not epidermal Langerhans cells, is responsible for initiating the unique T cell response. To evaluate the functional significance of these specific CD8 β+ T cells, the study evaluated the capacity of mice to resist infection by *Candida albicans*. Neutralization of IL-17A or depletion of CD8+ T cells is shown to increase *C. albicans* abundance. Although the mechanism of resistance to *Candida albicans* is unclear, mouse skin associated with *S. epidermidis* was shown to express more of the alarmins S100a8 and S100a9. These proteins have been implicated in a variety of functions including the capacity to induce neutrophil migration.

The authors speculate that many other specific skin commensals may have individual roles in educating the host adaptive immune response. Although by definition this interaction is evidence of mutualism, not commensalism, their finding is consistent with previous demonstrations of specific microbe interactions in the skin. For example, *S. epidermidis* was uniquely capable of inducing TRAF1 in keratinocytes (Lai et al., 2009) and *S. aureus* uniquely activated mast cells to exacerbate allergic responses (Nakamura et al., 2013). Furthermore, this study not only demonstrates the potential importance of specific bacteria on skin but also reinforces the idea that bacteria can act across the epidermis and interact with cells in the dermis.

Current knowledge of the mechanisms by which the microbiome participates in host defense is limited, but improving. The Naik et al. study shows that *S. epidermidis* participates in several different ways to directly and indirectly add to the innate and adaptive immune barrier to pathogens (Figure 1). Functional specificity seems to exist at both the species and strain level. It remains to be determined how these functions can be reconciled with the great diversity of organisms detected between individuals or how this knowledge can be translated into therapy. Regardless, these studies show again how bacteria participate in control of immunity and can exist in a mutually beneficial relationship with cells of the mammalian immune system.

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T_{FH}-IgA Responses Keep Microbiota in Check

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http://dx.doi.org/10.1016/j.chom.2015.01.009

In this issue of *Cell Host & Microbe*, Kubinak et al. (2015) demonstrate that gut microbiota-mediated signaling through MyD88 in $CD4^+$ T cells induces their differentiation into T follicular helper (T_{FH}) cells that promote affinity-matured microbiota antigen-specific immunoglobulin A (IgA) responses. These T_{FH}-driven IgA responses are essential for maintaining gut bacterial diversity and a healthy microbiota.

The healthy gut microbiota consists of functionally diverse species of bacteria and other microorganisms. Loss of this tremendous diversity, a condition termed dysbiosis, has been documented in patients with a host of diseases such as inflammatory bowel disease, autoimmune disease, asthma, food allergy, diabetes, obesity, liver cirrhosis, and autism. Several factors, including host genetics, use of antibiotics, diet, and inflammatory conditions, have been shown to decrease diversity of the microbiota and induce disease-related dysbiosis. In contrast to our understanding of these diversity-diminishing insults, the mechanisms responsible for the stable maintenance of diverse species in the gut during the steady state remain relatively unclear. Although the composition of the microbiota between individuals is highly variable at lower

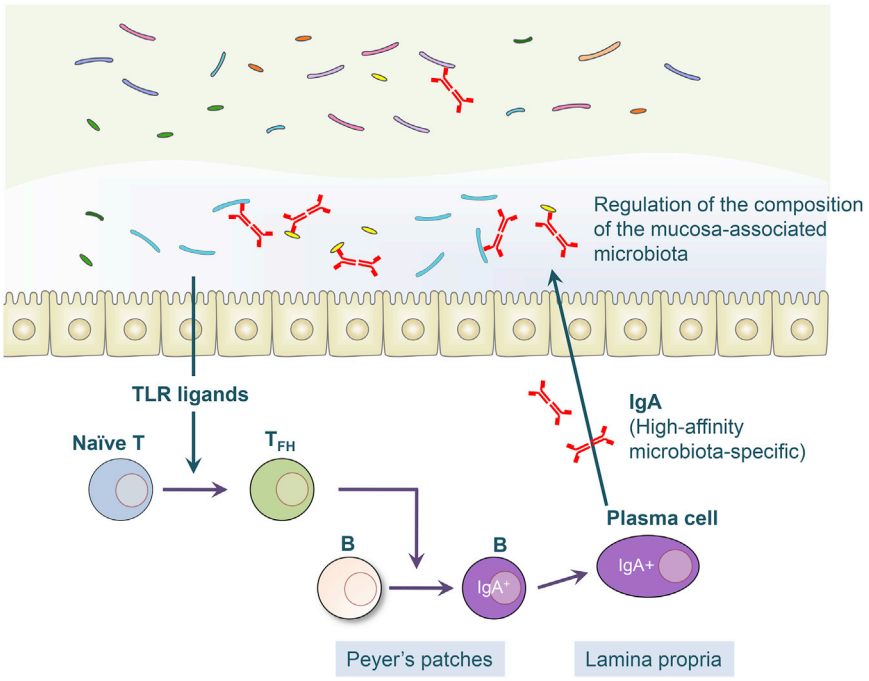

Figure 1. TLR Ligands Derived from the Gut Microbiota Activate MyD88-Dependent Signaling in CD4$^+$ T Cells

Activated CD4$^+$ T cells differentiate into T_{FH} cells, which then instruct B cells to differentiate into high-affinity microbiota-specific IgA-expressing cells in Peyer's patches. The secretory IgA produced by their plasma cell progeny in the lamina propria mainly binds to the bacteria located in the mucus layer close to the gut epithelium. This series of events is essential for keeping the entire microbiota symbiotic and diverse.

taxonomic levels, it is similar at the phylum level. Moreover, the intestinal mucosa-associated surfaces are predominantly colonized by a similar phylogenetic core (Nava and Stappenbeck, 2011). In addition, the overall composition of microbial genes is largely shared among individuals (Qin et al., 2010). Therefore, common host factors are likely to play important roles not only in selection of the microbiota community but also in maintaining its diversity.

Not surprisingly, the immune system has been proposed to be one of the key factors that affect the composition of the microbiota. Indeed, there are clear examples of development of dysbiotic gut microbiota in mice genetically deficient in immune system genes and, conversely, instances where certain members of the microbiota regulate the development of specific subsets of immune cell populations and establish the set-point for the steady-state immune system (Ivanov and Honda, 2012). Considering their long history of co-evolution, the gut microbiota and the host immune system regulate each other in a way that makes the relationship mutually beneficial. Indeed, the commensal microbiota educates the immune system to establish a robust mucosal barrier system. In turn, the immune system, thus educated by the commensals, acts to maintain their indigenous members by preventing further colonization with other microbes, including pathogens and commensals. Furthermore, the commensally educated immune system becomes tolerogenic and has suppressive activity against inflammation, thereby presumably contributing to maintenance of the symbiotic community, because potentially pathogenic microorganisms often prefer inflammatory conditions, while commensals such as Bacteroides and Firmicutes do not. In this issue of *Cell Host & Microbe*, Kubinak et al. (2015) demonstrate that the gut microbiota promotes the differentiation of T follicular helper (T_{FH}) cells and that these induced T_{FH} cells play essential roles in controlling the mucosa-associated bacterial communities and in maintaining a healthy, diverse microbiota through production of high-affinity microbiota-specific IgA.

T_{FH} cells are a distinct subset of CD4$^+$ T cells characterized by their expression of the transcription factor Bcl6, the B cell follicular homing chemokine receptor CXCR5, and the immune modulatory co-stimulatory molecules ICOS and PD-1. In the gut, T_{FH} cells localize in the germinal centers (GCs) of Peyer's patches and mesenteric lymph nodes and promote class switch recombination and somatic hypermutation in GC B cells to produce high-affinity IgA. Kubinak et al. first show that mice with a CD4$^+$ T cell-specific deficiency of the *Myd88* gene (T-MyD88$^{-/-}$ mice) have defects in gut T_{FH} cells, GC B cells, and mucosal IgA. MyD88 is an adaptor protein used by most Toll-like receptors (TLRs) to activate the NF-κB signaling pathway. Germ-free (GF) mice have similar defects, whereas oral administration of GF mice with a TLR2 ligand reverses these defects. Therefore, microbiota-derived TLR ligands are responsible for the activation of MyD88-dependent signaling in T cells, which is required for T_{FH} and IgA$^+$ B cell development in the gut.

Importantly, T-MyD88$^{-/-}$ mice have a decreased percentage of IgA-bound gut bacteria. In wild-type (WT) mice, IgA binds about 4% of the entire bacterial community, whereas less than 1% of bacteria are coated with IgA in T-MyD88$^{-/-}$ mice. Moreover, the composition of IgA-bound bacterial species is different between WT and T-MyD88$^{-/-}$ mice. In WT mice, IgA preferentially binds members of the microbiota that colonize in close proximity to the gut epithelial layer (Figure 1). In contrast, IgA-bound fractions are similar among mucosa-associated and fecal communities in T-MyD88$^{-/-}$ mice. In WT mice, the mucosa-associated communities are usually less variable than luminal communities among individuals because of the selective pressure imposed by microbiota-specific IgA. This selective pressure is lost in T-MyD88$^{-/-}$ mice, and as a result the composition of the mucosa-associated microbiota is highly variable across individual mice and is different from that of WT mice even after cohousing of mutant and WT mice. In particular, mucolytic bacteria, such as members of the Desulfovibrionaceae, Mucispirillum, and Ruminococcus genera, are significantly enriched in the mucosa of T-MyD88$^{-/-}$ mice. Therefore, TLR signaling in T cells governs the magnitude

and nature of IgA responses, thereby affecting the host-mediated selection of microbial communities in the gut. Accordingly, T-MyD88$^{-/-}$ mice display increased susceptibility to colitis. The disease predisposition of T-MyD88$^{-/-}$ mice could be shown to be due to the microbiota dysbiosis, because disease severity was significantly decreased after transfer of fecal microbiota from WT mice. This observation is consistent with a recent report showing that IgA coats colitogenic members of the microbiota and maintains immune homeostasis (Palm et al., 2014). It is noteworthy that Kubinak et al. further demonstrate a significant positive correlation between the relative abundance of GC B cells and the diversity of the mucosal bacterial community. Therefore, a stronger GC and IgA response promotes microbiota diversity, presumably by exploiting targeted bacteria and creating a habitable niche for rare bacterial species (Figure 1).

Several genetically modified mice with defects in the production of IgA in the gut have been used to explore the role of IgA in mucosal immune protection. T-MyD88$^{-/-}$ mice provide a valuable opportunity to understand the previously unexplored role of high-affinity microbiota-specific IgA driven by the microbiota-induced T_{FH} cells in selective control of the mucosa-associated community. It remains unknown where CD4$^+$ T cells encounter TLR ligands, how TLR signaling in CD4$^+$ T cells leads to T_{FH} cell development, and why IgA selectively targets mucosa-associated members. Because most of the IgA induced by T_{FH} cells is specific for microbiota antigens (Kubinak et al., 2015; Kawamoto et al., 2014; Palm et al., 2014), T_{FH} cells generated by the microbiota are also likely to be specific for microbiota antigens. Therefore, dendritic cells (DCs) are likely to play a role in skewing the initial commitment of CD4$^+$ T cells toward the T_{FH} subset. In this context, it has been shown that goblet cells deliver luminal antigen to CD103$^+$ DCs (McDole et al., 2012) and that CD103$^+$ DCs patrol the epithelium and capture bacteria attaching to its surface (Farache et al., 2013). Therefore, DCs localizing to the epithelial layer may sense and capture the mucosa-associated commensals to skew the TCR repertoire and the differentiation of CD4$^+$ T cells toward the T_{FH} subset. In any case, the finding by Kubinak et al. can be used to tailor therapies; for example, oral administration of a mixture of microbiota-specific high-affinity IgAs can be an effective therapy to treat microbiota-driven disease by restoring microbiota diversity.

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Hedgehog: Linking Uracil to Innate Defense

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http://dx.doi.org/10.1016/j.chom.2015.01.010

The ability of the gut epithelium to defend against pathogens while tolerating harmless commensal organisms remains an important puzzle. In this issue of *Cell Host & Microbe*, Lee et al. (2015) reveal how pathogen-secreted uracil acts at two steps to induce ROS via the Hedgehog pathway.

Epithelial barriers represent essential lines of defense against tissue invasion by bacterial and viral pathogens. For a sterile barrier such as the alveolar epithelium of the lung, this challenge boils down to keeping the pathogens and their effectors out. In the setting of a diverse natural ecosystem in the gut, the problem is significantly more complicated. Although pathogenic species must be prevented from invading the host or causing local tissue damage, beneficial or symbiotic bacteria comprising the commensal microbiota require tolerance. Thus, both the innate and adaptive (in vertebrates) immune systems must somehow distinguish friend from foe and respond accordingly.

Drosophila has emerged as an important model genetic system for analyzing gut homeostasis. The *Drosophila* gut