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Innate-like lymphocytes in intestinal infections

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Structured Abstract

Purpose of review—The mechanisms of immunity against intestinal pathogens are not well understood. Innate-like lymphocytes are a group of recently discovered cells that do not fit into either side of the historical innate-adaptive classification. They are enriched in the intestinal mucosa and participate in gut homeostasis and defense against infections. We will review recent developments in innate-like T lymphocytes and innate lymphoid cells (ILCs), specifically as they relate to responses to intestinal infections.

Recent findings—Recent studies have uncovered further details into antigen presentation to γδ T cells and mucosal-associated invariant T (MAIT) cells, the role of invariant natural killer T cells and MAIT cells in intestinal infections, and how ILCs maintain gut homeostasis and protection.

Summary—Innate-like lymphocytes play a major role in the critical early response to intestinal infections and maintaining gut homeostasis. Further studies of the roles these cells play in the human intestinal mucosa will aid in the development of therapeutics against intestinal infections.

Keywords

innate-like lymphocytes; gamma delta T cells; mucosal-associated invariant T cells; invariant natural killer T cells; innate lymphoid cells

Introduction

The human intestinal tract is home to over 100 trillion microorganisms, outnumbering the cells in our body by at least 10 to 1, with more than 1000 different species known to inhabit it [1]. The challenge of intestinal immunity is to maintain the equilibrium between the host commensal microbes, while providing protection from potentially invasive pathogens. Adaptive immune responses, while powerful at later stages of infection, require significant

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Conflicts of Interest

None.

time for clonal expansion of their low frequency, antigen-specific precursors before they can exert their effects. Innate and innate-like cells, however, with higher numbers of cells at the time of infection bearing pre-formed receptors, can respond quickly, and provide protective immunity even in cases where an adaptive immune response has not yet formed due to lack of antigen exposure, as is the case with newborns.

Since the discovery of natural killer (NK) cells over 40 years ago, a number of cell types have been discovered that, based on ontogenic and functional characteristics, blur the lines distinguishing the historical classifications of innate and adaptive immune responses (Table). Within these “in-between” cells lie a number of innate-like lymphocytes that may act to bridge the gap between the two arms. γδ T cells, mucosal-associated invariant T (MAIT) cells, and invariant natural killer T (iNKT) cells all utilize restricted T cell receptor rearrangements, which recognize conserved microbial elements presented on MHC-like molecules as opposed to the peptide-MHC complexes that activate classical αβ T cells. In addition, the recently defined innate lymphoid cells (ILCs), which include NK cells, help fill the gap among lymphocytes that do not fall into the classical categories of T, B, or myeloid lineage cells. Many of these cells participate in the first line of immune defense and are important mediators that modulate subsequent adaptive responses. In this review, we will focus on recent advances in the field of innate-like T lymphocytes and ILCs, with a particular emphasis towards studies examining their roles in protection against intestinal pathogens.

γδ T cells

γδ T cells are a subset of T cells which express a TCR γ chain in combination with a TCR δ chain. In humans, peripheral γδ T cells most frequently utilize the Vγ9 and Vδ2 chains, and represent 1–5% of T cells in healthy adults [2], but can reach up to 50% of T cells in a matter of days following an infection [3]. γδ T cells are enriched in the human intestine, mostly as intra-epithelial lymphocytes. In contrast to αβ T cells which are MHC-restricted, γδ T cells can recognize antigens in both MHC-dependent and MHC-independent ways.

γδ T cells are activated by both microbial- and host-derived compounds. They recognize the microbial compound (E)-4-hydroxyl-3-methyl-but-2-enyl pyrophosphate (HMB-PP)[4], an essential metabolite in isoprenoid biosynthesis, generated by the majority of gram negative bacteria and some gram positive bacteria. They also recognize host-derived phosphoantigens such as isopentenyl pyrophosphate. Recent work has focused on the mechanism behind phosphoantigen sensing and presentation, and several studies have identified butyrophilins as responsible for presenting HMB-PP [5–9]. Once activated, γδ T cells have a range of functions, such as killing infected or stressed target cells, priming CD4 and CD8 T cells, providing B cell help, inducing DC maturation, and promoting survival of neutrophil and monocytes [10].

Recent studies have demonstrated the role that γδ T cells play in limiting transepithelial pathogen invasion. Edelblum et al [11] observed that higher numbers of S. typhimurium are seen in the gut of TCR δ defective mice, and that migration of γδ IELs was critical to their function. This effect may be related to their influence on the intestinal mucus layer, as Kober

et al [12] found that γδ deficient mice had alterations in goblet cells and crypt length in the small intestine. A later study by the same group showed that γδ deficient mice displayed an altered O-glycan profile in the small intestine compared to wild type littermates [13]. Further evidence for the importance of γδ T cells in combating intestinal infections comes from research on necrotizing enterocolitis (NEC) [14]. Comparison of NEC ileal resections with non-NEC controls showed that γδ T IELs are reduced in NEC, and associated with decreased RORC, a Th17 transcription factor. The authors postulated that IL-17 produced by γδ T cells plays a role in promoting intestinal barrier production early in life, and provided support for this by demonstrating an increase in severity of experimental gut injury in TCRδ deficient mice.

There is increasing evidence that γδ T cells may share characteristics of, and possibly influence, the adaptive αβ T cell response. Sheridan et al [15] showed that the mucosal γδ T cell response following oral *Listeria monocytogenes* was retained long term and underwent extensive expansion upon oral challenge, displaying memory-like characteristics. Furthermore, γδ T cells may also act by their influence on αβ T cells in the gut, as McCarthy et al [16] showed that Vγ9δ2 T cells display gut homing potential upon microbial activation and populate the human intestinal mucosa. These γδ T cells mediated their effect via TNF-α and IFN-γ upon antigen exposure, and enhanced inflammation by stimulating production of IFN-γ and T-bet expression in colonic αβ T cells.

Taken together, γδ T cells likely play an important role in maintaining gut homeostasis and immunity to pathogens, though most studies of intestinal γδ T cells are limited to mouse models and their results must be interpreted with the limited homology between mouse and human γδ T cells in mind.

MAIT cells

Mucosal-associated invariant T (MAIT) cells are a recently identified T cell subset important in the defense against bacteria at mucosal surfaces. They express an invariant TCR α chain (Vα7.2-Jα33/12/20 in humans, Vα19-Jα33 in mice) and variable but restricted TCR β chains. MAIT cells are primarily found in mucosal tissues, such as the liver, lung, mesenteric lymph nodes, and intestinal epithelium [17]. In human peripheral blood, they constitute approximately 1–10% of total T lymphocytes [18], but are far less frequent in wild type mice, and essentially non-existent in germ-free mice. In the human intestine, they are located in both the lamina propria and as part of the IEL compartment [19]. Only recently has the ligand for MAIT cells been identified as belonging to a class of transitory intermediates of the riboflavin synthesis pathway [20], which are produced by many bacteria and yeast, but not viruses. These vitamin B metabolites are presented on the surface by the non-polymorphic MHC class I related protein (MR1) [21]. In addition to activation of MAIT cells through the T cell receptor, it has recently been shown that MAIT cells can be activated by IL-12 and IL-18 in a TCR-independent manner [22]. MAIT cells are capable of releasing IFN-γ, TNF-α, and IL-17 in response to stimulation, and recent studies have demonstrated that they also possess cytotoxic activity [23, 24], killing infected cells via granzyme b and perforin [24].

Several recent studies have examined the adaptive capacity of human MAIT cells, which despite their invariant Vα chain, features variability in both Jα and Vβ chains usage [25]. Gold et al [26] found that among MAIT cells, different pathogen-specific responses were characterized by distinct TCR usage, both between and within individuals. MAIT cells clones with distinct TCRs were also found to respond differently to a riboflavin metabolite. Their heterogeneity may allow MAIT cells to fine tune their response to bacterial metabolite variants in the gut [27]. Soudais et al [28] observed that in mice, most if not all of the MAIT cell ligands in *E coli* are related to the riboflavin biosynthetic pathway and display very limited heterogeneity.

HIV infection can result in longstanding damage to the intestinal epithelial barrier and translocation of microbial products from the gut lumen. Several recent studies have revealed that in HIV infection, peripheral blood MAIT cells are decreased [29–34], possibly due to activation of MAIT cells by translocated microbial products [35]. Such a reduction in MAIT cells is noted in elite controllers [32], and does not recover even after successful ART, though long term ART leads to restoration of MAIT cells in the colon but not the peripheral blood [30]. The possibility remains that decreases of MAIT cells in peripheral blood may be a consequence of migration of MAIT cells to affected tissue, instead of or in combination with depletion of MAIT cells through activation.

Data on the role of MAIT cells in immune responses against intestinal infections are limited. Our group [36] has shown that in *Vibrio cholerae* infection, circulating MAIT cells are activated, and that in children, but not adults, the frequency of MAIT cells are decreased for at least 90 days after infection. We also found an association of MAIT cells with increases in LPS-specific class switched antibody responses. This finding is in agreement with a previous finding that MAIT cells are associated with increased antibody-secreting cell response to *Shigella* LPS in humans given an experimental *Shigella* vaccine [23].

Despite their sizable presence in the intestinal mucosa, our knowledge of the mechanisms underlying MAIT cell proliferation and effect are limited by the lack of suitable animal models. MAIT cells have been proposed to be a potential target of mucosal vaccination [37], and further study on such interventions is needed.

iNKT cells

Invariant natural killer T cells (iNKT) are a subset of T cells which are so named because they express cell surface markers associated with NK cells, such as CD161 in humans or NK1.1 in mice [38], but also possess an invariant αβ T cell receptor (TCR). They represent approximately 1% of intraepithelial lymphocytes in both human and mice, and approximately 0.1 % of human T cells in peripheral blood [39]. In contrast to classical T cells, iNKT cells recognize lipids and glycolipids presented by CD1d, a nonpolymorphic MHC protein expressed on intestinal epithelial cells [40]. iNKT cells mediate their effector function primarily through rapid cytokine release following activation [39], including both Th1 (IFN-γ and TNF-α), Th2 (IL-1, IL-4, and IL-13), and Th17 (IL-17, IL-22) cytokines [38, 41]. They have also been shown to enhance B cell responses through both cognate and noncognate mechanisms [42].

While much work on iNKT cells has focused on their role in anti-tumor and autoimmunity, several studies have identified their importance in modulation of immune responses against viral infections [43]. Most recently, in a neonatal mouse model, Zhu et al [44] demonstrated that enterovirus 71 (EV71) infection led to activation of iNKT cells, through a TLR3-mediated mechanism. They found that iNKT cells are involved in protection against EV71 infection, and that CD1d is essential for this protection. Similarly, in a murine model of oral *Salmonella typhimurium* infection, Selvanantham et al [45] found that infected mice had higher frequency of iNKT cells in the lamina propria, and that iNKTs produce IFN-γ, in a process mediated by the cytosolic peptidoglycan receptors Nod1 and Nod2. Much remains to be determined in how this rare cell type may be involved in defense against intestinal pathogens in humans.

ILCs

Innate lymphoid cells (ILCs) is a collective term for cells with lymphoid morphology that do not contain rearranged antigen receptors and which lack myeloid-specific phenotypic markers [46]. They do not directly recognize antigens, but instead respond to changes in cytokine expression profiles as a result of infection. Group 1 ILC, which includes classic NK cells and ILC1, are responsive to cytokines such as IL-12 and IL-18 [38], and produce IFN-γ. Group 2 ILC (ILC2) respond to IL-25, IL-33, and TSLP and produce Th2 cytokines such as IL-4, IL-5 and IL-13 [38]. These cells have been mainly studied in the lung [47], though they also participate in intestinal immune responses against helminth infections by production of IL-13 and promotion of type-2 immunity. [48].

Group 3 ILCs (ILC3) are involved in the development of intestinal lymphoid organs, and reside primarily in the small intestine lamina propria. These cells express RORγt, and respond to IL-23 and IL-1β via production of IL-22 and IL-17 [49]. The production of IL-22 by ILC3s has been shown to mediate protection against bacterial pathogens [50], and ILC3s can directly stimulate $CD4^+$ T cells [51] and also interact with B cells to aid in T cell-independent antibody production [52].

There is increasing evidence that ILC3s are critically involved in intestinal homeostasis. Mortha et al [53] showed that ILC3s are the primary source of GM-CSF in the gut, and that deficient production of GM-CSF led to reduced Treg numbers and impaired oral tolerance. ILC-driven GM-CSF production was dependent on the ability of macrophages to sense microbial signals and produce IL-1β. Similarly, Hepworth et al [54] showed that loss of RORγt+ ILCs were associated with dysregulated adaptive immune responses against commensal bacteria and low-grade systemic inflammation, and found that ILCs act as APCs and limit commensal bacteria-specific CD4 T cell responses by inducing cell death via MHC class II-dependent mechanisms [54]. On the other hand, Korn et al [55] observed that CD4 T cells were found to regulate the number and function of IL-22-producing ILCs and production of antimicrobial peptides. Additionally, recent reports by Goto et al [56] and Pickard et al [57] showed that microbial signals leading to production of IL-22 by ILC3s induce intestinal epithelial cell fucosylation. Through experiments using fucosylation-deficient mice, they also showed that fucosylation contributes to protection against *Salmonella typhimurium* infection and host tolerance of *Citrobacter rodentium*. Taken

together, ILC3 mediates protection against intestinal pathogens through interactions with both microbes and host epithelium.

Unfortunately, nearly the entire body of knowledge on intestinal ILCs is based on studies in animal models, and studies examining the activity of ILCs in the human intestine are needed.

Conclusion

The functions of innate-like lymphocytes, long overshadowed by studies on adaptive immunity, have steadily increased in recent years as appreciation grows for their important roles in gut microbial homeostasis and early responses against intestinal infections. However, much work remains to be done in determining the nature of their interactions with the adaptive immune system, particularly their influence on B cells and humoral immunity. Such work could critically inform the development of interventions targeting these cells, with potential applications in diverse fields such as vaccinology, oncology, and autoimmunity.

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Key Points

- γδ T cells are intraepithelial lymphocytes that recognize phosphoantigens and migrate to sites of transepithelial invasion.
- MAIT cells account for up to 10% of T cells in humans, including the intestinal lamina propria, and recognize a microbial vitamin B metabolite, and may have adaptive capacity.
- iNKT cells recognize glycolipids and modulate the immune response to intestinal pathogens in murine models.
- ILC3s reside primarily in the intestinal lamina propria and play diverse roles in intestinal homeostasis, including the production of GM-CSF, antigen presentation to CD4 cells, and epithelial cell fucosylation.

Table

Prominent innate-like lymphocytes present in the intestine

Cell type	Locations & frequencies	TCR	Recognized antigen	Activating cytokines	Cytokines produced	Functions in intestinal immunity
γδ	-Blood (1–10% of T cells in humans) -Gut (25–60% of T cells in humans) -Thymus, Spleen	Vγ9δ2 (humans) Vδ1 Vδ2 Vγ4δ5	-HMB-PP (Vγ9δ2) -MICA, CD1c, lipohexapeptides (Vδ1) -ULBP4 (Vδ2) -EPCR (Vγ4δ5)	IL-1β IL-23	IFN-γ TNF-α IL-17 IL-4	-Lysis of infected/stressed cells -Cytokine/chemokine production -B cell help -Priming of αβ T cells -DC maturation -Regulation of stromal cell function
MAIT	-Blood (1–10% of T cells in humans, ~0.1% in mice) -Gut (LP, PP) -Liver (~30% of T cells in humans) -Lungs	-Vα7.2-Jα33/12/20, Vβ2/13.2 (humans) -Vα19-Jα33, Vβ6/8 (mice)	-Vitamin B metabolites	IL-12 IL-18	IFN-γ TNF-α IL-17	-Anti-bacterial immunity -Cytokine production -Lysis of infected cells
iNKT	-Blood (0.1–0.2% in humans) -Liver (<1% of T cells in humans, ~10–20 % in mice) -Gut, Lung, Spleen, Bone Marrow, Thymus	Vα24-Jα18, Vβ11 (humans) Vα14-Jα18, Vβ2/7/8.2 (mice)	-Endogenous and bacterial-derived glycolipids -α-galactosyl ceramide -β-galactosyl ceramide	IL-12 IL-18 IL-23 IL-1β IL-7 IL-25	Th1 (IFN-γ, TNF-α) Th2 (IL-1, IL-4, IL-13) Th17 (IL-17, IL22)	-Recognition of endogenous lipid antigens upregulated by DC upon TLR activation -Enhance priming of antigen-specific B and T cell responses -Cytokine production
ILC3	-Gut (LP, PP)	N/A	N/A	IL-7 IL-15 SCF (cKit) IL-23 IL-1β	IL-17 IL-22	-Stimulation of antimicrobial peptide RegIIIγ from epithelial cells by ILC-derived IL-22 -Regulating gut CD4 T cell resposnes -Maintenance of epithelial barrier function -Promoting formation of Peyer's patches and lymph nodes during embryogenesis (LTi)