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Communication between the microbiota and mammalian immunity

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Abstract

Mammalian immune systems evolved within a diverse and dominant microbial world, forcing reciprocal interactions between the two. Adaptive immunity enacts specific responses against microbes. These antigen specific responses have classically been studied in the context of pathogenicity, however are now known to have significant effects on our resident microbes. In turn, microbes employ an arsenal of mechanisms to influence development and specificity of host immunity. Understanding these complex reactions will be necessary to develop microbiota based therapies to prevent or treat disease. Here we review the literature detailing the cross-talk between resident microbes with a focus on the specificity of the host response and the microbial molecules that influence them.

Specificity of immune responses toward commensals

The GI tract harbors a highly complex microbial community that actively communicates with the intestinal immune system, significantly impacting host health. The adaptive arm of the immune system, comprised of T and B lymphocytes, interact with this microbial community to both prevent microbial invasion and pathogenesis while also preventing detrimental immune responses toward commensal microbes. Classically, T and B cells react to foreign molecules, or antigens, via their T and B cell receptors, and therefore their responses are considered to be highly specific to target precise organisms. Within the intestine there is a vast amount of dietary and microbial antigens that can continuously stimulate intestinal lymphocytes. This constant stimulation promotes immune processes to maintain a beneficial interaction with the microbiota, but can also promote pathogenic inflammatory responses. Whether these commensal induced responses are specific to the gut bacteria themselves or result in “bystander” immunity is still being evaluated. A number of reviews have recently and comprehensively described the current literature that summarizes the generalized immune responses that are induced by commensal microbes (1, 2). In this section, we will analyze the cell types and specificity of these responses.

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Dictating specificity: Major histocompatibility complex (MHC)

T cells detect antigens presented by glycoproteins encoded by major histocompatibility genes (MHC). T cells express co-receptors, CD8 and CD4, that interact with MHC I and II, respectively. MHC presentation of antigens to T cells serves as the basis for initiating antigen specificity. Several studies have demonstrated that the composition of the microbiota is dependent on the types of MHC alleles expressed by the host (3–7). MHC genes are some of the most diverse loci in the human genome and different alleles have distinct antigen presentation properties. As MHC/T cell interactions are the basis for all adaptive immunity, it is not surprising that MHC genetic variation impacts susceptibility to infectious diseases and autoimmune diseases (8). One of the mechanisms for this was recently attributed to how MHC influences assembly of the microbiota. Using mice expressing distinct MHC loci, we demonstrated that resident microbial communities were shaped differently depending on the MHC expressed. Different MHCll alleles altered antigen-specific antibody (IgA) responses in the gut, resulting in distinct microbial communities. These communities provided significantly different levels of protection against the enteric pathogen, *Salmonella typhimurium* (4).

Recently, MHC/microbiota interaction has been shown to protect mice against type I diabetes (T1D). In humans, MHC variation is the strongest genetic variant linked to T1D (8). Consistent with humans, the expression of a particular MHC allele (Eα complex) in the non-obese diabetic (NOD) mouse model of T1D protected mice from disease (9). The mechanism had been a mystery until recently when Silverman and colleges showed that this protection is mediated by the intestinal microbiota. Their first clue was that NOD mothers expressing the protective allele could transfer protection to their offspring without the allele. They then demonstrated that different antibiotics ameliorated the protective effect (6), demonstrating that commensal bacteria underlie this protection. These recent studies offer the first mechanistic evidence that diseases affected by MHC genetic variation may be regulated by microbiota alterations.

Antigen acquisition and antigen presenting cells.

A network of antigen presenting cells are responsible for acquiring and coordinating antigen-specific immune responses and mononuclear phagocytes, particularly dendritic cells, are central to this process (Figure 1). Dendritic cells are found throughout the intestine, but are concentrated in the lamina propria and lymphoid tissues that include Peyer’s patches and isolated lymphoid follicles in the small intestine and the draining mesenteric lymph node. There are 3 main DC groups found in the gut and they are differentiated by the expression of three surface markers, the α_ECD103 integrin, CD11b and CX3CR1 (10). In the small intestine, the majority of the DCs are CD103+CD11b+ and are located in both the lamina propria and CD103+CD11b− are primarily located in Peyer’s Patches (11). These dendritic cells are migratory, constantly sampling both dietary and commensal antigens and trafficking them to the MLN to activate T cells (12, 13).

There are a number of pathways that deliver antigens to these DCs. Mucus secreting goblet cells transports low molecular weight antigens to CD103+ DCs in the small intestine (14), specialized M cells overlaying Peyer’s patches allow passage of antigens and microbes to

Peyer's patch DCs, and pathogens that breach the epithelial cell layer. CD103+ CD11b+ DCs express high levels of the CCR7, which is required for migration of these DCs from mucosal tissues to the MLN (12, 15). CCR7 expressing DCs have also been shown to transport commensal microbes from the intestine to the MLN to stimulate commensal antigen-specific responses (16).

In the colon, the primary DC population is CD103−CD11b+ and also expresses the fractalkin receptor CX3CR1, though they also have important functions in the SI (17). Unlike CD103+ DCs, these cells are macrophage-like and arise from monocyte progenitors (12, 18) and been shown acquire antigen in ways distinct from CD103+ cells. Niess et al. used GFP-CX3CR5 mouse models to show that these cells extend cellular projections from the lamina propria, between epithelial cells, and into the intestinal lumen to sample microbial antigens, a process that required CX3CR1 expression (19). Unlike CD103+ DCs, CD103−CD11b+CX3CR1+ require microbial signals for development and are depleted in germ free mice (20). Also distinct from CD103+ DCs, these macrophage-like DCs do not express high levels of CCR7 and do not traffic to the MLN under homeostatic conditions (12). However, Diehl et al. demonstrated that these cells upregulated CCR7 and migrate to the MLN when the microbiota is depleted by antibiotics. This suggests microbial signals suppress CCR7 expression on these DCs, preventing migration, and potentially aberrant immune activation (21). CD103+ and CD103−CD11b+CX3CR1+ DC populations have also been shown to cooperate to acquire them to the MLN and CD103−CD11b+ CX3CR1+ DCs were shown to transfer antigens to CD103+ DCs, which transport them to the MLN (22).

Interestingly, there are inherent differences in the way these DC groups activate T cells (Figure 1). For example, CD103+ DCs are particularly adept at inducing Treg differentiation by secreting Treg inducing molecules, including retinoic acid and TGF-β (23). Specific DCs also maintain different T helper cell populations in the gut. CD103+CD11b+ DCs are required for maintaining Th17 cells, while CD103+CD11b− DCs were recently demonstrated to maintain Th1 responses (24–26). CD103−CD11b+ CX_3CR1 DCs induce both Th1 and Th17 responses (21, 24).

A non-classical antigen presenting cell that is important for mediating T cell responses are innate lymphoid cells (ILCs) (27). Particular subset of ILCs, called CCR6 ILC3, express MHCII that serve an important regulatory role in intestinal immune homeostasis. Selective deletion of MHCII in CCR6 ILC3 cells increased effector T cells in the intestinal lamina propria, increased inflammatory cytokine secretion, and increased intestinal inflammation (28–30)(Goto et al., 2014; Hepworth et al., 2013).These cells present intestinal antigens on MHCII to effector T cells, but instead of inducing cell proliferation, they induce apoptosis (29). In this manner, CCR6 ILC3 MHCII antigen presentation serves a novel immune suppressive function in the intestine.

Commensal antigen-specific responses

After phagocytosing and processing antigen, DCs present antigens to T cells and promote their differentiation. A complex combinations of signals from DCs, intestinal microbes, intestinal epithelial cells, and other immune cells dictate T cell responses, altering susceptibility to pathogens and inflammatory diseases. Commensal microbes induce many

of these antigen-specific T cells, and several T cell subsets, such as T helper 17 cells and inducible T regulatory cells, are severely depleted in germ free animals (31, 32). Specific antigen-specific immune interactions are difficult to study due to the complexity of the microbial community. Those that have been described reveal important features of commensal microbes that induce or modulate antigen-specific immune responses.

Th17 cells are particularly important for mucosal immunity, and genetic mutations disrupting Th17 development or function is associated with increased mucosal fungal infections (Okada et al., 2015; Puel et al., 2011) and Th17 deficient mice are more susceptible to intestinal *Citrobacter rodentium* infection (33–35)(Mangan et al., 2006). Th17-defining cytokines, IL-17 and IL-22, promote intestinal barrier function, and induce both antimicrobial peptide and IgA secretion (36). These inflammatory T cell populations also contribute to a number of pathogenic inflammatory conditions, that include inflammatory bowel disease, multiple sclerosis, and arthritis, so their origins are of great interest (37). Intestinal Th17 levels are highly dependent on the microbiota composition, and genetically identical mice from different mouse vendors have can drastically different Th17 levels (31). In this particular case, a single commensal organism, segmented filamentous bacteria (SFB), drove this Th17 response and most SFB-induced Th17 cells are SFB-specific (38). Using TCR hybridomas from SFB-colonized mice, Yang and colleges showed that the majority of the Th17 TCRs specifically recognize SFB antigens (39). Further, SFB Th17 responses require MHCII expression on dendritic cells and specifically require CD103−CD11b+CX3CR1+ DCs (30, 40).

Why does SFB preferentially induce Th17 differentiation? Two recent studies demonstrated that a key feature of SFB required for Th17 induction is its close association with the gut epithelial cells (41, 42). Using mouse and rat-specific SFB strains, Atarashi and colleges found that only strains matching their original host could induce Th17 cells, and this was due to species-specific adherence (41). SFB adherence induced the expression of serum amyloid proteins (SAA1/2), and the reactive oxygen producing protein Duox2 in epithelial cells (38, 41, 42). SAA1, in particular, directly enhanced IL-17A and IL-17F induction by Th17 cells, and also acts on dendritic cells to promote Th17 induction (41, 42).

Regulatory T cells are also induced and regulated by the microbiota and play a vital role in preventing pathogenic inflammation (43). Commensal microbes induce Tregs through number of innate immune and metabolic signaling pathways (discussed later in this review), but do Tregs recognize commensal antigens? To explore this question, two studies took advantage of mouse models with limited but diverse TCR repertoires and compared Treg TCR sequences in different lymphoid tissues (44, 45). These studies demonstrated that intestinal Tregs utilized a distinct set of TCRs compared to other lymphoid tissues and found that these Treg TCR repertoires were significantly altered in germ-free or antibiotic-treated mice. In addition, both groups found that colonic Treg hybridomas specifically recognize diverse commensal bacteria (44, 45). Together, these findings demonstrate that a large portion, if not the majority, of intestinal Tregs recognize commensal antigens.

Mechanisms by which commensal influence specificity of the immune response

Commensals, such as SFB, have been associated with a number of autoimmune diseases. Autoimmune diseases are characterized by inappropriate responses to self antigen and thus it is unclear how commensals might influence these specific immune responses. Here we describe three potential mechanisms that have been highlighted in recent literature, expansion of T cells expressing dual TCRs, bystander activation and molecular mimicry (Figure 2) While GF mice have been shown to be resistant to the development of EAE, mono-association with SFB alone induces worsened disease that was associated with induction of (46) model of arthritis in GF mice and introduction of SFB was sufficient to induce development of Th17 and T follicular helper cells (T_{FH}) to initiate disease (37)(47). Lung pathology is a significant complication and cause of mortality in individuals with rheumatoid arthritis (RA) (48). SFB was shown to exacerbate lung pathology in the K/BxN model of arthritis and this was dependent on Th17 cells (49). SFB was shown to preferentially expand T cells expressing two TCRs, one TCR was specific for SFB and the other for self-antigen. This provides a novel mechanism by which commensal bacteria might influence autoimmunity, through expansion of T cells expressing TCRs against self peptides.

Another mechanism by which commensals might influence the specificity of the immune response that leads to autoimmunity is through molecular mimicry. Recently, a peptide that is part of a bacterial integrase within the *Bacteriodes* genes was identified that is identical to a self pancreatic antigen known to elicit inflammation in a mouse model (50). Indeed, this bacterial antigen could be presented by MHCI to stimulate CD8+ T cells. Extending their findings to humans, the authors found the T cells isolated from individuals with type 1 diabetes (T1D) and Crohn's disease expanded in response to this bacterial antigen (50). Interestingly, T cells specific for this antigen were shown to be protective in a model of colitis, suggesting that these T cells were preserved within the host because they promoted tolerance in the gut. However, this represents an example of how commensal organisms within the gut might express antigens that cause expansion of T cells against other antigens, either self or foreign.

Up to this point we have analyzed the immune responses elicited by the microbiota through a rather classical lens. However, is it really possible that all microbes in the gut activate specific immune responses against themselves? Recent evidence suggests that commensals can also induce responses that are directed against other commensals, what is often referred to as bystander activation (51). Gomes-Neto et. al. recently demonstrated that *Helicobacter bilis* colonization directs Th17 responses against other members of the microbiota, but not to itself (52). By utilizing the defined ASF microbiota community, this group identified specific microbes targeted by *H. bilis*-induced Th17 responses. Interestingly, removing Th17-targeted bacteria from the community resulted in Th17 responses against a different collection of microbes, suggesting that *H. bilis* can alter T cell responses to a broad range of microbes (52). What mechanisms may drive these bystander responses? One possibility is that microbes or treatments that broadly alter intestinal permeability or cytokine milieu. For example, commensal microbes transiently escape the intestine during a *Toxoplasma gondii* infection and induce long-lived memory Th1 responses (53). Similarly, IBD is associated with Th1 responses specific for commensal flagella proteins in the intestine (54). Innate

immune signaling on T cells has been found to induce bystander effects. Stimulation of T cell TLRs by *Bacteriodes fragillis* promotes Treg differentiation (55–57). Recently, the direct TLR stimulation of T cells was found to induce arthritis during a *Borrellia* infection, the causative agent of Lyme disease (58).

Specificity of intestinal IgA responses

One of the primary functions of activated T cells is to induce and modulate intestinal antibody response. In the gut, the primary secreted immunoglobulin is IgA, which is produced by IgA plasma cells in the lamina propria and transported across the epithelial cell lay via the polymeric Ig receptor (pIgR) (59). IgA plasma cells develop through T cell dependent (TD) and T cell independent (TI) pathways. TI responses develop in the LP or in isolated lymphoid follicles and result from the direct response of B cells to free or DC-delivered antigens (60). Differentiation of these B cells into IgA plasma cells is then induced by multiple signals from DCs and epithelial cells. T cell dependent IgA induced in the PP and requires a specific group of T helper cells, call T follicular helper cells (Tfh). Tfh cells interact with MHCII-presented antigens on B cells in germinal centers (GC) to promote IgA PC development (61). New techniques that combine flow cytometry with 16S sequencing has revealed exciting insights into how IgA interacts with the microbiota, the microbial community that is bound by IgA, and relative role of TD and TI IgA responses in targeting intestinal microbes (summarized in Figure 3) (55, 62–65).

Recent work from Bendelac and colleges suggests that most of the IgA bound to commensal is TI-generated. Bunker et al. found that T cell deficient mice had similar levels of IgA coated bacteria throughout their intestine, and the bacterial community bound to IgA was largely similar to WT animals (65). They also demonstrated that IgA interaction is primarily dictated by its location within the intestine; microbes preferentially colonizing the SI are highly coated by IgA, while colon-resident bacteria are not (Figure 3)(65). In a subsequent study, this group demonstrated that IgA plasma cells have a propensity to secrete poly-reactive microbiota-targeting antibodies (66). They cloned and created monoclonal antibodies (mAbs) from sorted IgA plasma cells and compared their specificities to mAbs cloned from naïve B cells. The majority of IgA-derived mAbs bound a broad range of intestinal microbes, while mAbs from naïve B cells did not display this microbiota-reactivity (66). Together, these studies suggest that the majority of the intestinal IgA-bound bacteria are targeted in a non-specific manner. It is still unclear, however, how these TI responses shape the microbiota and alter interactions with the host. Interestingly, microbiota-reactive mAbs primarily bind to bacteria isolated directly from mice, and microbes cultured from this community no longer bound IgA-derived mAbs. This suggests that intestinal microbes either express, or are coated with molecules the bind polyreactive IgA specifically in the gut. Indeed, IgA-derived mAbs bound to a variety of bacterial glycans, raising the interesting possibility that intestinal IgA acts as an innate, perhaps glycan-recognizing, immune response toward microbiota (66). Notably, TD responses appeared to be required for IgA interaction with two mucosal-associated bacteria, SFB and *Mucispirillium,* and these organisms were not coated by TI IgA (65). Perhaps these organisms have mechanisms to avoid innate IgA interactions and may offer interesting microbes to explore how TI IgA impacts host/microbe interaction.

While TD IgA may not be the primary source of IgA interacting with intestinal microbes, several studies have demonstrated that these responses are important for shaping the microbial community. Disrupting T cells, B cells reduces diversity in the intestinal microbiota (62). To identify specific T cell responses required for maintaining fecal microbiota diversity, Kawamoto et. al., transferred different T cell populations into T cell deficient animals. They found that Foxp3 Tregs as the key T cell population that promotes diversity. Tregs are able to become T follicular regulatory cells in the PP, promoting germinal center formation and boosting IgA plasma cells in the SI. Interestingly, the Treg-shaped microbiota could also boost TD IgA responses when transferred to germ free mice (62). This suggests that there is a positive feedback loop, where TD IgA responses shape a microbiota that further promotes these immune responses. In this study, TD responses promoted Clostridia diversity, likely by suppressing *Lachnospiraceae* overgrowth (62), and Clostridia species are known to induce Tregs in the gut (32). In addition, our lab demonstrated that disruption of the T cell MyD88, a signaling protein required for the innate immune Toll like receptor signaling, is required for maintaining Tfh cells. Decreased Tfh cell number resulted in significant alterations to the tissue-associated microbial community and exacerbated colitis, which was dependent on changes to the microbiota (55). Therefore, TD induced IgA may not be the primary source of IgA interacting with intestinal microbes but it is important for in shaping the intestinal microbial community and impacting host health (Figure 3).

What is the functional difference between TD and TI IgA? The only documented difference so far is their specificity, with TD IgA having undergone affinity maturation while TI antibodies have not. Intestinal IgA serves multiple protective roles that include direct killing, opsonizing, and agglutination (59), and strength of IgA interaction likely effects each of these functions. For example, IgA prevents Salmonella Typhimurium from fully separating after cell division, preventing spread and promoting clearance. Only vaccine-induced, high-avidity IgA induces chain formation (67). In addition, IgA can directly modulate microbial behavior in the gut and is typically dependent TD IgA. A single specific IgA antibody developed against a *Bacteriodes thetaiodomicron* capsule epitope can suppress gene transcription required for its production in vivo (68). In addition, mice lacking TLR5, an innate immune receptor detecting bacterial flagella, have reduced flagella-specific IgA and a corresponding increase in microbiome expression of flagella genes (69). These examples suggest that strength and selectivity of IgA responses significantly regulate host/microbe interactions in the gut and these features may differentiate TD and TI responses.

Commensal regulation of host immunity

Just as pathogens have evolved elegant ways to subvert host immunity, commensals have evolved just as intricate mechanisms to control it. Over the last several years, a variety of molecules and metabolites that are produced by the microbiota produced have been identified to directly influence the mammalian immune response. These molecules have been classified by others into 3 specific categories and, here, we introduce a fourth (70). These are 1) specialized secreted microbial molecules 2) microbial modified host molecules 3) metabolism of dietary compounds and 4) and structural microbial components. The most well-known microbial modified host molecules (category 2) are bile acids and their effects

on the immune system have been reviewed extensively by others (70–72). Therefore, here we will focus on the other 3 categories of microbial compounds.

Specialized secreted molecules

Fecalibacterium prauznitzii is a gut organism that is found in high abundance within the intestine of many individuals (73, 74). Loss of *F. prauznitzii* is predictive for relapse of Crohn's disease after surgery and has been demonstrated to protect from the development of colitis in pre-clinical animal models of IBD (73). Recently, a protein termed microbial anti-inflammatory molecule (MAM) was identified in the supernatants of *F. prauznitzii* cultures(75). Seven peptides were shown to be a part of the *F. prauznitzii* MAM protein and induce IL-10 *in vitro*. As the technology to genetically manipulate *F. prauznitzii* does not exist, the ability to study MAM in detail is difficult. To get around this, the cDNA for this protein was placed into a plasmid and transfected into *Lactococcus lactis* (76). Animals treated with the MAM expressing *L. lactis* strain were protected from the induction of colitis using two-independent models. Mechanistically, MAM was shown to inhibit the activation of NF-kB which led to reductions in Th1 and Th17 responses in the gut. Other proteins having similar activity have been isolated from *Bifidobacterium animalis* subsp. lactis, however are less characterized (77). Thus, loss of *F. prauznitzii* or *Bifidobacterial* species within the intestine of individuals, as is seen in patients with Crohn's disease, would exacerbate inflammation and worsen disease symptoms due to a failure to down-regulate inflammation.

Staphylococcus epidermidis is a common commensal found on skin. While ligation of TLR signaling on keratinocytes elicits potent inflammation, *S. epidermidis,* despite expression of TLR ligands, does not elicit inflammatory responses from these cells (78). Based on this, it was hypothesized that *S. epidermidis* expressed a molecule that would antagonize TLR signals. Indeed, a small molecule secreted from *S. epidermidis* was identified that could selectively antagonize TLR3 signals. Lipoteichoic acid (LTA) is produced in a cellular form that is found within the membrane and an exocellular form that is secreted and can be recovered in a small molecule fraction (<10kDa). Both forms of LTA isolated from *S. epidermidis* could selectively suppress TLR3 induced inflammation, which is induced, in this study, by wounding the skin. TLR3 suppression mediated by *S. epidermidis* occurred through TLR2 signaling. Therefore, *S. epidermidis* is able to limit cutaneous skin inflammation during wound healing. This same group also identified that this molecule was able to elicit anti-microbial peptide expression that could prevent growth of *Staphlococcus aureus* (79). Since *S. epidermidis* is a common organism that is associated with sepsis, use of the organism itself as a probiotic would not be advisable (80). However, it is tempting to speculate the use of a highly purified form of *S. epidermidis* LTA as a naturally occurring anti-inflammatory in a skin cream that might help wounds heal faster and/or prevent growth of pathogenic organisms.

More recently, Powrie and colleagues identified a large polysaccharide found within the supernatants of *Helicobacter hepaticus* cultures that also induces anti-inflammatory responses(81). *H. hepaticus* can be a peaceful resident of the commensal microbiota, however if the host is deficient in the anti-inflammatory cytokine, IL-10, *H. hepaticus* elicits

inflammation and causes a chronic colitis (82). *H. hepaticus* was recently shown to induce IL-10 in gut macrophages without a corresponding increase in pro-inflammatory cytokines. This suggested that *H. hepaticus* might selectively induce anti-inflammatory responses. Through a series of *in vitro* experiments, the authors narrowed down a secreted polysaccharide from *H. hepaticus* cultures as being responsible for induction of IL-10. Interestingly, induction of IL-10 by this polysaccharide was dependent on signaling through TLR2 and MyD88 as is seen with *B. fragilis* and *S. epidermidis* (56).

While these molecules seem to be specific to these organisms, other common microbial products, such as ATP, can also direct host immunity. Over a decade ago, it was reported that ATP from commensal bacteria could elicit Th17 responses within the gut (83). Indeed, fecal ATP levels in GF mice were significantly reduced when compared to SPF mice and administration of ATP to GF mice was sufficient to induce Th17 responses within the gut. ATP was sensed by P2X receptors on a specific subset of $CD70^{high}CDllc^{low}$ dendritic cells to induce this inflammatory pathway. More recent studies have shown a role for bacteria derived ATP for induction of T_{FH} cells. P2rx7 is a receptor that binds to ATP and disruptions to this receptor cause weight gain in animals (84). $P2rx7^{-/-}$ T_{FH} cells were sufficient to recapitulate this phenotype, suggesting that T_{FH} cells are directly responsive to ATP (85). To prove that T_{FH} cells were influenced by microbially-produced ATP the authors performed an elegant experiment in germfree mice. They constructed a mutant of *E. coli* that expressed an apyrase so that all ATP produced by the microbe would be hydrolyzed and no extracellular ATP could be generated. GF animals were colonized with a control *E. coli* or the apyrase expressing *E. coli* and T_{FH} cells and IgA were monitored. Animals that were colonized with ATP deficient bacteria had increased T_{FH} and *E. coli* specific IgA responses compared to controls. These data suggest that ATP produced by commensals can serve to limit host antibody responses that functionally impact the composition of the microbiota leading to metabolic defects. It is likely that a multitude of organisms secrete ATP, therefore it is unclear how ATP would differentially drive IL-17 versus T_{FH} responses within gut. Perhaps the location of the ATP, or the specific cell type that is detecting the ATP would drive these differential outcomes (86).

In addition to detection of bacterially produced molecules through receptor mediated interactions, microbes are also known to make proteases that can directly destroy host proteins such as IgA (59). *Lactobacillus paracasei* has beneficial effects within the mammalian gut and is one of the members of a probiotic termed VSL#3 (87). Feeding animals VSL#3 during colitis, significantly downregulates inflammation and ameliorates colitis symptoms (88). This activity was shown to be reliant in part on a molecule that was secreted by *L. paracasei*. Further analysis identified this molecule as a serine protease that can degrade an array of pro-inflammatory chemokines such as IP-10 (89, 90). Disruption of this bacterial protease in the organism lead to a defect in IP-10 degradation and a failure to protect from colitis. Similarly, a commensal yeast strain known to ameliorate colitis induction in animals, *Saccharomyces boulardii*, was reported to secrete a protease that degrades toxin A produced by *Clostridium difficile* and protects from enteritis(91). Thus, commensal microbes express and secrete molecules that can actively degrade inflammatory cytokines as a mechanism to maintain tolerance within the intestine.

Dietary metabolites

There are several metabolites that arise from microbial metabolism of dietary compounds. These include, short-chain fatty acids (SCFAs), amino acid metabolites such as tryptophan and arginine, flavonoids and polyamines. SCFAs, include propionate, butyrate and acetate and are a result of fermentation by the microbiota. These metabolites have been demonstrated to induce Treg responses and thus down-regulate inflammation (32, 92). SCFAs also serve as a source of energy for intestinal epithelial cells and influence barrier function (93, 94). These particular metabolites have been extensively reviewed elsewhere (70, 72) and therefore will not be covered in depth within this review.

Tryptophan metabolites

Changes to microbial derived tryptophan metabolites are beginning to emerge in a number of human diseases (95–98). The microbiota metabolizes dietary tryptophan to indole as well as multiple indole derivatives including indole-3-acetate, indole-3-aldehyde, indole-proprionic acid (IPA), indole acetic acid, indoxyl-3-sulfate, and indole acrylic acid. Multiple organisms have been shown to metabolize tryptophan including *E. coli*, Lactobacillus species and Clostridia species such *Clostridia sporogenes*.

Indole itself was demonstrated to influence intestinal epithelial cell gene expression patterns, mucin production and enhanced tight junctions. Indole, indole-3-acetate, indole-3-aldehyde and tryptoamine have all been identified to act on the aryl-hydrocarbon receptor (AHR)(99). AHR activation can lead to expansion of innate lymphoid cells and IL-22 production leading to the development of intestinal lymphoid follicles (100–102). Mammals produce the enzyme indoleamine 2,3,-dioxygenase (IDO) to degrade tryptophan. To investigate host-extrinsic mechanisms of tryptophan degradation, Romani and colleagues utilized $IDO^{-/-}$ mice, which increases tryptophan availability to gut microbes(103). In these animals, *Lactobacilli* become expanded and produce copious amounts of indole-3-aldehyde. This metabolite directly upregulated expression of IL-22 through AHR and provided colonization resistance from *C. albicans* infection (103).

Polymorphisms in Card9 are found in individuals with IBD (104). Card9 is a signaling molecule that lies downstream of Dectin-1 and is activated by fungal cell wall components. $Card9^{-/-}$animals are more susceptible to colitis and this is dependent on the microbiota, as transfer to a GF recipient causes worsened colitis (95). The microbiota formed within these animals displayed the inability to metabolize tryptophan. In particular, indole-3-acetic acid was significantly lower in $Card9^{-/-}$ animals. As these tryptophan metabolites are known to bind AHR, the authors administered a known AHR agonist to $Card9^{-/-}$ and this ameliorated colitis (95). This studies suggests that loss of specific microbial metabolites can exacerbate disease.

Tryptophan metabolites have also been shown to function at extra-intestinal sites such as the central nervous system(96). IFN-β was shown to limit inflammation associated with a pre-clinical animal model of multiple sclerosis and its activity was in part dependent on AHR expression within astrocytes. A diet lacking tryptophan worsened disease, while replacement of the microbial metabolite, indole-3 sulfate, ameliorated disease. Indole-propionic acid and

indole-3-aldehyde had similar protective effects. To directly demonstrate that gut bacterial metabolism can influence extra-intestinal immune responses, Sonnenburg and colleagues identified the gene cluster in *C. sporogenes* responsible for metabolizing tryptophan to indole-propionic acid. Colonization of animals that lack this gene cluster fail to generate IPA and this causes enhanced T cell activity and antibody circulation within the blood(105). IPA is a known agonist for the pregnane X receptor (PXR) and thus the mechanism of action of this metabolite might be PXR dependent as has been shown within the gut (106). Thus, intestinal microbial metabolites can get into circulation where they bind to AHR and limit CNS inflammation.

Mucus serves as an energy source for multiple microbes within the gut and mucin-degraders can have both beneficial and detrimental consequences to the host (107, 108). To identify organisms that degrade mucins Xavier and colleagues utilized a computational approach (98). This screen lead to multiple organisms within the Clostridales order and 36 of them were able to grow on mucin. Further testing identified strains that were protective during DSS colitis, one of which was *Peptostroptococcus russellii*. Genome sequencing of this organism identified that it contained the fldA/BC loci known to be responsible for producing tryptophan metabolites. *P. russellii* made indoleacrylic acid which prevented intestinal permeability and down-regulated inflammatory responses.

Biogenic amines

Microbial metabolism of amino acids can produce biogenic amines through de-carboxylation. These include cadaverine (from lysine), agamatine, spermine and spermidine (from arginine) and histamine (from histidine). Most of these amines can also be made by the host and therefore, the literature on microbiota derived biogenic amines and there influence on the host is still in its infancy(109). Many of these biogenic amines however are known to have important consequences to the host. Purified agmatine administered to rats after the induction of cerebral ischemia significantly reduced brain infarction and minimized neuro-inflammation (110). Similarly, agmatine treatment attenuated fever associated with LPS administration (111) and its metabolite, spermine, protected mice from lethal sepsis and had suppressive immune effects (112, 113). With the known contribution of the microbiota to CNS health and development, this might be but one mechanism by which the microbiota can influence CNS health that has yet to be explored.

Histamine is another biogenic amine that has recently been shown to have beneficial effects on the immune system. Purified histamine cultured with intestinal explants suppresses IL-18 induction, demonstrating an anti-inflammatory role for this metabolite (113). Other studies identified a histamine secreting microbe could down-regulate inflammation. There are four G-protein coupled receptors encoded within humans that recognize histamine. Loss of the histamine receptor 2(HR2) in animals leads to the activation of multiple pro-inflammatory cytokines within the gut. A histamine secreting microbe, *Lactobacillus rhamnosus,* suppresses the production of TNF-α and GM-CSF within the gut in a HR2 dependent manner (114). Thus, metabolic conversion of dietary amino acids by the microbiota can have pervasive effects on the host immune system.

While most of the functional metabolites described above provide some benefit to the host, not all microbial metabolites fall into this category. Choline is a quaternary amine required for multiple biological processes in mammals. Metabolism of choline by the gut microbiota results in the production of trimethylamine (TMA)(115). TMA is absorbed by the intestine and can further be metabolized in the liver into trimethylamine-N-oxide (TMAO). TMAO levels have been positively correlated with several diseases including diabetes, atherosclerosis, non-alcoholic fatty liver disease and impaired renal function (116–118). TMAO injection into animals causes activation of NF-κB and elicits inflammation with the aorta. Additionally, microbes that utilize dietary choline within the gut, limit its bioavailability to the host (119). This could be especially harmful during pregnancy, where the fetuses need for dietary choline is significantly high. To test this, Balskus and collegues colonized dams with high levels of choline-consuming microbes which produced offspring with behavioral alterations. Thus, microbes can also compete for host nutrients to the host detriment.

Molecules that are part of the microbe structure

As an immune defense strategy, recognition of molecules exclusively expressed by micro-organisms is an elegant mechanism of sensing invasion and eradicating potential infection. Immune responses elicited upon detection of foreign bacterial molecules by host immune systems has been studied extensively and served as the basis for the many of the paradigms that have been identified to differentiate between ‘self’ and ‘non-self’. However, many of these same foreign molecules that are known to trigger sterilizing immunity are also expressed by commensal organisms and are now known to prime the development of steady state immune responses. This has led to speculation that perhaps many of these receptors evolved, at least in part, to initiate tolerance against commensal microbes(120, 121).

Some of the most commonly studied structural bacterial molecules are peptidoglycan (PGN), lipopolysaccharide (LPS) and flagellin. PGN can be recognized by a number of receptors including TLR2, NOD1, NOD2, NLRP3 through hexokinase (122), and PGN recognition proteins (PGRPs)(123) while LPS and flagellin are known to stimulate TLR4 and TLR5 respectively. These commensally derived molecules are found in abundance within the gut, but can also be found circulating within the blood where they have been shown to prime immunity against pathogenic infection and in some cases, induce tolerant immune responses against commensals.

PGN is recognized by a number of host receptors and polymorphisms within many of these genes, including TLR2 and Nod2, are associated with IBD in humans (124–126). Disruption of any one of these receptors in mice leads to increased susceptibility to colitis in multiple studies. However, in many cases, these results are contentious and either depend on the type of colitis model used or the facility in which the experiments were performed. As an example, TLR2 deficient animals are more susceptible to damage associated models of colitis induced by the chemical DSS, and provision of a synthetic TLR2 agonist to wild-type mice can ameliorate mucosal inflammation in this same model. However, in models of more chronic intestinal inflammation, such as the T cell transfer model of colitis, TLR2 does not have an effect on the development of disease (127). These disparate results could be

explained by the different models used, as one is mediated by epithelial damage and the other is mediated by chronic T cell inflammation. However, changes in the microbiota composition from facility to facility might also result in these differences (128). As colitis results, in part, from a loss of tolerance to commensal bacteria, the composition of the microbiota is imperative to the severity of disease. Indeed, certain microbial compositions are sufficient to worsen colitis while others are protective. A common theme amongst animals that lack PGN recognition, is that the composition of the microbiota was significantly different when compared to wild-type animals. This is true of TLR2$^{-/-}$ animals (129), NOD2$^{-/-}$(128, 130, 131), and PGRP1–4$^{-/-}$(123) animals. Similarly, a deficiency in receptors recognizing flagellin (132) and LPS (133) have reported changes to the structure of the microbiota in mutant mice. While differences in microbial composition due to mutations within host immunity is more of a rule, rather than an exception; changes in composition are not always required for exacerbated disease development. Thus, it is important to perform co-housing, germfree transplants, and/or antibiotic disruptions to demonstrate causality of the microbiota. This has been done in experiments using TLR5 (132) and PGRP1–4(123) deficient animals. To prove that the composition of the microbiota was sufficient to influence disease severity, the microbiota from mutant mice was transplanted into wild-type GF recipients. GF mice receiving the transplant from mutant animals developed worsened disease than GF mice receiving a transplant from the healthy animals. As the microbiota differs in various animal facilities, this may provide an explanation for disparate results found in the same mutant mice from different institutions.

While commensal cell wall components seem to be important in dictating microbial composition within the gut, commensal cell wall products have also been detected in circulation. Here they are reported to directly prime immune responses and protect from infection associated damage. Animals treated with antibiotics have a significantly increased susceptibility to influenza that includes delayed viral clearance and enhanced bronchiole damage (134). Loss of commensal bacteria upon antibiotic treatment impaired the induction of anti-viral immunity within peritoneal macrophages. Viral infection is in part sensed through dsRNA binding to TLR3. Remarkably, intra-nasal administration of synthetic dsRNA (poly I:C) to antibiotic treated animals restored their ability to mount anti-viral immunity and clear viral infection. Similarly, PGN was identified within circulating blood and shown to prime neutrophils within the bone marrow (135). GF mice have undetectable levels of PGN within blood and have increased susceptibility to *Streptococcus pnenmonia* and *Staphlococcus aerus*. Oral administration of PGN to GF mice is sufficient to restore neutrophil function and protect from infection. These results demonstrate that commensal bacteria provide tonic signaling that can prime extra-intestinal immune responses.

Sphingolipids are a distinctive group of membrane lipids that are made up of long-chain, monounsaturated, di-hydroxy amine structures. These lipids are critical components of the plasma membrane in mammals, but are also found on certain bacterial and fungal organisms. Bacterial sphingolipids are predominantly produced by organisms within the phylum *Bacteriodetes*, but can also be found in the fungal cell walls of *Saccharomyces* and *Candida* species (136). Interestingly, invariant natural killer T cells (iNKT) recognize nonpolymorphic CD1d glycosphingolipids, demonstrating recognition of these molecules by host immune systems (137). *Bacteriodetes* are largely found associated with mammalian

hosts and therefore one group sought to determine whether bacterial produced sphinolipids influenced host immune system development. They identified a gene encoded in *Bacteroides fragilis* that possessed significant homology with the eukaryotic enzyme serine palmitoyltransferase (SPT)(138), which is the first enzyme involved in sphingolipid biosynthesis. Germfree mice have increased iNKT cells within the colonic lamina propria, mono-associations of GF animals with *B. fragilis* could decrease this population to the same levels as specific pathogen free (SPF) mice. Deletion of the enzyme involved in sphingolipid synthesis in *B. fragilis* failed to reduce the population of iNKT found in GF mice, indicating that bacterial sphingolipids negatively regulation host iNKT populations. An overabundance of iNKT cells within the gut could be detrimental to the host during intestinal disease. Treatment of animals with the purified *B. fragilis* sphingolipid protected animals from the development of colitis, indicating a beneficial role for bacterial sphingolipids.

Polysaccharide A (PSA) is one of eight polysaccharides that are found in the capsule of the prominent commensal species, *B. fragilis*. PSA is part of the capsule of *B. fragilis* but it also secreted in outer membrane vesicles, where it can be delivered to host cells. PSA has been shown in multiple studies to act as an agonist for TLR2 and induce tolerogenic responses (56, 139, 140). The use of purified PSA can protect animals from the development of intestinal colitis and multiple sclerosis (140, 141). *B. fragilis* is known to associate closely within intestinal crypts and disruption of PSA in *B. fragilis* fails to induce host Tregs and *B. fragilis* can no longer associate with the intestinal epithelium (56). The effects of PSA have been discussed elsewhere(70), but the many studies on this one commensal molecule serve as an example of the powerful therapeutic potential that can be uncovered through the detailed study of commensal organisms.

While less abundant within the gut, fungal species are indeed relevant during intestinal development and disease. Multiple polymorphisms within genes that recognize fungal cell wall components have been found in individuals with IBD, including Dectin-1 and Card9 (142). However, Nod2 is one of the most commonly found mutations within individuals with Crohn's (143). It is known to be stimulated by PGN and most studies to date have focused on Nod2 recognition of PGN. However, Nod2 has also been reported to be stimulated by fungal chitin, an essential cell wall component found within most fungal organisms (144). Stimulation through NOD2 with chitin elicits anti-inflammatory IL-10 production, suggesting that tonic signaling through Nod2 by fungal organisms can elicit tolerogenic responses within the gut. Fungal cell wall mannan is also highly immune stimulatory as is the target of multiple C-type lectin and TLR innate immune receptors (145). Recently, fungal mannan was sufficient to rescue exacerbated colitis and increased susceptibility toward influenza in antibiotic-treated mice, in a process that required TLR4 (146). Fungal organisms can also express specialized polysaccharides that can influence host responses. Although rarely discussed within the context of commensalism, *Cryptococcus neoformans*, also expresses an immune-suppressive polysaccharide capsule comprised of glucuronoxylomannan (GXM) and galactoxylomannan (GalXM). Both GXM and GalXM have multiple anti-inglammatory properties and include inhibiting TLR4 signaling, promoting macrophage secretion of FasL to promote T cell apoptosis (147). While *C. neoformans* is widely studied as a pathogen that causes high mortality in immune-compromised patients, it rarely induces disease in healthy individuals. *C. neoformans*

prevalent environment and likely encountered often by individuals and therefore might influence steady state responses in the host. Indeed, the use of GXM was recently found to be therapeutically useful in models of sepsis (148). Thus, eukaryotic species residing at mucosal surfaces can also directly impact host immunity.

While much work has been done already to decipher how gut microbes influence their mammalian hosts, much remains to be done. With hundrends of distinct organisms from various kingdoms of life, little is known about the interactions that occur between them and consequences to the disease state. Given the importance of these microbes to human health it is likely that treatments to many diseases might be uncovered within our own GI tract.

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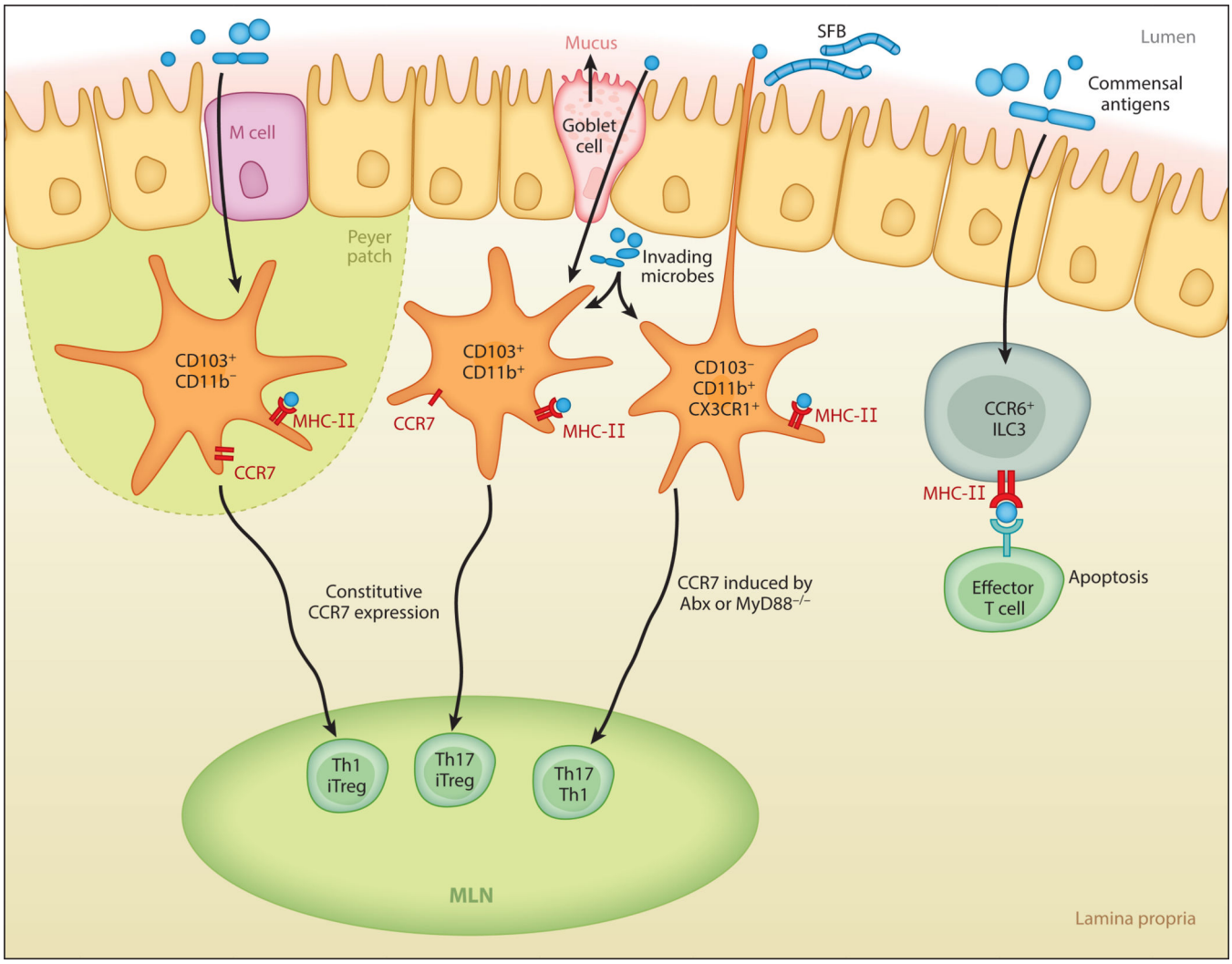

Figure 1: Important antigen-presenting cells in the gut.

The main DC populations in the gut are CD103+CD11b−, CD103+CD11b+, and CD103−CD11b+CX_3CR1+ DCs. CD103+ DCs acquire antigens through specialized M cells, transport through goblet cells, invading microbes, and even from CD103−CD11b+CX_3CR1+ DCs. These DCs constitutively express CCR7 and transport antigens to the MLN for T cell activation. CD103−CD11b+CX_3CR1+ DCs can directly sample intestinal microbes by sending cellular projections through the epithelial cell layer. CD103−CD11b+CX_3CR1+ DCs are not migratory under normal conditions, but upregulate CCR7 and migrate to the MLN after antibiotic-disruption of the microbiota, or in MyD88$^{-/-}$ mutant mice. These DC populations are required for inducing different T cell responses. CD103+ DCs are particularly good at inducing Treg differentiation. CD103+CD11b− DCs are required for Th1 responses, while CD103+CD11b− DCs are required for Th17 responses. CD103−CD11b+CX_3CR1+ DCs are able to induce both Th1 and Th17 responses, and are required for SFB-specific Th17 responses. Finally, CCR6 expressing ILC3 cells suppress commensal-specific T cells by presenting MHCII-bound commensal antigens and inducing T cell apoptosis.

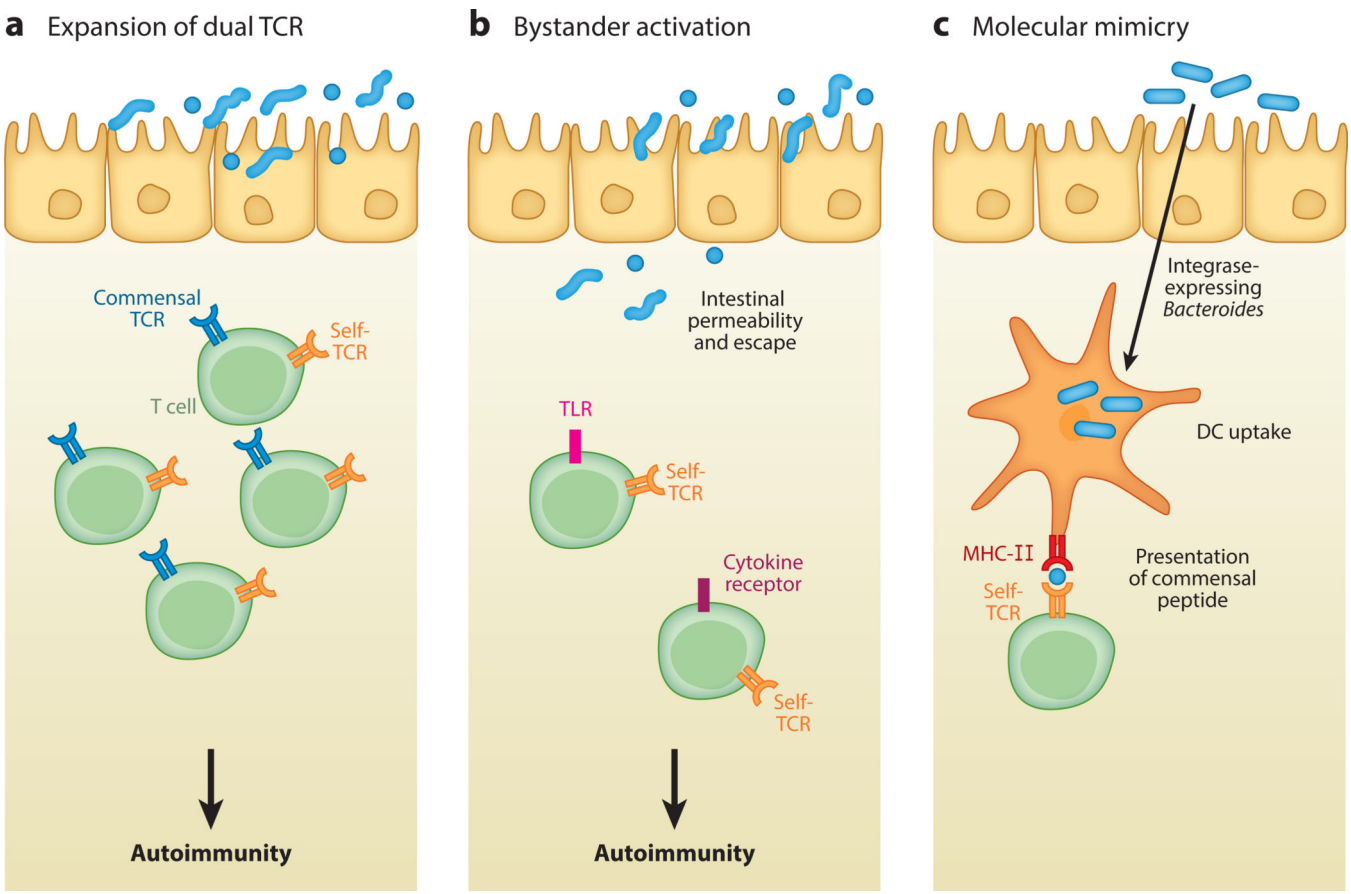

Figure 2:

How commensals can dictate immune specificity. **(A)** Organisms within the gut can expand populations of T cells that express two TCRs, one TCR that recognizes the commensal itself and one that reacts against self peptide. Migration of these T cells to host tissues could cause pathology and autoimmunity. (**B**) Both CD4+ and CD8+ T cells can be activated independently of their TCR. In this scenario, a commensal organism may induce a particular cytokine or be detected directly by T cells through toll-like receptors (TLRs). (**C**) Commensal organisms might express epitopes that mimic self peptides known to drive autoimmunity. Self reactive T cells would then be activated by these antigens in the gut and subsequently traffic to tissues and elicit autoimmunity.

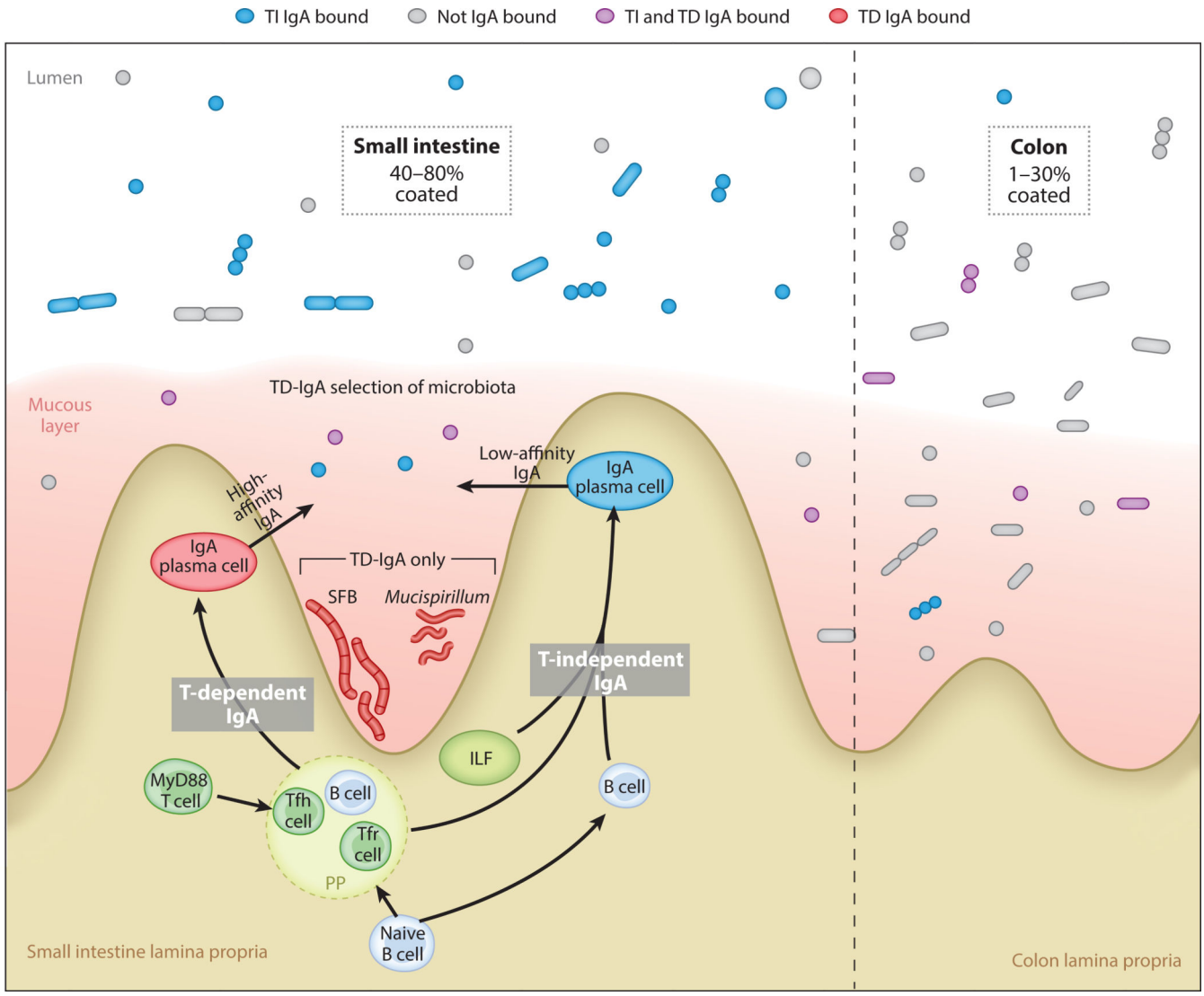

Figure 3: TD and TI IgA interactions in the gut.

T-cell dependent (TD) IgA arises from antigen-specific Tfh/germinal center B cell interactions in the PP and results in highly affinity sIgA. For T cell-independent IgA, naïve B cells can mature into IgA-secreting plasma cells in the PP, isolated lymphoid follicles, or in the lamina propria, resulting in low-affinity, polyreactive sIgA. Most of the IgA coating intestinal microbes comes from TI-IgA secretion. The propotion of IgA-coated bacteria is highest in the SI (40–80%) and decreases in the colon and feces (1–30%). TD-IgA is required for shaping mucosal-associated microbial communities and has been shown to control *Ruminococcus*, *Lachnospiraceae*, *Desulfobibrionaceae*, and *Mucispirillum* populations. Interestingly, the mucus or tissue associated bacteria, *Mucispirillum* and SFB are specifically coated by TD-IgA.