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The Intestinal Microbial Community and Inflammatory Bowel Diseases

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Abstract

Based on molecular, genetic, epigenetic, biochemical and microbiological analyses it is increasingly possible to identify individual disease-related characteristics that define disease pathogenesis, disease disposition or prognosis as well as the efficacy of therapeutic strategies ('personalized medicine/precision medicine'). In this context, the global human microbiome project, aimed at deciphering the complete set of genes of the microbiota, i.e., the individual's complete microbial community, was established in 2007 and has meanwhile developed into a major field of biomedical research. In particular, the intestinal microbial community has turned out to play a major role in human health and disease. In this context, the following comment addresses novel insights into its contribution to the pathogenesis, prevention and treatment of inflammatory bowel diseases (IBD). Beyond IBD, the intestinal microbial community is involved in numerous other, common, non-gastrointestinal diseases, such as obesity/metabolic syndrome and atherosclerosis as well as in health, in particular in immunity, making it one of the most dynamic current topics in biomedical research.

Keywords

Genome-wide association studies, Human microbiome project, Microbiota, Personalized medicine

Introduction

The basic aspects of molecular and cell biology are not only integral part of biomedical research but are also increasingly translated into 'personalized/precision medicine' with clinical relevance for the diagnosis, treatment and prevention of human diseases. Apart from the international human genome organization (HUGO) project that identified the complete sequence of the human genome about 15 years ago [1,2] and the international haplotype map (HapMap) project initiated in 2005 to identify, based on genome-wide association studies (GWAS) in ethnically different populations, single nucleotide polymorphisms (SNPs) and their association with specific human diseases and individual phenotypic characteristics, respectively [3,4], a third global consortium, the human microbiome project (HMP), was established in 2007 [5-9]. The HMP and the 'Metagenomics of the Human Intestinal Tract (Meta-HIT) Consortium Europe' aim at the sequencing of all microbes (eukaryotes, archaea, bacteria and viruses) that inhabit specific body sites (Table 1). Recent data demonstrate that specific compositions of the microbial community are associated with health and disease [5-9] and suggest that the detailed characterization, function and variation of the microbial community will reveal important commensal host-microbe as well as microbe-microbe interactions with diagnostic, therapeutic and preventive implications [10,11].

Intestinal microbial community

In recent years the intestinal microbial community has been studied in great detail. The colonization of the human gut begins at birth, is characterized by a successively changing composition and eventually becomes relatively stable in adulthood [12]. Important factors for the composition of the intestinal microbial community are, among others, diet lifestyle and exposure to drugs/

Table 1: Human microbial communities.

Body sites	References
Mouth-throat-airways	[5,6]
Stomach	[5,6]
Intestine	[5,6]
Urogenital system	[5,6]
Skin	[5,6]

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antibiotics. In this context it appears that the administration of low-dose penicillin early in life has lasting effects on the body mass index (obesity) through alteration of the intestinal microbial community [13,14]. Recent evidence further suggests that human genetic variation also influences the abundance of specific members of the intestinal microbial community [15].

The intestinal microbial community is highly variable from person to person but family members tend to have more similar microbes than unrelated individuals, possibly due to shared environmental factors and genetic similarities. Recent studies indicate that certain intestinal microbial communities are not only associated with different chronic diseases but may play a causative role in disease pathogenesis [5-9]. This is, last but not least, supported by the fact that the transplantation of intestinal microbes from diseased animals/humans to healthy recipients results in phenotypic disease characteristics, e.g., in kwashiorkor [16].

A causal relationship between the intestinal microbial community and an increasing number of human diseases, have been identified to date (Table 2). In addition, intestinal microbes play a central role in drug metabolism, e.g., of sulfasalazine, levodopa and irinotecan, both with respect to efficacy and to undesired side effects.

The inflammatory bowel diseases (IBD) in humans include ulcerative colitis (UC) and Crohn disease (CD). These are characterized by inflammation limited to the mucosal layer of the colon in UC and the transmural involvement of the gastrointestinal tract, including extraintestinal sites in CD. While the pathogenesis of IBD is not fully understood [17], it is clear that its pathology depends among others on the intestinal microbial community [18,19]. Further, a case-control study identified 'IBD-specific' alterations of the intestinal microbiota that may serve as biomarkers for the prediction of disease predisposition, activity/severity and responsiveness to therapy [20,21].

Host genes with effects on the composition of the intestinal microbiota are the IgA locus and the HLA genes as well as the defensin genes, the NOD2 gene, the resistin-like molecule beta gene, the apolipoprotein I gene, the MEFV gene and the myeloid differentiation primary response protein 88 gene. The three components -environment host genetics and the microbial community- interact to maintain homeostasis in the intestine [6]. The disruption of the stability of this interaction may be a trigger for disease development. Two recent publications shed a new light on the pathogenesis of IBD through the change of the intestinal microbial composition involving two different pathways: helminth infection [22] and lipocalin-2 expression [23], respectively.

Helminth infection, microbial community and IBD

Epidemiologic studies demonstrated a major increase of the incidence of IBD in the developed world, suggesting a change in the environment, including an alteration of the intestinal microbiome [24] and a decreased exposure to intestinal parasites, such as helminths [25]. In mice deficient for the CD susceptibility gene Nod2 ($Nod2^{-/-}$/knockout) [26], it could be demonstrated that small intestinal abnormalities develop in the face of a sustained colonization with the inflammatory bacterium *Bacteroides vulgatus*, an ubiquitous member of the intestinal microbial community [27]. Chronic infection of Nod2 mice with the parasitic worm *Trichuris muris*, however, inhibited colonization with inflammatory *Bacteroides species* and promoted the establishment of a protective microbial environment enriched in *Clostridiales* [22]. Further, the authors demonstrated that individuals from helminth-endemic regions harbour a similar protective microbial community and deworming treatment reduced *Clostridiales* and increased *Bacteriodales*, resulting in an increased IBD incidence. These data support

Table 2: Intestinal microbial community in health and diseases (examples).

Health/Disease(s)	Reference(s)
Adaptive immunity	[28]
Atherosclerosis/Thrombosis	[29-32]
Autoimmunity/Allergies	[33]
Colorectal carcinoma	[34]
Immune-mediated inflammatory	[35]
Diseases	
Inflammatory bowel diseases	[22,23,35,36]
Multiple sclerosis	[37]
Rheumatoid arthritis	[38]
Psoriasis	[39]
Innate immunity	[40]
Kwashiorkor	[16]
Liver diseases	[41]
Metabolic syndrome/Obesity	[42-46]
Neurodevelopmental, psychiatric and neurodegenerative diseases	
Autism	[47,48]
Depression	[47,49]
Alzheimer disease, parkinson disease	[47,50,51]

the hygiene hypothesis whereby certain individuals are genetically susceptible to the consequences of a changing intestinal microbial community that favours IBD development.

Lipocalin-2 protection from IBD and colon cancer

Lipocalin-2 (Lcn2) is an antimicrobial peptide with high mucosal and fecal concentrations in patients with IBD. It is produced by various cell types, including epithelial cells, and acts as an antimicrobial defence mediator by binding to a subset of bacterial siderophores, thereby preventing bacterial iron acquisition and growth of siderophore-dependent strains. While it has been implicated in several biologic processes, such as acute phase response, erythropoiesis and iron metabolism, its functional role in contributing to IBD development remained unclear.

To decipher the role of Lcn2 in colon inflammation, mice double deficient in Lcn2 and IL-10 ($Lcn2^{-/-}$/$IL10^{-/-}$ double knockout) were generated and compared to single knockouts and wild-type animals. The experimental data indicate that Lcn2 expression protects from early onset colitis and the spontaneous emergence of right-sided colonic tumours that result from IL-10 deficiency. The inflammation is driven by IL-6 which also controls tumorigenesis. The $Lcn2^{-/-}$/$IL10^{-/-}$ double knockout mice showed major alterations of their intestinal microbial community, especially with respect to the facultative pathogenic *Alistipes spp*. These contribute to inflammation and tumorigenesis as shown by the transmissibility of the phenotype and the protection by antibiotic therapy. Taken together, the authors demonstrate that Lcn2 protects against intestinal inflammation and tumorigenesis in the face of an altered intestinal microbial composition [23].

Conclusions and Perspectives

Recent advances in cell and molecular biology resulted in an increasingly detailed understanding of the pathogenesis of gastrointestinal diseases, including IBD. Apart from an increasing number of host genetic susceptibility loci and environmental factors, the individual microbial community is central for the barrier between microbes and hosts and for the mucosal homeostasis. In this context the mucosal immune responses to luminal dietary and/or microbial antigens play a major role. A thorough understanding of IBD pathogenesis depends on the one hand on the detailed characterization of the host's mucosal defence and response mechanisms and on the other hand on the careful analysis of the complex dynamics of the intestinal microbes.

The two recent publications discussed above [22,23], give a first glimpse into the complex mechanisms underlying the protection from IBD by the intestinal microbial community, i.e., by its modification through chronic helminth infection in susceptible hosts or by changing the microbial composition that results in a reduction of bacterial species with inflammatory and tumorigenic potential thereby increasing Lcn2 expression. These findings suggest a highly intricate interplay between the host and the microbial community in IBD pathogenesis and may eventually contribute to IBD prevention and therapy in humans.

Beyond IBD, the intestinal microbial community is involved in numerous other, common, non-gastrointestinal diseases, such as obesity/metabolic syndrome and atherosclerosis as well as in health, in particular in immunity, making it to one of the most dynamic areas of biomedical research.

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