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Low diversity gut microbiota dysbiosis: drivers, functional implications and recovery

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Dysbiosis, an imbalance in microbial communities, is linked with disease when this imbalance disturbs microbiota functions essential for maintaining health or introduces processes that promote disease. Dysbiosis in disease is predicted when microbiota differ compositionally from a healthy control population, but only truly defined when these differences are mechanistically related to adverse phenotypes. For the human gut microbiota, dysbiosis varies across diseases. One common manifestation is replacement of the complex community of anaerobes typical of the healthy adult gut microbiome with a community of lower overall microbial diversity and increased facultative anaerobes. Here we review diseases in which low-diversity dysbiosis has been observed and mechanistically linked with disease, with a particular focus on liver disease, inflammatory bowel disease, and *Clostridium difficile* infection.

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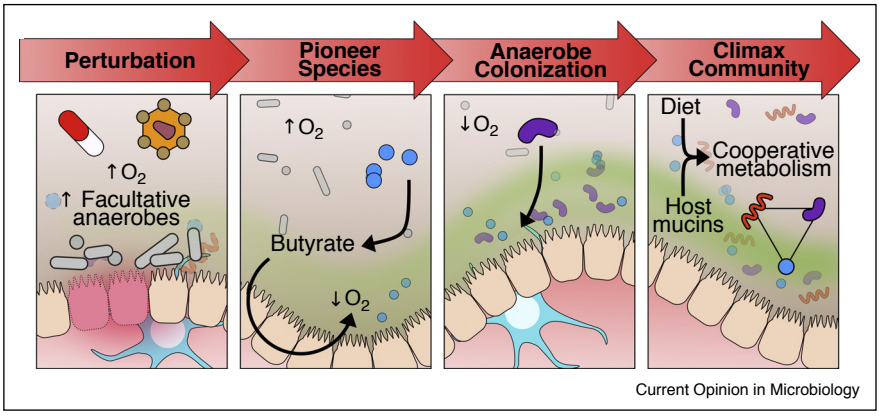
Introduction

The bacterial community of the human distal intestine is one of the richest microbial environments on earth, consisting of $>10^{12}$ cells and hundreds of species [1]. The healthy adult gut microbiota is typically dominated by anaerobic members of the Firmicutes and Bacteroidetes phyla and is known to provide key functions for maintaining health, including production of metabolites that promote immune homeostasis and competitive exclusion of pathogens [2]. This complex community establishes during the first two to three years of life through a process similar to ecological succession [2], in which the community follows a path from sterility through a systematic series of turnover of early successional 'pioneer' species before reaching a relatively stable complex community that is dominated by anaerobes (Figure 1). Remarkably, this path is very conserved in diverse geographic and socioeconomic settings [3]. In the perinatal period, facultative anaerobes such as Proteobacteria, Lactobacilli and Enterococcus species colonize as well as particular anaerobes such as Bifidobacteria. With the introduction of solid foods, dramatic shifts occur with expansion of strict anaerobes such as the Clostridiales and Bacteroidales (Table 1) [4].

Dysbiosis, or imbalance of the microbiome, may have diverse compositional and functional attributes in different disease contexts [5•]. In many different diseases, however, the dysbiotic gut microbiome has been described to have a reduction in the proportion of anaerobes that are typically abundant in health and an increased proportion of facultative anaerobes, including Proteobacteria and Bacilli. Such low-diversity, disease-associated microbiomes can resemble the gut microbiome of infants (younger than ~2 years of age) compositionally [2,6,7]. While it may be surprising that the gut microbiome of a very sick adult would resemble that of a perfectly healthy infant, this observation may be explained by the concept of 'secondary succession' where a dramatic disturbance that wipes out a complex community (such as a forest fire) results in the observation of similar early succession, or 'pioneer' species [2,6]. A low diversity, facultative anaerobe-dominated community observed in the adult gut thus may be considered a bioindicator of disturbance with age-dependent implications for health. Low-diversity microbiota, with increases in proportions of facultative anaerobes, have been observed with acute diarrheal disease [8], Inflammatory Bowel Disease (IBD) [7], *Clostridium difficile* infection (CDI) [9], liver disease [10,11], and in cancer patients [12]. In cancer patients who undergo allogeneic stem cell transplantation, this 'infant-like' microbiome was associated with all-cause mortality following stem cell transplant [12]. Since this particular type of dysbiosis may be common in many disease settings,

Figure 1



Recovery from disturbance through secondary succession. An insult (e.g. antibiotics) raises intraluminal oxygen concentrations leading to a bloom of facultative anaerobes. One factor in recovery may be oxygen-tolerant anaerobes that are able to colonize and reestablish butyrate production. Colonocyte metabolism of butyrate depletes luminal oxygen allowing for further colonization by anaerobes. Interdependent metabolic networks of the anaerobes are restarted and the mature, complex climax community of the healthy adult gut is reached.

research into drivers, functional consequences, and therapeutic strategies of recovery may have particularly far reaching implications. Dysbiosis can potentially take many different forms, therefore we use the term 'low-diversity dysbiosis' to specifically refer to a microbiome characterized by low diversity and increased proportions of facultative anaerobes (Table 1).

Drivers of low-diversity dysbiosis

Low-diversity dysbiosis may be driven by many factors that differ by disease context. One known contributor to low-diversity dysbiosis is broad-spectrum antibiotics. Individuals with recurrent CDI (rCDI) often have microbiome states consistent with low-diversity dysbiosis [9] and CDI is strongly associated with antibiotic exposure [13]. Epidemiologic studies have identified clindamycin, cephalosporins, and fluoroquinolones as significant risk factors for CDI [14]. However, CDI is also more common in certain populations, including the elderly, individuals with IBD [15], with liver disease [16] and with blood cancers [17]. Thus, the factors that predispose an individual to low-diversity dysbiosis and associated opportunistic infections are varied.

Table 1

Bacterial families that dominate the adult human gut in health and during low-diversity dysbiosis

Healthy	Low-diversity dysbiosis
Firmicutes	Firmicutes
Clostridia	Bacilli
Clostridiales	Lactobacillales
Lachnospiraceae (Clostridia XIVa)	Lactobacillaceae
Ruminococcaceae (Clostridia IV)	Streptococcaceae
	Enterococcaceae
Bacteroidetes	Proteobacteria
Bacteroidia	Gammaproteobacteria
Bacteroidales	Enterobacteriales
Bacteroidaceae	Enterobacteraceae
Prevotellaceae	

One factor that may also lead to dysbiosis in disease contexts is host genetics, such as in the case of IBD. IBD is characterized by chronic, relapsing inflammation with an unknown etiology and is currently separated into ulcerative colitis (UC) and Crohn's disease (CD) [18]. Individuals with IBD can have microbial compositions characteristic of low-diversity dysbiosis [18,19]. However, the dysbiosis observed with IBD can be more complex: for instance, one study showed low-diversity dysbiosis to be commonly observed in ileal CD but not colonic CD or UC [7,20]. Drivers of dysbiosis in the context of IBD are not known, but studies have illustrated a genetic component as one factor. 20–50% of monozygotic twins are concordant for CD versus 10% concordance in dizygotic twins [21] and more than 200 susceptibility loci have been identified as associated with either UC or CD. Many of these loci are implicated in other immune-related diseases and are linked with innate immunity, epithelial barrier function, and microbial recognition [22,23•]. For example, NOD2 is involved in peptidoglycan recognition and variations in the gene are linked to increased risk of CD [24].

Cross-talk between the gut and other organs may also drive the development of low-diversity dysbiosis (Figure 2). Liver cirrhosis is characterized by compositional features typical of low-diversity dysbiosis; namely a reduction in anaerobic bacterial families that typically dominate the healthy gut with corresponding increases in facultative anaerobes (Table 1) [10,11,25]. One factor that may drive gut microbiota shifts in low-diversity dysbiosis