Comparative Immunology, Microbiology and Infectious Diseases 43 (2015) 36–49

Contents lists available at ScienceDirect

Comparative Immunology, Microbiology and Infectious Diseases

journal homepage: www.elsevier.com/locate/cimid

Review

Dysbiotic gut microbiome: A key element of Crohn's disease

Styrk Furnes Øyri[a,1], Györgyi Műzes[b], Ferenc Sipos[b,*]

[a] Faculty of Medicine, Semmelweis University, Szentkirályi Street 46, 1088 Budapest, Hungary
[b] 2nd Department of Internal Medicine, Semmelweis University, Szentkirályi Street 46, 1088 Budapest, Hungary

ARTICLE INFO

Article history:
Received 5 June 2015
Received in revised form 6 October 2015
Accepted 22 October 2015

Keywords:
Gut microbiome
Dysbiosis
Crohn's disease
Pathogenesis
Immune system
Therapeutic aspects

ABSTRACT

Since the first publication on "regional ileitis", the relevance of this chronic inflammatory disease condition termed finally as Crohn's disease is continuously increasing. Although we are beginning to comprehend certain aspects of its pathogenesis, many facets remain unexplored. Host's gut microbiota is involved in a wide range of physiological and pathological processes including immune system development, and pathogen regulation. Further, the microbiome is thought to play a key role in Crohn's disease. The presence of Crohn's-associated variants of *NOD2* and *ATG16L* genes appears to be associated not only with alterations of mucosal barrier functions, and bacterial killing, but the gut microbiota, as well, reflecting a potential relationship between the host's genotype and intestinal dysbiosis, involved in disease etiology. This review aims to characterize some exciting new aspect of Crohn's disease pathology, focusing mainly on the role of intestinal microbes, and their interplay with the immune system of the host.

Contents

* Corresponding author. Tel.: +36 1 2660926; fax: +36 1 2660816.
E-mail addresses: styrkoyri@gmail.com (S.F. Øyri), muzes.gyorgyi@med.semmelweis-univ.hu (G. Műzes), dr.siposf@gmail.com (F. Sipos).
[1] Present address: ENT Department, Stavanger University Hospital, PO Box 8100, 4068 Stavanger, Norway.

http://dx.doi.org/10.1016/j.cimid.2015.10.005
0147-9571/

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC), the main clinical phenotypes of idiopathic, relapsing-remitting inflammatory bowel disease (IBD) are systemic disorders affecting the gastrointestinal (GI) tract with frequent extraintestinal manifestations [1]. IBD, as a polygenic immune disorder with complex multifactor etiology, generally is arising in susceptible individuals in whom upon environmental triggers a sustained disturbed, deleterious mucosal immune reaction is provoked toward commensal microbiota [2]. In IBD the epithelial barrier function is critical for the disease onset. Since the epithelium is densely inhabited by a resident microbial flora, the role of native immunity is particularly appreciated in recognizing and distinguishing commensal enteric bacteria from the invading ones, and thus, in maintaining tolerance and homeostasis [2]. Subsequently, the chronic unrestrained inflammatory response is mainly driven by a disintegrated host immune regulatory network. In CD development the host genetic susceptibility also represents an important etiologic factor [3,4]. Many of the recently identified genetic risk loci in CD are related to various cell types and pathways, suggesting the involvement of fairly different aspects of host immune responses in the IBD phenotype. Missing heritability in CD cannot be simply explained by genetic alterations [2]. Moreover, the fact of the worldwide considerable increase in disease incidence and prevalance emphasizes the importance of additional, environmental and epigenetic contributions [5,6]. The interplay of genes regulating immune functions is strongly affected by the environment, especially intestinal resident microbiota. On the basis of genetic alterations in CD impaired sensing and handling of intracellular bacteria by the innate immunity, being closely interrelated with the autophagic and unfolded protein pathways seem to be the most relevant pathophysiologic features [7].

2. Microbiome of the gut

Although distinct microbial communities inhabit all body surfaces exposed to the environment (e.g. the skin, nasal cavity, vagina, and mouth), the greatest and most varied microbial population resides in the intestine [8]. This complex microbial community consists of an array of bacteria, viruses, archaea, and microeukaryotes [9]. The GI tract harbors 10^{14} microbes which collectively make up the microbiome of the gut. Possibly more than 500–1000 separate taxa are part of the microbiome and estimates indicate that for every somatic cell in the human body, ten bacterial cells exist; most of which are located in the intestine [10–12]. The intestinal microbiota has lately been the subject of much research and an increasing amount of evidence implies that the microbiota is involved in a wide range of physiological and pathological processes in the host. The microbial community of the GI tract plays an important part in human metabolism, immune system development, and pathogen regulation. Correspondingly, the microbiome is thought to be involved in the pathogenesis of numerous diseases and pathogenic processes, including: IBD; asthma and atopy; neoplasia; insulin resistance; obesity; and atherosclerosis [13–19].

2.1. Normal gastrointestinal microbiome profile

The normal microbiota of the GI tract may be defined according to diversity of microbial composition (i.e. richness and evenness), and functional features. Previously, culture-based techniques were employed to investigate the microbial composition of the intestine; however, due to the challenging nature of gut bacteria (i.e. most required strict anaerobic conditions) only a fraction of these microbes can be cultured. After the introduction of more sensitive culture-independent methods, culturing has become less favored [20,21]. New molecular-oriented techniques involving large-scale high-throughput DNA sequencing enable wider identification of the microbiota structure and functional capacity. The *16S rRNA* gene is present in all prokaryotes and is therefore suitable for sequencing studies targeting the gastrointestinal microbiome. Furthermore, different taxa may be identified due to the presence of variable domains [22]. While *16S rRNA* studies rely on techniques such as PCR amplification or direct sequencing of a specific gene to investigate the compositional diversity of the microbiota, metagenomic studies analyze all genes of a distinct ecological community to provide an understanding of both the composition and functional capacity of microbes [23]. Additionally, microbial function may be studied more extensively by analyzing the abundance and diversity of proteins (metaproteomics), RNA content (metatranscriptomics), and presence of metabolites (metabolomics) [23]. Eckburg et al. conducted a comparative analysis of *16S rRNA* gene sequences from fecal and mucosal samples retrieved from three healthy subjects [24]. One archaeal and 395 bacterial phylotypes were singled out. Detected bacterial phylotypes were predominantly those of the *Bacteroidetes* and *Firmicutes*, and considerable variations in the *Bacteroidetes* phylotypes existed between the three subjects. Additionally, some sequences were related to the *Actinobacteria*, *Proteobacteria*, *Verrucomicrobia*, and *Fusobacteria*. Interestingly, in two of the subjects the majority of the mucosal bacterial composition was significantly different from the corresponding fecal bacterial composition, indicating that the structure of the microbiota varies axially through the GI tract from the mucosa to the lumen [24]. Several studies published in association with the Human Microbiome Project, have broadened our knowledge and understanding of the microbiome [25,26]. Turnbaugh et al. conducted a study describing microbial populations in the feces of dizygotic and monozygotic twins concordant for obesity and leanness [25]. Although interpersonal variations in bacterial phylotypes existed, a large collection of microbial genes were shared among the subjects of the study. This implied the existence of a functional core (i.e. a core microbiome) conserved at the gene level regardless of individual differences observed in the gut microbial composition [25]. A study by Qin et al., involving 124 random European subjects, further substantiated the findings of Eckburg et al. and Turnbaugh et al. [11,24,25]. *Firmicutes* and *Bacteroidetes* phyla accounted for the majority of the microbes found in stool samples, and approximately 38% of an individual's total microbial gene pool was shared with 50% of the other subjects in the study [11]. Moreover, a study by Harrell et al. found differences between the mucosa-associated and luminal microbes, also noting that bowel-preparations (i.e. colonic lavage) modified the diversity of the mucosal microbiota [26]. Through a large cohort study, the Human Microbiome Project Consortium aimed to describe the ecology of different communities of microbes found in humans. Samples were collected from different body sites, including the vagina (in women), skin, and oropharynx of 242 healthy adults [27]. The microbiota of the lower intestine was evaluated on the basis of stool samples. As previous studies had implied, the richest and most varied microbiome was that of the lower GI tract; and the *Bacteroidetes* and *Firmicutes* phyla were the predominant phylotypes found in the intestinal samples (i.e. the stool samples). Additionally, the cohort described a somewhat even arrangement of various metabolic pathways across body habitats and individuals, although variations in the relative predominance of bacterial genera and species were observed among the subjects [27].

2.2. Variations within the normal intestinal microbiome: Distribution, longitudinal and axial differences

The density of microorganisms differs longitudinally along various points of the GI tract, with the lowest numbers of colony