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Emerging roles for antigen presentation in establishing host-microbiome symbiosis

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Abstract

Trillions of beneficial bacteria inhabit the intestinal tract of healthy mammals from birth. Accordingly, mammalian hosts have evolved a series of complementary and redundant pathways to limit pathologic immune responses against these bacteria, while simultaneously protecting against enteric pathogen invasion. These pathways can be generically responsive to the presence of any commensal bacteria and innate in nature, as for IL-22-related pathways. Alternatively, specific bacterial antigens can drive a distinct set of adaptive immune cell responses, including IgA affinity maturation and secretion, and a recently described pathway of intestinal selection whereby MHCII + ILC3 deletes commensal bacteria-reactive CD4 T cells. These pathways can either promote or inhibit colonization by specific subsets of commensal bacteria, and cooperatively maintain intestinal homeostasis. In this review, we will highlight recent developments in understanding how these diverse pathways complement each other to cooperatively shape the symbiotic relationship between commensal bacteria and mammalian hosts.

Keywords

IL-22; IgA; microbiota; innate lymphoid cells; bacterial infection

Animals have evolved in the presence of a remarkably dense community of commensal prokaryotes that inhabits the gastrointestinal (GI) tract from birth. In humans, these commensal organisms, dominated by bacteria, likely outnumber the host at the cellular level (1). Intestinal commensal bacteria contribute to a wide variety of physiological and disease processes. Accordingly, the relationship between mammalian hosts and commensal bacteria must be tightly regulated and highly sophisticated. On one hand, commensal bacteria provide important developmental cues, contribute to nutrient harvest from the host diet and protect the host against infection (2). In contrast, multiple chronic infectious, inflammatory and metabolic diseases are associated with significant changes in the composition or

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anatomical localization of commensal bacteria; these changes often contribute to disease progression through metabolic effects or activation of the mammalian immune response (3). While our understanding of host-commensal bacteria relationships is still rapidly evolving, it is abundantly clear that further interrogation of these pathways will provide a greater understanding of human health and guide the development of novel therapeutic approaches in chronic human diseases (4).

Recent technological advances have led to a revolution in our understanding of the relationship between commensal bacteria populations and the human host. In striving to understand the factors that directly underlie healthy versus dysregulated host-commensal bacteria interactions, it has become clear that multiple pathways are acting cooperatively. Commensal bacteria themselves have adapted to exploit resources from the host diet and colonize specific niches in the intestinal tract and associated lymphoid tissues (5, 6). In parallel, mammals have co-evolved a variety of mechanisms to prevent inflammation targeted at innocuous commensal bacteria while simultaneously protecting against tissue invasion by pathogens. Notably, these include both innate pathways (typified by IL-22 responses and barrier maintenance by mucus secretion and epithelial tight junctions), and adaptive pathways that require antigen presentation (including IgA responses, regulatory T cell responses and innate lymphoid cell-mediated selection of commensal bacteria-specific CD4 T cells). Here, we will discuss recent advances in understanding these phenomena, with a particular highlight on the role of host antigen presentation pathways in maintaining intestinal homeostasis.

Distinct antigen-dependent and antigen-independent host pathways regulate symbiosis with commensal bacteria

The mucosal immune system provides a crucial barrier against infections. However, immune responses targeting potential pathogens must exhibit prudent specificity and regulation to prevent chronic inflammation and tissue damage. An estimated 40 trillion commensal bacteria inhabit the colon, all of which have the potential to induce inflammation. Hence, diverse and multi-layered mechanisms have evolved in the host to prevent pathologic, commensal-bacteria-dependent inflammation, while still maintaining mucosal barrier function. Recent work has greatly expanded our understanding in this area.

It is striking that the host has developed processes to both support and inhibit the survival of commensal bacteria. In particular, several host pathways such as IL-22, mucous production and IgA are highly regulated by the presence of commensal bacteria, exhibit a range of bacterial specificities, and function to limit pathogenic tissue invasion by inhibiting bacterial survival and bacterial access to the epithelium. In contrast, complementary host pathways have evolved to simultaneously support bacterial colonization and limit chronic inflammation by restraining immune responses against commensal bacteria-derived antigens. These pathways are typified by commensal bacteria-dependent regulatory T cell (Treg) development (extensively reviewed elsewhere) (7), and by a novel selection pathway involving group 3 innate lymphoid cells (ILC3s) that directly limits T cell reactivity to commensal bacteria-derived antigens through antigen presentation and major

histocompatibility complex class II (MHCII). These seemingly contradictory host activities (either supporting or inhibiting commensal bacteria populations by differentially regulating specific immune cell subsets) cooperatively maintain a healthy homeostatic relationship between mammalian hosts and commensal bacteria.

Moreover, the host must adapt to dynamic changes in commensal bacteria populations over a lifetime with an appropriate balance of pro- and anti-bacterial activities. This balance is reflected in host pathways that process and present commensal bacteria-derived antigens. The classic example of such a process is the development of specific IgA antibodies that sequester bacteria from the host epithelium (8). Until recently, a pro-bacterial, antigen-dependent counterpart to the IgA process was not known. The recent discovery of tolerogenic antigen presentation by ILC3s has brought balance to our understanding of host responses to commensal bacterial antigens. Here, we will review the pro- and anti-bacterial host responses, both antigen-independent and antigen-dependent, that collaborate to maintain a healthy relationship between mammalian hosts and commensal bacteria.

Antimicrobial peptides, mucus, and IL-22 are critical innate mediators of homeostatic host-commensal bacteria interactions

IL-22 is an important host-derived factor that is elicited by commensal bacteria and subsequently critically orchestrates host-commensal bacteria symbiosis. An explosion of interest in IL-22 biology in recent years has driven a greater understanding of its function. IL-22 plays a multifaceted role in regulating intestinal homeostasis, through limiting infections by enteric pathogens, regulating the composition of commensal bacteria populations, and influencing anatomical segregation of commensal bacteria from the mammalian immune system (9). In contrast to IgA, however, IL-22 is not known to interact with commensal bacteria directly, and does not respond in an antigen-specific manner. The IL-22 receptor is restricted to non-hematopoietic cells and highly enriched on hepatocytes, keratinocytes, airway epithelium and intestinal epithelial cells (9). Here, we will highlight the substantial recent advances in our understanding of: the impact of IL-22 on enteric bacteria; the mechanisms by which enteric bacteria promote IL-22 responses; and the influence of IL-22 on regulating enteric bacteria in the context of health and disease.

IL-22 is recognized as an essential contributor to epithelial tissue homeostasis and protection against inflammatory disease. In the absence of IL-22, mice are susceptible to intestinal damage and inflammation, including mouse models of dextran sodium sulfate (DSS) exposure, naïve T cell transfer, and graft versus host disease (10–14). In many of these models, it was demonstrated that ILC3-derived IL-22 protects against inflammation by supporting the Lgr5+ intestinal stem cell population (12, 15). These data suggest that IL-22 generally supports epithelial barrier function by supporting the continual regeneration of the epithelium. In contrast, it was recently reported that IL-22 signaling could be pathogenic in other models of intestinal inflammation, such as following anti-CD40 monoclonal antibody (mAb) administration and *Toxoplasma gondii* infection (16, 17). In the anti-CD40 mAb model administration to immunodeficient mice, ILC3-derived IL-22 is thought to recruit and activate inflammatory monocytes and neutrophils, contributing to tissue damage and inflammation (17). Crucially, the anti-CD40 mAb mouse model of intestinal inflammation

lacks all T and B cells, and it's been suggested that Treg-dependent modulation of inflammation would normally blunt the pathologic inflammation (18). Interestingly, evidence has also arisen to support a role for IL-22 in limiting sensitization to food allergens. In a germ-free mouse model, it was reported that colonization by a handful of *Clostridia* species, but not a *Bacteroides* species, could abrogate systemic responses to oral peanut allergens; this protective effect was found to depend on IL-22 induction, which was observed only in the *Clostridia*-colonized mice (19). Together, these findings argue that IL-22 signaling is crucial for preventing pathologic inflammation, but can become dysregulated and promote inflammation when the adaptive immune system is impaired. Evidence also suggests that the local cytokine milieu may influence the protective versus pathologic functions of IL-22, as co-expression of IL-17 can synergistically promote tissue inflammation (20). Therefore, it will be important to consider IL-22 in the context of immune-deficient patients, which is a frequent presentation of very early onset IBD, or in the context of adult IBD patients where IL-17 is abundantly co-expressed (21–23).

IL-22 may modulate inflammation through several distinct mechanisms including regulation of tissue repair, induction of anti-microbial peptides, and modulation of the composition or anatomical containment of commensal bacteria. For example, IL-22 has a well-documented role in limiting enteric bacterial infection and translocation. Further, depletion of ILCs, a primary source of IL-22, leads to systemic dissemination of otherwise innocuous commensal bacteria, and this phenotype can be rescued by administration of exogenous IL-22 (24). Genetic deletion of IL-22 can lead to a state of dysbiosis, with increased susceptibility to DSS (25). We have recently shown that IL-22 is required for colonization by lymphoid tissue-resident commensal bacteria (LRCs) (6). Given the fact that LRC colonization protects mice from DSS-induced pathology, defective LRC colonization and luminal bacteria dysbiosis may partially contribute to increased DSS susceptibility of *Il22*$^{-/-}$mice. IL-22 also plays a crucial and well-documented role in innate immune responses to *Citrobacter rodentium*, a murine-specific model of attaching and effacing enteric bacterial pathogens such as *E. coli* O157:H7. IL-22 knockout mice are highly susceptible to infection by *C. rodentium* (26). This susceptibility pattern was evident even on a Rag2$^{-/-}$ background, suggesting an innate source of functional IL-22 in this infection model. Furthermore, it was shown that IL-22 induces production of anti-microbial peptides (AMPs) in colonic tissues, and *C. rodentium* susceptibility in IL-22-deficient mice could be partially rescued by administration of the AMP RegIIIγ (26). Subsequently, the innate source of protective IL-22 was found to be the ILC3 cell population in this model (27). Further analysis shows that the LTi-like ILC3 subset, in particular, is the relevant IL-22 source (17, 28).

The critical contribution of ILC3-derived IL-22 in innate immunity against an enteric bacterial pathogen that represents such an important public health burden has motivated careful analyses of both the regulation of IL-22 in infection, and the mechanisms by which IL-22 limits infection. It is clear that IL-23 is an important effector upstream of the IL-22 response in this infection model (26). A recent report extensively characterized the source of IL-23 in *C. rodentium* infection, and found that CX_3CR1^+ macrophages are the dominant source in this setting (29). In contrast, a prior study found that $CD103^+$ dendritic cells produce IL-23 that elicits AMP production in an IL-22 dependent manner upon stimulation with bacterial flagellin (30). In combination, these studies argue that multiple enteric

phagocytes may produce IL-23 in response to diverse signals with different tropisms in the enteric lamina propria, but IL-22 appears to be a critical integrator of these signals. These findings are in agreement with previous reports that CX_3CR1^+ macrophages are required for the *C. rodentium*-elicited IL-22 response (31). Further supporting the paradigm that IL-22 is primarily tissue-protective, the CX_3CR1^+-dependent ILC3-IL-22 response is found to ameliorate intestinal tissue damage induced by *C. rodentium* infection (32). Notably, ILC3s themselves also appear to exhibit positive feedback by further stimulating ILC3 production of IL-22 via lymphotoxin receptor signaling (33, 34).

Beyond the prototypical attaching and effacing enteric pathogen, *C. rodentium*, enteric IL-22 is increasingly being appreciated as a modulator of other infection models as well. *Toxoplasma gondii* infection at high dose causes acute inflammation of the ileum, or ileitis, in an IL-22-dependent manner (16). Recent work showed that IL-22 in this setting directly elicits IL-18 in the ileum. Although IL-18 was required for effective clearance of *C. rodentium*, IL-22-dependent IL-18 expression was found to contribute to inflammatory pathology during *T. gondii* infection (35). Interestingly, IL-18 was also found to elicit further ILC3 production of IL-22 in a positive-feedback loop in the small intestine in *T. gondii* infection. Surprisingly, aryl hydrocarbon receptor (Ahr)-deficient mice, which exhibit impaired ILC3 development, were recently found to develop increased intestinal pathology relative to wild-type mice during *T. gondii* infection (36). This increased pathology correlated with T cell hyperactivity. These seemingly contradictory data might be explained by an IL-22-independent role for ILC3 in suppressing T cell responses (37). IL-22 also plays an important role in defense against *Clostridium difficile*. It was recently shown in mice that *C. difficile* infection allows the translocation of commensal bacteria and opportunistic pathogens to the liver and the lung, and IL-22 aids in the clearance of these disseminated bacteria through a complement-dependent mechanism (38). Finally, it was recently shown that IL-22 levels correlate with protection from *Staphylococcus aureus* pneumonia. Remarkably, the presence of SFB was shown to correlate with *S. aureus* protection, since SFB stimulates IL-22 production (39). Together, these data suggest that enteric IL-22, elicited by the presence of specific commensal bacteria, can have important impact on systemic host immunity.

While experiments with the *C. rodentium* infection model or bacterial flagellin demonstrated that IL-23 acutely activates IL-22 expression in ILC3s, several other signals may contribute to IL-22 production. Experiments with germ-free mice compared to conventional SPF mice showed that commensal bacteria are required for the development of $NKp46^+$ ILC3 cells, and that even IL-23 stimulation *ex vivo* is not sufficient to promote ILC3-derived IL-22 in the absence of the microbiota (40). Re-colonization of GF mice with commensal bacteria led to the development of $IL\text{-}22^+$ $NKp46^+$ ILC3 cells within 1–2 weeks. Based on comparison of fetal and weanling expression of IL-22 in the gut, it's also been suggested that microbiota-elicited IL-25 from the epithelium actually suppresses $IL\text{-}22^+$ ILC3 cells after birth (41). Beyond IL-23, an additional signal may be required for peak IL-22 expression; one study recently identified the chemokine CXCL16, constitutively expressed by CX_3CR1^+ macrophages, as a candidate for this second signal, since ILC3s require CXCR6 (the CXCL16 receptor) for proper development of IL-22 responses (42). Stimulation with IL-1β also contributes to IL-22 secretion (43). This result was recently confirmed with an ILC3-

like cell line *in vitro*, where IL-2 and IL-23 were also required for maximal IL-22 production (44). Recent evidence also suggests that IL-1α contributes to IL-22 production elicited by murine rotavirus (45). Interestingly, while IL-22 acts strongly on epithelial cells, evidence of epithelial cell feedback on the ILC3-IL-22 pathway was recently described. In particular, the NF-κB inhibitor IKKβ in intestinal epithelial cells (IECs) is required for induction of ILC3-derived IL-22 upon infection. In its absence, overproduction of TSLP by IECs suppresses ILC3 production of IL-22 and renders mice more susceptible to infection- or chemical-induced intestinal tissue damage (46). Within ILC3s themselves, the developmental factor Id2 was also recently shown to be required for continued ILC3 homeostasis and IL-22 responses to *C. rodentium* (47). These important advances in understanding IL-22 responses will be crucial for informing the development of therapeutic that modulate the IL-22 pathway for use in infection and inflammatory disease. Much exciting work remains to be done to understand the key points of regulation and the feedback in this pathway.

The role of ILC3-IL-22 pathway in directly stimulating AMP production in the epithelium is well documented, but exciting recent developments have also highlighted distinct mechanisms by which IL-22 may modulate the enteric commensal bacteria population. For example, a recently described subset of commensal bacteria, termed lymphoid-resident commensals (LRCs), is uniquely able to colonize the enteric lymphoid tissues of the healthy humans, primates, and mice (48). IL-22 plays a crucial role in regulating LRC colonization of the host. When IL-22 is acutely depleted from wild-type mice, LRCs can translocate systemically (24). When IL-22 is genetically deleted, however, LRCs cannot colonize mice due to the outgrowth of competing bacteria (6). Furthermore, in Ahr-deficient mice, it was discovered that a lack of ILC3 and IL-22 led to increased SFB colonization, which in turn led to increased inflammatory Th17 responses (49). More recently, it was determined that SFB elicits the serum amyloid A proteins 1 and 2, which may limit bacterial growth in an ILC3 and IL-22 dependent manner (50). This phenomenon is highly restricted to the ileum, and may be a general response to bacterial adherence to IECs (51). These data suggest a complex regulatory connection between epithelial-adherent commensal bacteria, ILC3 and Th17 cell responses, and the subsequent generation of AMPs and other epithelial factors that may shape the commensal bacteria community. The importance of this regulatory network for host health is emphasized by the finding that SFB overgrowth in the absence of ILC3s affects host susceptibility to diet-induced obesity (52). Conversely, it's also been demonstrated that diet-induced obesity inhibits IL-23-elicited IL-22 production and renders mice susceptible to *C. rodentium*, highlighting the complexity of the linkage between obesity, IL-22, and mucosal immunity (53). Adding another interesting layer to this regulation, several groups recently described a connection between the ILC3-IL-22 pathway and IEC glycosylation patterns, with important impact for the host-commensal bacteria relationship. IL-22 receptor-deficient mice exhibited severe microbial dysbiosis and were highly susceptible to *C. rodentium* infection, and this phenotype could be rescued by the administration of fucosylated oligosaccharides (54). It was determined that IEC fucosylation is driven by ILC3-derived IL-22 and is also required for resistance to *S. typhimurium* (55). Finally, it was demonstrated that Toll-like receptor (TLR) ligands induce dendritic cells to secrete IL-23, which stimulates the ILC3 production of IL-22 and underlies the upregulation

of the fucosyltransferase 2 (Fut2) gene in IECs (56). These studies all agree in showing a remarkable impact of IEC-intrinsic Fut2 activity in dictating the population of commensal bacteria that thrive in the lumen, presumably by selecting for commensal bacteria that are capable of metabolizing fucosylated oligosaccharides. Together, these data show that enteric phagocytes produce IL-23 to induce IL-22 production by ILC3s, and this single regulatory event has incredibly wide-ranging impacts on host-commensal bacteria homeostasis by activating IEC production of both negative regulators and positive regulators of bacterial growth. Particular subsets of commensal bacteria can also regulate this IL-22 response, presumably by activating IEC-intrinsic signals upon adhering to the epithelium. This remarkable and intimate feedback between the mammalian host and the enteric commensal bacteria is in keeping with the view that both parties of this relationship have co-evolved regulatory mechanisms to thrive together.

Among all the diverse effector functions of IL-22 at the epithelium, the dominant role of fucosylation suggests that the chemical environment at the barrier between the host epithelium and the commensal bacteria plays a key role in maintaining host-commensal bacteria homeostasis. It is not surprising, then, that the host-derived mucus layer that dominates this environment is a critical player in this homeostasis. The epithelial mucus layer develops and matures in response to the presence of the microbiota over a period of several weeks (57). Continued maintenance of a healthy mucus layer appears to be sensitive to the specific makeup of the commensal bacteria population, as the mucus thins out upon dietary perturbation of a healthy microbiota (58). Interestingly, it was recently shown that MUC2, the dominant mucus protein, actively drives intestinal dendritic cells toward tolerogenic responses (59), arguing that mucus functions extend beyond providing a simple physical barrier. In fact, mucus can also play an active role in modulating host immune responses. Developments in understanding the role of mucus in host-commensal bacteria homeostasis have been extensively reviewed elsewhere (60).

IgA responds to enteric bacteria to sequester them from the immune system

Human adults typically secrete multiple grams of IgA into the gastrointestinal tract each day, an amount that exceeds all other antibodies combined (61). Notably, IgA is present at functional levels in human breast milk, and appears to contribute protective immune functions in neonatal mammals (62). While the potential importance of IgA in human immunity has been recognized for several decades, progress in understanding the biological function of IgA has been complicated by the fact that its regulation is highly complex, as well as the observation that selective IgA deficiency in humans is often asymptomatic due to complementary upregulation of other immunoglobulins (63). Despite these challenges, considerable advances have recently been made in understanding the development and functional consequences of IgA responses.

Several lines of evidence, primarily from studies in mice, argue for a crucial role of IgA in modulating host-commensal bacteria relationships, with important implications for host health. In neonatal mice, for example, a lack of enteric IgA – achieved by genetic deletion of the pIgR gene, which is required for IgA secretion – led to increased levels of the opportunistic bacterium, *Ochrobactrum anthropi*, translocating to the mesenteric lymph node

(mLN), and increased tissue damage upon dextran sodium sulfate (DSS)-elicited inflammation (64). Strikingly, this phenotype correlated with the genotype of the dam rather than the neonate, arguing that maternal IgA in the breast milk is required for protection from opportunistic bacteria and maintenance of tissue repair in suckling mice. In further support of a host-protective role for enteric IgA secretion, a recent study characterized a particular IgA-degrading commensal bacteria community, which was stably transmissible to other mice, and antibiotic-sensitive (65). Remarkably, adoption of this IgA-degrading microbiota led to stable low levels of enteric IgA and a dramatically increased susceptibility to inflammatory tissue damage. This low-IgA, inflammation-sensitive phenotype correlated with increased colonization by bacteria of the *Sutterella* genus, suggesting complex feedback between IgA levels, host-commensal bacteria homeostasis, and resistance to inflammation (65). Moreover, another recent report investigated the role of IgA-coated commensal bacteria in driving intestinal inflammation. In this study, fecal bacteria samples from IBD patients were sorted based on levels of IgA coating; upon introduction of either highly-IgA-coated or uncoated bacteria into germ-free (GF) mice, it was found that highly-IgA-coated bacteria colonization led to increased host susceptibility to inflammatory tissue damage elicited by DSS (66). Importantly, FISH staining suggested that highly-IgA-coated bacteria were able to colonize the mucus layers, closely apposed to the intestinal epithelium (66). In contrast to the findings outlined above, which suggest that IgA predominantly functions to sequester bacteria from host tissues, it has also recently been suggested that IgA may facilitate the colonization of intestinal lymphoid tissues by specific subsets of bacteria (48). Together, these important findings imply that IgA may function as a diffusible extension of the mucosal barrier: by targeting, with varying degrees of specificity and efficacy, the commensal bacteria that are capable of living in close contact with more inflammatory elements of the mucosal immune system, IgA prevents uncontrolled colonization or dissemination, as well as subsequent tissue inflammation.

Reflecting the immense diversity of bacteria to which enteric IgA must respond over a lifetime, the regulation of IgA production and affinity maturation is multi-faceted. ‘Natural IgA’ is constitutively secreted even in GF mice, but the re-introduction of commensal bacteria in this setting leads to a rapid upregulation of IgA secretion (67). In agreement with this, the full IgA complement from the mature human ileum is dominated by somatically-mutated, antigen-specific IgA+ plasmablasts, displaying reactivity to enteropathogenic and commensal microbes as well as self antigens (68). The microbiota of an individual is expected to drift considerably over time, responding to changes in diet, infections, and antibiotic treatments, among other factors (69). A recent analysis has confirmed that commensal bacteria-specific IgA+ ‘memory’ plasma cells persist well beyond the withdrawal of the antigenic commensal bacterium, and yet new B cell clones can continuously develop against newly presented bacteria, for example in the case of enteric infection (70). Within the GF mouse model, the IgA response depends on the uptake of live commensal bacteria by dendritic cells (DCs), which then migrate to the mLN and induce IgA production by B cells (71). Interestingly, the induction of specific IgA depends on iNOS activity, which is typically considered a pro-inflammatory factor. Evidence points to a role for both DC- and B cell-intrinsic iNOS activation in IgA responses (72, 73).

While it's clear that T cells are not strictly required for IgA responses, a T cell-dependent pathway does support IgA development (8). A host of recent work has begun to dissect this pathway. Interestingly, Treg cell-intrinsic MyD88 contributes to IgA responses and prevents translocation of commensal bacteria to the liver and the lung (74). Moreover, abrogation of this pathway skews the pattern of reactivity against commensals; whereas IgA typically coats mucosal- and epithelial-associated commensals preferentially, this bias is lost when MyD88 is deleted in Treg cells (75). These mice also showed increased susceptibility to DSS. In a distinct mode of T cell-dependent IgA regulation, Th17 and/or T follicular helper cells also support high-affinity IgA development through the production of IL-21 (76, 77). A new report has also highlighted a requirement for eosinophils in IgA production, which may contribute to IgA development through both T cell-dependent and –independent pathways (78). Interestingly, some commensal bacteria seem more prone to elicit T cell-dependent IgA responses, while others are biased toward T cell-independent IgA development (79). Moreover, T cell presence does not affect the expression of CD11b in IgA+ plasma cells, which was recently reported as a marker of vigorous proliferation and copious IgA secretion. The complexity and the overlapping layers of IgA regulation emphasize the broad role that IgA must play in maintaining host-commensal bacteria homeostasis, while also presenting an ongoing challenge for the field (80).

Aside from simply triggering host-mediated IgA responses, commensal bacteria also appear to play an active role in these responses, with important impacts on host health. Segmented filamentous bacteria (SFB), which are well-known inducers of Th17 cells in the intestine, also appear to induce development of isolated lymphoid follicles in mice lacking Peyer's patches (PP), which serve as a site of IgA induction in these mice (81). In contrast, *E. coli* does not show the same capability, implying that some commensal bacteria may actually drive non-canonical modes of IgA induction. Furthermore, a potential bacteria-specific positive feedback loop was recently described (82). In this study, it was shown that a non-invasive *Salmonella* strain was highly coated by IgA, and subsequently was trafficked preferentially to PPs, where it induced even greater production of fecal IgA upon subsequent enteric antigen challenge (82). It was also demonstrated in this study that different mouse strains show different levels of polyreactive IgA secretion in the GF state, which further argues that stochastic IgA responses, potentially dependent on host genotype, may lead to divergent commensal communities and thus to divergent host phenotypes. In a similar vein, another group recently showed that proteobacteria-directed IgA responses are required for the development of a mature microbiota (dominated by Firmicutes and Bacteroidetes phyla) from the immature, pro-inflammatory, proteobacteria-enriched microbiome (83). In order to minimize the potential host genetic component of IgA responses in a human enteropathy, the Gordon group recently examined a cohort of twins discordant for Kwashiorkor (84). IgA-coated bacteria from the Kwashiorkor donors drove considerable enteropathy when transplanted into GF mice, but this pathology could be rescued by IgA-coated bacteria from the healthy donors (84). Given the recent suggestion of a stochastic IgA positive-feedback loop (65, 82), the data from Kwashiorkor-discordant twins suggests that disease development may also be stochastic, and reinforces the notion that IgA-dependent homeostatic processes can potentially modulate disease processes in humans. Remarkably, it was very recently shown that administration of bacteria-accessible oligosaccharides (derived

from bovine milk) could also ameloriate the metabolic defects cause by IgA-coated bacteria from Kwashiorkor donors, without significantly shifting the population of the bacteria (85). This remarkable finding further argues that IgA-coating alone, even within a disease state, may not strictly mark host-detrimental bacteria. The complex feedback between host IgA responses and commensal bacteria suggests that increasingly complex models (beyond GF mice mono-colonized with a single bacterium) will be required to design new therapies for chronic diseases associated with commensal bacteria.

ILC3s in host-commensal bacteria homeostasis: a novel role for antigen presentation

ILC3 cells are an innate immune cell subset with key emerging roles in regulating intestinal health and disease (86). A subset of ILC3s, termed lymphoid tissue inducer (LTi) cells, were initially highlighted for their essential role in the development of secondary lymphoid tissues, including small intestine Peyer's patches and peripheral lymph nodes (87). ILC3s thus play an indirect role in facilitating IgA responses directed from these tissues. ILC3s elicit these developmental effects by the production of TNF protein family members including Lymphotoxin-α and –β and RANKL, which spawn chemokine gradients contributing to the development of unique T- and B-cell zones in lymphoid tissue (88–90). ILC3s are also required for the formation of isolated lymphoid follicles (ILFs) in the intestine, in a process that depends on the presence of commensal bacteria (91). This observation suggests that the role of ILC3s in lymphoid tissue development continues through adulthood and may play a crucial – though indirect – role in host-commensal bacteria homeostasis. In further support of this concept, it's recently been shown that ILC3 lymphotoxin responses contribute to both T-cell-dependent and T cell-independent IgA responses, discussed further in the prior section (92). Interestingly, within the context of *C. rodentium* infection, it was recently shown that IL-22 is regulated downstream of ILC3 lymphotoxin responses to maintain colonic lymphoid tissue organization (33).

Exciting recent evidence argues that ILC3s can regulate homeostatic host-commensal bacteria relationships through modulation of host adaptive immunity, in a pathway that appears to be independent of IL-22 and lymphotoxin. For example, one recently described pathway involved microbiota-dependent crosstalk between macrophages and ILC3s. In this case, it was shown that commensal bacteria stimulate IL-1β production by macrophages, which stimulates the IL-1 receptor on ILC3s to stimulate release of Csf2, which subsequently stimulates Treg maintenance through the development of IL-10- and retinoic acid-producing phagocytes (93). It's also been shown, using RORγ-deficient mice and bone marrow chimeras, that ILC3s are required for memory CD4 (but not CD8) T cell survival (94). Moreover, it's recently been shown that ILC3s can regulate CD4 T cells in an IL-1β- and antigen-dependent manner (95). These results together suggest that ILC3 cells can, both directly and indirectly, impact T cell homeostasis. Given the crucial role of regulatory T cells in maintaining intestinal homeostasis, these findings support the notion that ILC3 cells also play a key role in this homeostasis. In support of this, it was shown that MHCII depletion in ILC3 cells led to increased Th17 cell differentiation, independent of SFB (96).

Recent work from our laboratory has more closely investigated the role of ILC3 antigen presentation via MHCII in directly modulating T cell responses, particularly in the context

of intestinal homeostasis. In a recent study, we demonstrated that loss of ILC3 (achieved via genetic deletion of RORγ) results in chronic, low-grade inflammation (typified by elevated, commensal bacteria-specific serum IgG responses) driven by the microbiota. However, this could not be recapitulated by targeting classical ILC3-dependent pathways, such as IL-22 or IL-17 (97). Instead, a subset of $CCR6^+$ ILC3 cells were shown to highly express major histocompatibility complex class II (MHCII), and *in vitro* these cells were capable of processing and presenting model antigens. However, ILC3 did not express classical co-stimulatory molecules and failed to induce CD4 T cell proliferation. In mice, lineage-specific deletion of MHCII resulted in spontaneous chronic intestinal inflammation in a microbiota-dependent manner (97). This microbiota-driven inflammation was associated with increased pro-inflammatory Th17 cells in the colonic tissues and could be transferred into lymphocyte-deficient hosts by T cell adoptive transfers. These data argue that ILC3-intrinsic MHCII directly limits T cell responses to commensal bacteria in order to prevent chronic intestinal inflammation.

More recent work has supported this notion, highlighting a likely mechanism of ILC3-orchestrated ‘intestinal selection’ against commensal bacteria-specific CD4 T cells. This study utilized TCR transgenic mice displaying T cell reactivity against a commensal bacteria flagellin antigen, termed CBir1 (98). Notably, transfer of pre-activated CBir1 T cells into mice expressing either no MHCII, or only ILC3-intrinsic MHCII, showed that CBir1 CD4 T cells were reduced in number in the mLN and intestine of mice expressing ILC3-intrinsic MHCII (37). This reduction was specific to effector, but not regulatory, CBir1 T cells. $MHCII^+$ ILC3 cells could bind large amounts of IL-2 and induce CBir1 CD4 T cell death *in vitro*. Since T cell death could be rescued by exogenous IL-2 or constitutive STAT5 activation in this setting, it is proposed that ILC3 cells induce T cell death by sequestration of crucial pro-survival cytokines from T cells (37). Finally, examination of Crohn’s disease patients showed an inverse correlation between ILC3 MHCII expression and disease state, Th17 cell frequencies, and commensal bacteria-specific IgG titers (37). These data strongly argue that ILC3-intrinsic MHCII functions to limit pathologic Th17 cell responses to commensal bacteria and prevent chronic inflammation in the intestinal tract of healthy humans. More importantly, these data support that this process may become disrupted in human IBD. This conclusion is supported by a recent unbiased RNA sequencing study of human ILC populations (99). Here, it was shown that one subset of human ILC3 cells expressed multiple HLA-encoding transcripts and associated enzymes to process antigens, but neither of the costimulatory molecules CD80 and CD86 were expressed within this cluster.

Going forward, it will be important to dissect the contribution of the different ILC3 effector functions to human health and disease. A better understanding of these connections will be crucial for the development of therapies for multiple diseases, including cancer, IBD, and enteric infection (86, 100). For example, a recent study in a macaque model of HIV infection showed depleted ILC3 numbers in the intestine, which may be causally connected to the increased levels of bacterial translocation observed in HIV patients (101). Another recent study in a humanized mouse model of HIV showed a similar decrease in ILC3 numbers, which was dependent on plasmacytoid DCs and was reversed by anti-retroviral therapy (102). These recent findings argue that ILC3 effector function may play a host-protective

role in the pathology of HIV. However, the relative contributions of ILC3-derived IL-22, ILC3 contributions to lymphoid tissue development, and ILC3 suppression of T cell responses are currently unknown. Interestingly, another recent study examined the impact of MHC polymorphisms on the host-commensal bacteria homeostasis and host susceptibility to infection. Here, it was shown that unique host MHC genotypes underlie unique populations of commensal bacteria, with a range of susceptibility to enteric infections among the different commensal populations (103). Although a role for ILC3s was not examined in this context, the primary role of ILC3 MHCII in modulating intestinal homeostasis would suggests that ILC3s may play a causative role in this context. Finally, it was recently reported that RORγ inhibition can selectively deplete pathogenic inflammatory Th17 cells, but not ILC3s (104). This result emphasizes that careful design and evaluation of immune cell-targeted therapies holds great promise for the treatment of inflammatory disease in the intestinal tract. Future efforts to therapeutically exploit ILC3 cells and their effector pathways will be important to consider moving forward. A continuing challenge remains, however, in carefully elucidating the relevant effector pathways at work in different pathologies, and a further challenge will be the development of therapies that might specifically target one ILC3 effector pathway while leaving others (such as IL-22 signaling, lymphotoxin responses, or intestinal selection) intact.

Conclusions and future directions

In summary, recent efforts focused on host IgA, IL-22, and ILC3 pathways have greatly informed our understanding of the dialogue between mammalian hosts and their intestinal commensal bacteria. IL-22 is driven by generic bacterial signals and thus is not antigen-specific, but it induces both pro-commensal bacteria pathways (such as fucosylated oligosaccharides that may feed a subset of commensal bacteria) as well as anti-commensal bacteria pathways (such as mucus and AMP secretion). Mammals have developed an ILC3 antigen presentation pathway that supports commensal bacteria survival (and limits chronic inflammation) by eliminating inflammatory T cells that recognize commensal bacteria. In contrast, a countervailing host response involves the development of antigen-specific IgA antibodies that serve to limit bacteria from colonizing niches in close proximity to host tissues. Going forward, it will be important to delineate the factors that control the competition (or collaboration) between these two pathways – for example, it is not known whether IgA antigens and ILC3 intestinal selection antigens overlap significantly, and it’s unclear how ILC3s obtain commensal bacterial antigens in the first place. Furthermore, the tendency of a given commensal bacterium to induce IgA responses, ILC3 intestinal selection, or both, is currently unknown. Clearly, modulation of these antigen-dependent pathways could be of great therapeutic benefit. For example, IgA responses contribution to pathogen resistance, while ILC3 responses described above may ameliorate inflammatory bowel disease, infection, and HIV-associated pathology. While many important questions remain concerning the host-commensal bacteria dialogue, we are highly optimistic regarding the long-term therapeutic potential of targeting these antigen-specific pathways.

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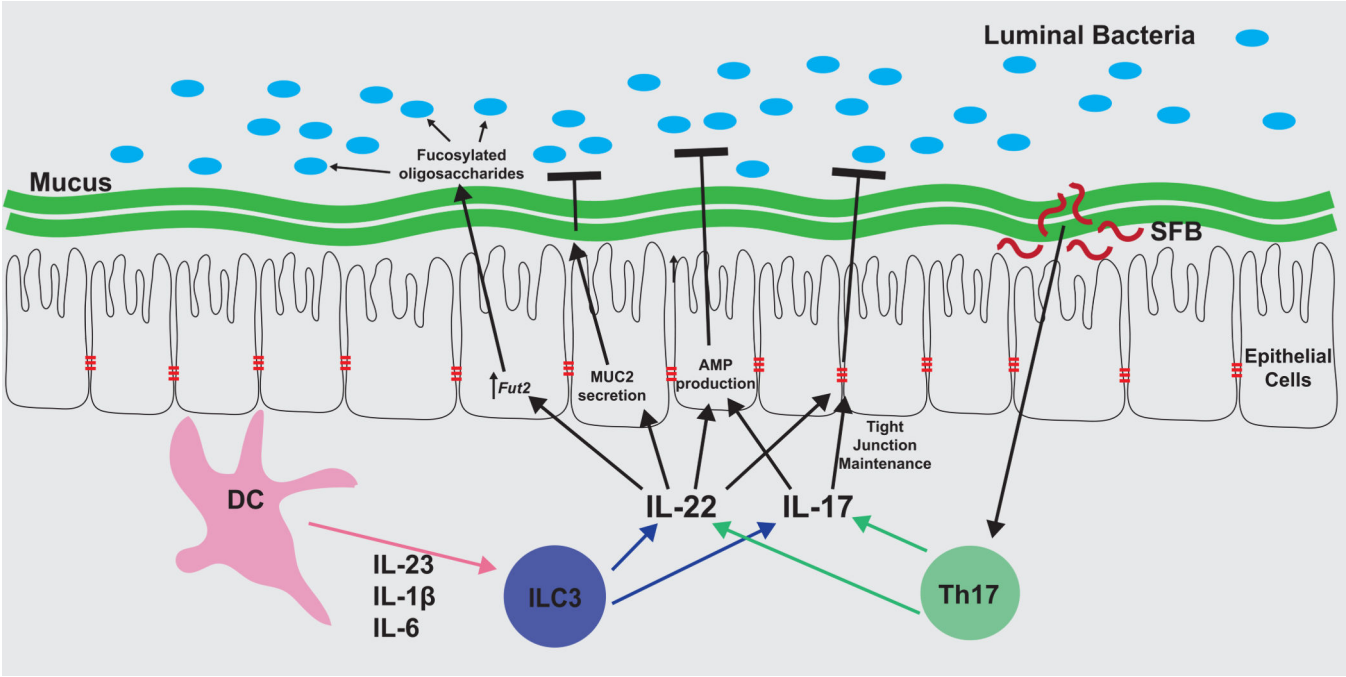

Figure 1. Antigen-independent mammalian pathways regulate host-commensal bacteria symbiosis

IL-22 is a master regulator of antigen-independent pathways that respond to and modulate the microbiota. IL-22 integrates multiple commensal bacteria-dependent signals, and coordinates diverse responses emanating from the intestinal epithelium. Dendritic cells sense commensal bacteria and release cytokines (IL-23 most notably, as well as IL-1β and IL-6) that stimulate IL-17 and IL-22 production by ILC3 cells. Th17 cells are also stimulated to produce IL-17 and IL-22 by inflammatory signals or, in the steady-state, segmented filamentous bacteria (SFB). IL-17 can induce AMP production and maintenance of epithelial tight junctions. IL-22 is sensed by intestinal epithelial cells, which respond by: secreting mucus to enforce a physical barrier between host and bacteria; maintaining tight junctions to prevent bacterial translocation into tissues; producing anti-microbial peptides (AMPs) that selectively target commensal bacteria; and producing highly fucosylated oligosaccharides, which provide metabolic benefits to specific subsets of commensal bacteria.

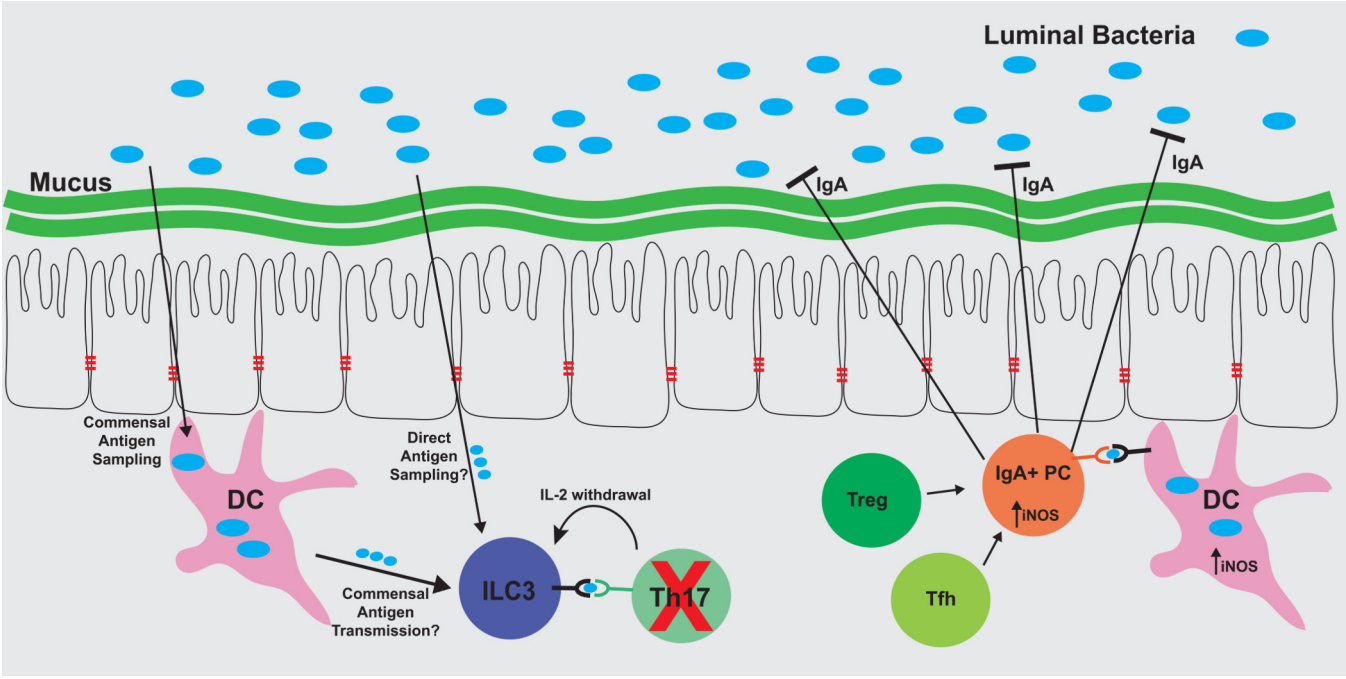

Figure 2. Antigen-dependent host pathways serve both to limit and also to protect commensal bacteria populations

ILC3 cells and IgA^+ plasma cells each respond to commensal bacteria antigens, but ILC3 serves to limit host responses to these antigens, while IgA functions to limit colonization of these bacteria. ILC3 cells acquire antigen through an unknown mechanism, and present commensal bacteria-derived antigens through MHCII, but they do not express co-stimulatory molecules, and instead bind important pro-survival cytokines including IL-2. As a result, ILC3 cells induce apoptosis of T cells reactive to commensal bacteria. In parallel, antigen-specific IgA^+ is induced in lymphoid tissues in a DC- and iNOS-dependent manner. T cells can also contribute to antigen-specific IgA responses. Antigen-specific IgA is secreted into the intestinal lumen, where it coats antigenic bacteria and inhibits bacterial colonization of the intestinal epithelium and mucus layers.