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# The intestinal $\gamma\delta$ T cells: functions in the gut and in the distant organs

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Located in the frontline against the largest population of microbiota, the intestinal mucosa of mammals has evolved to become an effective immune system.  $\gamma\delta$  T cells, a unique T cell subpopulation, are rare in circulation blood and lymphoid tissues, but rich in the intestinal mucosa, particularly in the epithelium. *Via* rapid production of cytokines and growth factors, intestinal  $\gamma\delta$  T cells are key contributors to epithelial homeostasis and immune surveillance of infection. Intriguingly, recent studies have revealed that the intestinal  $\gamma\delta$  T cells may play novel exciting functions ranging from epithelial plasticity and remodeling in response to carbohydrate diets to the recovery of ischemic stroke. In this review article, we update regulatory molecules newly defined in lymphopoiesis of the intestinal  $\gamma\delta$  T cells and their novel functions locally in the intestinal mucosa, such as epithelial remodeling, and distantly in pathological setting, e.g., ischemic brain injury repair, psychosocial stress responses, and fracture repair. The challenges and potential revenues in intestinal  $\gamma\delta$  T cell studies are discussed.

## KEYWORDS

mucosal immunity, intestinal  $\gamma\delta$  T cells, lymphopoiesis,  $\gamma\delta$  T-epithelial remodeling, and gut  $\gamma\delta$  T-brain injury repair

**Abbreviations:** AhR, Aryl hydrocarbon receptor; AKR1B10, Aldo-keto reductase 1B10; BTNL, butyrophilin-like; cTECs, cortical thymic epithelial cells; DC, dendritic cells; DN, double negative; DSS, dextran sulfate sodium; GALT, gut-associated lymphoid tissues;  $\gamma\delta$ IELs, intraepithelial  $\gamma\delta$  lymphocytes; IBD, inflammatory bowel disease; ICZ, indolo[3,2-b] carbazole; IECs, intestinal epithelial cells; IELs, intraepithelial lymphocytes; ILC3, type 3 innate lymphoid cells; MHC, major histocompatibility complex; MLNs, mesenteric lymph nodes; PAS, period clock-AhR nuclear transporter (Arnt)-single-minded; PB, peripheral blood; PBMCs, peripheral blood mononuclear cells; PPs, Peyer's patches; RUNX3, runt-related transcription factor 3; TCR, T-cell receptor; TGF- $\beta$ , transforming growth factor  $\beta$ ; VCAM-1, vascular cell adhesion molecule-1.

# 1 Introduction

The gut mucosa composed of the epithelium, basement membrane, and lamina propria separates a milieu enriched with various microbes and food antigens from the submucosa clear of any external pathogens (1). The intestinal epithelium consists of a single layer of intestinal epithelial cells (IECs), which represents the largest epithelial barrier of adult mammals, up to 200 ~ 400 square meters in humans (2); gut commensals are the largest microbiota on earth, up to 10<sup>12</sup> microbes/gram contents in the colon (3). Therefore, the gut mucosa faces a constant threat of luminal pathogens, and the intestinal epithelium is an important barrier for the prevention of harmful substance invasion and a vital regulator of intestinal immunity (4).

The intestine has the most complex immune system and the largest repertoire of immune cells in the body, which consists of mesenteric lymph nodes (MLNs), Peyer's patches (PPs), diffuse lymphoid structures (e.g., cryptopatches in lamina propria) and immune cells (Figure 1) (5, 6). T cells are scattered in lamina propria, named lamina propria lymphocytes, or reside between epithelial cells, referred to as intraepithelial lymphocytes (IELs) (7, 8). T cells are divided into αβ T and γδ T cells based on heterodimer surface receptors, i.e., T-cell receptor (TCR). TCR of αβ T cells consists of one α chain and one β chain while γδ T cells contain a γ

chain and a δ chain. Intestinal intraepithelial T cells include αβ T and γδ T cells (known as γδIELs) (9, 10). In mouse intestinal epithelium, Vγ5<sup>+</sup> γδ T (Garman's System (11)) cells are most abundant (12), but Vδ1 Vγ2<sup>+</sup> γδ T cells are rich in the human epithelium (13, 14).

Different from the classic and well-known CD4<sup>+</sup> helper and CD8<sup>+</sup> cytotoxic αβ T cells, γδ T cells are unique and MHC-unrestricted (15, 16). They have a wide range of functional plasticity through a variety of mechanisms, including the production of cytokines (e.g., IFN-γ, TNF-α, and IL-17) and chemokines (e.g., IP-10 and lymphokines), release of perforin and granzymes, and interaction with epithelial cells, monocytes, dendritic cells (DC), neutrophils, and B cells as well (15, 17–20). Therefore, γδ T cells can function as innate immune cells to serve as the first line of intestinal defense, but also shape early adaptive immune responses in anti-infection immunity (21). In the intestine, γδ T cells are the critical component of mucosal immunity, regulating epithelial homeostasis and immune response and participating in various physiological and pathological processes, such as inflammatory bowel disease (IBD) (22, 23).

γδ T cells are now a hot topic, and several impressive articles review the key functional roles of the γδ T cells in transplantation (24), anti-viral infection (25), and responses to the gut microbiota (26), as well as the γδ TCR in diagnosis and prognosis of

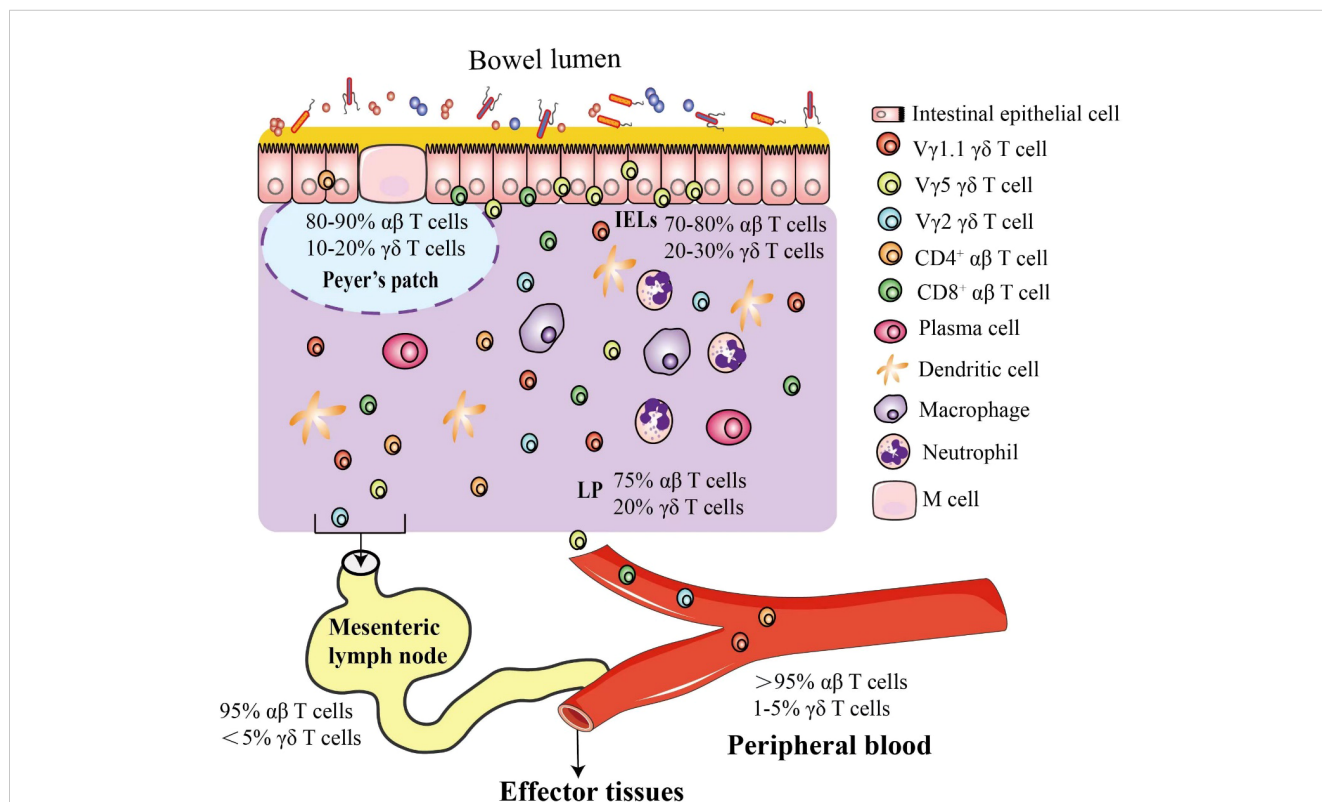


FIGURE 1

Mouse intestinal γδ T cells. The intestinal epithelium is composed of a single layer of cells that separate microbes in the lumen from the lamina propria. In response to high risk of pathogen invasion, the most complex immune system evolves in the intestine, including γδ and αβ intraepithelial lymphocytes interspersed throughout the epithelium and a plethora of immune cells in the lamina propria, such as γδ T cells, αβ T cells, dendritic cells, macrophages and neutrophils. In mice, the γδ T cells are classified by different Vγ chains, and the Vγ5<sup>+</sup> γδ T cells are most popular intraepithelial γδ T cells in the intestinal epithelium. Most T cells in peripheral blood (PB) are αβ T cells, and γδ T cells account for about 1-5% (55~120 γδ T cells/μL), but in the intestinal mucosa, specific subsets of γδ T cells are enriched as shown.

hematologic tumors (27). Ribot, et al. reviewed the physiology and surveillance of  $\gamma\delta$  T cells in secondary lymphoid organs and peripheral tissues (28), and Rampoldi, et al. nicely discussed the different talks with gut microbiota of the intestinal  $\gamma\delta$  T cells in three layers, i.e., intestinal intraepithelial  $\gamma\delta$  T cells, lamina propria  $\gamma\delta$  T cells and Peyer's patch  $\gamma\delta$  T cells (29). However, the intestinal  $\gamma\delta$  T cells may also function in the distant organs (30). This article discusses the current updates of intestinal  $\gamma\delta$  T cells in terms of their development and functions inside and outside the intestine with focus on novel functions of  $\gamma\delta$  T cells in the distant organs.

## 2 Intestinal homing of $\gamma\delta$ T cells

Intestinal homing of  $\gamma\delta$  T cells is regulated by several key factors. In mice, the  $V\gamma 5^+$   $\gamma\delta$  T cells express chemokine receptor CCR9 and integrin  $\alpha E\beta 7$ ; the CCR9 receptor binds CCL25, a chemokine highly expressed by IECs, promoting intestinal homing of  $V\gamma 5^+$   $\gamma\delta$  T cells (31–34). CCL25 and CCR9 deficient mice show a specific decrease of  $\gamma\delta$ IELs (33, 34). Integrin  $\alpha E$ , also known as CD103, dimerizes with  $\beta 7$  to form a receptor complex that binds to E-cadherin expressed on IECs, promoting entry and residence of  $\gamma\delta$ IELs in the intestinal epithelium (7, 35, 36). Either  $\alpha E$  or  $\beta 7$  deficiency reduces  $\gamma\delta$ IEL number, but a greater decrease occurs in  $\beta 7$  deficient mice as  $\beta 7$  can also dimerize with integrin  $\alpha 4$  to form a lymphocyte homing receptor integrin  $\alpha 4\beta 7$  (37–40). The  $\alpha 4\beta 7$  receptor has two natural ligands. One is the mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1) specifically expressed on the endothelium of high endothelial venules in the gut and gut-associated lymphoid tissues (e.g., Peyer's patches) (41, 42); the other is vascular cell adhesion molecule-1 (VCAM-1) expressed on stimulated endothelial cells of blood vessels, peripheral lymph nodes, and bone marrow (43). The CCL25 enhances the affinity of  $\alpha 4\beta 7$  for MAdCAM-1, but reduces the binding to VCAM-1, whereas CXCL10 works oppositely. These two chemokines distinctly regulate the active conformation of  $\alpha 4\beta 7$  and selective binding to MAdCAM-1 or VCAM-1 (39). The  $\alpha E$  expression on  $\gamma\delta$ IELs is regulated by the CCL25-CCR9 axis (44, 45), as well as transforming growth factor  $\beta$  (TGF- $\beta$ ) and runt-related transcription factor 3 (RUNX3) (46, 47).

A novel subset of  $\gamma\delta$  T cells that express both gut-homing integrins CD103 ( $\alpha E$ ) and  $\alpha 4\beta 7$  ( $CD103^+$  and  $\alpha 4\beta 7^{\text{high}}$ ) has been identified in gut-draining MLNs and in intestinal epithelial and lamina propria compartments of mice with T cell-mediated colitis and spontaneous chronic intestinal inflammation (48). The  $CD103^+$  and  $\alpha 4\beta 7^{\text{high}}$   $\gamma\delta$  T cells are generated in MLNs and then mobilize to the intestine as they also express the CCR9 receptor with IEC-expressed CCL25 as a ligand (31). This subset of  $CD103^+$   $\alpha 4\beta 7^{\text{high}}$   $\gamma\delta$  T cells precede inflammation, and adoptive transfer of the  $CD103^+$   $\alpha 4\beta 7^{\text{high}}$   $\gamma\delta$  T cells dramatically enhances the accumulation of Th1 (INF $\gamma$ )/Th17 (IL-17) cells in the intestine and severity of the disease. The  $CD103^+$   $\alpha 4\beta 7^{\text{high}}$   $\gamma\delta$  T cells are thus also named inflammatory  $\gamma\delta$  T cells ( $i\gamma\delta$  T). In addition,  $CD103^+$   $\alpha 4\beta 7^{\text{high}}$   $\gamma\delta$  T cells display a distinct transcriptional profile with a broad expression of cytotoxic mediators and NK cell receptors, which may endorse their inflammatory ability

through induction of apoptosis and barrier dysfunction of intestinal epithelial cells (48).

## 3 Lymphopoiesis of intestinal $\gamma\delta$ T cells

Gut mucosa is a main site of extrathymic lymphopoiesis of T cells, populating mostly  $\gamma\delta$  T cells (49–52). Interaction between IECs and mucosal lymphocytes is important in the regulation of intestinal lymphopoiesis of T cells. In mice,  $V\gamma 5^+$   $\gamma\delta$  T cells expand and transit to a mature phenotype from immature in the intestinal epithelium within the first few weeks after implanted (14). Factors that are critical for the proliferation, survival, and homeostatic maintenance of  $\gamma\delta$  T cells in the intestine include IL-7, IL-15, butyrophilin-like molecules, aryl hydrocarbon receptor, and aldo-keto reductase 1B8 (AKR1B8) (Figure 2). Interestingly, gut microbiota does not influence the expansion and maturation of the  $\gamma\delta$  T cells in the intestine, but stimulates their function, such as granzyme expression (53, 54).

### 3.1 Butyrophilin and butyrophilin-like molecules

After homing in the intestine,  $\gamma\delta$  T cells are shaped by butyrophilin-like (BTNL) molecules that are expressed on the surface of IECs (14, 55). By definition, butyrophilin-like proteins are similar to butyrophilin (BTN) which has two members in mice and six members in humans (56). BTNL family consists of six members in rodents and five in humans (57, 58). Several BTN/BTNL molecules are involved in immune regulation (59, 60). For instance, human BTN3A1 mediates the response of peripheral blood  $\gamma\delta$  T cells to low-molecular-mass microbial and endogenous metabolite phosphoantigens (61, 62), while SKINT1, a butyrophilin-like member expressed specifically by suprabasal keratinocytes shapes murine dendritic epidermal T cells (DETCs), i.e.,  $V\gamma 3^+$   $\gamma\delta$  T cells (63). In the gut of mice, intestinal  $V\gamma 5^+$   $\gamma\delta$  T cells expand and mature *via* regulation of BTNL1 and BTNL6 heterocomplexes expressed on the surface of enterocytes (14). In this process, the BTNL1 and BTNL6 complex selectively promotes the phenotypic conversion of immature  $V\gamma 5^+$   $\gamma\delta$  T cells and selective outgrowth of the mature  $V\gamma 5^+$   $\gamma\delta$  T cells (14, 64). The BTNL1/BTNL6 complexes are expressed by post-mitotic (differentiated) enterocytes interspersed with IELs, but not by replicating epithelial progenitors, where no IELs reside. The shaping process of the intestinal  $V\gamma 5^+$   $\gamma\delta$  T compartment seems unique by BTNL and is not affected by the thymus, lymph nodes, and Peyer's patches, or by gut microbiota and dietary protein antigens (14). In humans, it is that the BTNL3 and BTNL8 complexes expressed by intestinal epithelial cells shape the  $V\delta 2^- V\gamma 4^+$   $\gamma\delta$  T cell compartment in an organ-specific manner (14), whereas BTNL2 is a negative regulator (65). Recently, it has been reported that BTNL molecules may function through direct binding to their respective  $\gamma\delta$  TCRs (66, 67). Once established in the intestine,  $\gamma\delta$  T cells rely on IEC-expressed IL-15 and dietary AhR ligands for their maintenance and survival (68–70).

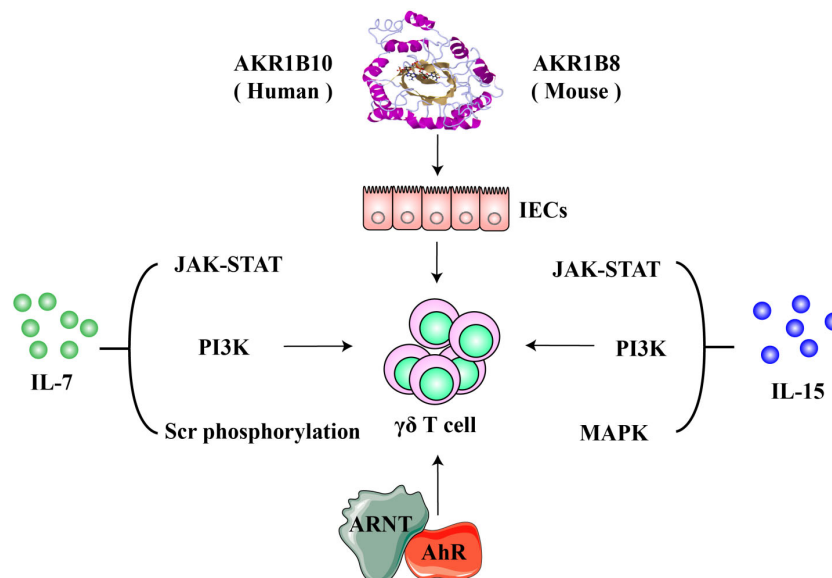


FIGURE 2

Molecules involved in the lymphopoiesis and functions of  $\gamma\delta$  T cells. IL-7 and IL-15 are critical cytokine signaling pathways that regulate the proliferation and survival, development and maturation of  $\gamma\delta$  T cells. Aryl hydrocarbon receptor (AhR) modulates  $\gamma\delta$  T cells via the AhR nuclear translocator (ARNT)-mediated signaling; AKR1B8 (AKR1B10 in humans) may exert regulatory effects on  $\gamma\delta$  T cells through an intestinal epithelial cell-mediated mechanisms.

### 3.2 IL-7 and IL-15 as key cytokines for lymphopoiesis and functions of $\gamma\delta$ T cells

In the intestine, IL-7, expressed by IECs and required for  $\gamma\delta$  T cell lymphopoiesis (71, 72), signals through a heterodimer IL-7 receptor (IL-7R) composed of a unique  $\alpha$  chain (IL-7R $\alpha$ ) and a common  $\gamma$  chain (CD132) (73–75). Binding to IL-7R, IL-7 activates JAK-STAT, PI3K, and Src phosphorylation signaling pathways to regulate target gene expression, including up-regulation of anti-apoptotic genes Bcl-2, Bcl-xL and Mcl-1 and down-regulation of pro-apoptotic genes Bax and Bak. This contributes to the survival function of IL-7, with so-called trophic effects on lymphoid progenitors and mature lymphoid cells (76–78). In mice, intestinal  $\gamma\delta$  T defects induced by IL-7 deficiency are restored by targeted expression of IL-7 in enterocytes (79). The ectopic expression of IL-7 in enterocytes does not restore  $\gamma\delta$  T cells defective in other tissues induced by the IL-7 deficiency, such as the thymus (79). IL-7R is also found in lymphocytes isolated from lamina propria and recombinant IL-7 can stimulate their growth (72). Therefore, locally expressed IL-7 plays a critical role in innate immunity against infections, such as *Citrobacter rodentium*, a mouse extracellular enteric pathogens like the human enteropathogenic *Escherichia coli* and enterohemorrhagic *Escherichia coli* (80).

IL-15 is also essential for the repertoire of intestinal  $\gamma\delta$  T cells. IL-15 signals through an IL-15 receptor (IL-15R) complex consisting of an IL-15R $\alpha$  chain, an IL-2R $\beta$  (CD122), and a  $\gamma$  chain. IL-15 could signal through either trans-presentation or cis-presentation. In the trans-presentation, IL-15 binds to IL-15R $\alpha$  and forms an IL-15/IL-15R $\alpha$  complex, which is then presented to the IL-15R $\beta\gamma$  complex on the membrane of neighboring cells, while IL-15 assembles a cis quaternary complex with IL-15R $\alpha$ , IL-2R $\beta$ , and  $\gamma$

on the cells in the cis-presentation (81, 82). The flexibility of IL-15 $\alpha$  allows the interface of IL-15 ligand-receptor to be identical in either *cis* or *trans* (81, 83). Upon binding to its receptors, IL-15 activates JAK-STAT, PI3K, and MAPK pathways, induces expression of anti-apoptotic Bcl-2 and proto-oncogenes c-Myc, c-Fos, c-Jun, c-Myc, and NF- $\kappa$ B, and promotes cell proliferation and maturation (83–86). IL-15 and IL-15R $\alpha$  are expressed by enterocytes and dendritic cells in lamina propria, forming an IL-15/IL-15R $\alpha$  complex trans-presented to  $\gamma\delta$  T cells (87, 88). IECs are the main source of IL-15 in the intestine, and IEC-specific IL-15 knockout leads to a decrease in  $\gamma\delta$  T percentage and absolute number in the intestine and to impairment of functional maturation, such as the decrease in granzyme B expression, whereas IL-15 knockout in blood vascular endothelial cells (BECs) and hematopoietic cells does not affect intestinal  $\gamma\delta$  T cells (88). IEC-specific knockout of IL-15 also leads to a decrease of  $\gamma\delta$  T cells in lamina propria, but not in the thymus. The IL-15 knockout in BECs/hematopoietic cells has no effects on  $\gamma\delta$  T cells in the thymus either, indicating the organ specificity of the expressed IL-15 cytokine. In addition, the intestinal  $\gamma\delta$  T cells in IEC-specific IL-15 knockout mice exhibit reduced survival, but increased apoptosis due to reduced Bcl-2 but increased Fas expression (88). In mice and humans, IL-15 promotes the proliferation and cytotoxic capacity of  $\gamma\delta$  T cells, enhancing antitumor activity (89). Human V $\delta$ 2<sup>+</sup> T cells isolated through TCR-crosslinking or activated by isopentenyl pyrophosphate (IPP) exhibit strong inhibition on the  $\alpha\beta$  T cell proliferation, and IL-15 can greatly enhance the inhibitory phenotype of V $\delta$ 2<sup>+</sup> T cells (90). The authors believe that pharmacologic activation and expansion of V $\delta$ 2<sup>+</sup> T cells through the V $\delta$ 2 TCR yields potent killer activity and suppression of  $\alpha\beta$  T cell responses as well. Makkouk, et al. recently reported that secreted IL-15 can sustain the proliferation and

antitumor activity of  $V\delta 1^+$  T cells engineered with GPC-3.CAR (91). Dendritic cell (DC) vaccine demonstrates therapeutic effects on acute myeloid leukemia, and IL-15 secreting DC cells yield more efficacy through activation of the innate cytotoxic capacity of  $\gamma\delta$  T cells (92). Together IECs act as a IL-15 niche to regulate the development, function, and homeostasis of the intestinal  $\gamma\delta$  T cells.

### 3.3 Aryl hydrocarbon receptor and dietary ligands

Aryl hydrocarbon receptor (AhR) is a ligand-activated cytosolic transcription factor receptor that uses dioxin or aromatic (aryl) hydrocarbon and endogenous indole derivative (e.g., kynurenine) as ligands. Upon binding to ligands, AhR is dissociated with chaperones, translocated into the nucleus, and dimerized with AhR nuclear translocator (ARNT) to drive the expression of target genes. The AhR signaling regulates immunity, stem cells, and cellular differentiation, involved in developmental and pathological processes (93–97). In the intestine and skin, AhR plays a crucial regulator in the survival and maintenance of  $\gamma\delta$  T cells (70). AhR deficiency or absence of AhR ligands leads to increased apoptosis and striking loss of over 95% of  $\gamma\delta$  T cells in the intestine, coupled with subsequent dysbiosis of gut microbiota and vulnerability to epithelial damage, whereas the  $\gamma\delta$  T cell subset in lymph nodes, spleen or thymus is not affected; proliferation of  $\gamma\delta$  T cells is normal, but survival is decreased in AhR deficient mice (70).

AhR contains two highly conserved, period clock-AhR nuclear transporter (Arnt)-single-minded (PAS) domains, which are primarily evolved to sense environmental changes in energy (98). Therefore, AhR activity can be regulated by dietary components, such as tryptophan-derived phytochemical I3C in cruciferous vegetables, which is converted into high-affinity AhR ligands, indolo[3,2-b] carbazole (ICZ) and 3,3-diindolylmethane (DIM) (99). Yet it is difficult to determine the exact nature of potential dietary AhR ligands due to the chemical complexity of diet, but a study has indeed shown that feeding C57BL/6 mice with a standard diet (5021-3 Autoclavable Rodent Lab Diet) significantly induces expression of the AhR target gene, *Cyp1a1*, compared to a synthetic purified diet (AIN-76A Purified Rodent Diet); consistently, mice fed with the synthetic diet exhibit a significant decrease in  $\gamma\delta$  T cells in the small intestine compared to mice with the standard diet. In contrast, dietary supplementation of phytochemical I3C in mice fed with the synthetic diet activates AhR and induces *Cyp1a1* expression, coupled with recovery of  $\gamma\delta$  T cells in the small intestine (70).

### 3.4 Aldo-keto reductase 1B10/aldo-keto reductase 1B8

Aldo-keto reductase 1B10 (AKR1B10) is a cytosolic protein that is specifically expressed in the intestinal epithelial cells, where it protects host cells from luminal and cellular carbonyl lesions and promotes fatty acid/lipid synthesis, regulating AKT and ERK

signaling pathways (100–102). Aldo-keto reductase 1B8 (AKR1B8) is the orthologue in mice of human AKR1B10 (103). AKR1B10 expression is lost or markedly reduced in ulcerative colitis and associated colorectal cancer (104); siRNA-mediated silencing of AKR1B10 inhibits epithelial cell proliferation (105) and targeted disruption of AKR1B8 locus leads to abnormal self-renewal of the intestinal epithelium and high susceptibility to dextran sulfate sodium (DSS)-induced colitis and associated tumorigenesis (104). More importantly, AKR1B8 deficient mice in naïve status demonstrate severe abnormalities in  $\gamma\delta$  T cell development and function, accompanied by abnormal antigen presentation and effector T cell development (106).

### 3.5 Other molecules and factors

G protein-coupled receptor GPR18 regulates  $\gamma\delta$  T cell abundance in the gut and the positioning next to epithelial cells, rather than to lamina propria (107, 108). In sharp contrast, GPR55 negatively regulates intestinal  $\gamma\delta$  T cells as GPR55 deficient mice show an increase in the number and migration of  $\gamma\delta$  T cells, and their crosstalk with epithelial cells as well (109).

Intestinal flora does not have effects on the development and proliferation of  $\gamma\delta$  T cells (53), but affects their function, promoting  $\gamma\delta$  T cytotoxicity and antimicrobial function, such as the expression of regenerating islet-derived protein 3 Gamma (RegIII $\gamma$ ) (110, 111). RegIII $\gamma$  (RegIII $\alpha$  in humans) is an antimicrobial peptide (AMP) that inhibits Gram-positive bacteria (112, 113). The intestinal  $\gamma\delta$  T cells thus act as an early responder that restricts the intestinal bacterial penetration into mucosa after epithelial injury.

## 4 TCR ligands and activation of intestinal $\gamma\delta$ T cells

The  $\gamma\delta$  TCRs are the main molecules on the surface of  $\gamma\delta$  T cells involved in the recognition of antigens and pathological conditions, and the complementarity defining region 3 (CDR3) comprises the most diversity of the receptors (114). However, in striking contrast to  $\alpha\beta$  T cells which are activated in an MHC-restricted manner, the majority of  $\gamma\delta$  T cells are activated in an MHC-independent mechanism, requiring neither MHC-mediated antigen presentation, nor co-receptor interaction (114). The antigens recognized by most  $\gamma\delta$  T cells remain baffling, which may be derived from the high challenges in the identification of the  $\gamma\delta$  TCR antigens. As the lack of general restricting molecules, the antigens could be any molecules present on the cell surface or in the surrounding extracellular space, such as proteins, carbohydrates, lipids, and nucleic acids. This extremely increases the complexity of antigen identification. In addition, the affinity of  $\gamma\delta$  TCRs to their antigens is low at micromolar levels and thus classical strategies of protein biochemistry for antigen identification may not be applied (115). Alternative methods, such as blocking antibodies and genetic approaches, are tedious and labor-intensive, and usually need prior knowledge of possible candidates (115–118). Despite these hurdles,

proceedings of  $\gamma\delta$  TCR antigen identification have been achieved, and  $\gamma\delta$  TCR antigens identified thus far include MHC-like molecules, such as MHC-Ib molecule T10/T22 (114, 119), lipid antigen-presenting molecules CD1-c and CD1-d, cell stress-induced Annexin A2 and ephrin receptor A2 (EphA2), and butyrophilin molecules (Figure 3). Please read the review article (114) for more details on  $\gamma\delta$  TCR antigens.

BTNL1 and BTNL6 heterodimers are involved in the shaping of  $V\gamma5^+$   $\gamma\delta$ IELs in the mouse gut, whereas the BTNL3 and BTNL8 complex is involved in the development of human intestinal  $V\gamma4^+$   $\gamma\delta$ IELs (14). Recent work has revealed the direct binding and interaction mode of BTNL proteins with their respective  $\gamma\delta$  TCRs through germline-encoded  $V\gamma4$  complementarity-determining region 2 (CDR2) and HV4 loops in variable  $\gamma$ -chain (66, 67). The other CDRs are not involved in BTNL protein binding, but are available for clonally specific ligand binding, such as CD1-d.

## 5 Functions of intestinal $\gamma\delta$ T cells in the gut and distant organs

The intestinal  $\gamma\delta$  T cells have been a hot topic of intestinal immunity, and novel functions of this special type of cells, in the gut and distant organs, have been increasingly revealed.

## 5.1 Intestinal $\gamma\delta$ T cell functions in the gut

Located in the mucosa, the intestinal  $\gamma\delta$  T cells are the first immune cells to appear in many bacterial infections and shape adaptive immune response, being a critical component of intestinal mucosal immunity (Figure 3). Table 1 summarizes the main functions of the intestinal  $\gamma\delta$  T cells with references.

### 5.1.1 Homeostasis and barrier function of the intestinal epithelium

Intestinal  $\gamma\delta$  T cells modulate homeostasis of intestinal epithelium by expression of keratinocyte growth factor 1 (KGF-1). KGF-1, also called FGF-7, promotes proliferation, maturation, and injury repair of IECs and regulates tight junctions and mucosal permeability (120–122). In mice,  $V\gamma5^+$   $\gamma\delta$  T cells are necessary and sufficient for integrity maintenance of the epithelial tight junctions after enteric infection, such as *Salmonella enterica* (123). In *TCR $\delta$* <sup>-/-</sup> ( $\gamma\delta$  T cell deficiency) and *KGF-1*<sup>-/-</sup> mice, the proliferation and migration of intestinal epithelial cells are decreased, and the permeability of intestinal mucosa is increased (121, 123). These mice are sensitive to colitis induced by DSS with severe epithelial damage and impaired injury repair (120–122). The intestinal  $\gamma\delta$  T cells also produce IL-22 (124), which can stimulate the secretion of antimicrobial peptides (AMP) from IECs and contribute to the

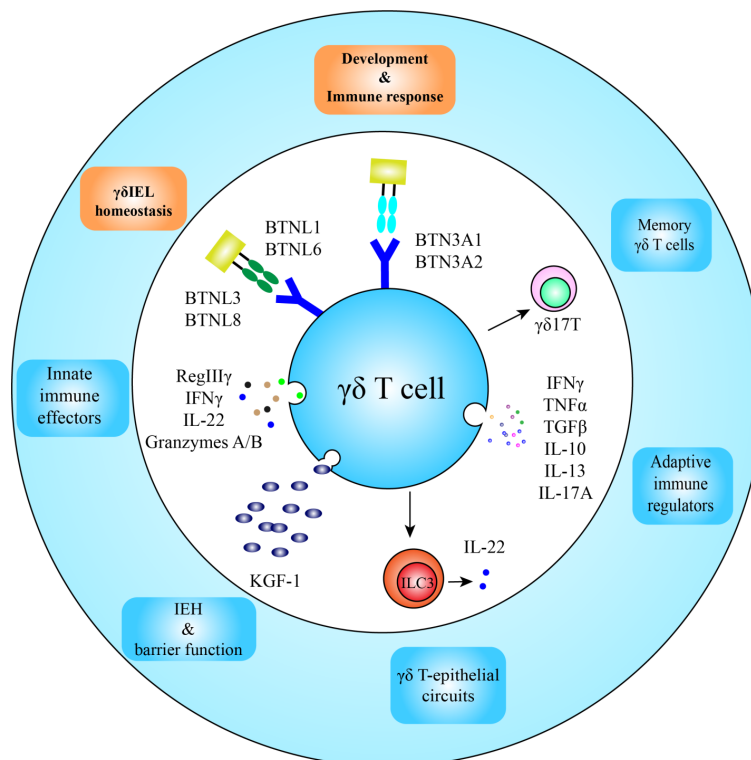


FIGURE 3

Function and development of intestinal  $\gamma\delta$  T cells. After homing in the intestine, butyrophilin and butyrophilin-like molecules participate in development and homeostatic maintenance of  $\gamma\delta$  T cells; and located in the frontline of the intestinal defense, intestinal  $\gamma\delta$  T cells are the first immune responders to appear in infection spots, functioning as innate immune effectors and adaptive immune regulators as well. Intraepithelial  $\gamma\delta$  T cells also secrete KGF-1 and IL-22 for intestinal epithelial homeostasis (IEH) and integrity of the epithelium. Some  $\gamma\delta$  T cells in the lamina propria may obtain long-lived memory phenotypes.

TABLE 1 Functions of intestinal  $\gamma\delta$  T cells in the gut and distant organs.

Locations	Functions	References
In the gut	Homeostasis and barrier function of the intestinal epithelium	(114–119)
	Surveillance of intestinal infections	(49, 104, 105, 120–138)
	Epithelial cell remodeling and responding to diets	(139, 140)
	Development and progression of colorectal cancer	(105, 114)
	Ischemic brain injury repair	(24, 141, 142)
In the distant organs	Psychosocial stress responses	(143)
	Fracture repair	(144)

repair of injury (125). Therefore, the intestinal  $\gamma\delta$  T cells play an important role in homeostasis and wound repair of the intestinal mucosa.

### 5.1.2 Surveillance of intestinal infections

Intestinal  $\gamma\delta$  T cells are dynamic and constantly migrate within epithelium *via* occludin-mediated cell–cell contact to perform surveillance of epithelium (126, 127). At steady status,  $\gamma\delta$  T cells distribute in the middle region of intestinal villi, where they reside between the basement membrane and epithelial layer, but also migrate to the intercellular space between IECs for short-time surveillance. An individual  $\gamma\delta$  T cell surveys a large area and contacts numerous IECs in a short time (54, 127). In response to the invasion of bacteria or parasites,  $\gamma\delta$  T cells gather in pathogen-rich areas rapidly and reduce normal surveillance behavior, accompanied by increase of “flossing” movements into lateral intercellular space between the IECs (54, 127, 128). The exact function of  $\gamma\delta$  T cell flossing is unknown yet, but its association with pathogen invasion suggests a crucial role in infection control and epithelial repair. MyD88 signaling in IECs is a key regulator in sensing invasive pathogens and subsequent behavioral changes of  $\gamma\delta$  T cells; specific blockage of the MyD88 signaling pathway in IECs rigorously blunts the  $\gamma\delta$  T cell response (54, 110). Gut commensals have no effects on  $\gamma\delta$  T cell number, but may contribute to their distribution within villi and to their migratory behavior and antimicrobial activity (54, 110, 111). In short,  $\gamma\delta$  T cells survey epithelial integrity, whereas IECs dictate  $\gamma\delta$  T cell behavior and facilitate adaptation in the intestinal milieu.

Microbial infection constitutes a major challenge that the intestinal epithelium encounters. Anti-infection immunity of  $\gamma\delta$  T cells includes innate and adaptive responses, and the anatomical location of intestinal  $\gamma\delta$  T cells grants them a privilege to isolate and restrict microbial pathogens from the entrance into the systemic compartment, building up the frontline of defense. Intestinal  $\gamma\delta$  T cells can express AMP (e.g., RegIII $\gamma$ ) to control pathogens (110) or IL-22 to promote AMP expression by IECs (129).  $\gamma\delta$  T cells also express cytolytic factors, e.g., granzyme A and B and perforin to lyse infected or transformed intestinal cells (111, 130–132). Activated  $\gamma\delta$  T cells can also prevent potentially against intracellular pathogens through an interferon-mediated mechanism, including IFN $\gamma$ , type I (IFN $\alpha$ ), and type III interferons (133, 134). Cytotoxic potentials of  $\gamma\delta$  T cells are regulated by cell surface receptors, e.g.,  $\gamma\delta$ TCR and

NKG2D (natural killer group 2D) (135, 136), and DNAX accessory molecule-1 (DNAM-1), leukocyte function-associated antigen-1 and co-stimulatory receptor CD27 are involved in the cytotoxicity of  $\gamma\delta$  T cells (137).

In addition to the innate response, intestinal  $\gamma\delta$  T cells quickly recruited to the inflammatory sites also shape the early immune events through secretion of a variety of cytokines to promote recruitment and activation of dendritic cells, phagocytes, neutrophils, B cells, and conventional T lymphocytes (19, 138). Cytokines secreted by intestinal  $\gamma\delta$  T cells include IFN $\gamma$ , TNF $\alpha$ , TGF $\beta$ , IL-10, IL-13, IL-17A and prothymosin  $\beta$ 4 (7). IFN $\gamma$ , TNF $\alpha$ , and IL-17A are important pro-inflammatory factors whereas IL-10, TGF $\beta$ , KGF-1, and prothymosin  $\beta$ 4 are anti-inflammatory cytokines, promoting healing and integrity of intestinal epithelium (7, 17, 122, 139–141, 145). Therefore, intestinal  $\gamma\delta$  T cells play a dual role in microbial infection, i.e., inhibiting microbial invasion by induction of inflammation in the early stage but limiting excessive inflammation and tissue damage in the later stage. In the different stages of colitis, therefore, intestinal  $\gamma\delta$  T cells seem to play a different role, i.e., a pathogenic role in the early stage, but a protective role in the later stage (142, 143).

### 5.1.3 Epithelial cell remodeling responding to diets

Enzymes and transporters required for carbohydrate digestion and absorption are induced by high-carbohydrate diets, coupled with changes in specialized enterocyte subsets (144). Carbohydrate transcriptional re-programming and epithelial cell remodeling on demand occur rapidly within 5 days of high carbohydrate feeding in mice, and intestinal  $\gamma\delta$  T cells play a crucial role in this process through suppression of IL-22 expression by type 3 innate lymphoid cells (ILC3s) (144). In response to carbohydrate diets, tissue localization, transcriptome, and behavior of  $\gamma\delta$  T cells enriched at the barrier surface of the intestine are changed. In the intestine, the intraepithelial  $\gamma\delta$  T cells are abundant and closely interact with epithelial cells whereas the lamina propria  $\gamma\delta$  T cells are a minor population of CD45<sup>+</sup> lymphocytes (146). The  $\gamma\delta$  T cells in different tissue compartments respond differentially to high carbohydrate diets. The lamina propria  $\gamma\delta$  T cells increase in frequency and number in high-protein feeding, but intraepithelial  $\gamma\delta$  T cells move more rapidly. RNA-seq analysis indicates that  $\gamma\delta$  T cells in both the epithelium and lamina propria compartments demonstrate transcriptional changes, particularly in

lamina propria  $\gamma\delta$  T cells that emerge with the greatest differentials of the transcriptome. Additionally,  $\gamma\delta$  T cells move to the crypt base in response to high-carbohydrate diets to influence the transcriptome and remodeling of epithelial cells through interaction with progenitors in the crypt base (144). This  $\gamma\delta$  T-mediated epithelial remodeling may represent an important mechanism of intestinal adaptation to environmental changes.

### 5.1.4 Development and progression of colorectal cancer

It is well known of the surveillance of the  $\gamma\delta$  T cells in transformed intestinal cells through the expression of cytolytic factors, but their temporal contribution to the development and progression of colorectal cancer is unclear (111). A recent study revealed that most  $\gamma\delta$  T cells resident in pre-malignant or non-tumor colon tissues host a cytotoxic signature, while the  $\gamma\delta$  T cells infiltrated in tumor tissues exhibit a pro-tumorigenic profile; the roles of  $\gamma\delta$  T cell subsets in pro- and anti-tumor activity are associated with distinct usage of the V $\gamma\delta$  gene of the T cell receptor in both humans and mice (147). This novel work addresses an important question on the intestinal  $\gamma\delta$  T cells as a double-edged sword in colorectal cancer.

## 5.2 Intestinal $\gamma\delta$ T cell functions in pathological settings of distant organs

Although located in the intestine, recent studies have revealed that the intestinal  $\gamma\delta$  T cells are important regulators of pathological settings in distant organs.

### 5.2.1 Intestinal $\gamma\delta$ T cells and ischemic brain injury repair

A subpopulation of  $\gamma\delta$  T cells develops a long-lasting memory phenotype and adaptive responses (148). Recent studies indicated that commensals in the gut may yield an impact on the recovery of ischemic brain injury in mice through an interleukin-17 (IL-17) producing memory  $\gamma\delta$  T (named  $\gamma\delta 17T$ ) mediated mechanism (30). Intestinal dysbiosis induced by antibiotics leads to changes in homeostasis of intestinal  $\gamma\delta 17T$  and T<sub>reg</sub> cells and trafficking of these gut effector T cells to leptomeninges after stroke, thus influencing the outcome of acute brain injuries. This is a pioneer study in the special gut-brain axis. Recently, Wang, *et al.* reported that electro-acupuncture could regulate the  $\gamma\delta$  T and Treg cells in the ischemic brain and small intestine and thus exerts protective a role on ischemic stroke (149). More recently, Piepke and colleagues reported that IL-10-mediated IL-17 production is a key factor that limits stroke lesions, and may be a potential target for stroke management (150).

### 5.2.2 Intestinal $\gamma\delta$ T cells and psychosocial stress responses

Gut microbiota trains the intestinal immune system to facilitate the maintenance of gut homeostasis; the gut microbiota also mediates the stress-induced impairment of brain function. A recent report proposed that the intestinal  $\gamma\delta$  T cells are important

mediators in the axis of gut microbiota-stress-brain function impairment (151). A specific *Lactobacillus* species of gut microbiota drives the differentiation and meningeal accumulation of colonic  $\gamma\delta 17T$  cells and thus modulates behavioral vulnerability to chronic social stress through a mechanism mediated by the dectin-1 signaling pathway.

### 5.2.3 Intestinal $\gamma\delta$ T cells and fracture repair

In fracture repair, IL-17 produced locally by  $\gamma\delta$  T cells and Th17 cells drives the inflammatory phase. Dar, *et al.* reported recently that the gut microbiota-mediated expansion and migration to the callus of intestinal  $\gamma\delta$  T and Th17 cells are involved in fracture repair (152). The S1P-receptor-1 (S1PR1) signaling pathway regulates egress and homing to the callus of the Th17 cells; and deletion of the  $\gamma\delta$  T cells and microbiome (by antibiotics) and blockade of Th17 cell influx into the callus impair the fracture repair, suggesting the importance of  $\gamma\delta$  T and Th17 cells activation and trafficking in fracture repair. It is recently understood that IL-17A secreted by  $\gamma\delta$  T cells stimulate the proliferation of mesenchymal progenitor cells and differentiation of osteoblasts to accelerate bone formation and fracture healing; in IL-17A deficient mice, the bone fracture repair is impaired (153).

## 6 Concluding remarks

The intestinal mucosa of mammals has evolved an amazing immune compartment to protect the host from pathogenic attacks. The intestinal  $\gamma\delta$  T cells represent a specific population of cells that function in the maintenance of epithelial homeostasis, barrier integrity, damage repair, and rapid compartmentalization of microbial pathogens. In response to infections, intestinal  $\gamma\delta$  T cells function as innate immune cells to restrict microbial pathogens from systemic spreading and then shape early adaptive immune responses through the recruitment of neutrophils and activation of phagocytes and dendritic cells. Therefore, intestinal  $\gamma\delta$  T cells are key regulators of mucosal physiology and pathology in disease settings. The intestinal  $\gamma\delta$  T cells may also deliver effects on distant organs, such as brain stroke and fracture repair and psychosocial stress responses.

A mysterious question is that  $\gamma\delta$  T cells are activated independently of MHC and thus antigens of  $\gamma\delta$  TCR, as lack of restricting molecules, could be different types of molecules on the cell surface or in surrounding extracellular space. Gut microbiota would be an exciting area for the exploration of microbially originated antigens/ligands. IELs regulate both the intestinal immunity and microbiota and are thus located at top of the hierarchy that guards intestinal health. How IELs regulate homed  $\gamma\delta$  T cells would then be another interesting topic. Yet some epithelial-originated molecules, such as IL-7, IL-15, BTNL, and AhR have been characterized, but identification of AKR1B10 as a novel molecule that mediates the development and function of intestinal  $\gamma\delta$  T cells implies a warranty of further investigation. New technologies developed to date, such as single-cell RNA-seq (154) and RNAscope<sup>®</sup> *in situ* hybridization combined with immunohistochemistry (155), would add avenues to understand  $\gamma\delta$  T cells in the frontline of intestinal immunity. The



gut microbiota, circadian rhythms, sex hormones, and neurotransmitters are all regulatory factors of intestinal  $\gamma\delta$  T cells (156); it is challenging but intriguing to boost the beneficial and protective roles of  $\gamma\delta$  T cells but tame their proinflammatory action.

## Author contributions

G-QL researched data and wrote the draft. JX performed the revisions. WZ drew figures. WL and LL contributed to the revisions of figures. XZ and DC substantially contributed to the discussion of content and reviewed/edited/finalized the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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