Unsettling Facts of Life: Bacterial Commensalism, Epithelial Adherence, and Inflammatory Bowel Disease

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A fascinating and unsettling fact of life, perhaps better known to the GASTROENTEROLOGY readership, is our cohabitation with an astonishing diversity and abundance of colonic bacteria. The human large intestine contains hundreds of culturable bacterial species,[1–3] and morphologic and molecular analysis suggest an equal number of unculturable species.[4–6] Although the characterization of these bacteria is incomplete, it is clear that there are a lot of them. For individuals on a Western diet, colonic bacteria exceed 50% of fecal solids.[7] At 10^{13} to 10^{14} organisms, humans on a cellular basis are perhaps only 10% human.

Gut bacteria directly contribute to both energy salvage and metabolic support of the local mucosa, particularly through bacterial hydrolysis and fermentation of carbohydrate and peptide components of the feces.[8,9] However, commensal bacteria also pose ongoing risks to the host. Bacterial products, particularly cell wall and outer membrane components stimulatory to the innate immune system, may initiate or aggravate mucosal inflammation in the susceptible host.[10,11] Inflammation, and deficient or unfavorable metabolic products, also contribute to intestinal disorders ranging from flatulence to cancer. The regulation of microbial make-up and activity is thus a critical aspect of gut homeostasis. A major mode of regulation is interbacterial, through processes such as nutrient competition and quorum sensing.[12] In fact, the manipulation of enteric microflora by diet and microbial competition forms the basis of emerging pre- and probiotic therapies.[13,14]

More subtly, coevolution has yielded reciprocal host-bacterial regulatory mechanisms at the mucosal surface. For example, high-throughput molecular analysis of intestinal colonization by *Bacteroides thetaiotaomicron* reveals striking changes in bacteria metabolism on one hand, and modulation of epithelial functions on the other, including nutrient absorption, mucosal barrier fortification, and xenobiotic metabolism.[15,16] One aspect of such reciprocal recognition is glycan-based bacterial-epithelial adherence. However, adherence poses profound hazards to the host— excessive bacterial retention, accumulation of toxic or proinflammatory bacterial products, or mucosal invasion. Accordingly, adherence is attenuated through diverse host processes including mucus production, secretory IgA, maintenance of local metabolic barriers, antibacterial molecules, and active cellular processes.[9,16,17]

In this issue of GASTROENTEROLOGY, Swidsinski et al.[18] report a striking disturbance of adherence attentuation in chronic colitis. Using a clever in situ assay for mucosa-associated bacteria, the investigators find that most patients with persistent colitis (inflammatory bowel disease [IBD] and indeterminate colitis) were distinguished from control groups (self-limited colitis and asymptomatic subjects) by more frequent and excessive levels of such bacteria. The bacteria were diverse phylogenetically, and were not distinguishable from the predominant fecal microbiota in healthy individuals. Enteric bacteria play an essential role in human Crohn's disease and model chronic colitis.[11] Mutation of a bacterial sensing gene, *N0D2*, accounts for a major genetic locus of Crohn's disease susceptibility.[19–21] How do the present findings help us better understand the role of bacteria in chronic colitis?

First, a confounding issue in such studies is the effect of disrupted mucosa on local bacterial behavior. At sites of active inflammation, bacteria may encounter dysfunctional or absent epithelium, with gross changes to barriers attenuating invasion and exposure of stromal sites for bacterial adhesion. However, in a careful morphologic and ultrastructural examination, Swidsinski et al.[18] uncover little evidence for these modes of bacterial invasion. In fact, the most abundant bacterial recovered are from intact rather than inflamed mucosal sites. Hence, the phenotype reflects a disorder that appears to directly enhance bacterial-epithelial adhesion.

What mechanisms might account for the excessive bacterial adhesion? Some studies have reported novel adhesive bacteria species in IBD, but these were limited to strains of *E. coli*.[22–24] In the present work, a diversity of bacterial species share the trait of epithelial adhesion. This could be explained by a primary mucosal disorder, such as impaired host attentuation processes or aberrant epithelial glycan expression.[25–27] A role for such mucosal dysfunction deserves exploration from cell biology and genetic perspectives, particularly because the phenotype among individuals is heterogeneous within each patient group. However, recent work by Shoemaker et al.[28] points to an alternate explanation. Among intestinal microflora, there is remarkably promiscuous sharing of expressible genes and horizontally transmissible ele-

ments.[28] One might speculate that the excessive epithelial adhesion by diverse bacterial species in such patients could reflect the exchange and positive selection for a promiscuous adhesin-bearing episome.

Are these adherent bacteria the inducers of mucosal inflammation, or are they nonpathogenic correlates of colitis? The present study does not address this important question, but it is surprisingly challenging to resolve. In murine models of chronic colitis dependent on ambient enteric bacteria, monoassociated bacterial pathogens are only now being identified. In the few cases where representative bacterial species are established (e.g., *B. vulgatus*, *H. hepaticus*, *E. faecalis*), they are highly restricted to individual models, and their bacterial virulence traits are entirely unknown.[29–32] The present study's design also does not address the potential role of minor microbial components or the major cohort of nonculturable bacteria as disease factors.

Swidsinski et al.[18] describe an apparently global disturbance of host-bacterial interaction in chronic colitis, involving both inflamed and uninvolved mucosa, and diverse bacterial species. The findings reflect a relationship gone awry, but leave open whether host or bacteria is to blame. Confirmation of this striking observation, and delineation of its mechanism, may provide a new perspective on therapeutic strategies to restore the physiologic host-bacterial interaction.

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