

PERSPECTIVE

Investigating regional-specific gut microbial distribution: an uncharted territory in disease therapeutics

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The gastrointestinal (GI) tract is crucial for nutrient digestion and absorption. Longitudinally segmented into the mouth, esophagus, stomach, duodenum, jejunum, ileum, cecum, and colon, each region plays a critical role in these processes and hosts trillions of symbiotic microbiota with diverse functions (Donaldson et al., 2016). Moreover, as the body's largest endocrine organ, the GI tract orchestrates host metabolic regulation via a complex crosstalk between the host and microbiota, mediated by gut hormones, bioactive peptides, and microbiota-modified metabolites (Ahlman and Nilsson, 2001; Donaldson et al., 2016).

Conventionally, it was believed that only a limited number of microbiota in the oral cavity could move beyond their original location and colonize other regions of the GI tract, potentially causing metabolic disorders. However, recent studies have increasingly demonstrated that microbes residing in the oral cavity are significantly linked to systemic diseases (Baker et al., 2024; Peng et al., 2022), including metabolic and GI disorders (Read et al., 2021). Interestingly, some studies have found that the atypical colonization of oral microbes in the lower intestinal tract could contribute to GI immune (Atarashi et al., 2017) and glycolipid metabolic disorders (Kunath et al., 2022; Vonaesch et al., 2022). While the driving mechanism behind microbial migration warrants further investigation, these findings underscore the fact that microbial dislocation in the gut occurs much more frequently than previously anticipated.

The small intestine, including the duodenum, jejunum, and ileum, serves as the primary site for nutrient processing, with each segment displaying distinct

metabolic patterns. Physiological factors, including enzymes such as pepsin and gastric lipase from the stomach, bile acids (BAs) from the liver, and trypsin, amylase, and carboxypeptidase from the pancreas, modulate the functionality of these segments (Peters, 1970; Treherne, 1967). Consequently, the upper intestine's local microenvironment influences the survival, colonization, and proliferation of microbiota, resulting in a lower bacterial density due to factors such as oxygen presence, rapid transit time, variable pH, and enzymatic activity (Kastl et al., 2020; Martinez-Guryn et al., 2018). Notably, aging significantly alters the gut microbiota signatures of the small intestine, potentially becoming microbial hallmarks of aging in the future (Leite et al., 2021). On the other hand, the large intestine, comprising the cecum and colon, harbors the most abundant bacteria due to its thicker mucus layer and favorable conditions for microbial growth (Evans et al., 1988; Marteau et al., 2001; Pereira and Berry, 2017). The variations in physiological characteristics (such as epithelial structure and intestinal motility), microenvironments (aerobic/anaerobic), and pH levels along the GI tract contribute to the biogeographic distribution of the microbiota, which has already been systematically reviewed before (de Vos et al., 2022; Martinez-Guryn et al., 2019).

Recent multi-omics studies have revealed significant differences in microbial composition, host proteins, metabolome, and phages among different regions of the GI tract (Folz et al., 2023; Shalon et al., 2023; She et al., 2024). These findings underscore the spatial heterogeneity of the microbiota, metabolites, and immune response across different segments of the intestine. Consequently,

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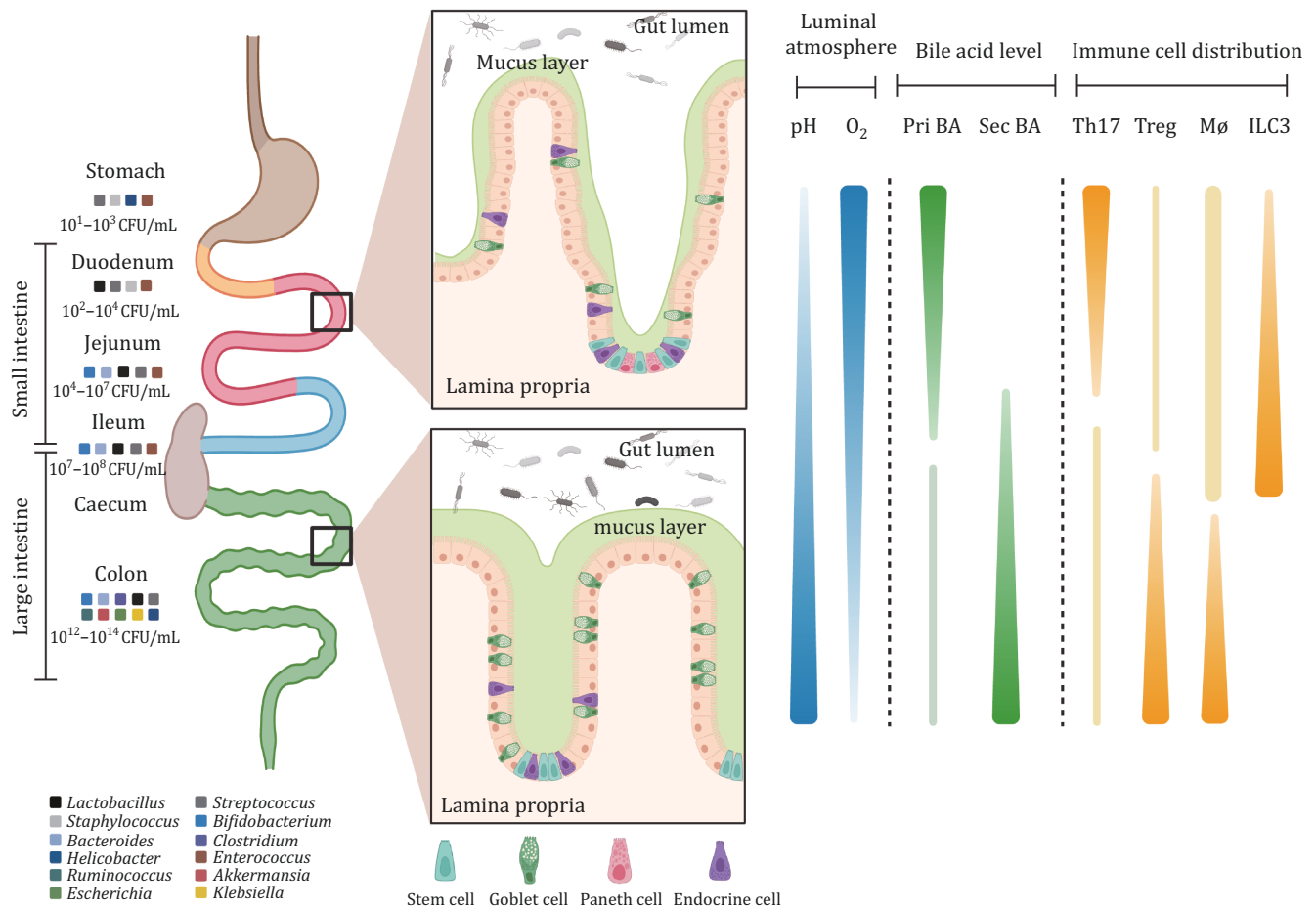


Figure 1. The longitudinal microbial distribution and other physiological characteristics of GI tract. The left side illustrates the bacterial composition and colony-forming units (CFU/mL) in different regions of the gut, from the stomach to the colon. The middle insets provide detailed views of the epithelial structure in the small intestine and colon, showing key cell types such as stem cells, goblet cells, Paneth cells, and endocrine cells, along with the lamina propria and the mucus layer. The right side illustrates the luminal atmosphere parameters (pH, oxygen levels), bile acid concentration (primary and secondary bile acids), and the distribution of key immune cell types along the GI tract. The gradients represent variations in these factors across different regions of the intestine. Pri BA, primary bile acid; Sec BA, secondary bile acid; Th17, T helper 17 cells; Treg, regulatory T cells; M ϕ , macrophages; ILC3, type 3 innate lymphoid cells.

the displacement of bacteria from their native niches can occur in response to diverse physiological and pathological stimuli. Disruption of the microbiota-intestinal immune homeostasis ultimately leads to systemic metabolic dysregulation and contributes to metabolic and GI diseases. Manipulating gut microbiota redistribution may offer a novel therapeutic approach for metabolic diseases.

The longitudinal distribution and functionality signatures of microbiota and metabolites along the gastrointestinal tract

The gastrointestinal tract include longitudinal segments (i.e., stomach, duodenum, jejunum, ileum, cecum, and colon), and each region play critical roles in digestion and absorption processes of dietary nutrients, meanwhile,

as the largest endocrine organ regulating host metabolism through various gut hormones and bioactive peptides (Ahlman and Nilsson, 2001; Donaldson et al., 2016) (Fig. 1). The small intestine which could be further divided into three segments (duodenum, jejunum, and ileum, each with distinct metabolic patterns), is responsible for the digestion and absorption of dietary nutrients. These physiologic functions were affected by many physiological factors, such as pepsin and gastric lipase from the stomach, bile acids (BAs) from the liver, trypsin, amylase, and carboxypeptidase secreted from the pancreas (Peters, 1970; Treherne, 1967). The microenvironment of each gut segment affects the survival, colonization, and amplification of microbial organisms, the upper small intestine harbors a lower abundance of bacteria as the O_2 contents, transit time, pH levels, and presence of digestive enzymes (Kastl et al., 2020; Martinez-Guryn

et al., 2018). Apart from these intestinal physiologic factors, a recent study found that natural aging significantly altered the gut microbiota signatures of the small intestine (Leite et al., 2021), which may become the hallmarks of aging from the microbial perspective in the future. Interestingly, host genetic variations attributed by the individual diversity in immune-related pathways could greatly impact the microbial composition in different human body sites (Blekhman et al., 2015).

The large intestine which included the cecum and colon, harbors the most abundant bacteria owing to their thicker mucus layer and luminal microenvironment suitable for microbial growth (Evans et al., 1988; Marteau et al., 2001; Pereira and Berry, 2017). Moreover, the characteristics of bacteria along the gastrointestinal tract have been reviewed in some papers (Donaldson et al., 2016; Martinez-Guryn et al., 2019). The physiologic properties, colonization preference of microbes, and gut luminal microenvironment determine the longitudinal distribution of gut microbiota and its related metabolites along the gastrointestinal tract (Table 1). Therefore, when bacteria did not colonize in their original location, after exposure to various external physiological or pathological stimuli, it may lead to the occurrence of metabolic or gastrointestinal diseases. We reckon that the longitudinal distribution of gut microbiota in each intestinal segment is disturbed in metabolic and gastrointestinal diseases, which contributes to the onset and progression of the diseases.

Stomach

About forty years ago, the stomach was generally regarded as a microbiologically sterile organ because its microenvironment was considered inhospitable for bacterial growth (Yang et al., 2013). With the advancement of modern technology, it was gradually recognized that some specific bacteria existed in the stomach (i.e., *Helicobacter pylori*), and the abnormal increase of certain pathogenic bacteria can lead to the occurrence of diseases (de Vos et al., 2022; Hunt et al., 2015). The microenvironment of acidity pH, high levels of digestive enzymes, oxygen content, and peristalsis speed resulted in relatively lower bacterial abundance (Hunt et al., 2015). Therefore, the α diversity was decreased and the aero- and acid-tolerant taxa were enriched in the healthy stomach. Dominant members of the phylum bacteria in the stomach were Proteobacteria, Firmicutes, Bacteroidetes, Fusobacteria, and Actinobacteria (Kaźmierczak-Siedlecka et al., 2022). The gut microbiome composition and functions varied along the gastrointestinal tract. Besides, studies have suggested that the crosstalk between the gut microbiome of the stomach and the microbiota in the lower gastrointestinal tract contributes to disease development. The patients carried *Helicobacter pylori* also had an extremely low relative abundance of several

Bifidobacterium species in the lower gut of those with aggressive gastric diseases (Devi et al., 2021). Bile reflux gastritis and the higher intragastric pH values have been implicated with the etiopathogenesis of gastritis and gastric cancer, which lead to the elevated concentration of conjugated and secondary BAs (Li et al., 2019; Wang et al., 2022) and the enrichment of pathogenic bacterium (Jin et al., 2022a; Noto et al., 2022). Besides, several oral pathogenic bacteria were related to the persistence of atrophy and intestinal metaplasia in the stomach, such as *Peptostreptococcus*, *Streptococcus*, *Parvimonas*, *Prevotella*, *Rothia*, and *Granulicatella* (Kaźmierczak-Siedlecka et al., 2022; Rajilic-Stojanovic et al., 2020). The occurrence of pathogenic bacterial thriving in patients with bile reflux and the translocation of oral pathogens both contributed to the etiopathogenesis of gastric or other gastrointestinal disorders, which also provides us with an idea to treat the related diseases by focusing on bacterial longitudinal displacement.

Duodenum

The duodenum received the chyme from the stomach and alternately contracted, and relaxed, which moved the food to the following intestinal segments. The contraction of the duodenum helped the product in the intestine transported to the jejunum quickly. Primary bile acids were synthesized from the cholesterol in the liver and temporarily stored in the gallbladder (Jia et al., 2018). After the meal, they were secreted into the duodenum with pancreatic juices to facilitate digestion and absorption of dietary lipids and nutrients (Jia et al., 2018). Meanwhile, bile acids had certain bactericidal effects, as the main regulator of microbial activity (An et al., 2022). Besides, due to the relatively higher oxygen content in this intestinal segment, coupled with the presence of gastric acid and various digestive juices, and the shorter transit time, the abundance of the duodenal bacterial load is relatively low, approximately between 10^2 and 10^4 CFU/mL (Simon and Gorbach, 1984). Limited by sampling methods, the study focused on the small intestinal flora, especially the duodenal flora was much more difficult than that of feces. As for the microbial composition, the common duodenal microbiota phyla include Firmicutes, Proteobacteria, and Actinobacteria (Sroka-Oleksiak et al., 2020). Shanahan et al. confirmed the presence of duodenal mucosa-associated microbiota, dominated by the genus of *Streptococcus*, *Prevotella*, *Veillonella*, and *Neisseria* in the lower level, with newly developed encased biopsy forceps (Shanahan et al., 2016).

Studies have shown that elevated pH levels resulting from hypoacidity and reduced BA secretion can lead to bacterial overgrowth in the duodenum, including many oral pathogenic bacteria, such as *Rothia mucilaginosa*, *Streptococcus salivarius* and *Granulicatella adiacens* (Filardo et al., 2022). This suggested a disordered longitudinal

Table 1. The relationship between regional-specific microbiota, metabolites, and diseases.

Metabolite	Key microbial species	GI tract location	Disease
	<i>Bacteroidia</i> , <i>Gammaproteobacteria</i> , <i>Clostridia</i> , <i>Bacilli</i> , <i>Alphaproteobacteria</i> , <i>Actinobacteria</i> , <i>Campylobacteria</i> , <i>Fusobacteria</i> , <i>Negativicutes</i> , <i>Erysipelotrichia</i> , <i>Lentisphaeria</i> , <i>Coriobacteriia</i> , <i>Mollicutes</i> , <i>Chlamydiae</i> , <i>Deltaproteobacteria</i> , <i>Verrucomicrobiae</i> and <i>Saccharimonadia</i>	Duodenum	Hyperglycemia (Darra et al., 2023)
	<i>Streptococcus</i> , <i>Prevotella lineages</i> , <i>Fusobacteria</i> , <i>Veillonella</i>	Duodenum	Functional dyspepsia, gastric emptying (Shanahan et al., 2023)
	<i>Escherichia coli</i> , <i>Prevotella salivae</i> , <i>Neisseria</i>	Duodenum	Celiac disease (Constante et al., 2022)
Bile acids			
DCA, LCA	<i>Clostridium</i> , <i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Bacteroides</i>	Distal small intestine and colon	CRC (Gérard, 2013; Ridlon et al., 2016b)
Iso-DCA	<i>Eubacterium lentum</i> , <i>Clostridium perfringens</i> , <i>Ruminococcus gnavus</i>	Distal small intestine and colon (Wahlström et al., 2016)	
Allo-bile acids	<i>Eubacterium</i>	Distal small intestine and colon	HCC (El-Mir et al., 2001)
UDCA	<i>Clostridium</i>	Distal small intestine and colon	Cholesterol gallstone, PBC and PSC (Ridlon and Bajaj, 2015)
HDCA	Unidentified Gram-positive rod	Putative: Distal small intestine and colon	MASLD (Madsen et al., 1976; Kuang et al., 2023)
SCFAs			
Acetate	<i>Akkermansia muciniphila</i> , <i>Bacteroides spp.</i> , <i>Bifidobacterium spp.</i>	Colon	IBD, CRC (Imhann et al., 2018; Louis et al., 2014; Macfarlane and Macfarlane, 2003)
Propionate	<i>Coprococcus catus</i> , <i>Eubacterium hallii</i> , <i>Bacteroides spp.</i>	Colon	IBD, CRC (Louis et al., 2014; Macfarlane and Macfarlane, 2003; Sun et al., 2017)
Butyrate	<i>Coprococcus comes</i> , <i>Coprococcus eutactus</i> , <i>Anaerostipes spp.</i>	Colon	IBD, CRC (Louis et al., 2014; Macfarlane and Macfarlane, 2003; Sun et al., 2017)
Tryptophan metabolites			
Indole	<i>Achromobacter liquefaciens</i> , <i>Bacteroides ovatus</i> , <i>Bacteroides thetaiotamicron</i>	Putative: colon	IBD, metabolic syndrome, obesity (Agus et al., 2018; Devlin et al., 2016)
Indole derivatives	<i>Bacteroides spp.</i> , <i>Clostridium spp.</i> , <i>Escherichia coli</i>	Putative: colon	Metabolic syndrome, obesity (Agus et al., 2018; Devlin et al., 2016)
Kynurenines'	<i>Lactobacillus spp.</i> , <i>Pseudomonas aeruginosa</i> , <i>Pseudomonas fluorescens</i>	Putative: colon	IBD, IBS, metabolic syndrome, obesity (Agus et al., 2018; Vujkovic-Cvijin et al., 2013)
Tryptamine	<i>Clostridium sporogenes</i> , <i>Ruminococcus gnavus</i>	Putative: colon	Depression, ASD (Kałużna-Czaplińska et al., 2019; Williams et al., 2014)
Serotonin (5-hydroxytryptamine)	Indigenous spore-forming bacteria	Putative: colon	IBS, metabolic syndrome, obesity, depression, ASD (Fung et al., 2019; Kałużna-Czaplińska et al., 2019; Yano et al., 2015)
Imidazole propionate	<i>Aerococcus urinae</i> , <i>Streptococcus mutans</i> , <i>Anaerococcus prevotii</i> , <i>Adlercreutziaae equolifaciens</i> , <i>Eggerthella lenta</i> , <i>Lactobacillus paraplantarum</i> , <i>Brevibacillus laterosporus</i> , <i>Shewanella oneidensis</i>	Putative: colon	T2DM (Koh et al., 2018)

Table 1. Continued

Metabolite	Key microbial species	GI tract location	Disease
Others			
Dopamine	<i>Enterococcus</i> , <i>Lactobacillus</i>	Jejunum	Parkinson's disease (van Kessel et al., 2019)
Dopamine	<i>Enterococcus faecalis</i> , <i>Enterococcus faecium</i>	Intestine	Parkinson's disease (Maini Rekdal et al., 2019)
Histamine	<i>Morganella morganii</i> , <i>Escherichia coli</i>	Intestine	Asthma (Barcik et al., 2017)
TMAO	<i>Clostridia</i> , <i>Proteus</i> , <i>Shigella</i> , and <i>Aerobacter</i>	Colon	CVD (Gatarek and Kaluzna-Czaplinska, 2021; Subramaniam and Fletcher, 2018)

DCA, deoxycholic acid; LCA, lithocholic acid; UDCA, ursodeoxycholic acid; HDCA, hyodeoxycholic acid; CRC, colorectal cancer; HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; MASLD, metabolic-associated steatotic liver disease; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; ASD, autism spectrum disorder; TMAO, trimethylamine N-oxide; CVD, cardiovascular disease.

distribution of the oral microbiota to the distal gut, resulting in duodenal dysbiosis and pathological conditions. Another study reported that the oral normal microflora like *Shuttleworthia* and *Rothia* are overrepresented at the distal duodenum in patients with alcoholic liver disease, implying that some microbes shifting down into the duodenum was implicated in the progression of alcoholic liver disease (Maccioni et al., 2020). Besides, the gut microbial structure of duodenal mucosa was closely related to type 2 diabetes (T2DM) and obesity (Darra et al., 2023; Sroka-Oleksiak et al., 2020). Emmanouil et al. compared the duodenal microbiota samples of the patients with obesity and healthy controls through 16S rDNA sequencing and found that obese individuals had a significant increase in anaerobic genera (Angelakis et al., 2015). Meanwhile, the metabolism pathway of glycerophospholipid and the pathway of sucrose phosphorylase were downregulated in obese individuals (Angelakis et al., 2015). Furthermore, bariatric surgery and duodenal mucosal resurfacing (DMR) surgery showed that the proximal small intestine is the key contributor to post-operative metabolic benefits, which involved the displacement of duodenal microbiota (Liou et al., 2013; van Baar et al., 2021). It is worth noting that, diets induced mucosa-associated microbiota dysbiosis varied across the intestinal tract. Studies based on the porcine metabolic syndrome model have shown that *Lactobacillus johnsonii*, which had an anti-obesity effect by preventing inflammation and mucosal barrier disruption (Yang et al., 2020), was elevated at the duodenum and decreased at the cecal and rectal luminal regions (Xu et al., 2022).

Jejunum

The intestinal segment of the jejunum is an important site for the digestion and absorption of dietary lipids. Dietary lipids digested in the duodenum are further absorbed in the jejunum as fatty acids. The small intestine especially the jejunum was responsible for the

majority of dietary nutrients digestion and absorption, also having profound effects on the host physiology (El Aidy et al., 2015; Ermund et al., 2013). However, few studies have investigated the composition of intestinal flora in the jejunum because of the limited access to obtain jejunal intestinal contents or tissue in healthy individuals, and most of the investigations have focused on the large intestine or feces. Complex interactions of oxygen level, nutrient bioavailability, pH, bile acid contents, gastrointestinal motility, mucus, and immune factors contribute to the low levels of diversity and richness of gut bacteria in the jejunum, approximately between 10^4 and 10^7 CFU/mL (Simon and Gorbach, 1984). The common sampling method such as the endoscope needed to pass through the oral cavity and upper gastrointestinal tract, which will cause confusion and contamination of samples. In a study investigating the jejunal bacterial microbiota from fasting obese patients by surgery, the jejunal bacteria richness was relatively lower, approximately 10^3 – 10^4 CFU/mL (Villmones et al., 2022). Under normal physiological conditions, the intestinal barrier of the jejunum protects the internal circulation environment from destruction by pathogenic intestinal bacteria, including physical barriers (epithelial cells, tight junctions), chemical barriers (mucus layer, antimicrobial peptide), immunological barriers (such as secretory immunoglobulin A (sIgA)), and the competitive effect of commensal microbiota. Cani et al. observed an increase in circulating lipopolysaccharides (LPS) level in mice fed a high-fat diet (HFD) for 4 weeks, which further contributed to the increased inflammatory response during obesity development. This metabolic alteration occurs because of the disruption of the jejuno-intestinal physical barrier (Cani et al., 2007).

Ileum

The ileal microbial load was estimated 10^7 – 10^8 CFU/mL compared with the upper intestinal tract, accompanied

by increased facultative and strict anaerobes (Hayashi et al., 2005). As for the ileal-harbored bacteria, most taxa of the Enterobacteriaceae and the Bacilli class of the Firmicutes, and relatively high abundances of *Enterococcus*, *Lactobacillus*, *Clostridium*, *Streptococcus* were found in ileum from human samples (Ahmed et al., 2007; Boojink et al., 2010; Donaldson et al., 2016; Hayashi et al., 2005; Wang et al., 2005). Similarly, the compositional and functional fluctuations of the lower small intestinal microbes were largely unexplored due to the inaccessibility of the biological specimens. Recently, researchers found that the human gut microbiota in the distal small intestine would react flexibly like changing the biomass of the whole microbes or the proportions of subspecies in response to the nutritional status, providing a novel understanding of the host-gut microbiome crosstalks (Yilmaz et al., 2022).

Beyond the roles of digestion and absorption of dietary nutrients, the ileum was widely involved in regulating the host's metabolic homeostasis through the gut microbiome-host interactions. BAs, synthesized by the hepatic enzymes from cholesterol, were the key participants. The hepatic primary BAs would conjugate taurine or glycine, forming the conjugated primary BAs, then were secreted into the intestinal tract when the gallbladder contracted after meals. The conjugated BAs would be deconjugated by the bile salt hydrolase (BSH) from the gut microbiota in the ileum. And the bile acids that reached the lower small intestine would be reabsorbed into the portal vein by passive and active transport including the apical sodium bile acid transporter (ASBT) and recirculated to the liver (Jia et al., 2018).

Many nuclear receptors were expressed in the distal ileum, including farnesoid X receptor (FXR), G-protein-coupled bile acid receptor 1 (GPBAR1, TGR5), G-protein-coupled receptor 43 (GPR43), and vitamin D receptor (VDR) (Fiorucci et al., 2021). The intestinal FXR-liver axis played an important role in the regulation of hepatic bile acid synthesis and glycolipid metabolism (Sun et al., 2021). The fibroblast growth factor 15/19 (FGF15/19) was released from the ileal enterocytes when the FXR signaling was inhibited, further, the hepatic cholesterol 7 α -hydroxylase (CYP7A1), the rate-limiting enzyme of the bile acid synthetic pathway, was downregulated (Inagaki et al., 2005). Besides, the bile acid-intestinal FXR-ceramide axis also played a part in glucose and lipid metabolism, preventing the development of metabolic-associated steatotic liver disease (MASLD), insulin resistance, and even diabetes when the intestinal FXR signaling was depleted (Chen et al., 2022; Gonzalez et al., 2016; Wu et al., 2021). TGR5 was another BA-bound receptor activated by multiple conjugated and unconjugated BAs, the glucagon-like-peptide 1 (GLP-1) would be released when the TGR5 in enteroendocrine L cells was activated (Ahmad and Haeusler, 2019; Pols et al., 2011). Hyocholic

acid species (HCAs), a special group of BAs from pig, could strongly stimulate the secretion of GLP-1 through a distinct inhibited FXR and activated TGR5 mechanism in enteroendocrine cells simultaneously (Makki et al., 2023; Zheng et al., 2021) to promote insulin secretion and further maintain glucose homeostasis (Albaugh et al., 2019), besides, ileal FXR signaling pathway was involved in the therapeutic effects of hyodeoxycholic acid (HDCA) for MASLD (Kuang et al., 2023). Another endogenous bile acid, cholic acid-7-sulfate (CA7S), increased after the sleeve gastrectomy, inducing the GLP-1 secretion by activating the TGR5 (Chaudhari et al., 2021). Besides, short-chain fatty acids (SCFAs) also could trigger the secretion of GLP-1 from intestinal L cells by activating the GPR43/41, exerting beneficial effects on obesity and diabetes (Tolhurst et al., 2012). L-arabinose, a microbiota-accessible carbohydrate (MAC), could increase the relative abundance of microbiota-derived SCFAs, which will further activate the GPR43/GPR41 from the distal ileum (Tomioka et al., 2022). Another nuclear receptor, VDR, was highly expressed in the ileum, and activated by the lithocholic acid (LCA) and 3-oxo-LCA, 6-oxo-LCA (Makishima et al., 2002). LCA would increase the ileal expression of *Cyp24a1* and *Cyp3a11*, which were responsible for the detoxification of LCA (Adachi et al., 2005; Ishizawa et al., 2018). Besides, lack of the VDR in Paneth cells would contribute to the impaired anti-bacterial capability, increasing the inflammatory responses (Lu et al., 2021).

Colon

The thicker colonic outer and inner mucus layers allowed the inhabitant of larger biomass of anaerobic microbiota up to 10^{12} – 10^{14} CFU/mL compared with the small intestine (Sommer and Bäckhed, 2013). Given the microenvironment and physiological properties, the colon was enriched in the families *Bacteroidaceae*, *Prevotellaceae*, *Lachnospiraceae*, and *Ruminococcaceae* (Flint et al., 2012).

In a physiological state, the majority of dietary carbohydrates, lipids, and proteins would be emulsified, digested, and absorbed in the small intestine, and few would escape this process reaching the colon. Besides, the un-digestible dietary fibers would pass through the gastrointestinal tract all the way to the colon because of the lack of host enzymes that could break down the fibers. Under the fermentation of dietary carbohydrates by some bacteria including genera *Bacteroides*, *Prevotella*, *Parabacteroides*, and *Alistipes* (Flint et al., 2015), the microbiota-derived SCFA could fuel the colonocytes, mitigate the inflammation, and served as signaling molecules (Koh et al., 2016). The deficiency of SCFA was closely related to the progression of diabetes, and supplementation of SCFA producers could alleviate the disturbance of glucose metabolism to some extent

(Zhao et al., 2018), which implied targeting the dietary fibers-gut microbiota-SCFA to treat metabolic diseases would be a feasible approach (Canfora et al., 2019).

The colon was the dominant site for the secondary metabolism of the primary BAs that escaped from the enterohepatic circulation in the distal ileum. After the deconjugation of conjugated BAs by BSH, primary unconjugated BAs like cholic acid (CA) and chenodeoxycholic acid (CDCA) would be 7α -dehydroxylated to form the deoxycholic acid (DCA) and LCA respectively by a series of BA-inducible (bai) enzymes from *C. scindens*, *C. hiranonis* and *C. hylomonae* (Funabashi et al., 2020; Ridlon et al., 2016a). Another commensal bacteria *Faecalicatena contorta* S122 was recently found to efficiently convert CA/CDCA to DCA/LCA respectively (Jin et al., 2022b). Apart from the deconjugation, and dehydroxylation forms of BA transformation, oxidation and epimerization were also the other secondary metabolisms of BAs by gut microbiota (Devlin and Fischbach, 2015). A large number of oxo-, epi- and iso-BA derivatives metabolized by gut microbiota have been identified, recent studies reported that LCA could be metabolized into the trace cluster of BA, 3-oxoLCA, and isoLCA by the gut microbiota isolated from human feces, including 12 bacterial genera (Song et al., 2020). Another study identified a special secondary BA, isoalloLCA, produced by the *Odoribacteraceae* strains after which were screened in the centenarians (Sato et al., 2021). As for BA epimerization, the microbial 7α -hydroxysteroid dehydrogenase (7α -HSDH) and 7β -HSDH could convert the CDCA to ursodeoxycholic acid (UDCA) (Heinken et al., 2019) and DCA to iso-DCA (Song et al., 2021) respectively.

GI locations: determinant of microbial properties in health and diseases

In recent decades, microbiome research has primarily focused on the large intestine (colon) and fecal samples, revealing their role in maintaining metabolic homeostasis. However, emerging evidence suggests that the upper intestinal regions, particularly the small intestine (duodenum, jejunum, and ileum), plays a significant role in this balance. Studies have found distinct microbiota in the jejunum and ileum compared to the colon (Zmora et al., 2018), with the proximal small intestine (stomach and duodenum) showing greater response to external stimuli than the distal small intestine (jejunum and ileum) (Seekatz et al., 2019). Additionally, research has shown rapid changes in ileal microbiota biomass and sub-strains in response to feeding status compared to the relatively stable colonic microbiota (Yilmaz et al., 2022). These findings warrant in-depth investigation into the role of the small intestine in regulating host metabolism.

The distribution of the microbiota is closely related to its function and can significantly impact host metabolism

in both normal and abnormal conditions (Tropini et al., 2017). The circadian rhythm, a fundamental physiologic process, is regulated by core clock transcription factors, which in turn affects cellular processes and helps the body adapt to daily oscillations (Roenneberg and Merrow, 2016; Takahashi, 2017). Disturbances in the diurnal rhythmicity of host-gut microbiota interactions contribute to metabolic dysfunctions (Thaiss et al., 2015, 2016). Studies have shown that a HFD can cause changes in the composition and gene expression of the microbiota in the small intestine, particularly the ileum, which plays a crucial role in regulating host circadian rhythms (Dantas Machado et al., 2022). HFD also impairs the expression of the antimicrobial peptide Reg3 γ in the distal small intestine, disrupting the rhythmicity of the gut microbiota and leading to metabolic dysregulation (Frazier et al., 2022). Additionally, recent research has demonstrated that diet can modulate the function of the small intestine barrier through the diet-microbiota-small intestine MHC class II-IL-10 axis, highlighting its importance in developing interventions for gut inflammatory diseases (Tuganbaev et al., 2020). Interestingly, targeting microbial choline trimethylamine lyase inhibition has been shown to improve metabolic status by reshaping circadian rhythms (Schugar et al., 2022).

In various pathological conditions, the gut microbiota has been closely linked to a cluster of diseases, such as obesity, diabetes, MASLD, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and celiac disease (CeD) (de Vos et al., 2022).

In IBD, chronic inflammation affects the entire GI tract and is accompanied by disruptions in gut microbiota composition. A recent review has highlighted the importance of reclassification of Crohn's disease (CD) into ileum-dominant and colon-dominant types based on site-specific changes in pathophysiological characteristics (Atreya and Siegmund, 2021). However, the contribution of the small intestine to IBD pathogenesis, particularly in CD, has been overlooked. An emerging study revealed that the microbial composition of the colon partially resembles that of the small intestine, including specific pathobionts found in the small intestine that are relevant to disease phenotypes (Ruigrok et al., 2021). This suggests that metabolic dysregulation in the small intestine may precede and potentially contribute to colonic disorders.

Small intestinal bacterial overgrowth (SIBO) occurs when there is an overload of non-native or native bacteria in the duodenum and jejunum. SIBO is closely associated with conditions such as IBS, MASLD, and T2DM, characterized by abnormal concentrations of bacteria in the upper small intestine and corresponding clinical manifestations (Skrzydło-Radomańska and Cukrowska, 2022). Many factors contributing to the occurrence of SIBO, including gastric acid secretion

deficiency, bilio-pancreatic insufficiency, anatomical modifications by surgery, intestinal dysmotility, impaired intestinal mucosal integrity, and a dysfunctional ileocecal valve, have been systematically reviewed elsewhere (Bushyhead and Quigley, 2022). SIBO has a relatively high prevalence in gastrointestinal disorders like IBS, IBD, and CeD. In metabolic diseases, obesity is linked to an elevated risk of SIBO, with a prevalence rate of 26% in obese individuals compared to 6% in healthy controls (Ierardi et al., 2016; Roland et al., 2018). SIBO may play a contributing role in the onset and development of obesity. Additionally, approximately 35% of individuals with chronic MASLD exhibit SIBO, indicating its presence throughout different stages of liver diseases (Gudan et al., 2022). Increased intestinal permeability is associated with a higher incidence of SIBO in MASLD patients, suggesting a potential role in the pathogenesis of MASLD (Miele et al., 2009). The mechanisms by which SIBO contributes to MASLD need further investigation. Pathophysiological influences of SIBO include mucosal injury induced by bacteria and competition for dietary nutrients, leading to maldigestion and malabsorption (Bushyhead and Quigley, 2022). Recent research has shown that individuals with SIBO have reduced microbial diversity and disruptions in the ecological network of the duodenal microbiota, with notable elevations of *E. coli* and *Klebsiella* strains, potentially triggering inflammatory immune response (Leite et al., 2023). Therefore, therapeutic strategies for metabolic diseases with concurrent SIBO should focus on reconstructing the small intestinal microbiota to restore the regulation of metabolites and the intestinal immune-mediated metabolic signaling pathways.

It is important to note that the relationship between SIBO and disease remains a subject of ongoing debate, raising the question of whether SIBO contributes to the onset of certain diseases or as a consequence of underlying pathologies. This “chicken or egg” situation complicates our understanding of SIBO’s role in disease progression. Conditions such as impaired gut motility, immune dysfunction, or altered intestinal anatomy may predispose individuals to SIBO, suggesting that it could be a secondary effect. However, SIBO itself may exacerbate disease by promoting inflammation or disrupting normal nutrient absorption. Further research, particularly longitudinal studies, is needed to clarify this bidirectional relationship and determine whether SIBO is a driver of disease or a consequence.

CeD, an autoimmune enteropathy mediated by T cells, occurs in genetically predisposed individuals with the absence of gluten metabolism-related genes (Abadie et al., 2011). A longitudinal prospective cohort study examining fecal samples from children at high risk of developing CeD revealed that altered microbial signatures occurred before the onset of the disease (Leonard et al.,

2021). Notably, the predominant site of CeD is localized in the small intestine, where specific compositional and functional changes in the duodenal microbiota have been linked to impaired gluten degradation (Caminero et al., 2016; Constante et al., 2022). These findings emphasize that the GI location is a determinant for the composition and functionality of microbiota in CeD.

The pivotal role of GI location and its resident microbiota in the development and progression of diseases, such as MASLD, T2DM, obesity, and other GI disorders, needs to be reevaluated. The spatial distribution of gut microbiota along the GI tract has profound effects on host physiology by influencing the microbiota–metabolites–immune system interaction (Fig. 2). Understanding the longitudinal shifts of gut microbiota along the GI tract during disease progression is essential for conducting mechanistic studies and developing effective intervention approaches.

Disrupted microbial distribution in metabolic disease onset: insights from bile acid metabolism

BAs are synthesized from cholesterol in the liver through a series of complex enzymatic pathways. After a meal, BAs are secreted into the small intestine along with pancreatic enzymes and undergo further metabolism by the gut microbiota, leading to the diversification of the BA pool. In the physiological state, microbial transformations of BAs, such as deconjugation, hydroxylation, and epimerization. These transformations play a crucial role in nutrient absorption and maintaining intestinal metabolic and immune homeostasis.

Changes in dietary patterns or other external pathophysiological factors can significantly alter the BA profile, affecting both its biosynthesis and secretion processes (Zheng et al., 2017). These alterations can reduce the anti-bacterial effect of BAs in the upper small intestine, allowing certain microbial populations to thrive in these regions and deviate from their original ecological niches, potentially contributing to SIBO (Fig. 3). The displacement of microbiota can cause the deconjugation of conjugated BAs in advance, resulting in a reduced proportion of conjugated BAs reaching the distal small intestine, while untimely deconjugated BAs may diffuse into the circulation via passive transport. These changes in the BA profile disrupt the regulatory effects of conjugated/unconjugated and primary/secondary BAs on BA-related receptors, leading to the malfunction of BA-mediated host glucose and lipid metabolism by disrupting intestinal FXR signaling and the TGR5-GLP-1 axis. Additionally, the displacement of microbiota can trigger intestinal immune responses, disrupting the homeostasis of the intestinal immune system and inducing intestinal inflammation in the proximal small intestine. These dysregulations

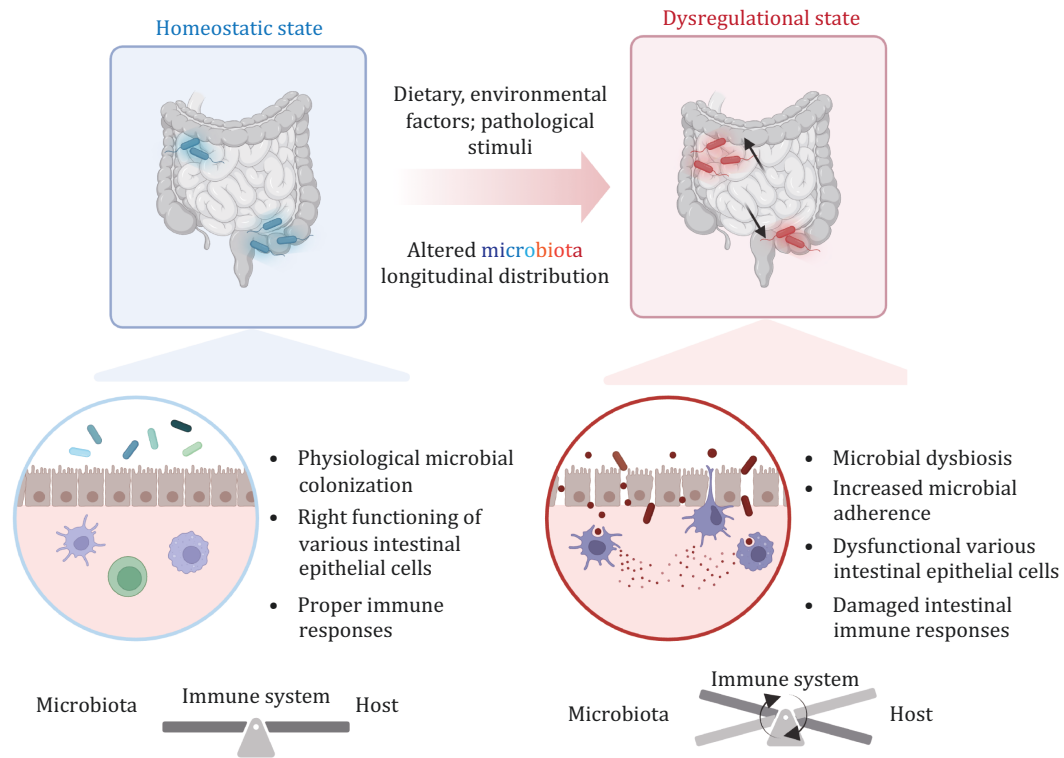


Figure 2. The disruption of gut longitudinal microbial distribution contributed to the host metabolic dysregulation. Various dietary, environmental, and pathological stimuli would lead to the altered GI longitudinal microbiota distribution, which disrupts the microbiota–metabolites–immune response homeostatic state.

may further fuel the progression of various metabolic diseases, including obesity, T2DM, MASLD, and GI disorders.

Recently, studies have identified novel microbial-mediated biosynthetic conjugated forms of BAs (Mohanty et al., 2024a; Ridlon and Gaskins, 2024) in the intestine, such as acylated- (Liu et al., 2024; Nie et al., 2024), amino acid conjugated- (Quinn et al., 2020; Rimal et al., 2024) and polyamine conjugated BAs (Mohanty et al., 2024b), with unexpectedly high levels observed in the small intestine, although their precise physiological functions still require further elucidation. Importantly, whether dislocated microbiota in the proximal small intestine could lead to the production of these newly identified and yet more uncharted forms of BAs remain unclear. Additionally, the existence of regional-specific microbiota-mediated BA metabolism along the GI tract warrants further exploration and detailed investigation.

Targeting the redistribution of gut microbiota for preventive and therapeutic intervention

This review outlines different strategies for modulating the distribution of gut microbiota along the GI tract, providing insights and guidance for the development of effective therapeutic approaches that target the longitudinal displacement of gut microbiota. These therapeutic

strategies can be broadly classified into two main categories: anatomical modifications of the microbiota through surgery and ecological control achieved by introducing exogenous bacteria or metabolites into the gut ecosystem (Fig. 4A). Moving forward, we aim to explore innovative interventional and therapeutic strategies that target the manipulation of longitudinal gut microbial distribution, which merit further investigation and attention.

Anatomical modifications

How does gastric bypass surgery specifically alter the microbiota composition of the small intestine? Bariatric surgery has emerged as a highly effective treatment strategy for obesity and T2DM, leading to significant reductions in body weight, blood glucose levels, and improved insulin sensitivity (Kirwan et al., 2022; Mingrone et al., 2021; Schauer et al., 2017). The two most commonly performed bariatric surgeries are vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB). VSG involves the removal of a large portion of the stomach, while RYGB re-routes the intestinal tract, bypassing the stomach, duodenum, and proximal jejunum. Notably, the postoperative metabolic improvements have been linked to changes in BAs profiles and gut microbiota composition in both human and rodent models. These metabolic changes include elevated levels of total and specific serum BAs (McGavigan et al.,

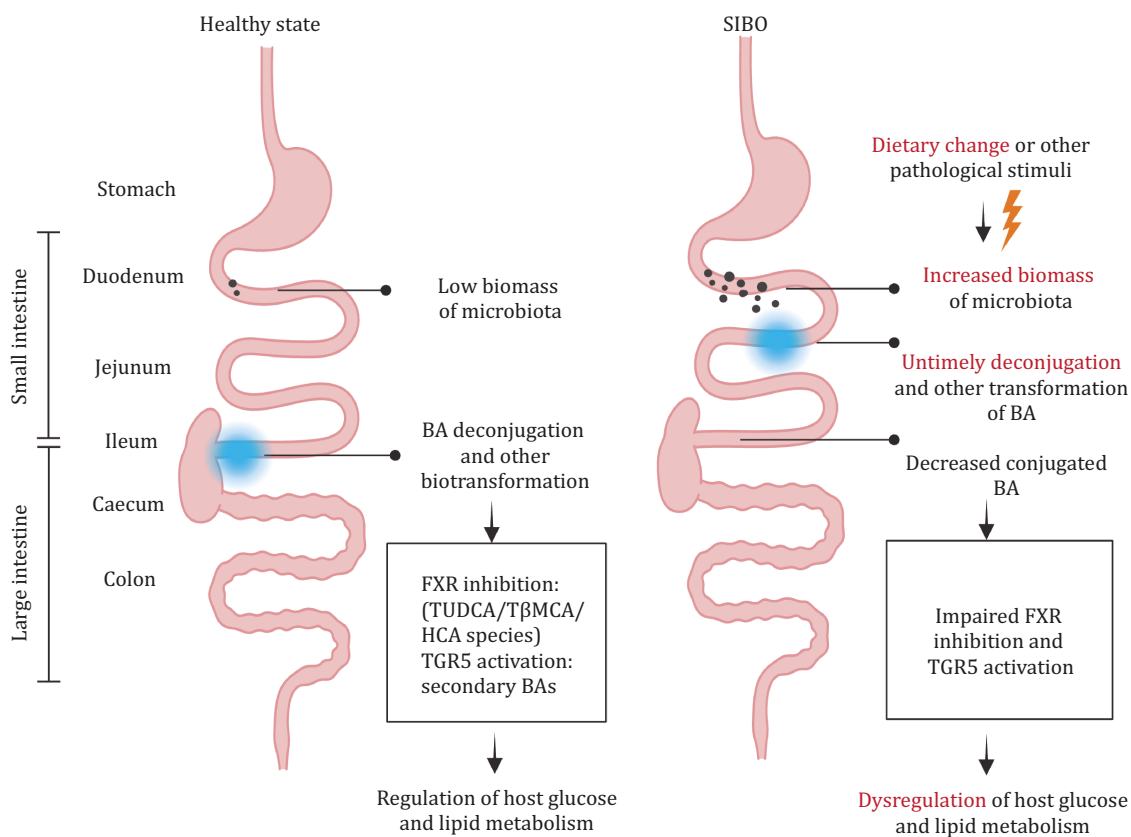


Figure 3. Dislocation of microbiota contributes to bile acid-mediated impaired host metabolism: a scenario that possibly happens in SIBO. Bile acids are normally metabolized (deconjugation and other biotransformation) in the lower small intestine, especially in the terminal ileum. When the SIBO occurs, bile acids are untimely deconjugated and transformed by the overgrown microbiota in the upper small intestine, which results in the less conjugated bile acids reaching the terminal ileum, impairing the regulation of bile acids on the glucose and lipid metabolism by targeting the critical receptors such as FXR and TGR5. BA, bile acid; FXR, farnesoid X receptor; TGR5, G-protein-coupled bile acid receptor 1; TUDCA, tauroursodeoxycholic acid; TβMCA, tauro-β-muricholic acid; HCA, hyocholic acid.

2017; Myronovych et al., 2020; Patti et al., 2009; Ryan et al., 2014), as well as alterations in the composition and function of the gut microbiota, which may contribute to improved glucose metabolism (Dang et al., 2021; Fouladi et al., 2019). A recent study demonstrated that germ-free mice receiving gut microbiota from post-RYGB surgery patients on a Western diet exhibited enhanced insulin sensitivity, characterized by a reshaped gut microbiota structure (increased *Akkermansia muciniphila* or *Blautia*) and metabolomic profiles (increased tryptophan-derived metabolites) (Yadav et al., 2023). The gut microbiota appears to be a key determinant in the regulation of glucose metabolism following RYGB (Debédát et al., 2022). More importantly, we reckoned that bariatric surgery especially RYGB, specifically and significantly altered the microbiota composition of the small intestine owing to the more rapid and pronounced changes in nutrient flow, bile acid metabolism, gut transit time, and oxygen levels compared with distal intestine. The anatomical alteration reduced exposure of ingested food to gastric

acids, digestive enzymes, and BAs in the bypassed section, creating an environment less favorable for certain bacteria while promoting others. The reduction in bile acid exposure in the upper small intestine can decrease the growth of bile-sensitive bacteria and increase bile-resistant ones. Besides, RYGB accelerated the transit of food through the small intestine, reducing the time food spent in this region. This limited the growth of bacteria that rely on slow transit and fermentation. These alterations led to shifts in bacterial populations, favoring species that adapt to the new metabolic and environmental conditions, ultimately contributing to improved metabolic health and weight loss.

Ecological control

From an ecological perspective, the introduction of exogenous agents such as probiotics, prebiotics, phages, and fecal microbiota transplantation (FMT) can compete with the dislocated microbiota for nutrition, thereby regulating the ecological balance and facilitating the

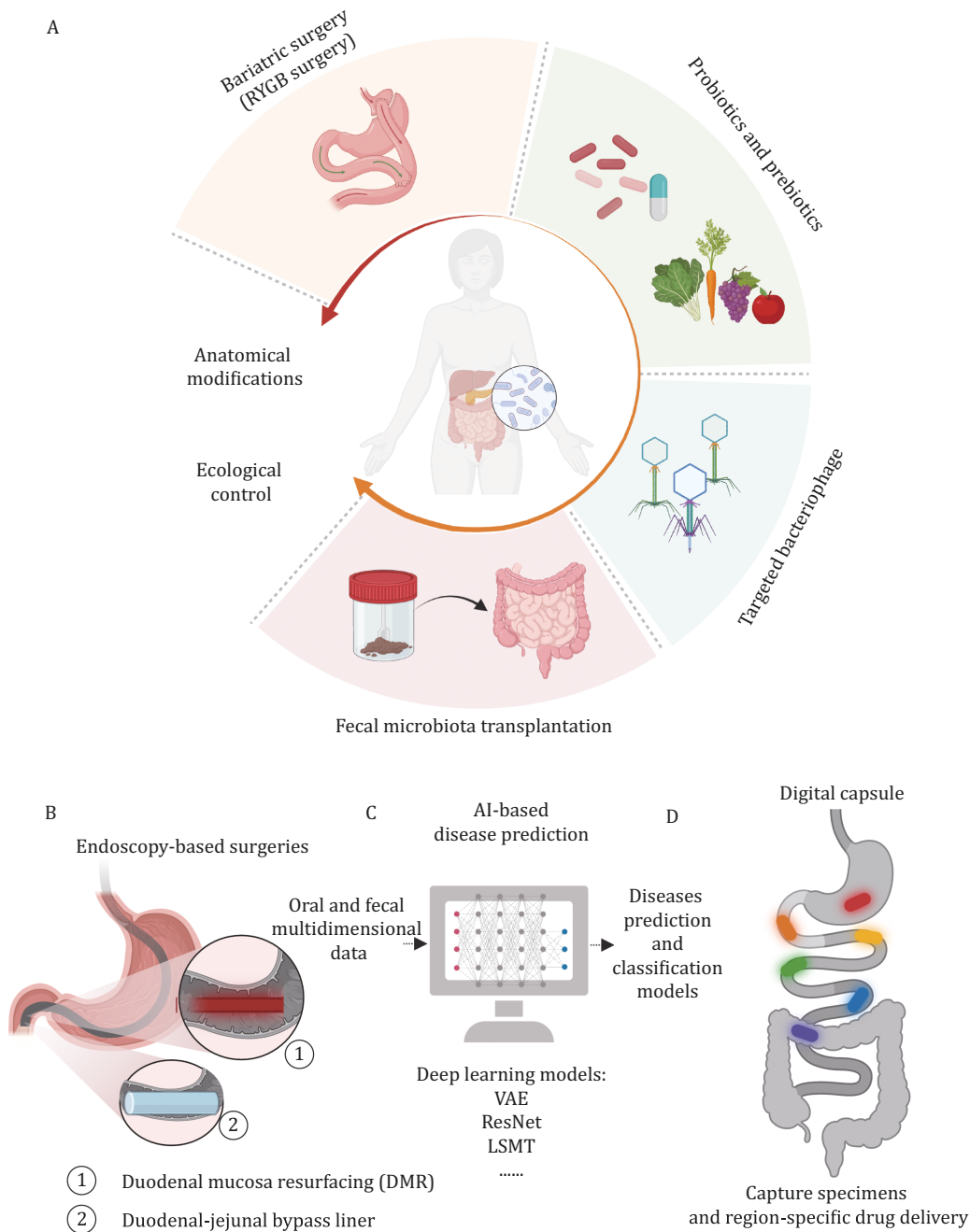


Figure 4. Ways to redistribute the gut longitudinal microbiota. (A) The traditional ways to redistribute the GI longitudinal microbial distribution including RYGB surgery, probiotics/prebiotic intervention, targeted bacteriophage, and FMT. (B) Endoscopy-based surgeries including duodenal mucosa resurfacing (DMR) (hydrothermal ablation of duodenal mucosa) and duodenal-jejunal bypass liner (endoscopically implanted 60 cm impermeable fluoropolymer sleeve) procedures to functionally deprive the duodenal mucosa. (C) Employing the oral and fecal microbial multidimensional data to construct artificial intelligence (AI)-based deep-learning prediction models. (D) Digital capsules to capture regional-specific human GI biospecimens and deliver drugs.

decolonization of pathogenic or dislocated microbiota from their ecological niches. This process not only promotes the re-establishment of beneficial microbial communities but also has the potential to alleviate metabolic diseases and GI disorders.

FMT has emerged as a promising therapeutic approach for GI diseases, particularly for recurrent *Clostridioides difficile* infection (rCDI), where it has demonstrated a

high therapeutic response (Hui et al., 2019; Ianiro et al., 2018; Quraishi et al., 2017). The efficacy of FMT is not only dependent on the microbial composition and functions of the donor microbiota in the recipient (Porcari et al., 2023), but also on the specific GI colonization site, which significantly impacts therapeutic outcomes. For instance, FMT using wild boar microbiota has been shown to modulate the structure of jejunal gut

microbiota and alleviate HFD-induced obesity (Zhu et al., 2022). Additionally, self-reinoculation in rodents significantly altered the composition and function of the gut microbiota in the small intestine, with less pronounced effects on the large intestine, while unconjugated BAs were found to be predominant in the small intestine of non-coprothetic mice (Bogatyrev et al., 2020). In another study, whole-intestinal microbiota transplantation (WIMT) from pigs was found to better promote small intestinal epithelial development and reduce systemic inflammatory response compared to conventional FMT, which predominantly represents gut microbiota from the large intestine (Li et al., 2020). Therefore, these findings underscored the fact that applying fecal microbiota to reconstitute the intestinal microbial ecology in patients is inappropriate, given the significant differences in microbiota distribution along the GI tract. It also highlighted the importance of the specific GI colonization site in determining the efficacy of FMT. Additionally, this suggests that WIMT may be a more effective approach in the future for reconstructing a healthy ecological relationship between host and microbiota.

The efficacy and heterogeneity of probiotics, prebiotics, and phage-based therapies across different regions of the GI tract have been extensively reviewed (Sorbara and Pamer, 2022; Strathdee et al., 2023). To enhance their effectiveness and minimize potential adverse effects, it is crucial to develop targeted microbiota or drug delivery systems that enable site-specific release and action. The design and modification of bioinspired oral delivery systems, which can improve efficacy, have been comprehensively reviewed elsewhere (Zhang et al., 2023). A cutting-edge study recently employed an advanced 18-strain commensal bacterial consortium, named the “F18-mix,” to target and eliminate pathogenic Enterobacteriaceae strains, specifically *Klebsiella pneumoniae* and *Escherichia coli*, in the gut (Furuichi et al., 2024). These pathogenic bacteria often persist in the intestinal tract due to disruptions caused by antibiotic treatments, leading to inflammatory conditions such as IBD. The application of the F18-mix represents a promising alternative to traditional antibiotic therapies, particularly in combating infections caused by drug-resistant strains of *Klebsiella* and *E. coli*. Furthermore, the development of personalized probiotic interventions customized to an individual’s unique gut microbial composition and dietary patterns holds great potential for optimizing gut health and proactively preventing pathogen overgrowth in the future.

Future direction

Recent advancements in endoscopy-based interventional approaches provide a novel therapeutic strategy for T2DM, which has garnered significant attention. The

duodenum is increasingly recognized as the metabolic center, and Western diets high in fat can cause hyperplasia of the duodenal mucosa, leading to impaired lipid and glucose metabolism (Ghosh et al., 2018; Gniuli et al., 2010; Nguyen et al., 2015; Rubino et al., 2006). The DMR procedure, which aims to ablate the duodenal mucosa through hydrothermal means, has emerged as a potential new treatment for glycemic control. Multiple international multi-center DMR clinical trials have demonstrated the efficacy of DMR surgery in durably improving insulin sensitivity and multiple metabolic indicators such as HbA1c and HOMA-IR in T2DM patients, without reported adverse effects to date (Mingrone et al., 2022; van Baar et al., 2020, 2022). Notably, changes in the longitudinal distribution of gut microbiota may contribute to the morphological and functional reshaping of the duodenal mucosa, although the causal relationship between them remains elusive and requires further investigation. Additionally, glycemic remission after DMR surgery may potentially be linked to the suppression of microbial overgrowth and the rectification of its subsequent detrimental effects on mucosal immune and glycolipid metabolism. Another technique duodenal-jejunal bypass liner shows promising clinical outcomes in treating T2DM and obesity by mimicking the functional deprivation of proximal small intestine of RYGB surgery while being less invasive (Ryder et al., 2023). Studies have demonstrated significant reductions in body weight, HbA1c levels, systolic blood pressure, and cholesterol in patients who have undergone this treatment (Ryder et al., 2023). Additionally, it has led to reduced insulin dosages or even discontinuation for some patients. Despite these positive results, there are safety concerns, particularly related to gastrointestinal bleeding and liver abscess formation, which have led to early removal in some cases. Nevertheless, with proper monitoring, the risks appear manageable. Looking forward, duodenal-jejunal bypass liner has the potential to become a widely available treatment option for patients with refractory uncontrolled T2DM and obesity, especially as demand for noninvasive metabolic treatments grows. Consequently, the restoration of regional-specific host-microbiota homeostasis through endoscopy-based therapeutic approaches holds great promise in the treatment of metabolic disorders (Fig. 4B).

The limited accessibility of human biospecimens from the upper GI tract, such as the duodenum and jejunum, necessitates more feasible methods for early detection and intervention in cases of disrupted gut microbial distributions. Recent research has shown the similarities between oral and fecal microbiota, and has shown that changes in oral microbial composition often precede the clinical manifestations of diseases (Yang et al., 2023). These findings suggest that oral microbes may serve as potential biomarkers for early-stage disease detection. Integrating

multidimensional data from oral and fecal samples into disease prediction models can help depict microbial trajectories during disease progression (Hernández Medina et al., 2022). Techniques like variational autoencoders (VAE) (Allesøe et al., 2023; Gomari et al., 2022; Nissen et al., 2021), and residual neural networks (ResNet) are utilized for this purpose (Buerger et al., 2022; Michel-Mata et al., 2022; Wang et al., 2024). By utilizing these approaches, it becomes possible to depict the microbial trajectory during disease progression and identify individuals in the early stages of the disease (Fig. 4C). In addition to this, the development of micro-capsules that respond to intestinal pH value (Shalon et al., 2023) or external magnet field (Sun et al., 2024) may revolutionize the ways biospecimens are collected for early detection and personalized intervention in the future (Fig. 4D).

Summary

The GI tract is a complex ecosystem with distinct gut microenvironments in each segment. These regions act as unique ecological niches with specific microbial composition and functions. The interactions between the host and microbiota influence the production of microbial metabolites, which play a vital role in regulating intestinal immune homeostasis and host metabolism. Understanding the pathophysiological significance of gut microbiota in different GI regions is crucial for developing targeted therapies.

Traditionally, fecal specimens have been used to assess gut and host metabolism. However, this approach does not fully capture the metabolic processes in the upper intestinal tract. The roles of microbial spatial organization and metabolic capacity in the small intestine have been overlooked in the understanding of metabolic diseases including obesity, DM, MASLD, IBD, and so on. Obtaining biological information from the small intestine is essential for unraveling host-microbiota interactions.

Each segment of the GI tract, with its resident gut microbiota, serves as a distinct functional ecological niche that regulates metabolic homeostasis. Disruption of the gut microenvironment can lead to the dislocation of gut microbiota along the GI tract, as seen in SIBO. This dislocation disrupts the balance between microbiota, metabolites, and the intestinal immune response, affecting metabolic homeostasis.

Conventional interventions like probiotics, prebiotics, surgery, FMT, and endoscopy-based procedures aim to correct the dislocation of gut microbiota, restoring the natural ecological niche and its functions. These interventions show promise in treating metabolic and GI disorders.

In the long term, prevention is prioritized over treatment. Integrating multidimensional microbial data,

including oral and fecal samples, into AI-powered deep-learning prediction models can identify individuals at risk of developing diseases before clinical symptoms emerge. This approach holds potential for microbial data-driven precision medicine.

Conflict of interest

The authors declare no competing interests.

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Data availability

Not applicable.

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