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Enteric Infection and Inflammation Alter Gut Microbial Ecology

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Abstract

The complex microbial community residing within the intestine plays important roles in host defense. However, the impact of enteric infection and inflammation on this resident community has not been fully explored. In this issue of *Cell Host & Microbe*, Lupp and coworkers reveal that the composition of the intestinal microbiota changes in distinctive ways in response to infection and inflammation.

Starting at birth, the epithelial surfaces of the human body are colonized by communities of microorganisms. In the adult human body, the total number of microbial cells can outnumber human cells by an order of magnitude. The majority of these microbial cells reside within digestive tract communities, where they reach extremely high densities (10^{11} to 10^{12} cells/ml). The intestinal microbial community (microbiota) of both humans and mice consist of only a few bacterial phyla (deep phylogenetic lineages), dominated by the phyla Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. These few deep lineages terminate in a multiplicity of shallow lineages, comprising hundreds of bacterial species and thousands of strains (Eckburg et al., 2005; Ley et al., 2005).

Studies in humans and rodent models have revealed that the gut microbiota impacts upon a wide range of host biological processes. These include aspects of both innate and adaptive immunity, metabolism of dietary nutrients and xenobiotics, cell renewal in the intestinal epithelium, as well as intestinal angiogenesis and motility (Dethlefsen et al., 2006; Ley et al., 2006). The gut microbiota has also been implicated in the etiology of a spectrum of human diseases, including inflammatory bowel disease (IBD), colorectal cancer, allergies, and obesity (Dethlefsen et al., 2006). There is, therefore, considerable interest in understanding the organizational principles underlying gut microbial ecology during homeostasis, disease, and other events.

Two salient events that can occur within the intestine are the invasion of pathogenic microorganisms and inflammation. In the natural setting, both infection and inflammation take place within an intestinal ecosystem that already contains a complex microbiota. The microbiota is not a passive bystander during these events, as specific members of the gut microbiota can contribute to pathogen exclusion (Reid et al., 2001) and can also help suppress (and sometimes promote) inflammation (Sansonetti, 2004). Study of enteric

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infection and inflammation has historically focused on the mechanisms utilized by invading pathogens to establish infection, as well as the host mechanisms that permit and/or defend against infection. In contrast, investigations of how the overall structure of the intestinal microbiota is impacted by infection and inflammation have only recently been initiated (Kuehl et al., 2005), and many questions remain unanswered. For example, how is the composition of the normal microbiota affected by inflammation and/or invasion by foreign microbes? Can these microbial communities subsequently reestablish their original structure? What are the organizing principles that determine these changes in microbial community structure? As reported in this issue,Lupp et al. (2007) have used a panel of mouse models of intestinal infection and inflammation to address these questions. By monitoring the composition of intestinal bacterial communities as a function of pathogen infection and inflammation, they call attention to several emerging themes in gut microbial ecology.

First, different bacterial species can display different abilities to colonize a host and induce inflammation. Introduction of the human enteric pathogen *Campylobacter jejuni*, or mouse enteric pathogens *Citrobacter rodentium* (Lupp et al., 2007) or *Helicobacter hepaticus* (Kuehl et al., 2005) into wild-type mice resulted in robust colonic colonization by the respective pathogen. In contrast, nonpathogenic *Escherichia coli* failed to establish a robust colonization following introduction into the intestines of wild-type mice (Lupp et al., 2007). Among the pathogens that were able to colonize, only *C. rodentium* elicited a robust inflammatory response and subsequent clearance from the gut, while *C. jejuni* and *H. hepaticus* sustained elevated colonic densities without stimulating an inflammatory response (Kuehl et al., 2005; Lupp et al., 2007). The traits required for a foreign bacterium to establish and sustain a robust colonization in the gut are therefore separable from those required to stimulate inflammation.

Second, intestinal inflammation results in reduced intestinal microbial density. Colonization by *C. rodentium* and the resulting inflammatory response were associated with a significant decrease in overall colonic bacterial density. Reduced bacterial density was also observed in an intestinal inflammation model based on oral administration of dextran sodium sulfate (DSS). In both of these cases, reduced microbial density was associated with a reduction in the relative abundance of the bacterial phylum that dominated the respective community prior to the onset of inflammation (Lupp et al., 2007). In contrast, infection with pathogens that establish colonization but do not evoke a robust inflammatory response (i.e., *C. jejuni* and *H. hepaticus*) did not result in appreciable changes in the composition of the respective original community (Kuehl et al., 2005; Lupp et al., 2007). This indicates that inflammation is sufficient to reduce microbial density and induce gross alterations in the colonic microbiota; however, more detailed analyses will be required to reveal the subtle details of these changes. It will also be of interest to determine the functional consequences of these inflammation-induced changes in microbial community composition.

Third, intestinal inflammation is associated with an overgrowth of aerotolerant bacteria. Lupp et al. (2007) observed that *C. rodentium* colonization caused robust inflammation and concurrent enrichment of aerotolerant Gamma-Proteobacteria. Inflammation induced by DSS treatment in wild-type mice resulted in enrichment of *Enterococcus faecalis*, an

aerotolerant member of the Firmicutes phylum (Lupp et al., 2007). Overgrowth of aerotolerant bacteria has also been observed in patients suffering from IBD (Gophna et al., 2006), suggesting that this could be a nonspecific response to conditions associated with enteric inflammation. It remains unclear if such alterations in microbial community structure are a cause and/or consequence of inflammation in IBD. However,Lupp et al. (2007) observe that the nonpathogenic Gamma-Proteobacterium *E. coli* is only able to establish a robust colonization in the presence of inflammation (induced either by DSS treatment or loss of the anti-inflammatory cytokine IL-10), suggesting that inflammation can be sufficient for aerotolerant bacteria to colonize the gut.

Finally, the composition of the original microbial community is largely restored following clearance of the enteric pathogen. *C. rodentium* colonization resulted in a rapid reduction in microbial density and altered community composition, followed by clearance of the pathogen over the next few weeks. Strikingly, the composition and density of the colonic microbial community after pathogen clearance was very similar to the composition of the community that preceded infection (Lupp et al., 2007). This underscores the presence of strong organizing principles in gut community composition that specify the relative abundance of different microbial taxa. This is consistent with previous observations that a foreign microbial community (a zebrafish gut microbiota dominated by phylum Proteobacteria) introduced into a germ-free mouse is subsequently modified by the host gut habitat such that members of bacterial phyla that dominate the normal mouse gut microbiota (i.e., Firmicutes) are markedly amplified (Rawls et al., 2006). Deciphering the organizing principles that determine the structure of the gut microbiota during homeostasis and disease remains an important goal for future investigation.

Lupp et al. (2007) demonstrate that predictable changes in microbial community composition can be associated with specific events within the gut ecosystem; they observed that intestinal inflammation is associated with decreased microbial density and enrichment of aerotolerant bacteria. This raises the attractive possibility that different types of disease and perturbation of the gut ecosystem might have distinct and reproducible effects on microbial community structure and function. This notion is supported by the recent observation that the intestines of obese individuals display distinct differences in the relative abundance of dominant bacterial phyla compared to lean counterparts (Ley et al., 2005). Such disease-specific microbial fingerprints will provide critical frames of reference for understanding the etiology of intestinal and extra-intestinal diseases.

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