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Why related bacterial species bloom simultaneously in the gut: Principles underlying the “Like will to like” concept

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Summary

The large intestine is host to a complex ecological community composed predominantly of obligate anaerobic bacteria belonging to the classes Bacteroidia and Clostridia. This community confers benefit through its metabolic activities and host interactions. However, a microbial imbalance (dysbiosis) characterized by a decreased abundance of Clostridia and a bloom of facultative anaerobic Proteobacteria is commonly observed during inflammation in the large bowel. Here we review recent insights into the principles that favor simultaneous increases in the abundance of closely related species belonging to the Proteobacteria during inflammation, which provides important clues for the rational design of strategies to treat dysbiosis.

Introduction

Our large bowel is host to a complex microbial community (microbiota) composed predominantly of obligate anaerobic bacteria belonging to the phyla Bacteroidetes (class Bacteroidia) and Firmicutes (class Clostridia), while members of the phyla Proteobacteria and Actinobacteria are commonly present in low abundance. Preservation of a balanced microbiota is important for maintaining immune homeostasis, providing nutrients, and conferring resistance against infection (reviewed in (Brestoff and Artis, 2013; Brown *et al.*, 2013; Chu and Mazmanian, 2013; Kamada *et al.*, 2013)). However the general principles that either help conserve a balanced microbial community structure or lead to its disruption during episodes of disease are just beginning to be unraveled.

Maintenance of a balanced microbiota in the large bowel has recently been likened to lawn care, in that severe incidents can take the ecosystem back to bare earth where weed-like species can run wild (Lozupone *et al.*, 2012). The resulting microbial imbalance (dysbiosis) is characterized by phylum-level changes in the community structure, which often includes an increased prevalence of facultative anaerobic bacteria belonging to the Proteobacteria and a decreased relative abundance of obligate anaerobic Clostridia (Fig. 1). In other words, conventional wisdom holds that a balanced gut microbiota (i.e. the lawn) occupies an intestinal niche, which can only support a bloom of Proteobacteria (i.e. of weeds) after it has been vacated. While this metaphor has some appeal, a more mechanistic understanding of the underlying processes is desirable for the rational design of potential intervention

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strategies. Here we review recent mechanistic insights into the processes that lead to phylum-level changes in microbial communities that inhabit the lower gastrointestinal (GI) tract.

***Similis simili gaudet* (like takes pleasure in like)**

The principle underlying phylum-level changes in the microbiota composition is that closely related bacterial species bloom simultaneously in the large bowel. This concept was first noted in studies showing that mice harboring microbial communities characterized by a high abundance of commensal *Escherichia coli* (phylum Proteobacteria) are more susceptible to infection with related enteric pathogens, including *Salmonella enterica* (Stecher *et al.*, 2010), and *Campylobacter jejuni* (Haag *et al.*, 2012). The observation that the presence of closely related bacterial species increases the likelihood that a new bacterial species can enter the gut-associated microbial community has become known as the “like will to like” hypothesis (Stecher *et al.*, 2010), a phrase that has its origin in the Latin *similis simili gaudet*. A possible explanation for this observation is that certain environmental conditions might impose selective forces that confer a fitness advantage upon all members of a phylogenetic group. However the identities of these selective forces are not immediately obvious.

Natural variation in microbial communities inhabiting the lower GI tract of laboratory mice provide clues about possible drivers of phylum-level change in the microbiota composition. Profiling of gut-associated microbial communities from conventional laboratory mice shows that they fall into one of two clusters, termed ‘enterotypes’. One enterotype is characterized by a higher overall diversity and a dominance of Clostridia over Bacteroidia. The second enterotype exhibits lower species diversity, a lower relative abundance of Clostridia and a markedly increased relative abundance of Proteobacteria. Interestingly, the latter enterotype is associated with mice exhibiting low-level intestinal inflammation, as indicated by increased fecal calprotectin levels (Hildebrand *et al.*, 2013)(Fig. 1). Although the concept of human enterotypes has recently been called into question (Koren *et al.*, 2013), the above correlation points to a possible connection between intestinal inflammation, an increased prevalence of Proteobacteria and a decreased abundance of Clostridia within the microbial community.

Inflammation alters microbial communities inhabiting the lower GI tract

Evidence that the inflammatory host response does, in fact, promote an overgrowth of Proteobacteria comes from studies on dysbiosis in mouse models of colitis. Investigation of the mechanism leading to dysbiosis reveals that the inflammatory host response induced by enteric bacterial pathogens, by a chemical trigger, or by genetic predisposition increases the relative luminal abundance of facultative anaerobic bacteria, most commonly members of the family Enterobacteriaceae (phylum Proteobacteria) (Garrett *et al.*, 2010; Lupp *et al.*, 2007) (Fig. 1). Similarly, ileitis induced by the protozoan parasite *Toxoplasma gondii* results in dysbiosis characterized by an uncontrolled expansion of Enterobacteriaceae within the community (Molloy *et al.*, 2013; Raetz *et al.*, 2013; Haag *et al.*, 2012). Some pathogens within the family Enterobacteriaceae use their virulence factors to cause inflammation,

thereby gaining a luminal growth advantage (Kamada *et al.*, 2013; Barman *et al.*, 2008; Lupp *et al.*, 2007; Stecher *et al.*, 2007). Finally, antibiotic treatment has recently been shown to trigger low-level intestinal inflammation (Włodarska *et al.*, 2011; Atarashi *et al.*, 2008), which is at least in part responsible for the enhanced ability of commensal *E. coli* to colonize the large bowel of streptomycin-treated mice (Spees *et al.*, 2013).

The principle that conditions of intestinal inflammation are commonly associated with a bloom of Proteobacteria and/or a decreased prevalence of Clostridia also surfaced in a number of studies on a variety of human illnesses (Fig. 1). For instance, microbial communities in patients with Crohn's disease (CD), a disorder of unknown etiology that can manifest as ileitis or colitis, exhibit an increased prevalence of Enterobacteriaceae and a depletion of Clostridia (Baumgart *et al.*, 2007; Frank *et al.*, 2007; Gophna *et al.*, 2006; Seksik *et al.*, 2003). One of the gravest complications in premature infants is the development of necrotizing enterocolitis (NEC), a disease associated with a bloom of Enterobacteriaceae in the gut (Normann *et al.*, 2013). Human immunodeficiency virus (HIV)-infected individuals can develop chronic diarrhea and an elevated inflammatory tone of the intestinal mucosa without an identified infectious cause, a condition termed HIV enteropathy. A recent study suggests that HIV enteropathy is accompanied by an increased abundance of Alphaproteobacteria, Betaproteobacteria, and Gammaproteobacteria within gut-associated microbial communities (Vujkovic-Cvijin *et al.*, 2013). Finally, changes in the microbiota composition are observed during irritable bowel syndrome (IBS), a condition, which often follows surgery or repeated courses of antibiotics and is characterized by low-level intestinal inflammation and diarrhea. Changes in the microbiota composition reported from IBS patients include a depletion of Clostridia and a bloom of Proteobacteria belonging to the families Enterobacteriaceae, Pasteurellaceae and Pseudomonadaceae (Carroll *et al.*, 2012; Kerckhoffs *et al.*, 2011; Saulnier *et al.*, 2011; Krogius-Kurikka *et al.*, 2009; Matto *et al.*, 2005).

Collectively, these observations are consistent with the idea that the inflammatory host response imposes selective forces that act on closely related organisms, thereby instigating phylum-level changes in gut-associated microbial communities (Fig. 1). However, the question arises whether the identity of these selective forces are the same for each phylogenetic group. In other words, are the factors responsible for increasing the relative abundance of Proteobacteria during inflammation also responsible for a depletion of Clostridia? As outlined below, the answer is likely to be no.

How the host response feeds Proteobacteria

Recent mechanistic insights suggest that the inflammatory host response enhances growth of Proteobacteria by a mechanism that involves production of reactive oxygen species and reactive nitrogen species. As these antimicrobial compounds diffuse away from the epithelium, they react to form respiratory electron acceptors, such as tetrathionate or nitrate, which become available in the lumen during inflammation (Lopez *et al.*, 2012; Winter *et al.*, 2010). Pathogenic *S. enterica* and commensal *E. coli* can use electron acceptors produced as a by-product of the inflammatory host response to support their growth by anaerobic respiration, which leads to their uncontrolled expansion in the lumen of the large bowel

(Rivera-Chavez *et al.*, 2013; Spees *et al.*, 2013; Winter *et al.*, 2013b; Lopez *et al.*, 2012; Winter *et al.*, 2010). Anaerobic respiration provides a fitness advantage because it enables facultative anaerobic bacteria to use non-fermentable substrates or fermentation end products as carbon sources, which enables them to sidestep the competition over fermentable nutrients with obligate anaerobic Bacteroidia and Clostridia (Thiennimitr *et al.*, 2011)(Fig. 2). These data suggest that by producing electron acceptors as a by-product, the host response selectively feeds facultative anaerobic bacteria, which explains the increased prevalence of Proteobacteria within the microbial community during inflammation (Winter *et al.*, 2013a).

There are likely additional mechanisms that contribute to changes in the microbial community structure during inflammation. For example, the process expected to be responsible for the reduced prevalence of obligate anaerobic Clostridia during inflammation is likely distinct from anaerobic respiration, because members of this group lack the terminal oxidoreductases needed to use electron acceptors produced by the host response (reviewed in (Fischbach and Sonnenburg, 2011)). The identities of the negative selective forces that explain why the prevalence of Clostridia is sometimes reduced during inflammation remain to be worked out. Furthermore, these selective forces are not likely to act on all members of this class, because *Clostridium difficile* and some members of the family Lachnospiraceae can increase their prevalence within the community during intestinal inflammation (Chassaing *et al.*, 2013).

Concluding remarks

Although our understanding of factors responsible for the dynamics of gut-associated microbial communities during inflammation is still incomplete, clues gained from studying a bloom of Proteobacteria provides first mechanistic insights into the ‘like will to like’ concept. Our current understanding of the processes responsible for increasing the prevalence of Proteobacteria within the community suggest one of the driving forces is that the host response alters the nutritional environment in the lumen of the lower GI tract. The ‘like will to like’ hypothesis predicts that these changes in the nutritional environment impose similar selective forces on closely related organisms, thereby causing them to bloom simultaneously (Stecher *et al.*, 2010). Consistent with this postulate, the increased availability of exogenous electron acceptors during inflammation is expected to provide an anaerobic respiration-dependent fitness advantage upon facultative anaerobic Proteobacteria, but not upon obligate anaerobic Bacteroidia and Clostridia. The resulting bloom of Proteobacteria during inflammation is arguably one of the most robust ecological patterns observed in the lower GI tract (Fig. 1). Competition between related bacterial species likely arises during this process, especially when they occupy very similar metabolic niches (Deriu *et al.*, 2013; Maltby *et al.*, 2013). Nonetheless, analysis of gut-associated microbial communities suggests that multiple species belonging to the same phylum commonly coexist in this environment.

At a first glance, the above mechanism seems to suggest that clearing the niche might not be necessary, because production of electron acceptors by the inflammatory host response would be expected to support an outgrowth of Proteobacteria even in the presence of a

balanced community of obligate anaerobic bacteria. However, an additional factor that needs to be considered is the ability of a balanced microbial community to actively contribute to immune homeostasis in the intestine (Atarashi *et al.*, 2011). Clostridia in particular are credited with generating large quantities of short-chain fatty acids (SCFAs) during fermentation of complex carbohydrates in the large bowel. In turn, SCFAs stimulate receptors on regulatory T cells, which results in the resolution of inflammation and maintenance of immune homeostasis (Smith *et al.*, 2013). Thus clearing Clostridia from the niche, for example by antibiotic treatment, might be necessary to first elevate the inflammatory tone of the mucosa (Atarashi *et al.*, 2008) before Proteobacteria can increase their abundance through growth by anaerobic respiration (Spees *et al.*, 2013). Even though these skirmishes are still adequately portrayed by the lawn care metaphor (Lozupone *et al.*, 2012), it is becoming increasingly clear that the host immune system – akin to a gardener – plays a critical role in shaping microbial communities in the lower GI tract. Furthermore, elucidation of the mechanisms underlying these complex relationships between the host and its microbiota identifies anaerobic respiration as a potential target for intervention strategies.

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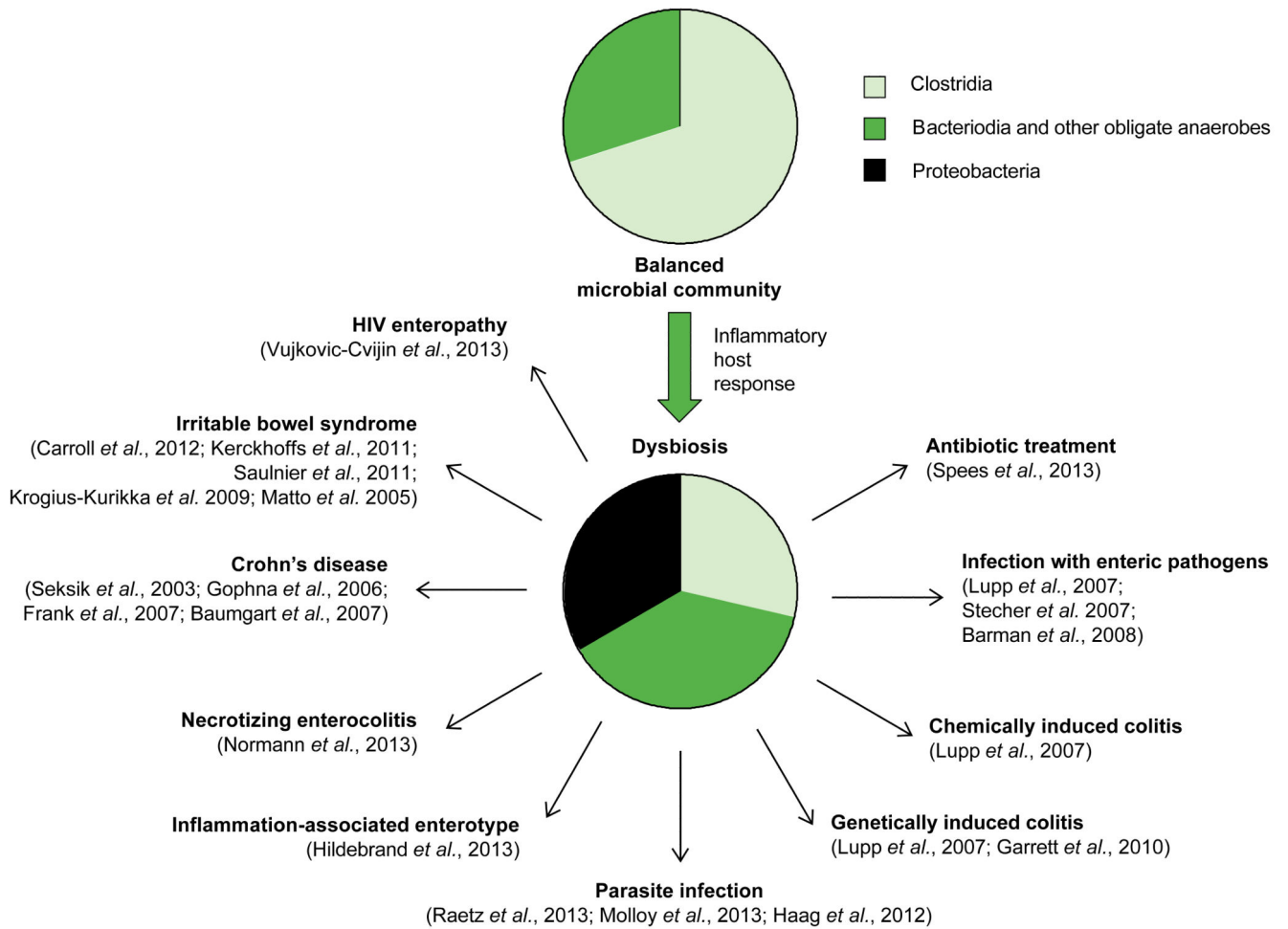


Figure 1.

Changes in gut-associated microbial communities commonly associated with inflammation of the lower GI tract. Pie charts provide a schematic illustration of the balanced microbial community structure of the healthy lower GI tract (top) and the imbalanced microbial community structure (dysbiosis) associated with inflammation of the large bowel (bottom). Black arrows point to recent studies suggesting that this association between the inflammatory host response and dysbiosis is a conserved ecological pattern observed in the lower GI tract.

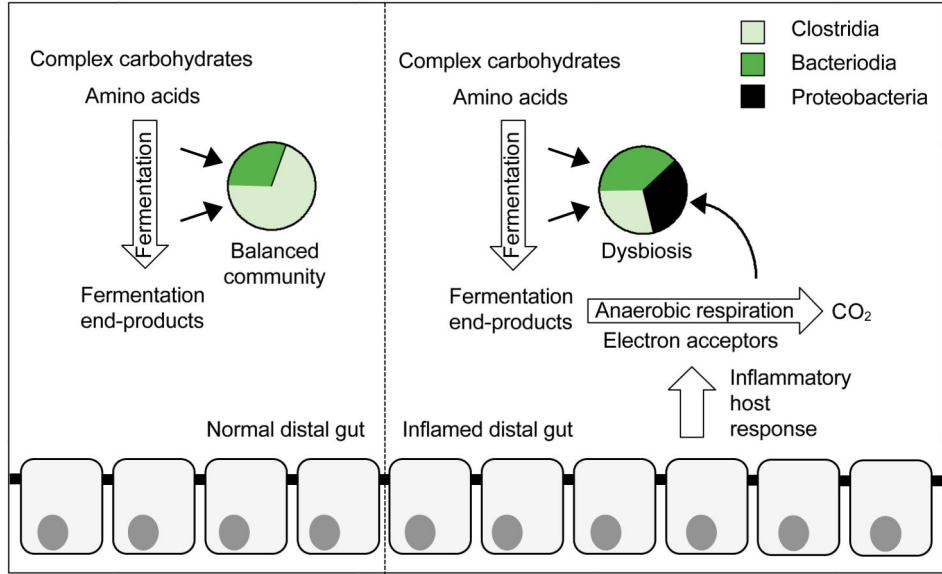


Figure 2.

The host inflammatory response provides a growth advantage for Proteobacteria.

Pie charts provide a schematic illustration of the balanced microbial community structure of the healthy lower GI tract (left) and the dysbiosis associated with inflammation (right). In the absence of inflammation, complex carbohydrates and amino acids support growth of obligate anaerobic bacteria by fermentation (left). The inflammatory host response enables facultative anaerobic bacteria to consume fermentation end products, thereby increasing their prevalence within the community (right).