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The role of the microbiota in shaping infectious immunity

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Abstract

Humans are meta-organisms that maintain a diverse population of microorganisms on their barrier surfaces, collectively named the microbiota. Since most pathogens either cross or inhabit barrier surfaces, the microbiota plays a critical and often protective role during infections, both by modulating immune system responses and by mediating colonization resistance. However, the microbiota can also act as a reservoir for opportunistic micro-organisms that can 'bloom', significantly complicating diseases of barrier surfaces by contributing to inflammatory immune responses. Here, we review our current understanding of the complex interactions between the host, its microbiota and pathogenic organisms, focusing in particular on the intestinal mucosa.

Infection Seen Through the Eyes of the Bacteria

With the advent of next generation sequencing technologies, our understanding of the complex relationship between the host and its resident microbes has been fundamentally changed. The microbes that inhabit our barrier surfaces are not the result of random colonization, but are shaped by interactions with the host and are therefore unique to each tissue site [1]. We have evolved in the context of microbial colonization; therefore there are multiple host functions dependent upon cues derived from the microbiota [2]. Not least of these is the immune system, which can sense the microbiota directly via their expression of Microbe-Associated Molecular Patterns (MAMPs), enzymatically derived metabolites and foreign antigens [3]. Thus the immune system relies upon the microbiota for protection against invading pathogens, but this close relationship comes with a significant risk in that if it becomes perturbed, responses against the microbiota can contribute to disease. The microbiota has been shown to contribute in a significant way to a wide variety of diseases, however for chronic inflammatory diseases, such as Inflammatory Bowel Disease (IBD), no single microbial organism has been isolated and shown to be causative [3]. In fact, it is not at all clear that we can define a healthy microbiota versus an unhealthy microbiota at the level of individual bacterial strains and instead it may be more effective to discuss a core metagenome of genes derived from multiple organisms that are necessary for functional metabolism and may be altered during disease [4]. This is not to say that strain level

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identities are not important as well, as microbial pathogenesis is defined by the specific metabolism and pathogenicity factors of the invading microbe. However, all host-microbe interactions are contextual and all infectious disease relies on the combinatorial interaction between the microorganism, the host and the environment [5, 6]. Therefore, to understand the immune/microbiota relationship, we must understand infection as a disruptive microbial colonization strategy amongst many other strategies that is significantly dependent upon contextual factors outside of the specific interaction between the pathogen and the host. Examples of the contextuality of infection abound and have become more obvious with our deeper understanding of host and microbial genetics. It has been known for many years that specific genetic conditions are associated with susceptibility to micro-organisms that are innocuous (or 'commensal') in most people [5]. A prime example of this effect is the susceptibility of patients with defects in the IL-17 signaling pathway to fungal invasion [7]. In addition to host genetics, the outcome of a specific host microbial interaction is dependent upon the community of micro-organisms that share the host. For example, a stable microbiota can resist invasion by potentially pathogenic organisms via a mechanism termed colonization resistance [8]. The microbiota is also critical to the development and maintenance of both the innate and adaptive immune response [9, 10]. Infection is a stressor that can strain the relationship between the microbiota and the host, in some instances chronically, and may have significant impacts on long-term health. In this review we will discuss how the host relationship with the microbiota is critical in the control of infection, although it is interesting to note that they can enhance infections in some cases (Text box 1). Conversely, because the immune response and microbiota are intertwined we will discuss how infection can alter the homeostatic relationship between these two factors, leading to inflammation.

TEXT BOX 1

Inter-Kingdom interactions that Promote Infection

While the microbiota can block infection via a variety of mechanisms, specific pathogens rely upon interactions with microbes for infection. For instance, some enteric viruses are dependent upon the presence of the bacterial microbiota for efficient infection [119–121]. In particular, poliovirus and some retroviruses bind to LPS present on the surface of Gram-negative bacteria, which is necessary for binding of the virus to its host's cell surface target and for subversion of host immunity [122, 123]. In the murine model of norovirus infection, the microbiota reduces IFN γ signaling preventing clearance [124]. Intriguingly, some enteric worms also 'sense' the microbiota so that they can infect the correct intestinal compartment. Specifically, *Trichuris* eggs have the ability to respond to LPS, which initiates hatching, insuring that the worms infect the small intestine [125]. Whether such 'inter-kingdom' interactions are the norm for enteric viruses and parasites is not known, but will be an interesting area for future investigation.

Colonization Resistance Through Direct Bacterial Competition and the Modification of Innate Immunity

Beyond its effects on metabolism and tissue development, the microbiota has multiple overlapping roles in modulating host immunity. A healthy microbiota is a critical barrier against the outgrowth of opportunistic infections as is evident by the incidence of opportunistic enteric infections after the use of broad-spectrum antibiotics. This function of the microbiota in preventing the bloom of aggressive organisms is termed colonization resistance [8, 11]. The most clinically relevant example of colonization resistance is nosocomial *Clostridium difficile* infection following antibiotic administration [12]. Infection with *C. difficile* is often refractory to antibiotic therapy, but in recent years, replacement of the microbiota via the physical transplantation of the microbiota of a healthy donor has been shown to be a powerful treatment in *C. difficile* infection [13]. The curative effects of fecal transplant are believed to be in part ecological and may be mediated via the modification of host bile salts that inhibit the outgrowth of *C. difficile* [14]. Identification of the organisms responsible for limiting *C. difficile* outgrowth may allow for the first targeted microbiota therapeutics [14]. In other cases, such as the murine infection models of *Citrobacter rodentium* or *Salmonella enterica serovar typhimurium*, direct competition between related micro-organisms for nutrients is important for colonization resistance [15, 16]. The production of bacteriocins that target other species of bacteria, is important in determining dominance in bacterial communities and may be a critical factor in colonization resistance [17, 18]. Colonization resistance can also be mediated indirectly via the modulation of the host innate immune response. Specifically, Toll-like Receptor (TLR) sensing of the microbiota by enterocytes is necessary for the production of certain anti-microbial peptides (AMPs) and for the fucosylation of small intestinal epithelial cells by Fut2, both of which can limit specific infections [19–22] (Figure 1). Additionally, TLR7 mediated activation of IL-22 from a subset of innate lymphoid cells can also contribute to protection against antibiotic-induced outgrowth of *Enterococcus faecalis* [23]. Interestingly, these innate responses do not always target the bacteria initiating the TLR response implying that the microbiota and immune response can work together via these innate mechanisms to eliminate some organisms (AMPs) while feeding others (fucosylation) [19]. Whether these are generalizable concepts or whether mechanisms of colonization resistance are unique to specific organisms will be an important area for future research.

Innate Immune Modulation by the Microbiota Affects Infectious Immunity

As discussed above, innate immune activation by the microbiota can induce potent innate immune responses that provide colonization resistance. The microbiota can also induce innate immune mechanisms that directly target infection and it is believed that a breakdown in this system allows for penetration of the mucosal barrier and the development of IBD [24]. The importance of the microbiota for both colonization resistance and innate immunity is emphasized by the increased susceptibility of infants, who are born sterile, to enteric infections. Perhaps unsurprisingly then, many immune cells including dendritic cells and innate lymphocytes, (including most ILC subsets, mucosal-associated invariant T cells and $\gamma\delta$ intraepithelial lymphocytes) develop without the necessity for the microbiota because

these cells must protect initially ‘naked’ barriers [25–27]. Conversely, intestinal macrophage number and differentiation state is dependent upon microbiota-driven replenishment of macrophages from Ly6C⁺ monocytes [28]. Critically, the microbiota is required for the replenishment of monocyte-derived macrophages, which are important for protection against GI infections such as *Toxoplasma gondii* [29]. The production of neutrophils and monocytes in the bone marrow is also dependent upon the microbiota and as a result germ-free mice are more susceptible to systemic infections [30]. As barrier sites become colonized with the microbiota, the immune response must become educated as to the tonic level of signaling associated with colonization with microorganisms. Mammals become colonized with bacteria and viruses during birth, and have evolved to down-regulate TLR3 and TLR4 in the intestinal epithelial cells, macrophages and dendritic cells to prevent overt inflammation [31–33]. Interestingly, as the GI tract becomes colonized by the microbiota, stimulation via Toll-like receptors ‘educates’ the intestine to tonic levels of microbial interaction via the modification of TLR signaling molecules such as IRAK1 [34]. Presumably this ‘gearing’ of innate immune responses prevents pathological immune responses against the microbiota. In support of this notion, many of the genes associated with IBD are related to innate immunity and bacterial colonization of premature infants, who are developmentally unprepared, can lead to significant complications such as necrotizing enterocolitis [35, 36].

The Microbiota Directs Priming of the Adaptive Immune Response

Innate immune cells not only provide rapid protection against invasion but also serve as a bridge between microbes and the adaptive immune system, made up of T and B cells. Thus the microbiota is required for steady-state priming of the adaptive T cell response to counter infection. The mucosal immune system is unique, likely because of the dual requirement for vigilance against invasive organisms coupled with the necessity to maintain homeostasis with respect to the multitude of antigens associated with food and the microbiota. As a general rule for the intestine, lamina propria-derived antigen presenting cells traffic only to mucosal associated lymphoid tissue (MALT) and not beyond, so as to prevent potentially damaging systemic immune responses against the microbiota [37]. Instead it is believed that intestine-derived dendritic cells present microbiota-derived antigens in the MALT to foster homeostatic relationships with respect to the microbiome via the induction of T_{regs}, Th17 T cells and IgA secreting plasma cells (Figure 1). Secretion of antibodies is an important mechanism for the immune system to mediate change upon the microbiota [38].

Accordingly, production of secreted IgA requires intestinal microbes and is significantly reduced in germ-free mice [39]. The importance of secreted antibodies is perhaps evident from the fact that the average person secretes grams of IgA and IgM every day and a combination of antibodies against the microbiota and innate immune signaling responses is required to contain the intestinal microbiota and prevent systemic immune activation [40, 41]. IgA binding also predisposes bacteria to be taken up by M cells into Peyer’s Patches, possibly engaging a feed-forward mechanism via which early binding of bacteria with IgA begets higher affinity responses and can facilitate clearance [42, 43]. Such a feed-forward mechanism is potentially important in the context of an opportunistic member of the microbiota, who, due to modest and intermittent interaction with the host have only engendered low affinity B cell responses that can be re-activated upon outgrowth and

invasion. IgA specificity does seem to be concentrated on those organisms most likely to cause disease in both patients suffering from Crohn's Disease and Environmental Enteropathy (EE) [44, 45]. The microbiota-driven B cell immune response is not limited to the induction of IgA alone, as certain members of the microbiota appear to be capable of inducing IgG and IgM responses. For example, IgG responses against *Enterobacteriaceae* from the microbiota appear to be able to limit sepsis caused by more invasive strains and can be passed from mother to child via the neonatal Fc Receptor, possibly to limit the early interactions with colonizing microbes [46, 47]. Additionally, IgM responses raised against intestinal *E. coli* that are cross-reactive to *Plasmodium* can be effective in limiting malaria infection [48]. Thus, a variety of antibody types combine to control the microbiota and prevent the outgrowth of opportunistic strains, though the effector mechanisms remain unclear. Of note, such compensatory effects between isotypes are likely to explain the fact that phenotypes associated with IgA deficiency are usually mild in both mice and humans. Certainly IgM and IgG can activate clearance mechanisms such as complement and opsonization (though how these work in the intestinal lumen is not clear), but IgA cannot. Perhaps IgA, via steric blocking and hindrance is not used to kill bacteria but instead to modify gene expression and shape the behavior of the microbiota [49]. Indeed, IgA is often targeted to the flagella of bacteria in the GI tract, perhaps indicating an effort to promote sessile organisms and limit planktonic bacteria, which in some strains are more invasive and immunogenic [50]. A better understanding of the antibody response and associated effector mechanisms will be critical to our understanding of the immune/microbiome relationship and may yield opportunities for precision therapeutic targeting of members of the microbiota.

Priming of the mucosal T cell immune response by the microbiota has also been shown to be necessary for the host immune response to infection. CpG DNA, the ligand for TLR9 is important for driving the steady-state Th1 and Th17 immune responses of the small intestine, contributing to protection against parasitic infection [51]. In mouse colonies colonized with segmented filamentous bacteria (SFB), IL-23 production by dendritic cells and IL-1 β production by macrophages induces the expression of IL-17A and IL-22 by SFB-specific T cells and innate lymphoid cells (ILCs) that provide modest bystander protection against adherent bacterial pathogens such as *Citrobacter rodentium* [52–58]. While the mechanism of protection against adherent luminal pathogens is not clear, both T_{regs} and Th17 cells have been shown to support IgA responses and IL-17 up-regulates Pigr and AMPs, indicating a multi-faceted approach (Figure 1) [59–63]. Clearance of *C. rodentium* also involves aspects of colonization resistance because once antibodies drive the bacteria away from the surface of the intestine, a healthy microbiota assists clearance via competition for nutrients, in this case simple sugars [15]. Thus a combination of innate and adaptive mechanisms combines to clear luminal intestinal infections. In the skin, the local microbiota also plays a critical role in priming the immune response prior to infection. Tonic Toll receptor signaling provided by the microbiota is necessary for the production of IL-1 β in the skin which activates T cells [64, 65]. Indeed, a paucity of Th1 and Th17 T cells in the skin of GF mice causes increased susceptibility to cutaneous infection with *Leishmania major* and *Candida albicans* [64, 65]. As the microbiota varies enormously amongst different skin sites, this priming does not seem to require colonization with specific microbial strains but

instead seems to rely on MAMPs such as TLR ligands found on many microbes. In terms of the ecology of the microbiota, it is however possible that some species shape the composition and function of the whole community. Whether such 'keystone' organisms and or products that have functions that belie their abundance are required for immune protection or alternatively whether there are mechanisms to measure and sample the microbiota more holistically is an important area of future research.

Despite the fact that antigen-specific T and B cell responses are limited to the MALT, the microbiota can also affect the systemic immune responses. For instance, colonization with SFB drives Th17 responses at distal sites and has been shown to contribute to disease in multiple models of autoimmunity [61, 66]. SFB also increases lung Th17 T cell responses aiding in protection against fungal infection [67]. Germ-free (GF) mice have significantly depressed anti-viral and anti-bacterial T cell responses at sites distal to the intestine such as the lung, leading to decreased clearance [30, 68, 69]. In each of these studies the systemic effect of the microbiota appears to be related to the development and activation-state of innate dendritic cells, macrophages and neutrophils by either bacteria or bacterial products. The exact mechanisms of the systemic action of the microbiota remain unclear, but recent studies using radio-labelled bacteria provide evidence of the systemic reach of the microbiota and provide hope for how we might develop therapies based upon specific bacterial products [70]. The systemic immune defects of germ-free animals may also be related to the fact that in contrast to conventionally reared animals, GF mice are significantly shifted towards Th2 immunity, characterized by the production of IL-4, IL-5 and IL-13 from T cells and the production of IgE from B cells [71]. Reconstitution of GF mice with *Bacteroides spp.* is sufficient to shift the microbiota away from a Th2 state, reducing disease in models of atopy and perhaps priming the response against invasive bacteria and viruses [71, 72]. It will be important to determine if differential acquisition of intestinal bacteria might contribute to the differences in atopic and infectious disease susceptibility between high and low income countries via modulation of the immune response [73].

Role of the Microbiota in Controlling Immunopathology

The microbiota is also important for the resolution of the immune response following infection. A commonality of cellular immune responses is a massive proliferation of responding cells that needs to be resolved to prevent immunopathology. The mechanisms driving contraction of the immune response are still not completely clear, but include competition for homeostatic survival signals and more active regulatory mechanisms that are programmed to terminate the host response. The microbiota may be critical to both of these mechanisms. For example, the termination of T cell immune responses is believed to be partly controlled via competition for homeostatic cytokines such as IL-2, IL-7 and IL-15. In the small intestine, both IL-7 and IL-15 are induced by the presence of the microbiota, though how any given configuration of the microbiota affects expression of these cytokines is unknown [74, 75]. IL-15 in particular is critical in the development of celiac disease and thus the microbiota's effect in supporting its expression may be critical to disease etiology [76]. Further research is necessary to determine how exactly signals from the microbiota control these cytokines that regulate T cell and innate lymphoid cell survival. The microbiota can also be important in limiting pathology associated with infection. Inflammatory

monocytes are important mediators of protection in the immune response to the GI parasite *Toxoplasma gondii* [29]. Recently, a regulatory role for inflammatory monocytes has been appreciated. Specifically, the production of the critical immunoregulatory molecules IL-10 and prostaglandin requires activation by bacteria from the microbiota that are known to translocate during this infection [77]. Critically, in the absence of inflammatory monocytes or if prostaglandin is blocked, mice succumb to neutrophil-driven immunopathology.

Regulatory T cells are also critical in maintaining immune homeostasis and resolving infection-induced immune responses in the GI tract [78]. Both mouse models where T_{regs} are ablated and IPEX patients who carry mutations in their FoxP3 gene develop severe colitis [79]. The microbiota is critical in the maintenance and development of the intestinal-resident T_{reg} population [80]. In particular, a set of organisms in the Clostridia class is necessary and sufficient to support the colonic T_{reg} population and conversely Tregs support these bacteria via shaping the IgA repertoire [81, 82]. One mechanism via which these organisms support colonic T_{regs} is via the provision of short chain fatty acids (SCFA). SCFA are produced by the breakdown of complex carbohydrates, such as fiber, by the microbiota and are a primary source of energy for the enteric epithelium. Increased levels of SCFA have been shown to induce colonic T_{regs} and limit innate immune cell driven inflammation both locally in the gut and distally in the lung [83–87]. Interestingly, during enteric worm infections that rely on T_{regs} for chronic infection, the worm pushes the host microbiota towards increased production of SCFA [88]. In contrast, the microbiota also drives colonic T_{regs} that express ROR γ t and these cells actually limit anti-helminth infection via regulation of T cell activation and differentiation [89, 90]. How intestinal metabolites affect ROR γ t expression in intestinal Tregs is not known and will be critical to understanding how immune responses to enteric infection are regulated. Two of the most critical mediators of immunoregulation secreted by T_{regs} are IL-10 and TGF β . Interestingly, signals from the microbiota help to drive IL-10 production from Tregs, and TGF β production in DCs [91, 92]. IL-36 γ is another microbiota-dependent molecule that has been shown to assist in repair and regulation and it will be interesting to determine its importance in restoring homeostasis following infection [93]. Thus, taken together, the microbiota and its products are critical mediators of not only protection against infection, but also the resolution of immune responses.

It stands to reason that if the microbiota is contributing to immunoregulation, a shift in the microbiota may inhibit curative resolution in chronic inflammatory conditions. It is now believed that for diseases like IBD and EE, that effective treatments will involve intervention at the level of the microbiota in addition to the host and diet [94, 95]. Indeed, in mouse models, EE depended upon a combination of a shift in the microbiota and a diet low in fat and protein [44, 96]. Fecal transplant has also been attempted as a treatment for IBD, with somewhat mixed results that perhaps are an indication that shifts in the microbiota are a symptom rather than an underlying cause of the disease [97]. Alternatively, given the complexity of IBD pathology, an approach combining efforts to modulate immune-driven inflammation in addition to the microbiota might be more effective.

Infection Shifts the Relationship Between the Host and the Microbiota

As we have seen, the microbiota supports the immune response and modifies the response to infection significantly. However, as discussed above, the microbiota and infection are not always separable entities and regardless of the particulars, the immune system must reset homeostasis to prevent chronic inflammation. Most infectious organisms enter and proliferate at mucosal sites and therefore pose a particular problem for the immune system because the microbiota and inciting organism are not always easily discriminated. One hypothesis on how the immune response is targeted is that there are certain behaviours that are not characteristic of benign organisms, such as cytoplasmic invasion and membrane rupture which can be sensed by sensors such as NOD-like receptors (NLRs) to allow for discrimination [98, 99]. However, perturbation of the microbiota can lead to the emergence of opportunistic pathogens or cause the translocation of otherwise innocuous bacteria systemically and how the immune system deals with these shifts is not fully known. For instance, intestinal inflammation and in particular infection has been associated with a narrowing of microbe diversity and an outgrowth and invasion of the host with opportunistic bacteria, such as *Enterobacteriaceae* [96, 100–104]. One might suspect that severe shifts in the microbiota may also induce shifts in the metabolites that are produced and that these may be measured as surrogates for health of the microbiota. Indeed, as previously discussed, SCFA support colonic T_{regs} but recent results indicate that innate immune signaling may be modified by metabolites as well. The inflammasome is a multi-molecular complex important for the post-translational processing of the inflammatory cytokines IL-1 β and IL-18. Metabolites associated with healthy (taurine) and disrupted (spermine and histamine) microbiomes have been shown to modulate the function of the inflammasome and downstream IL-18 and AMP production, possibly explaining how some configurations of the microbiota can predispose to intestinal inflammation [105]. Similar metabolites were disrupted in a mouse model of microbiota-driven enteropathy, perhaps hinting that these shifts are consistent to multiple perturbations of the host/microbiota relationship [96]. How microbiota-derived metabolites shift and modulate immunity at times of infection is not known, but is a fascinating area for future investigation.

Infection also modifies the T cell response against the microbiota. For instance *T. gondii* infection induces microbiota and food-specific T cells to adopt a Th1 fate, in contrast to the Th17 and T_{reg} responses associated with homeostasis [78, 100, 106, 107]. Conversely, the canonical Th17 T cell response against SFB was not modified by intestinal infection with *Listeria monocytogenes* [58, 108]. Therefore, perhaps unsurprisingly, the T cell response against the microbiota is shaped by infection and is contextual to the inciting inflammatory insult, the specific biology of the resident organisms and host genetics. Nonetheless, it is clear that effector CD4 T cells raised against the microbiota are a common occurrence due to infection and other inflammatory insults. How the immune system maintains these cells in quiescence long-term is an important outstanding question and should be addressed in the context of genetic backgrounds known to contribute to chronic barrier diseases such as IBD and psoriasis.

Infection with enteric pathogens such as *Yersinia pseudotuberculosis* can also cause damage and induce ‘immunological scarring’, which disrupts intestinal immune responses and

inflames local fat depots by deviating the homeostatic flow of antigen-presenting cells carrying bacterial products to the tissue [109]. Thus, by changing the flow of information from the intestine to the lymphoid tissue, infection-induced scarring can shift both homeostatic and infectious immune responses, which underscores the importance of the proper cellular flow from the GI tract for host/microbiota health.

Taken together, these changes to the host/microbiota relationship due to infection, including: the activation of microbiota-specific T cells, shifts to the diversity and composition of the microbiota and immunological scarring form the basis of a hypothesis wherein infection can lead to chronic disease long-after the inciting organism has been cleared (Figure 2). Indeed, experiments in mouse models have shown clearly that viral infection predisposes to significantly worse pathology in the context of Crohn's Disease-related mutations in ATG16L1 [110]. Oral *Yersinia enterocolitica* infection in mice deficient for TLR1, a key innate immune receptor, can also induce a shift in the microbiota towards a pro-inflammatory state. This change pre-disposes animals to colitis, perhaps linking infection, genetics and a shift in the microbiota [111]. Additionally, Crohn's Disease in particular shows many of the characteristics of an infection-modulated microbiota/host relationship, including the invasion of the mesenteric fat by members of the microbiota and immune cells in addition to a shift in the composition of the microbiota towards reduced diversity and an increased fraction of *Enterobacteriaceae* [112–114]. There is some evidence that infection and in particular *Campylobacter jejuni* infections can pre-dispose to the development of chronic inflammatory disease [115, 116]. Specifically, patients with a history of GI infection are more likely to develop Irritable Bowel Syndrome and IBD, though these findings are confounded by the possibility that those people who are pre-disposed to development of intestinal disease may be prone to infection as well [117, 118]. Only through a better understanding of how infectious history may shape the microbiota and therefore mucosal immunity will we begin to understand this complex relationship.

Concluding Remarks

The era of next generation sequencing has given us enormous new insight into the diverse set of organisms that inhabit our barrier surfaces but has also led to many new questions (see Questions box). Large clinical studies and controlled animal models have just begun to show us how these organisms and their gene products may be important modulators of the host, both contributing to and protecting against chronic inflammatory disease. One of the most important systems modified by the microbiota is the immune system and accordingly the microbiota is critical in the response to infection. As we begin to understand the unique interactions of the members of the microbiota with the immune system, the hope is that we will understand how the system is governed. However, understanding how a diverse consortium of bacteria interacts with the immune system in a shifting environment is beyond our current capabilities. Therefore, identifying surrogates of a healthy microbiota/host relationship, such as metabolites and how they control the system will be critical to our understanding and to the development of therapeutics that do not require the complicated provision of live organisms. Our newfound microbial knowledge has also shifted how we understand the nature of infectious disease. It can be argued that pathogens and 'commensal' organisms are merely two different approaches to the same problem of the need to colonize a

broad range of hosts. For instance, both benign colonization and pathogenicity can be characteristic of two genetically identical organisms, depending upon the host and the environment. Through the discovery of the TLRs that sense microbial patterns and more recently the NLRs, that provide information on cellular damage and cytoplasmic invasion, we now understand the basic framework within which the immune system determines the threat associated to any given organism. If we can come to the understanding of how the adaptive immune system is shaped by organisms with such behavioural plasticity without developing chronic pathological immune responses, it will be an enormous step forward for our comprehension of the function of mucosal immune system. In addition, opportunistic infections and 'blooms' of resident bacteria and chronic immune responses are associated with many of the most intractable diseases afflicting humankind today, so a better understanding of their etiology is critical for novel targeted therapies that treat the root cause.

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Questions?

1. What are the key metabolites and bacterial products that control immune system–microbiota interactions? We have seen metabolites that shape mutualism, but are there metabolites that indicate a perturbation of the microbiota and induce inflammation? Can these metabolites be leveraged as mucosal adjuvants?
2. Do pathogens modulate the microbiota to limit immunity to gain access to the host?
3. What is the core metagenome and does the immune system assess the health of the metagenome via metabolites?
4. Does previous carriage of opportunistic organisms such as *C. difficile* and *E. coli* affect the immune response upon outgrowth and infection? How does the adaptive immune system handle such shifts in behavior and is immune plasticity an effort to deal with ever shifting bacterial behavior?
5. How exactly does the immune system modify the microbiota? IgA does not generally kill bacteria, so is IgA shaping bacterial behavior? Are there other mechanisms to shape bacterial behavior, that have yet to be discovered? How else might shifts in the microbiota be mediated?
6. Do infections predispose to chronic inflammation via shifting the immune system–microbiota relationship? What is the best way to intervene? In situations where genetics are contributing to disease (IBD for example), is fecal transplant a viable therapeutic option, or do we need to first target the ecological causes (nutrients, inflammatory molecules) of the shift in the microbiota?

Trends page

1. Pathogenicity, particularly amongst bacteria in the gastrointestinal tract, is contextual, and depends both on the host genetics and the other microorganisms present. Many organisms shift between benign and pathogenic states according to their environment
2. The microbiota can work in concert with the host immune system to limit infection via two main mechanisms: colonization resistance and tonic activation of both the innate and adaptive immune response
3. Infection can shift the host – microbiota relationship significantly, possibly contributing to chronic inflammatory disease.

Figure 1. Innate and Adaptive Immune Responses Against the Microbiota

A) Sensing of the microbiota by innate immune receptors engenders multiple mechanisms to foster the host/microbiota relationship and clear invasive organisms. LPS signaling induces the fucosylation on the surface of the intestine which supports the healthy microbiota and limits invasion by *Proteobacteria* such as *Citrobacter*. Microbial signals also induce IL-23 from dendritic cells and IL-1 β from macrophages which, in turn activates IL-17A and IL-22 from ILCs and T cells, leading to the production of antimicrobial peptides (AMPs) that can kill intestinal bacteria. B) Dendritic cells carrying antigens from the microbiota traffic from the intestine to the mesenteric lymph nodes (MLN) where they predominantly drive the differentiation of regulatory T cells (T_{regs}) and Th17 T cells. Both T_{regs} and Th17 T cells are capable of inducing the differentiation and class switching of IgA producing plasma B cells which secrete large amounts of dimeric IgA (sIgA). IL-17 produced by Th17 cells also drives the production of the polymeric-Ig receptor (pIgR), allowing for greater secretion of IgA into the intestinal lumen. The microbiota directly shapes this interaction with metabolites such as short-chain fatty acids (SCFA), which drives the production of T_{regs} from migratory dendritic cells.

Figure 2. Shifts in the Host-Microbiota Relationship Induced by Infection

A) Infections, particularly those that cause translocation of the microbiota, can lead to the activation of inflammatory microbiota and pathogen-specific T cells. B) Infection-induced traffic of effector T cells, neutrophils (NΦ) and inflammatory monocytes (IM) can drive significant inflammation in the GI tract via the production of cytokines such as tumor necrosis factor (TNFα) and interferon-γ (IFN) -γ in addition to the secretion of nitrate and superoxide compounds into the intestinal lumen, driving shifts in the microbiota. C) Shifts in the microbiota, induced by infection lead to increased penetration of the host tissue and thereby further driving chronic inflammation and interfering with healing. D) Some infections, (*Yersinia pseudotuberculosis*) can induce immunological scarring that is compounded by chronic inflammation and dysbiosis, and reduces the fidelity of traffic through the lymphatics to the lymph node, leading to further inflammation in the adipose tissue.