Interactions between the intestinal microbiota and innate lymphoid cells

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Keywords: microbiota, intestinal immunity, *Bacterioides fragilis*, polysaccharide A, innate lymphoid cell, lymphoid tissue inducer cell

Abbreviations: AHR, aryl hydrogen receptor; APC, antigen-presenting cell; CCR, CC-chemokine receptor; DC, dendritic cell; Foxp3, forkhead box P3; GF, germ-free; IBD, inflammatory bowel disease; IFN, interferon; Ig, immunoglobulin; IL, interleukin; ILC, innate lymphoid cell; ILF, isolated lymphoid follicle; LT, lymphotoxin; LTi, lymphoid tissue inducer; MHC, major histocompatibility complex; MLN, mesenteric lymph node; NCR, natural cytotoxicity receptor; NK, natural killer; NOD, nucleotide-binding oligomerization domain–containing; PP, Peyer's patch; PSA, polysaccharide A; ROR, retinoic acid-related orphan receptor; SFB, segmented filamentous bacterium; SLO, secondary lymphoid organ; SPF, specific pathogen-free; TCR, T cell receptor; Th, T helper; TLR, Toll-like receptor; TNBS, trinitrobenzenesulfonic acid; TNF, tumor necrosis factor; Treg, regulatory T cell; WT, wild-type

The mammalian intestine must manage to contain 100 trillion intestinal bacteria without inducing inappropriate immune responses to these microorganisms. The effects of the immune system on intestinal microorganisms are numerous and well-characterized, and recent research has determined that the microbiota influences the intestinal immune system as well. In this review, we first discuss the intestinal immune system and its role in containing and maintaining tolerance to commensal organisms. We next introduce a category of immune cells, the innate lymphoid cells, and describe their classification and function in intestinal immunology. Finally, we discuss the effects of the intestinal microbiota on innate lymphoid cells.

Introduction

The mammalian gastrointestinal tract is home to 100 trillion bacteria (the microbiota),^{1,2} and the amount of genetic material contained by the microbiota (the microbiome) is perhaps 100 times the total amount of host genetic material.³ A growing body of evidence is establishing the key role of the mammalian gut flora in both health and disease.² The commensal flora plays a critical role in normal functioning of the host. Germ-free (GF) animals have deficits in systems ranging from digestion and metabolism⁴ to angiogenesis⁵ to cognitive development.⁶ In humans, the microbiome differs substantially in health and disease,^{7,8} and effects exerted by the microbiota are associated with obesity,^{9–14} colon cancer,^{15–17} asthma,^{18,19} inflammatory bowel disease (IBD),^{7,20,21} and cardiovascular disease.^{22,23} We are

beginning to understand in greater detail the mechanisms behind and significance of these differences. Early studies of the gut flora primarily used crude comparisons of GF and conventional specific pathogen-free (SPF) animals; however, we now know that host–bacterial interactions are highly specific²⁴ and that in many cases particular organisms, rather than the general bacterial load, are responsible for normal host development in a given mammalian species.^{25–30}

One aspect of host–microbial interactions that has attracted particular interest pertains to the immune system, especially the intestinal immune system, which interacts most directly with the microbiota.^{2,31} This review will first discuss the intestinal immune system and the role of the intestinal immune system in containing and defending against intestinal bacteria, with special emphasis on innate lymphoid cells (ILCs). We will then discuss the effects the microbiota has on the immune system in general and ILCs in particular. Unlike previous reviews on this topic, which have mostly focused on ILC classification and function in health and disease, this review will focus on the molecular mechanisms by which the microbiota influences ILCs and vice versa, and will attempt to address some of the controversies in the field and areas where the published data appear to conflict.

Intestinal Immunity

Background

The intestine has the dual function of nutrient absorption and protection against potential pathogens. These two tasks have conflicting demands. Optimal absorption requires a large surface area and selective permeability to nutrients through a thin epithelial layer. However, a large surface area increases exposure to luminal bacteria, and the thinness of the epithelium increases the possibility of bacterial invasion. Thus, the intestinal immune system must be robust enough to defend a one-cell-thick epithelial layer. At the same time, it must not initiate inappropriate immune

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Submitted: 08/17/2013; Revised: 11/19/2013; Accepted: 11/20/2013;
Published Online: 12/16/2013
<http://dx.doi.org/10.4161/gmic.27289>

Table 1. Categories and functions of innate lymphoid cells

Cell type	Tissues	Activated by	Primary mediators	Function and disease associations	References
NK cell	SLO Blood	IL-12 IL-18 NCRs	IFN- γ Perforin Granzymes Fas ligand	Tumor immunity Antiviral immunity Systemic inflammation	64–69
ILC1	Intestine		IFN- γ	Colitis	59, 61
ILC2	Airway/lung Intestine Mesentery	IL-25 IL-33	IL-5 IL-13 Amphiregulin	Airway hypersensitivity Postinfection homeostasis Antihelminth immunity	73–78, 80
LTi cell	SLO Intestine	IL-1 β IL-7 IL-23 AHR	IL-17 IL-22 LT CD30L OX40L	Colitis Intestinal infection SLO development T cell maintenance	95–96, 99, 110–112
NCR ⁺ ILC3	Intestine		IL-22	Colitis Intestinal infection	83, 96, 99
NCR ⁻ ILC3	Intestine		IL-17 IL-22 IFN- γ	Colitis Postinflammatory colon cancer	81, 100

Abbreviations: AHR, aryl hydrogen receptor; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; LT, lymphotoxin; LTi, lymphoid tissue inducer; NCR, natural cytotoxicity receptor; SLO, secondary lymphoid organ. Note: This table is not intended to be exhaustive. Shown are the major categories of ILCs along with their locations in the body, the molecules that induce cytokine production, the mediators (cytokines and others) primarily responsible for their immune effects, and their known functions and roles in disease.

responses to the commensal bacteria that reside in the intestinal lumen, as these responses may result in inflammatory diseases such as IBD.^{31,32} Accordingly, it is important for the intestinal immune system to maintain an appropriate balance of pro- and anti-inflammatory factors.³³

The intestinal immune system consists of highly organized structures—namely Peyer's patches (PPs), mesenteric lymph nodes (MLNs), and isolated lymphoid follicles (ILFs)—that are associated with the lamina propria and epithelial cells of the intestine.³⁴ PPs are secondary lymphoid organs (SLOs) of the intestine that facilitate the sampling of luminal antigens. Murine PPs consist of B cell follicles surrounding a T cell zone.³⁵ These follicles are surrounded by a subepithelial dome, which is in turn surrounded by a follicle-associated epithelium that is exposed to the intestinal lumen.³⁵ PPs differ from peripheral lymph nodes in that they are not fed by afferent lymph vessels;³⁶ instead, the follicle-associated epithelium consists of a large number of M cells, specialized epithelial cells that transcytose macromolecules and microorganisms into the subepithelial dome.^{37–39} This transcytosis allows antigen-presenting cells (APCs) in the subepithelial dome to sample antigens from the bacteria that are most proximal to the epithelium.³⁸ The APCs next can either present these antigens to T cells locally within the PP or migrate to the MLNs and present the antigens there.^{40,41} The T cells can then be activated, as can B cells through partially T cell-independent mechanisms.⁴² While these PP- and MLN-activated lymphocytes do enter the bloodstream through the thoracic duct,^{43,44} both T⁴⁵ and B⁴³ cells then return to the intestinal lamina propria, and this return to the gut may limit systemic inflammation.^{46,47} APCs also play an important role in balancing activation and tolerance: some APC populations primarily produce proinflammatory cytokines, while others have a more regulatory role.^{40,48–51}

B cell activation in the PPs and MLNs helps the host contain the microbiota. Activated B cells differentiate and produce secretory immunoglobulin (Ig) A, which is the main intraluminal antibody. IgA helps control the growth of the intestinal bacteria and prevents microbial adhesion to epithelial cells,^{42,52} but acts primarily locally and does not induce systemic inflammation.⁵³ IgA is produced in the PPs and MLNs, as previously discussed. The other major source of intestinal IgA is the ILF.⁵⁴ ILFs consist of large groups of B cells in addition to other, smaller cell populations such as dendritic cells (DCs) and lymphoid tissue inducer (LTi) cells (to be discussed in greater detail below).³⁴ The B cells in ILFs primarily generate IgA not through T cell co-activation, but rather through a T cell-independent mechanism involving lymphotoxin (LT) signaling and LTi cell-stromal cell interactions.^{54,55}

Innate lymphoid cells

The ILC is a component of the intestinal immune system that has recently attracted tremendous attention. ILCs are a diverse class of immune cells defined by three criteria: lymphoid morphology on microscopy; absence of recombination-associated, gene-mediated antigen receptors (i.e., T and B cell receptors); and absence of myeloid and DC markers.⁵⁶ ILCs play an important role in the innate immune system through cytokine production and other miscellaneous functions.^{57,58} The ILC nomenclature has recently been standardized, with classification of the cells into three groups based on cytokine production profile.⁵⁶ We will focus primarily on group 3 ILCs, which have the best-characterized role in intestinal immunity, but will briefly discuss the other groups as well (Table 1).

Group 1 ILCs are analogous to T-helper (Th) 1 cells in that they produce interferon (IFN)- γ but not other cytokines associated with Th17 cells, such as interleukin (IL)-17 or IL-22.^{56,58} Group 1

ILCs express the transcription factor T-bet^{59,60} and respond to the cytokines IL-12 and IL-18.^{59,61-63} The prototypical group 1 ILC is the natural killer (NK) cell, which is the best-characterized of all ILCs.^{64,65} NK cells are named for their cytotoxic effects on virus-infected cells^{66,67} and tumor cells;⁶⁸⁻⁷⁰ these effects are mediated through mechanisms involving perforin, granzymes, and the Fas ligand.^{64,65} During specific stages of development,⁶⁵ NK cells also produce IFN- γ in the setting of systemic inflammation⁷¹ and after activation of the natural cytotoxicity receptors (NCRs) NKp46 (found in mice and humans) and NKp44 (humans).⁷² In addition to NK cells, group 1 ILCs include a class of cells called ILC1s⁵⁶ that accumulate in the intestine during colitis in mice and humans and are a major source of innate IFN- γ under such conditions.^{59,61} Group 2 ILCs (ILC2s) are defined as cells that produce Th2-associated cytokines.⁵⁶ They express the transcription factor GATA3,^{73,74} respond to IL-25 and IL-33,⁷³⁻⁷⁸ and are found in the lungs,^{73,75} gut,^{75,76} and adipose tissue.⁷⁴ ILC2s protect against helminthic infection^{74,76} and also play an important role in the airways⁷⁹ by driving airway hypersensitivity induced by influenza virus,⁷⁸ ovalbumin, and dust mites⁷⁷ through IL-5 and IL-13.^{77,78} In addition, ILC2s are critical for tissue healing and for restoration of lung and airway homeostasis after infection with influenza virus.⁸⁰

Group 3 ILCs are characterized by production of the Th17 cytokines IL-17 and IL-22, though they may also produce other cytokines, such as IFN- γ .^{56,81} Like Th17 cells, group 3 ILCs produce cytokines in response to IL-1 β and IL-23^{82,83} and express varying levels of the transcription factor retinoic acid-related orphan receptor (ROR) γ t and, sometimes, T-bet.⁸⁴⁻⁸⁶ IL-17 and IL-22 are both important regulators of intestinal and systemic immunity. IL-17 is typically proinflammatory and stimulates neutrophil homing, granulocyte and macrophage growth and differentiation, and acute-phase reactant production.⁸⁷ This cytokine usually exacerbates inflammatory diseases⁸⁸ but confers protection against fungal and certain bacterial infections.⁸⁹⁻⁹¹ IL-22, in contrast, promotes tissue healing by inhibiting apoptosis, increasing cell cycle progression, and inducing mitogenic factor production.^{87,92} IL-22 also induces epithelial cells to produce the antimicrobial peptides RegIII β and RegIII γ ⁹³ as well as mucin;⁹⁴ these products kill microbes and maintain the barrier between host and bacteria (Fig. 1). While IL-22 generally protects against infectious^{95,96} and inflammatory⁹⁷ diseases, it also drives colon cancer under certain circumstances.⁹⁸

IL-22 is responsible for many of the effects of group 3 ILCs in health and disease. Through IL-22, ILCs mediate experimental colitis,⁹⁹ drive inflammatory colon cancer,¹⁰⁰ and protect against infection by the intestinal pathogens *Citrobacter rodentium*⁹⁵ and *Salmonella enterica* serovar Typhimurium.⁸² Group 3 ILCs are important not only in the setting of infection or inflammation but also in the steady-state, in which they contain luminal bacteria through IL-22-dependent mechanisms.¹⁰¹ In the absence of ILCs, there is greater dissemination of bacteria (especially *Alcaligenes* species) to the spleen and liver, with resultant systemic inflammation and elevated serum cytokine levels (Fig. 1). Of note, even in mice with T and B cells, ILCs are necessary for containing these bacteria. ILC-produced IL-17

Figure 1. Effects of ROR γ t⁺ innate lymphoid cells (ILCs) on the microbiota. ILCs kill and inhibit bacteria by producing interleukin 22 (IL-22), with subsequent downstream effects on epithelial cells (ECs). In addition, they induce the formation of isolated lymphoid follicles (ILFs) through the induction of lymphotoxin $\alpha\beta_2$ (LT- $\alpha\beta_2$) and subsequent IgA production and bacterial suppression. Finally, ILCs signal to CD4⁺ T cells through major histocompatibility complex class II (MHC II) and suppress T cell responses to the microbiota.

is also physiologically important in defense against fungal infection⁸⁹ and may drive certain models of colitis.⁸¹ In addition to exerting cytokine-dependent effects, group 3 ILCs modulate intestinal immunity through major histocompatibility complex class II (MHC II)-mediated antigen presentation to CD4⁺ T cells (Fig. 1).¹⁰² Such antigen presentation does not cause T cell proliferation, but rather induces T cell tolerance to commensal bacteria; mice lacking MHC II expression in ILCs develop spontaneous colitis.¹⁰²

The best-characterized group 3 ILC is the LT α i cell. LT α i cells are named and best known for their role in the generation of SLOs, such as lymph nodes and the white pulp of the spleen, during embryogenesis.¹⁰³ During fetal development, LT α i cells migrate to nascent SLOs, where stromal cells activate them through IL-7 and the tumor necrosis factor (TNF)-related activation-induced cytokine (TRANCE), inducing them to express LT- $\alpha\beta_2$.^{104,105} LT- $\alpha\beta_2$ signals to the LT- β receptor on stromal cells, which causes stromal cells to express the homing molecules CC-chemokine ligand 19, CC-chemokine ligand 21, and CXC-chemokine ligand 13;¹⁰⁶ these ligands recruit T cells, B cells, and APCs into spatially distinct T zones and follicles.¹⁰⁷ PP development is similar, except that IL-7 plays a larger role in this process than in lymphoid development¹⁰⁵ and DCs rather

Figure 2. Effects of the microbiota on RORγt⁺ innate lymphoid cells (ILCs). Intestinal bacteria stimulate ILCs through antigen-presenting cell (APC)-produced interleukin 1β (IL-1β) and IL-23 and epithelial cell (EC)-produced IL-7 and also inhibit ILCs through EC-produced IL-25. Intestinal bacteria may also directly induce ILC activity through the aryl hydrogen receptor (AHR) and natural cytotoxicity receptors (NCRs).

than stromal cells activate LT production and are themselves an important source of LT.¹⁰⁸ LTⁱ cells also signal through LT to induce the maturation of intestinal cryptopatches into ILFs, which are a source of subsequent secretory IgA production as previously discussed (Fig. 1).^{53,54,109} In addition to these roles in induction, LTⁱ cells residing in the SLOs of adult mice co-stimulate T cells through CD30L and OX40L.¹¹⁰ This co-stimulation is required for activated T cell survival^{111,112} and maintenance of T cell memory against pathogens.¹¹³ Finally, like other group 3 ILCs, both splenic¹¹⁴ and intestinal⁸⁵ LTⁱ cells produce IL-17 and IL-22.

In addition to LTⁱ cells, there are other group 3 ILCs that are collectively known as ILC3s.⁵⁶ One subset expresses RORγt and the NCRs NKp46 (in mice and humans) and NKp44 (in humans only) and produces large amounts of IL-22^{83,96,115} but little or no IL-17.^{96,115} Another NCR[−] group produces IL-17, IL-22, and IFN-γ.⁸¹ Interestingly, one paper has identified a common gamma chain-independent response in a subset of splenic ILCs in which these cells produce IL-17 and IL-22 in response to flagellin and lipopolysaccharide.¹¹⁶ While human ILCs are less well understood than their murine counterparts, it is known that human group 3 ILC subsets can produce IL-22 alone or both IL-17 and IL-22.¹¹⁷⁻¹²⁰

The developmental relationship between these different ILC populations is unclear. There is certainly some plasticity between

different types of ILCs in humans. Human NCR⁺ and NCR[−] group 3 ILCs can differentiate into ILC1s.⁶¹ In addition, human LTⁱ cells can differentiate into NKp44⁺ and NKp46⁺ ILC3s both in vitro when cultured with stromal “feeder” cells, IL-7, and IL-15 and in vivo when injected into lymphocyte-deficient mice.^{121,118} Interestingly, the same is not the case in mice: Eberl and colleagues found that, under similar in vitro conditions, neither adult nor embryonic LTⁱ cells differentiate into ILC3s.⁸⁵ Investigation to clarify the lineage relationships of the different types of ILCs in different species is ongoing.

Effects of Gut Flora on Innate Lymphoid Cells

Background

We have discussed how the intestinal immune system influences and contains intestinal bacteria. However, host-microbial interactions are two-way, and the microbiota affects the host immune system as well. We will now consider some general principles regarding microbial effects on the host and will then describe the details of these effects on ILCs.

In addition to nonimmunologic deficits,³¹ GF mice have abnormal intestinal immunity, with smaller PPs, fewer IgA-secreting B cells and CD8⁺ intraepithelial lymphocytes, and decreased production of antimicrobial peptides.²⁷ Systemically, GF mice have a pronounced Th2 skew: a greater proportion of CD4⁺ T cells produce Th2 cytokines such as IL-4 in GF mice than in conventional mice.²⁷ Most of these immunologic changes are rapidly reversible upon introduction of a normal mouse microbiota.^{26,122} Interestingly, though, some of the effects of the intestinal flora are programmed very early after birth and persist even when the flora is altered later in life; this point is best illustrated by NKT cell migration to the colon.¹²³

There appears to be considerable specificity in host-microbial interactions, as our lab recently showed while investigating the effects of intestinal colonization with a mouse microbiota or a human microbiota on murine intestinal immunity.²⁴ The microbiotas were similar at the phylum level (the Bacteroidetes and Firmicutes dominated in both), but diverged at the genus level in the Firmicutes and at the operational taxonomic unit level in the Bacteroidetes. These differences in the microbiota resulted in drastically different immune phenotypes. The mouse microbiota nearly restored intestinal T cell numbers and fully restored T cell proliferation to SPF levels. However, the human microbiome did not change either T cell numbers or proliferation relative to GF status. Interestingly, these effects were limited to gut-associated compartments: splenic T cell numbers were identical in all groups.

Given that genus- and species-level differences in the microbiota can result in radically different immunologic phenotypes, it will be important to identify specific organisms and groups of organisms that drive these differences. One such organism is *Bacteroides fragilis*. While in the clinical setting *B. fragilis* is often found in infections, most notably abdominal abscesses,^{124,125} it is also a member of the normal human microbiota.¹²⁶ Its effects on the immune system are primarily attributable to polysaccharide A (PSA), one of its eight capsular

polysaccharides.^{32,126} Capsular polysaccharides in general are important for normal bacterial growth and have attracted a great deal of attention as potential vaccine targets.¹²⁷⁻¹³¹ PSA in particular is necessary for *B. fragilis* colonization of its intestinal “niche,”¹³² though other bacterial products may also be necessary for this process.¹³³ In addition, PSA, either purified and orally gavaged or produced by intestinal bacteria, regulates the systemic murine Th1/Th2 balance²⁷ and induces the development of IL-10-producing forkhead box P3⁺ (Foxp3⁺) regulatory T cells (Tregs).²⁸ The effects of this IL-10 production are not apparent in the steady-state,¹³⁴ but in the setting of inflammation, IL-10 confers protection against murine colitis²⁸ and experimental autoimmune encephalomyelitis.^{135,136} PSA is recognized by host TLR2^{132,134} (unpublished data) and, after endosomal processing, can bind to MHC II.¹³¹ Another bacterium that drives immune development is the segmented filamentous bacterium (SFB), which is critical for the development of Th17 cells²⁶ and the pathogenesis of Th17-associated diseases in the gut¹³⁷ and other tissues.^{88,138,139} Finally, as another mechanism by which molecules produced by the commensal flora may influence the intestinal immune system, short-chain fatty acids upregulate Treg numbers and IL-10 production in the colon but, interestingly, not the small intestine, spleen, MLN, or thymus.¹⁴⁰ A major mediator of this process is G-protein coupled receptor 43, which recognizes acetate and propionate¹⁴¹ and inhibits histone deacetylases.¹⁴⁰

In addition to these instances in which a single organism drives immune maturation, there are other examples in which groups of bacteria are required for a similar effect. Specific *Clostridium* species are required for Treg development.²⁵ Clostridia are the most numerous gram-positive spore-forming organisms in the intestine¹⁴² and constitute 10–40% of the normal microbiota, even though certain species, such as *C. perfringens* and *C. difficile*, can cause disease.¹⁴³ Honda and colleagues identified a collection of 46 *Clostridium* strains native to the murine intestine¹⁴⁴ whose introduction into GF mice increased by more than 3-fold (relative to the results in untreated GF mice) the number and proportion of CD4⁺ cells in the colon, liver, lung, and spleen²⁵ that produce IL-10, a cytokine critical for protection against colitis.¹⁴⁵⁻¹⁴⁷ The introduction of these 46 clostridial strains even into SPF mice resulted in decreased susceptibility to dextran sodium sulfate colitis (a Th1 and Th17 cytokine-driven colitis in the disease stage investigated¹⁴⁸) and oxazolone colitis (Th2 cytokine-driven^{149,150}).²⁵ This group later rationally selected a group of 17 human *Clostridium* strains that also induced IL-10-producing Foxp3⁺ Tregs and protected against 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis and ovalbumin-induced diarrhea.¹⁵¹ Of note, it appears that a certain number of strains are required. Cocktails of three murine strains led to a much smaller effect than did the combined 46 strains.²⁵ Monocolonization with any one of the 17 human clostridial species failed to induce Tregs relative to GF status, and colonization with a mix of three or five of these species did not induce as many Tregs as the full 17-species cocktail did.¹⁵¹

As has been discussed, specificity in host–microbial interactions is driven by genus- or even species-level differences.²⁴ However, an important question arises: what is the molecular

mechanism of this specificity? There are several possibilities. Microbial pattern recognition receptors that are characteristic of the innate immune system are not generally considered specific enough to recognize such differences.¹⁵² However, the aryl hydrogen receptor (AHR), which recognizes various natural products including those from bacterial tryptophan metabolism, offers a counter-example: when AHR is activated by one particular ligand, it induces Treg development, whereas AHR activation by a different ligand induces Th17 cell development.¹⁵³ Another potential source of specificity is T cell receptor (TCR) recognition of bacterial antigens. The substantial differences between TCRs of colonic Tregs and those of thymic-derived natural Tregs suggest that differentiation of naïve T cells into Tregs may be driven by local antigens, and intestinal Treg TCRs do, in fact, recognize bacterial antigens.¹⁵⁴ Interestingly, recognition of bacterial antigens by these same TCRs on naïve T cells preferentially induces these T cells to differentiate into Tregs rather than effector cells.¹⁵⁴ Perhaps under certain circumstances bacteria can induce naïve T cells to differentiate into other T cell subsets as well.

A final possibility relates to the proximity of bacteria to host tissues. Some bacterial species, for a variety of organism-specific reasons, form closer associations with the host than others, and this greater proximity may cause greater exposure to bacterial products, recognition of bacterial antigens, or activation of host danger-associated pattern receptors.¹⁵⁵ It is certainly plausible that bacteria in the center of the intestinal lumen have less influence on intestinal immunity than those in close proximity to epithelial cells. Interestingly, the bacteria that are most physically associated with intestinal crypts are surprisingly similar in the murine colon and the invertebrate midgut and are far more similar between species than the total microbiota, which suggests that this core group of closely associated organisms co-evolves with its hosts.¹⁵⁶ There is no direct evidence for this proximity hypothesis, since it is not yet possible to control the spatial organization of the gut flora without modifying other factors. Nevertheless, notable bacteria that influence host immune development, such as SFB²⁶ and clostridial species,²⁵ appear on electron microscopy to have direct contact with epithelial cells. *B. fragilis* PSA-induced immunomodulation may also be location-specific. In *B. fragilis*–monocolonized mice, a small proportion of all *B. fragilis* organisms are in close proximity to colonic epithelial cells. However, in mice monocolonized with PSA-deficient bacteria, this population of tissue-associated organisms is far smaller; it increases to normal levels with oral administration of PSA.¹³² Depletion of Foxp3⁺ Tregs decreases the size of this tissue-associated population, while IL-17 blockade increases it. These findings imply that IL-17 would normally hinder *B. fragilis* association with the colon and that PSA induces Foxp3⁺ Tregs that downregulate IL-17 production and enhance this association. As a final example, mice deficient in the nucleotide oligomerization domain-containing (NOD)-like receptor P6 are susceptible to dextran sodium sulfate colitis, and this susceptibility is transmissible to wild-type (WT) mice through the gut flora.¹⁵² This colitis susceptibility phenotype is associated with greater frequency of Prevotellaceae and association of these organisms in intestinal crypts.¹⁵² Clearly, further investigation—perhaps

including the development of new tools—will be necessary to better establish the extent to which and the mechanisms by which intestinal geography influences immunologic phenotype,¹⁵⁵ but this proximity hypothesis shows promise as one explanation for the specificity of host-bacterial interactions.

In humans, too, there are associations between gut flora and intestinal immunity, though the direction of causality is much more difficult to establish in humans than in mice. The prototypical disease that illustrates this association is IBD, which comprises the subsets of Crohn disease and ulcerative colitis and is believed to arise from breakdown of immune tolerance to the microbiota.^{143,157-159} Humans with IBD have polymorphisms in genes associated with the immune system¹⁶⁰ as well as intestinal microbiomes that differ markedly from those of healthy controls.⁷ For instance, enteroadhesive *Escherichia coli* colonizes a greater proportion of Crohn patients than of healthy controls,²⁰ and *Faecalibacterium prausnitzii*, a human commensal that produces anti-inflammatory effects in murine colitis models, is associated with a lower risk of recurrence in Crohn.²¹ Given these associations, treatments directed at the microbiota may be useful in IBD patients. A recent meta-analysis has found that some antibiotics slightly decrease the likelihood and shorten the duration of IBD relapses.¹⁶¹ Conversely, the VSL#3 probiotic, which consists of defined cultures of four *Lactobacillus*, three *Bifidobacterium*, and one *Streptococcus* species, moderately increases the chance of establishing remission and decreases the risk of relapse in ulcerative colitis.^{162,163} Overall, these findings suggest that the microbiota regulates inflammation in human IBD. However, the significance of its role and the therapeutic value of targeting it remain unclear.

ILC numbers and cytokines

Having introduced some general principles regarding the effects of the gut flora on the immune system, we will now discuss the numerous effects that intestinal bacteria have on ILCs, starting with the role of these organisms in determining ILC numbers and cytokine production (Fig. 2). We will focus on group 3 ILCs, but clearly the microbiota can influence other cells as well. For instance, human NK cells express the microbial pattern receptors Toll-like receptor (TLR) 2,¹⁶⁴ TLR3, and TLR9,¹⁶⁵ and human group 3 ILCs express TLR2,¹¹⁷ so both cell types may directly recognize bacterial components. (Murine ILCs do not appear to express TLRs.¹⁶⁶) Furthermore, commensal bacteria induce host epithelial cells and APCs to produce cytokines such as IL-6, IL-7, IL-12, IL-15, type 1 IFNs, and TNF- α , and this microbe-driven effect is required for full NK cell activation.^{167,168} The effects of commensal organisms on ILC2s have yet to be directly verified.

Two early studies found that GF mice had very few ROR γ t⁺ small-intestinal group 3 ILCs and that these cells produced little IL-22.^{96,115} ILC numbers could be fully restored by colonization of GF mice with an SPF intestinal flora within 15 d.¹¹⁵ In addition, when ROR γ t⁺ NKp46⁺ ILC3s from SPF mice were cultured with IL-23, the percentage of cells producing IL-22 increased dramatically from around 15% to 35%.¹¹⁵ However, very few ILC3s from GF mice produced IL-22 even at baseline (< 5%), and the percentage of IL-22⁺ cells did not increase following IL-23 stimulation. Consistent with those findings,

epithelial cells from GF mice produced very low levels of *Reg3b* and *Reg3g* transcripts, which encode for RegIII β and RegIII γ , two antimicrobial peptides produced by epithelial cells in response to IL-22 signaling.⁹³ Recolonization of adult GF mice with a conventional flora normalized expression of these peptides within 1–2 wk.¹¹⁵ Together, these two studies demonstrate that the intestinal microbiota is necessary for the development of ROR γ t⁺ ILC3s and stimulates IL-22 production by these cells.

Other investigators, however, have found no differences in ILC numbers in mice with different microbiotas. Eberl and colleagues investigated this question using a “fate-map” mouse model—with which the progeny of a cell type can be tracked throughout life—to follow the fetal precursors of ROR γ t⁺ ILCs.⁸⁵ When the investigators treated mice with streptomycin, ampicillin, and colistin starting from day 7 after birth, there was no change in the composition of any ROR γ t⁺ group 3 ILC classes. Furthermore, the proportions of the different ROR γ t⁺ subsets among all ROR γ t⁺ cells were similar in GF and SPF mice.⁸⁵ Another paper from the same group described the investigation of cell numbers, rather than proportions, in GF mice and SPF mice and found no differences in numbers of ROR γ t⁺ CD4⁺ LTi cells or ROR γ t⁺ NCR⁺ ILC3s in GF and SPF mice or after antibiotic treatment starting from one day before birth.⁹⁹ A separate study found that the proportion of NCR⁺ ILCs among ROR γ t⁺ ILCs was identical in SPF and GF mice.⁸³

Perhaps the discrepancies in these findings have to do with how cells were quantified. That there are fewer ROR γ t⁺ ILCs may mean either that there are fewer ILCs or that fewer ILCs express ROR γ t, and the microbiota could theoretically affect either or both of these variables. Diefenbach and colleagues readdressed this question, using fate-map mice in which any descendant of ROR γ t⁺ precursors—even if it had subsequently lost ROR γ t expression—could be identified.¹²¹ The researchers found that the microbiota’s effect on ROR γ t⁺ cell numbers reflected less ROR γ t expression rather than lower cell numbers: GF and SPF fate-map mice had similar numbers of LTi cells and NCR⁺ ILC3s, but ROR γ t expression was lower in the GF mice. A major mechanism behind this effect was microbial stabilization of ROR γ t expression through the induction of host cell production of IL-7,¹²¹ which drives development of group 3 ILCs.^{169,170} Antibiotic treatment decreased both the number of intestinal *Il7* transcripts and ROR γ t expression in ILCs, and IL-7R^{-/-} mice had decreased numbers of LTi cells and NCR⁺ ILC3s.¹²¹ Together these results suggest that the microbiota influences not ILC development, but rather ROR γ t expression, through IL-7 signaling (Fig. 2).

Gut flora-induced differences in T-bet expression constitute a mechanism by which the gut flora may influence ILC numbers.⁸⁶ In mice, CCR6⁺ ROR γ t⁺ ILCs develop largely before birth (i.e., before bacterial colonization of the intestine), do not express the Th1-associated transcription factor T-bet, do not express NKp46, and produce IL-17A, IL-17F, and IL-22 independent of T-bet; this population is most similar to the traditional fetal LTi cell population. In contrast, CCR6⁻ ROR γ t⁺ ILCs develop and proliferate mostly after birth (i.e., after bacterial colonization). At birth, these cells are essentially all T-bet⁻, but around two weeks

of age, a population of CCR6⁺ T-bet⁺ RORγt⁺ cells develops from T-bet⁺ progenitors. Intestinal microbiota and IL-23 both induce T-bet expression, which in turn increases Nkp46 expression and IFN-γ production. That is, the number of CCR6⁺ RORγt⁺ cells depends on the intestinal microbiota. This provides another mechanism by which the microbiota may influence group 3 ILC numbers. However, the molecular mediators responsible T-bet induction by the microbiota remain to be identified.

ILC3s express NCRs, which can be directly activated by specific microbial products such as influenza virus hemagglutinin¹⁷¹ and cell surface antigens of *Mycoplasma*-infected cells and represent another mechanism by which the microbiota may influence ILCs.^{172,173} NCRs, which in conventional NK cells cause cytotoxic granule release and IFN-γ production,⁷² also appear to upregulate ILC function. One recent paper investigating human ILCs found that Nkp44 signaling influences RORγt⁺ ILC signaling through a mechanism synergistic with that mediated by cytokines.¹⁷⁴ The authors found that Nkp44 activation alone caused ILCs to produce TNF but not IL-22, while IL-1, IL-7, and IL-23 preferentially induced IL-22 but not TNF. However, activating Nkp44 antibodies and IL-1, IL-7, and IL-23 synergized to induce large amounts of TNF and IL-22 secretion. An earlier paper found that even in the absence of Nkp46 murine ILCs produce IL-22;¹⁷⁵ however, the earlier paper did not investigate the effects of Nkp46 activation on ILCs and does not conflict with the above paper on human ILCs.

Finally, there are other speculative mechanisms by which the microbiota may influence the intestinal immune system that may not be physiologically significant. The gut flora induces APCs to produce IL-1β and IL-23,¹⁷⁶⁻¹⁷⁸ which enhance IL-17 and IL-22 production by ILCs (Fig. 2).^{82,83,114} In addition, group 3 ILCs express AHR,¹⁷⁹ which recognizes, among other things, products of bacterial tryptophan metabolism.¹⁸⁰

Although in the previously described examples the microbiota activates group 3 ILCs, there is evidence that it may also inhibit them. Eberl and colleagues identified IL-25 as a negative regulator of ILC cytokine production.⁹⁹ In small-intestinal LTi cells and NCR⁺ ILC3s, *Il22* expression in the steady-state was 1–2 orders of magnitude higher in GF mice than in their SPF counterparts. In addition, the proportion of IL-22-producing cells upon ex vivo stimulation with IL-23 was higher in GF mice than in SPF mice, and also in mice treated with streptomycin, colistin, and ampicillin from birth than in untreated mice. The authors found that the microbiota induces production of IL-25 by epithelial cells and that adding recombinant IL-25 decreases the in vitro ability of ILCs to produce IL-22 (Fig. 2). Reynders et al. also investigated IL-22 production by small-intestinal LTi cells and NCR⁺ ILC3s, in this case after ex vivo stimulation with IL-23.⁸³ The proportion of cells producing IL-22 in this setting was about 2-fold higher in GF than in SPF mice, and recolonization of GF mice with a conventional flora restored IL-22 production to SPF levels within 5 wk.

These discrepant findings—i.e., that the microbiota can either activate or inhibit ILCs—may be partially attributable to differences in the microbiotas of the SPF mice in these studies. The dominant effect of the microbiota may differ widely depending on its composition. For example, in a microbiota with many

organisms containing flagellin, which induces intestinal DCs to produce IL-23,¹⁷⁶ bacterium-induced upregulation of IL-23 stimulation may be substantial and, as a result, that particular microbiota may predominantly activate ILCs. In contrast, a more “regulatory” microbiota that induces large amounts of IL-25 production may predominantly inhibit ILCs. This explanation, however, does not fully account for the differences in the studies cited: GF mice, which have an identical (i.e., absent) microbiota in all facilities, had very different levels of IL-22 production and expression in the papers cited.^{96,99,115} Nevertheless, it is certainly possible that, in other settings, different microbiotas have different immunomodulatory effects. To better understand these effects, it will be important to identify specific organisms that influence ILC function and to define the mechanisms by which they do so.

Lymphoid tissue development

The development of lymphoid tissues such as SLOs and ILFs is a unique and important function of RORγt⁺ ILCs.^{103,181} This process is largely microbe-driven and involves NOD1.⁵⁴ While investigating microbe-associated pattern receptors in the setting of ILF formation, Bouskra et al. found that the number of ILFs in both the small intestine and the colon was substantially decreased in GF mice from that in SPF mice.⁵⁴ They attempted to identify types of organisms responsible for this effect by monocolonizing 8-wk-old GF mice with individual bacterial species. Specific gram-negative organisms, including *E. coli*, increased the number of ILFs above GF levels, but the gram-positive *Lactobacillus acidophilus* did not. Consistent with that finding, mice treated from birth until 8 wk of age with colistin, which targets gram-negative bacteria, had fewer ILFs than mice treated with vancomycin, which targets gram-positive bacteria. The investigators found that peptidoglycan is a major mediator of this effect. Mice lacking NOD1, which recognizes peptidoglycans from gram-negative bacteria, had fewer small-intestinal ILFs and hypertrophic cryptopatches, indicating defective maturation from cryptopatches to ILFs, and mice monocolonized with WT *E. coli* had more ILFs than GF mice or mice monocolonized with an *E. coli* strain that produces very small amounts of peptidoglycan. Of note, in the colon of NOD1^{-/-} mice, there were actually more ILFs and more hypertrophically mature ILFs, which suggested that the greater bacterial load in the colon triggers NOD1- and peptidoglycan-independent pathways to induce ILF maturation; these other pathways remain to be identified. Still, these results indicate that NOD1 recognition of gram-negative bacterial products such as peptidoglycan is critical for LTi cell localization and induction of ILF development as well as for ILF maturation.

In contrast, Mebius and colleagues found that while—consistent with the previous paper—a greater proportion of ILFs were immature in GF mice, colonic ILF numbers were equal in GF and SPF mice.¹⁸² These results suggest that colonic bacteria are actually unnecessary for LTi cell induction of ILFs. However, antibiotic treatment with streptomycin, ampicillin, and colistin from embryonic day E14 to postpartum day 14 did not affect colonic ILF numbers or maturation, possibly due to incomplete depletion of colonic bacteria. These results are consistent with a classic paper demonstrating that small-intestinal cryptopatch numbers are normal in GF mice.¹⁸³

In addition to NOD1, another mechanism by which the microbiota may influence ILF development is AHR.⁵⁸ Kiss et al. found that there were virtually no ILFs in AHR-deficient mice.¹⁷⁹ While newborn AHR^{-/-} mice have normal numbers of group 3 ILCs, by 8 wk of age the AHR^{-/-} mice in this study had several times fewer group 3 ILCs than their WT counterparts. This difference indicates that while AHR is dispensable for prenatal ILC development, it is important for expansion or survival of ILCs postnatally. ILCs from AHR-deficient mice demonstrated decreased proliferation, perhaps because AHR stabilized the expression of Kit, a receptor kinase important for ILC proliferation. The authors identified indole-3-carbinol, a product of hydrolysis of a phytochemical, as an AHR ligand and critical regulator of ILF formation and ILC proliferation,¹⁷⁹ which indicates that diet too likely influences lymphoid tissue development. While, citing earlier studies,¹⁸³ they reasoned that bacterial AHR ligands are unlikely to have a similar effect, they did not rule out that possibility experimentally, and it may be that the microbiome may play a role in ILF formation through AHR.

Conclusions

In this review, we have discussed the intestinal immune system and its effect on the gut flora, focusing primarily on ILCs, a heterogeneous class of lymphocytes that are critical components of the innate immune system. The gut flora clearly has profound

effects on intestinal ILC function. Microbiota-induced IL-7 and IL-25 regulate ILC cytokine production, and the microbiota may also signal ILCs more directly through NOD1 and AHR. Our understanding of ILC development, function in health and disease, and interactions with the intestinal microbiota has expanded tremendously in the last several years. In the future, it will be important to identify more specific host and bacterial molecules involved in bacteria-ILC interactions, as these cells and the bacterial molecules could ultimately become targets of therapeutic agents. Likewise, identifying the precise organisms that interact most closely with ILCs will help us target the microbiota, perhaps with probiotics or antibiotics, to modulate the role of ILCs in disease. Finally, with the exception of NK cells, human ILCs are far less well characterized than their murine counterparts. We have already identified intriguing differences between human and murine ILCs, and further exploration of human ILC biology may yield interesting insights relevant to human health.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

Acknowledgments

We thank Dr Suryasarathi Dasgupta and Dr Neeraj K Surana for critical discussion of this manuscript and Julie B McCoy for her excellent editorial work.

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