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Regulation of the adaptive immune system by innate lymphoid cells

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Abstract

Innate lymphoid cells (ILCs) are a group of lymphocytes that promote rapid cytokine-dependent innate immunity, inflammation and tissue repair. In addition, a growing body of evidence suggests ILCs can influence adaptive immune cell responses. During fetal development a subset of ILCs orchestrate the generation and maturation of secondary lymphoid tissues. Following birth, ILCs continue to modulate adaptive immune cell responses indirectly through interactions with stromal cells in lymphoid tissues and epithelial cells at barrier surfaces. In this review we summarize the current understanding of how ILCs modulate the magnitude and quality of adaptive immune cell responses, and in particular focus on recent evidence suggesting that ILCs can also directly regulate $CD4^+$ T cells. Further, we discuss the implications that these pathways may have on human health and disease.

The innate lymphoid cell family

Recent evidence has implicated innate lymphoid cells (ILCs) as critical regulators of innate immunity and inflammation at mammalian barrier surfaces, including the skin, airways and gastrointestinal tract [1-4]. Although ILCs lack antigen-specific receptor rearrangement they exhibit strikingly similar transcription factor profiles and cytokine-producing capabilities as $CD4^+$ T cells, suggesting that ILCs may act as an innate counterpart to the $CD4^+$ T helper (Th) cell arm of the adaptive immune system. In line with this, both ILCs and T cells develop from common lymphoid progenitors in a process dependent upon the transcriptional regulator T cell factor-1 (TCF-1) and the common γ-chain cytokine receptor [5-9]. Further mirroring $CD4^+$ T cells, mature ILCs can be grouped based on expression of lineage-specifying transcription factors and a defined profile of effector cytokines [1,3,4]. Group 1 ILCs parallel Th1 cells in their expression of the transcription factor T-bet, production of IFN-γ in response to interleukin (IL)-12, and ability to mediate immunity to intracellular pathogens and tumors [3,10,11]. Group 2 ILCs parallel Th2 cells in their expression of the transcription factor GATA-3, production of the cytokines IL-5, IL-9 and IL-13 in response to IL-25, IL-33 and thymic stromal lymphopoietin (TSLP), and ability to mediate allergic inflammation and immunity to helminth infection [9,12-14]. Finally, group 3 ILCs parallel Th17 cells in their expression of retinoic acid-related orphan receptor gamma (RORγt), production of IL-17A and IL-22 in response to IL-23 and IL-1β, and ability to maintain intestinal epithelial barrier function, drive tissue inflammation and mediate immunity to

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extracellular bacteria [15-21] (reviewed in [1,2,22]). Given the ability of ILCs to respond rapidly to stimulation, it has been hypothesized that ILCs represent a critical early source of cytokines prior to the initiation of an adaptive immune response. For example, RORγt$^+$ group 3 ILC-derived IL-22 is required for innate immunity to the enteric pathogen *Citrobacter rodentium* [17,18,21], prior to the generation of a robust IL-22$^+$ CD4$^+$ T cell response, which may be required for late-stage resolution of infection [23]. In addition, emerging evidence suggests group 3 ILCs may also play a significant role in modulating the adaptive immune system by promoting the generation, organization and maintenance of secondary lymphoid tissues, maintaining intestinal barrier function, and via direct interactions with adaptive immune cell populations. In this review, we will summarize the current understanding of how group 3 ILCs regulate adaptive immune cell populations through direct and indirect mechanisms, and discuss the implications of these findings for human health and disease.

Regulation of secondary lymphoid tissues by lymphoid tissue inducer cells

Group 3 ILCs encompass a heterogeneous family of RORγt-expressing innate lymphocytes that produce IL-22 and/or IL-17A [16,17,24,25]. One subset of group 3 ILCs, termed lymphoid tissue inducer (LTi) cells, were first described by Mebius and colleagues as CD4$^+$ CD3$^-$ hematopoietic cells that collect at sites of lymphoid tissue development prior to birth and were proposed to act as initiators of lymphoid organogenesis [26]. Subsequent studies confirmed that LTi cells were required for the formation of secondary lymphoid tissues during fetal development including peripheral lymph nodes and Peyer's patches in the small intestine [27]. These tissues provide an organized environment for antigen presentation of both foreign and self antigens to adaptive immune cells, permitting the generation of protective immune responses to pathogens, orchestration of affinity maturation and the induction of peripheral tolerance [28].

Central to their ability to orchestrate the development, maturation and maintenance of secondary lymphoid tissues, LTi cells express multiple members of the tumor necrosis factor (TNF)-family of proteins, including the lymphotoxin-α and -β subunits and RANKL (TRANCE) which confer the unique lymphoid tissue inducing function of this ILC subset [29-32]. In particular, expression of the surface-bound lymphotoxin heterotrimer ($LT\alpha_1\beta_2$) on LTi cells allows for interactions with lymphotoxin-β receptor (LTβR) on stromal organizer cells and induces stromal cell expression of chemokines and adhesion markers, including CXC-chemokine ligand 13, CC-chemokine ligand 19 (CCL19), CCL21, MAdCAM-1 and VCAM-1. These stromal cell responses act to recruit innate and adaptive immune cells expressing the cognate receptors (CXCR5, CCR7) and integrins (α4β7) to the site of the primitive lymph node [28]. The chemokine gradients induced by LTi cells during secondary lymphoid organogenesis further act to segregate the incoming lymphocytes, allowing for formation of discrete B- and T- cell zones, required for optimal humoral immune responses [33]. Indeed, transfer of $LT\alpha_1\beta_2$-expressing LTi cells to $LT\alpha^{-/-}$ mice is sufficient to induce segregation of B- and T- cell zones [33], confirming that LTi cells are an essential source of lymphotoxin and act to orchestrate lymph node architecture. Thus, prior to birth, LTi cells promote the generation of defined lymphoid environments that are necessary for optimal adaptive immune cell responses throughout life.

Indirect regulation of adaptive immune cell responses by group 3 ILCs

In addition to their role during fetal development, group 3 ILCs play equally critical roles in the maturation and maintenance of secondary lymphoid tissues during adult life (Figure 1). For example, $LT\alpha_1\beta_2$-expressing group 3 ILCs in the intestine of adult mice indirectly regulate the function of the adaptive immune system via interactions with VCAM-1 and

IL-7 expressing stromal cells, resulting in the formation and retention of discrete group 3 ILC clusters known as cryptopatches and subsequent chemokine-dependent recruitment of innate and adaptive immune cell populations to form mature intestinal lymphoid structures known as isolated lymphoid follicles (ILFs) [34,35]. Interestingly, this process is dependent upon the presence of commensal bacteria in the intestine, suggesting that bacteria-derived signals promote ILC-mediated formation and maturation of secondary lymphoid structures in the adult intestine [34]. Furthermore, the maturation of ILFs is required for optimal production of IgA by intestinal B cells [36], which is important for mucosal host defense through regulation of commensal bacteria populations [37-39]. One recent study demonstrated that RORγt$^+$ ILCs act to orchestrate the adaptive immune system through two distinct pathways in order to promote production of intestinal IgA (Figure 1). First, expression of the membrane-bound lymphotoxin heterotrimer ($LT\alpha_1\beta_2$) by RORγt$^+$ ILCs was required for T-cell independent IgA production via modulation of dendritic cell function. Second, RORγt$^+$ ILC secretion of soluble lymphotoxin-α trimers ($sLT\alpha_3$) was found to be required for T cell-dependent IgA production by lamina propria B cells through the regulation of T cell homing to the intestine [40]. Further, $LT\alpha_1\beta_2$-expressing group 3 ILCs also promote the restoration of secondary lymphoid tissue architecture following the disruption of immune cell homeostasis during viral or pathogenic bacterial infections [41,42]. Collectively, these studies suggest that group 3 ILCs drive the maturation and maintenance of secondary lymphoid organs during adult life, and that these pathways are critical to orchestrate adaptive immune cell responses to both pathogens and commensal microorganisms.

Group 3 ILCs may also modulate host adaptive immune cell responses towards commensal bacteria via cytokine-mediated regulation of intestinal barrier function (Figure 2). For example, depletion of ILCs or neutralization of IL-22 in immunodeficient *Rag1*$^{-/-}$ mice results in impaired anatomical containment of specific commensal bacteria species resident in lymphoid-tissues, and the onset of pro-inflammatory adaptive immune cell responses directed against commensal bacteria that disseminated to systemic tissues [19]. In addition, it has recently been shown that loss of RORγt$^+$ ILC-intrinsic aryl hydrocarbon receptor (Ahr) expression results in the ablation of IL-22 production by ILCs and an outgrowth of segmented filamentous bacteria (SFB), a strain of commensal bacteria attached to the epithelial surface of the small intestine that has previously shown to induce robust Th17 cell responses [43-45]. Consistent with this, the increased abundance of SFB in the intestinal tract resulted in elevated frequencies of pro-inflammatory Th17 cells and the onset of spontaneous colitis [45]. Thus, in line with previous studies demonstrating that ILC-derived IL-22 is a crucial innate regulator of intestinal barrier integrity and bacterial containment [17-19,21], IL-22-producing ILCs also appear to indirectly regulate CD4$^+$ T cell responses and intestinal homeostasis by modulating the composition and anatomical containment of commensal bacteria.

Direct regulation of adaptive immune cell responses by group 3 ILCs

In addition to their roles in indirectly regulating the adaptive immune system, emerging evidence suggests that RORγt$^+$ ILCs may also act to directly regulate the adaptive immune system through multiple pathways (Figure 3). For example, human IL-22-producing ILCs have been shown to co-produce B-cell activating factor (BAFF) [46], a positive regulator of B cell function, suggesting ILCs located in lymphoid tissue may directly promote B cell responses. Furthermore, a series of studies by Lane and colleagues demonstrated that RORγt$^+$ ILCs express CXCR5 and CCR7 and respond to cognate chemokines produced by stromal cells by forming distinct clusters at intra-follicular regions of secondary lymphoid tissues [47,48], which was hypothesized to facilitate their ability to regulate adaptive immune cell responses at these sites. Indeed adult group 3 ILCs expressing the TNF-family

members OX40L and CD30L were found to be present in these ILC clusters and acted to maintain memory CD4+ T cells following *Listeria monocytogenes* infection or protein immunization, via direct interactions with the corresponding receptors OX40 and CD30 on memory $CD4^+$ T cells [48-51]. Consistent with a failure to maintain memory $CD4^+$ T cell responses, mice lacking both CD30L and OX40L are unable to sustain germinal center formation or long-lived antibody responses, and exhibit a loss of memory $CD4^+$ T cells in the intestinal tract [48,50,52].

In addition, we have recently shown that $ROR\gamma t^+$ group 3 ILCs may also act to directly regulate immune cell homeostasis in the intestine through the expression of major histocompatability complex class II (MHCII) and direct interactions with commensal bacteria-responsive $CD4^+$ T cells. Mice with an $ROR\gamma t^+$ ILC-intrinsic deletion in MHCII developed dysregulated $CD4^+$ T cell responses towards commensal bacteria and spontaneous intestinal inflammation [53]. Interestingly, although $MHCII^+$ $ROR\gamma t^+$ ILCs were able to efficiently pick up, process and present exogenous antigens *in vitro*, they were unable to induce $CD4^+$ T cell proliferation, possibly due to their lack of co-stimulatory molecule expression, suggesting $MHCII^+$ $ROR\gamma t^+$ ILCs may act to inhibit rather than promote T cell responses in this context [53]. Recent evidence also suggests interactions between $ROR\gamma t^+$ ILCs and $CD4^+$ T cells may be bidirectional. *Rag1*$^{-/-}$ mice were found to have higher numbers of group 3 ILCs and increased levels of IL-22 and anti-microbial peptides in the intestine [54]. This phenomenon could be reversed upon transfer of purified-$CD4^+$ T cells, suggesting T cells may also act to regulate ILC numbers and function [54].

Despite these advances, it remains unclear when or where group 3 ILCs act to modulate $CD4^+$ T cell responses. Previous studies have shown that $ROR\gamma t^+$ ILCs are found clustered at the interface of the B- and T- cell zones in lymph nodes and spleen and that these cells interact with $CD4^+$ T cells following priming by dendritic cells [33,48,51]. Further work is needed to determine whether group 3 ILCs preferentially regulate antigen-specific $CD4^+$ T cells or whether these pathways are active in the context of infectious, inflammatory or autoimmune diseases. Interestingly, in regard to their regulation of $CD4^+$ T cell responses to commensal bacteria, $ROR\gamma t^+$ group 3 ILCs are constitutively present at intestinal sites where luminal antigen is sampled, such as Peyer's patches, ILFs and cryptopatches. These lymphoid structures are organized around specialized epithelial cells called microfold cells (M cells), which play critical roles in the immunosurveillance of intestinal luminal microorganisms (Reviewed in [55]), provoking the hypothesis that commensal bacterial antigens sampled through M cells may be taken up by neighboring $MHCII^+$ $ROR\gamma t^+$ ILCs. Additionally, subcapsular sinus macrophages, which filter circulating antigen in the spleen, were recently shown to transfer antigen-containing blebs to IL-17A-expressing innate-like lymphocytes [56], although it remains to be seen whether $ROR\gamma t^+$ ILCs may acquire antigen in this manner.

Regulation of adaptive immune cell responses by group 1 or group 2 ILCs

Although less well-defined, emerging evidence suggests that group 1 or group 2 ILCs may also influence adaptive immune cell responses. Group 2 ILCs can induce B cell proliferation and enhance IgA production via the secretion of IL-5 and IL-6 [9], and regulate barrier function in the lung via production of amphiregulin [57]. Group 2 ILCs have also been reported to express MHCII under some circumstances [13,53], and transfer of group 2 ILCs can enhance Th2 responses in recipient mice [13,58], although the contribution of MHCII in this process is currently unknown. In addition, classical NK cells, a subset of group 1 ILCs, can modulate the magnitude of $CD4^+$ T cell responses via both direct and indirect mechanisms dependent on their expression of NK-cell receptors, such as NKp46 [59-62]. Of note, a subset of group 3 ILCs also express NKp46, although it is currently not known

whether NKp46$^+$ group 3 ILCs can also regulate CD4$^+$ T cell responses via similar mechanisms. Taken together, these data suggest that the broader ILC family may act to regulate CD4$^+$ T cell and B cell responses during infectious or inflammatory settings. Further work is needed to determine whether other ILC subsets can also modulate CD4$^+$ T cells via direct interactions and to determine whether the ability of ILCs to inhibit or enhance adaptive immune responses occurs in a context-dependent manner.

Implications for human health and disease

Recent evidence suggests that altered ILC populations in humans are associated with the pathogenesis and progression of numerous chronic infectious and inflammatory diseases [1,2,10,11,58,63-70]. While the potential contribution of dysregulated ILC-derived cytokine production to innate immunity, inflammation and tissue repair in these diseases is relatively well appreciated [2,22], it is also possible that altered ILC responses may contribute to disease progression by significantly influencing adaptive immune cell responses. For example, alterations in group 3 ILC responses have recently been associated with both inflammatory bowel disease (IBD) and HIV infection [10,63-66,69,70]. In the context of IBD, dysregulated ILC responses may directly contribute to intestinal inflammation through impaired IL-22 production and increased IL-17A and IFN-γ production [1,10,11,66,69,70], although these altered ILC responses may also contribute to disease progression through impaired regulation of pro-inflammatory CD4$^+$ T cell responses to commensal bacteria, perhaps via MHCII. In the context of HIV infection, a loss of ILCs may also result in increased pro-inflammatory CD4$^+$ T cell responses to commensal bacteria at mucosal sites, which would increase the availability of activated CD4$^+$ T cells for viral infection and replication, thus contributing to disease progression.

In support of an important role for ILCs in modulating adaptive immunity in human disease, a recent study reported that therapeutic administration of a monoclonal antibody directed against CD25 targeted group 3 ILCs, resulting in reduced pathologic adaptive immune cell responses [67]. This report provides compelling evidence of a role for ILCs in human disease pathogenesis, and further implicates ILCs as therapeutic targets due to their ability to modulate adaptive immune cell responses. Further interrogation of the interactions between ILCs and the adaptive immune system may also inform the design of next generation vaccine strategies, given the potential importance of ILCs in maintaining CD4$^+$ T cell memory responses and high affinity antibody production [48,50-52]. Taken together, these studies highlight the need for a better understanding of how ILCs regulate the adaptive immune system in order to develop novel therapeutic strategies aimed at boosting immunity to pathogens while limiting human disease associated with inappropriate inflammatory responses to commensal bacteria, allergens or self-antigens.

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Abbreviations used

NK	Natural killer
MHCII	major histocompatibility complex class II

IL	Interleukin
IFN-γ	Interferon gamma
Th	T helper
TSLP	thymic stromal lymphopoietin
IgA	Immunoglobulin A
HIV	Human immunodeficiency virus

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Highlights

- Innate lymphoid cells (ILCs) are critical regulators of immune responses in lymphoid and barrier tissues.
- ILCs modulate adaptive immune cell responses indirectly through cytokine-mediated regulation of stromal cells and epithelial cells.
- ILCs can also directly regulate adaptive immune cells via MHCII or other cell-surface bound molecules.
- ILC regulation of adaptive immune cells may be of clinical relevance in a wide range of chronic human inflammatory diseases.

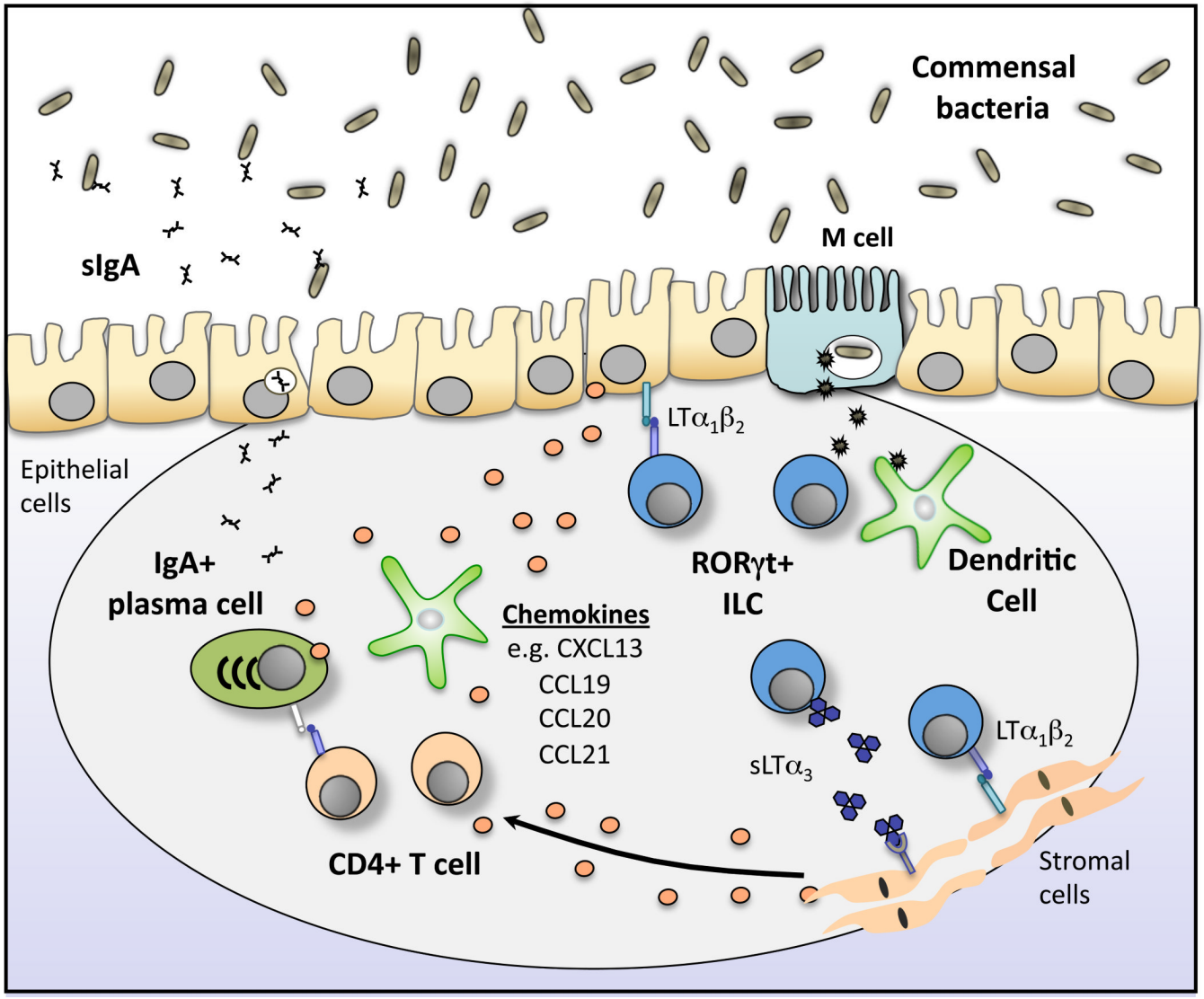

Figure 1. RORγt$^+$ ILCs orchestrate the formation of gut associated lymphoid tissue and the induction of IgA

RORγt$^+$ ILCs orchestrate the formation of secondary lymphoid tissues in the intestine in response to commensal bacteria-derived signals. Lymphotoxin-mediated interactions with epithelial cells and stromal cells induce the production of chemokines, including CCL19, CCL20 CCL21 and CXCL13, which attract DCs, B cells and T cells to the intestine to form Peyer's patches and isolated lymphoid follicles (ILFs). This process is critical for the induction of IgA production by resident B cells. In addition M cells present in these lymphoid tissues sample antigen from the lumen and deliver to antigen-presenting cells in the underlying lymphoid tissue, possibly including MHCII$^+$ ILCs.

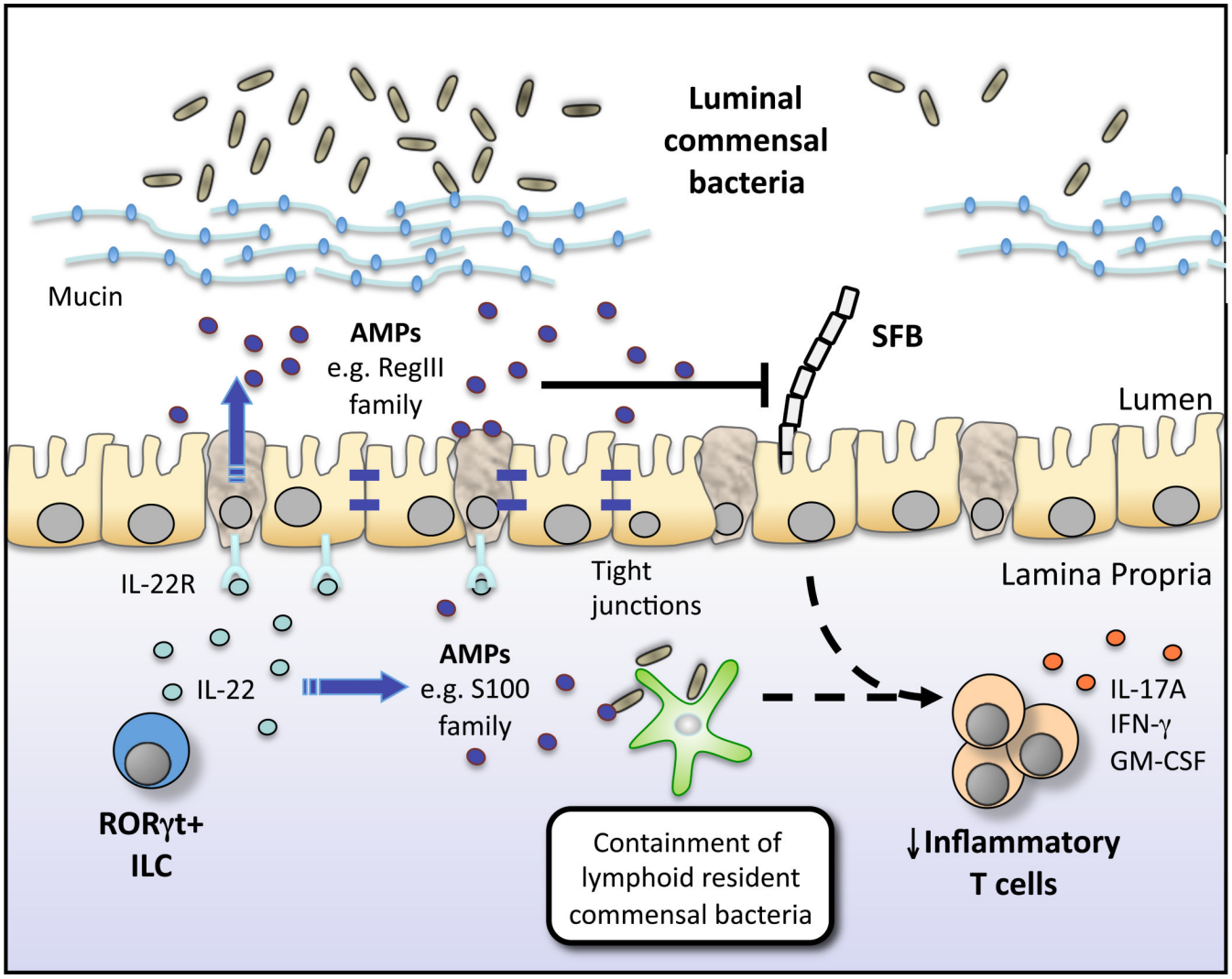

Figure 2. RORγt$^+$ ILCs regulate intestinal adaptive immune responses via IL-22

RORγt$^+$ ILCs regulate epithelial barrier function and immune homeostasis in the intestine via the production of interleukin (IL)-22. ILC-derived IL-22 acts on epithelial cells and secretory cells to regulate epithelial barrier integrity and induce the production of antimicrobial peptides (AMPs) such as RegIIIγ and S100 family proteins, as well as mucins, which spatially segregate commensal bacteria from the epithelial barrier. ILC-derived IL-22-dependent pathways further regulate the growth of specific commensal bacteria species that are intimately associated with the host, such as segmented filamentous bacteria (SFB) and *Alcaligenes/Achromobacter* spp. Collectively, these responses limit the development of pathologic CD4$^+$ T helper cell responses and intestinal inflammation.

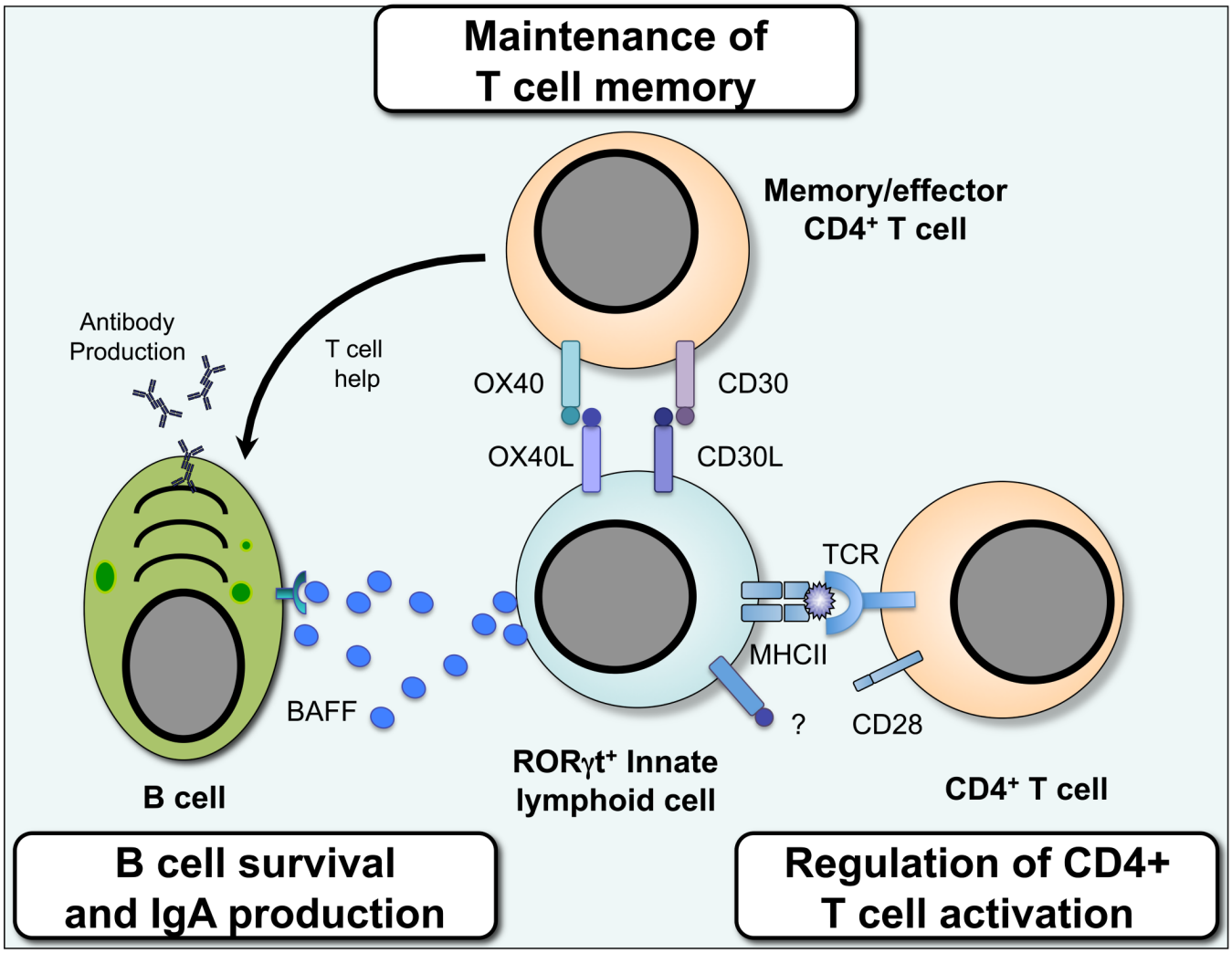

Figure 3. Direct regulation of adaptive immunity by RORγt$^+$ ILCs

Group 3 ILCs expressing the transcription factor RORγt directly interact with CD4$^+$ T cells through receptor mediated cell-cell contact. ILCs regulate the magnitude and quality of the CD4$^+$ T cell response via presentation of antigen in the context of MHC class II. In the steady state ILCs lack co-stimulatory molecule expression and appear to limit CD4$^+$ T cell responses, however it remains to be tested whether ILCs can promote T cell proliferation under inflammatory settings. Furthermore, ILCs are located at distinct sites within the spleen and lymph nodes and act to critically regulate the survival of recirculating memory CD4$^+$ T cells via interactions between ILC-expressed OX40L and CD30L and cognate receptors expressed by activated T cells. Finally, the ability of ILCs to regulate adaptive immune cell responses is not limited to T cells alone as ILCs may also produce cytokines and growth factors, including B cell-activating factor (BAFF), which support the function of B cells in lymphoid tissues.