Best Practice & Research Clinical Gastroenterology 30 (2016) 3–15

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

1

Dysbiosis in gastrointestinal disorders

Christopher Chang, MD, PhD, Assistant Professor [1],
Henry Lin, MD, Professor and Chief of Medicine *

New Mexico VA Health Care System, Division of Gastroenterology and Hepatology, University of New Mexico School of Medicine, United States

Keywords:
Dysbiosis
Microbiota
Microbiome
Metagenomics
Metabolomics
Obesity
Nonalcoholic fatty liver disease
Inflammatory bowel disease
Irritable bowel syndrome

A B S T R A C T

The recent development of advanced sequencing techniques has revealed the complexity and diverse functions of the gut microbiota. Furthermore, alterations in the composition or balance of the intestinal microbiota, or dysbiosis, are associated with many gastrointestinal diseases. The looming question is whether dysbiosis is a cause or effect of these diseases. In this review, we will evaluate the contribution of intestinal microbiota in obesity, fatty liver, inflammatory bowel disease, and irritable bowel syndrome. Promising results from microbiota or metabolite transfer experiments in animals suggest the microbiota may be sufficient to reproduce disease features in the appropriate host in certain disorders. Less compelling causal associations may reflect complex, multi-factorial disease pathogenesis, in which dysbiosis is a necessary condition. Understanding the contributions of the microbiota in GI diseases should offer novel insight into disease pathophysiology and deliver new treatment strategies such as therapeutic manipulation of the microbiota.

Introduction

One hundred trillion microbes are in and on us where we interface with the environment, with the gastrointestinal tract as the most colonized organ [1]. This human microbiota is comprised of bacteria,

* Corresponding author. 1501 San Pedro Dr. SE, Medicine Service, Box 111, Albuquerque, NM 87108, United States. Tel.: +1 505 265 1711x4511; fax: +1 505 256 2803.
E-mail addresses: CChang1@salud.unm.edu (C. Chang), HELin@salud.unm.edu (H. Lin).
[1] Tel.: +1 505 265 1711x5154.

http://dx.doi.org/10.1016/j.bpg.2016.02.001
1521-6918/

archaea, fungi, and viruses that constitute diverse ecosystems within us. Our full appreciation of the richness and diversity of the microbiota was previously constrained by culture-based methods which failed to identify fastidious, non-culturable bacteria that constitute the majority of our cohabitants. Over the past decade, with the development of high throughput sequencing methodologies and bioinformatics analyses, the enormity, complexity and diverse functions of the gut microbiota have become apparent [2]. However, despite the exponential growth in identifying the constituents of our GI tract microbiota and the genes encoded within their genomes (i.e. the gut microbiome), the definition of a "healthy" gut microbiota remains elusive. Table 1 provides a glossary of key terms used in this review and in the current literature. What is clear from research thus far is that alterations in the composition or balance of the intestinal microbiota, or dysbiosis, are associated with many GI and autoimmune disease susceptibilities. The question still remains, is intestinal dysbiosis a cause or effect of these diseases? Consequently, the precise mechanisms by which the dysbiosis could trigger or promote disease pathogenesis constitute an area of intense research focus. In this paper, the contribution of intestinal dysbiosis will be reviewed in select diseases and can run the spectrum of disease association or effect, to *necessary* for disease, to *sufficient* to cause the disease or select disease phenotypes. Animal experiments, in which gut microbiota or their metabolites from a diseased host transferred into "normal" hosts reproduce disease features or the disease itself, provide the strongest evidence yet of dysbiosis causing a disease. The literature in gut dysbiosis increasingly demonstrates that the microbiome is often a necessary contributor, if not sufficient itself, to mediate disease development and/or progression.

Intestinal microbiota and its development

Based on 16S rRNA gene based approaches, the distal gut microbiota consists of over 1000 bacterial species, dominated by the phyla Bacteroidetes and Firmicutes, and to a lesser extent Acinetobacteria, Verrucomicrobia, and Proteobacteria [3]. The trillions of microbes in the gut outnumber the total number of human cells in our body by a ratio of over 10:1. Moreover, the gut microbiome encodes an estimated 10 million nonredundant genes, thus dwarfing the estimated 25,000 genes comprising the human genome. With the sheer enormity and complexity of the intestinal microbiota and microbiome, it is unsurprising that interindividual and intraindividual variation exists and reflects many external influences [2]. In addition, a "healthy" microbiota or microbiome does not hinge on one or a group of microbes or their genes. Rather, bacterial diversity or richness of the microbiota and a greater repertoire of metabolic functions encoded by the microbiome are associated with greater overall health. For example, reduced bacterial diversity was observed in feces of infants that developed necrotizing enterocolitis [4], and in those at increased later risk of allergic disease at school age [5]. Furthermore, reduced bacterial species richness was noted in Crohn's disease patients, compared to healthy controls [6], and a similar pattern was found in monozygotic twin pairs discordant for Crohn's disease [7]. In contrast, greater diversity and richness corresponded to better nutritional status and overall health in an elderly population [8]. Metabolic pathways enriched in the microbiome of healthy adults are involved in hydrogen and methane production, spermidine biosynthesis, methionine degradation,

Table 1
Glossary.

Microbiota: A microbial community, including bacteria, archaea, eukaryotes, and viruses, which occupy a given habitat.
Dysbiosis: Alteration of the microbiota from the normal, healthy state. A condition of microbial imbalances rather than equilibrium of "good" and "bad" microbes.
Microbiome: The totality of microbes, their genetic elements or genomes, and environmental interactions in a defined environments. Their collective genomes would constitute a metagenome. Term now commonly used to refer to the collective genomes present in members of a given microbiota.
Metagenomics: The genomic analysis applied to all the microorganisms of a microbial ecosystem without previous identification. Encompasses culture-independent studies of the structures and functions of microbial communities and their interactions with the habitats they occupy to understand their biological diversity.
Metabolomics: The characterization of metabolites generated by one or more organisms in a given physiological and environmental context. Mass spectroscopy, nuclear magnetic resonance, or other analytical methods commonly used.