2 as a mediator for extracellular electron transfer to the anode of microbial fuel cell systems (Khan et al., 2012), indicating that gut microbiota also rely on vitamins as nutrients for survival. About 83% Actinobacteria genomes contain biotin transporter although they lack biotin biosynthesis genes (Magnúsdóttir et al., 2015). Most Firmicutes contain roles for the conversion of DHF to THF, suggesting that they might depend on the uptake of vitamins. Similarly, most of Actinobacteria and half of Firmicutes genomes contain riboflavin transporter role though *de novo* biosynthesis pathway is absent in these bacteria. 1,2-Propanediol produced by *Akkermansia muciniphila* could support the growth of *Eubacterium hallii*, which in turn provided *Akkermansia muciniphila* with cobamide (Belzer et al., 2017). These genome annotations associated with vitamin biosynthesis and transporters and cross-feeding relationship all support the fact that gut microbiota could affect B vitamins production and metabolism.

Effects of gut microbiota on fat soluble vitamins

Vitamin K could be produced by gut microbiota. *Bacillus subtilis*, *Veillonella*, *E. coli* and *Shigella* are reported to produce vitamin K (Stacchiotti et al., 2021). Vitamin K produced by intestinal bacterial contributes to 10%–50% of human vitamin K requirements. In addition, modification of the gut microbiota to produce vitamin K functions as new therapeutic approach for bone quality (Castaneda et al., 2020). However, gut microbiota could not contribute to other fat-soluble vitamins. Daily requirements for vitamins A, D and E are mainly from dietary intake.

Proteins or metabolites (bile acids) produced by gut microbiota regulate vitamin A transport into intestinal epithelial cells by FXR and RXR expression; in addition, enzymes from gut microbiota promote the retinoids production from β-carotenoids (Srinivasan and Buys, 2019). The role of gut microbiota in vitamin D status and biological functions through FGF23 activity directly or metabolites (bile acids and SCFAs) or enzymes indirectly have been well summarized elsewhere (Steinert et al., 2020). Lithocholic acid (as metabolites from bacteria) binds VDR to compete with vitamin D, thereby affecting vitamin D metabolism. Some hydroxylase expressed by bacteria might take part in hydroxylation of vitamin D. On the other hand, the absorption and transportation of fat-soluble vitamins take place in the epithelial cells similarly to fats, which are usually under the help of bile acids. SCFAs also play an important role in the barrier functions of the intestine. Thus, microbiota-producing metabolites might affect fat soluble vitamins metabolism through the intestinal epithelial function of hosts. Taken together, although direct shreds of evidence are less to support the effect of gut microbiota on fat soluble vitamin metabolism, enzymes, metabolites, and receptors from gut microbiota as well as intestinal barrier of the hosts are all potentially involved in the regulation mechanism indirectly.

The role of vitamins-gut microbiota crosstalk in host immunity or related diseases

It has been reported that the estimated prevalence of NAFLD is 25.2% in the general population and more than 50% in the diabetic and obese group (Bugianesi and Petta, 2022). The incidence and prevalence of IBD have rapidly increased worldwide and now is a global disease (Park and Cheon, 2021). Both of these two diseases are associated with complex interplay among immunological, metabolic and microbial factors. Hence, we mainly summarize the role of vitamin-gut microbiota crosstalk in human NAFLD and IBD diseases in this section.

IBD

The gut microbiota is involved in the development and progression of IBD by interacting with host immunity (Glassner et al., 2020; Huang et al., 2022b). It is found that vitamin B1, riboflavin, thiamin, biotin, folate, vitamin B12, vitamins A and C are significantly lower in patients with IBD. Furthermore, vitamin B5 is particularly depleted in the gut during IBD (Lloyd-Price et al., 2019). A recent review has indicated that a high prevalence of vitamin D deficiency, lower vitamin B2 and C are linked to patients with IBD, and they proposed that the effect of vitamin D on IBD is mediated by controlling gut microbiota composition through antimicrobial peptides (Pham et al., 2021a). B vitamins could be produced by gut microbiota via *de novo* synthesis. These imply the crosstalk between vitamins and gut microbiota in IBD disease. Most studies also address the role of vitamins-gut microbiota crosstalk in the development and treatment of IBD. Vitamin D deficiency causes a decrease in the diversity of butyrate production bacteria in IBD, while butyrate is thought to reduce inflammation and maintain the balance between Th17 and Treg cells (Battistini et al., 2020), indicating that vitamin D modulates inflammatory response in the host mediated by intestinal microbiota. In addition, early vitamin D deficiency could lower the abundance of *Clostridium* XIVa and *Bacteroides* to inhibit optimal Treg cell expansion, which improves the susceptibility to colitis in mice (Cantorna et al., 2019). Also, nicotinamide has been demonstrated to increase the proportion of *Odoribacter*, *Flexispira*, and *Bifidobacterium*, restoring the composition of gut microbiota and derived SCFAs production, which protects barrier function of the intestine by regulating immune cytokines, and consequently ameliorate chronic colitis in mice (Kang et al., 2021). In this regard, vitamins themselves could act as powerful signaling molecules to develop mitigation function on IBD via remodeling gut microbiota and intestinal homeostasis.

NAFLD

The liver is the main site for fat soluble vitamins metabolism, and most B vitamins serve as coenzyme factors during the process of lipid metabolism. Interestingly, vitamin status is related to NAFLD. Indeed, each vitamin could be contained, while folic acid, vitamins A, C, D and E accounted for a large portion regarding the role of vitamins in NAFLD (Abe et al., 2021). Additionally, there is evidence that the occurrence and development of NAFLD is associated with imbalance of gut microbiota, which is called the gut-liver axis (Zhao et al., 2023). Clinical trials have suggested that an oral intake of 1,000 mg d^{-1} vitamin C for 12 weeks increases the diversity of intestinal microbiota and the relative proportion of beneficial bacteria, which contribute to improve liver function and other metabolic parameters in NAFLD patients through gut-liver axis (He et al., 2021). Animal study with vitamin D intraperitoneal injection has supported this concept, and vitamin D remodels the gut microbiota, alleviates hepatic lipid accumulation and inflammatory response in HFD-induced NAFLD mice (Zhang et al., 2023). Consistently, vitamin D treatment is demonstrated to ameliorate HFD-induced hepatic injury *in vivo* and *in vitro* via suppressing pyroptosis and restoring gut microbiota dysbiosis by increasing *lactobacillus* and reducing *Acetatifactor*, *Oscillibacter*, and *Flavonifractor* relative abundances (Zhang et al., 2021c). Similarly, vitamin E also ameliorates NAFLD/NASH by suppressing hepatic lipid deposition, lipid peroxidation and inflammation (Nagashimada and Ota, 2019). Collectively, although limited direct shreds of evidence support the relationship between vitamin E and gut microbiota in NAFLD disease, it might be possible that vitamin E is involved in the regulation of gut redox potential as the antioxidant just like vitamin C.

Of note, carbohydrate-restricted diet treatment in obese humans with NAFLD could decrease hepatic *de novo* lipogenesis, and increase folate-producing *Streptococcus* as well as serum folate levels, suggesting that gut bacteria might contribute to the beneficial effects of dietary folic acid on lipid metabolism disorder diseases (Mardinoglu et al., 2018). Specifically, folic acid restores depleted hepatic one-carbon metabolism and the diversity of gut microbiota, thereby improving hepatic metabolism via sirt1-dependent mechanism (Xin et al., 2020). Vitamin B6 and B12 play key roles in the conversion of different coenzymes forms of folic acid, and they interact with each other to develop the function in one-carbon unit metabolism, therefore vitamin B6 and B12 might develop function in NAFLD disease from the perspective of one-carbon metabolism.

In addition, dietary folic acid increases acetic acid and propionic acid in cecal, which is negatively related to gene expression about cell proliferation and differentiation in abdominal fat (Liu et al., 2023). Acetic acid and propionic acid down-regulate lipid contents in adipocytes from humans with obesity and diabetes (Naraoka et al., 2018). Subcutaneous acetate injection decreases triglyceride concentrations in plasma and absolute weight of adipose tissue in rabbits (Liu et al., 2019). Therefore, all of these highlight their potential interactions among folic acid, gut microbiota, SCFAs on lipid disorders (Figure 15). Although we did not find direct evidence to clarify their causal relationship using fecal bacteria transplantation under folic acid diets, the mechanism that folic acid regulating lipid disorders is linked to gut microbiota could be illustrated to some extent based on most references.

Conclusions and perspectives

Although there are contradictory results, the existing data

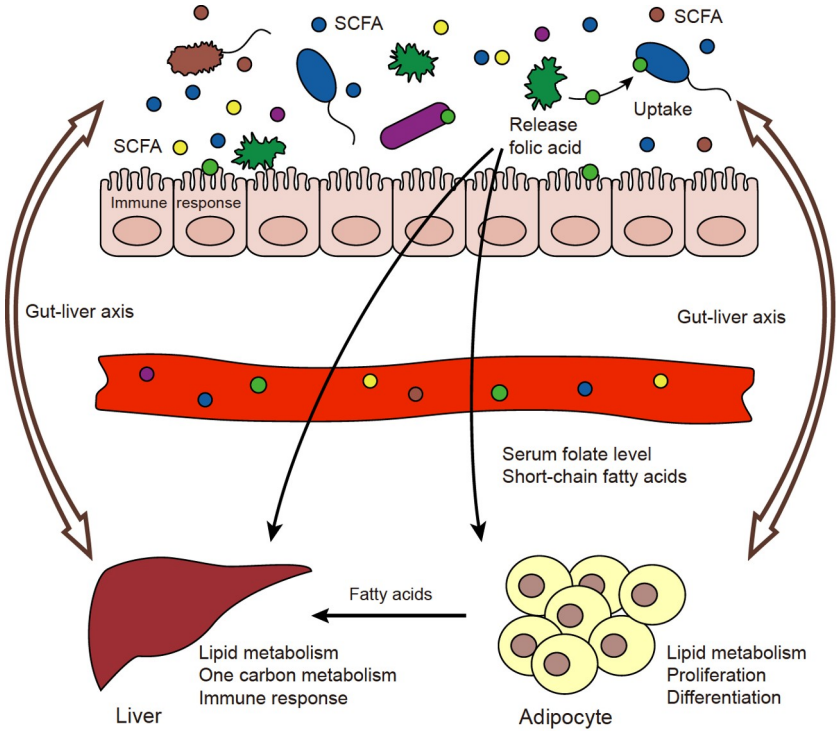

Figure 15 Schematic depicting the crosstalk among microbiota, folic acid, and NAFLD/obesity. Folic acid could affect hepatic lipid metabolism and cell proliferation and differentiation in adipose tissue through portal venous circulatory system. In addition, folic acid also indirectly develops its function in lipid regulation or immune response mediated by gut microbiota and their metabolites (SCFAs) via the gut-liver axis.

demonstrate that the bacterial transformation of dietary constituents plays critical roles in host health and diseases. Dietary nutrients shape the function of gut microbiota and exert powerful regulatory effects on the host. This increased understanding of diet-microbes-host interactions suggests the manipulation of nutrients intake and gut microbes is a powerful way to modulate host health. Therefore, delineating the molecular mechanisms of diet-gut microbe crosstalk and host immunity will facilitate to formulate dietary regulation strategies or gut microbiota manipulation methods, and provide a practical basis for targeted intervention and treatment of related diseases.

The tripartite diet-microbiota-host crosstalk is complex and multidirectional. In different host states (health or disease), the dominant nutrients may change, and there are complex and dynamic interactions between different nutrients. Therefore, dietary recommendations designed to tackle diseases need to be based on conclusive medical evidence. Owing to the host's need to continuously consume an appropriate level of macronutrients and micronutrients to maintain normal life activities, untangling the cooperation mode of different nutrients in a specific host state stands at the first step in formulating reasonable dietary recommendations. Moreover, we should note that diet is not the only stimuli that mediate the host state by disturbing the gut microbial ecosystem. For example, there is compelling evidence that the ABO blood types influence the community structure of gut bacteria as well as feedback on the host (Zmora et al., 2019). Thereby, it is difficult to separate physiological effects that are caused by a diet-altered microbiota from those that are directly caused by the diet and from those in which microbiota alterations are merely a bystander or secondary effect (Wang and Wang, 2022). As such, information on diet-gut microbiota-host interactions needs to further validate, refine, and innovate. We need to move from simply making associations among diets or gut microbial taxa and host phenotype toward elucidating the mechanisms, namely, identifying key microorganisms for the fermentation of specific dietary constituents, untangling the fermentation pathway, deciphering the mechanism of action of metabolites and consequently attempting to assemble meaningful and applicable conclusion. On this basis, the intervention means to enhance, introduce, or eliminate specific functionality genes or taxa selectively in the digestive tract could provide a possibility for treating diseases.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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