Best Practice & Research Clinical Gastroenterology xxx (2017) 1–7

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

journal homepage: https://ees.elsevier.com/ybega/default.asp

Diet, microbiome, and colorectal cancer

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ARTICLE INFO

Article history:
Received 28 July 2017
Accepted 3 September 2017

Keywords:
Microbiome
CRC
Diet

ABSTRACT

The scientific interests in the colorectal cancer (CRC) associated microbiome have increased significantly in the past decade. Mechanistically, several members of the human microbiome and products thereof have been implicated as inductors of the pathogenic inflammation related to CRC. Conversely, the activities of the human intestinal microbial community influenced by specific diet might confer a protective effect against the CRC risks and progression. As the microbiome is both a key contributor and one of the tools to prevent CRC, the current review gives a summary of the CRC-associated microbiome and the dietary strategies relevant to CRC. As more evidences become available, new microbiome-based treatments and specific diets may emerge to reduce the CRC risk and improve CRC patients' quality of life.

1. Introduction

Cancer remains one of the major challenges facing human health care. The intense research efforts of the last three decades have resulted in profound insight into the molecular basis of oncological disease, and have spawned a bewildering number of novel treatment modalities. In some cases, there have been spectacular successes, where previously untreatable cancers associated with rapid mortality have become manageable, with notable examples including gastrointestinal stromal tumors [1]. However, transformative therapies are not the norm. In general, many new forms of treatment appear only useful in a subset of patients, are prone to side effects, and provide only a limited benefit in terms of enhanced survival, while simultaneously being associated with very substantial reduction in the quality of life. The duty is increasingly clear to manifest our ability to efficiently stratify patients so that they receive the most effective therapeutics, and experience the greatest benefits in quality of life. Studies on the entire set of bacteria and fungi colonizing the human gut (microbiome and mycobiome) will be instrumental to provide evidence-based solutions of these serious concerns. Microbiome has recently emerged as an important regulator of many critical processes relevant to cancer, but is only beginning to be seriously studied in the context of colorectal cancer (CRC) [2].

2. Human microbiome and intestinal fungi: new insights from the application of Next Generation Sequencing approaches

The human body is home to an array of microbial species whose primary function in the various human ecosystems remains unclear. The human gastrointestinal (GI) tract on its own harbors a complex microbial community that is estimated to contain approximately 100 trillion cells, belonging to at least 1000 species [3]. The GI tract microbial community (gut microbiota) has co-evolved with the host, establishing a relatively stable and homeostatic community structure in the course of interactions with each other as well as with the host. The gut microbiota play major roles in sustaining the healthy state of humans, such as to protect the host against the overgrowth of pathogens, to shape the developing innate and adaptive immunity, to extract energy, and to produce nutrients for the host [4].

Exciting new insights in the microbiome research are results of improvements in Next Generation Sequencing (NGS) techniques that allow analyzing large populations of microbiota in a culture-independent manner. Two NGS approaches have been wildly used to profile the human bacterial population. One is based on the 16S ribosomal RNA (rRNA) gene that is highly bacteria-specific and conserved between bacterial species, apart from some variable regions. These variable regions allow for taxonomic classification. This approach is dependent on PCR amplification of a part of the 16S rRNA gene followed by sequencing or array-based (HITChip) profiling methods. Since this approach is based on PCR

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http://dx.doi.org/10.1016/j.bpg.2017.09.007
1521-6918/

amplification, selection biases are introduced. Furthermore, taxonomic profiling on basis of 16S rRNA gene will not directly result in functional profiling. The second approach used to profile the human bacterial population is shotgun sequencing or metagenomics. This approach is based on direct sequencing of the DNA sample isolated from the bacterial population. It is a more elaborate method compared with the 16S rRNA-based profiling, but generates more and less biased information. Furthermore, metagenomics allows for taxonomic profiling as well as profiling of gene functions and pathways.

In 2011, the European MetaHit consortium published the first in depth description of the human gut microbiome based on metagenomics data obtained from 39 individuals [5]. The human gut microbiome is composed of a few highly abundant species (mainly from the Firmicutes and Bacteroidetes phyla) and many low abundant species. This "long tail" of low abundant species bring gene functions into the ecosystem that may or may not be beneficial to the host. For example, *Bacteroidetes* and *Firmicutes* are two predominant phyla among them, while *Proteobacter*, *Actinobacteria*, *Fusobacteria*, and *Cyanobacteria* are other minor constituents. Importantly, most microbial functions reside in the low abundant phyla [6]. Furthermore, the authors could identify three main clusters (designated as enterotypes) on basis of the phylogenetic profiles that were independent of the geographical origin of the samples. A year later, the American Human Microbiome Project (HMP) consortium published their first report based on 16S data from 242 individuals including deep sequencing metagenomics data of a subset of them [7]. This paper showed that the human gut microbial community is composed of several thousand species and, based on metagenomics data, these species account for close to a million genes. A follow up HMP consortium paper showed that there is a high variability in microbial composition among individuals, although the variability in gene functions is remarkably lower. This lower variation could be ascribed to the housekeeping core of the bacterial community, whereas higher variability was detected in lower abundant gene functions and pathways [8]. The potential of the gut microbiota as a diagnostic tool and therapeutic target has also been highlighted. Using a low-error 16S ribosomal RNA amplicon sequencing method, in combination with whole-genome sequencing of >500 cultured human bacterial intestinal isolates, the bacterial strain composition has been determined in fecal samples of 37 U.S. adults sampled for up to 5 years. Importantly, the study has demonstrated a high level of stability (decades) for most strains in an individual and for family members [9].

These studies have set the microbiome research field in terms of biology and technical approaches. Alongside them, many initial association and case-control studies have been performed that linked microbial communities, especially that in the gut, with diseases and traits such as obesity [6], Crohn's disease [10], diabetes [11], and colorectal cancer [2,6,12]. The inherited weakness of the association studies was their inability to demonstrate if certain microbial profile is the result or the cause of a trait. Nonetheless the initial large-scale correlations studies were very instrumental to generate specific hypothesis and direct further research. In a few studies, however, causative relations have been identified. For example, the conversion of L-carnitine from red meat into substrates that are indicative to promote atherosclerosis by intestinal microbiota in mice [13]. Furthermore, two studies have demonstrated that the microbial composition of genetically obese mice was different from that of their litter mates and that the "obese microbiome" had a higher capacity to gain energy from the diet [14,15]. Furthermore, increased levels of *Enterobacteriacea* and reduced bacterial diversity are hallmark of the obesity-associated microbiome shown to be more efficient at energy extraction [15]. For metabolic syndrome, levels of *Escherichia coli et. rel.*, were significantly increased in small intestinal biopsies, which may be successfully treated using transplantations of intestinal bacteria [16]. A paper by Koren et al. (2012) [17], has reported on changes to the microbiota during pregnancy by analyzing the relative abundance of different gut bacteria in the stools of 91 Finnish women and their children. During the first and third trimesters of pregnancy, remarkable differences in the microbiome developed that were not related to diet, treatment with antibiotics, the presence or absence of gestational diabetes, or pre-pregnancy body mass index. Data suggested that other factors, such as the state of the host immune or endocrine systems, may actively contribute to the observed shift further supporting the notion that host is able to drive changes to the microbiome intended to support host metabolism and the immune system [17]. Further studies elucidating how changes to the microbiome might positively or negatively affect host would be of obvious value for designing novel, rational therapies and preventive measurements.

Next to the human microbiome, the human fungal and yeast microbial community (mycobiome) has been recently appreciated as complex and important for health [18]. Although some fungi are associated with the human skin, the majority of the interactions of the human host with the yeast and the fungi are taking place in the intestine. Studies identified hundreds of different types of fungi in oral and colonic microbiota [18,19]. Some of these are understudied and of unknown significance to the microbiota, while others are quite well-known. Using deep sequencing analysis it has been confirmed that *Saccharomyces cerevisiae* is a highly abundant fungus in the human gut [20]. Other recent studies have similarly shown that *S. cerevisiae* DNA can be detected in oral and intestinal mucosa of healthy individuals. Most fungi are resident to both skin, genital, and gastrointestinal mucosa without causing diseases. For examples, in healthy individuals *Candida* species are often part of the fungal microbial community in colon [18,20]. While commensal *Candida* can become pathogenic, this typically happens only in immune suppressed individuals. The use of neoplastic and immune suppressed drugs, broad-spectrum antibiotics, and interlining diseases like pancreatitis are among the factors for the increased rate of *C. albicans* reported recently [20]. Therefore, defects in the immune system, genetic predisposition, breached mucosal barrier and microbial dysbiosis can all contribute to the *C. albicans* infection and invasion. Upon a defect in the fungal recognition, specific pathogenic species can gain access to the host tissues to increase the severity of the inflammation [18]. Anti-fungal drug during inflammation can be effective in controlling the intestinal inflammation. It is, however, currently not know if the non-pathogenic fungi can also increase the severity of the inflammation or this is a trait to the pathogenic *Candida*-like population. This is important not only for the treatments of inflammatory disease in the intestine, but also in the context of the host protection against systemic fungal infections, which can have deadly outcomes due of the late diagnostic and limited treatment options [21].

Components of the commensal microbiota are probably involved in controlling fungal growth. Studies in mice have shown increased *Candida* colonization in the stomachs of antibiotic-treated mice [22,23], and germfree mice are highly susceptible to *Candida* infection [24]. Similarly, prolonged antibiotic treatment in humans can predispose to fungal infections [20]. It indicates the utmost importance of the bacterial community acting as a barrier against the outgrowth of the fungal pathogens. Commensal fungi, however, can also protect the host from bacterial pathogens. For instance strains of *S. cerevisiae boulardii* have been successfully used for the treatment of *Clostridium difficile*-induced diarrhea and in *Salmonella*-induced gastroenteritis [25]. The mechanism of protection seems to be a combination of direct competition with intestinal pathogens, interaction with the host immune system, and

Please cite this article in press as: Konstantinov SR, Diet, microbiome, and colorectal cancer, Best Practice & Research Clinical Gastroenterology (2017), http://dx.doi.org/10.1016/j.bpg.2017.09.007