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Review Article

Characteristics of $CD8^+$ and $CD4^+$ Tissue-Resident Memory Lymphocytes in the Gastrointestinal Tract

Pan Li,[1] Yixi Zhang,[1] Yanping Xu,[1] Hongcui Cao,[2] and Lanjuan Li[2]

[1]*State Key Laboratory for the Diagnosis and Treatment of Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Rd, Hangzhou, Zhejiang 310003, China*
[2]*Jinan Microecological Biomedicine Shandong Laboratory, Jinan, Shandong 250117, China*

Correspondence should be addressed to Hongcui Cao; hccao@zju.edu.cn and Lanjuan Li; ljli@zju.edu.cn

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Tissue-resident memory T cells (TRMs) are plentiful in the memory T cell pool and persist in barrier sites without recirculating. Increasing evidence has shown that some kinds of $CD8^+$ TRMs and $CD4^+$ TRMs are resident in the gastrointestinal tract (GI), playing an important role in the context of microbiota-immune interactions, infections, maintenance of tissue homeostasis, and tumor surveillance. Although sharing some similar phenotypes, functional properties, and transcriptional regulation with other tissue-TRMs, gastrointestinal tract TRMs (GI-TRMs) have unique phenotypic and functional characteristics reshaped by the local microenvironment. In this review, we will summarize current knowledge on the regulation, maintenance, and function of the $CD8^+$ TRMs and $CD4^+$ TRMs in GI, exploring how these cells contribute to local immune defense, tissue homeostasis, and tumor surveillance.

1. Introduction

Memory T cells are mainly responsible for mediating an immediate response to the recurrent incoming antigens that are derived from pathogens, tumor, or tissue local proteins, which limit the spread of infectious agents and finally provide effective protection for the host. They have been traditionally classified as central memory T cells (TCMs) and effector memory T cells (TEMs). Once recognizing antigen, TCMs undergo rapid and robust proliferation, differentiate into effector cells, and then migrate from secondary lymphoid organs (SLOs) to the infectious site. TEMs recirculate between the blood and peripheral tissues and are involved in immune surveillance and protection [1–3]. In addition to these conventional memory T cells, recent studies have confirmed that tissue-resident memory T cells (TRMs) occupy in tissues (e.g., the gastrointestinal tract (GI) [4], brain [5], and liver [6, 7]) without recirculating (Table 1). Their major function is to prevent previously encountered pathogens from accumulating and invading in tissues. Compared to circulatory counterparts, TRMs show stronger and quicker antigen-specific response to tissue infection.

Notably, GI is not only a place for metabolic activity and nutrient storage, but it also contains a complicated immunological system. Enriched with abundant immune cells and a myriad of commensal microbiota, GI acts as a habitat for the dynamic interactions among the host mucosal nonimmune system, immune system, commensal microbiota, and their metabolites [8, 9]. It evolved highly specialized structures and cellular components to support this balance. Structurally, GI contains a mucus layer that acts as a physical barrier to prevent the entry of foreign antigens. The mucus layer is further classified with a single-cell thick epithelial layer and lamina propria, enriching with a specialized immune network [10]. $CD4^+$ and $CD8^+$ gastrointestinal tract TRMs (GI-TRMs) play a dominant role in barrier homeostasis with their potent cytotoxicity, functional plasticity, and robust abilities to sense and respond to diverse signals derived from food, commensals, and pathogens. This review will elaborate the phenotypes and functional characteristics of GI-TRMs,

Table 1: The subsets of memory T cells.

Subset	Phenotype	Location	Circulation	Cytokine secretion
TCM (central memory T cell)	$CD44^+$, $CD62L^+$, $CD27^+$, $CD28^+$, $CD127^+$, $CD69^{+/-}$, $CD103^-$, $CD11a^{+/-}$, $KLRG1^-$, $CX3CR1^-$, $CCR7^+$, $perforin^-$, and granzyme B^-	Lymph nodes, spleen, blood, and bone marrow	High	Poor
TEM (effector memory T cell)	$CD44^+$, $CD62L^-$, $CD127^{+/-}$, $CD69^-$, $CD103^-$, $CD11a^{+/-}$, $KLRG1^+$, $CX3CR1^+$, $CCR7^-$, $perforin^+$, granzyme B^+, CCR8&10$^+$(skin), and $CCR9^+$ (GI)	Spleen, lymph nodes, blood, GI, lung, heart, liver, skin, reproductive tract, and adipose tissue	High	Prompt
TRM (tissue-resident memory T cell)	$CD44^+$, $CD62L^-$, $CD127^{+/-}$, $CD69^{+/-}$, $CD103^{+/-}$, $CD11a^+$, $KLRG1^-$, $CX3CR1^{+/-}$, $CCR7^-$, $perforin^{+/-}$, granzyme $B^{+/-}$, $CCR8^+$(skin), $CCR9^+$ & $LAMP^+$ (GI), and $CCR6^+$ (lung)	Liver, lung, GI, skin, reproductive tract, and brain	Low	Prompt

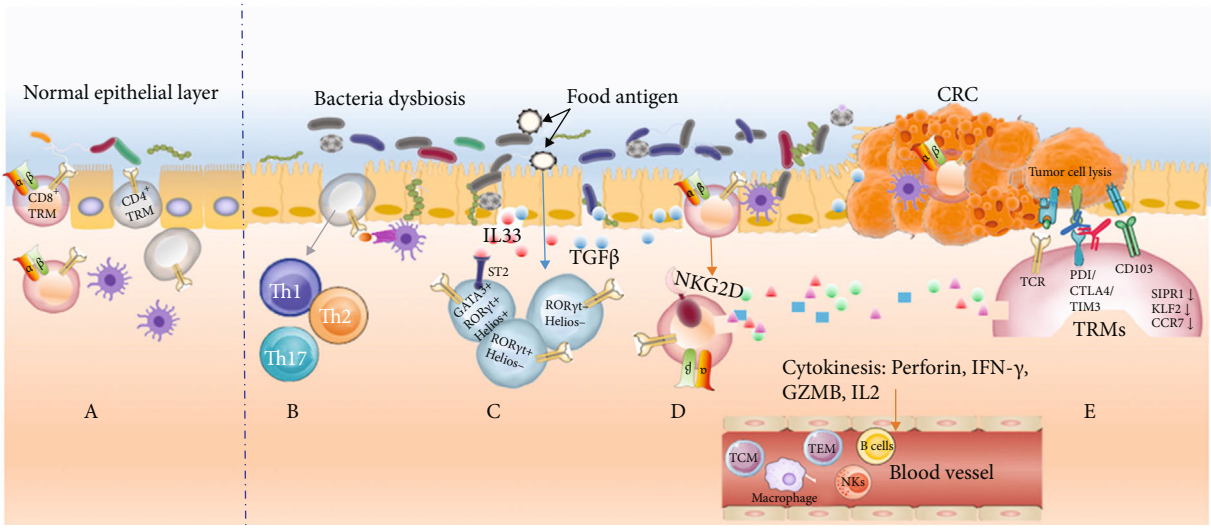

Figure 1: Classification and features of GI-TRMs. Stimulated by antigens, T cells are primed in the draining lymph nodes by professional antigen-presenting dendritic cells (DCs). Followed by GI recruitment and pathogen clearance, partial of them differentiates into memory subsets and resident in local for a long time. Meanwhile, some subsets of TRMs exist at birth. The TRMs providing immediate and potent immune response to the recurrent antigens or infection. GI-TRMs developed unique phenotypic and functional characteristics reshaped by the local microenvironment such as surface marker and transcriptional regulation factors.

which let us better understand the role of GI-TRMs in physiological and pathological situations in GI diseases.

1.1. General Background of TRMs. TRMs are widely spread in the entire length of the intestine and are enriched in the lamina propria (LP) and the epithelial layer. Following by the primary infection of the tissues, TRMs have specifically developed their functional features and resident mechanisms by expressing some markers, such as CD103, CD49a, CD44, and CD69 [11–13]. However, not all of these markers are expressed in all populations of TRMs, indicating the nuance among different TRM subsets (Figure 1).

CD103 interacts with E-cadherin on epithelial cells to facilitate the positioning, retention, and the shape of TRMs within the epithelium. $CD103^-$ skin TRMs were observed in decreased quantity and increased motility relative to the wild-type counterparts [2, 14]. Moreover, CD103 signals upregulate the chemokine receptors, such as CCR5, which is a key chemokine receptor for $CD8^+$ T cells to reach the airways in the microenvironment of lung cancer [15]. In addition, the interaction between CD103 and CCL25 via chemokine receptor CCR9 promoted the expression of CD103 on $CD8^+$ T cells in the intestine [16]. CD49a, on the other hand, plays a pivotal role in the development or survival of TRMs in the gut intraepithelial layer through binding to the extracellular matrix components, such as collagen and laminin [17, 18]. The blockage of CD49a prevented the lymphocytes adhesion to collagens and subsequent tumor necrosis factor (TNF) release [19]. A reduced TRM in gut infiltration and gut pathology was observed in a murine model with graft-versus-host disease (GVHD) by blocking CD49a [20]. CD44 may also be beneficial for TRMs via interacting with hyaluronic acid, though it is conventionally thought as the activation and memory marker of newly generated TEMs [21–23]. CD69 is a marker that indicates the T cell receptor (TCR) stimulation and is quickly downregulated in active circulating T cells. However, it consistently expresses on TRMs, resisting sphingosin-1-

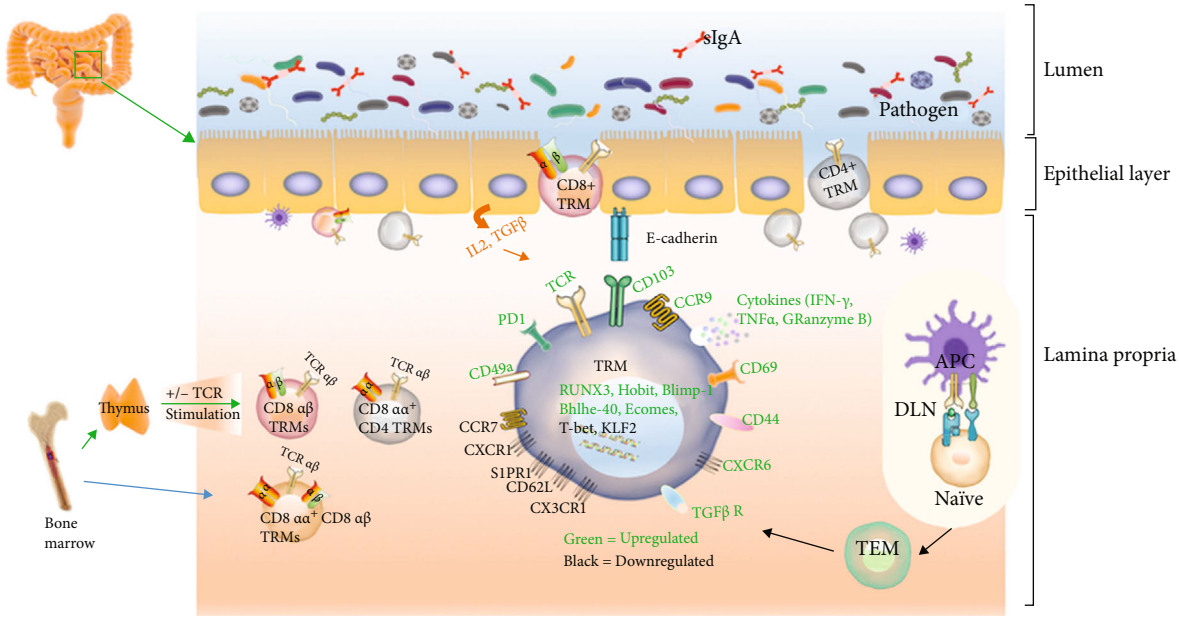

Figure 2: Functions of GI-TRMs. (a) GI-TRMs are capable of providing the front-line defenses against pathogens at the most vulnerable entry port. (b) $CD4^+$ TRMs are retained in the tissues and can be reactivated locally following reinfection. $CD4^+$ TRMs are expanded and can become effector Th1, Th17, or Th2-type cells that mediate rapid clearance of the infection. (c) Small intestine lamina propria Tregs are differentiated into all three subtypes based on the expression of RORγt (Rorc), GATA3, and Helios: $ROR\gamma t^-Helios^-$ Tregs primarily generated in response to dietary macromolecules and are proposed to be helpful in containing childhood allergies. $GATA3^+Helios^+$ Tregs expressed ST2 receptor that interacts with tissue damage-induced alarmin IL-33 to tissue repair. $ROR\gamma t^+Helios^-$ Tregs were involved in establishing tolerance towards local microbes. (d) Upon antigen resensitization or CRC, $CD8^+$ TRMs could express NK receptors (e.g., CD94 and NKG2D), exerting a NK-like function as well as producing granzyme B and inflammatory cytokines. (e) GI-TRMs employed myriad mechanisms for CRC clearance such as constitutively expressed granzyme B, IFNγ, perforin, and IL-2 and played a cytotoxic role. Meanwhile, GI-TRMs recruited circulating memory $CD8^+$ T cells, B cells, and other lymphocytes to the sites of tumor.

phosphate- (S1P-) mediated tissue egress, and thereby confers early tissue retention until TRM differentiation is complete [24, 25]. The knockout of CD69 destroyed the establishment of TRMs in herpes simplex virus-infected mouse skin [26]. However, partial $CD69^+$ T cells can return to the circulation, which indicates CD69 might not be a compulsory marker for residency. Besides, TRMs also lack lymph node (LN) homing receptors (CD62L and CCR7) that ensure their resident in local tissue [27].

TRMs have been proved to express a unique pattern of transcription factors (TFs) compared to their circulating counterparts. As major transcriptional regulators of TCM and TEM cells, T-bet expression is highest in short-lived effector cells, but in terms of tissue-resident T cells, the overexpression of T-bet hinders the formation of TRMs [28]. The downregulation of T-bet is necessary for the survival and proliferation of $CD8^+CD103^+$ TRMs in the lung [29]. In addition, it has been shown thatT-betTFs control two cytokines, transforming growth factor-β (TGF-β) and interleukin-15 (IL-15), which are essential for the development and survival of $CD8^+CD103^+$ TRMs [30]. These two signaling pathways play an important role in the maintenance of TRMs. The Hobit-Blimp1 transcriptional module is selectively upregulated in TRMs of the skin, gut, liver, and kidney in mice, compared to that in peripheral T cells [31, 32]. By inhibiting tissue egress-associated genes, Hobit enhances the maintenance of the TRMs. The deficiency of Hobit almost completely abolished the establishment of $CD8^+$ TRMs in the gut [33]. Besides, Runx3 is an essential factor for the formation of TRM populations, supports the expression of critical tissue-residency genes, and inhibits genes related to tissue egress and recirculation [34, 35]. In addition, basic helix-loop-helix family member E40 (Bhlhe40) is reported as a critical regulator of TRM survival and activity in the contexts of both infection and cancer, by driving the expression of a myriad of residency-promoting genes such as *Itgae* and *Cxcr6* [36]. Finally, both the Notch family of signaling receptors and the aryl hydrocarbon receptor (AhR) transcription factors are involved in maintaining the retention of TRM cells [26, 37, 38].

1.2. Phenotypic and Functional Characteristics of GI-TRMs. The presence of TRMs is quite important in GI to provide an immediate protection (Figure 2(a)). If TCMs and TEMs are the only memory T cell subsets, several processes are required including pathogen-derived antigens disseminating/presenting to the SLOs and immune cell recruitment around inflammatory sites. Thus, the time-consuming process is not able to provide an immediate protection after the initial infection. On the contrary, TRMs can utilize the advantage of tissue residency to respond quickly, which may benefit for the cleaning of infection. TRM subsets can be reshaped by GI local microenvironments and consequently develop tissue-specific phenotypes and functions

[39]. Here, we focus on the unique properties of GI-resident $CD8^+$ TRMs, $CD4^+$ TRMs, and their roles in GI-related diseases.

1.3. $CD8^+$ GI-TRMs. Normally, effector $CD8^+$ T cells are generated during infection with foreign antigens and undergo an activation stage that allows their entry into various peripheral tissues. The migration of effector $CD8^+$ T cells into the intestinal mucosa might be associated with local activation, due to the presence of intestinal homing molecules induced by lymphoid tissue. Partial memory $CD8^+$ T cells stayed at the GI after the first infection and can provide immediate response against the reinfection at the same site. For example, following by the lymphocytic choriomeningitis mammarenavirus (LCMV) infection, early effector $CD8^+$ T cells in the spleen upregulated the expression level of $\alpha4\beta7$ integrin and CCR9 and migrated into the intestinal epithelium. In the intestine, these T cells reduced the expression of $\alpha4\beta7$, and some of them differentiated into $CD8^+$ TRMs and exist in the tissue for a long time. The whole process happened within a week of the initial LCMV infection [40].

There are two main subsets of $CD8^+$ TRMs residing in the intestine: $TCR\alpha\beta^+CD8\alpha\beta^+$ TRMs and $TCR\alpha\beta^+CD8\alpha\alpha^+$ TRMs. $TCR\alpha\beta^+CD8\alpha\beta^+$ TRMs can reside in the tissue for a long time and are originated from antigen-experienced peripheral $CD8^+$ T cells. In comparison with the splenic counterparts, $TCR\alpha\beta^+CD8\alpha\beta^+$ TRMs showed a constitutive expression of granzyme B, CD69, CD103, and $\beta7$ integrin, along with less secretion of TNF-α and interferon-γ (IFN-γ) in LCMV-infected mice [41]. Moreover, resting $TCR\alpha\beta^+CD8\alpha\beta^+$ TRMs in human can express natural killer (NK) receptors (e.g., CD94 and NKG2D), exerting a NK-like function as well as producing granzyme B and inflammatory cytokines [42]. Although the role of $TCR\alpha\beta^+CD8\alpha\beta^+$ TRMs in mucosal immunity is less clear, they have been reported to be associated with the pathogenesis of celiac disease in human [43]. In the celiac disease progression, intestinal epithelial cells (IECs) increase the expression levels of IL-15 and the ligands of NKG2D. IL-15 subsequently upregulated NKG2D on $TCR\alpha\beta^+CD8\alpha\beta^+$ TRMs, which induce TRMs attacking IECs. The TCRs of TRMs are necessary for the acquisition of NK cell receptor expression and killer activity; however, the potential role of their antigen specificity in such TRM-facilitated pathology awaits further exploration (Figure 2(d)) [44, 45]. "Natural" $TCR\alpha\beta^+CD8\alpha\alpha^+$ TRMs exist at birth, comprising one third of intraepithelial lymphocyte population but decreasing with advanced age [46, 47] . $TCR\alpha\beta^+CD8\alpha\alpha^+$ TRMs are highly heterogeneous with diverse major histocompatibility complex (MHC) class I restriction. Their development is significantly impaired in $\beta2$-microglobulin-deficient mice and is partially affected in classical (H2-K and H2-D) or nonclassical (Qa2 or CD1d) MHC-deficient mice [1, 48, 49]. In the differentiation process via responding to self-antigens, $TCR\alpha\beta^+CD8\alpha\alpha^+$ TRMs acquire a cytotoxic phenotype and gut-homing capacity without the stimulation of any foreign antigens [45].

The regulation of TRMs is associated with cytokines such as TGF-β, TNF, and interleukin-33 (IL-33). TGF-β is conventionally thought to induce the CD103 expression on $CD8^+$ T cells. It drives the development of TRMs in the lung and gut by a SMAD4-independent signaling pathway [50]. However, recent researches showed that the developments of $CD103^-$ $CD8^+$ T cells in the lamina propria were more affected by IL-12 and type I IFN rather than TGF-β [51]. Furthermore, IL-33, TNF, and TGF-β can integrately induce the expression of CD69 and CD103 (a T cell-like phenotype) of $CD8^+$ T cells [52–54].

In the aspect of transcriptional regulation, GI-TRMs share similar characteristics with TRMs from other tissues. For instance, Hobit and Blimp-1 take part in the maturation of TRMs, genetic deficiency of them almost completely abolished the establishment of $CD8^+$ TRMs in the gut [33]. KLF2 is a transcription factor that positively correlates to the genes related to the recirculation of SLOs (e.g., S1P1). It is downregulated in TRMs, which further reduced the expression of receptors for S1P in the aspect of gene regulation. Thus, the residency of TRMs depends on the gene-regulated activity, rather than an antagonization by CD69 [55]. Besides their generality, AhR is an important transcription factor of $CD8^+$ GI-TRMs and the activity of AhR is determined by the aromatic hydrocarbon ligands from leafy vegetables in food. This suggests the GI microenvironment may serve as an important factor for the differentiation of TRMs [56].

$CD8^+$ GI-TRMs produce a fast and effective protective immune response against invading pathogens, avoid harmful inflammation, and provide host protection.$CD8^+$ TRMs express high levels of Ki67 and granzyme B, showing their proliferative and cytotoxic potential [57]. Thus, vaccines that elicit TRMs yield higher immune response than do vaccines that elicit systemic immunity. This phenomenon was confirmed in skin- and genital tract-related tumors [58, 59]. Besides, $CD8^+$ GI-TRMs must have unique properties in intestine transplantation, as the incidence of high ratio of GVHD and bacterial infection in the first month after transplantation (67.7% patients) [36, 60, 61]. In summary, further exploration is required for the understanding of the exact phenotypic or functional characteristics of GI-resident $CD8^+$ T cells.

1.4. $CD4^+$ GI-TRMs. Like $CD8^+$ TRMs, $CD4^+$ TRMs also provide immediate protection from recurrent antigens and infections. However, the phenotype, function, and maintenance of these subsets in infection remain unclear. There are several differences between $CD4^+$ and $CD8^+$ TRMs in the aspects of tissue localization, marker expression, and cytokines that drive the establishment of TRMs. Further exploration of these differences will benefit for understanding the identification and differentiation of $CD4^+$ TRMs.

Naive $CD4^+$ T cells can expand and differentiate into different subsets of T helper (TH) cells after infection. These different subsets of TH cells have varied functions in circulation, SLOs, and infected tissues [62]. After clearing infection, most of these effector cells undergo apoptosis process, while a small part of them differentiate into memory cells and persist in the tissue for a long time to provide immediate and potent immune response to the recurrent antigens or infection [63].

After migrating to tissues, effector-memory T cells acquired the expression of integrins and adhesion molecules, such as CD44 and/or CD103, thus to retain as $CD4^+$ TRMs [64]. $CD4^+$ TRMs mainly reside in human large intestine and murine intestinal regions close to the cecum, and vast majority of them that are resident in the lamina propria express CD69 [65]. Unlike the high expression level of CD69, the expression of CD103 may vary in different tissues [66–69]. The roles of IL-2, IL-15, and IL-7 have been well documented in conventional $CD4^+$ T cell biology [70]. IL-2 is an important driven factor for the primary proliferation of activated effector $CD4^+$ T cells [71]. Moreover, IL-2 is an indispensable cytokine to maintain the residency of Tregs and take part in the intestine immunologic homeostasis [72]. Besides, the IL-2 receptor (IL-2R) signaling pathway is required for the establishment of $CD4^+$ TRMs. The lack of IL-2R signaling disables the migration of activated $CD4^+$ T cells into the lung in viral pulmonary infection and allergic asthma settings [73–75]. The initial T cell activation requires IL-15; however, the long-term survival of $CD4^+$ TRMs depends on late IL-15 signals. IL-7 signal interacts with the intestinal extracellular matrix and is involved in the recruitment or survival of $CD4^+$ TRMs [76]. The incoming pathogenic bacteria can drive the differentiation of $CD4^+$ TRM populations within the lamina propria, such as *Listeria monocytogenes*-driven $CD4^+$ memory TRMs [77, 78]. The Th1 TRMs in a *Listeria monocytogenes*-infected model can be induced and accumulated in the lamina propria and epithelium. Of note, their residency is independent with IL-15 [79]. Th2 TRMs can also be found in the lamina propria and peritoneal cavity in a *Heligmosomoides polygyrus*-infected model [80]. Segmented filamentous bacteria (SFB) infection in mice can induce the differentiation of Th17 in the lamina propria and these Th17 cells respond to pathogens by producing IL-17 and IL-22 [81]. Commensal microbiota can induce resident Tregs as well. Murine gut resident Tregs can be driven by some specific strains of *clostridium* located within murine intestine, although these bacteria are originated from humans (Figure 2(b)) [82, 83]. In addition, skin-resident TRMs are induced by localized *Staphylococcus epidermidis*, which specifically strengthens the epithelial barrier function and prevents the overgrowth of heterologous microorganisms, including *Candida albicans* [84]. Similarly, *Aspergillus fumigatus* sensitization induces a $CD103^{lo}CD69^{hi}CD4^+$ TRM population and increases IL-5 and IL-13 production in the lung to promote the allergic process [85].

GI resident Tregs exert a suppressive function like peripheral Tregs and can be differentiated into three subsets based on the expression of RORγt (Rorc), GATA3, and Helios: $GATA3^+$ $Helios^+$ Tregs, $ROR\gamma t^+$ $Helios^-$ Tregs and $ROR\gamma t^-$ $Helios^-$ Tregs (Figure 2(c)) [86]. $GATA3^+Helios^+$ Tregs express ST2 receptor that interacts with tissue damage-induced alarmin IL-33 [87, 88]. Thus, they are involved in the inflammatory suppression and tissue repair by secreting amphiregulin. $ROR\gamma t^+Helios^-$ Tregs involved in the regulation of Th2 and Th1/Th17 mediated immunity [89]. $ROR\gamma t^-Helios^-$ Tregs have been identified as a novel subset and may be related to dietary antigens, indicated by their localization [90]. Furthermore, a novel function subset of siTregs is identified from the intraepithelial lymphocyte (IEL) population. Lamina propria Tregs move to epithelial compartment, and some of them do not express Foxp3 anymore, meanwhile with diminished expression of ThPOK (encoded by *Zbtb7b*) to gain expression of $CD8\alpha\alpha^+$. The frequencies of $CD4^+CD8\alpha\alpha^+$ Tregs are decreased in chronic intestinal inflammation patients, suggesting its potential regulatory function [91, 92].

Transcription factors such as Runx3, T-bet, and KLF2 are also involved in the regulation of $CD4^+$ TRMs; however, the regulation of them is comparatively less known. The PR zinc finger domain 1 (PRDM1) was highly expressed by intestinal $CD4^+$ TRMs, which has been implicated in pathogenic Th17 cell responses in Crohn's disease [93]. Hobit and Blimp-1 were found to drive $CD4^+$ TRMs to control intestinal inflammation [93–96]. As systemic and tissue-retained memory $CD4^+$ T cells are long-lived in tissues and exhibit more polyclonality than $CD8^+$ T cells, the immunization approaches that are capable of inducing their differentiation may play a significant role in persistent protection. Th1 cells can provide the protection to the host against the viruses and intracellular bacteria. Recent evidence has shown that IFN-γ-secreting TRMs are important for providing long-term protection against these insults. The same evidence was shown in the parasite field, which indicated that Th2 and Th1-type TRMs defend against extracellular and intracellular parasites, respectively [97–99]. However, there are several questions to answer. Firstly, the underlying mechanism that controls the development or specific activation of effector Th1, Th2, and Th17 from $CD4^+$ TRMs in GI followed by reinfection with foreign pathogens has not been well documented. Secondly, the generation of Th1, Th2, and Th17 subtypes of $CD4^+$ TRMs is controversial. It remains unclear whether they are originally resident in GI, or they are induced by the reinfection activity. Finally, the impact of local microbiota on the differentiation of $CD4^+$ TRMs requires further exploration.

1.5. TRM Functionality in Local Diseases and Implications for Immunotherapies. TRMs reside in GI for a long time; more importantly, they express many TCM-like and effector T cell-like markers that relate to the homeostatic proliferation and survival. Thus, it is not surprising to find that they play important roles in immune regulation in the contexts of chronic inflammation and tumor [100–102].

Current researches reported that the numbers and percentages of $CD8^+$ TRMs of IELs were significantly decreased in inflammatory bowel disease (IBD) tissues compared to that in human healthy controls [101]. $CD8^+$ TRMs expressed high intracellular levels of Ki67 and granzyme B, showing their proliferative and cytotoxic potential, and are increased in CD intestinal mucosa [57]. $CD4^+CD69^+$ cells were observed to accumulate in the colon of IBD patients compared to that in control donors [103]. Besides, compared to circulating counterparts, microbiota-reactive $CD4^+$ TRMs were more inclined to display both Th17 and Th1 characteristics in IBD [33, 104]. In addition, there was another unique subset of $TNF\alpha^+$ $IL\text{-}17A^+$ $CD4^+$ TRMs,

which was enriched in Crohn's disease and produced more IL-17A and TNFα. This subset participated in the local inflammation immunity and is mainly regulated by the transcription factors PRDM1. Chronic inflammation is caused by continued activating immune system as the incidence of repeated antigens. Thus, TRMs act as gatekeepers to alert the host once reinfection happened, as well as assist the clearance of antigens.

As a typical digestive tract cancer, colorectal cancer (CRC) is one of the third worldwide cancers. Many researches reported the existence of TRMs in CRC tissues, but the prognostic significance and clinical implications of TRMs in CRC are still underexplored. There is a $CD8^{+-}$ $CD103^{+}$ population that accounts around one-third of $CD45^{+}$ cells, with the coexpression of CD69, fatty acid synthase (FAS), human leukocyte antigen (HLA)-DR, and CD38 in CRC tissues. The cell number of $CD8^{+}CD103^{+}$ TRMs in the tumor epithelium is 27-fold larger than that in normal epithelium. Based on single-cell ribonucleic acid (RNA) sequencing analysis, colorectal tumor-infiltrated $CD8^{+}CD103^{+}$ T cells expressed cytolytic molecules (such as GZMA, GZMB, GZMH, and recombinant perforin 1 (PRF1)), immune checkpoint molecules, activation- or exhaustion- associated molecules (e.g., programmed cell death-1 (PD-1), lymphocyte activation gene 3 protein (LAG3), T cell immunoglobulin and mucin-containing molecule-3 (TIM-3), and CD39), and proliferation markers [105, 106].The underlying mechanism of how TRMs are specifically associated with CRC has not been well documented. However, suggested by the mechanisms of how TRMs control microbial infection, one speculation is that the tissue-specific expression of homing and adhesion molecules by TRMs may assist TRMs exerting the antitumor effects [107–109]. This hypothesis is supported by the accumulating evidences. Along this line, CD103 expression on T cell clones contributes to their expression of E-cadherin in infiltrated tumor islets. Moreover, colon carcinoma-specific T cell that was extracted from tumor-infiltrating lymphocytes (TILs) of a colon carcinoma patient could enhance the secretion of TGF-β by the stimulation of antigen. And the tumor-derived TGF-β subsequently promoted the CD103 expression on T cells [110]. In another model, CD103 expression on $CD8^{+}$ T cells which was induced by TGF-β promoted the lysis of E-cadherin-transduced pancreatic tumor cells (Figure 2(e)) [50, 111]. Consistently, the knockout of CD103 prevented the T cell infiltration and diminished tumor rejection in murine models [112, 113].

In addition, with persistent infection, GI-TRMs continue to express mucosal-homing $\alpha4\beta7$ integrin, which can interact with mucosal address in cell adhesion molecule-1 (MAdCAM-1), a molecule that was a marker of vascular endothelial cells in the intestinal lamina propria. The interconnection was very important for the positioning of TRMs in the gut wall and subsequent immune protection [114].The deficiency of $\alpha4\beta7$ integrin impacted the subset composition of TRMs in gut-associated lymphoid tissues, further showing an altered immune response against CRC [16, 115–118]. Furthermore, deleting CD49a impaired the tumor control in several mouse cancer models [113, 119].

On the other hand, $CD8^{+}$ TRM-secreted IFN-γ also exerted suppressed tumor cell division, improved the activation of other population of lymphocytes, and inhibited the resistance to the chemotherapy that resulted from tumor-associated fibroblast [120, 121]. Additionally, $CD8^{+}$ TRM-secreted IFN-γ affected the tumor architecture and prevented the metastatic spread, by triggering the formation of fibronectin [122]. Moreover, by the secretion of chemokines and cytokines, GI-TRMs recruited other immune cells, as well as initiated the activation of local resident dendritic cells (DCs) and macrophages [11, 123, 124]. In this way, GI-TRMs could prime tumor-specific T cells in draining lymph nodes to control the development of tumor.

As shown by the correlation of TRMs, virus, chronic infection, and cancers, TRMs may be ideal candidates for the diagnosis and treatment of related diseases. One potential application is vaccine. Traditional vaccine normally triggers the responses of circulating T cells, rather than tissue-resident T cells. The activation of tissue-resident T cells depends on the route of immunization [59, 125, 126]. Vaccination by direct intracolorectal (i.c.r.) administration showed enhancing immunity of large intestinal mucosa in animal models. However, the delivery method was not impractical in human. Oral administration is the most frequently used with advantages of safety, simplicity, and convenience. However, the efficacy may be significantly abolished by the upper gastrointestinal tract [127–129]. Therefore, researches aiming the delivery of vaccine in GI to activate the local TRMs need further exploration. In addition, the complicated intestinal microbiome might affect the vaccination response in different individuals. At the end of this line, the poor understanding of the correlation of local microbiome, resident T cells, and vaccine immune response significantly hinders the development of vaccination.

Another application for TRMs is tumor immunotherapy. Many attentions have been paid to expand TRMs *in vitro* for adoptive cellular therapies or assist the immune cells in developing TRM-like characteristics [130, 131]. However, due to the poor proliferation of $CD103^{+}$ TRMs *in vitro* and loss of the therapeutic properties of TRMs, the strategy of transferring TRMs into tumor tissue might not show a satisfactory result in cancer treatment and there is still a long way to go [132]. One potential solution is to use tumor-derived DCs that do impart TRM properties to T cells, and it would be useful to exploit this property for DC inducing TRM expansion *in vitro* [113, 133]. Finally, as TRMs express some typical inhibitory receptors (e.g., PD-1, Lag3, and Tim3), they might be a potential target in checkpoint inhibition therapy. Clinical trials have shown the efficacy of PD1-blocking antibodies in metastatic CRC, and two of them (pembrolizumab and nivolumab) have been approved by the Food and Drug Administration (FDA) [134–136].

2. Conclusion

As discussed above, GI-TRMs are capable of providing the front-line defenses against pathogens at the most vulnerable entry port. They are additionally responsible for the integrity of the mucosal border, as they can prevent the uncontrolled

infiltration of immune cells and unwanted immune responses. In addition, GI-TRMs and GI-microbiota may be involved in the homeostasis of other tissues, such as the liver [137], brain [138, 139] by gut-liver axis, and gut-brain axis. Moreover, GI-TRMs may be associated with Coronavirus disease 2019 (COVID-19), as the acute respiratory syndrome shows GI-dependent local immune system imbalance [140, 141]. A deeper and more comprehensive understanding of GI-TRMs may shed light on the potential therapeutic strategies for diverse diseases.

Although the biological characteristics of TRMs may be beneficial in multiple diseases, there still exist several questions. The first challenge is that the criteria of sampling and related analytical methods are hard to make out, due to the complexity of GI. The markers that are frequently analyzed in current human CRC are not uniquely expressed in TRMs, which makes it difficult to define a genuine TRM subset in TILs [142, 143]. In animal models, it is still not applicable to construct an appropriate mouse model that targeted TRM-specific genes and completely depleted already differentiated TRMs. The paucity of mouse model leads to difficulties in obtaining detailed preclinical and clinical details. Therefore, it is hard to gain a deeper understanding of TRM biology and its function in disease, which might hinder the development of its application such as in IBD and CRC treatment. However, these problems might be solved by recent emerging technology such as single-cell RNA sequencing [144] and cytometry by time-of-flight (CyTOF) [145] which may provide a more accurate insight. Besides, since chronic inflammation is associated with CRC, a deeper understanding of what specific role in IBD and the possible physiological consequences of TRM persistence is required.

Data Availability

All data analyzed during this study are included in this article.

Conflicts of Interest

The authors declare no conflict of interests for this article.

Authors' Contributions

All authors listed have made substantial, direct, and intellectual contribution to the work and approved it for publication. P.L. organized the database and drafted the manuscript. Y.Z. and Y.X. performed critical revision of the manuscript. H.C. and L.L contributed to the final approval of the version to be published, all authors provided critical feedback and helped shape the manuscript. All authors contributed to the manuscript revision, read, and approved the submitted version.

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