Large Intestine and Its Microbiota

Subjects: Gastroenterology & Hepatology

Contributor: Ivan Kushkevych

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.

Keywords: intestinal microbiome ; sulfate-reducing bacteria ; hydrogen sulfide ; inflammatory bowel diseases ; 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 10^{13}–10^{14} bacteria in the human gut, with about 10^{13} 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 Table 1.

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

Domain/Phylum	Examples of Genera	Main Function
Phylum: *Bakteroidetes*	***Bacteroidetes*, *Prevotella*, *Xylanibacter***	**Degradation complex glycans**
Phylum: *Firmicutes*	***Ruminococcus*, *Clostridium*, *Lactobacillus*, *Roseburia*, *Eubacterium*, *Faecalibacterium***	**Probiotics, butyrate producers**
Phylum: *Actinobacteria*	***Collinsella*, *Bifidobacterium***	**Probiotics**

Domain/Phylum	Examples of Genera	Main Function
Phylum: *Proteobacteria*	*Desulfovibrio*	Sulfate-reducing bacteria
Phylum: *Verrucomicrobia*	*Akkermansia*	Degradation of mucin
Domain: *Archaea*	*Methanobrevibacter*	Methanogenesis

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 fatty acids, and gases, including CH_4, NH_3, H_2, CO_2, and H_2S [7][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 B_{12}. 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[7]. 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 H_2 composition of the flatus is up to 40% and appears to be exclusively of microbial origin[10]. H_2 is produced by various intestinal microorganisms. The main producers are *Bacteroides* and *Clostridium*. There are three main microbial pathways by which H_2 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 (CO_2) 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 H_2 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].

References

1. Ahmed, I.; Niaz, Z. Ulcerative Colitis. In Ulcerative Colitis. Epidemiology, Pathogenesis and Complications; IntechOpen: London, UK, 2011; pp. 1–12.
2. Ho, G.-T.; Boyapati, R.; Satsangi, J. Ulcerative colitis. Medicine 2015, 43, 276–281.
3. Kushkevych, I.; Dordević, D.; Vítězová, M. Toxicity of hydrogen sulfide toward sulfate-reducing bacteria Desulfovibrio piger Vib-7. Arch. Microbiol. 2019, 201, 389–397.
4. Kushkevych, I.; Kotrsová, V.; Dordević, D.; Buňková, L.; Vítězová, M.; Amedei, A. Hydrogen Sulfide Effects on the Survival of Lactobacilli with Emphasis on the Development of Inflammatory Bowel Diseases. Biomolecules 2019, 9, 752.
5. Vilela, E.G. Evaluation of inflammatory activity in Crohn's disease and ulcerative colitis. WJG 2012, 18, 872.
6. Gibson, G.R.; Macfarlane, S.; Macfarlane, G.T. Metabolic interactions involving sulphate-reducing and methanogenic bacteria in the human large intestine. FEMS Microbiol. Ecol. 1993, 12, 117–125.
7. Cummings, J.H.; Macfarlane, G.T. Colonic microflora: Nutrition and health. Nutrition 1997, 13, 476–478.
8. Cummings, J.H.; Macfarlane, G.T.; Macfarlane, S. Intestinal bacteria and ulcerative colitis. Curr. Issues Intestig. Microbiol. 2003, 4, 9–20.
9. Malik, T.A. Inflammatory Bowel Disease. Surg. Clin. N. Am. 2015, 95, 1105–1122.
10. Gibson, G.R.; Cummings, J.H.; Macfarlane, G.T. Growth and activities of sulphate-reducing bacteria in gut contents of healthy subjects and patients with ulcerative colitis. FEMS Microbiol. Lett. 1991, 86, 103–112.
11. Kushkevych, I.V. Kinetic Properties of Pyruvate Ferredoxin Oxidoreductase of Intestinal Sulfate-Reducing Bacteria Desulfovibrio piger Vib-7 and Desulfomicrobium sp. Rod-9. Pol. J. Microbiol. 2015, 64, 107–114.
12. Kushkevych, I.V. Activity and kinetic properties of phosphotransacetylase from intestinal sulfate-reducing bacteria. Acta Biochim. Pol. 2015, 62, 103–108.
13. Kushkevych, I. Isolation and Purification of Sulfate-Reducing Bacteria. In Microorganisms; Blumenberg, M., Shaaban, M., Elgaml, A., Eds.; IntechOpen: London, UK, 2020; ISBN 978-1-83880-187-8.
14. Kushkevych, I.; Kollar, P.; Suchy, P.; Parak, T.; Pauk, K.; Imramovsky, A. Activity of selected salicylamides against intestinal sulfate-reducing bacteria. Neuro Endocrinol. Lett. 2015, 36 (Suppl. 1), 106–113.
15. Kushkevych, I.; Fafula, R.; Parák, T.; Bartoš, M. Activity of Na+/K+-activated Mg2+-dependent ATP-hydrolase in the cell-free extracts of the sulfate-reducing bacteria Desulfovibrio piger Vib-7 and Desulfomicrobium sp. Rod-9. Acta Vet. Brno 2015, 84, 3–12.
16. Kushkevych, I.; Kováč, J.; Vítězová, M.; Vítěz, T.; Bartoš, M. The diversity of sulfate-reducing bacteria in the seven bioreactors. Arch. Microbiol. 2018, 200, 945–950.
17. Pitcher, M.C.; Cummings, J.H. Hydrogen sulphide: A bacterial toxin in ulcerative colitis? Gut 1996, 39, 1–4.

18. Yuan, Y.; Hunt, R.H. Systematic Reviews: The Good, the Bad and the Ugly. Am. J. Gastroenterol. 2009, 104, 1086–1092.

19. Ergal, İ.; Fuchs, W.; Hasibar, B.; Thallinger, B.; Bochmann, G.; Rittmann, S.K.-M.R. The physiology and biotechnology of dark fermentative biohydrogen production. Biotechnol. Adv. 2018, 36, 2165–2186.

20. Rittmann, S.K.-M.R.; Seifert, A.H.; Bernacchi, S. Kinetics, multivariate statistical modelling, and physiology of CO2-based biological methane production. Appl. Energy 2018, 216, 751–760.

21. Dordević, D.; Jančíková, S.; Vítězová, M.; Kushkevych, I. Hydrogen sulfide toxicity in the gut environment: Meta-analysis of sulfate-reducing and lactic acid bacteria in inflammatory processes. J. Adv. Res. 2020, 27, 55–69.

22. Kushkevych, I.; Dordević, D.; Kollár, P. Analysis of physiological parameters of Desulfovibrio strains from individuals with colitis. Open Life Sci. 2019, 13, 481–488.

23. Kováč, J.; Vítězová, M.; Kushkevych, I. Metabolic activity of sulfate-reducing bacteria from rodents with colitis. Open Med. 2018, 13, 344–349.

24. Kushkevych, I.; Vítězová, M.; Kos, J.; Kollár, P.; Jampílek, J. Effect of selected 8-hydroxyquinoline-2-carboxanilides on viability and sulfate metabolism of Desulfovibrio piger. J. Appl. Biomed. 2018, 16, 241–246.

25. Kushkevych, I.; Dordević, D.; Vítězová, M. Analysis of pH dose-dependent growth of sulfate-reducing bacteria. Open Med. 2019, 14, 66–74.

26. Kushkevych, I.; Castro Sangrador, J.; Dordević, D.; Rozehnalová, M.; Černý, M.; Fafula, R.; Vítězová, M.; Rittmann, S.K.-M.R. Evaluation of Physiological Parameters of Intestinal Sulfate-Reducing Bacteria Isolated from Patients Suffering from IBD and Healthy People. JCM 2020, 9, 1920.

27. Kushkevych, I.; Dordević, D.; Vítězová, M. Possible synergy effect of hydrogen sulfide and acetate produced by sulfate-reducing bacteria on inflammatory bowel disease development. J. Adv. Res. 2020, 27, 71–78.

28. Stange, E.F. Inflammatory bowel diseases. Preface. Dig. Dis. 2013, 31, 269.

29. Boyapati, R.K.; Rossi, A.G.; Satsangi, J.; Ho, G.-T. Gut mucosal DAMPs in IBD: From mechanisms to therapeutic implications. Mucosal. Immunol. 2016, 9, 567–582.

30. Head, K.; Jurenka, J.S. Inflammatory bowel disease. Part II: Crohn's disease--pathophysiology and conventional and alternative treatment options. Altern. Med. Rev. 2004, 9, 360–401.

31. Ek, W.E.; D'Amato, M.; Halfvarson, J. The history of genetics in inflammatory bowel disease. Ann. Gastroenterol. 2014, 27, 294–303.

32. Boirivant, M.; Cossu, A. Inflammatory bowel disease: Inflammatory bowel disease. Oral Dis. 2012, 18, 1–15.

33. Juyal, G.; Sood, A.; Midha, V.; Thelma, B.K. Genetics of ulcerative colitis: Putting into perspective the incremental gains from Indian studies. J. Genet. 2018, 97, 1493–1507.

34. Molodecky, N.A.; Kaplan, G.G. Environmental risk factors for inflammatory bowel disease. Gastroenterol. Hepatol. (N. Y.) 2010, 6, 339–346.

35. Koloski, N.-A.; Bret, L.; Radford-Smith, G. Hygiene hypothesis in inflammatory bowel disease: A critical review of the literature. World J. Gastroenterol. 2008, 14, 165–173.

36. Sonnenberg, A. Occupational distribution of inflammatory bowel disease among German employees. Gut 1990, 31, 1037–1040.

37. Macfarlane, M.J.; Hopkins, G.T.; Ma, S. Bacterial Growth and Metabolism on Surfaces in the Large Intestine. Microb. Ecol. Health Dis. 2000, 12, 64–72.

38. Macfarlane, S.; Steed, H.; Macfarlane, G.T. Intestinal bacteria and inflammatory bowel disease. Crit. Rev. Clin. Lab. Sci. 2009, 46, 25–54.

39. Savage, D.C. Microbial Ecology of the Gastrointestinal Tract. Annu. Rev. Microbiol. 1977, 31, 107–133.

40. Carbonnel, F.; Jantchou, P.; Monnet, E.; Cosnes, J. Environmental risk factors in Crohn's disease and ulcerative colitis: An update. Gastroenterol. Clin. ET Biol. 2009, 33, S145–S157.

41. Campieri, M. Bacteria as the cause of ulcerative colitis. Gut 2001, 48, 132–135.

42. Sands, B.E. Inflammatory bowel disease: Past, present, and future. J. Gastroenterol. 2007, 42, 16–25.

43. Clavel, T.; Haller, D. Bacteria- and host-derived mechanisms to control intestinal epithelial cell homeostasis: Implications for chronic inflammation: Inflamm. Bowel Dis. 2007, 13, 1153–1164.

44. Ng, S.C.; Shi, H.Y.; Hamidi, N.; Underwood, F.; Tang, W.; Benchimol, E.; Panaccione, R.; Ghosh, S.; Wu, J.; Chan, F.; et al. Evolving Trends in the Epidemiology of IBD in the 21st Century: A Systematic Review of Population-Based

Studies: 594. Am. J. Gastroenterol. 2017, 112, S319–S320.

45. Sánchez de Medina, F.; Romero-Calvo, I.; Mascaraque, C.; Martínez-Augustin, O. Intestinal Inflammation and Mucosal Barrier Function: Inflamm. Bowel Dis. 2014, 20, 2394–2404.
46. Guarner, F.; Malagelada, J.-R. Role of bacteria in experimental colitis. Best Pract. Res. Clin. Gastroenterol. 2003, 17, 793–804.
47. Li, X.; Bi, Y. How Many Human and Bacteria Cells Are in the Human Body? Infect. Dis. Transl. Med. 2017, 1–2.
48. Pushpanathan, P.; Mathew, G.; Selvarajan, S.; Seshadri, K.; Srikanth, P. Gut microbiota and its mysteries. Indian J. Med. Microbiol. 2019, 37, 268.
49. Ziemer, C.J. Newly Cultured Bacteria with Broad Diversity Isolated from Eight-Week Continuous Culture Enrichments of Cow Feces on Complex Polysaccharides. Appl. Environ. Microbiol. 2014, 80, 574–585.
50. Schroeder, B.O. Fight them or feed them: How the intestinal mucus layer manages the gut microbiota. Gastroenterol. Rep. 2019, 7, 3–12.
51. Johansson, M.E.V.; Gustafsson, J.K.; Holmén-Larsson, J.; Jabbar, K.S.; Xia, L.; Xu, H.; Ghishan, F.K.; Carvalho, F.A.; Gewirtz, A.T.; Sjövall, H.; et al. Bacteria penetrate the normally impenetrable inner colon mucus layer in both murine colitis models and patients with ulcerative colitis. Gut 2014, 63, 281–291.
52. Cummings, J.H. Short chain fatty acids in the human colon. Gut 1981, 22, 763–779.
53. Rowland, I.; Gibson, G.; Heinken, A.; Scott, K.; Swann, J.; Thiele, I.; Tuohy, K. Gut microbiota functions: Metabolism of nutrients and other food components. Eur. J. Nutr. 2018, 57, 1–24.
54. Couto, M.R.; Gonçalves, P.; Magro, F.; Martel, F. Microbiota-derived butyrate regulates intestinal inflammation: Focus on inflammatory bowel disease. Pharmacol. Res. 2020, 159, 104947.
55. Mauerhofer, L.-M.; Pappenreiter, P.; Paulik, C.; Seifert, A.H.; Bernacchi, S.; Rittmann, S.K.-M.R. Methods for quantification of growth and productivity in anaerobic microbiology and biotechnology. Folia Microbiol. 2019, 64, 321–360.
56. Roy, C.C.; Kien, C.L.; Bouthillier, L.; Levy, E. Short-Chain Fatty Acids: Ready for Prime Time? Nutr. Clin. Pract. 2006, 21, 351–366.
57. Treem, W.R.; Ahsan, N.; Shoup, M.; Hyams, J.S. Fecal short-chain fatty acids in children with inflammatory bowel disease. J. Pediatr. Gastroenterol. Nutr. 1994, 18, 159–164.
58. Hill, M.J. Intestinal flora and endogenous vitamin synthesis. Eur. J. Cancer Prev. 1997, 6, S43–S45.
59. Martens, H.; Barg, M.; Warren, D.; Jah, J.-H. Microbial production of vitamin B 12. Appl. Microbiol. Biotechnol. 2002, 58, 275–285.
60. Tremaroli, V.; Bäckhed, F. Functional interactions between the gut microbiota and host metabolism. Nature 2012, 489, 242–249.
61. Duncan, S.H.; Holtrop, G.; Lobley, G.E.; Calder, A.G.; Stewart, C.S.; Flint, H.J. Contribution of acetate to butyrate formation by human faecal bacteria. Br. J. Nutr. 2004, 91, 915–923.
62. Gonçalves, P.; Martel, F. Butyrate and Colorectal Cancer: The Role of Butyrate Transport. CDM 2013, 14, 994–1008.
63. LeBlanc, J.G.; Chain, F.; Martín, R.; Bermúdez-Humarán, L.G.; Courau, S.; Langella, P. Beneficial effects on host energy metabolism of short-chain fatty acids and vitamins produced by commensal and probiotic bacteria. Microb. Cell Fact. 2017, 16, 79.
64. Oliphant, K.; Allen-Vercoe, E. Macronutrient metabolism by the human gut microbiome: Major fermentation by-products and their impact on host health. Microbiome 2019, 7, 91.
65. Clausen, M.R.; Mortensen, P.B. Kinetic studies on colonocyte metabolism of short chain fatty acids and glucose in ulcerative colitis. Gut 1995, 37, 684–689.
66. Moeinian, M. Beneficial effect of butyrate, Lactobacillus casei and L-carnitine combination in preference to each in experimental colitis. WJG 2014, 20, 10876.
67. den Besten, G.; Lange, K.; Havinga, R.; van Dijk, T.H.; Gerding, A.; van Eunen, K.; Müller, M.; Groen, A.K.; Hooiveld, G.J.; Bakker, B.M.; et al. Gut-derived short-chain fatty acids are vividly assimilated into host carbohydrates and lipids. Am. J. Physiol. Gastrointest. Liver Physiol. 2013, 305, G900–G910.
68. Al-Asmakh, M.; Anuar, F.; Zadjali, F.; Rafter, J.; Pettersson, S. Gut microbial communities modulating brain development and function. Gut Microbes 2012, 3, 366–373.

69. De Vadder, F.; Kovatcheva-Datchary, P.; Goncalves, D.; Vinera, J.; Zitoun, C.; Duchampt, A.; Bäckhed, F.; Mithieux, G. Microbiota-Generated Metabolites Promote Metabolic Benefits via Gut-Brain Neural Circuits. Cell 2014, 156, 84–96.
70. Abdel Azim, A.; Rittmann, S.K.-M.R.; Fino, D.; Bochmann, G. The physiological effect of heavy metals and volatile fatty acids on Methanococcus maripaludis S2. Biotechnol. Biofuels 2018, 11, 301.
71. Frost, G.; Sleeth, M.L.; Sahuri-Arisoylu, M.; Lizarbe, B.; Cerdan, S.; Brody, L.; Anastasovska, J.; Ghourab, S.; Hankir, M.; Zhang, S.; et al. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. Nat. Commun. 2014, 5, 3611.
72. Louis, P.; Flint, H.J. Formation of propionate and butyrate by the human colonic microbiota. Environ. Microbiol. 2017, 19, 29–41.
73. Levitt, M.D.; Bond, J.H. Volume, composition, and source of intestinal gas. Gastroenterology 1970, 59, 921–929.
74. Figliuolo, V.R.; Coutinho-Silva, R.; Coutinho, C.M.L.M. Contribution of sulfate-reducing bacteria to homeostasis disruption during intestinal inflammation. Life Sci. 2018, 215, 145–151.
75. Christl, S.U.; Murgatroyd, P.R.; Gibson, G.R.; Cummings, J.H. Production, metabolism, and excretion of hydrogen in the large intestine. Gastroenterology 1992, 102, 1269–1277.
76. Wolf, P.G.; Biswas, A.; Morales, S.E.; Greening, C.; Gaskins, H.R. H2 metabolism is widespread and diverse among human colonic microbes. Gut Microbes 2016, 7, 235–245.
77. Florin, T.H.J.; Neale, G.; Goretski, S.; Cummings, J.H. The Sulfate Content of Foods and Beverages. J. Food Compos. Anal. 1993, 6, 140–151.
78. Suarez, F.; Furne, J.; Springfield, J.; Levitt, M. Insights into human colonic physiology obtained from the study of flatus composition. Am. J. Physiol. 1997, 272, G1028–G1033.