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Dysbiosis in intestinal inflammation: Cause or consequence

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ABSTRACT

The intestinal microbiota encompasses hundreds of bacterial species that constitute a relatively stable ecosystem. Alteration in the microbiota composition may arise from infections, immune defects, metabolic alterations, diet or antibiotic treatment. Dysbiosis is considered as an alteration in microbiota community structure and/or function, capable of causing/driving a detrimental distortion of microbe-host homeostasis. A variety of pathologies are associated with changes in the community structure and function of the gut microbiota, suggesting a link between dysbiosis and disease etiology. With an emphasis in this review on inflammatory bowel diseases (IBD), the non-trivial question is whether dysbiosis is the cause or consequence of inflammation. It is important to understand whether changes in microbial ecosystems are causally linked to the pathology and to what extend disease risk is predicable based on characteristic changes in community structure and/or function. Local changes in tissue integrity associated with focal areas of inflammation may result in the selection of a dysbiotic bacterial community associated with the propagation of a disease phenotype. This review outlines the role of dysbiosis in intestinal inflammation with particular focus on IBD-relevant gnotobiotic mouse models, the factors implicated in the development of dysbiosis and the means available to investigate dysbiosis in the context of human diseases.

1. Intestinal microbiota in health—Structure and function

The mammalian intestine is inhabited by a dense and diverse bacterial community, including bacteria, archaea, viruses, yeasts and protozoa, known as the microbiota (Human Microbiome Project Consortium, 2012). The mammalian gut microbiota comprises several hundred different bacterial species, many of which have a beneficial effect on the host and correspond to up to 10^{12}–10^{14} organisms/g of colon content, exceeding the number of eukaryotic cells in a ratio of 10:1 (Round and Mazmanian, 2010). Only recently, Sender et al. (2016) proposed an innovative reanalysis of an established "fact" stating that the number of bacteria in the human body and the number of human cells rather represents a 1:1 ratio based on differences in the estimated colon volume and body cell count of a "reference man" (Sender et al., 2016). The totality of all microbial genes of the intestinal microbiota is called the metagenome and latest estimations suggest a reference catalogue of 9.9 million genes (Sommer and Backhed, 2013; Li et al., 2014). The host maintains a complex compartmentalization to confine the huge load of bacteria in the gastrointestinal tract by exploiting a single layer of polarized intestinal epithelial cells (IECs). The intestinal epithelium is a key modulator of intestinal immunity and plays an instrumental role in mucosal homeostasis through the integration of microbial signals and interaction with immunocompetent cells (Haller et al., 2000; Mowat and Agace, 2014). The adult intestinal microbiota is dominated by the two phyla Bacteroidetes and Firmicutes accompanied at much lower abundance by Actinobacteria and Proteobacteria (Eckburg et al., 2005; Human Microbiome Project Consortium, 2012; Lozupone et al., 2012; Lozupone et al., 2013). Overall, more than 1000 different bacterial species were detected in human fecal samples and biopsies (Human Microbiome Project Consortium, 2012). Despite the high inter-individual variability of the intestinal microbiota in healthy people and the respective problems in identifying a reference microbiota, metagenomic analysis revealed a core functional gut microbiome consisting in approximately 60 bacterial gene families shared by individual subjects with differences in bacterial phylotypes (Turnbaugh and Gordon, 2009; Human Microbiome Project Consortium, 2012). Therefore, a microbiome associated with the healthy host contains a shared gene set necessary to perform important biochemical reactions for host physiology, including degradation of xenobiotic substances, vitamin biosynthesis, fermentation of indigestible polysaccharides into beneficial short-chain fatty acids (SCFA), immune development and maintenance of intestinal homeostasis (Turnbaugh et al., 2009; Qin et al., 2010; Kau et al., 2011; Human Microbiome Project Consortium, 2012;

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Lozupone et al., 2012; Buttó et al., 2015). Under physiological conditions the microbiota is highly resilient to perturbations, including moderate fluctuations in response to a change in dietary-patterns, short-term applications of drugs or antibiotics. These factors, so-called exposomal components, might temporarily or permanently modify the microbiota composition leading the bacterial ecosystem to stabilize within a new "alternative state" (Faust et al., 2015). The ability of the microbiota to adapt to alterations in the intestinal milieu maintains intestinal homeostasis. In addition, a variety of host factors, including gender, genotype, age, psychological stress and health status have been reported to shape the intestinal microbiota (Dominguez-Bello et al., 2010; Claesson et al., 2012).

2. Dysbiosis in intestinal inflammation

Given the co-evolution of microbiota and host, the crucial role of the microbiota in maintaining intestinal homeostasis is evident. A variety of pathologies are associated with changes in the community structure and function of the gut microbiota, suggesting a link between dysbiosis and disease etiology (Swidsinski et al., 2008; Abu-Shanab and Quigley, 2010; Adams et al., 2011; Qin et al., 2012; Kamada et al., 2013b; Le Chatelier et al., 2013; Ridaura et al., 2013; Schwabe and Jobin, 2013; Serino et al., 2014; Kostic et al., 2015). Dysbiosis is considered as an alteration in microbiota community structure and/or function, capable of causing/driving a detrimental distortion of microbe–host homeostasis that specifically initiates or propagates disease (Manichanh et al., 2006; Frank et al., 2007; Willing et al., 2010; Lepage et al., 2011). Loss of species richness correlates with disease activity in various studies and subsets of IBD patients (Gevers et al., 2014), however the "egg or hen" question related to the cause or consequence in the context of inflammation-driven changes in the microbiota remains unanswered. In addition and similar to IBD, other immune-mediated pathologies such as Type-1 diabetes also show low species richness at disease-onset questioning the specificity of this readout in IBD (Kostic et al., 2015).

3. Dysbiosis in IBD

The pathogenesis of inflammatory bowel diseases (IBD) appears to involve a primary defect in innate immune mechanisms associated with impaired mucosal barrier function and/or bacterial clearance at the epithelial interface. Loss of bacterial compartmentalization and immune tolerance leads to a life-long risk for inadequate and recurrent adaptive immune activation towards luminal gut antigens and the development chronic tissue damage (Bouma and Strober, 2003; Mowat, 2003; Allez and Mayer, 2004; Sartor, 2008; Asquith and Powrie, 2010). Dysbiosis in IBD is characterized by the decrease in overall species richness and α-diversity, often characterized by the alteration in Firmicutes abundance, especially reduction in *Lachnospiraceae*, such as *Roseburia* and Clostridium cluster XIVa and IV, with *Faecalibacterium prausnitzii* as a prominent representative species (Frank et al., 2007; Sokol et al., 2008, 2009; Willing et al., 2009; Gevers et al., 2014; Lopez-Siles et al., 2015). On the other hand, *Veillonellaceae* seem to be overrepresented (Gevers et al., 2014). At the same time, Bacteroidetes, *i.e. Bacteroides fragilis and Bacteroides vulgatus* gain in abundance (Takaishi et al., 2008), with concomitant overrepresentation of Fusobacteria (Strauss et al., 2011; Gevers et al., 2014) and Proteobacteria (Frank et al., 2007; Rehman et al., 2010; Lepage et al., 2011; Strauss et al., 2011; Barnich et al., 2013; Minamoto et al., 2015). A recent analysis of a large cohort (RISK) including 447 treatment-naïve new-onset pediatric CD and 221 non-IBD control samples confirmed the association between disease severity and low species richness (α-diversity) (Gevers et al., 2014). Interestingly, overall community structures only differed between patients and controls when correlated with ileal gene expression, suggesting that individual patterns of microbiota composition or function are linked to host responses including disease phenotype, activity and location (Haberman et al., 2014). Despite the availability of data from these larger cohorts, consensus about specific disease-relevant taxa in IBD is still hampered. Meta-analyses of combined 16S-sequence datasets from all the cross-sectional studies might help to increase sample size, however knowledge extraction from this approach is heavily confounded by technical differences in sample collection, storage and extraction as well as age, geographic location, medication and disease phenotypes/activity of the various study individuals (Lozupone et al., 2013). Due to this noise in the datasets it seems unlikely that in the absence of mechanistic understanding the sole description of microbial communities including their gene repertoires will identify IBD-relevant phylotypes or disease-conditioning bacterial networks across a broader range of patients.

4. Characteristic features and effectors of dysbiosis

Dysbiosis displays changes in the microbial composition, including (i) loss of function (*i.e.* reduced bacterial diversity and reduction in indicator species), (ii) gain of function (*i.e.* expansion of pathobionts), and (iii) change in microbial functional properties (Buttó et al., 2015). Alterations in microbiota composition might result from the exposure to endogenous components, such as genetic susceptibility, and exogenous factors including, antibiotics (Keeney et al., 2014; Vangay et al., 2015), drugs (Syer and Wallace, 2014), psychological and physical stress (Cryan and Dinan, 2012; Collins, 2014), radiation (Sheikh Sajjadieh et al., 2012; Nam et al., 2013), exposure to pathogens and dietary changes (Day and Lopez, 2015; Kaakoush et al., 2015; Lee et al., 2015a; Lee et al., 2015b; Lee et al., 2016). In the current review we focus on host genetic predisposition in IBD and pathogenic bacteria as drivers of inflammation.

5. Endogenous effectors of dysbiosis

5.1. Genetic susceptibility in IBD

IBD include the two main phenotypes Crohn's disease (CD) and ulcerative colitis (UC) both characterized by intermittent conditions of chronic and relapsing inflammation in the entire gastrointestinal tract or colon, respectively. Disease initiation and perturbation is triggered by environmental factors in genetically susceptible individuals (Podolsky, 2002; Schirbel and Fiocchi, 2010). Genome-wide association studies (GWAS) identified a variety of target genes that point towards a disruption of microbe–host interactions including genetic loci associated with microbial sensing and clearance as well as resilience mechanisms to cope with accumulating cell stress (Jostins et al., 2012; Liu et al., 2015). Defects in these functions lead to a dysfunctional mucosal interface and chronic activation of adaptive immune effectors and ultimately to dysbiosis, potentially due to different mechanisms, such as (i) microbial factors, (ii) loss of barrier function (*CDH1, MUC19*), (iii) failure to maintain intestinal epithelial cell homeostasis (*XBP1; ORMDL3*) specifically targeting Paneth cells, (iv) loss of innate mechanisms for microbial clearance (*NOD2, ATG16L1, IRGM*), (v) shift towards aggressive immune responses and loss of tolerance (TNFS15, *IL-10RB, IL-23R*), and (vi) persistence of pathogenic antigens (Jostins et al., 2012; Liu et al., 2015). Despite environmental triggers being thought to play the dominant role in the etiology of IBD (Renz et al., 2011; Kaplan, 2015), the identification of genetic risk factors paved the way to a better understanding of the defects in host defense mechanisms implicated in the IBD phenotype (Buttó et al., 2015). A recent analysis of a variety of different