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REVIEW

The intestinal microbiota: its role in health and disease

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Abstract The intestinal microbiota (previously referred to as "intestinal flora") has entered the focus of research interest not only in microbiology but also in medicine. Huge progress has been made with respect to the analysis of composition and functions of the human microbiota. An "imbalance" of the microbiota, frequently also called a "dysbiosis," has been associated with different diseases in recent years. Crohn's disease and ulcerative colitis as two major forms of inflammatory bowel disease, irritable bowel syndrome (IBS) and some infectious intestinal diseases such as *Clostridium difficile* colitis feature a dysbiosis of the intestinal flora. Whereas this is somehow expected or less surprising, an imbalance of the microbiota or an enrichment of specific bacterial strains in the flora has been associated with an increasing number of other diseases such as diabetes, metabolic syndrome, non-alcoholic fatty liver disease or steatohepatitis and even psychiatric disorders such as depression or multiple sclerosis. It is important to understand the different aspects of potential contributions of the microbiota to pathophysiology of the mentioned diseases.

Conclusion: With the present manuscript, we aim to summarize the current knowledge and provide an overview of the different concepts on how bacteria contribute to health and disease in animal models and—more importantly—humans. In addition, it has to be borne in mind that we are only at the very beginning to understand the complex mechanisms of host-microbial interactions.

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Introduction

The normal microbiota of humans consists of a few eukaryotic fungi, viruses, and some archaea that colonize the lower intestinal tract [68, 79]. By far, the most prominent component of the normal microbiota, however, is bacteria [148, 154]. They are the most numerous and obvious microbial components of the normal flora. Up to 100 trillion (10^{14}) microorganisms [166] per human colonize the intestinal tract making about 2 kg of the body weight. They represent at least 300–1000 different species [57, 166].

Interestingly, at present, no one is able to exactly determine how many bacterial species might really be represented in an intestinal microbiota probe. This is dependent on the mathematical algorithm used for the analysis and the cutoff for similarity of the 16S RNA sequence (usually 97 % sequence identity is chosen to demarcate different "species" and define a so-called operational taxonomic unit (OTU) [117]) [124]. However, the knowledge on microbial composition has greatly increased with the use of culture-independent analysis methods. Culture-dependent methods in the past have been hampered by the fact that the majority of bacterial species cannot be cultured under aerobic conditions. Anaerobic conditions are hard/impossible to maintain. Only a short contact with oxygen may kill several species thereby leading to conditions that further decrease vitality of other species. Thus, culture methods are not suited to really give us an overview over the complete intestinal flora of a human individual.

Culture-independent methods mainly employ variations in genes that are common in all bacteria with, however, species-

specific differences, such as 16S RNA [46, 161, 167, 168]. While these culture-independent methods such as restriction fragment length polymorphism (RFLP) analysis or pyro-sequencing have enabled a more in-depth study of the microbial composition in the human intestine with higher precision, little is known how the complex composition is modulated and how environmental factors such as nutrition, medication use, way of life, toxins, and other exogenic factors such as smoking might change the balance between different microbial species [26, 201]. Besides environmental influences, there are other influences on the composition of the intestinal microbiota. Among those are genetic influences. There is obviously an adaptation between the genetic structure of the host and the genetic composition of the bacteria [11, 80, 137, 153, 197]. Based on the genetic background, metabolites are synthesized by the bacteria as well as the host [195]. Those metabolites will cross-react and influence each other [195], indicating that the metabolic activity of host and commensal bacteria also needs to be in a tight balance. An extremely rare though nevertheless impressive illustration of host-microbial metabolic interaction is the so-called gut fermentation syndrome (auto-brewery syndrome), where an overgrowth with specific microbes may induce considerable and clinically relevant ethanol blood levels in the absence of any alcohol intake [36]. Another aspect that influences the bacterial composition is the age of the host, the gender, the area of living, the amount of stress perceived, the extent of regular physical exercise, the climate, and other influences that have been mentioned before [120, 213].

Bacteria select their environment

It is well known that bacteria have environmental preferences and that certain bacteria only colonize certain areas of the body [66, 131, 214]. This may be due to an interaction with surface molecules on the respective tissue cells. Table 1 gives a list of specific bacterial strains and their preferred tissue of adherence.

It was well established from disease description, which was then further analyzed by molecular methods, that for example *Corynebacterium diphteriae* mainly colonizes the throat epithelium [125]. This is the reason why diphtheria as a disease is mainly a throat disease. On the other hand, *Neisseria gonnorhoeae* mainly colonizes the urogenital epithelium and this is the reason why this is a veneric disease [204]. Contrastingly, there are bacterial species such as *Vibrio cholerae*, the bacterium causing cholera disease, that mainly colonize the small intestinal epithelium. *Staphylococcus aureus* has a preference for the nasal membranes and *Staphylococcus epidermidis* for the skin.

Bacteria have found their ecological niche in the human body and have selected attachment molecules where they have an advantage above other bacteria [39, 62, 112]. For some of the bacterial species, both the bacterial ligands for attachment at the host cell or tissue receptor have been identified [16, 141, 184]. This is illustrated in Table 2.

Streptococcus pyogenes uses its protein F to bind to the amino terminus of fibronectin which is largely expressed on the pharyngeal epithelium [191]. *Neisseria gonorrhoeae* has N-methylhenyl-alanine pili that bind to glucosamine-galactose carbohydrate residues on proteins mainly in the urethral and cervical epithelium. *Escherichia coli* has type 1 fimbriae that bind certain carbohydrates on either the intestinal epithelium or the urethral epithelium [4, 12, 30, 211]. Their binding sites are to some extend carbohydrate specific [4, 12, 30, 211].

Certainly, there are many more bacterial ligands from bacteria that are harder to culture. Protein expression of bacterial species that cannot be cultured obviously cannot be investigated. So far, we only have cDNA sequences from those bacteria. As there is no knowledge on protein composition of the bacterial wall of those bacteria species, the host cell receptor or tissue receptor cannot be identified. Most of those bacteria live in the intestinal lumen or are attached to the intestinal epithelial cells.

In general, the forms of bacterial colonization are either mutualistic, commensalistic, or opportunistic [178]. *Mutualism* means that both organisms benefit from the coexistence. Most of the intestinal bacteria therefore are not commensalistic (despite the fact that they are called commensals) but mutualistic, because both, the bacteria and the human organism, benefit from their existence [11]. In a *commensalistic* situation, one organism benefits and the other is neither helped nor harmed. If our intestinal bacteria would be commensalistic, this would mean that they profit but the human body has no profit. In most scenarios and situations, this is not the case: The relationship between colonizing bacteria and the human body most frequently is a mutualistic one. *Opportunistic* would mean that under normal conditions, the microbe does not cause disease but if conditions become conductive, it can cause disease. Opportunistic infections can

Table 1 Tissue preferences of some well-known bacteria

Bacteria	Tissue preference
Staphylococcus epidermidis	Skin
Staphylococcus aureus	Nasal membranes
Streptococcus salivarius	Mouth, tongue
Corynebacterium diphtheriae	Throat
Vibrio cholerae	Small intestinal epithelium
Escherichia coli	Small intestinal epithelium
Neisseria gonorrhoeae	Urogenital epithelium

Table 2 Bacterial ligands and interacting host proteins (examples)

Bacterium	Bacterial ligand for attachment	Host cell or tissue receptor	Attachment site
Streptococcus pyogenes	Protein F	Amino terminus of fibronectin	Pharyngeal epithelial cells
Streptococcus salivarius	Lipoteichoic acid	Unknown	Tongue epithelial cells
Streptococcus pneumoniae	Cell-bound protein	N-acetylhexosamine-galactose disaccharide	Mucosal epithelium
Staphylococcus aureus	Cell-bound protein	Amino terminus of fibronectin	Mucosal epithelium
Neisseria gonorrhoeae	N-methylphenyl-alanine pili	Glucosamine-galactose carbohydrate	Urethral/cervical epithelium
Enterotoxic *E. coli*	Type 1 fimbriae	Species-specific carbohydrate(s) (e.g., mannose)	Intestinal epithelium
Uropathogenic *E. coli*	Type 1 fimbriae, P-pili (pap)	Complex carbohydrate, Globobiose linked to ceramide lipid	Urethral epithelial cells and upper urinary tract
Bordetella pertussis	Fimbriae ("filamentous hemagglutinin")	Galactose on sulfated glycolipids	Respiratory epithelium
Vibrio cholerae	N-methylphenylalanine pili	Fucose and mannose carbohydrate	Intestinal epithelium

be induced by *Staphylococcus aureus* and others that usually only become infectious when they enter the body whereas there is no problem with colonization on the skin or even in the intestine.

Why do we have bacterial colonization in the intestine?

The number of bacteria found throughout the gastrointestinal tract differs from the esophagus to the rectum (Fig. 1). Whereas the number of bacteria in the esophagus and the stomach is low with 10^1 to 10^3 bacteria per milliliter, already in the upper small intestine the number of bacteria clearly increases. Per gram of small intestinal content, the number of bacteria is 10^3 to 10^4, which is still low. However, there is a steady increase of bacterial concentration toward the lower small intestine. In the ileum and in the terminal ileum, there are 10^8 to 10^9 bacteria per gram content. Finally, in the colon, there are 10^{12} to 10^{14} bacteria per gram of feces (Fig. 1).

Those bacteria should not enter the body and there are several mechanisms to protect body integrity and to form a barrier against invasion of bacteria. First of all, the epithelium of the intestinal mucosa forms a monolayer with intercellular contacts that inhibit the passage of bacterial products and potential antigens through this monolayer barrier. Nevertheless, this barrier becomes leaky and single cells are extruded as shown by Alistair Watson and co-workers, causing hole-like structures in the intestinal barrier which therefore is not completely mechanically tight [121, 205, 206].

To maintain barrier integrity, several other mechanisms are necessary [60, 136, 146, 193] (Table 3). One is gut motility which prevents the long-term interaction between certain bacteria and small mucosal areas. A further important mechanism is the secretion of mucins by goblet cells as well as chloride secretion. Also, defensins are very effective in preventing the invasion of bacteria into the mucosa [207]. Defensins are like human antibiotics that can kill bacteria due to partial destruction of the cell wall. The mucin layer that is above the mechanical barrier of the epithelial cells usually contains defensins bound to the mucin structure. This mucin layer above the brush or the membrane of the epithelial cells usually is almost sterile; no bacteria are found close to the epithelial cells. However, this mucus is colonized in chronic intestinal inflammation such as Crohn's disease or ulcerative colitis [42, 185–187] (Fig. 2). Furthermore, there is a competition between different bacterial strains at the mucosal surface. Usually, mucus-layer-attached bacteria are more host-friendly as luminal bacteria. A decreasing number of those beneficial bacteria may induce growth, adhesion, and invasion of pathogenic bacteria. This is the reason why *Clostridium difficile* usually only can induce colitis when the number of beneficial bacteria is diminished by antibiotic treatment.

If the potential migration and translocation of bacteria across the intestinal barrier is such a big problem for the human body, why is the intestinal lumen colonized with bacteria at all? The normal flora synthesizes and excretes vitamins in excess of their own needs and contributes to vitamin delivery to the human body [80]. Among those vitamins are vitamin K, vitamin B12, and other B vitamins (see Table 4). The normal flora also prevents the colonization by pathogens. This is facilitated by competition for attachment sites or by a competition for essential nutrients. For example, important insights have been derived from *Salmonella* studies that clearly show that *Salmonella* is not very infective in a mouse that has a colon colonized with normal commensal bacteria [15]. Only when the number of bacteria is decreased

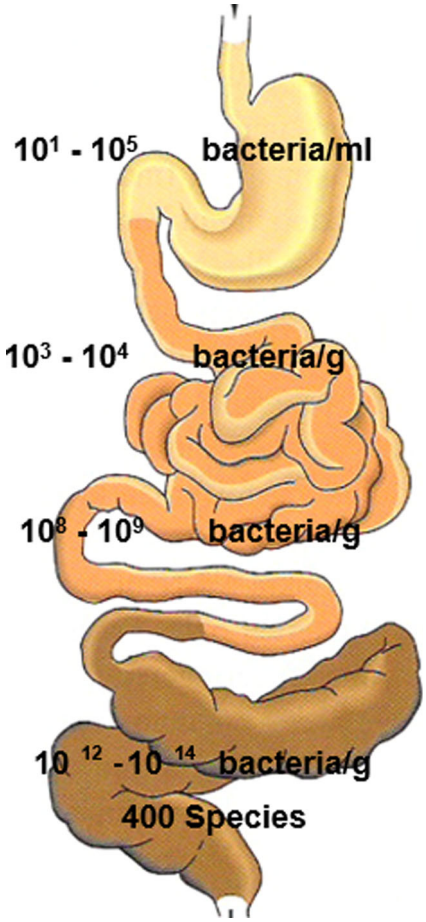

Fig. 1 Numbers of bacteria per segment of the GI tract in healthy individuals

by antibiotic treatment or in germ-free animals that *Salmonella* can already cause disease in very low numbers [15, 71, 182].

In addition, the intestinal bacteria produce a variety of substances ranging from peroxides to highly specific other metabolic products that support epithelial growth and metabolism. Without bacterial colonization, some of the digestive enzymes would not be induced sufficiently. In various animal experiments, Jeff Gordon's group has shown that the colonization with bacteria dramatically induces genes in the epithelial cells which are mandatory for physiological digestive process [81].

Table 3 Mechanisms for maintenance of intestinal barrier integrity

- Gut motility
- Chloride secretion
- Cell-cell contacts
- Secretion of mucin by goblet cells
- Defensin and cytokine production
- Luminal microbiota (products of bacterial metabolism, mutualistic bacteria)

Furthermore, the normal flora stimulates the development of the adaptive immune system[30] and the lymphatic tissue, for example, the Peyer's patches in the GI tract [13, 14]. The cecum of germ-free mice is enlarged and thin walled and the lymphatic structures are underdeveloped. Functioning lymphatic structures, however, are important during intestinal infections. Furthermore, the normal microbiota stimulates the production of cross-reactive antibodies (mainly IgA) which are secreted into the gut lumen [210]. As those antibodies are cross-reactive, they also prevent from bacterial infections. Moreover, microbial products may harbor a direct immune-regulatory potential, as for instance shown with polysaccharide A (PSA) produced by *Bacteroides fragilis* (a ubiquitous and mutualistic organism in the gut) that may modulate and correct systemic T cell deficiencies and TH1/TH2 imbalance [126] as well as T helper cell subsets and potentially other immune cell populations. Thus, the normal flora induces a protective mechanism for preventing infections of the GI tract.

Is there a specific role of the bacterial flora in childhood?

The gut is colonized by bacteria during the first hours of life. This colonization induces gene expression and subsequent functions on the intestinal mucosa that are important for digestions and nutrition [10, 80, 85]. Intestinal angiogenesis may also be regulated by the gut microbiota [181] indicating that the microbiota has also a role in local micro- and macrocirculation.

In addition, the human intestinal flora has an important role in shaping the immune system [108]. It profoundly influences the formation of lymphatic structures and the differentiation of lymphocytes [63].

The interaction of intestinal microbiota with the immune system may further be important in the prevention of allergic and atopic diseases. In children with atopic disease, again, an "imbalance" of the intestinal flora has been described [27, 144]. Interestingly, children with the presence of eczema had an even more diverse intestinal flora as compared to control subjects [133]. Children with eczema in this analysis had an increased abundance of the *Clostridium* clusters IV and XIVa, which are typically abundant in adults [133]. Again, it is unclear whether these finding are only associated with the disease or in any causal relationship. On the other hand, risk genes identified for atopic diseases include a number of genes relevant for the barrier function of the skin, again indicating a role for bacteria [58]. The skin microbiome is altered at least during acute exacerbations of the disease [98]. Whereas, indeed, the majority of studies point to an association between microbiota and especially the gut microbial composition and atopic diseases, no specific harmful or protective microbes could be identified so far [145].

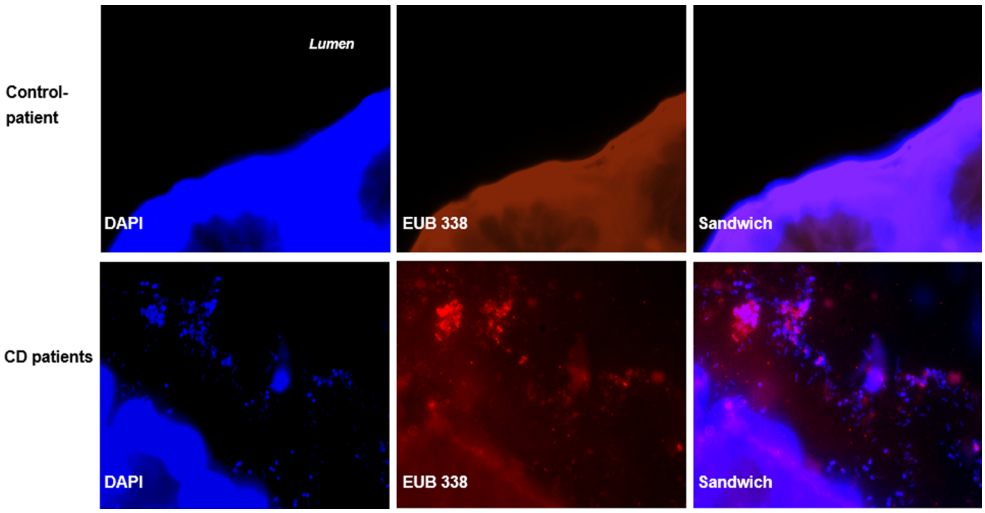

Fig. 2 Colonization of the mucus barrier above the intestinal epithelial cells in health subjects and patients with CD. DAPI stains DNA, EUB338 is a pan-bacterial marker. The *sandwich picture* shows the colonization of the CD patient's mucus layer by living bacteria

A direct epidemiological link between the exposure to microorganisms (which are assumed to influence mutualistic microbial composition and immune system development in the host) in early childhood and prevalence of chronic immune-related disorders is suggested by the hygiene hypothesis [9]. This inverse correlation between exposure to microbes and infectious diseases in childhood has for instance been shown with the occurrence of inflammatory bowel disease and is one of the most prominent explanations for the increasing incidence in recent years [64, 149].

Which diseases are associated with changes of the bacterial flora?

There is a growing list of non-infectious diseases that have been associated with the composition of the bacterial flora. Among them are chronic inflammatory bowel diseases, namely Crohn's disease and ulcerative colitis, metabolic syndrome, non-alcoholic steatohepatitis, irritable bowel syndrome, atherosclerosis, rheumatoid arthritis, and colorectal carcinoma. Interestingly, shifts in intestinal microbial composition have also increasingly been described in lifestyle factors, not only in disease states, such as for instance an increased gut microbial diversity associated to heavy exercise (professional rugby players) [34]. It appears plausible that this list of environmental factors having an impact on microbial composition will grow in the next years.

Table 4 Positive effects of bacterial colonization of the intestine

- Synthesis and excretion of supplementary vitamins, e.g., vitamin K and vitamin B12 (the amount of this supplementary "intake" derived by microbial production, however, is not sufficient to cover the necessary total amount)
- Prevention of colonization by pathogens by competition for attachment or nutrients
- Metabolomic activities (production of growth factors for epithelial cells, secretion of peroxides or bacteriocidins to inhibit other bacteria)
- Stimulation of the development of lymphoid structures (Peyer's patches) and T cell differentiation, correction of T cell imbalances
- Induction of production of cross-reactive antibodies (IgA, secreted into the gut lumen).

Inflammatory bowel disease

The two most frequent and clinically most important forms of inflammatory bowel diseases (IBDs) are Crohn's disease and ulcerative colitis [75, 169]. They are chronic relapsing intestinal inflammations. More than 160 genetic factors (single-nucleotide polymorphisms, SNPs, in more than 160 genes are associated with an increased odds ratio to develop the disease) contribute to an increased risk to develop both diseases [90, 109]. However, these genetic risk factors are not disease specific [109]. The individual odds ratio of several genetic risk factors is low and there is clear evidence that environmental factors must contribute to the onset of both inflammatory diseases [158, 169]. Moreover, while the genetic pool largely remained stable within the last decades, incidence and prevalence have shown an impressive increase in the majority of epidemiologic studies all over the world and even more pronounced in threshold countries [127], further indicating a prominent role of environmental factors.

IBDs are multifactorial diseases but there definitely is an important role for bacteria. "Dysbiosis" has been detected in both diseases that is most pronounced when the inflammation is active. Alterations and changes of the predominant species of the fecal bacteria in the colon of IBD patients have been demonstrated by many groups [55, 92, 119, 151, 173, 183]. While some of the alterations observed may even be conflicting between studies, there are certain distinctive changes that have been reproduced in the scientific literature. For instance,

a decrease of *Faecalibacterium prausnitzii* and butyrate-producing *Roseburia hominis* is clearly associated with Crohn's disease (CD) [19, 73, 89, 119] and has interestingly also been found in healthy relatives of CD patients [73]. Usually, the changes are summarized in a reduction of "diversity" [52, 92, 128, 139]. A more "diverse" flora usually is regarded to be beneficial; subsequently, OTUs are statistically analyzed by "diversity indices"; however, in fact, we have no clue so far what this could mean on a functional level.

In addition, there is a reduced expression and biochemical changes of mucins in the colon of Crohn's disease and ulcerative colitis patients [6, 18, 96]. Important studies demonstrated a reduced production of defensins (antimicrobial peptides that are mainly secreted by Paneth cells) [7, 32, 97, 138, 171] and some authors such as Fellermann, Wehkamp, Stange, and colleagues have called Crohn's disease a "defensin deficiency disease" [61, 86, 208].

Fecal microbiota transplantation, as an attempt to radically address disturbed microbial composition and diversity, is discussed controversially in these diseases. While some authors and small case reports/series reported a clear benefit, others could not find a beneficial effect and even saw adverse events in IBD patients such as fever or diarrhea [5, 41, 103].

Most of the genetic risk factors for IBD are layers in the innate immune system that is responsible for the acute defense against invading bacteria [109, 110]. Among those risk genes are pattern recognition receptors such as *NOD2*, *TLR4*, *CARD8*, *CARD9*, or *NLRP3* as well as autophagy genes such as *ATG16L1*, *IRGM*, and *LRRK2* which destroy bacteria when they have entered the epithelial cells in the process called autophagy. Further, risk factors for Crohn's disease can be found in the antibacterial response as for example in the defensin system (see above). Also, elements that are responsible for the maintenance of the epithelial barrier integrity (*IBD5*, *DLG5*, *PDGER4*, *DMBT1*, and *XBP1*) have been identified. In addition, there are aspects that mainly orchestrate the adaptive immune system, but they may be secondary to those defects in the innate immune response.

Interestingly, a number of the components that have been identified to be genetic risk factors in IBD also were found in other diseases such as systemic lupus erythematosus (*PTPN22*), ankylosing spondylitis (*ERAP2*), psoriasis (*PTPN22*), asthma (*IBD5*), type 2 diabetes (*GCKR*), coeliac disease (*PTPN2*), type 1 diabetes (*PTPN22*), leprosy (*NOD2*), rheumatoid arthritis (*PTPN22*), and multiple sclerosis (*PTGER4*, *STAT3*). This may indicate a link between those diseases and the intestinal microbiota [109, 110]. For instance, the critical role of *NOD2* on intestinal microbial composition was revealed in a *NOD2*-deficient mouse model, where microbial alterations were found already at an early weaning stage [153].

In 2010, we could show that indeed an increased amount of the bacterial wall compound LPS can be found inside the lamina propria of Crohn's disease patients that carry the *NOD2* variants in their mucosa [100]. *NOD2* variants also are responsible for increased risk to suffer from severe intestinal graft versus host disease after stem cell transplantation [70, 76–78, 102, 105, 159]. This further indicates that the bacteria and the bacterial invasion are crucial in the onset of mucosal inflammation. Further, evidence comes from the finding that antibacterial therapy by antibiotics might decrease the risk for intestinal inflammation [94].

Irritable bowel syndrome

The potential role of the intestinal microbiota in the pathogenesis of IBS has come into the focus of attention only in recent years. One of the reasons for this relatively long deferment might be based on the very nature of the "functional" fundament of the definition of IBS [132], rather precluding a well definable and identifiable anatomical or physiological alteration. However, at the very latest with the large double-blind randomized-controlled trial from Pimentel and colleagues using rifaximine, a non-absorbable derivate of rifamycine, a critical role of the gut microbiota in IBS was suggested by the main finding of the study. Significantly, more patients in the verum group reached the primary end point, i.e., the proportion of patients with a relief of global IBS symptoms [147]. Several years ago, one of the first studies characterizing microbial composition in patients with IBS from Finland found significant differences in the microbial composition of IBS patients, including several distinctive alterations on the level of genera, such as for instance *Coprococcus*, *Collinsella*, and *Coprobacillus* [93]. Further studies confirmed variations of microbial alterations in IBS patients compared to controls [29, 35, 150, 156], also observable in childhood IBS [165] suggesting—besides a new therapeutic target—also a diagnostic potential of distinctive microbial fingerprints to accurately identify IBS and differentiate this condition from other gastrointestinal diseases [150].

Colorectal cancer

The intestinal microbiota also seems to play an important role for the development of colorectal cancer (CRC). A recent, excellent review highlighted the insights we have on the role of the intestinal microbiota in CRC so far [84]. Components of the intestinal bacterial flora are thought to generate "genotoxic stress to promote genetic and epigenetic alterations" in the intestinal epithelial cells finally leading to cancer [84, 172]. Distinctive alterations in colorectal cancer microbiota composition, such as an increase of *Fusobacterium* sequences, have been described [101], although in these descriptive studies of microbial composition, the issue of either primary causative

event or secondary phenomenon cannot be resolved. However, animal models appear to be an important means of elucidating this question. For instance, dysbiosis induced by *NOD2* deficiency in mice resulted in an increased predisposition to colitis-associated dysplasia and cancer [40].

In an animal model of colorectal cancer, Jobin and coworkers provided evidence that mono-colonization with the commensal *Escherichia coli NC101* promoted invasive CRC [88]. They further identified specific genes of this bacterium that are involved in the promotion of CRC: The deletion of a so-called "genotoxic island" from the DNA of this *Escherichia coli* strain NC101 decreased tumor multiplicity and invasion in the mouse model [8].

Other types of cancer

The impact of the microbiome on the development of liver cancer may be either direct or indirect. An indirect pathway would primarily contribute to metabolic syndrome and NASH (see below). The translocation of bacterial products across the intestinal barrier into the portal vein blood that contribute to senescence of stellate cells could be a direct contribution [174]. However, in liver cancer, deconstructing the distinctive pathogenetic role of the microbiota remains challenging, as obesity per se increases the risk for several cancers [157], including those of the liver.

Polymorphisms in the *NOD2* gene which is a pattern recognition receptor and the first identified and long-known susceptibility factor for CD have been shown to be associated with an increased risk for a number of different cancers besides CRC [118] (for a meta-analysis, see [114], for a review, [25]). Among them is gastric cancer [203], but also urothelial cancer [69] or breast cancer [83]. On the other hand, there are studies that could not confirm this association [104, 194] making these findings somewhat disputable.

The gut microbiota may help to shape the immunological anti-cancer response as some anti-cancer therapies seem to lose efficacy in germ-free animals [198].

Metabolic syndrome

Whereas it might be obvious that bacteria can contribute to intestinal inflammation such as IBD, it seems to be a little bit more surprising that the microbiota also has been associated to metabolic diseases such as diabetes [1, 3, 22, 23, 47, 50, 56, 72, 209], metabolic syndrome [31, 189, 199], or non-alcoholic steatohepatitis [74, 212]. There is a worldwide pandemia of obesity and recent data show that 69 % of the US adults above 20 years are overweight or obese (Central for Disease Control; *www.cdc.gov*). In general, in those patients, an increase in *Firmicutes* and *Actinobacteria* is found and a decrease in *Bacteroidetes* which is paralleled in human and mice [91, 111, 192].

Interestingly, the obese phenotype has shown to be transmissible via the fecal microbiota [113, 155, 192]. A microbiota extracted from obese mice and transferred to lean mice was followed by a significant weight gain in the lean mice. Unfortunately, it does not work in the opposite direction [155, 192]. Microbiota from lean mice does not cause a weight loss in obese mice. Nevertheless, the modification of the gut microbiota is already discussed as a future treatment strategy for obesity. At present, we cannot tell whether this is just hype or whether it will be a promise for the future. Preliminary data from a smaller trial in humans, rather focusing on insulin resistance than body weight, suggested, however, only a very modest effect [200].

There are distinctive changes in the composition of the major phyla. Phylum refers to a taxonomic rank in biology below the rank kingdom including *Archaebacteria* and *Eubacteria* from the domain *Bacteria*. Regarding phyla, there is an increase in energy extraction in *Firmicutes*-rich gut microbiota [192]. However, the relationship is most likely more complex than just an increased *Firmicutes*-to-*Bacteroidetes* ratio. No correlation to abundance of major phyla in structured weight loss programs in humans has been described [164]. On the other hand, the success in weight loss is higher in individuals that are rich in *Bacteroides fragilis*, *Lactobacilli*, and *Bifidobacteria*.

To date, knowledge on the mechanisms and host-microbial interactions behind a weight gain is sparse. Potential proposed explanations include an influence of intestinal bacteria and archaea on the expression of genes involved in energy metabolism [81]: There is a transcriptional response of epithelial genes upon bacterial colonization. When the altered genes are more closely looked at that are increased upon bacterial colonization, they are responsible for nutrient absorption, mucosal barrier fortification, xenobiotic metabolism, angiogenesis, and intestinal maturation. In addition, bacteria may mediate hormonal changes modulating satiety and energy harvest (such as for instance via G protein receptors) [106] or induce a chronic inflammatory state [28, 65, 82].

Rheumatic diseases

There is increasing evidence that the bacterial flora also may contribute to the onset of rheumatic diseases [24]. As mentioned before, IBD and rheumatic diseases share common risk loci such as *PTPN2* or *PTPN22* [107]. Similar to what has been described for IBD, an interaction between genetic and environmental risk factors seems to be pathophysiologically relevant in rheumatic diseases [170]. Similar to other diseases, distinctive intestinal microbial alterations in patients with rheumatoid arthritis compared to healthy humans have been

described, such as a lower abundance of *Bifidobacteria* and bacteria of the *Bacteroides-Porphyromonas-Prevotella* group, *Bacteroides fragilis* subgroup, and *Eubacterium rectale–Clostridium coccoides* group [196].

Allergies and atopic diseases

The microbiota composition of children with atopic diseases has been found to be altered as compared to controls (for details see above). The "training" of the intestinal immune system by gut bacteria appears as an important step in the development of immune reactions during childhood. As previously mentioned, there are, however, no definite microbial taxa associated with the occurrence of distinctive allergic diseases. In a randomized trial of oral supplementation of a bacterial lysate (between week 5 and end of month 7), infant colonization with clostridia was shown with an increased risk of developing atopic dermatitis in the subsequent 6 months [142]. However, currently, no specific taxonomic microbial members are consistently found to be a risk factor for allergic diseases, having older siblings and mode of delivery, both factors having clearly shown to influence intestinal microbial composition and appear to modulate atopy risk [143]. This represents an indirect proof for the importance of microbial composition in the pathogenesis of atopy.

Heart disease

A recent review highlighted the important role the intestinal microbiota might have for the development of various heart diseases [160]. Patients with inflammatory bowel diseases appear to have a higher risk—interestingly above all in women—for coronary heart disease and cerebrovascular events [177] despite a lower prevalence of "classical" risk factors, indicating additional links between the gut and the cardiovascular system. An impaired intestinal barrier function followed by bacterial translocation and presence of bacterial products in the circulation may contribute to atherosclerosis and chronic heart failure (CHF) as recent data indicate [160]. This association is further suggested by an interesting study investigating microbial composition in atherosclerotic plaques that showed a clear correlation to the microbial composition of the hosts' oral cavity [99].

Psychiatric disorders

An alternation of the composition of the human microbiota has been found in a mouse model of depression [140] as well as in patients with depressive symptoms [51, 130]. However, it has to be kept in mind that depression is associated with a number of changes in behavior such as food consumption, diet, and physical activity that may influence the composition of the gut microbiota.

Changes of the gut flora furthermore have been found in mouse models [45] as well as patients with autism [44, 115, 202]. Also, stress perception may have a significant influence on human microbiota [135].

It is too early to interpret these findings. They may, however, open a sight on diseases that seemed to have no connection to intestinal functions.

Possibly the most robust evidence for a brain modulating capacity of the intestinal microbial composition in humans so far comes from a randomized trial of *Bifidobacteria* supplementation, where significant changes in task performances and activity in brain regions important for the procession of emotion and sensation were observed in correlation to shifts in intestinal microbial composition in those women receiving the verum preparation [190].

What environmental factors drive the composition of the microbiota?

Nutrition certainly is responsible for some aspects of microbiota composition [2, 43, 59, 123, 148, 162, 163, 176, 215]. Individuals that change their living conditions also change the microbial composition of the intestinal flora. For example, the change from a mixed diet to a vegetarian diet causes changes in the microbial flora [95]. Moreover, the intestinal microbiota appears to only to be associated with Kwashiorkor (a disease state of severe malnutrition)—rather, transplant experiments using mouse models suggest a direct pathogenetic and causative role of microbial composition, as the phenotype appeared to be inducible by transplantation [179]. Antibiotic treatment has also been shown to induce alterations on microbial composition [48, 49, 87]. The sustainability of this effect is not fully understood. However, as the induced disturbances have been shown to increase the risk in children to develop IBD years or even decades after intake [175, 188], it appears plausible to consider long-term (potentially lifetime) shifting. Aside from these rather intuitively plausible modulating factors, other influences on microbial composition, where the causative link appears more obscure, have been identified, such as physical activity [34] or excessive alcohol use [129].

Interestingly, the microbial composition of the gut has been shown to be different in the elderly [33, 122]. So far, it remains to be established whether these differences in composition and temporal stability are directly linked to differences of the physiology in the elderly or rather a sort of summation effect from modulating factors (including environmental) during the whole human life span.

On the other hand, there are influences that only recently have been recognized. While in utero the entire organism is

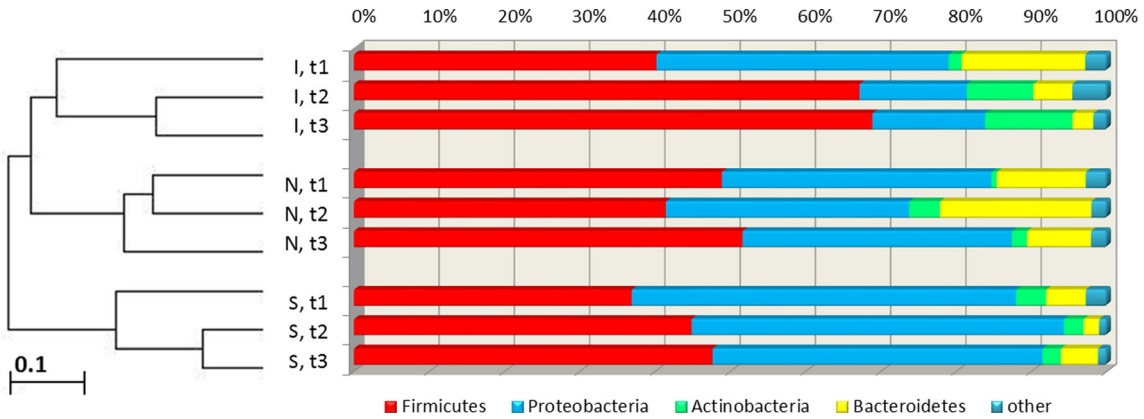

Fig. 3 Intestinal microbial composition (major phyla of the gut microbiota) 1 week before (*t1*) as well as 4 (*t2*) and 8 weeks (*t3*) after smoking cessation in the intervention group (*I*) compared to the non-smoking (*N*) and smoking (*S*) control groups with the same intervals but without abrupt change in smoking habits. Percentages of major phyla are shown for the three time points. A significant increase in fractions of *Firmicutes* and *Actinobacteria* and a decrease in fractions of *Proteobacteria* and *Bacteroidetes* can be observed in the intervention group with a stable composition in the control groups. On the *left*, a phylogenetic tree is shown, to illustrate the earlier separation of the samples in the intervention group prior and after smoking cessation, i.e., closer to the root of the tree

sterile, initial colonization of the newborn with microorganisms does not occur after birth as often incorrectly assumed but indeed during the very process of passage through the vaginal birth canal [53], a distinctive ecosystem with its own evolutionary history toward its current microbial composition dominated by *Lactobacillus* and *Prevotella* spp. [54, 152]. Thus, delivery mode, i.e., conventional vaginal birth (VB) versus Cesarean section (C-section), has a key impact on primal intestinal bacterial colonization and thus composition of the pioneer human intestinal microbiota [20, 54, 67].

It always has been reported that there is an average weight gain after smoking cessation of 7–8 kg [134]. Usually, it has been attributed to an increased food intake as an oral substitution for the smoking. However, data from one of the largest population-based primary prevention trial on this topic, the Multiple Risk Factor Intervention Trial, revealed that successful quitters gained weight despite the fact that they consumed less calories and had a healthier diet compared to the continuous smokers or recidivists, who did not gain weight [180].

Interestingly, smoking also has detrimental effects in Crohn's disease, whereas in ulcerative colitis, smoking seems to be protective [17, 37, 38, 116]. There is a low incidence of ulcerative colitis especially early onset forms in smokers and a more severe disease course may appear after smoking cessation. Subsequently, we were interested in studying the composition of the intestinal microbiota upon smoking cessation. Thus, we performed a study in 10 healthy smoking subjects and a control group of 10 subjects that continued smoking or were non-smokers [21]. The observational period was 9 weeks, including five study visits to collect stool samples. An intensive counseling by physicians and psychologists was performed. Food diary controlled the food intake and strict adherence to smoking cessation was verified by carbon monoxide exhalation monitoring. Interestingly, using different microbial approaches to investigate microbial composition and quantify specific strains, including 454-pyrosequencing and fluorescence in situ hybridization, we found significant shifts of microbial composition from phyla to genera in the intervention group after smoking cessation (Fig. 3). In the intervention group, there was a significant increase of *Firmicutes* and *Actinobacteria* whereas there was a decrease of *Proteobacteria* and *Baceroidetes*. In contrast, in the two control groups, there was a stable microbial composition. This increase in *Firmicutes* and *Actinobacteria* was associated with the weight gain despite a stable intake of calories in those subjects undergoing smoking cessation [21].

Summary

We have only started to understand the importance and the impact of our microbiota for health and disease. Many diseases have been associated with an imbalance or dysbiosis of the microbial composition such as IBD, rheumatoid diseases, atopic diseases, cancer, metabolic syndrome, and even psychiatric disease. So far, these findings are descriptive. A deeper understanding of the interactions will be necessary to finally come to new therapeutics to treat those chronic diseases. A promising hint that this may indeed be possible in the future is the clinical success of FMT (a radical, though very unspecific, approach) for recurrent *Clostridium difficile* colitis. For obvious reasons, other diseases will require more specific approaches. It will be important to neither raise exaggerated expectations nor make unbalanced or enthusiastic promises at present. We should bear in mind that we still need to further carefully elucidate the mechanisms by which the bacterial flora contributes to health and disease and learn how this knowledge must may be translated to overcome various

obstacles still present in the creation of targeted microbial treatment approaches for the multitude of human diseases associated with altered microbial composition. Otherwise, the hype about the microbiota will soon be over and we will have missed an important chance.

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