Shaping the immune system by commensal bacteria in the gut

The human intestine is colonized with hundreds of phylotypes of nonpathogenic commensal bacteria that have co-evolved with humans over many millennia. These bacteria, which grow to extremely high densities in the colon, appear to be beneficial to humans by preventing the overgrowth of pathogenic microorganisms, by digesting polysaccharides that can then be more easily absorbed, and, most important, by shaping the mucosal immune system. However, the interactive processes between commensal bacteria and the host and the specific bacteria that colonize the intestine and are responsible for these beneficial effects are poorly characterized.

These very important questions have been addressed by two recent studies—one by Gaboriau-Routhiau *et al*.,[1] the other by Ivanov *et al*.[2]—and by a Commentary by Ivanov and Littman in this issue of *Mucosal Immunology*.[3] The two earlier papers both show that a single, specific commensal bacterial microbe—a *Clostridia*-related species called segmented filamentous bacteria (SFB)—has a profound role in shaping the immune system and enhancing the development of T helper type 17 (Th17) cells. In the absence of SFB—for example, in germ-free mice—Th17 cells failed to develop, but replenishment of this single phylotype in mice fully restored the development of Th17 cells, fulfilling Koch's postulates that the development of Th17 cells requires an infectious agent. Given that Th17 cells develop in a reciprocal relationship with regulatory T cells, are important in host defense against bacteria and fungi, and are essential for the development of inflammatory bowel disease, the acquisition of SFB in the gastrointestinal tract appears to represent an important event in the development of the host. The Commentary by Ivanov and Littman provides further perspective on this topic.

SFB have eluded detection and been invisible to microbiologists because these bacteria are not culturable by current standard culture techniques and can be identified only with new molecular methods that amplify by reverse transcription–polymerase chain reaction and sequence bacterial 16S ribosomal RNA. These new 16S ribosomal RNA methodologies, which indicate that the majority of the intestinal bacteria are in fact not culturable, have dramatically changed microbiology and redefined the bacterial communities present in the gut and the environment.

These two provocative studies showing that SFB have profound effects in shaping the immune system evoke many additional questions. For example, are the SFB identified in mouse Th17 cell development also important for human Th17 cell development? In the study by Gaboriau-Routhiau,[1] administration of normal human colonic bacteria to germ-free mice did not induce the expansion of the Th17 subset, indicating that SFB are not part of the human intestinal microbiome, although more extensive studies of human gastrointestinal bacteria need to be performed. Also, would SFB, if given to humans, induce human Th17 cell development, or do other bacterial phylotypes perform this function in humans? Moreover, have SFB or SFB-related bacteria been eliminated from the human intestinal microbiome, and has the human intestinal microbial community changed dramatically over the past several decades, in response to improved "hygiene," to changes in the human diet, or to increased use of antibiotics? And are these changes responsible for the significant increase in the prevalence of autoimmune diseases, including inflammatory bowel disease, or for the increase in the prevalence of asthma and allergy that have occurred in the past two to three decades? What are the specific molecular mechanisms by which SFB induce Th17 cells and affect dendritic cells, epithelial cells, or other host cells, and can these be replicated by specific SFB molecules? Finally, do other bacterial species affect the expansion of SFB, and are there specific intestinal bacteria responsible for the development of regulatory T cells, Th1 cells, or Th2 cells?

Understanding the specific gastrointestinal bacterial species that shape the immune system, and the specific pathways by which such bacteria interact with the host, could clearly lead to the development of novel beneficial therapies for many diseases. We look forward to additional studies of nonculturable microbes, as well as studies of how these microbes affect the mucosal immune system.

Dale T Umetsu, Associate Editor

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2. Ivanov, I.I., Atarashi, K., Manel, N., Brodie, E.L., Shima, T., Karaoz, U. *et al.* Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell* **139**, 485–498 (2009).
3. Ivanov, I.I. & Littman, D.R. Segmented filamentous bacteria take the stage. *Mucosal Immunol* **3**, 209–212.