Chapter

Intestinal Microbiomics in Physiological and Pathological Conditions

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Abstract

Microbiomics represents a new science studying the microbiome, consisting of all the microorganisms of a given community. This new science collects data about all the members of the microbial community and quantifies the molecules responsible for the structure, function, and dynamics of the microbiome. The human microbiome plays a very important role in the healthy state and in a variety of disease states. The human microbiome knowledge has evolved during the last decades and nowadays one can consider that, in particular, the gut microbiota is seen as a significant organ holding 150 times more genes compared to the human genome. This chapter will focus on discussing the normal and modified phyla and species of the gut microbiome in a variety of conditions, providing a better understanding of host-microbiome interactions. We will highlight some new associations between intestinal dysbiosis and acute or chronic inflammatory and metabolic diseases.

Keywords: microbiomics, gut microbiome, microbiota, dysbiosis, eubiosis

1. Introduction

Microbiomics is the science that distinguishes the structure, role, and passage of molecules involved in the microbial group [1]. In the "omics" era, it became more and more clear that gut microbiota is probably impacting the entire metabolism of the host. The study of the microbial community in their own habitat allows us to understand the complex interactions between microorganisms and the molecules responsible for their maintenance and correct functioning [1]. The microbiome, considered the metagenome of the microbiota, consists of the genetic material of bacteria, fungi, protozoa, and viruses, which can be found on the skin or hair surfaces, on mucosal surfaces (oral, intestinal, airways [2], vaginal [3]); uterus [4], eyes [5], and lungs [6]) [7].

Humans and microorganisms have coexisted for millennia under symbiotic relationships [7]. Any alteration in the human microbiome can lead to an imbalance stated, called dysbiosis, which influences the evolution of different conditions [8]. Dysbiosis can occur due to a series of factors like environment conditions (cold temperatures, poor economic status), treatment with antibiotics, probiotics intake, acute or chronic infections, or even the immune status of the host [9].

The gut microbiota is responsible for generating biologically active metabolites, with important roles in homeostasis, but also in pathophysiological processes [7].

Gut microbiota is involved in maintaining the immunological barrier, providing nutrients, and generating energy [10].

2. Structure and dynamics of the healthy adult microbiota

Oral microbiota was described to be dominated by *Streptococcus*, followed by *Haemophilus* (buccal mucosa), *Actinomyces* (supragingival plaque), and *Prevotella* (near the subgingival plaque) [11, 12]. *Porphyromonas gingivalis (P. gingivalis)*, a bacterium that colonizes the oral mucosa, was found through immunohistochemical techniques in 61% of the cancerous esophageal tissue examined. Thus, experts suggest it is a potential biomarker for assessing cancer progression. Originally located in the mouth, *Fusobacterium nucleatum* is linked with colonic adenocarcinoma development, strong evidence of its tumor protective role against the immune system cells arises from recent research [13].

Skin microbiota differs between different topographical regions, being under the influence of lifestyle conditions, hygiene, and antibiotic use. The microorganisms present on the skin are involved in the pathophysiology of different dermatological conditions, such as atopic dermatitis, psoriasis, acne, and seborrheic dermatitis. In a study conducted by Grice et al., although based on a limited number of subjects, the most frequent phyla identified were *Actinobacteria, Firmicutes, Proteobacteria* and *Bacteroidetes* and the most common genera were *Corynebacteria (Actinobacteria), Propionibacteria (Actinobacteria)*, and *Staphylococci (Firmicutes)*. Propionibacterium species preponderate in sebaceous locations, *Corynebacteria* in moist locations, while *Staphylococci* species were present in significant amounts in both sebaceous and moist sites [14]. Regarding dry areas, high levels of *beta-Proteobacteri*a and *Flavobacteriales* were observed [14]. Although human skin microbiota consists mostly of bacteria, several types of fungi are also present. A combination of the genera: *Malassezia, Aspergillus, Cryptococcus Rhodotorula*, and *Epicoccum* was found located mostly in the foot skin area [15].

The vaginal microbiome is dominated by bacteria that can produce lactic acid, mostly *Lactobacillus* species (*Lactobacillus iners*, *Lactobacillus crispatus*, *Lactobacillus gasseri, Lactobacillus jensenii*), coexisting with other types of bacteria, such as *Gardnerella, Atopobium, Megasphaera, Eggerthella, Aerococcus, Alloiococcus, Streptococcus, Leptotrichia/Sneathia, Prevotella, Papillibacter* and anaerobic microorganisms [16]. They lower the local pH due to lactic acid production and have bacteriostatic and bactericidal properties [17, 18]. The uterine microbiome is similar in composition to the vaginal population with a predominance of *Lactobacillus* colonies together with *Bifidobacterium, Gardnerella, Prevotella,* and *Streptococcus* types of microorganisms. Uterine dysbiosis due to contraceptive medication usage, untreated or chronic bacterial vaginosis, or other physiological factors can lead to fertility issues (loss of fetal implantation ability, bacterial overpopulation, and uro-genital

infections) [4]. The uterine microbiome and the interactions between the microbiome and the human reproductive system are currently being studied for enhancing the current approach to assist reproductive techniques, by targeting specific phyla and the results are promising [19].

The predominant bacterial genera found in the eyes conjunctiva and ocular surface are gram-positive pathogens like *Staphylococcus, Streptococcus, Propionibacterium, Diphtheroid* bacteria, and *Micrococcus*. While gram-negative genus is mostly found in the gut, anaerobes or fungi are rarely observed in this particular site. It is unclear how the intraocular immune environment and microbiome interact to control inflammatory eye disorders like uveitis [20].

Airways are largely populated by *Actinobacterium (Corynebacterium, Aureobacterium,* and *Rhodococcus)*, but there is a significant microbiome diversity difference between nasopharynx microbiota and pharynx commensal bacterial population. *Corynebacterium, Aureobacterium, Rhodococcus*, and *Staphylococcus*, including *S. epidermis, Staphylococcus capitis, Staphylococcus hominis, Staphylococcus haemolyticus, Staphylococcus lugdunensis,* and *Staphylococcus warneri,* compose the majority of the nasal microbiota [2].

Although previously believed that the lungs are sterile, and the first evidence of commensal bacterial population in the lungs where initially attributed to contamination from upper airways through bronchoscopy, it is now clear that the majority of lung microbiota consists of *Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria,* and *Actinobacteria* and alterations at this level can be linked to lung diseases (asthma, chronic obstructive pulmonary disease, and chronic suppurative lung disease) occurrence [6].

The human gut hosts thousands of microbial species [21], which have a gene pool larger than the human genome, which determined its name as a metagenome [22, 23]. There are two major phyla, *Bacteroidetes* and *Firmicutes*, representing 90% of the total bacterial species found in the human gut, the remaining 10% consisting of *Actinobacteria, Cyanobacteria, Fusobacteria, Proteobacteria,* and *Verrucomicrobia* [7, 23].

Several factors can alter the composition and evolution of gut microbiota over the years. Firstly, differences between newborns are noted: babies delivered vaginally have gut microbiota consisting of *Lactobacillus, Prevotella, and Atopobium*, while, in comparison, the gut of babies delivered by caesarian section has maternal epidermal microflora, mostly represented by *Staphylococcus* [18, 23]. With age, anaerobic microorganisms become more abundant, with significant concentrations of *Bifidobacteria* and *Clostridia* in teenagers when compared to adults and higher levels of facultative anaerobes in the elderly [10]. The microbiota of infants was observed to be rich in *Clostridium coccoides* and *Clostridium leptum*, while elevated levels of *Escherichia Coli* and *Bacteroidetes* were observed in older people [10, 23].

Changes in the gut microbiota composition are in correlation with the physiological age-related processes. A systematic review conducted by Badal and colleagues presented some of the microbiota variations throughout the years. In older subjects, alpha diversity of the microbial taxa, functional pathways, and metabolites were enhanced, while beta diversity fluctuated significantly through different age groups. *Akkermansia* was described to be relatively plentiful with aging, while *Faecalibacterium, Bacteroidaceae,* and *Lachnospiraceae* were relatively diminished [24]. Elders possess different properties and functions of the microbiota: decreased activity of carbohydrate metabolism pathways and amino acid synthesis, higher production of short-chain fatty acids (SCFA) and butyrate derivatives (gamma-aminobutyric acid - GABA and DL-3-amino isobutyric acid) [24, 25].

For older people with ages ranging from 66 to 80 years old, lower levels of *Bifidobacterium*, *Faecalibacterium*, *Bacteroides*, and *Clostridium* cluster XIVa were noted. However, elevated aggregations of the *Akkermansia* and *Lactobacillus* group were detected in the cluster of people over 80 years old, compared with adults. Moreover, lower fecal SCFA concentrations were associated with aging, with statistical significance [26].

Diet plays a major role in the diversity of the human gut microorganisms and David et al. [27] compared plant-based diet microbiome with animal produce consumption microbiome and concluded that a shift in diet from mostly fibers to high fats and proteins can lead to only 24 hours to an increased population of *Alistipes, Bilophila* and *Bacteroides* and decreased levels of *Firmicutes (Roseburia, Eubacterium rectale,* and *Ruminococcus bromii)* known for their ability to metabolize dietary plant polysaccharides [27]. Several studies comparing the African diet with European food underline the same conclusion: different food components can alter the human gut microbiota very quickly and in different ways, leading to variability in the microorganism population found in the digestive tract [28, 29].

3. The role of the microbiota in specific diseases and conditions

3.1 Inflammatory bowel disease

Inflammatory Bowel Disease (IBD) defines a group of chronic disorders that includes Crohn's disease (CD) and Ulcerative colitis (UC). Though they are two different diseases, they both affect the intestinal tract and are characterized by intestinal inflammation with periods of remission and relapse [30]. The incidence of IBD is consistently growing in the recent few decades, having a peak onset age between 15 and 35 years that was initially described in the western populations, and now is also more frequent in other countries, as processed food and animal-based diets are overtaking the plant-based diet [31].

The etiology of IBD is an important subject of discussion as it is not fully understood. The key ways proposed as mechanisms for developing inflammation in IBD are the genetic susceptibility and environmental factors that interact with the immune system. Thus, the host gives an inappropriate immune response to changes of the gut microbiome and modulates inflammation and disease involvement and activity [32, 33].

The interaction between the host and different environmental factors, such as infections, smoking, dietary habits, psychological stress, medications, and alcohol consumption leads to alterations in the balance between gut microbiota and the genetically predisposed host. This imbalance changes the complex interactions of the immune system and products of the commensal microbiota that trigger immune responses using inflammatory mediators and signaling pathways. Hence, prolonged imbalance of the gut microbiota (including the microbiome, mycobiome, virome, and protozoa) with changes of the composition with a decrease of the commensal phyla and increase of potential pathological microorganisms, defined as dysbiosis, induce the alterations and dysregulations of mucosal barrier [34–36].

The dysfunction of the mucosal immune barrier has been shown in mouse studies that can regulate the development of T regulatory (T reg) cells and T helper 17 (Th17) cells with important differentiation in healthy and sick subjects. The activation of Th17 cells is important in bacterial and fungal infections, releasing pro-inflammatory

interleukine (IL) 17 cytokines, important in the pathogenesis of colitis. T reg cells play an important role in the suppression of inflammation through transforming-growth factor B (TGF-B), interleukine (IL) 35, and IL10. The deficiency of T reg cells leads to inflammation and IBD [33, 37–39]. Their role is important against *Citrobacter rodentium* and *Salmonella enterica* and was shown to be decreased in *Bacteroides* increased microbiome. Also, *Clostridium* clusters showed the ability to act on the differentiation of T reg cells [34, 37, 40, 41].

The dysbiosis occurring in IBD affecting bacterial microbiota is the most studied section of the gut microbiota. The most frequent phyla that are seen in healthy subjects are *Bacteroides, Bifidobacterium spp, Fecalibacterium spp, Firmicutes spp, Roseburia spp, Actinobacteria, and Verrucomicrobia* are regarded as over 90% of the gut microbial families [30, 32, 34]. Patients affected by IBD, in general show a decreased presence of mentioned phyla and an increase in *Proteobacteria spp, Escherichia coli spp*, *Fusobacterium spp, Ruminococcus spp, Pasteurellaceae spp, Veillonellaceae, Campylobacter spp,* and *Clostridioides spp*. There have been shown differences in composition and diversity regarding UC and CD, regarding also the extension of disease, aggressivity, and activity, thus being able to use the microbiome changes as a biomarker for disease activity and response to treatment [30, 34].

Regarding composition and diversity, there is a common agreement that in CD patients is a greater degree of dysbiosis compared to UC. Studies using 16 s rRNA sequencing characterized the gut microbiome in IBDs, showing a decrease of *Anaerostipes, Methanobrevibacter, Fecalibacterium* (especially *F.prausnitzii*), *Peptostreptococcaceae, Collinsella, Bifidobacteria* (especially *Bifidobacterium adolescentis*), *Dialister invisus, Clostridioides* cluster XIVa, *Bacteroides fragilis, Roseburia, Firmicutes* and *Erysipelotrichales* in CD and an increase of *Proteobacteria (Campylobacter), Yersinia enterocolitica, Bacteroides (vulgatus, fragilis), Helicobacterhepaticus, Mycobacteria spp, Enterobacteriaceae* (pathogenic *E.coli, Shigella*), *Ruminococcus gnavus, Veillonellaceae, Fusobacteriaceae,* and *Pasteurellaceae*, in human and animal models [30, 34].

These bacterial taxa are different from those expressed in UC, where a decrease of *Roseburia, Eubacterium, Faecalibacterium, Akkermansia, Bifidobacterium* and an increase *Helicobacteraceae, Mucispirillum, Desulfovibrio, Clostridioides ramnosum,* and *Porphyromonas* differentiate from common alterations of the microbiome seen in both CD and UC [34, 35, 42, 43].

Regarding disease phenotype, there have been a few studies about a range of specific gut bacteria changes associated with different patterns in CD. Li et al. [44] showed that individuals with ileal CD showed an increase in *Actinobacteria spp* and *Firmicutes/Bacillus* and a decrease in *Ruminococcus spp* [44]. Also, this phenotype was associated with an absence of *Roseburia* and *F. prausnitzii*, and an increase of *E. coli* [45]. In addition, decreased presence of *F. prausnitzii* in patients with ileal resection in CD, showed an increase in recurrence [46].

The regulation of gut mucosal immunity and host immune response is made through bacterial physiology and interaction on cell growth and interaction with metabolites produced by the microbiome. The stability of mucosal inflammation is disrupted in IBDs with the alteration of immunomodulatory metabolites such as SCFAs (acetate, propionate, and butyrate), bile acids, and tryptophan metabolites. SCFAs are mostly represented by acetate and are produced by *Bacteroidetes* and *Firmicutes*, and there has been demonstrated an important reduction in IBDs while associated also with reduced SCFA-producing bacteria such as *F. prausnitzii, R.intestinalis*. Another study also demonstrated decreased specific taxa for CD as *Phascolarctobacterium* and *Roseburia* and for UC *Leuconostocaceae spp* [32, 38, 47].

Given the alterations of gut microbiota and metabolites in IBD, there have been developed and proposed several management strategies for controlling the microbiome. Probably the most studied approach is using probiotics, which are bacterial species that may promote the maintenance of the immunological balance [48]. The effectiveness of probiotics in improving IBD evolution has been exhibited using different strains of *Lactobacillus, Bifidobacterium, Streptococcus,* and *Saccharomyces*. Their efficacy was seen in maintaining remission in UC patients by reducing pro-inflammatory cytokines and restoring normal gut microbiota. Nevertheless, the use of probiotics in CD showed little or no implication [31, 48, 49]. Often administered with oral probiotics, are the substrates, such as fructooligosaccharides, pectins, starch, and fibers, targeting microbiome composition by aiding the development of normal gut microbiota [50].

The use of antibiotics for their role in the modulation of microbiota is controversial. They function by decreasing the concentrations of different bacteria in the gut and reducing tissue invasion and translocation, acting also on metabolism with a decrease of pro-inflammatory metabolites and an increase of SCFAs. However, the non or very little selectivity character of antibiotics alter also the composition of some beneficial bacterial strains and their use is kept for septic and infectious complications, such as *Clostridioides difficile* infection [32, 48, 51, 52].

An important method of influencing the microbiome is Fecal Microbiota Transplantation (FMT), a very attractive method with significant rates of success, that is known from as early as fourth century [53]. As well as probiotics, FMT was better studied and showed important results in UC, and less in CD [34, 54, 55]. In UC, in mild-to-moderate cases, usage is still modest as it managed to induce response and remission in 20–55% of cases being comparable with active treatment as reflected in decreasing Mayo score and reducing symptoms [54, 56]. An important use of FMT is also recommended in recent guidelines for recurrent infection [57]. It remains a subject of future studies' better selection of FMT donors as currently being no possibility of predicting the success of a given donor to an IBD patient, thus defining an "ideal" donor [53].

The changes in lifestyle and diet represent the most common intervention on the microbiome, and of paramount interest being the first recommendation and the easiest to accept the measure. Diets rich in vegetables, fermented foods probiotic-rich (kimchi, kefir, yogurt, and pickled vegetables), fibers, and prebiotics have a positive impact on intestinal barrier health and microbiome balance [35, 50]. Currently, there are some diet recommendations for IBD and the most studied diets are Low Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (FODMAP), Crohn's disease exclusion diet, and Mediterranean diet (MD). A low FODMAP diet was found to have a good improvement in disease clinical scores in mild cases of IBD that are associated with IBS (Irritable Bowel Syndrome). MD characterized by low saturated fat, high monounsaturated fat, fiber, high vitamin B, C, E, and moderate ethanol intake showed in a few studies on CD patients' improvements of the quality of life and mild reducing fecal calprotectin an serum CRP [35, 58–61]. Another diet studied is a plant-based diet that exerts anti-inflammatory effects, composed of whole grains, cereals, fruits, vegetables, and nuts showed good improvements regarding symptoms, lowering serum CRP, overall WBC, but with the price of requiring supplementation of micronutrients [31, 62].

3.2 Acute and chronic pancreatitis

Acute pancreatitis (AP) is defined as an inflammatory condition of the pancreas following the injury of the pancreatic serous acini, leading to premature activation

of digestive enzymes (trypsin, chymotrypsin, lipase, and elastase) [63]. The clinical severity of AP cases depends on their complications, which can be localized (sterile or infected peri/pancreatic necrosis) or systemic (transient or persistent organ failure) into mild, moderate, severe, and critical AP [64]. The evolution of AP can be summarized in three stages: (1) local inflammation of the pancreas; (2) systemic inflammatory response syndrome; and (3) multiple organ dysfunction syndrome [65–67].

The revised Atlanta classification identifies two main stages of AP: (a) interstitial edematous pancreatitis and (b) necrotizing pancreatitis (NP) [68].

Although often overlooked, the gut microbial community and the gut barrier integrity disruption were described as aggravating factors responsible for the amplification of the initial inflammatory process accompanying AP [69]. Apparently, according to Liu et al. 2008 in AP patients, with mild and severe forms, there is an early gut mucosal dysfunction, leading to the development of multiple organ dysfunction [70]. The mucus layer integrity in the gut lining is lost after the onset of AP as shown by Fishman et al. 2014, leading to the failure of the gut barrier, apparently due to mechanisms independent of the activity of the pancreatic proteases in the intestinal lumen [71]. Pancreatic necrosis is accompanied by a lot of inflammatory cytokines and determines multiple changes in the gut such as a decrease in intestinal motility, favoring bacterial overgrowth and malnutrition and followed by gut barrier failure and increased permeability [72]. The intestinal permeability is highly increased in severe forms of AP and favors a poor prognosis.

The gut mucosal secretions also contain important quantities of secretory IgA, a key immunoglobulin that prevents the adhesion of pathogens and is responsible for the maintenance of immune homeostasis [73]. Usually, the amount of sIgA found in the small intestine is directly correlated with bacterial eubiosis and diversity. A decrease in sIgA is often correlated with low bacterial diversity in the small intestine and increased permeability and bacterial translocation leading to severe AP and infection [74].

The study by Yu et al. 2020 performed the 16S rRNA sequencing of gut microbiota species from fecal samples obtained through rectal swabs from 80 patients and described a correlation between gut microbiota and the severity of AP [75].

The microbiota profile was different, depending on the severity grade. In mild AP the main two phyla *Bacteroidetes* and *Firmicutes* were identified. *Bacteroides, Escherichia-Shigella,* and *Enterococcus* species were dominant while *Blautia* was highly decreased. *Finegoldia, Eubacterium hallii*, and *Lachnospiraceae* were considered to be potential diagnostic biomarkers for this stage of AP. In moderately severe AP, *Anaerococcus* was the most significantly increased and *E. hallii* the most decreased species, while in severe AP, *Enterococcus* was the most significantly increased and *E. hallii* the most decreased species. *Proteobacteria* phylum was the most increased in both, moderately severe and severe AP [75]. This study is impaired by several limitations such as possible contamination due to rectal swab samples and secondly by the impossibility to determine if microbiota dysbiosis is due to the presence of AP or is the main factor determining the AP severity. These findings are in correlation to those of the multihospital prospective clinical study performed by Tan et al. 2015 who describe dramatic alterations of the microbiota, determined by real-time quantitative polymerase chain reaction, in mild and severe forms of AP [76]. *Enterobacteriaceae* and *Enterococcus* were found to be increased by 3.2 and 9.3%, respectively, while the beneficial strains like *Bifidobacterium* were decreased by 9.2% in the severe forms of AP compared to mild forms [76]. The drawbacks of this study consist in the small sample size of patients with AP included and the lack of modern techniques like

high-throughput sequencing. Another study performed by Zhu et al. 2019 describes the reduction of other beneficial strains like *Blautia* in patients with severe AP [77].

The gut mucosal lining is affected by dysbiosis mainly through the metabolites produced by certain bacterial species. *Firmicutes* and *Bacteroidetes* are mainly responsible for the production of short-chain fatty acids (SCFAs), mainly acetate, propionate, and butyrate, the main energy source of enterocytes, colonocytes, and hepatocytes [78]. SCFAs are very important for the maintenance of tight junctions between the intestinal epithelial cells and also for the mucosal immune barrier [79]. In AP patients, there is a decrease in SCFAs promoted by dysbiosis and moreover, because of the decreased pH, it creates the condition for potential pathogenic and pathogenic bacteria, such as *E. coli* and *Shigella,* to grow and aggravate the evolution [80].

Experimental studies performed on mice suggested that microbiota regulation by fecal transplantation might reduce the damage at the intestinal barrier level and create a more stable evolution, preventing severe forms [80, 81]. Ding et al. 2021 showed in a randomized, controlled study registered at https://clinicaltrials.gov (NCT02318134) that the fecal microbiota transplantation had no beneficial effects in the evolution of severe forms of AP and moreover, the intestinal permeability might have been adversely affected [82].

Chronic pancreatitis (CP) is defined as a progressive and irreversible inflammation of the pancreas that leads to pancreatic exocrine insufficiency (PEI) and diabetes mellitus [83]. A normal pancreatic function provides antimicrobial peptides, bicarbonate, and digestive enzymes that are necessary for digestive function but also for the maintenance of healthy microbiota [84, 85].

The evidence accumulated in recent years regarding pancreatic exocrine deficiency advocates for small intestinal bacterial overgrowth (SIBO) and gut dysbiosis-reduced diversity, and increased abundance of opportunistic pathogens [86, 87]. Capurso et al. 2016 also demonstrated in a meta-analysis that one-third of patients with CP have SIBO [88]. A study by Ní Chonchubhair et al. 2018 evaluated the relationship between SIBO and clinical symptoms in CP and found that SIBO was present in 15% of chronic pancreatitis patients [89]. Frost et al. 2020 recently determined the intestinal microbiota composition by bacterial 16S ribosomal RNA gene sequencing and found reduced alfa and beta microbial diversity index and an increased abundance of opportunistic pathogens in patients with CP. They found in CP cases an increase in abundance of *Enterococcus* and *Bacteroides* and an absolute reduction of *Faecalibacterium* and *Prevotella* [86]. Talukdar et al. 2017 also described in their study a reduction of *Fecalibacterium prausnitzii* and *R. bromii* in CP without and with diabetes. Apparently, the gut barrier integrity is disrupted due to low *Fecalibacterium* levels and this favors the passage of bacterial endotoxins in circulation followed by subsequent alterations in the functionality of beta pancreatic cells [90].

As the studies indicated, there are some significant alterations in the composition and function of the gut microbiota in patients with AP and CP, leading to severe forms of disease and in correlation with a poor prognosis. The disturbance of the gut microflora equilibrium needs to be further explored in close correlation with the gut mucosal integrity and systemic inflammatory status.

3.3 Colorectal cancer

Colorectal cancer (CRC) is the third most frequent cancer worldwide with more than 1.9 million new cases and 930.000 deaths reported in 2020. It is predicted that

by 2040, the burden of the disease will be increased to 3.2 million cases per year and 1.6 million deaths per year. [91] Approximately 90% of CRC cases are sporadic [92], and various environmental and genetic factors contribute to CRC tumorgenesis [93]. Studies show that only a small percentage of CRC cases are genetically predisposed [93, 94], underlining the importance of environmental factors in the development of CRC. Diets rich in red and grilled meat, tobacco, high alcohol intake, disruption of circadian rhythm, and preexisting conditions, such as obesity, inflammatory bowel disease, and diabetes, have been associated with CRC. [95] In addition, the intestinal microbiota is getting more and more recognition among environmental factors implicated in the development of CRC, evidence dating as early as the 1960s. One study published in the late 1960s demonstrated that glucoside cycasin failed to produce its carcinogenic effect in germ-free mice and was only able to induce cancer in conventional rats. [96] In 1975 Reddy et al. showed that a large dose of 1,2-dimethylhydrazine induced multiple colonic tumors in 93% of the conventional rats included in the study, whereas 1,2-dimethylhydrazine-induced colonic tumors were observed in only 20% of the germ-free mice. [97] Moreover, subcutaneous administration of azoxymethane led to an increased incidence of colonic tumors in germ-free rats, indicating that intestinal bacterial populations can alter the carcinogenic effects of certain compounds in the colon [98].

Studies on humans, that have analyzed both mucosal and fecal samples, demonstrate that the gut microbiota of CRC patients differs significantly from that of healthy subjects, CRC patients presenting diminished richness and bacterial diversity [99–101]. Also, Chen et al. 2012 observed that the microbial composition in cancerous tissue is significantly different from that found in the intestinal lumen [102]. Numerous bacteria have been correlated with CRC in spite of variations in intestinal microbiota [99, 100].

B. fragilis, a bacteria that colonizes most humans [103] *F. nucleatum, Prevotella intermedia, Parvimonas micra, Porphyromonas asaccharolytica, Alistipes finegoldii,* and *Thermanaerovibrio* are bacteria identified by one meta-analysis to be enriched in CRC [104]. In 2019 two more meta-analyses investigating the fecal metagenome in CRC have been published, expanding the list of CRC-enriched bacteria [105, 106].

Not only has an increase in the population of *F. nucleatum* been associated with CRC, but also it is thought to promote disease progression [107]) and its presence in CRC tissues might be indicative of a worsen prognosis [108, 109]. A recent study found increased levels of *P. intermedia* and *F. nucleatum* in adenocarcinomas compared with paired adenomatous polyps. The presence of this bacteria was shown to exert an additive effect on the migration and invasion of CRC cells and was also associated with lymph node involvement and distant metastasis [110].

Increased levels of *Enterococcus faecalis, E. coli,* and *Peptostreptococcus anaerobiusi* in CRC patients in comparison with healthy controls was also reported by several authors, but the exact mechanisms by which these bacteria promote cancer development is still to be determined [100].

The enriched bacteria are also associated with reduced levels of benefic bacteria, such as *Clostridium butyicum and Streptococcus thermophilus*, [104] bacteria belonging to the genus *Roseburia* and other butyrate-producing bacteria [111]. *Wang et al. 2012* highlight that the decrease in butyrate-producing bacteria and the opportunistic pathogen multiplication might be responsible for the structural imbalance of gut microbiota in patients suffering from CRC [111]. Short-chain fatty acids (SCFAs) are fermentation end products produced by bacteria, with butyrate being the most intensively studied SCFA. Apart from being considered the energy source for

colonocytes, they also promote the apoptosis of cancer cells [112]. The amount of SCFAs produced by the microbiota is however insufficient to inhibit CRC development and probiotic supplementation might result in increased SCFAs. One *in vitro* study showed that *Lactobacillus fermentum* NCIMB 5221 was able to increase SCFAs production, thus exerting antiproliferative effects against Caco-2 cancer cells and promoting normal epithelial cell growth [113]. Resistant starch (RS) is part of starch that is fermented into SCFAs in the cecum and this process leads to pH decrease. Prebiotic supplementation with RS has been demonstrated to reduce the proliferation of epithelial cells in the colon and rectum [114, 115]. Moreover, the administration of synbiotics, meaning the combinations of prebiotics and probiotics has also been investigated. In one RCT patients with a history of CCR received a synbiotic preparation composed of oligofructose-enriched inulin and two probiotics *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12. The synbiotic intervention resulted in significantly reduced colorectal proliferation, an increase in the number of beneficial bacteria, cytokine production modulation (decreased interleukin (IL) 2 and increased IFN-gamma production), and a decreased genotoxins exposure, which translates into a reduction in DNA alterations [116].

The role of the intestinal microbiota in CRC tumor progression is also supported by the differences in bacterial composition between patients with early-stage adenomas and those in advanced stages with definitive CRC [92].

Nevertheless, the CRC microbiome is also characterized by an imbalance in the composition of the viral and fungal species [92, 99]. A higher viral load has been observed in tumors compared to normal tissue of CRC patients [92]. Although some studies have identified cytomegalovirus, John Cunnningham virus, and human papilloma virus in CRC tumor samples, the data are however inconsistent [99]. Shotgun metagenomic analyses of viromes of fecal samples identified 22 viral taxa that differentiate the CRC virome from one of healthy controls [117]. Trans kingdom crosstalk between bacteria and viruses may play an important role in CRC tumorigenesis, as some studies indicate [118]. Although less studied, differences in terms of fungal composition were also observed [119, 120].

Existing studies suggest that several carcinogenesis mechanisms involved in the development of CRC are intimately linked to the gut microbiota. Among studies, authors have insisted on the mechanisms of inflammation, oxidative stress, pathogenic bacteria, genotoxins, and biofilm [100]. Studies have demonstrated that some bacterial species, such as *F. nucleatum* [121] and *P. anaerobius* [122], can induce a pro-inflammatory immune microenvironment, which leads to the progression of colorectal neoplasia. The immunomodulatory capacity of probiotics has led scientists to investigate probiotics in the management of CRC. Oral administration of a mixture of six viable strains of *Lactobacillus* and *Bifidobacterium* in patients with CRC 4 weeks after surgery resulted in a significant pro-inflammatory cytokine reduction compared to placebo administration. The levels of tumor necrosis factor (TNF-α), IL-6, IL-10, IL-12, IL-17A, IL-17C, and IL-22 were significantly reduced, and no severe adverse reactions were reported [123]. After comparing the intestinal microbiota of CRC patients with that of healthy patients, one study analyzed the possibility of preventing colorectal carcinogenesis by modulating the composition of the intestinal bacterial population using *L. gasseri*. Probiotic administration resulted in an increase in the *Lactobacillus* population and a decrease in the amount of *Clostridium perfringens* as well as a shift in fecal pH toward acidosis along with an increase in IL-1 and natural killer (NK) cell activity values starting with week 4 [124].

Additionally, through their adhesion capacities, pathogens and their virulence factors adhere to the intestinal epithelial cells (IECs) and promote tumor formation [122, 125–127]. Also, the gut microbiota can modulate the immune system response by stimulating the production of chemokine in tumoral cells with the purpose of recruiting T lymphocytes [128]. Moreover, bacterially produced genotoxins, exert DNA damage in IECs, which can further initiate carcinogenesis. For example, *E. coli* produces the genotoxin colibactin [129, 130] which is reported to induce transient DNA damage in epithelial cells [130]. Similarly, *Salmonella* damages the DNA in IECs by producing typhoid toxin [131]. Inflammation can lead to increased levels of ROS (reactive oxygen species) and RNS (reactive nitrogen species), its negative impact translating into DNA damage and the development of mutations. *E. faecalis* [132], *P. anaerobius* [133], *E. coli,* and enterotoxigenic *B. fragilis* [134, 135] promote ROS production by colonic cells. Enterotoxigenic *B. fragilis,* through its metalloprotease toxin and its effect on IL-17 pathway, is believed to promote carcinogenesis in colonic cell population [136, 137]. Microbiota, also found as a biofilm at the surface of the colon mucosa, can promote colonic tumor cell proliferation through modulating interleukin 6 and STAT3 signaling pathways [138, 139].

3.4 Cardiovascular disease

The abnormal interactions between the microbiota and the host compromise homeostatic mechanisms. Most cardiovascular risk factors, such as age, obesity, diet, and lifestyle, can generate gut dysbiosis, which is associated with intestinal inflammation and poor integrity of the intestinal barrier [7, 23].

Diets rich in fat lead to the stimulation of mast cells from the intestinal mucosa, generating inflammatory mediators, such as histamine, which can amplify intestinal permeability [140]. However, high carbohydrate diets can also raise intestinal permeability and endotoxins [141].

Cardiovascular diseases (CVD), the number one cause of death worldwide, are influenced by smoking, dyslipidemia, diabetes mellitus, and arterial hypertension [23].

Dysbiosis is involved in numerous pathophysiological chains of events, leading to different conditions, and cardiovascular afflictions making no exception. The perturbation of the gut microbiota can favor a pro-inflammatory state in the human body, therefore promoting the atherosclerotic process [7, 23, 142].

Atherosclerosis is, unfortunately, a frequent chronic inflammatory process, which comprises endothelial dysfunction, dysfunction of vascular smooth muscle cells differentiation, infiltration with inflammatory cells, and subendothelial lipid accumulation [143].

Microorganisms, such as *Chlamydophila* pneumoniae, *P. gingivalis, Helicobacter pylori*, Influenza A virus, Hepatitis C virus, cytomegalovirus, and human immunodeficiency virus, were associated with a high risk for developing CVD [23, 144]. Infections can influence atherosclerosis through arterial wall inflammation, favoring plaque formation, or through the production of pro-inflammatory mediators, which are the result of infections of various sites in the body [23, 145].

High blood levels of lipopolysaccharides (LPS) have been linked to adverse cardiac events in patients with CVD such as atrial fibrillation [146]. LPS are endotoxins, byproducts of gut microbiota that can reach systemic circulation through the intestinal mucosa [147]. A decrease in gut bacteria, such as *Bacteroides spp*, has been negatively correlated with atherosclerotic plaque progression and endothelial dysfunction, thus promoting inflammation [148].

Atherosclerosis is associated with trimethylamine-N-oxide (TMAO), a vasculotoxic metabolite resulting from L-carnitine, choline, and phosphatidylcholine. TMAO was indicated to promote the development of aortic lesions in apolipoprotein E (apoE) in mice by modifying bile acid profiles. TMAO inhibits the production of bile acids through the farnesoid X nuclear receptor (FXR) and small heterodimer partner (SHP) [149].

Elevated serum levels of TMAO have been shown to predict CVD outcomes in heart failure. Individual TMAO formation is dependent on microbial gut composition. A red meat diet consumption rich in choline and an omnivorous diet with high carnitine may account for TMAO levels elevation [150]. In an observational study of 155 patients with heart failure, elevated plasma levels of TMAO were found in chronic HF patients with higher levels in NYHA class III and IV and were associated with worse prognoses [151].

Microbiota in the colon metabolizes secondary bile acids (BA) from un-recycled bile acids through bile-salt hydrolase (BSH). BA synthesis is an important pathway for cholesterol elimination, thus having an athero-protective function. Composition of bile acids is altered in heart failure patients with a decrease in the primary to secondary bile acids ratio. A decrease in BSH levels subsequently causes cholesterol buildup and progression of CVD. Microbial BSH modulates stimulation of hepatic FXR, which acts as a bile acid signaling receptor and a potential target for bile acid therapy in reducing cardiovascular complications [152, 153].

Moreover, probiotic supplements may improve intestinal balance and select probiotics could have a cardioprotective role. Altered bacterial diversity was observed in two heart failure with reduced ejection fraction (HFrEF) cohorts with an increase in *Prevotella* genus and a decrease in genera belonging to *Lachnospiraceae* family and *Rumminococcaceae Faecalibacterium* and *Bifidobactericeae Bifidobacterium* [154]. Similar cohorts had increases in pathogenic bacteria, such as *Campylobacter, Shigella, Yersinia enterolytica*, and *Candida* species, associated with an increase in gut permeability [155]. The *Firmicutes/Bacteroidetes* ratio (F/B) in hypertensive patients is higher than in the normotensive individuals, by lower levels of *Bacteroidetes* [156]. *Roseburia*, one of the main producers of butyrate, is diminished in hypertensive patients. However, *Roseburia* can also produce linoleic acid, which has anti-inflammatory properties and a possible role in lowering blood pressure values, together with linolenic acid [156–159]. According to CARDIA study, *Robinsoniella* and *Catabacter* were positively associated with hypertension [160].

Animal studies suggest that gut dysbiosis is associated with arterial hypertension both directly and indirectly. Change in microbial diversity such as the ratio of *Firmicutes* to *Bacteroidetes* in the intestine yields a potential mechanism in hypertension formation and a pathway for future treatment. By fermentation of fibers, these bacteria produce short-chain fatty acids (SCFAs) such as propionate and butyrate [161].

SCFAs play an important role in homeostasis, including blood pressure variations, through their interaction with certain receptors: G-protein-coupled receptors (GPCRs), such as Gpr41 or Olfr78. Studies on mice null for Olfr78 led to the conclusion that those animals were hypotensive, while mice null for Gpr41 were hypertensive [162].

In a metabolomic analysis of prehypertensive and hypertensive patients, it was shown that overgrowth of opportunistic bacteria, such as *Klebsiella* and *Prevotella copri,* was present in prehypertensive (pHTN) patients compared to healthy individuals, where higher levels of *Faecalibacterium*, *Bifidobacterium*, *Roseburia* and *Butyrivibrio* were found. This suggests alteration of the microbial profile occurs

well before clinical findings. Probiotics and antibiotics could be proven as potential therapies for BP. Furthermore, small-scale fecal transplant from hypertensive patients to germ-free mice has led to higher blood pressure levels compared to controls [163].

Atrial fibrillation (AF) is another important CVD that has been linked in recent studies with dysbiosis. Patients with persistent AF manifest an increase in *Ruminococcus, Streptococcus,* and *Enterococcus,* and bacteria, such as *Faecali bacterium, Oscillobacter,* and *Biliophilus,* were decreased [164]. An imbalance of microbiota leads to damage in the intestinal barrier function that in turn can promote atrial electrical remodeling by increasing the activity of NLRP3 inflammasome [165, 166].

A metagenomic analysis by Zhang et al. 2021 in a cohort of patients with AF showed that species with SCFA-synthesis enzymes such as *Coprococcus catus* and *Firmicutes bacterium* were decreased in the gut of AF patients compared to controls. Furthermore, homeostasis of gut microbiota metabolites such as bile acids can modulate the risk of AF [167].

3.5 Obesity and diabetes mellitus

The microbiota of obese individuals significantly differs in composition and function from that of healthy individuals [168]. Thus, the microbiota of obese people is characterized by an increased ratio of *Firmicutes* vs. *Bacteroidetes*, mainly *Ruminiococcus, Candida*, and *Lactobacillus* [169, 170], increased amount of *Actinobacteria*, which produce SCFA and *Proteobacteria* [171]. Human studies have shown that obese people had more *Firmicutes* and approximately 90% fewer *Bacteroidetes* and a low-fat or low-carbohydrate diet can restore the *Firmicutes* to *Bacteroidetes* ratio but never be the same as the people that were lean from the beginning [169]. Some other studies demonstrated that a higher caloric intake increased *Firmicutes* by 20% and reduced *Bacteroidetes* by 20%, leading to a gain in body weight [172]. Studies on infants observed that obese children have a lower level of *Bifidobacterial* and a higher level of *Staphylococcus aureus* [173].

As it is already known, the diet has an important role in modulating microbiota composition, in both healthy and obese people. Some types of diets, like the Western diet, can modify microbiota, especially by increasing *Firmicutes* levels, leading to dysbiosis, metabolic stress, and obesity [174, 175]. Compared to the Western diet, a diet based on dietary fiber, plant polysaccharides, and lower fat and animal protein is characterized by a lower level of *Firmicutes* and a higher level of *Bacteroidetes* [28, 176]. Importantly, some mice and human studies underlined that a high-fat/high-sugar Western diet can modify the microbiota in just 1 day [177, 178]. Chen J et al. 2019 have shown that dietary intake has more impact on microbiota changes in mice than genetic etiology [179]. Moreover, Pols et al. 2011 have demonstrated that an improper diet has significantly negative consequences leading to the disappearance of species and strains of microbiota [180].

The obesity-microbiota relationship and its mechanisms have been studied for a long time [168] Many studies have shown that alterations in the microbiota community modify the process of energy extraction from food and consequently the adiposity of the body [176]. The gut microbiota of obese people has a larger capacity for absorbing energy from meals, thus their gut bacteria lead to weight growth [170]. Some studies have shown that gut microbiota can influence adiposity by modulating host gene expression, metabolic and inflammatory pathways, and gut-brain axis [181]. Inflammation mediated by gut microbiota can increase circulating lipopolysaccharide (LPS) levels and gut permeability and thus adipose tissue inflammation,

commonly seen in obesity [182]. Microbiota metabolites like SCFA are increased in obese people, being involved in glucose homeostasis (improving glucose sensitivity) and lipid metabolism through free-fatty acid receptors, leading to activation of hepatic gluconeogenesis and lipogenesis [183] and inhibition of fatty acid oxidation in muscles [184]. Nondigestible carbohydrates can increase SCFA levels, which can modify the level of enteric hormones [185]. Alterations of the microbiota can reduce organisms that temper CD36 expression, such as products produced by *Clostridia*, which can increase lipid absorption, leading to obesity and metabolic syndrome [186]. Microbiota dysbiosis can reduce fasting-induced adipose factor expression, being involved in lipoprotein lipase (LPL) activation with lipid accumulation in adipose tissue [187]. Gut bacteria influence two key signaling pathways, glycemic reaction component binding domain, and cholesterol control component related proteins causing fat accumulation in the liver, where lipids can be then absorbed via visceral fat, thanks to LPL [170]. A lack of dietary fiber and poorly digestible carbohydrates reduce the diversity of bacterial flora [188]. Some studies have shown that lower microbiota diversity is associated with increased abdominal adiposity [189], but can be reversible in humans with cardiorespiratory fitness [190]. Human studies underlined that obese humans have a low fecal bacterial diversity, promoting adiposity, dyslipidemia, impaired glucose homeostasis, and higher low-grade inflammation [191]. Hormonal, neurological, and immunological pathways connect the brain with the microbiota [170]. Microbiota can modulate the synthesis of neuropeptides like dopamine, which regulate gastrointestinal function and thus can influence cognitive activity and increase hunger [192]. Among the metabolites secreted by the microbiota, serotonin, and γ-aminobutyric acid (GABA) control appetite and body weight regulation [193]. Alterations of the intestinal microbiota can modify the secretion of gastrointestinal hormones, such as glucagon-like-peptide-1 (GLP-1), which is involved in food intake control [194]. The dysbiosis of the microbiota in obese people can increase the level of acetate, enhancing the secretion of glucose-stimulated insulin and ghrelin, consequently increasing obesity [195]. Some studies underlined that the risk of obesity is associated with prenatal and perinatal antibiotic use by influencing microbial colonization and maturation [196].

Obesity-microbiota relationship and especially dysbiosis is associated with the risk of developing some other health problems, like diabetes mellitus (DM) [168, 197].

Schwartz et al. 2016 included for the first time gut microbiota modification as a mechanism implicated in DM [198]. The gut microbiota has an important role in influencing the immunologic system and developing type 1 DM (T1DM), as also as in developing metabolic disorders such as type 2 DM (T2DM) [197]. DM is considered an inflammatory clinical entity, characterized by inflammatory mechanisms that involve lipid accumulation, cytokines synthesized by a dysfunctional adipose tissue, a dysregulated immune system, as also as increased levels of inflammatory markers, such as C-reactive protein, Tumor Necrosis Factor-α, interleukins 6, 17 and 23, and Transforming Growth Factor β [199–201].

Studies have underlined that SCFAs, bile acid, branched-chain amino acids, imidazole propionate, and LPS have an important role in DM, among these the release of LPS with pro-inflammatory effects and decrease in SCFA production is the phenomena discussed in DM patients [197, 202].

In the case of dysbiosis, the LPS secreted by gram-negative bacteria from the gut generates a low-grade inflammatory state by interacting with type 4 toll-like receptors, increasing the risk of insulin resistance [203]. Physiological, the intestinal wall prevents the passage of LPS into the systemic circulation. High-fat diets increase the

permeability of the intestinal wall and LPS circulation, by influencing the distribution of binding protein complexes and excessive and chronic production of biliary acids [197]. LPS binds then with the lipopolysaccharide-binding proteins and interacts with a membrane protein of differentiation 4, allowing the activation of TLR. A signaling cascade is then stimulated and focal adhesion kinase is phosphorylated and activated. In systemic circulations, LPS binds the TLR-4 in the membranes of immune and adipose cells, including pancreatic betta-cells, releasing TNF-α, IL-1, and IL-6, which can induce insulin resistance [204, 205].

Increased levels of *Firmicutes* in obese individuals, as was already mentioned, generate energy harvest, positive energy balance, and higher caloric bioavailability, leading to weight gain [197]. Modifications of *Firmicutes* to *Bacteroidetes* ratio have also been present in DM patients, being characterized by increased levels of *Bacteroidetes* [206], which are associated with decreased levels of *Akkermansia municiphila* [207]. Studies have observed an increased level of *Clostridium* and *Veillonella* genre in kids with T1DM, which ferment glucose and form propionate, succinate, and acetate from lactate and increase gut permeability [208]. Patients with DM and chronic pancreatitis have a low level of *Fecalibacterium prausnitzii*, which has anti-inflammatory properties and stimulate the synthesis of binding proteins [209]. Low levels of *R. bromii* have been observed in patients with DM, leading to the production of butyrate and energy [210]. T2DM is characterized especially by increased levels of *Bifidobacterium* and *Bacteroides* and to a lesser extent by *Faecalibacterium, Akkermansia, Roseburia, Ruminococcus, Fusobacterium,* and *Blautia* [211]. In patients with gestational diabetes mellitus, it was observed an increase in *Firmicutes* levels and a decrease in *Bacteroidetes* and *Actinobacteria* levels [212].

SCFAs are involved in T2DM by their immunomodulatory functions, but also stimulate the secretion of peptides that regulate the appetite and satiety, like GLP-1, the YY peptide, and ghrelin [213, 214]. In dysbiosis induced by a high-fat diet, it has been observed a decreased level of *Lactobacillus* and an increased level of *Bacteroides, Bukholderia*, and *Clostridium*, leading to an increased level of GLP-1 [215] and SCFA acetate, which affects insulin secretion, leading to obesity, hyperlipidemia, and insulin resistance [197, 216]. Studies have shown that increased levels of *Eubacterium* and *Roseburia* intestinalis in association with abnormal production and absorption of propionate, as also as postprandial insulin secretion and propionate generation in feces stimulated by butyrate, can increase the risk of T2DM [202].

Gut microbiota plays an important role in obesity and DM, especially in the case of dysbiosis, which influences the inflammatory and immune response, but also their pathophysiology. Throughout life gut microbiota is influenced by a lot of factors and has an important role in energy balance, being connected to obesity. Greater levels of LPS and lower levels of SCFA are the main characteristics of DM patients. Many mechanisms implicated in an obesity-microbiota-DM relationship were discussed in studies, a lot of them being still unwell known, so future research needs to investigate the function of the intestinal flora and its link to obesity and DM [170, 217].

3.6 Dermatological conditions

The skin, together with the intestinal epithelium, represent the largest interfaces between the body and the external environment, being the place where the most important processes of immune tolerance take place, allowing their colonization with essential commensal microorganisms that form the skin and gut microbiota [218, 219]. Thus, their alterations are associated with the appearance or progression of

numerous inflammatory dermatological diseases, such as psoriasis, atopic dermatitis (AD), hidradenitis suppurativa (HS), acne, rosacea, alopecia areata, skin cancers, and seborrheic dermatitis [218]. Although most research groups have focused on the changes in the skin microbiota associated with dermatological diseases, recent studies have also observed alterations also in intestinal microbiota, probably through the systemic modulations determined by secreted molecules with the hormonal role and through the cells of the immune system [219, 220].

One of the most studied dermatological conditions associated with changes in the intestinal microbiota is psoriasis, a chronic inflammatory dermatosis, characterized by numerous pruritic, erythematous-scaly patches and plaques, distributed especially on the extension areas, associated or not with articular involvement [221]. Thus, a study conducted on a group of 30 patients with psoriasis and 30 healthy volunteers that evaluated the composition of the intestinal microbiota, observed that, although there is no difference statistically significant in terms of the type of bacteria in the analyzed samples (alpha diversity), their proportion is statistically significantly different between the two groups. Thus, the group with psoriasis showed an increase in the proportion of the families *Veillonellaceae* and *Ruminococcaceae* ($p < 0.05$) and of the genera *Faecalibacterium* and *Megamonas* ($p < 0.05$) compared to the healthy group [222]. The number of some of the microorganisms (*Bacteroides, Escherichia*, respectively *Dialister*) also seems to correlate negatively with different paraclinical markers like complement 3 (C3) ($p < 0.01$) respectively Interleukin 2 Receptor (IL2R) ($p < 0.001$). Moreover, *Prevotella*, respectively *Phascolarctobacterium* positively correlates positively with the level of C3 ($p < 0.01$), respectively IL2R ($p < 0.001$) [222]. Tan et al. 2015, observed a decrease in the classes of microorganisms *Mollicutes* and *Verrucomicrobiae* and the genus *Akkermansia* (species *Akkermansia muciniphila*), as well as an increase in the genera *Enterococcus* and *Bacteroides* in a study conducted on a group of 14 patients with psoriasis and 14 healthy volunteers [223].

Another study conducted by Hidalgo-Cantabrana et al. 2019 on a group of 19 patients with psoriasis and 20 healthy patients also highlighted the presence of the same phyla as in a healthy population, similar to the studies above. However, unlike Tan et al. [76], the populations of *Bacteroidetes* and *Proteobacteria* were lower than in the control group ($p < 0.001$), and *Actinobacteria* and *Firmicutes* were in a larger number ($p < 0.001$). This study also highlighted a decrease in *Verrucomicrobacteria* [224]. Scher et al. 2015 evaluated the variability of the microbiota in patients with early psoriatic arthritis, compared to patients with psoriasis and healthy patients, and found a decrease in *Akkermansia* and *Ruminoccocus* in those with psoriatic arthritis compared to patients with psoriasis. In the latter, a decrease in *Bacteroidetes* and *Coprobacillus* was observed. Also, lower levels of medium-chain fatty acids (involved in cell signaling) were found in patients with psoriatic arthritis ($p < 0.05$) and in those with psoriasis ($p < 0.01$) compared to the control group [225].

Regarding atopic dermatitis (AD), numerous studies evaluate both the changes in the microbiota, as well as the impact of the administration of probiotics on the evolution and severity of the disease. Thus, it was found that 1-week-old newborns who were later diagnosed with IgE-mediated eczema showed a decrease in *Enterobacteriaceae, Escherichia-Shigella* (statistically insignificant), and *Ruminococcaceae* ($p = 0.0047$). It was also found that the mothers of these children had an increased level of microorganisms from the *Bacilli* class and the *Streptoccocus* genus [226, 227]. AD was also associated in patients under 20 years, with a decrease in *Clostridium, Streptococcus, Enterobacteriaceae,* and *Bifidobacterium* ($p = 0.006$). Moreover, more severe forms of the disease were associated with a lower number of

Bifidobacterium ($p = 0.046$) and a higher number of *Bacteroides* ($p = 0.0443$) compared to children with average manifestations of AD [228]. Another study carried out on a pediatric population (28 children aged 6 months old with AD) demonstrates the existence of a statistically significant correlation between the severity of the disease and the decrease in the number of bacterial species in the microbiota ($r = -0.54$, $p = 0.002$). Moreover, the administration of hydrolyzed casein in these patients led to an improvement in the clinical score and the composition of the microbiota [229].

Another dermatological condition with a significant impact on the quality of life, in which the microbiota seems to play an important role is hidradenitis suppurativa (HS). Thus, in those patients, a decrease in the diversity of the intestinal bacterial flora was also found, but with an increase in *Ruminoccocus gnavus*, which also appears to increase in other inflammatory digestive or articular diseases [230]. Kam et al. also observed a decrease in the phylum *Firmicutes* compared to the healthy population ($p = 0.03$), with changes in the genera *Lachobacterium* and *Veillonella* in the same direction ($p = 0.019$, respectively $p = 0.005$). The genera *Biophila* and *Holdemania* were found in a higher proportion of these patients, although the small number of patients on which the study was conducted (3) makes it difficult to interpret the data [231]. Another difference between the microbiota of HS patients compared to healthy ones was highlighted by Lam et al. 2021 in a study carried out on 17 patients with HS. He observed colonization with *Robinsoniella* only in patients with HS, not in the healthy group, but also a greater number of microorganisms from the *Sellimonas* genus in these patients. The latter was also associated with the presence of several inflammatory joint diseases [232].

The immunological, neurological, and biochemical interrelations between skin and gut, explained by the existence of the skin-gut axis are also reflected in the way in which microbiota alterations are present in various dermatological inflammatory pathologies. Although the current studies show changes in the proportions of bacteria from the intestinal microbiota, the small groups of patients, as well as the contradictory data from some studies prevent us from drawing clear conclusions and associating changes in specific genera or species with certain diseases.

4. Conclusion and future perspectives

Although the complex mechanisms between gut dysbiosis and the etiology and progression of numerous systemic diseases are not fully understood and there are clear indications that gut homeostasis is very important. Future research is needed addressing also animal models and clinical trials to restore the microflora normal balance and gut mucosal barrier integrity in order to maintain health. As microbiomics develops as an equivalent of human genomics and the microbiome is seen as a second genome in the human body considered nowadays as a holobiont (the host organism and its microbiome), one can consider this as a very promising future step toward precision medicine. The continuous development of next-generation sequencing (NGS) technologies will allow us to gain new insights and perspectives about how to influence and modulate the microbiome through noninvasive procedures, such as prebiotics, probiotics, and dietary lifestyle changes.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and Abbreviations

AF	atrial fibrillation
AD	atopic dermatitis
apoE	apolipoprotein E
SCFAs	short-chain fatty acids
RS	resistant starch
TNF	tumor necrosis factor
IL	interleukin
NK	natural killer
IECs	intestinal epithelial cells
ROS	reactive oxidative species
RNS	reactive nitrogen species
CVD	cardiovascular disease
LPS	lipopolysaccharides
TMAO	trimethylamine-N-oxide
FXR	farnesoid X nuclear receptor
SHP	small heterodimer partner
BA	bile acids
BSH	bile-salt hydrolase
F/B	*Firmicutes/Bacteroidetes* ratio
GPCRs	G-protein-coupled receptors
GABA	aminobutyric acid
LPS	lipopolysaccharide
GLP-1	glucagon-like-peptide-1
DM	diabetes mellitus
T1DM	type 1 DM
T2DM	type 2 DM
HS	hidradenitis suppurativa
C3	complement 3
NGS	next-generation sequencing
pHTN	prehypertensive
HFrEF	heart failure with reduced ejection fraction

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References

[1] Kumar PS. Microbiomics: Were we all wrong before? Periodontology 2000. 2021;**85**(1):8-11. DOI: 10.1111/prd.12373

[2] Rasmussen TT, Kirkeby LP, Poulsen K, Reinholdt J, Kilian M. Resident aerobic microbiota of the adult human nasal cavity. APMIS. 2000;**108**(10):663-675. DOI: 10.1034/j.1600-0463.2000.d01-13.x

[3] Diop K, Dufour J-C, Levasseur A, Fenollar F. Exhaustive repertoire of human vaginal microbiota. Human Microbiome Journal. 2019;**11**:100051. DOI: 10.1016/j.humic.2018.11.002

[4] Toson B, Simon C, Moreno I. The endometrial microbiome and its impact on human conception. International Journal of Molecular Sciences. 2022;**23**(1):485. DOI: 10.3390/ijms23010485

[5] Dong Q, Brulc JM, Iovieno A, Bates B, Garoutte A, Miller D, et al. Diversity of bacteria at healthy human conjunctiva. Investigative Ophthalmology & Visual Science. 2011;**52**(8):5408-5413. DOI: 10.1167/iovs.10-6939

[6] Moffatt MF, Cookson WO. The lung microbiome in health and disease. Clinical Medicine (London, England). 2017;**17**(6):525-529. DOI: 10.7861/clinmedicine.17-6-525

[7] Ionescu RF, Enache RM, Cretoiu SM, Cretoiu D. The interplay between gut microbiota and miRNAs in cardiovascular diseases. Frontiers in Cardiovascular Medicine. 2022;**9**:856901. DOI: 10.3389/fcvm.2022.856901

[8] Parello CSL. 6 - Microbiomics. In: Sonis ST, Villa A, editors. Translational Systems Medicine and Oral Disease. United Kingdom: Academic Press, Elsevier Inc.; 2020. pp. 137-162. DOI: 10.1016/B978-0-12-813762-8.00006-2

[9] Feng Q, Chen W-D, Wang Y-D. Gut microbiota: An integral moderator in health and disease. Frontiers in Microbiology. 2018;**9**:151. DOI: 10.3389/fmicb.2018.00151

[10] Mariat D, Firmesse O, Levenez F, Guimarăes V, Sokol H, Doré J, et al. The firmicutes/bacteroidetes ratio of the human microbiota changes with age. BMC Microbiology. 2009;**9**:123. DOI: 10.1186/1471-2180-9-123

[11] The Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature. 2012;**486**(7402):207-214. DOI: 10.1038/nature11234

[12] Segata N, Haake SK, Mannon P, Lemon KP, Waldron L, Gevers D, et al. Composition of the adult digestive tract bacterial microbiome based on seven mouth surfaces, tonsils, throat and stool samples. Genome Biology. 2012;**13**(6):R42. DOI: 10.1186/gb-2012-13-6-r42

[13] Jia G, Zhi A, Lai PFH, Wang G, Xia Y, Xiong Z, et al. The oral microbiota - a mechanistic role for systemic diseases. British Dental Journal. 2018;**224**(6):447-455. DOI: 10.1038/sj.bdj.2018.217

[14] Grice EA, Kong HH, Conlan S, Deming CB, Davis J, Young AC, et al. Topographical and temporal diversity of the human skin microbiome. Science. 2009;**324**(5931):1190-1192. DOI: 10.1126/science.1171700

[15] Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. Nature Reviews

Microbiology. 2018;**16**(3):143-155. DOI: 10.1038/nrmicro.2017.157

[16] Ling Z, Kong J, Liu F, Zhu H, Chen X, Wang Y, et al. Molecular analysis of the diversity of vaginal microbiota associated with bacterial vaginosis. BMC Genomics. 2010;**11**:488. DOI: 10.1186/1471-2164-11-488

[17] Voravuthikunchai SP, Bilasoi S, Supamala O. Antagonistic activity against pathogenic bacteria by human vaginal lactobacilli. Anaerobe. 2006;**12**(5-6):221-226. DOI: 10.1016/j.anaerobe.2006.06.003

[18] Ravel J, Gajer P, Abdo Z, Schneider GM, Koenig SS, McCulle SL, et al. Vaginal microbiome of reproductive-age women. Proceedings of the National Academy of Sciences of the United States of America. 2011;**108**(Suppl 1):4680-4687. DOI: 10.1016/j.anaerobe.2006.06.003

[19] Franasiak JM, Scott RT. Reproductive tract microbiome in assisted reproductive technologies. Fertility and Sterility. 2015;**104**(6):1364-1371. DOI: 10.1016/j.fertnstert.2015.10.012

[20] Li JJ, Yi S, Wei L. Ocular microbiota and intraocular inflammation. Frontiers in Immunology. 2020;**11**:609765. DOI: 10.3389/fimmu.2020.609765

[21] Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;**464**(7285):59-65. DOI: 10.1038/nature08821

[22] Joseph J, Loscalzo J. Nutri(meta) genetics and cardiovascular disease: novel concepts in the interaction of diet and genomic variation. Current Atherosclerosis Reports. 2015;**17**(5):505. DOI: 10.1007/s11883-015-0505-x

[23] Novakovic M, Rout A, Kingsley T, Kirchoff R, Singh A, Verma V, et al. Role of gut microbiota in cardiovascular diseases. World Journal of Cardiology. 2020;**12**(4):110-122. DOI: 10.4330/wjc.v12.i4.110

[24] Badal VD, Vaccariello ED, Murray ER, Yu KE, Knight R, Jeste DV, et al. The gut microbiome, aging, and longevity: A systematic review. Nutrients. 2020;**12**(12):3759. DOI: 10.3390/nu12123759

[25] Tuikhar N, Keisam S, Labala RK, Imrat RP, Arunkumar MC, et al. Comparative analysis of the gut microbiota in centenarians and young adults shows a common signature across genotypically non-related populations. Mechanisms of Ageing and Development. 2019;**179**:23-35. DOI: 10.1016/j.mad.2019.02.001

[26] Salazar N, Arboleya S, Fernández-Navarro T, de Los Reyes-Gavilán CG, Gonzalez S, Gueimonde M. Age-associated changes in gut microbiota and dietary components related with the immune system in adulthood and old age: A cross-sectional study. Nutrients. 2019;**11**(8). DOI: 10.3390/nu11081765

[27] David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;**505**(7484):559-563. DOI: 10.1038/nature12820

[28] De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**(33):14691-14696. DOI: 10.1073/pnas.1005963107

[29] Schnorr SL, Candela M, Rampelli S, Centanni M, Consolandi C, Basaglia G, et al. Gut microbiome of the Hadza hunter-gatherers. Nature Communications. 2014;**5**:3654. DOI: 10.1038/ncomms4654

[30] Guo X, Huang C, Xu J, Xu H, Liu L, Zhao H, et al. Gut microbiota is a potential biomarker in inflammatory bowel disease. Frontiers in Nutrition. 2021;**8**:818902. DOI: 10.3389/fnut.2021.818902

[31] Antoniussen CS, Rasmussen HH, Holst M, Lauridsen C. Reducing disease activity of inflammatory bowel disease by consumption of plant-based foods and nutrients. Frontiers in Nutrition. 2021;**8**:733433. DOI: 10.3389/fnut.2021.733433

[32] Zuo T, Ng SC. The gut microbiota in the pathogenesis and therapeutics of inflammatory bowel disease. Frontiers in Microbiology. 2018;**9**:2247. DOI: 10.3389/fmicb.2018.02247

[33] Silva FA, Rodrigues BL, Ayrizono ML, Leal RF. The immunological basis of inflammatory bowel disease. Gastroenterology Research and Practice. 2016;**2016**:2097274. DOI: 10.1155/2016/2097274

[34] Santana PT, Rosas SLB, Ribeiro BE, Marinho Y, de Souza HSP. Dysbiosis in inflammatory bowel disease: Pathogenic role and potential therapeutic targets. International Journal of Molecular Sciences. 2022;**23**(7):3464. DOI: 10.3390/ijms23073464

[35] Sultan S, El-Mowafy M, Elgaml A, Ahmed TAE, Hassan H, Mottawea W. Metabolic influences of gut microbiota dysbiosis on inflammatory bowel disease. Frontiers in Physiology. 2021;**12**:715506. DOI: 10.3389/fphys.2021.715506

[36] Guzzo GL, Andrews JM, Weyrich LS. The neglected gut microbiome: Fungi, protozoa, and bacteriophages in inflammatory bowel disease. Inflammatory Bowel Diseases. 2022;**28**(7):1112-1122. DOI: 10.1093/ibd/izab343

[37] Jarmakiewicz-Czaja S, Zielińska M, Sokal A, Filip R. Genetic and epigenetic etiology of inflammatory bowel disease: An update. Genes. 2022;**13**(12):2388. DOI: 10.3390/genes13122388

[38] Tavakoli P, Vollmer-Conna U, Hadzi-Pavlovic D, Grimm MC. A Review of inflammatory bowel disease: A model of microbial, immune and neuropsychological integration. Public Health Reviews. 2021;**42**:1603990. DOI: 10.3389/phrs.2021.1603990

[39] Hisamatsu T, Kanai T, Mikami Y, Yoneno K, Matsuoka K, Hibi T. Immune aspects of the pathogenesis of inflammatory bowel disease. Pharmacology & Therapeutics. 2013;**137**(3):283-297. DOI: 10.1016/j.pharmthera.2012.10.008

[40] Shepherd FR, McLaren JE. T Cell immunity to bacterial pathogens: Mechanisms of immune control and bacterial evasion. International Journal of Molecular Sciences. 2020;**21**(17). DOI: 10.3390/ijms21176144

[41] Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, et al. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature. 2013;**500**(7461):232-236. DOI: 10.1038/nature12331

[42] Halfvarson J, Brislawn CJ, Lamendella R, Vázquez-Baeza Y, Walters WA, Bramer LM, et al. Dynamics of the human gut microbiome in inflammatory bowel disease. Nature Microbiology. 2017;**2**:17004. DOI: 10.1038/nmicrobiol.2017.4

[43] Yilmaz B, Spalinger MR, Biedermann L, Franc Y, Fournier N, Rossel J-B, et al. The presence of genetic risk variants within PTPN2 and PTPN22 is associated with intestinal microbiota alterations in Swiss IBD cohort patients. PLoS One. 2018;**13**(7):e0199664. DOI: 10.1371/journal.pone.0199664

[44] Li E, Zhang Y, Tian X, Wang X, Gathungu G, Wolber A, et al. Influence of Crohn's disease related polymorphisms in innate immune function on ileal microbiome. PLoS One. 2019;**14**(2):e0213108. DOI: 10.1371/journal.pone.0213108

[45] Alshehri D, Saadah O, Mosli M, Edris S, Alhindi R, Bahieldin A. Dysbiosis of gut microbiota in inflammatory bowel disease: Current therapies and potential for microbiota-modulating therapeutic approaches. Bosnian Journal of Basic Medical Sciences. 2021;**21**(3):270-283. DOI: 10.17305/bjbms.2020.5016

[46] Torun A, Hupalowska A, Trzonkowski P, Kierkus J, Pyrzynska B. Intestinal microbiota in common chronic inflammatory disorders affecting children. Frontiers in Immunology. 2021;**12**:642166. DOI: 10.3389/fimmu.2021.642166

[47] Morgan XC, Tickle TL, Sokol H, Gevers D, Devaney KL, Ward DV, et al. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. Genome Biology. 2012;**13**(9):R79. DOI: 10.1186/gb-2012-13-9-r79

[48] Banfi D, Moro E, Bosi A, Bistoletti M, Cerantola S, Crema F, et al. Impact of microbial metabolites on microbiota-gut-brain axis in inflammatory bowel disease. International Journal of Molecular Sciences. 2021;**22**(4):1623. DOI: 10.3390/ijms22041623

[49] Yang M, Gu Y, Li L, Liu T, Song X, Sun Y, et al. Bile acid–gut microbiota axis in inflammatory bowel disease: From bench to bedside. Nutrients. 2021;**13**(9):3143. DOI: 10.3390/nu13093143

[50] Akram W, Garud N, Joshi R. Role of inulin as prebiotics on inflammatory bowel disease. Drug Discoveries & Therapeutics. 2019;**13**(1):1-8. DOI: 10.5582/ddt.2019.01000

[51] Sartor RB, Wu GD. Roles for intestinal bacteria, viruses, and fungi in pathogenesis of inflammatory bowel diseases and therapeutic approaches. Gastroenterology. 2017;**152**(2):327-39.e4. DOI: 10.1053/j.gastro.2016.10.012

[52] Mu C, Zhu W. Antibiotic effects on gut microbiota, metabolism, and beyond. Applied Microbiology and Biotechnology. 2019;**103**(23):9277-9285. DOI: 10.1007/s00253-019-10165-x

[53] Stojek M, Jabłońska A, Adrych K. The role of fecal microbiota transplantation in the treatment of inflammatory bowel disease. Journal of Clinical Medicine. 2021;**10**(18):4055. DOI: 10.3390/jcm10184055

[54] Sokol H, Landman C, Seksik P, Berard L, Montil M, Nion-Larmurier I, et al. Fecal microbiota transplantation to maintain remission in Crohn's disease: A pilot randomized controlled study. Microbiome. 2020;**8**(1):12. DOI: 10.1186/s40168-020-0792-5

[55] Paramsothy S, Paramsothy R, Rubin DT, Kamm MA, Kaakoush NO, Mitchell HM, et al. Faecal microbiota transplantation for inflammatory bowel disease: A systematic review and meta-analysis. Journal of Crohn's and Colitis. 2017;**11**(10):1180-1199. DOI: 10.1093/ecco-jcc/jjx063

[56] Li Q, Ding X, Liu K, Marcella C, Liu X, Zhang T, et al. Fecal Microbiota transplantation for ulcerative colitis: The optimum timing and gut microbiota as predictors for long-term clinical outcomes. Clinical and Translational Gastroenterology. 2020;**11**(8):e00224. DOI: 10.14309/ctg.0000000000000224

[57] Kelly CR, Fischer M, Allegretti JR, LaPlante K, Stewart DB, Limketkai BN, et al. ACG Clinical guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. The American Journal of Gastroenterology. 2021;**116**(6):1124-1147. DOI: 10.14309/ajg.0000000000001278

[58] Chicco F, Magrì S, Cingolani A, Paduano D, Pesenti M, Zara F, et al. Multidimensional impact of mediterranean diet on IBD patients. Inflammatory Bowel Diseases. 2021;**27**(1):1-9. DOI: 10.1093/ibd/izaa097

[59] Gill PA, Inniss S, Kumagai T, Rahman FZ, Smith AM. The role of diet and gut microbiota in regulating gastrointestinal and inflammatory disease. Frontiers in Immunology. 2022;**13**:866059. DOI: 10.3389/fimmu.2022.866059

[60] Rapozo DC, Bernardazzi C, de Souza HS. Diet and microbiota in inflammatory bowel disease: The gut in disharmony. World Journal of Gastroenterology. 2017;**23**(12):2124-2140. DOI: 10.3748/wjg.v23.i12.2124

[61] Peppas S, Pansieri C, Piovani D, Danese S, Peyrin-Biroulet L, Tsantes AG, et al. The brain-gut axis: Psychological functioning and inflammatory bowel diseases. Journal of Clinical Medicine. 2021;**10**(3):377. DOI: 10.3390/jcm10030377

[62] Park S, Zhang T. A positive association of overactivated immunity with metabolic syndrome risk and mitigation of its association by a plant-based diet and physical activity in a large cohort study. Nutrients. 2021;**13**(7):2308. DOI: 10.3390/nu13072308

[63] Bhatia M. Inflammatory response on the pancreatic acinar cell injury. Scandinavian Journal of Surgery. 2005;**94**(2):97-102. DOI: 10.1177/145749690509400203

[64] Heckler M, Hackert T, Hu K, Halloran C, Büchler M, Neoptolemos J. Severe acute pancreatitis: surgical indications and treatment. Langenbeck's Archives of Surgery. 2021;**406**:521-535. DOI: 10.1007/s00423-020-01944-6

[65] Bhatia M. Acute pancreatitis as a model of SIRS. FBL. 2009;**14**(6):2042-2050. DOI: 10.2741/3362

[66] Carden DL, Granger DN. Pathophysiology of ischaemia-reperfusion injury. The Journal of Pathology. 2000;**190**(3):255-266. DOI: 10.1002/(SICI)1096-9896(200002)190:3<255::AID-PATH526>3.0.CO;2-6

[67] Bhatia M, Wong FL, Cao Y, Lau HY, Huang J, Puneet P, et al. Pathophysiology of acute pancreatitis. Pancreatology. 2005;**5**(2-3):132-144. DOI: 10.1159/000085265

[68] Thoeni RF. The revised Atlanta classification of acute pancreatitis: Its importance for the radiologist and its effect on treatment. Radiology. 2012;**262**(3):751-764. DOI: 10.1148/radiol.11110947

[69] Clemente JC, Manasson J, Scher JU. The role of the gut microbiome in systemic inflammatory disease. BMJ. 2018;**360**:j5145. DOI: 10.1136/bmj.j5145

[70] Liu H, Li W, Wang X, Li J, Yu W. Early gut mucosal dysfunction in patients

with acute pancreatitis. Pancreas. 2008;**36**(2):192-196. DOI: 10.1097/MPA.0b013e31815a399f

[71] Fishman JE, Levy G, Alli V, Zheng X, Mole DJ, Deitch EA. The intestinal mucus layer is a critical component of the gut barrier that is damaged during acute pancreatitis. Shock. 2014;**42**(3):264-270. DOI: 10.1097/shk.0000000000000209

[72] Capurso G, Zerboni G, Signoretti M, Valente R, Stigliano S, Piciucchi M, et al. Role of the gut barrier in acute pancreatitis. Journal of Clinical Gastroenterology. 2012;**46**(Suppl):S46-S51. DOI: 10.1097/MCG.0b013e3182652096

[73] PietrzakB,TomelaK,Olejnik-SchmidtA, Mackiewicz A, Schmidt M. Secretory IgA in intestinal mucosal secretions as an adaptive barrier against microbial cells. International Journal of Molecular Sciences. 2020;**21**(23):9254. DOI: 10.3390/ijms21239254

[74] Bunker JJ, Flynn TM, Koval JC, Shaw DG, Meisel M, McDonald BD, et al. Innate and adaptive humoral responses coat distinct commensal bacteria with immunoglobulin A. Immunity. 2015;**43**(3):541-553. DOI: 10.1016/j.immuni.2015.08.007

[75] Yu S, Xiong Y, Xu J, Liang X, Fu Y, Liu D, et al. Identification of dysfunctional gut microbiota through rectal swab in patients with different severity of acute pancreatitis. Digestive Diseases and Sciences. 2020;**65**(11):3223-3237. DOI: 10.1007/s10620-020-06061-4

[76] Tan C, Ling Z, Huang Y, Cao Y, Liu Q, Cai T, et al. Dysbiosis of intestinal microbiota associated with inflammation involved in the progression of acute pancreatitis. Pancreas. 2015;**44**(6):868-875. DOI: 10.1097/MPA.0000000000000355

[77] Zhu Y, He C, Li X, Cai Y, Hu J, Liao Y, et al. Gut microbiota dysbiosis worsens the severity of acute pancreatitis in patients and mice. Journal of Gastroenterology. 2019;**54**(4):347-358. DOI: 10.1007/s00535-018-1529-0

[78] Cho I, Blaser MJ. The human microbiome: At the interface of health and disease. Nature Reviews. Genetics. 2012;**13**(4):260-270. DOI: 10.1038/nrg3182

[79] Parada Venegas D, De la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, et al. Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Frontiers in Immunology. 2019;**10**:277. DOI: 10.3389/fimmu.2019.00277

[80] Li XY, He C, Zhu Y, Lu NH. Role of gut microbiota on intestinal barrier function in acute pancreatitis. World Journal of Gastroenterology. 2020;**26**(18):2187-2193. DOI: 10.3748/wjg.v26.i18.2187

[81] Li M, Liang P, Li Z, Wang Y, Zhang G, Gao H, et al. Fecal microbiota transplantation and bacterial consortium transplantation have comparable effects on the re-establishment of mucosal barrier function in mice with intestinal dysbiosis. Frontiers in Microbiology. 2015;**6**:692. DOI: 10.3389/fmicb.2015.00692

[82] Ding L, He C, Li X, Huang X, Lei Y, Ke H, et al. Efficacy and safety of faecal microbiota transplantation for acute pancreatitis: A randomised, controlled study. Frontiers in Medicine (Lausanne). 2021;**8**:772454. DOI: 10.3389/fmed.2021.772454

[83] Majumder S, Chari ST. Chronic pancreatitis. Lancet.

2016;**387**(10031):1957-1966. DOI: 10.1016/s0140-6736(16)00097-0

[84] Pitchumoni C. Interdependence of nutrition and exocrine pancreatic function. In: Vay Liang W. Go, et al., editors. The Pancreas: Biology, Pathobiology, and Disease. Second ed. New York: Raven Press Ltd; 1993. DOI: 10.1007/978-3-642-79167-3_48

[85] Pietzner M, Budde K, Rühlemann M, Völzke H, Homuth G, Weiss FU, et al. Exocrine pancreatic function modulates plasma metabolites through changes in gut microbiota composition. The Journal of Clinical Endocrinology & Metabolism. 2021;**106**(5):e2290-e22e8. DOI: 10.1210/clinem/dgaa961

[86] Frost F, Weiss FU, Sendler M, Kacprowski T, Rühlemann M, Bang C, et al. The gut microbiome in patients with chronic pancreatitis is characterized by significant dysbiosis and overgrowth by opportunistic pathogens. Clinical and Translational Gastroenterology. 2020;**11**(9):e00232. DOI: 10.14309/ctg.0000000000000232

[87] Akshintala VS, Talukdar R, Singh VK, Goggins M. The gut microbiome in pancreatic disease. Clinical Gastroenterology and Hepatology. 2019;**17**(2):290-295. DOI: 10.1016/j.cgh.2018.08.045

[88] Capurso G, Signoretti M, Archibugi L, Stigliano S, Delle FG. Systematic review and meta-analysis: Small intestinal bacterial overgrowth in chronic pancreatitis. United European Gastroenterology Journal. 2016;**4**(5):697-705. DOI: 10.1177/2050640616630117

[89] Ní Chonchubhair HM, Bashir Y, Dobson M, Ryan BM, Duggan SN, Conlon KC. The prevalence of small intestinal bacterial overgrowth in non-surgical patients with chronic pancreatitis and pancreatic exocrine insufficiency (PEI). Pancreatology. 2018;**18**(4):379-385. DOI: 10.1016/j.pan.2018.02.010

[90] Talukdar R, Jandhyala SM, Reddy R, Arutla M, Reddy D. Altered gut microbiota in patients with chronic pancreatitis is associated with gut barrier dysfunction and metabolic abnormalities. Clinical Gastroenterology and Hepatology. 2017;**15**:153. DOI: 10.1016/j.cgh.2016.09.023

[91] Morgan E, Arnold M, Gini A, Lorenzoni V, Cabasag CJ, Laversanne M, et al. Global burden of colorectal cancer in 2020 and 2040: Incidence and mortality estimates from GLOBOCAN. Gut. 2023;**72**(2):338. DOI: 10.1136/gutjnl-2022-327736

[92] Sánchez-Alcoholado L, Ramos-Molina B, Otero A, Laborda-Illanes A, Ordóñez R, Medina JA, et al. The role of the gut microbiome in colorectal cancer development and therapy response. Cancers (Basel). 2020;**12**(6):1406. DOI: 10.3390/cancers12061406

[93] Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. The New England Journal of Medicine. 2000;**343**(2):78-85. DOI: 10.1056/nejm200007133430201

[94] Czene K, Lichtenstein P, Hemminki K. Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish Family-Cancer Database. International Journal of Cancer. 2002;**99**(2):260-266. DOI: 10.1002/ijc.10332

[95] Rattray NJW, Charkoftaki G, Rattray Z, Hansen JE, Vasiliou V,

Johnson CH. Environmental influences in the etiology of colorectal cancer: The premise of metabolomics. Current Pharmacology Reports. 2017;**3**(3):114-125. DOI: 10.1007/s40495-017-0088-z

[96] Laqueur GL, McDaniel EG, Matsumoto H. Tumor induction in germfree rats with methylazoxymethanol (MAM) and synthetic MAM acetate. Journal of the National Cancer Institute. 1967;**39**(2):355-371. DOI: 10.1093/jnci/39.2.355

[97] Reddy BS, Narisawa T, Wright P, Vukusich D, Weisburger JH, Wynder EL. Colon carcinogenesis with azoxymethane and dimethylhydrazine in germ-free rats. Cancer Research. 1975;**35**(2):287-290

[98] Reddy BS, Narisawa T, Weisburger JH. Colon carcinogenesis in germ-free rats with intrarectal 1,2-dimethylhydrazine and subcutaneous azoxymethane. Cancer Research. 1976;**36**(8):2874-2876

[99] Wong SH, Yu J. Gut microbiota in colorectal cancer: Mechanisms of action and clinical applications. Nature Reviews Gastroenterology & Hepatology. 2019;**16**(11):690-704. DOI: 10.1038/s41575-019-0209-8

[100] Cheng Y, Ling Z, Li L. The intestinal microbiota and colorectal cancer. Frontiers in Immunology. 2020;**11**:615056. DOI: 10.3389/fimmu.2020.615056

[101] Saffarian A, Mulet C, Regnault B, Amiot A, Tran-Van-Nhieu J, Ravel J, et al. Crypt- and mucosa-associated core microbiotas in humans and their alteration in colon cancer patients. MBio. 2019;**10**(4):e01315-19. DOI: 10.1128/mBio.01315-19

[102] Chen W, Liu F, Ling Z, Tong X, Xiang C. Human intestinal lumen and mucosa-associated microbiota in patients with colorectal cancer. PLoS One. 2012;**7**(6):e39743. DOI: 10.1371/journal.pone.0039743

[103] Chung L, Thiele Orberg E, Geis AL, Chan JL, Fu K, DeStefano Shields CE, et al. Bacteroides fragilis toxin coordinates a pro-carcinogenic inflammatory cascade via targeting of colonic epithelial cells. Cell Host & Microbe. 2018;**23**(2):203-14.e5. DOI: 10.1016/j.chom.2018.01.007

[104] Dai Z, Coker OO, Nakatsu G, Wu WKK, Zhao L, Chen Z, et al. Multi-cohort analysis of colorectal cancer metagenome identified altered bacteria across populations and universal bacterial markers. Microbiome. 2018;**6**(1):70. DOI: 10.1186/s40168-018-0451-2

[105] Wirbel J, Pyl PT, Kartal E, Zych K, Kashani A, Milanese A, et al. Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. Nature Medicine. 2019;**25**(4):679-689. DOI: 10.1038/s41591-019-0406-6

[106] Thomas AM, Manghi P, Asnicar F, Pasolli E, Armanini F, Zolfo M, et al. Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation. Nature Medicine. 2019;**25**(4):667-678. DOI: 10.1038/s41591-019-0405-7

[107] Bashir A, Miskeen AY, Bhat A, Fazili KM, Ganai BA. Fusobacterium nucleatum: An emerging bug in colorectal tumorigenesis. European Journal of Cancer Prevention. 2015;**24**(5):373-385. DOI: 10.1097/cej.0000000000000116

[108] Mima K, Nishihara R, Qian ZR, Cao Y, Sukawa Y, Nowak JA, et al.

Fusobacterium nucleatum in colorectal carcinoma tissue and patient prognosis. Gut. 2016;**65**(12):1973-1980. DOI: 10.1136/gutjnl-2015-310101

[109] Wei Z, Cao S, Liu S, Yao Z, Sun T, Li Y, et al. Could gut microbiota serve as prognostic biomarker associated with colorectal cancer patients' survival? A pilot study on relevant mechanism. Oncotarget. 2016;**7**(29):46158-46172. DOI: 10.18632/oncotarget.10064

[110] Lo C-H, Wu D-C, Jao S-W, Wu C-C, Lin C-Y, Chuang C-H, et al. Enrichment of Prevotella intermedia in human colorectal cancer and its additive effects with Fusobacterium nucleatum on the malignant transformation of colorectal adenomas. Journal of Biomedical Science. 2022;**29**(1):88. DOI: 10.1186/s12929-022-00869-0

[111] Wang T, Cai G, Qiu Y, Fei N, Zhang M, Pang X, et al. Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. The ISME Journal. 2012;**6**(2):320-329. DOI: 10.1038/ismej.2011.109

[112] Molska M, Reguła J. Potential mechanisms of probiotics action in the prevention and treatment of colorectal cancer. Nutrients. 2019;**11**(10). DOI: 10.3390/nu11102453

[113] Imen K, Meenakshi M, Alaoui-Jamali MA, Prakash S. In-Vitro characterization of the anti-cancer activity of the probiotic bacterium lactobacillus fermentum NCIMB 5221 and potential against colorectal cancer. Journal of Cancer Science & Therapy. 2015;**07**:224-235. DOI: 10.4172/1948-5956.1000354

[114] van Munster IP, Tangerman A, Nagengast FM. Effect of resistant starch on colonic fermentation, bile acid metabolism, and mucosal proliferation. Digestive Diseases and Sciences. 1994;**39**(4):834-842. DOI: 10.1007/bf02087431

[115] Dronamraju SS, Coxhead JM, Kelly SB, Burn J, Mathers JC. Cell kinetics and gene expression changes in colorectal cancer patients given resistant starch: A randomised controlled trial. Gut. 2009;**58**(3):413-420. DOI: 10.1136/gut.2008.162933

[116] Rafter J, Bennett M, Caderni G, Clune Y, Hughes R, Karlsson PC, et al. Dietary synbiotics reduce cancer risk factors in polypectomized and colon cancer patients. The American Journal of Clinical Nutrition. 2007;**85**(2):488-496. DOI: 10.1093/ajcn/85.2.488

[117] Nakatsu G, Zhou H, Wu WKK, Wong SH, Coker OO, Dai Z, et al. Alterations in enteric virome are associated with colorectal cancer and survival outcomes. Gastroenterology. 2018;**155**(2):529-41.e5. DOI: 10.1053/j.gastro.2018.04.018

[118] Hannigan GD, Duhaime MB, MTt R, Koumpouras CC, Schloss PD. Diagnostic potential and interactive dynamics of the colorectal cancer virome. MBio. 2018;**9**(6):e02248-18. DOI: 10.1128/mBio.02248-18

[119] Luan C, Xie L, Yang X, Miao H, Lv N, Zhang R, et al. Dysbiosis of fungal microbiota in the intestinal mucosa of patients with colorectal adenomas. Scientific Reports. 2015;**5**:7980. DOI: 10.1038/srep07980

[120] Coker OO, Nakatsu G, Dai RZ, Wu WKK, Wong SH, Ng SC, et al. Enteric fungal microbiota dysbiosis and ecological alterations in colorectal cancer. Gut. 2019;**68**(4):654-662. DOI: 10.1136/gutjnl-2018-317178

[121] Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA,

Michaud M, et al. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host & Microbe. 2013;**14**(2):207-215. DOI: 10.1016/j.chom.2013.07.007

[122] Long X, Wong CC, Tong L, Chu ESH, Ho Szeto C, Go MYY, et al. Peptostreptococcus anaerobius promotes colorectal carcinogenesis and modulates tumour immunity. Nature Microbiology. 2019;**4**(12):2319-2330. DOI: 10.1038/s41564-019-0541-3

[123] Zaharuddin L, Mokhtar NM, Muhammad Nawawi KN, Raja Ali RA. A randomized double-blind placebo-controlled trial of probiotics in post-surgical colorectal cancer. BMC Gastroenterology. 2019;**19**(1):131. DOI: 10.1186/s12876-019-1047-4

[124] Ohara T, Yoshino K, Kitajima M. Possibility of preventing colorectal carcinogenesis with probiotics. Hepato-Gastroenterology. 2010;**57**(104):1411-1415

[125] Biarc J, Nguyen IS, Pini A, Gossé F, Richert S, Thiersé D, et al. Carcinogenic properties of proteins with pro-inflammatory activity from Streptococcus infantarius (formerly S.bovis). Carcinogenesis. 2004;**25**(8):1477-1484. DOI: 10.1093/carcin/bgh091

[126] Rubinstein MR, Wang X, Liu W, Hao Y, Cai G, Han YW. Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin. Cell Host & Microbe. 2013;**14**(2):195-206. DOI: 10.1016/j.chom.2013.07.012

[127] Gur C, Ibrahim Y, Isaacson B, Yamin R, Abed J, Gamliel M, et al. Binding of the Fap2 protein of Fusobacterium nucleatum to human inhibitory receptor TIGIT protects tumors from immune cell attack. Immunity. 2015;**42**(2):344-355. DOI: 10.1016/j.immuni.2015.01.010

[128] Cremonesi E, Governa V, Garzon JFG, Mele V, Amicarella F, Muraro MG, et al. Gut microbiota modulate T cell trafficking into human colorectal cancer. Gut. 2018;**67**(11):1984. DOI: 10.1136/gutjnl-2016-313498

[129] Arthur JC, Gharaibeh RZ, Mühlbauer M, Perez-Chanona E, Uronis JM, McCafferty J, et al. Microbial genomic analysis reveals the essential role of inflammation in bacteria-induced colorectal cancer. Nature Communications. 2014;**5**:4724. DOI: 10.1038/ncomms5724

[130] Cuevas-Ramos G, Petit CR, Marcq I, Boury M, Oswald E, Nougayrède JP. Escherichia coli induces DNA damage in vivo and triggers genomic instability in mammalian cells. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**(25):11537-11542. DOI: 10.1073/pnas.1001261107

[131] Martin OCB, Bergonzini A, D'Amico F, Chen P, Shay JW, Dupuy J, et al. Infection with genotoxin-producing Salmonella enterica synergises with loss of the tumour suppressor APC in promoting genomic instability via the PI3K pathway in colonic epithelial cells. Cellular Microbiology. 2019;**21**(12):e13099. DOI: 10.1111/cmi.13099

[132] Singh N, Gurav A, Sivaprakasam S, Brady E, Padia R, Shi H, et al. Activation of Gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. Immunity. 2014;**40**(1):128-139. DOI: 10.1016/j.immuni.2013.12.007

[133] Collins D, Hogan AM, Winter DC. Microbial and viral pathogens in colorectal cancer. The Lancet Oncology. 2011;**12**(5):504-512. DOI: 10.1016/S1470-2045(10)70186-8

[134] Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature. 2013;**504**(7480):446-450. DOI: 10.1038/nature12721

[135] Buda A, Qualtrough D, Jepson MA, Martines D, Paraskeva C, Pignatelli M. Butyrate downregulates $\alpha_2\beta_1$ integrin: A possible role in the induction of apoptosis in colorectal cancer cell lines. Gut. 2003;**52**(5):729. DOI: 10.1136/gut.52.5.729

[136] Boleij A, Hechenbleikner EM, Goodwin AC, Badani R, Stein EM, Lazarev MG, et al. The bacteroides fragilis toxin gene is prevalent in the colon mucosa of colorectal cancer patients. Clinical Infectious Diseases. 2015;**60**(2):208-215. DOI: 10.1093/cid/ciu787

[137] Wu S, Rhee K-J, Albesiano E, Rabizadeh S, Wu X, Yen H-R, et al. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nature Medicine. 2009;**15**(9):1016-1022. DOI: 10.1038/nm.2015

[138] Kortylewski M, Xin H, Kujawski M, Lee H, Liu Y, Harris T, et al. Regulation of the IL-23 and IL-12 balance by Stat3 signaling in the tumor microenvironment. Cancer Cell. 2009;**15**(2):114-123. DOI: 10.1016/j.ccr.2008.12.018

[139] Wang K, Kim MK, Di Caro G, Wong J, Shalapour S, Wan J, et al. Interleukin-17 receptor a signaling in transformed enterocytes promotes early colorectal tumorigenesis. Immunity. 2014;**41**(6):1052-1063. DOI: 10.1016/j.immuni.2014.11.009

[140] Scudamore CL, Jepson MA, Hirst BH, Miller HR. The rat mucosal mast cell chymase, RMCP-II, alters epithelial cell monolayer permeability in association with altered distribution of the tight junction proteins ZO-1 and occludin. European Journal of Cell Biology. 1998;**75**(4):321-330. DOI: 10.1016/s0171-9335(98)80065-4

[141] Zhang DM, Jiao RQ, Kong LD. High dietary fructose: Direct or indirect dangerous factors disturbing tissue and organ functions. Nutrients. 2017;**9**(4):335. DOI: 10.3390/nu9040335

[142] Cretoiu D, Ionescu RF, Enache RM, Cretoiu SM, Voinea SC. Gut microbiome, functional food, atherosclerosis, and vascular calcifications-is there a missing link? Microorganisms. 2021;**9**(9):1913. DOI: 10.3390/microorganisms9091913

[143] Lusis AJ. Atherosclerosis. Nature. 2000;**407**(6801):233-241. DOI: 10.1038/35025203

[144] Rosenfeld ME, Campbell LA. Pathogens and atherosclerosis: Update on the potential contribution of multiple infectious organisms to the pathogenesis of atherosclerosis. Thrombosis and Haemostasis. 2011;**106**(5):858-867. DOI: 10.1160/th11-06-0392

[145] Jonsson AL, Bäckhed F. Role of gut microbiota in atherosclerosis. Nature Reviews. Cardiology. 2017;**14**(2):79-87. DOI: 10.1038/nrcardio.2016.183

[146] Pastori D, Carnevale R, Nocella C, Novo M, Santulli M, Cammisotto V, et al. Gut-derived serum lipopolysaccharide is associated with enhanced risk of major adverse cardiovascular

events in atrial fibrillation: Effect of adherence to Mediterranean diet. Journal of the American Heart Association;**6**(6):e005784. DOI: 10.1161/JAHA.117.005784

[147] Yamashita T, Yoshida N, Emoto T, Saito Y, Hirata KI. Two gut microbiota-derived toxins are closely associated with cardiovascular diseases: A review. Toxins (Basel). 2021;**13**(5):297. DOI: 10.3390/toxins13050297

[148] Yoshida N, Yamashita T, Kishino S, Watanabe H, Sasaki K, Sasaki D, et al. A possible beneficial effect of Bacteroides on faecal lipopolysaccharide activity and cardiovascular diseases. Scientific Reports. 2020;**10**(1):13009. DOI: 10.1038/s41598-020-69983-z

[149] Ding L, Chang M, Guo Y, Zhang L, Xue C, Yanagita T, et al. Trimethylamine-N-oxide (TMAO)-induced atherosclerosis is associated with bile acid metabolism. Lipids in Health and Disease. 2018;**17**(1):286. DOI: 10.1186/s12944-018-0939-6

[150] Witkowski M, Weeks TL, Hazen SL. Gut microbiota and cardiovascular disease. Circulation Research. 2020;**127**:553-570. DOI: 10.3390/microorganisms9091913

[151] Trøseid M, Ueland T, Hov JR, Svardal A, Gregersen I, Dahl CP, et al. Microbiota-dependent metabolite trimethylamine-N-oxide is associated with disease severity and survival of patients with chronic heart failure. Journal of Internal Medicine. 2015;**277**(6):717-726. DOI: 10.1111/joim.12328

[152] Tang WHW, Li DY, Hazen SL. Dietary metabolism, the gut microbiome, and heart failure. Nature Reviews. Cardiology. 2019;**16**(3):137-154. DOI: 10.1038/s41569-018-0108-7

[153] Mutalub YB, Abdulwahab M, Mohammed A, Yahkub AM, Al-Mhanna SB, Yusof W, et al. Gut microbiota modulation as a novel therapeutic strategy in cardiometabolic diseases. Food. 2022;**11**(17):2575. DOI: 10.3390/foods11172575

[154] Kummen M, Mayerhofer CCK, Vestad B, Broch K, Awoyemi A, Storm-Larsen C, et al. Gut microbiota signature in heart failure defined from profiling of 2 independent cohorts. Journal of the American College of Cardiology. 2018;**71**(10):1184-1186. DOI: 10.1016/j.jacc.2017.12.057

[155] Pasini E, Aquilani R, Testa C, Baiardi P, Angioletti S, Boschi F, et al. Pathogenic gut flora in patients with chronic heart failure. JACC Heart Failure. 2016;**4**(3):220-227. DOI: 10.1016/j.jchf.2015.10.009

[156] Ionescu RF, Boroghina SC, Cretoiu SM. Is there a link between the gut microbiome and arterial hypertension. Journal of Hypertension Research. 2021;**7**:12-17

[157] Miura K, Stamler J, Nakagawa H, Elliott P, Ueshima H, Chan Q, et al. Relationship of dietary linoleic acid to blood pressure. The international study of macro-micronutrients and blood pressure study [corrected]. Hypertension. 2008;**52**(2):408-414. DOI: 10.1161/hypertensionaha.108.112383

[158] Tsukamoto I, Sugawara S. Low levels of linoleic acid and α-linolenic acid and high levels of arachidonic acid in plasma phospholipids are associated with hypertension. Biomedical Reports. 2018;**8**(1):69-76. DOI: 10.3892/br.2017.1015

[159] Djoussé L, Arnett DK, Pankow JS, Hopkins PN, Province MA, Ellison RC.

Dietary linolenic acid is associated with a lower prevalence of hypertension in the NHLBI family heart study. Hypertension. 2005;**45**(3):368-373. DOI: 10.1161/01.HYP.0000154679.41568.e6

[160] Sun S, Lulla A, Sioda M, Winglee K, Wu MC, Jacobs DR Jr, et al. Gut microbiota composition and blood pressure. Hypertension. 2019;**73**(5):998-1006. DOI: 10.1161/hypertensionaha.118.12109

[161] Jin M, Qian Z, Yin J, Xu W, Zhou X. The role of intestinal microbiota in cardiovascular disease. Journal of Cellular and Molecular Medicine. 2019;**23**(4):2343-2350. DOI: 10.1111/jcmm.14195

[162] Pluznick JL. Microbial short-chain fatty acids and blood pressure regulation. Current Hypertension Reports. 2017;**19**(4):25. DOI: 10.1007/s11906-017-0722-5

[163] Li J, Zhao F, Wang Y, Chen J, Tao J, Tian G, et al. Gut microbiota dysbiosis contributes to the development of hypertension. Microbiome. 2017;**5**(1):14. DOI: 10.1186/s40168-016-0222-x

[164] Lu D, Zou X, Zhang H. The relationship between atrial fibrillation and intestinal flora with its metabolites. Frontiers in Cardiovascular Medicine. 2022;**9**:948755. DOI: 10.3389/fcvm.2022.948755

[165] Wang L, Wang S, Zhang Q, He C, Fu C, Wei Q. The role of the gut microbiota in health and cardiovascular diseases. Molecular Biomedicine. 2022;**3**(1):30. DOI: 10.1186/s43556-022-00091-2

[166] Drapkina OM, Yafarova AA, Kaburova AN, Kiselev AR. Targeting gut microbiota as a novel strategy for prevention and treatment of hypertension, atrial fibrillation and heart failure: Current knowledge and future perspectives. Biomedicine. 2022;**10**(8):2019. DOI: 10.3390/biomedicines10082019

[167] Zhang J, Zuo K, Fang C, Yin X, Liu X, Zhong J, et al. Altered synthesis of genes associated with short-chain fatty acids in the gut of patients with atrial fibrillation. BMC Genomics. 2021;**22**(1):634. DOI: 10.1186/s12864-021-07944-0

[168] Ballini A, Scacco S, Boccellino M, Santacroce L, Arrigoni R. Microbiota and obesity: Where are we now? Biology (Basel). 2020;**9**(12):415. DOI: 10.3390/biology9120415

[169] Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proceedings of the National Academy of Sciences of the United States of America. 2005;**102**(31):11070-11075. DOI: 10.1073/pnas.0504978102

[170] Ahmad A, Riaz S, Tanveer M. Obesity and gut microbiota. In: Effect of Microbiota on Health and Disease. London: IntechOpen; 2022. DOI: 10.5772/intechopen.105397

[171] Ojeda P, Bobe A, Dolan K, Leone V, Martinez K. Nutritional modulation of gut microbiota - the impact on metabolic disease pathophysiology. The Journal of Nutritional Biochemistry. 2016;**28**:191-200. DOI: 10.1016/j.jnutbio.2015.08.013

[172] Jumpertz R, Le DS, Turnbaugh PJ, Trinidad C, Bogardus C, Gordon JI, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. The American Journal of Clinical Nutrition. 2011;**94**(1):58-65. DOI: 10.3945/ajcn.110.010132

[173] Kalliomäki M, Collado MC, Salminen S, Isolauri E. Early differences

in fecal microbiota composition in children may predict overweight. The American Journal of Clinical Nutrition. 2008;**87**(3):534-538. DOI: 10.1093/ajcn/87.3.534

[174] Di Domenico M, Pinto F, Quagliuolo L, Contaldo M, Settembre G, Romano A, et al. The role of oxidative stress and hormones in controlling obesity. Frontiers in Endocrinology (Lausanne). 2019;**10**:540. DOI: 10.3389/fendo.2019.00540

[175] Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. Cell Host & Microbe. 2008;**3**(4):213-223. DOI: 10.1016/j.chom.2008.02.015

[176] Davis CD. The gut microbiome and its role in obesity. Nutrition Today. 2016;**51**(4):167-174. DOI: 10.1097/nt.0000000000000167

[177] Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. The effect of diet on the human gut microbiome: A metagenomic analysis in humanized gnotobiotic mice. Science Translational Medicine. 2009;**1**(6):6ra14. DOI: 10.1126/scitranslmed.3000322

[178] Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011;**334**(6052):105-108. DOI: 10.1126/science.1208344

[179] Chen J, Thomsen M, Vitetta L. Interaction of gut microbiota with dysregulation of bile acids in the pathogenesis of nonalcoholic fatty liver disease and potential therapeutic implications of probiotics. Journal of Cellular Biochemistry. 2019;**120**(3):2713-2720. DOI: 10.1002/jcb.27635

[180] Pols TW, Nomura M, Harach T, Lo Sasso G, Oosterveer MH, Thomas C, et al. TGR5 activation inhibits atherosclerosis by reducing macrophage inflammation and lipid loading. Cell Metabolism. 2011;**14**(6):747-757. DOI: 10.1016/j.cmet.2011.11.006

[181] Maruvada P, Leone V, Kaplan LM, Chang EB. The human microbiome and obesity: Moving beyond associations. Cell Host & Microbe. 2017;**22**(5):589-599. DOI: 10.1016/j.chom.2017.10.005

[182] Chassaing B, Ley RE, Gewirtz AT. Intestinal epithelial cell toll-like receptor 5 regulates the intestinal microbiota to prevent low-grade inflammation and metabolic syndrome in mice. Gastroenterology. 2014;**147**(6):1363-77.e17. DOI: 10.1053/j.gastro.2014.08.033

[183] Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. Nature. 2016;**529**(7585):212-215. DOI: 10.1038/nature16504

[184] Helmink BA, Khan MAW, Hermann A, Gopalakrishnan V, Wargo JA. The microbiome, cancer, and cancer therapy. Nature Medicine. 2019;**25**(3):377-388. DOI: 10.1038/s41591-019-0377-7

[185] Murphy EF, Cotter PD, Healy S, Marques TM, O'Sullivan O, Fouhy F, et al. Composition and energy harvesting capacity of the gut microbiota: relationship to diet, obesity and time in mouse models. Gut. 2010;**59**(12):1635-1642. DOI: 10.1136/gut.2010.215665

[186] Petersen C, Bell R, Klag KA, Lee SH, Soto R, Ghazaryan A, et al. T cell-mediated regulation of the microbiota protects against obesity. Science.

2019;**365**(6451):eaat9351. DOI: 10.1126/science.aat9351

[187] den Besten G, Bleeker A, Gerding A, van Eunen K, Havinga R, van Dijk TH, et al. Short-chain fatty acids protect against high-fat diet-induced obesity via a PPARγ-dependent switch from lipogenesis to fat oxidation. Diabetes. 2015;**64**(7):2398-2408. DOI: 10.2337/db14-1213

[188] Wlodarska M, Thaiss CA, Nowarski R, Henao-Mejia J, Zhang JP, Brown EM, et al. NLRP6 inflammasome orchestrates the colonic host-microbial interface by regulating goblet cell mucus secretion. Cell. 2014;**156**(5):1045-1059. DOI: 10.1016/j.cell.2014.01.026

[189] Cani PD, Delzenne NM. The gut microbiome as therapeutic target. Pharmacology & Therapeutics. 2011;**130**(2):202-212. DOI: 10.1016/j.pharmthera.2011.01.012

[190] Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;**444**(7122):1027-1031. DOI: 10.1038/nature05414

[191] Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, et al. Richness of human gut microbiome correlates with metabolic markers. Nature. 2013;**500**(7464):541-546. DOI: 10.1038/nature12506

[192] Shajib MS, Khan WI. The role of serotonin and its receptors in activation of immune responses and inflammation. Acta Physiologica (Oxford, England). 2015;**213**(3):561-574. DOI: 10.1111/apha.12430

[193] Sandhu KV, Sherwin E, Schellekens H, Stanton C, Dinan TG, Cryan JF. Feeding the microbiota-gut-brain axis: Diet, microbiome, and neuropsychiatry. Translational Research. 2017;**179**:223-244. DOI: 10.1016/j.trsl.2016.10.002

[194] Delzenne NM, Cani PD, Daubioul C, Neyrinck AM. Impact of inulin and oligofructose on gastrointestinal peptides. The British Journal of Nutrition. 2005;**93**(Suppl 1):S157-S161. DOI: 10.1079/bjn20041342

[195] Torres-Fuentes C, Schellekens H, Dinan TG, Cryan JF. A natural solution for obesity: Bioactives for the prevention and treatment of weight gain. A review. Nutritional Neuroscience. 2015;**18**(2):49-65. DOI: 10.1179/1476830513y.0000000099

[196] Cox LM, Blaser MJ. Antibiotics in early life and obesity. Nature Reviews Endocrinology. 2015;**11**(3):182-190. DOI: 10.1038/nrendo.2014.210

[197] Salazar J, Angarita L, Morillo V, Navarro C, Martínez MS, Chacín M, et al. Microbiota and diabetes mellitus: Role of lipid mediators. Nutrients. 2020;**12**(10):3039. DOI: 10.3390/nu12103039

[198] Schwartz SS, Epstein S, Corkey BE, Grant SF, Gavin JR 3rd, Aguilar RB. The time is right for a new classification system for diabetes: Rationale and implications of the β-cell-centric classification schema. Diabetes Care. 2016;**39**(2):179-186. DOI: 10.2337/dc15-1585

[199] Zozulinska D, Wierusz-Wysocka B. Type 2 diabetes mellitus as inflammatory disease. Diabetes Research and Clinical Practice. 2006;**74**(2):98-107. DOI: 10.1016/j.diabres.2006.06.007

[200] Roohi A, Tabrizi M, Abbasi F, Ataie-Jafari A, Nikbin B, Larijani B,

et al. Serum IL-17, IL-23, and TGF-β levels in type 1 and type 2 diabetic patients and age-matched healthy controls. BioMed Research International. 2014;**2014**:718946. DOI: 10.1155/2014/718946

[201] Abdel-Moneim A, Bakery HH, Allam G. The potential pathogenic role of IL-17/Th17 cells in both type 1 and type 2 diabetes mellitus. Biomedicine & Pharmacotherapy. 2018;**101**:287-292. DOI: 10.1016/j.biopha.2018.02.103

[202] Zhang L, Chu J, Hao W, Zhang J, Li H, Yang C, et al. Gut microbiota and type 2 diabetes mellitus: Association, mechanism, and translational applications. Mediators of Inflammation. 2021;**2021**:5110276. DOI: 10.1155/2021/5110276

[203] Huang X, Yan D, Xu M, Li F, Ren M, Zhang J, et al. Interactive association of lipopolysaccharide and free fatty acid with the prevalence of type 2 diabetes: A community-based cross-sectional study. Journal of Diabetes Investigation. 2019;**10**(6):1438-1446. DOI: 10.1111/jdi.13056

[204] Gomes JMG, Costa JA, Alfenas RCG. Metabolic endotoxemia and diabetes mellitus: A systematic review. Metabolism. 2017;**68**:133-144. DOI: 10.1016/j.metabol.2016.12.009

[205] Matheus VA, Monteiro L, Oliveira RB, Maschio DA, Collares-Buzato CB. Butyrate reduces high-fat diet-induced metabolic alterations, hepatic steatosis and pancreatic beta cell and intestinal barrier dysfunctions in prediabetic mice. Experimental Biology and Medicine (Maywood NJ). 2017;**242**(12):1214-1226. DOI: 10.1177/1535370217708188

[206] Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One. 2010;**5**(2):e9085. DOI: 10.1371/journal.pone.0009085

[207] Endesfelder D, Engel M, Davis-Richardson AG, Ardissone AN, Achenbach P, Hummel S, et al. Towards a functional hypothesis relating anti-islet cell autoimmunity to the dietary impact on microbial communities and butyrate production. Microbiome. 2016;**4**:17. DOI: 10.1186/s40168-016-0163-4

[208] Murri M, Leiva I, Gomez-Zumaquero JM, Tinahones FJ, Cardona F, Soriguer F, et al. Gut microbiota in children with type 1 diabetes differs from that in healthy children: A case-control study. BMC Medicine. 2013;**11**:46. DOI: 10.1186/1741-7015-11-46

[209] Jandhyala SM, Madhulika A, Deepika G, Rao GV, Reddy DN, Subramanyam C, et al. Altered intestinal microbiota in patients with chronic pancreatitis: Implications in diabetes and metabolic abnormalities. Scientific Reports. 2017;**7**:43640. DOI: 10.1038/srep43640

[210] Remely M, Aumueller E, Merold C, Dworzak S, Hippe B, Zanner J, et al. Effects of short chain fatty acid producing bacteria on epigenetic regulation of FFAR3 in type 2 diabetes and obesity. Gene. 2014;**537**(1):85-92. DOI: 10.1016/j.gene.2013.11.081

[211] Gurung M, Li Z, You H, Rodrigues R, Jump DB, Morgun A, et al. Role of gut microbiota in type 2 diabetes pathophysiology. eBioMedicine. 2020;**51**:102590. DOI: 10.1016/j.ebiom.2019.11.051

[212] Ionescu R, Enache R, Cretoiu S, Bogdan G. Gut microbiome changes

in gestational diabetes. International Journal of Molecular Sciences. 2022;**23**:12839. DOI: 10.3390/ijms232112839

[213] Rahat-Rozenbloom S, Fernandes J, Cheng J, Wolever TMS. Acute increases in serum colonic short-chain fatty acids elicited by inulin do not increase GLP-1 or PYY responses but may reduce ghrelin in lean and overweight humans. European Journal of Clinical Nutrition. 2017;**71**(8):953-958. DOI: 10.1038/ejcn.2016.249

[214] Duran ALC, Medina MFD, Valdivieso MRA, Dunn MAE, Torres WPR, Barrera LNA, et al. Terapia incretinomimética: evidencia clínica de la eficacia de los agonistas del GLP-1R y sus efectos cardio-protectores. Revista Latinoamericana de Hipertensión. 2018;**13**(4):400-415

[215] Grasset E, Puel A, Charpentier J, Collet X, Christensen JE, Tercé F, et al. A specific gut microbiota dysbiosis of type 2 diabetic mice induces GLP-1 resistance through an enteric NO-dependent and gut-brain axis mechanism. Cell Metabolism. 2017;**25**(5):1075-90.e5. DOI: 10.1016/j.cmet.2017.04.013

[216] Perry RJ, Peng L, Barry NA, Cline GW, Zhang D, Cardone RL, et al. Acetate mediates a microbiome-brain-β-cell axis to promote metabolic syndrome. Nature. 2016;**534**(7606):213-217. DOI: 10.1038/nature18309

[217] Zhang S, Cai Y, Meng C, Ding X, Huang J, Luo X, et al. The role of the microbiome in diabetes mellitus. Diabetes Research and Clinical Practice. 2021;**172**:108645. DOI: 10.1016/j.diabres.2020.108645

[218] De Pessemier B, Grine L, Debaere M, Maes A, Paetzold B, Callewaert C. Gut-skin axis: Current Knowledge of the Interrelationship between Microbial Dysbiosis and Skin Conditions. Microorganisms. 2021;**9**(2):353. DOI: 10.3390/microorganisms9020353

[219] Ellis SR, Nguyen M, Vaughn AR, Notay M, Burney WA, Sandhu S, et al. The skin and gut microbiome and its role in common dermatologic conditions. Microorganisms. 2019;7(11):550. DOI: 10.3390/microorganisms7110550

[220] Coates M, Lee MJ, Norton D, MacLeod AS. The skin and intestinal microbiota and their specific innate immune systems. Frontiers in Immunology. 2019;**10**:2950. DOI: 10.3389/fimmu.2019.02950

[221] Nast A, Spuls PI, van der Kraaij G, Gisondi P, Paul C, Ormerod AD, et al. European S3-guideline on the systemic treatment of psoriasis vulgaris - update apremilast and secukinumab - EDF in cooperation with EADV and IPC. Journal of the European Academy of Dermatology and Venereology. 2017;**31**(12):1951-1963. DOI: 10.1111/jdv.14454

[222] Zhang X, Shi L, Sun T, Guo K, Geng S. Dysbiosis of gut microbiota and its correlation with dysregulation of cytokines in psoriasis patients. BMC Microbiology. 2021;**21**(1):78. DOI: 10.1186/s12866-021-02125-1

[223] Tan L, Zhao S, Zhu W, Wu L, Li J, Shen M, et al. The Akkermansia muciniphila is a gut microbiota signature in psoriasis. Experimental Dermatology. 2018;**27**(2):144-149. DOI: 10.1111/exd.13463

[224] Hidalgo-Cantabrana C, Gómez J, Delgado S, Requena-López S, Queiro-Silva R, Margolles A, et al. Gut microbiota dysbiosis in a cohort of

patients with psoriasis. British Journal of Dermatology. 2019;**181**(6):1287-1295. DOI: 10.1111/bjd.17931

[225] Scher JU, Ubeda C, Artacho A, Attur M, Isaac S, Reddy SM, et al. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. Arthritis & Rheumatology. 2015;**67**(1):128-139. DOI: 10.1002/art.38892

[226] West CE, Rydén P, Lundin D, Engstrand L, Tulic MK, Prescott SL. Gut microbiome and innate immune response patterns in IgE-associated eczema. Clinical and Experimental Allergy. 2015;**45**(9):1419-1429. DOI: 10.1111/cea.12566

[227] Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, Jenmalm MC. Low diversity of the gut microbiota in infants with atopic eczema. The Journal of Allergy and Clinical Immunology. 2012;**129**(2):434-40, 440.e1-2. DOI: 10.1016/j.jaci.2011.10.025

[228] Sator PG, Schmidt JB, Hönigsmann H. Comparison of epidermal hydration and skin surface lipids in healthy individuals and in patients with atopic dermatitis. Journal of the American Academy of Dermatology. 2003;**48**(3):352-358. DOI: 10.1067/mjd.2003.105

[229] Nylund L, Nermes M, Isolauri E, Salminen S, de Vos WM, Satokari R. Severity of atopic disease inversely correlates with intestinal microbiota diversity and butyrate-producing bacteria. Allergy. 2015;**70**(2):241-244. DOI: 10.1111/all.12549

[230] McCarthy S, Barrett M, Kirthi S, Pellanda P, Vlckova K, Tobin A-M, et al. Altered skin and gut microbiome in hidradenitis suppurativa. Journal of Investigative Dermatology. 2022;**142**(2):459-68.e15. DOI: 10.1016/j.jid.2021.05.036

[231] Kam S, Collard M, Lam J, Alani RM. Gut microbiome perturbations in patients with hidradenitis suppurativa: A case series. Journal of Investigative Dermatology. 2021;**141**(1):225-8.e2. DOI: 10.1016/j.jid.2020.04.017

[232] Lam SY, Radjabzadeh D, Eppinga H, Nossent YRA, van der Zee HH, Kraaij R, et al. A microbiome study to explore the gut-skin axis in hidradenitis suppurativa. Journal of Dermatological Science. 2021;**101**(3):218-220. DOI: 10.1016/j.jdermsci.2020.12.008