Large Intestine and Its Microbiota

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The large intestine (intestinum crassum) is the last part of the digestive tract ensuring the resorption of water, amino acids, bile acids, salts, vitamins and removes unabsorbed residues such as feces. This organ is 1.3–1.4 m long and 5–8 cm wide.

intestinal microbiome	sulfate-reducing bacteria		hydrogen sulfide	
inflammatory bowel diseas	ses	ulcerative colitis	meta-analysis	

1. Introduction

The large intestine (intestinum crassum) is the last part of the digestive tract ensuring the resorption of water, amino acids, bile acids, salts, vitamins and removes unabsorbed residues such as feces. This organ is 1.3–1.4 m long and 5–8 cm wide. The main sections of the large intestine are the caecum from which the appendix vermiformis, the colon, the rectum, and the anal canal analis extend. The intestinal wall consists of mucosa, mucosal ligament, muscle, and serosis.

The mucosa of the large intestine is smooth, slightly articulated. Kerckring's algae and intestinal villi, which are found in the small intestine, are absent in the large intestine. Lieberkühn's crypts have a tubular appearance and are significantly longer than in the small intestine. The epithelium of the colonic mucosa is single-layered cylindrical and consists of enterocytes and goblet cells, which are particularly abundant in the middle sections of Lieberkühn's crypts. Paneth cells are usually missing. Of the endocrine cells, the epithelium contains mainly EC cells (so-called enterochromaffin cells), which, among other things, synthesize serotonin. The intestinal epithelium is a physical barrier that coexists with intestinal microorganisms, ensuring the transport of substances and their regulation so that homeostasis is maintained^[45].

2. Intestinal Microbiota

There are approximately 10¹³–10¹⁴ bacteria in the human gut, with about 10¹³ cells in the human body^{[46][47]}. Thus, there are as many or up to ten times more bacteria in the human body than human cells alone^{[38][39]}. Bacteria in the large intestine are thought to make up almost 90% of the total human colonic microbiota^[48].

Profiling of the 16S rRNA gene sequence showed that bacteria of the strains *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, *Verrucomicrobia*, and also representatives of the

domain *Archaea* predominate. Bacterial strains of *Cyanobacteria*, *Fusobacteria* and *Spirochaete* are also present in the intestines, but in smaller numbers. The microbiota has an important metabolic, immunological, and protective function^[49].

The composition of the microbiome is therefore crucial because billions of bacterial individuals in the intestinal lumen can become a threat to the host organism with any change in conditions. Although metabolites produced by the microbiota affect various organs and systems in the body by signaling, symbiosis with the intestinal mucosa is necessary for their survival^[50]. The main representatives of intestinal bacteria are presented in <u>Table 1</u>.

Domain/Phylum	Examples of Genera	Main Function
Phylum: <i>Bakteroidetes</i>	Bacteroidetes, Prevotella, Xylanibacter	Degradation complex glycans
Phylum: Firmicutes	Ruminococcus, Clostridium, Lactobacillus, Roseburia, Eubacterium, Faecalibacterium	Probiotics, butyrate producers
Phylum: Actinobacteria	Collinsella, Bifidobacterium	Probiotics
Phylum: Proteobacteria	Desulfovibrio	Sulfate-reducing bacteria
Phylum: Verrucomicrobia	Akkermansia	Degradation of mucin
Domain: Archaea	Methanobrevibacter	Methanogenesis

Table 1. The main representatives of intestinal bacteria^[48].

The human body has well-developed mechanisms by which it effectively prevents the translocation of symbiotic or pathogenic microorganisms across the mucosal barrier, including mucus protection of the intestinal epithelium. Intestinal mucus has a highly organized glycoprotein network structure but also contains a stable proteome^[51]. Intestinal epithelial cells separate the intestinal lumen and deeper tissue structures that normally contain immune cells^{[52][53]}. By contacting or penetrating the epithelial barrier, microorganisms affect immune cells and can cause the induction of an immune response^[54].

Anaerobic colon bacteria break down carbohydrates and proteins through fermentation into gases and SCFAs^[55], which are a major source of energy for the colon epithelium^[52]. Saccharolytic bacterial fermentation produces generally beneficial metabolites. However, while under carbohydrate-limiting conditions, bacteria turn to alternative energy sources, leading to the production of other metabolites that might be harmful to human health^[53].

Indigestible polysaccharides present in, for example, fruits and vegetables pass without effective cleavage to the large intestine, where they are fermented to form SCFAs as products of bacterial metabolism^[54]. Low intake of indigestible polysaccharides results in reduced levels of SCFAs and their producers. An interesting finding was the fact that increased intake of fruits and vegetables is associated with a reduced risk of developing both UC and CD, and SCFAs could, therefore, be good candidates for deeper research into the regulation of the immune response

under the influence of various inducing factors^[56]. Decreased levels of SCFAs have been confirmed in children with IBD^[57].

The intestinal microbiota also has the significant proteolytic capacity, converting ingested food protein and endogenous protein from host enzymes and mucin to shorter peptides, amino acids and their derivatives, short and branched-chain [7] fatty acids, and gases, including CH₄, NH₃, H_{2} CO_2 , and H₂S ^[53]. Bacteroides and Propionibacterium are the dominant proteolytic species in fecal samples, with proteolysis also being common to Clostridia, Streptococci, Staphylococci, and Bacillus species^{[10][53]}.

Colon bacteria are also able to synthesize some vitamins, especially B vitamins, including biotin, cobalamin, folate, nicotinic acid, pantothenic acid, pyridoxine, riboflavin, and thiamine, and vitamin $K^{[53][58]}$. One of the first documented benefits of intestinal commensals for human metabolism was undoubtedly their confirmed ability to produce vitamin B₁₂. These vitamins are important for both bacterial metabolism and the host ^[59].

3. Short-Chain Fatty Acids

Indigestible polysaccharides, including cellulose and other substances, are fermented in the gut by anaerobic bacteria to obtain energy for microbial growth and production of short-chain fatty acids (SCFAs)^[60]. The three most abundant SCFAs detected in feces are acetate, propionate, and butyrate^[61].

Butyrate is important representative of SCFAs and plays a key role in maintaining intestinal epithelial homeostasis as a preferred source of energy for colonocytes and their growth stimulator^[62]. Previously published studies have found that 71% of the energy obtained by colonocytes is due to butyrate, which is preferentially produced by commensals, especially representatives of *Clostridia* sp. from the *Firmicutes* phylum strain^[63]. It is also used as an inhibitor of carcinogenesis, inflammation, and oxidative stress that stimulates mucus production and absorption of electrolytes and fluids and improves the barrier function of the intestinal epithelium^[62].

Butyrate also has anti-inflammatory effects by stimulating antigen-presenting cells to produce the cytokines TGF- β , IL-10, IL-18, and by inducing the differentiation of naive T cells into regulatory T cells. A mild anti-inflammatory effect was also demonstrated for acetate and propionate. These two molecules have the ability to suppress the production of proinflammatory cytokines by stimulating TLR 4^[64].

Butyrate metabolism is one of the current theories for the etiology of $UC^{[65]}$. It is thought that a lack of energy for colonocytes could lead to the onset of this disease^{[41][52]}. Butyrate has also been used experimentally in the treatment of colitis with numerous benefits for patients^{[54][66]}.

Propionate, like butyrate, can induce T-cell differentiation^[64]. Propionate is a source of energy for epithelial cells, but it is also transferred to the liver, where it plays a vital role in gluconeogenesis (IGN). A study in mouse models showed that after infusion of the propionate solution, 62% of this substance was used as a substrate for IGN throughout the body of the experimental animal. Glucose synthesis from propionate represents 69% of the total

IGN in the body^[67]. It is also increasingly considered an important molecule in satiety signaling due to interaction with the intestinal GPR 41 and GPR 43 receptors^{[53][68]}, also known as FFAR2 and FFAR3 fatty acid receptors, which may, in turn, activate intestinal IGN^{[53][69]}.

Acetate is the most abundant SCFA and is an important cofactor and metabolite for the growth of many microorganisms^{[61][70]}. In the human body, acetate is transported to peripheral tissues and is taken up by cholesterol metabolism and lipogenesis. Recent studies expect them to play a significant role in the central regulation of appetite ^[71]. SCFAs are demonstrably connecting the links between dietary routines, intestinal microbiota, and host energy metabolism^[67]. SCFAs are advantageous energy coverage of up to 10% of the daily caloric potential of the human body^[63].

Bacterial fermentation provides numerous intermediates, including fumarate, succinate, and lactate, but are commonly detected at low levels in the feces of healthy individuals due to their extensive use by other bacteria. For example, lactate is usually converted to propionate or butyrate by other bacteria and is therefore present at negligible levels in adult feces. However, in patients with UC, lactate can be detected in significantly higher amounts and could be a potential indicator of the disease^{[53][72]}. It has been shown that the control and manipulation of the intestinal microbiome can be an approach to the therapy and prevention of IBD^[7].

4. Intestinal Gases

The gas is a product of microbial fermentation in anaerobic ecosystems, including the digestive tract. However, some anaerobically growing species produce no $gas^{[53][73]}$. This is the case with common probiotics such as *Lactobacilli* and *Bifidobacteria*. It is therefore theoretically possible that probiotics or prebiotics can reduce the occurrence of gas in the intestines and also contribute to the suppression of some health problems^[10].

Most microbially generated gas includes CH_4 , NH_3 , H_2 , CO_2 , and H_2S , among others. The key harmful and potentially toxic components are sulfides, which act as precursors to other sulfur-based components^[Z]. However, sulfide is also an important signaling molecule for bacteria, plants, and mammals. In the human body, sulfide acts as a messenger for a variety of systems, including the central and peripheral nervous systems, the immune system, and the gastrointestinal tract. Sulfide gas enters and also leaves cells due to diffusion across the lipid membrane^[74].

The H₂ composition of the flatus is up to 40% and appears to be exclusively of microbial origin^[10]. H₂ is produced by various intestinal microorganisms. The main producers are *Bacteroides* and *Clostridium*. There are three main microbial pathways by which H₂ can be removed. These include sulfate dissimilation reduction, methanogenesis, and acetogenesis^[75].

The dissimilative reduction of sulfates is provided by SRB. These microorganisms use sulfate as an electron acceptor to dissimilation organic compounds and H_2 ^[76]. The most common genus SRB in the intestine is the genus *Desulfovibrio*. Sulfate can be ingested in the diet or released after microbial metabolism of sulfate mucins.

These are glycoproteins that line the gastrointestinal tract and act as a protective barrier between the mucosal surface and the luminal contents^[77].

The use of H_2 to reduce sulfate to sulfide has effects on overall gas production in the colon by reducing the amount of free H_2 , thereby helping to prevent excessive gas accumulation. However, the highly toxic nature of the H_2S produced can have pathological consequences for the host^[53]. The SRB group is described in more detail in Chapter 4.

Dissimilatory sulfate reduction: $4H_2 + SO_4^{2-} + H^+ \rightarrow HS^- + 4H_2O$

Methanogenesis is another mechanism of H_2 removal in the large intestine that also reduces the overall gas accumulation. Thus, methanogenic archaea and SRB compete for H_2 in the gut, and the process that dominates depends on the amount of sulfate available. When sufficient sulfate is available, SRB are more easily recovered by H_2 due to their higher affinity for the substrate^{[10][53]}.

Methanogenesis: $4H_2 + CO_2 \rightarrow CH_4 + 2H_2O$

For host health, acetogenesis is probably the most preferred way to recycle H_2 . The reason is the conversion of carbon dioxide (CO₂) and H_2 into acetate without releasing gas. However, this reaction is less energetically favorable than reduction by dissolving sulfate or methanogenesis ^[75].

Acetogenesis: $4H_2 + CO_2 \rightarrow CH_3COOH + 2H_2O$

 CO_2 is another quantitatively significant gas. CO_2 can represent between 5% and 50% of the total volume of the flatus and is recycled by methanogenesis and to a lesser extent by acetogenesis. Unlike H₂ and methane, CO_2 can be generated by a number of processes, not just bacterial metabolism^[78].

The absence of SRB, methanogens, and acetogens would cause the individual to produce 5–10 times more gas than usual. H_2 recycling by disulfilization reduction of sulfate generates H_2S , which is a cellular signaling molecule, but also a highly toxic substance for colon cells, and its production and amount is a cofactor of inflammatory bowel disease. The presence of methane in the colon has been linked to colorectal cancer, although this association may be due to disease rather than causation, as patients with these difficulties also suffer from slower intestinal passage through the colon, which benefits the growth of intestinal methanogens due to their slowly growing nature^[53].

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