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Inflammatory disease caused by intestinal pathobionts

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Environmental and intrinsic factors that alter microbiota structure can trigger aberrant immune responses. The resulting states of dysbiosis take many forms characterized by overrepresentation of pro-inflammatory organisms and pathobionts and loss of beneficial commensals further aggravating the inflammatory state. The pathogenic potential of the dysbiotic community can be linked to specific organisms in some cases but accumulating evidence suggests that intestinal inflammatory diseases are driven by collective functions of highly variable polymicrobial communities. Key challenges are to gain sufficient knowledge of the structure and function of a given disease-causing consortium to understand how inflammation is perpetuated, to identify the protective mechanisms lost in the absence of specific commensals and test interventions to shift a persistent dysbiotic community to a more benign state.

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Introduction

Enteric bacteria and their vertebrate hosts have coevolved over millions of years [1]. Colonization and development of a stable microbiota within the intestinal tract is crucial for host physiology and a fully functional immune system [2,3]. The intestinal epithelium is a single layer of cells that facilitates absorption of nutrients and vitamins. Remarkably this thin barrier also prevents pathogen invasion and dissemination of commensals. Coping with the trillions of microbes present in the gut lumen and continuous threats from newly ingested infectious and non-infectious organisms is a tremendous challenge for the mucosal immune system. Achieving a healthy steady state requires mounting an effective frontline defense while enabling the host to accommodate the symbiotic community. Intestinal epithelial cells (IECs) take an active role in both processes through perception of microbial signals and working in concert with immunocompetent cells from the underlying lamina propria. Preservation of homeostasis relies on highly efficient innate and adaptive mucosal immunity and continuous epithelial renewal.

Historically bacteria have been classified according to their relationship with the host: *commensal* or *pathogen*. However, as the field of human microbiome research has exploded in the last decade, more differentiated terms are needed to adequately describe the host–microbe commensal relationship (for an excellent discussion see Ref. [4••]). Homeostasis, and the composition and activities of the symbiotic community can be challenged by host genetics [5] or environmental factors such as diet [6,7•] or medication [8]. The altered host–microbe relationship can be defined as *dysbiosis* when the microbial shift has pathophysiological consequences. *Pathobionts* are members of the symbiotic community that expand as a result of the imbalance and exert pathogenic effects on the host.

Here I discuss how microbial dysbiosis contributes to the development and pathology of inflammatory diseases of the intestine, use recent advances with selected experimental models to illustrate microbial-driven pathologies and focus on the particular role of pathobionts in this dysregulated state.

Individualists vs. community level pathogenic potential

Antibiotics alter microbiota composition and functions producing both acute and long-lasting deleterious effects for the host [9]. Depletion of microbial density diminishes signaling to the intestinal mucosa, impairs colonization resistance and allows expansion by the antibiotic resistant population. A healthy human microbiota harbors a rich and diverse reservoir of resistance genes, which amplify dramatically during treatment [10]. Moreover, antibiotic use lowers resistance to intestinal domination by bacteria associated with hospital-acquired infections [11]. Overgrowth and dissemination to extraintestinal organs by highly resistant bacteria such as vancomycin-resistant Enterococci and multidrug-resistant Enterobacteriaceae create clinical problems that increasingly defy treatment [12,13].

The induced dysbiosis can also result in overgrowth of toxigenic members. The organisms causing antibiotic associated diarrhea remain unidentified in many cases,

yet antibiotic associated colitis is a disease model that has enabled single organisms and their specific pathophysiological effects to be causally linked to the development of inflammatory disorders. Resident members such as *Clostridium difficile* or *Klebsiella oxytoca* flourish under these conditions and their ability to produce protein or small molecule enterotoxins, once high microbial densities are reached [14], is responsible for some but not all forms of antibiotic associated colitis [15,16]. Although these organisms appear to exert their pathogenic properties individually, a complex interplay between pathobiont, microbial community, and host response actually determines disease outcome [17].

Other inflammatory diseases are instigated not by single organisms but by the collective activities of a multispecies community. Interactions between community members create synergies and determine the pathogenic potential of the consortium, such as the capacity to overgrow, produce noxious substances, sustain inflammation and support pathogens [18]. Hajishengallis and Lamont [4••] suggested the term *nososymbiocity* [*nosos* (Greek for disease) arising from host–microbe *symbiosis*] to describe the capacity of an indigenous community to cause disease in a context-dependent manner. The potential for a dysbiotic microbiota to induce an immune response that is uncontrolled and destructive is a key component in inflammatory mucosal diseases.

Crohn's disease (CD) and ulcerative colitis (UC) are two intestinal inflammatory conditions collectively called inflammatory bowel disease (IBD) that are caused by multiple factors involving host genetics, the environment, and microbes. Hallmark shifts in microbial abundances in CD are expansion of pathobiont microbes from Bacteroidetes and Enterobacteria and a concomitant depletion of symbiont microbes including Firmicutes, Bifidobacteria and Clostridia [19]. Nonetheless evidence implicating a single pathobiont has not emerged from studies of different IBD cohorts. Perturbation of the host–microbe commensal relationship is widely accepted as a leading factor driving the inflammatory tissue injury. Yet the microbial component of IBD has been more difficult to define primarily because the bacterial role in pathogenesis occurs indirectly, via stimulation of the immune system. The emerging view based on numerous studies is that collective interactions of the community drive disease through dysregulation of mucosal immunity and disruption of the mucosal barrier. The resulting loss of tolerance to antigens present in the commensal microbiota induces chronic intestinal inflammation and disease. Knowledge of how immunopathological communities become established has advanced dramatically (Figure 1). Functional mechanistic insights into how the host response shapes the microbial community and the consequences of these fluctuations are also beginning to emerge. The challenge remains to delineate the respective roles of community members to understand causalities between gut microbes and immunity.

Host genetic deficiencies and colonic microbial ecology

Large-scale genome-wide association studies reveal IBD as complex multigenic disorders [20]. The genetic variants that confer risk to IBD indicate the importance of genes involved in recognition and intracellular killing of bacteria including autophagy genes involved in bacterial clearance [21]. Although genetic polymorphisms associated with IBD predispose the host, it is increasingly appreciated that both genetic background and inflammation itself impacts the microbiota. The resulting shift in microbial structure and function is required for induction and perpetuation of chronic inflammation. As an illustration of this, both loss and hyperactivity of inflammasomes – complexes that act as steady-state sensors of pathogen-associated molecular patterns and regulators of the colonic microbiota – are linked to dysbiosis, pathobiont expansion and disease [22–24]. Lack of the inflammasomes NLRP6 and NLRP3, for example, results in dysbiosis marked by expansion of several specific taxa not found in wild type littermates [23,24]. The altered gut microbiota generated by inflammasome deficiency triggered an enhanced inflammatory response in the intestine and predisposed the host to IBD. Importantly, the colitogenic phenotypes were communicable to wild type mice through co-housing. Moreover, genetically susceptible mice treated with antibiotics to reduce the microbiota or those born via caesarian section then raised germ-free developed little or no colitis. Thus, genetic alterations play a role, yet it is the associated changes in microbial composition and pathogenic potential that are believed to regulate not only the rate of progression of IBD, but also colorectal cancer and multiple metabolic syndrome-associated abnormalities [25,26]. This interpretation raises the question of whether genetics predispose individuals to a less effective microbiota.

Role of the microbiota in the inflammatory cascade

Identifying the causal molecular mechanisms that enable pathobionts to contribute to disease development has been challenging but important insights are emerging. In the healthy intestine, there is normally a low oxygen level and a large obligate anaerobe population. Fermentation of complex polysaccharides supports anaerobic growth of the resident community. However, conditions and diseases leading to intestinal inflammation disrupt the microbiota composition severely [27,28]. Inflammatory conditions are mainly associated with an overall drop in species richness and an alteration in the abundance of several taxa [29,30]. Obligate anaerobes from the phyla Bacteroidetes and Firmicutes are lost and facultative anaerobes belonging to the Gammaproteobacteria increase. The bloom of Enterobacteriaceae is notably