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Trends in
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Review

Small intestinal microbiota: from taxonomic composition to metabolism

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The small intestinal microbiota (SIM) is essential for gastrointestinal health, influencing digestion, immune modulation, and nutrient metabolism. Unlike the colonic microbiota, the SIM has been poorly characterized due to sampling challenges and ethical considerations. Current evidence suggests that the SIM consists of five core genera and additional segment-specific taxa. These bacteria closely interact with the human host, regulating nutrient absorption and metabolism. Recent work suggests the presence of two forms of small intestinal bacterial overgrowth, one dominated by oral bacteria (SIOBO) and a second dominated by coliform bacteria. Less invasive sampling techniques, omics approaches, and mechanistic studies will allow a more comprehensive understanding of the SIM, paving the way for interventions engineering the SIM towards better health.

Highlights

Recent advances in sampling and -omics techniques allow a better characterization of the taxonomic composition and functional potential of the small intestinal microbiota (SIM).

The SIM is composed of a core microbiota present in high abundance along the entire small intestinal tract complemented with a set of segment-specific taxa.

The SIM plays an essential role in carbohydrate degradation, amino acid metabolism, lipid absorption, and micronutrient metabolism.

Small intestinal bacterial overgrowth can be classified in two subgroups, namely small intestinal oral bacterial overgrowth (SIOBO) characterized by an overgrowth of oropharyngeal Gram-positive bacteria, and coliform small intestinal bacterial overgrowth (SIBO) characterized by an overgrowth of *Enterobacteriaceae* such as *Escherichia* or *Klebsiella*. SIOBO may contribute to environmental enteric dysfunction and linear growth delay.

The understudied small intestinal microbiota

The human intestinal microbiota describes the sum of microorganisms – including bacteria, archaea, viruses, fungi, and eukaryotic parasites – that reside in our gastrointestinal tract (GIT). The microbiota is associated with overall host health and disease [1,2], as it is essential for critical functions including digestion, immune system regulation, and production of nutrients and metabolites [3,4]. Unsurprisingly, it has been shown that the gene content and metabolic capabilities of the microorganisms colonizing the GIT are more extensive than those of their human host [3,5].

In recent decades, the vast majority of studies have focused on the fecal microbiota which, owing to its noninvasive and convenient sample collection, served as a proxy for the colonic microbiota [6]. By comparison, the SIM is largely understudied, mostly due to its challenging accessibility, requiring invasive sampling procedures, thus posing ethical constraints [6]. Given these constraints, most of the samples characterizing the SIM to date have been collected from patients suffering from gastrointestinal disorders.

Currently, aspiration of the intestinal fluid, as well as biopsy and luminal brushing, are the most commonly used small intestinal sampling methods. In addition to their invasive nature, these sample collection techniques have several drawbacks such as cross contamination, bowel preparation, and restriction to the proximal small intestine [6]. Sampling during surgical procedures, or through ileostomy pouches, allows to minimise contamination but cannot be applied to healthy individuals [6]. Recently, less invasive techniques using ingestible sampling capsules have been developed. They might allow to profile the full length of the digestive tract with minimal physiological disturbances [7]. However, the inaccurate location of the sampled sites, as well as the potential contamination, are major limitations of these devices even though the coating is specifically designed to address these issues [7].

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From the duodenum to the colon, environmental variations promote distinct microbial communities with specialized metabolic functions [8–11]. In the small intestine, significant interactions take place between the microorganisms, the host, and the nutrients, making the SIM a major factor both in health and disease-related contexts.

This review aims at summarizing current knowledge on SIM composition and its impact on health and disease. Furthermore, the review aims to discuss gaps in our understanding of the community structure and the metabolic functions within the SIM.

Microbiota composition along the small intestinal tract

The small intestine is characterized by a fast transit time (2–5 h in the small intestine, 10+ h in the colon), a wide range of pH, and the presence of secretions from the body (Figure 1) [9,11,12]. Overall, these characteristics lead to a dynamic environment that is less diverse and less densely populated by microorganisms in comparison to the colonic microbiota [5,13]. From the duodenum to the large intestine, the typical concentration of bacteria increases from 10^3 to 10^{11} cells/ml, with the highest density found in the colon [5]. Furthermore, the small intestine has relatively high oxygen levels, which decrease from the duodenum to the ileum until anaerobic conditions prevail in the colon [14]. Additionally, the vascular system underneath the epithelium provides oxygenation of the intestinal tissue, creating an oxygen gradient between the mucosa and the lumen [10]. Facultative anaerobes regulate oxygen availability by gradually depleting the oxygen in the lumen [15,16]. These changing conditions, combined with the presence of dietary nutrients, create unique, specialized niches for microbial communities throughout the different sections of the small intestinal tract.

In recent years, several studies aimed to characterize the microbiome in the different sections of the small intestinal tract. However, for ethical reasons, most samples have been collected from patients suffering from intestinal disorders, including functional dyspepsia [17], irritable bowel syndrome (IBS) [18], cancer [19,20], celiac disease [21,22], Crohn's disease [23], ileostomy

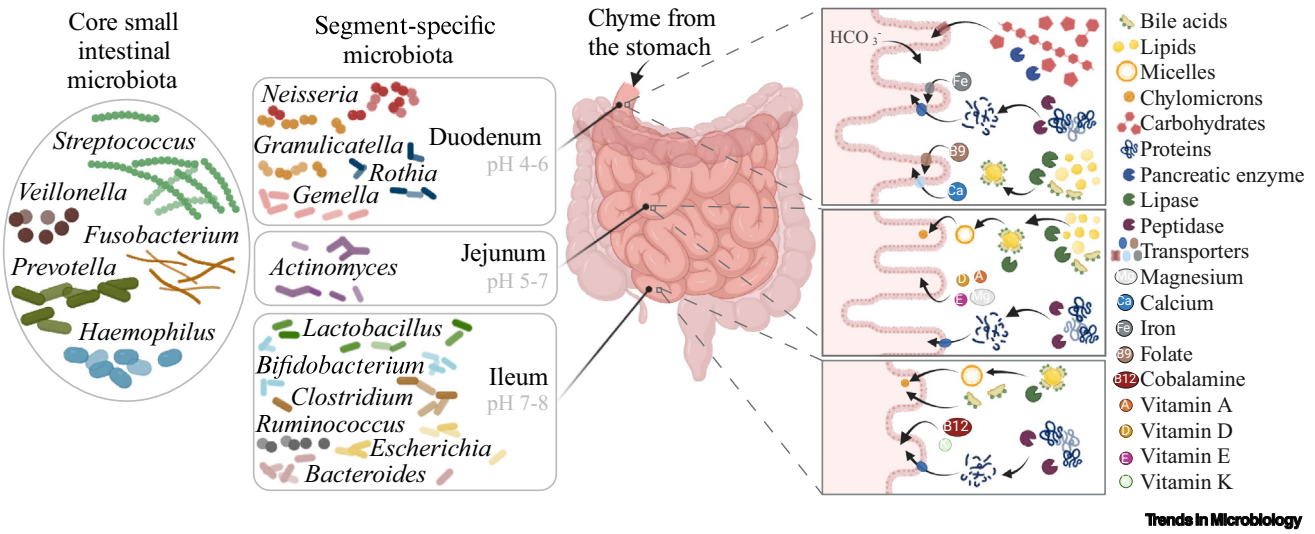

Figure 1. The small intestinal microbiota (SIM) and the sites of absorption of nutrients. The core SIM represents five bacterial genera found in high abundance and prevalence in the three segments of the small intestinal tract. The segment-specific microbiota shows genera found in higher abundance and prevalence in a specific segment. The boxes highlight the structure of each segment and the differences in enzyme degradation and absorption of essential nutrients, including carbohydrates, lipids, peptides, vitamins, and minerals.

[24,25], obesity [26], and stunting [27,28] (Table 1). Importantly, these diseases are influencing the microbiota composition and, to date, only a few studies have included healthy patients [7,17,23,29–31] (Table 1). This scarcity in 'healthy' SIM data, and the potential confounding effect due to a disease state, are leading to inconsistencies in the taxonomic composition. Nevertheless, general trends can be observed.

At the phylum level, the SIM is generally composed of *Bacillota* (formerly *Firmicutes*), *Bacteroidota* (formerly *Bacteroidetes*), *Pseudomonadota* (formerly *Proteobacteria*), *Fusobacteriota* (formerly *Fusobacteria*), and *Actinomycetota* (formerly *Actinobacteria*) [66] in varying abundances depending on the individuals and the study [27,36,43]. Other phyla such as *Verrucomicrobiota* (formerly *Verrucomicrobia*) [66] and *Saccharibacteria* (formerly TM7) are occasionally found [27,36,43]. Recently, two studies assessed the microbiome along the length of the GIT: Nagasue *et al*. analyzed mucosal samples from the stomach, duodenum, jejunum, ileum, rectum, and feces of 29 patients suffering from gastrointestinal symptoms [36], and Leite *et al*. mapped the small intestinal and fecal microbiota in 53 subjects [43]. Jointly, these studies showed that there are also important community differences along the GIT. While *Bacillota* dominate in the duodenum, *Pseudomonadota* abundance increase from the proximal to the distal part of the small intestinal tract. *Bacteroides* are more abundant in the ileum where the environmental conditions more closely resemble the colon and the feces [31,36,43].

As, to date, most studies used 16S rRNA gene amplicon sequencing to investigate taxonomic composition, the current resolution for a comparative analysis of the SIM is restricted to the genus level. At this taxonomic rank, *Streptococcus, Veillonella, Prevotella, Fusobacterium*, and *Haemophilus* can be identified as core members of the microbiota as these genera are consistently found in the small intestine regardless of the section sampled (Figure 1). The duodenum and jejunum's microbiota is similar in their composition and clearly distinct from the ileum [30,31,36,43]. In addition to the core microbiota, other segment-specific members commonly found include *Neisseria*, *Granulicatella*, *Gemella*, *Rothia*, and *Actinomyces* in the duodenum and the jejunum, and *Bacteroides*, *Escherichia–Shigella, Ruminococcus, Bifidobacterium, Clostridium*, and *Lactobacillus* in the ileum (Figure 1).

Besides the proximal–distal gradient of oxygen and nutrients along the GIT, a gradient for oxygen and secreted antimicrobials is present from the mucosa to the lumen. These gradients, alongside the mucus layer, create distinct niches across the transversal axis of the intestine [10,11,67]. To date, only very few studies aimed to characterize both the mucosal and luminal compartments of the small intestine [29,39,47,60]. Overall, they mostly observed differences in relative abundance, notably of *Streptococcus* and *Prevotella*, while the presence/absence of specific microbial taxa seems to be fairly similar in between these two sites [47,60]. These observations are likely explained by the constant renewal of the mucus layer shedding its associated bacteria in the lumen and the difficulty of collecting samples in this region of the GIT, which hampers a precise discrimination between samples and associated microorganisms from the mucosa and the lumen [53,67].

Taken together, these results suggest that five genera represent the core SIM and that additional community members differ in their presence and relative abundance in a specific segment. Importantly, despite the different origins and variety of diets of the sampled patients, the SIM composition seems widely similar across populations. Nevertheless, a better characterization at lower taxonomic levels is still warranted. In this regard, the recent development of non-invasive sampling techniques [7], and the lower cost of deep shotgun metagenomic sequencing, will create numerous opportunities to widen our understanding of the SIM.

Table 1. Characteristics of the studies characterizing the SIM[a,b]

Study	*n*	Medical conditions	Sampling technique	Sampling location[c]	Analysis technique[d]	Refs
Leite *et al*. 2023	505 38	SIBO	Aspiration	D	16S rRNA SMS	[32]
Shalon *et al.* 2023	15	–	Capsule-based sampling	D, J, I	16S rRNA SMS	[7]
Collard *et al.* 2022[e]	165	SIBO, S	Aspiration	D	Culture	[33]
Jiang *et al.* 2022	30	NLH	Biopsy	I	16S rRNA	[34]
Kelly *et al.* 2022	7	CF	Biopsy	I	16S rRNA	[35]
Maeda *et al*. 2022	47	C, H.pl	Aspiration	D	16S rRNA	[20]
Nagasue *et al.* 2022	29	GI	Brush	D, J, I	16S rRNA	[36]
Villmones *et al.* 2022	60	O	Swab	J	16S rRNA, culture	[37]
Vonaesch *et al.* 2022	128	S, EED	Aspiration	D	16S rRNA	[27]
Xia *et al.* 2022	61	C'sD	Swab	I	16S rRNA	[23]
Zheng *et al*. 2022	35	–	Brush and biopsy	D	16S rRNA	[29]
Barlow *et al.* 2021	250	GI	Aspiration	D	16S rRNA	[38]
Dreskin *et al.* 2021	–	–	Aspiration	D	16S rRNA	[39]
Leite *et al.* 2021	251	GI	Aspiration	D	16S rRNA	[40]
Schiepatti *et al.* 2021	37	CD	Biopsy	D	16S rRNA	[21]
Chen *et al.* 2020	36	EED	Aspiration	D	16S rRNA	[28]
Fukui *et al.* 2020	18	FD	Brush	D	16S rRNA	[17]
Gutierrez-Repiso *et al*. 2020	45	O	Swab	J	16S rRNA	[26]
Hussain *et al.* 2020	51	LC	Biopsy	D	16S rRNA	[41]
Leite *et al.* 2020	140	SIBO	Aspiration	D	16S rRNA	[42]
Leite *et al.* 2020	23	–	Aspiration	D, J	16S rRNA	[43]
Panelli *et al.* 2020	83	CD	Biopsy	D	16S rRNA	[22]
Gong *et al.* 2019	20	IM	Biopsy	D	16S rRNA	[44]
Raj *et al.* 2019	46	CLD	Biopsy	D	16S rRNA	[45]
Saffouri *et al*. 2019	126	GI	Aspiration	D	16S rRNA	[46]
Seekatz *et al.* 2019	64 46	–	Aspiration	D J	16S rRNA	[30]
Shin *et al.* 2019	76	SIBO	Aspiration and biopsy	J	16S rRNA	[47]
Zeichner *et al.* 2019	29	GI	Aspiration	J	16S rRNA	[48]
Mei *et al.* 2018	28	C	Biopsy	D	16S rRNA	[19]
Shanahan *et al*. 2018	102	GI	Biopsy	D	16S rRNA	[49]
Villmones *et al.* 2018	27	GI	Swab	I	16S rRNA	[50]
Vonaesch *et al.* 2018[d]	46	SIBO, S	Aspiration	D	16S rRNA	[51]
Zmora *et al.* 2018	29	–	Aspiration	D, J, I	16S rRNA SMS	[31]
Sjöberg *et al.* 2017	13	C'sD, UC	Aspiration	D	16S rRNA	[52]
Sundin *et al.* 2017	20	GI	Aspiration	J	16S rRNA	[53]
Chung *et al.* 2016	47	IBS	Biopsy	J	16S rRNA	[54]
D'Argenio *et al.* 2016	41	CD	Biopsy	D	16S rRNA	[55]
Giamarellos-Bourboulis *et al.* 2016	258	IBS	Aspiration	D	16S rRNA	[56]
Nistal *et al.* 2016	18	CD	Biopsy	D	16S rRNA	[57]
Angelakis *et al*. 2015	10	O	Aspiration	D	16S rRNA	[58]

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Table 1. (continued)

Study	*n*	Medical conditions	Sampling technique	Sampling location[c]	Analysis technique[d]	Refs
Dlugosz et al. 2015	51	IBS	Biopsy	J	16S rRNA	[59]
Li *et al*. 2015	9	–	Aspiration and biopsy	D	16S rRNA	[60]
Zhang *et al.* 2014	11	–	Biopsy	I	16S rRNA	[61]
Cheng *et al.* 2013	26	CD	Biopsy	D	qPCR	[62]
Wacklin *et al*. 2013	51	CD	Biopsy	D	16S rRNA	[63]
Nistal *et al.* 2012	28	CD	Biopsy	D	16S rRNA	[64]
Oh *et al.* 2012	19	SBT	Biopsy	I	16S rRNA	[65]
Zoetendal *et al.* 2012	8	GI, I	Aspiration	I	16S rRNA	[25]

[a]Abbreviations: C, cancer; CD, coeliac disease; CF, cystic fibrosis; CLD, chronic liver disease; C'sD, Crohn's disease; EED, environmental enteric dysfunction; FD, functional dyspepsia; GI, gastrointestinal tract symptoms; H.pl, *Helicobacter pylori* infection; I, ileostoma; IBS, irritable bowel syndrome; IM, intestinal metaplasia; LC, liver cirrhosis; NLH, nodular lymphoid hyperplasia; O, obesity; S, stunting; SBT, small bowel transplant; SIBO, small intestinal bacterial overgrowth; UC, ulcerative colitis; – healthy/no medical conditions reported.
[b]Inclusion criteria: study published since 2010, analyzing aspirates, biopsies, or brushing of the duodenum, jejunum, or ileum and/or ileal content from stoma pouches, characterizing the microbiota by either culture, qPCR, 16S rRNA gene amplicon, or SMS and including a characterization of the most prevalent and/or abundant genera of the small intestinal microbiota as a list and/or plot.
[c]Abbreviations: D, duodenum; J, jejunum; I, ileum.
[d]16S rRNA, 16S rRNA gene amplicon sequencing.
[e]These studies are, to a large extent, a subset of the samples analyzed in Vonaesch *et al*. 2022 [27].

Differences in the microbial community between the small and large intestine

To date, most studies focus on the analysis of fecal samples as a crude read-out of the overall lower GIT. This poses evident problems as the biotic and abiotic factors and, consequently, the ecosystems, vary along the length of the GIT. Not surprisingly, the overall community composition clearly differs along the digestive tract, and notably, between the duodenum and the feces (Table 2).

At the phylum level, *Bacillota* and *Pseudomonadota* are found in higher abundance in the small intestine, whereas *Bacteroidota* and *Bacillota* seem to dominate in the feces (Figure 2) [36,43,68]. Additionally, albeit the same main phyla are found in varying abundances, the exact composition at lower taxonomic levels differs within each compartment (Figure 2). Overall, studies

Table 2. Characteristics of the studies including small and large intestinal samples[a]

Study	*n*	Medical conditions	Sampling sites	Sample type	Analysis technique	Refs
Shalon *et al. 2023*	15	Healthy	D, J, PI, DI, AC	Capsule-based sampling	V4 16S rRNA gene sequencing	[7]
Vonaesch *et al. 2022*	150	Stunted	D, F	Aspirate	V4 16S rRNA gene sequencing	[27]
Nagasue *et al. 2022*	29	GIT symptoms	D, J, PI, DI, R, F	Brush	V4 16S rRNA gene sequencing	[36]
Leite *et al. 2020*	53	GIT symptoms	D, J, PI, F	Aspirate	V3–V4 16S rRNA sequencing	[43]
Seekatz *et al. 2019*	8	Healthy	D, J, F	Aspirate	V4 16S rRNA gene sequencing	[30]
Vuik *et al. 2019*	14	Abdominal symptoms	D, J, PI, DI, AC, DC, R	Biopsy	V3–V4 16S rRNA sequencing	[68]
Vonaesch *et al. 2018*[b]	46	Stunted	D, F	Aspirate	V4 16S rRNA gene sequencing	[51]
Zmora *et al. 2018*	25	Healthy	D, J, DI, AC, TC, DC, R, F	Aspirate, brush, biopsy	V4 16S rRNA gene sequencing, SMS	[31]

[a]Abbreviations: AC, ascending colon; D, duodenum; DC, descending colon; DI, distal ileum; F, feces; GIT, gastrointestinal tract; J, jejunum; PI, proximal ileum; R, rectum; TC, transverse colon.
[b]This study is, to a large extent, a subset of the samples analyzed in Vonaesch *et al*. 2022 [27].

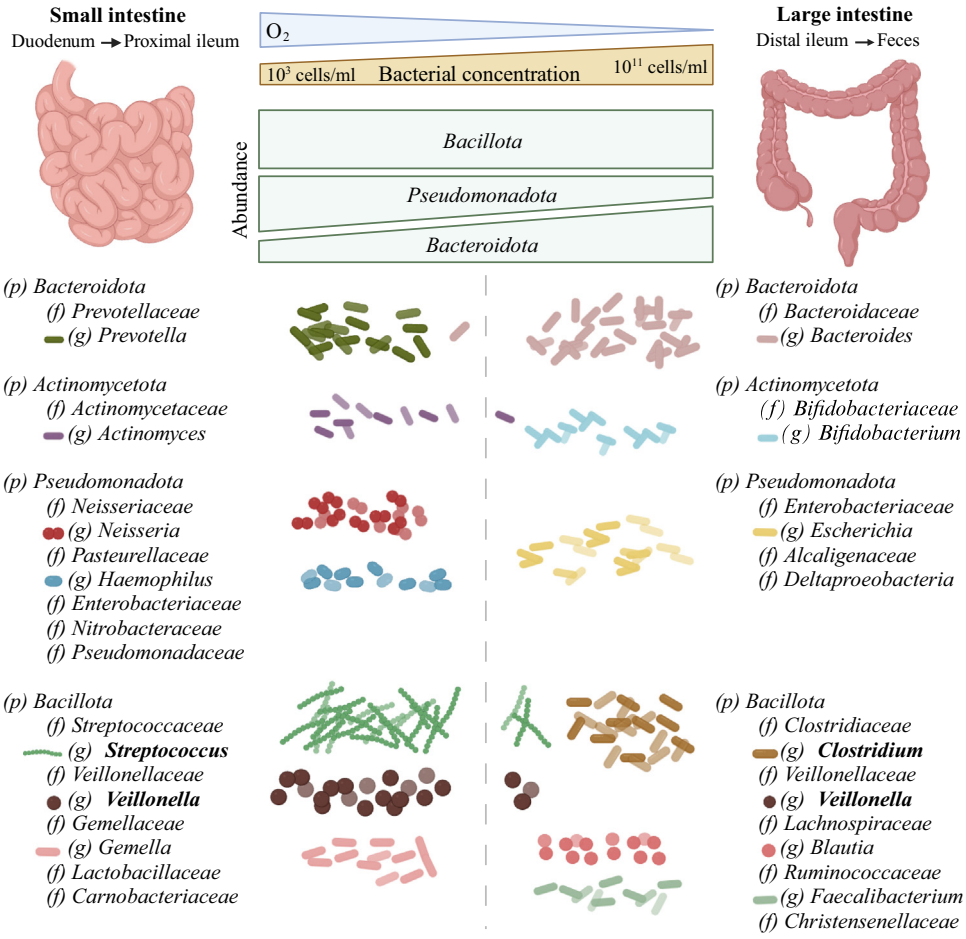

Figure 2. Differences between the small and the large intestinal microbiota. The figure summarizes the distribution of the three main phyla along the gastrointestinal tract (GIT). While *Bacillota* remains at a high abundance along the intestinal tract, *Pseudomonadota* abundance decreases and *Bacteroidota* abundance increases from the small to the large intestine. The two columns depict the different bacterial families and genera found in higher abundance and prevalence either in the small or the large intestine. While the same phyla are found in both sites, the microbiota composition within each phylum changes between the upper and lower part of the intestinal tract. Abbreviations: f, family; g, genus; p, phylum.

show that the SIM is mostly composed of fast-growing primary fermenters such as *Streptococcaceae* and *Lactobacillaceae* alongside secondary fermenters such as *Veillonellaceae* [30,36,43,51,68]. In the colon and feces, obligateanaerobes, including *Ruminococcaceae* and *Lachnospiraceae,* are found [30,36,43,51,68]. Furthermore, *Clostridiaceae* and *Bacteroidaceae* are rarely found in the duodenum and jejunum and show increasing relative and absolute abundances from the ileum to the feces [31,36,43,51]. Interestingly, *Streptococcaceae* and *Veillonellaceae* are found in both the small and large intestine, but in lower relative abundances in the feces [30,36,43,68].

Although, the GIT is often described as separate compartments, it is essential to emphasize that the digestive tract is a continuum. In this sense, several taxa are found along the whole length of the digestive tract, showing a transmission from the oral cavity to the intestines [69–71]. In healthy individuals, the oral microbiota is dominated by *Streptococcus*, *Haemophilus*, *Rothia*, *Neisseria*,

and *Veillonella* alongside other bacterial genera such as *Prevotella*, *Corynebacterium*, *Actinomyces*, *Fusobacterium, Granulicatella*, and *Gemella* depending on the oral niches and the individual [72]. These genera are observed throughout the whole length of the digestive tract, particularly in the small intestine, albeit in different abundance depending on the compartment [53,69,70]. While there are evident abundance and taxonomic differences at higher taxonomic ranks, it remains unclear if bacterial strains are continually transmitted and thus remain the same across the whole length of the digestive tract or if they locally adapt to their respective niches for long-term residency (Box 1). A better understanding of the bacterial strains' transmission mechanisms and colonization dynamics is of the outmost importance as ectopic colonization of oral bacteria is associated with several GIT diseases [27,28,73].

Role of the small intestinal microbiota in nutrient metabolism

Microbiota and carbohydrate degradation

Carbohydrates are major components of human diets, yet only a fraction of them can be digested using the body's own 17 pancreatic enzymes [74]. The majority of dietary fibers are processed by the intestinal microbiome through bacterially encoded enzymes degrading dietary glycans – carbohydrate-active enzymes (CAZymes) [75]. CAZymes have attracted a lot of interest in fecal microbiota studies [76], but their presence in the SIM has been scarcely explored. In 2012, Zoetendal *et al*. observed an enrichment in genes related to carbohydrate metabolism in five ileostomy effluent samples in comparison to fecal samples from two healthy subjects [25]. This suggests that simple carbohydrates are primarily digested and absorbed in the small intestine [11]. More recently, using six ileal and colonic stoma samples from cured colorectal cancer patients, Yilmaz *et al*. showed the temporal dynamic of the intestinal microbiota and metabolites during fasted and fed states using high-resolution untargeted mass-spectrometry. Interestingly, no changes in mono- and disaccharides were detected after a meal, suggesting a direct and complete uptake of these compounds in the small intestinal tract [24]. Thanks to the recent development of capsule devices collecting luminal contents from the small intestine and ascending colon, Shalon *et al*. evaluated the functional differences between the intestinal and fecal microbiota in 15 healthy individuals and showed the presence of CAZyme-encoding genes both in small intestinal and fecal samples (Figure 3) [7]. As bacterial carbohydrate degradation is of major importance for the host, more studies characterizing CAZymes in the SIM are needed, especially in the proximal part of the small intestine.

Box 1. Transmission of strains along the digestive tract

Clear differences exist at higher taxonomic ranks, from phylum to genus, between the different section of the GIT. However, the extend of bacterial transmission and colonization dynamics along the digestive tract remains largely uncharacterized. Indeed, further evidence is needed to define if bacterial strains are continuously transmitted from the oral cavity to the intestinal tract and thus remain the same across the whole length of the digestive tract or if they locally adapt to their respective niches for long-term residency. Recently, Gough *et al*. analyzed *Streptococcus salivarius* strains inferred from shotgun metagenomic data in 140 fecal samples from two different time points from a randomized control trial on cotrimoxazole intake in HIV-positive Zimbabwean children. They found that the strains were more similar to each other compared to reference strains derived from oral cavities from subjects from high-income countries, concluding that there might be niche-specific microbe adaptations [70]. On the contrary, using 753 public and 182 newly sequenced saliva and stool samples from 470 healthy and diseased individuals, Schmidt *et al*. suggested that microbial taxa flux from the oral cavity to the lower GIT is extensive in healthy individuals, leading to connected strain populations along the digestive tract [69]. Recently, Dubinsky *et al.* extended these observations in 21 healthy individuals by showing that even though three common human intestinal species from the terminal ileum, cecum, and descending colon had a distinct genome, they were interrelated and derived from a founder strain colonizing multiple sites [71]. While it is not excluded that these two phenomena coexist, and might also be different according to specific bacterial taxa and the health state of their host, it is crucial to better understand taxonomic variations along the digestive tract at lower taxonomic levels, especially as ectopic colonization of oral bacteria in the lower digestive tract has been previously associated with the exacerbation of several gastrointestinal diseases [27,28,73].

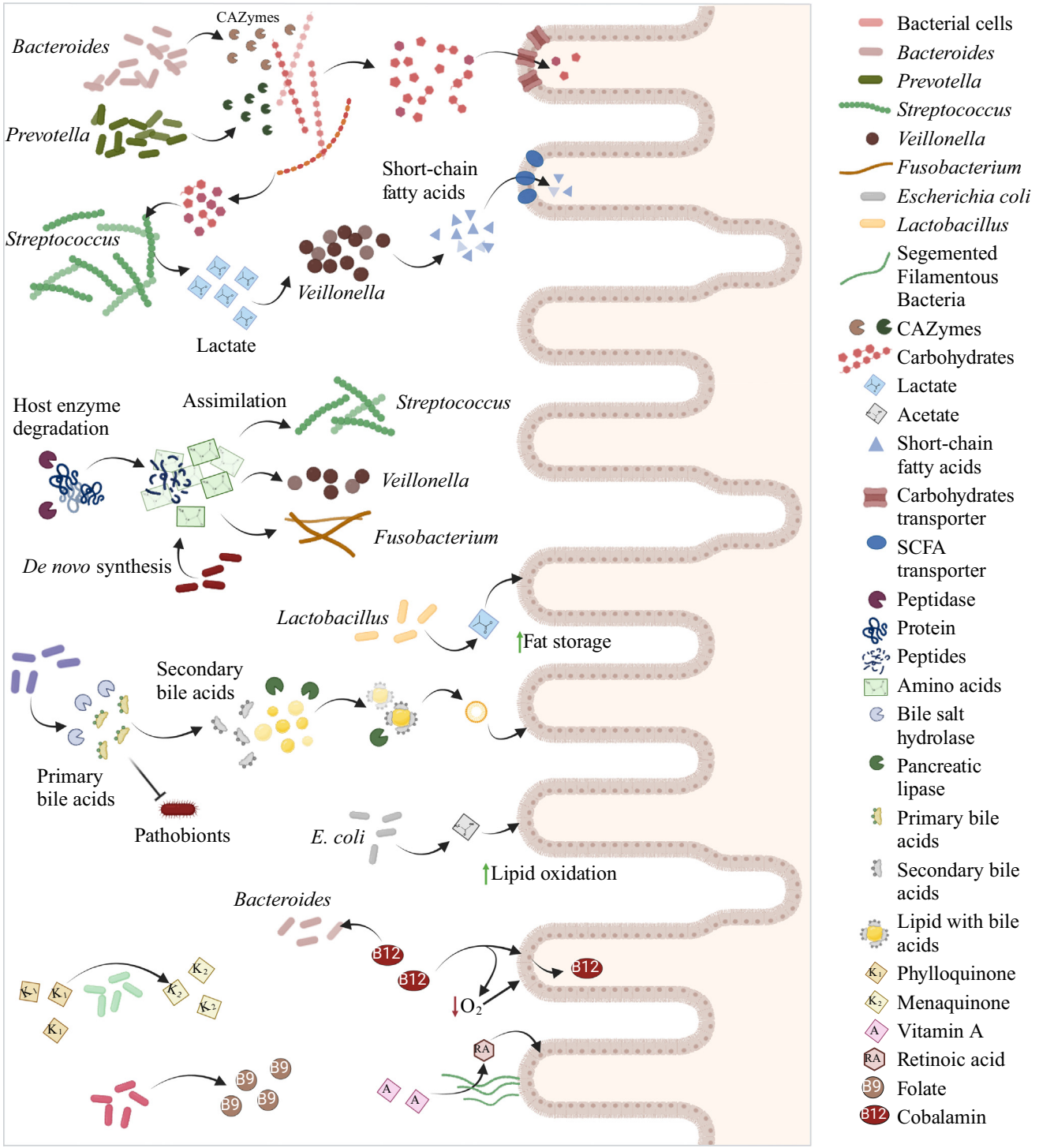

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Figure 3. Effects of the small intestinal microbiota (SIM) on macro- and micronutrient metabolism. *Bacteroides* and *Prevotella* produce carbohydrate-active enzymes (CAZymes) responsible for the degradation of carbohydrates in the small intestine. Lactate produced by lactic acid bacteria (LAB), such as *Streptococcus*, is utilized by *Veillonella* to produced short-chain fatty acids (SCFAs). While free amino acids are made available by the digestion of peptides by pancreatic enzymes, the

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Lactic acid bacteria (LAB), such as streptococci, are major members of the SIM and produce lactic acid as an end-product of simple carbohydrate fermentation [43,77,78]. Members of the SIM further work synergistically to produce fermentation end-products: *Veillonella* is able to use lactate as substrate, transforming it into the short-chain fatty acids acetate and propionate (Figure 3) [25,43,79]. This cross-feeding likely explains the co-occurrence of these two taxa and their high abundance in the small intestinal tract [25,80]. Overall, the role of LAB and *Veillonella* in the small intestine, while not fully understood, is evidently important for carbohydrate degradation and short-chain fatty acid production [81–83]. Ultimately, more experimental research is needed to elucidate in detail the molecular mechanisms of small intestinal glycan metabolism and unravel other taxa and taxonomic groups contributing to carbohydrate degradation.

Amino acid degradation, assimilation, and *de novo* synthesis

Amino acids (AAs) and peptides derived from ingested proteins are essential for human physiology as well as for bacterial growth. In a recent metabolomic study on 15 healthy subjects using ingestible capsules to sample the small intestine, Folz *et al*. showed that di- and tripeptide abundance decreased along the length of the small intestine suggesting their absorption in this part of the GIT [84]. Recent evidence suggests that the microbiota is able to both produce and metabolize AAs, even though the exact mechanisms and the net result between metabolism and anabolism are not yet fully elucidated [85,86]. For instance, in a randomized, cross-over, explorative study during which 16 ileostomy patients consumed fermented milk products or a placebo, microbial metabolism was shifted towards AAs [87]. Bacterial species, including *Fusobacterium, Streptococcus*, and *Veillonella*, have been reported to be able to assimilate and degrade AAs (Figure 3) [88], generating smaller peptides and free AAs, which then become available to the overall ecosystem and can be assimilated by the host and other bacterial species [89].

Additionally, bacterial species of the SIM might be able to carry out *de novo* AA synthesis (Figure 3). Zoetendal *et al*. found an enrichment in pathways for AA metabolism in the small intestine of five ileostomy patients in comparison to fecal samples from two healthy subjects [25]. Furthermore, Van den Bogert *et al*. found evidence of anabolic pathways for AA synthesis in small intestinal *Streptococcus* genomes [78]. The authors suggested that the limited availability of AAs in the small bowel might promote bacterial *de novo* synthesis, thus benefiting the host as well as cross-feeding bacteria within the intestinal ecosystem. More efforts are thus needed to understand the interplay between AAs, the SIM, and the host, especially in the context of a low-protein diet and insufficient nutrient intake.

Small intestinal microbiota, bile acids, and lipid metabolism

Dietary lipids constitute one of the main energy sources in humans [90]. In the duodenum, lipids are emulsified by bile acids (BAs) and hydrolyzed by lipases before being absorbed in the jejunum (Figure 1) [90]. Evidence from animal models indicates that the SIM is an essential actor in dietary lipid digestion and absorption within the small intestine [91,92]. In mice, the consumption of a high-fat diet (HFD) alters the SIM, including the microbial circadian clock, and leads to enhanced lipid absorption in the small intestinal tract, thus promoting diet-induced obesity [91,93].

microbiota contributes to the pool of free amino acids by *de novo* synthesis. *Streptococcus*, *Veillonella*, and *Fusobacterium* have been shown to take up free amino acids and use them for their own metabolism. Primary bile acids secreted in the duodenum are transformed into secondary bile acids by bacterial enzymes. The pool of bile acids provides resistance against pathobiont infection. Lipids are emulsified by bile acids and hydrolyzed by pancreatic bacterial lipases before being absorbed. *Lactobacillus* species increase fat storage via L-lactate production, and *Escherichia coli* increases lipid oxidation via acetate production. The microbiota plays an essential role in the conversion of phylloquinone (vitamin K_1) into menaquinone (vitamin K_2) as well as in the biosynthesis of folate (vitamin B_9). The absorption of cobalamin (vitamin B_{12}) in the ileum is reduced by members of the *Bacteroides* genus that compete with the host for B_{12} absorption. Cobalamin absorption was further shown to decrease oxygen levels in the lumen, indirectly controlling *Salmonella* Typhimurium infection. Production of retinoic acid from dietary vitamin A by segmented filamentous bacteria promotes defense against enteric infections.

Conversely, in case of undernutrition and environmental enteric dysfunction (EED), expression of genes implicated in lipid absorption is decreased in the duodenum, thus leading to reduced serum lipid levels and stunting [94,95]. Additionally, Vonaesch *et al*. demonstrated that duodenal bacterial isolates from stunted children from Madagascar and Central African Republic decrease lipid absorption both *in vitro* and in a mouse model [27]. Previous work demonstrated a link between several small intestinal bacteria and lipid metabolism: *Lactobacillus paracasei* promotes fat storage in enterocytes by producing L-lactate, while *Escherichia coli* promotes lipid oxidation by producing acetate (Figure 3) [92,96]. Furthermore, lipid absorption in the ileum is influenced by the presence of *Clostridium ramosum*, which upregulates the fatty acid translocase CD36 [97]. The expansion of *Desulfovibrio* and loss of *Clostridia* in the context of metabolic syndrome such as obesity thus alters the expression level of *cd36* and may lead to inappropriate lipid uptake [98]. Finally, *cd36* expression and lipid absorption were shown to be regulated by the circadian transcription factor Nfil3, itself regulated by the microbiota, notably Gram-negative motile bacteria [99].

Inherent to lipid metabolism, BAs, synthetized in the liver, are conjugated with glycine or taurine before being secreted in the duodenum [100]. Microbial enzymes, such as bile salt hydrolase (BSH), are known to increase the diversity of BAs by modifying primary BAs into secondary BAs which are reabsorbed in the ileum (Figure 3) [100]. Additionally, the increased BA diversity reduces inhibition of the farnesoid X receptor in enterocytes which consequently inhibits BA synthesis in the liver, making the microbiota a regulator of both BA metabolism and synthesis [101]. Consequently, alterations of the BA pool mediated by the microbiota were associated with nutritional disorders such as obesity and undernutrition [102,103]. Of note, deconjugation of taurocholic acid by BSH during consumption of a diet high in milk promotes the expansion of the pathobiont *Bilophila wadsworthia* [104]. By contrast, the pool of BAs provides resistance against pathobiont infections and profoundly shapes the microbiota as taxa differ in their inherent tolerance to given BAs (Figure 3) [100,105]. Taken together, these findings underscore the role of the microbiota in lipid and BA metabolism in the small intestine. Understanding the precise interactions between the SIM, BAs, and lipid absorption might lead to novel therapeutic strategies for the treatment of nutritional disorders.

Micronutrient synthesis by the small intestinal microbiota

Micronutrients are vitamins as well as minerals (calcium, iron, magnesium, phosphate) and trace elements essential for human physiology and mostly acquired from exogenous sources [11]. Water-soluble vitamins, such as folate (B9) and menaquinone (K_2), can be synthesized by intestinal bacteria, while other micronutrients must be acquired from the diet (Figure 3) [11,106]. Notably, Magnúsdóttir *et al*. predicted *in silico* that B vitamins were produced by 40–65% of the 256 most prevalent intestinal bacteria [107]. Additionally, the microbiota can affect micronutrient bioavailability and absorption [108]: ileal cobalamin (B_{12}) absorption is reduced by anaerobic bacteria, particularly *Bacteroides*, through B_{12} capture by surface-exposed lipoproteins [109]. Conversely, minerals and vitamins also modulate the microbiota composition in the lower GIT, as recently reviewed by Barone *et al*. [110]. Furthermore, dietary vitamins are involved in providing colonization resistance against pathogens. Recent studies in mice demonstrated that colonization by segmented-filamentous bacteria producing retinoic acid from dietary vitamin A promotes innate defense against *Citrobacter rodentium* and provides protection against rotavirus (Figure 3) [111,112]. B_{12} also indirectly controls *Salmonella* Typhimurium infection by regulating oxygen levels in the ileal lumen (Figure 3) [113]. Overall, much about the precise interactions between the SIM and micronutrients as well as the consequences they have for the host remain to be elucidated.

The small intestinal microbiota and gastrointestinal diseases

Several medical conditions, such as inflammatory bowel disease (IBD), IBS, and coeliac disease (CD), involve the small intestine. Changes in the intestinal microbiota in the context of IBD, IBS,

and CD have been covered at length in recent reviews [114–116]. These conditions have notably been shown to co-occur with small intestinal bacterial overgrowth (SIBO) [117]. Traditionally, SIBO has been defined as the presence of a bacterial count exceeding 10^5 colony-forming units per ml in the small intestine [117]. Despite the risk of contamination, small intestinal aspirates are considered as the gold standard procedure. However, noninvasive procedures, such as hydrogen or lactulose breath tests, are commonly used to diagnose SIBO, even though they lack specificity and sensitivity [117]. Bacteria regularly identified in SIBO patients can be classified in two subgroups, namely Gram-positive bacteria of oropharyngeal origin (termed here small intestinal oral bacterial overgrowth, SIOBO [27], also formerly referenced as upper aerodigestive tract SIBO, UAT SIBO [118]) and coliform Gram-negative bacteria (coliform SIBO), characterized mainly by an increased abundance of members of the genera *Escherichia* and *Klebsiella* [32,118].

SIOBO is observed in children suffering from linear growth delay as a consequence of undernutrition (i.e., stunting) and is believed to drive local inflammation and increase gut permeability [33,51,119,120]. In stunted children, ectopic colonization and overgrowth of oropharyngeal species, including *Lactobacillus*, *Streptococcus, Veillonella, Prevotella*, and *Gemella*, have been observed in the duodenum of stunted children and their absolute abundance has been linked to stunting severity [28,51]. Ectopic oral bacteria colonization in the small intestinal tract has equally been described in IBD [121]. While factors predisposing for SIOBO remain to be identified, SIOBO is clearly not due to the overgrowth of a single species but rather to the overgrowth of a consortium of strains [51].

Moreover, it has been proposed that SIBO and SIOBO may contribute to EED, a condition commonly characterized by villous atrophy, intestinal inflammation, malabsorption, and barrier dysfunction. This syndrome is highly prevalent in low- and middle-income countries and may contribute to stunting [27,28,51,119,122]. However, the etiology of EED is not clearly defined, and biomarkers of the different hallmarks are poorly correlated [123,124]. Overall, more research is needed to precisely define the role of SIBO and SIOBO in stunting, EED, and other gastrointestinal syndromes. A better knowledge of the source of the ectopically colonizing strains and the mechanisms leading to inflammation and malabsorption will be crucial to rationally engineer the microbiota in the future.

Concluding remarks and future perspectives

Due to challenges inherent to sampling, the small intestine has been less well characterized than other parts of the digestive tract, and consequently many questions remain open in the field. Previous data obtained from samples collected from patients suffering from intestinal diseases are of crucial importance yet need to be complemented with samples from healthy individuals. This will allow to better understand the broader ecosystem of the healthy small intestinal tract and to disentangle disease-associated signatures (see Outstanding questions).

Furthermore, studies characterizing the duodenum were conducted almost essentially in the USA [7,30,32,38,41,46–48,53,56,65], China [19,23,29,34,44,60], Europe [21,22,25,26,35,37,50,52,55,57–59,62–64], Australia [45], and Japan [17,20,36]. We found no studies characterizing the duodenum from the South American continent, and only two articles from the same study describing the duodenal microbiota composition in Madagascar and the Central African Republic [27,51]. Finally, only a single study described the duodenal microbiome in a lower-income Asian country, Bangladesh [28]. Even though the SIM composition remains widely similar across countries, this observation highlights the biased knowledge we have about the SIM composition and the need of including non-Western populations in future studies (see Outstanding questions).

Outstanding questions

What is the strain level composition of the small intestinal microbiota (SIM)?

What are the differences in taxonomic composition across geographies, age groups, diets, and disease status?

What are the sources and colonization dynamics of bacterial strains along the length of the digestive tract in health and disease-related contexts?

Can new, noninvasive, sampling techniques allow to repeatedly sample specific sections of the digestive tract, thus allowing for longitudinal analyses?

What is the taxonomic composition of small intestinal oral bacterial overgrowth (SIOBO) and coliform small intestinal bacterial overgrowth (SIBO)? What is the role of each condition in health and disease?

What are the underlying molecular mechanisms of nutrient–microbiota–host interactions observed in the small intestinal tract?

What is the metabolic potential and metabolic activity of the SIM along the small intestinal tract, in health as well as in different disease states?

How can we rationally engineer the small intestinal microbiota?

The recent advances in different omics techniques have so far been scarcely applied to study the SIM. The widely used 16S rRNA gene amplicon sequencing allows reliable taxa identification only at the genus level. While important conclusions can be drawn from this sequencing method, more precise and deeper sequencing is necessary to obtain a finer picture of the microbiota composition in the small intestine, notably allowing to infer strain-level differences (see Outstanding questions). Furthermore, functional profiling, using both metagenomic and metatranscriptomic sequencing, as well as metabolomic and metaproteomic approaches, will be essential to better characterize the functional potential and activity of the SIM (see Outstanding questions). Finally, we need experimental studies to elucidate the molecular mechanisms regulating nutrient metabolism. A combination of culture and multi-omics analyses will allow to better understand the interplay between the microorganisms, the nutrients, and the host, setting the bases to design appropriate interventions rebalancing the SIM towards a healthy state.

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Declaration of interests

No interests are declared.

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