eosinophils might selectively impact worm fitness during chronic infection. It will be helpful to recapitulate similar analysis of eosinophil-deficient mice in pathophysiological contexts such as helminth infection.

Recent work establishes a link between nutrient intake and eosinophil homeostasis (Nussbaum et al., 2013). Diet is an important factor regulating intestinal health, which in turn is thought to impact autoimmune and inflammatory disease susceptibility. The role of eosinophils in diet-related intestinal dysbiosis is unclear. It will be fascinating to learn how eosinophil function is directly affected by changes in availability of dietary metabolites such as in low-fiber, high-fat, restricted nutrient diets. The link between micronutrient deficiency and type 2 barrier immunity was recently highlighted (Spencer et al., 2014). The role of eosinophils in adapting dynamically to dietary changes and microbial presence or absence in the gut clearly could help elucidate mechanisms driving autoimmunity and inflammatory diseases, as well as infection and immunity in malnourished regions.

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Microbial Learning Lessons: SFB Educate the Immune System

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Segmented filamentous bacteria (SFB) contribute to immune-system maturation. In this issue of *Immunity*, Goto et al. (2014) and Lécuyer et al. (2014) provide evidence for how SFB induce antigen-specific T helper 17 cells and promote development of adaptive immunity at discrete mucosal sites.

Powerful signals from the microbiota instruct architectural and functional features of the mammalian immune system (Lee and Mazmanian, 2010). Though the human and mouse microbiota contain several hundred species, only a handful of microorganisms have been experimentally shown to have immune-modulating capabilities. Segmented filamentous bacteria (SFB) are unique, compared to other microbes, in their ability to induce germinal center activation in Peyer's patches (PPs) of mice (Talham et al., 1999), increase production of immunoglobulin A (IgA) (Klaasen et al., 1993), and contribute to the expansion and function of mucosal T cells (Umesaki et al., 1999). Unlike other T helper cell subsets, T helper 17 (Th17) cells, which have been linked to both mucosal resistance to enteric pathogens and to autoimmunity in mice, are acutely responsive to the microbiota and to SFB in particular. Germ-free animals are essentially devoid of gut Th17 cells (Ivanov et al., 2008), and interest in SFB was rekindled when two groups showed that this microbe specifically induced Th17 cells in the small intestine of mice (Ivanov et al., 2009; Gaboriau-Routhiau et al., 2009). Subsequent work showed that SFB promote Th17 responses at extraintestinal locations during autoimmune inflammation (Lee et al., 2011; Wu et al., 2010), and although the site of induction is unknown, a gut origin is likely. In this issue, two papers extend understanding of how specific members of the gut microbiota educate the mucosal immune system. Goto et al. (2014), and Lécuyer et al. (2014), show that SFB induce adaptive immune responses at specific, and unconventional, mucosal sites, likely involving a process that requires presentations of SFB antigens.

Mice and humans are born with an immature gut-associated lymphoid tissue (GALT) that develops simultaneously as a complex microbiota of several hundred bacterial species is forming after introduction to gut microbes after birth. The concurrent development of both the immune system and microbiota suggests that postnatal maturation of the host might, in part, depend on input from gut

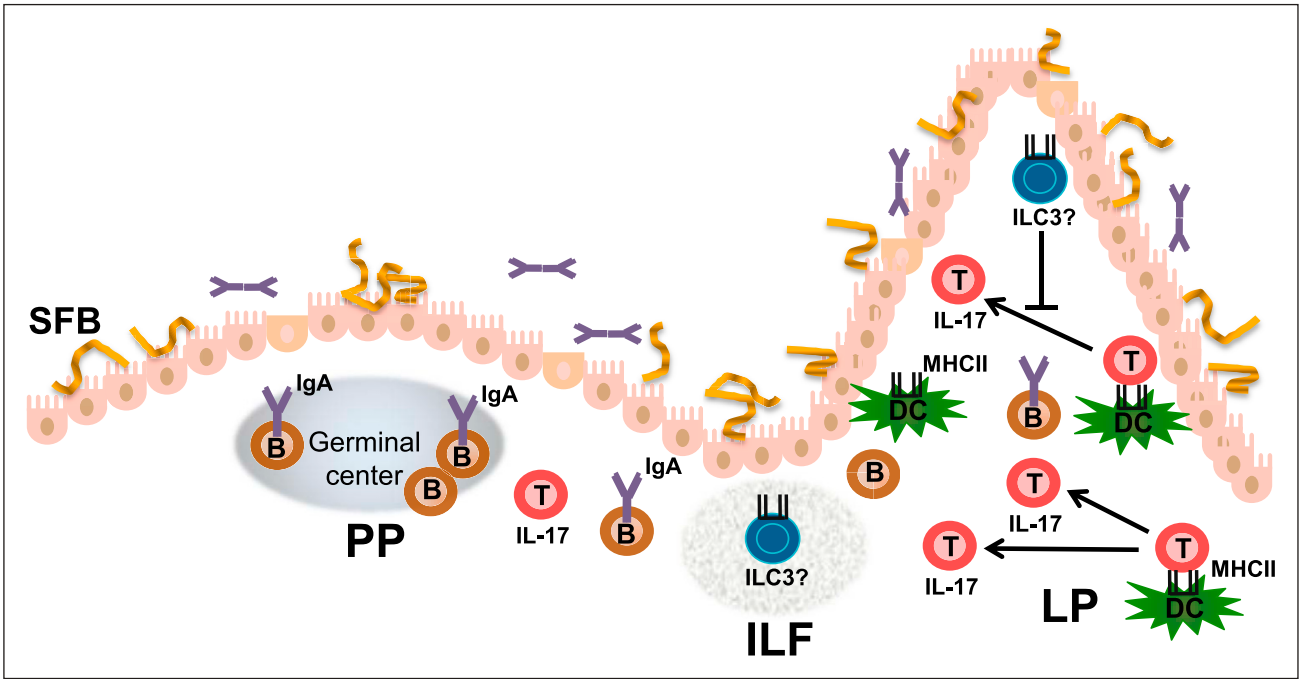

Figure 1. SFB Induce Adaptive Immune Responses at Several Mucosal Sites via Antigen Presentation
SFB are able to induce activation of germinal centers in PPs and drive formation of ILFs. IgA can be produced at these sites. In the absence of PPs and ILFs, SFB are still able to induce adaptive immunity, presumably at tertiary lymphoid sites in the LP. This process appears to be dependent on MHCII expression for DCs to induce Th17 cell development and for ILCs to inhibit Th17 cells.

bacteria. Indeed, adult germ-free animals display specific defects in both the physical architecture of the GALT, as well as in distinct immune cell subsets. Furthermore, not all bacteria are similar in their ability to induce developmental processes in mice. Lécuyer and colleagues focus on anatomical sites of induction for IgA-secreting and Th17 cells, comparing colonization of mice with SFB to a nonpathogenic strain of *Escherichia coli*. As mentioned, PPs are considered a major inductive site for activation of mucosal immunity in response to gut bacteria, although other secondary and tertiary immune sites—such as mesenteric lymph nodes (MLNs), the lamina propria (LP), and isolated lymphoid follicles (ILFs)—have also been implicated. Lécuyer and colleagues confirm that colonization of mice with SFB induces activation of germinal centers in PPs (Figure 1). Intriguingly, mice lacking PPs were still able to support production of IgA-secreting cells in response to SFB, albeit in reduced numbers compared to wild-type mice, whereas these structures remain required for adaptive immune responses to *E. coli*. In addition to PPs, the authors reveal that cryptopatch-derived ILFs are also dispensable for the development of IgA-secreting cells in response to SFB, suggesting that perhaps the LP or transiently induced tertiary lymphoid tissues might also be involved in responses to this unique microbe. Indeed, monocolonization with SFB, but not *E. coli*, resulted in the de novo development of tertiary lymphoid tissues in the LP that are distinct from cryptopatch-derived ILFs (which require the transcription factor RAR-related orphan receptor-γt [RORγt] for their formation). Presumably, in addition to PPs, tertiary lymphoid tissues, also found in mice with a complex microbiota, are the location for IgA responses in SFB monocolonized mice, a notion further supported by findings that MLNs or the spleen are not required for induction of adaptive immunity in response to SFB.

Lécuyer and colleagues also investigated the anatomical requirements for SFB-mediated induction of Th17 cells. In contrast to IgA, the Th17 cell response to SFB was at least partially antigen specific. PPs and cryptopatch-derived ILFs were fully dispensable for SFB-meditated interleukin-17 (IL-17) production from $CD4^+$ T cells. However, T cells from mice that are unable to form PPs, ILFs, and de novo tertiary lymphoid structures did not express IL-17 in response to SFB antigens, further suggesting these transient sites as being important for immune regulation by SFB. Nonspecific Th17 cells did appear in the MLNs of SFB monocolonized mice without organized mucosal lymphoid tissues, demonstrating that this microbe can elicit proinflammatory T cells that might impact immunity in systemic compartments. It is interesting to speculate whether these non-antigen-specific Th17 might be involved in extraintestinal autoimmune responses driven by SFB in animal models of multiple sclerosis and rheumatoid arthritis (Lee et al., 2011; Wu et al., 2010).

The notion that commensal bacteria can induce antigen-specific adaptive immunity in the gut is intriguing, and SFB offer a tool for investigating this concept. Cytokine signaling, partially regulated by the microbiota, likely plays a critical role in Th17 cell induction (Ivanov et al., 2009); however, whether other pathways including cell contact-dependent mechanisms are required has remained unknown. Goto and colleagues show that major histocompatibility complex II

(MHCII)-dependent presentation of SFB antigens to T cells is critical for the induction of mucosal Th17 cells (Figure 1). Similar to Lécuyer and colleagues, these authors show that gut Th17 cell responses can be both specific for SFB, or not, but that SFB-specific Th17 cell induction requires SFB. This suggests a critical role for antigen presentation. Indeed, SFB-specific Th17 cells are greatly reduced in the GALT of MHCII-deficient mice, whereas nonspecific Th17 cell proportions are unchanged in these animals, suggesting that cell contact is required for distinguishing between the development of populations with differing antigenic or antigen specificities. Goto and colleagues further demonstrate that restricting MHC deletion to intestinal dendritic cells (DCs) abrogates SFB-specific Th17 cell development, suggesting that $CD11c^+$ DCs process and present SFB antigens to $CD4^+$ T cells to initiate this process. The cytokine environment is important for both specific and nonspecific Th17 cells but ostensibly is not sufficient for the development of SFB-specific Th17 cells in the murine small intestinal LP. Though this study indicates that SFB-induced Th17 cells recognize proteins from SFB, the identity and characteristics of the antigens remain undefined. Nevertheless, it appears that most Th17 cells that are induced by SFB recognize antigens from this organism, in a response that is polyclonal and thus suggesting that numerous SFB antigens might be presented by MHCII on DCs.

In accord with the companion study, Goto and colleagues show that PPs and ILFs are dispensable for SFB-induced Th17 cells, further suggesting that the LP might be a site of induction for IL-17-producing $CD4^+$ T cells in the GALT. The authors propose a model whereby DCs in the small intestine acquire and present SFB antigens during the local priming of $CD4^+$ T cells. They further investigate other cell types that might be involved in antigen presentation, initially ruling out intestinal epithelial cells (IECs) that are known to express MHCII. Intriguingly, they identify MHCII expression on Lin^- $ROR\gamma t^+$ innate lymphoid cells (ILCs) and show that deletion of MHCII specifically in group 3 innate lymphoid cells (ILC3) results in increased proportions and numbers of small intestinal Th17 cells, even in the absence of SFB. Colonization of $ILC3^{\Delta MHCII}$ mice with SFB leads to a further enhancement of Th17 cells, with these cells having features of antigen specificity for SFB. Thus, MHCII expression on ILC3 cells seems to restrain Th17 cell development to both diverse gut bacteria and SFB. The dynamic relationship between DCs and ILCs, and the complex environments where these cells interact (e.g., PPs, ILFs, tertiary lymphoid structures) to mediate the potent effects of the microbiota are undefined but likely represent fascinating features of immune orchestration by gut bacteria.

These two studies expand our understanding for how a specific member of the mammalian microbiota regulates adaptive immune responses in the gut. Research into mechanistic aspects of host-microbial interactions with the immune system represents an exciting approach to expand our appreciation of this intricate and highly evolved relationship. SFB are a leading example of a microbe that has forged a deep evolutionary connection with mammals, having the unique adaptation to promote specific aspects of host immune development. It will be important to determine whether there are specific SFB antigens that drive IgA production and Th17 cells and/or how SFB create a cytokine environment along with antigen presentation to elicit their potent immune-modulating capabilities. The milieu SFB create also relates to the site of cell induction, which will require further exploration into the biology of tertiary immune structures, and cellular and molecular interactions between DCs, ILCs, and other cell types. Of critical importance will be the discovery of SFB molecules that activate an immunomodulatory process, perhaps signaling via pattern recognition receptors, G-protein-coupled receptors, or other pathways that "educate" DCs to present SFB antigens in a manner that enhances specific immune responses in defined anatomical locations. Discovering how commensal microbes promote development of specific features and functions within our immune system might teach us important lessons in how to harness the microbiota for medical benefit.

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