frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 09 March 2023
DOI 10.3389/fimmu.2023.1119383

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cancer Immunity and Immunotherapy, a section of the journal Frontiers in Immunology

RECEIVED 08 December 2022
ACCEPTED 27 February 2023
PUBLISHED 09 March 2023

CITATION
Liang M, Wang X, Cai D, Guan W and Shen X (2023) Tissue-resident memory T cells in gastrointestinal tumors: turning immune desert into immune oasis. *Front. Immunol.* 14:1119383. doi: 10.3389/fimmu.2023.1119383

Tissue-resident memory T cells in gastrointestinal tumors: turning immune desert into immune oasis

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Tissue-resident memory T cells (Trm) are a particular type of T cell subgroup, which stably reside in tissues and have been revealed to be the most abundant memory T cell population in various tissues. They can be activated in the local microenvironment by infection or tumor cells and rapidly clean them up to restore homeostasis of local immunity in gastrointestinal tissues. Emerging evidence has shown that tissue-resident memory T cells have great potential to be mucosal guardians against gastrointestinal tumors. Therefore, they are considered potential immune markers for immunotherapy of gastrointestinal tumors and potential extraction objects for cell therapy with essential prospects in clinical translational therapy. This paper systematically reviews the role of tissue-resident memory T cells in gastrointestinal tumors and looks to the future of their prospect in immunotherapy to provide a reference for clinical application.

KEYWORDS

tissue resident memory T, gastrointestinal tumor, anti-tumor response, cancer immunotherapy, tumor immune microenvironment

1 Introduction

Immunotherapy has developed rapidly in the past few years and has become one of the first-line treatment strategies in gastrointestinal tumors, of which immune checkpoint inhibitors (ICIs) are the representative drug and have achieved promising therapeutic effects by activating the exhausted immune cells. T cells, especially $CD8^+$ T cells, are the main effector cells of the anti-tumor immune response. Memory T cells are the main T cell subsets that exert anti-infection and anti-tumor immune response due to their contact with infection and/or tumor

Abbreviations: MSI, Microsatellite instability; CRC, Colorectal cancer; CTLs, Cytotoxic T lymphocytes; Trm, Tissue-resident memory T cells; Tcm, Central memory T cells; Tem, Effector memory T cells; Tex, Exhausted T cells; Tas, Tumor antigen-specific T cells; TAA, Tumor-associated antigen; TCR, T cell receptor; IELs, Intraepithelial lymphocytes; MDSC, Myeloid-derived suppressor cells; S1P, sphingosine-1-phosphate; TLS, Tertiary lymphoid structure; ICI, Immune checkpoint inhibitor; ICB, Immune-checkpoint blockade; VLA-1, Very late antigen-1; FFA, Free fatty acid; EBVaGC, Epstein–Barr virus-associated gastric cancer.

antigens (1). These cells can form long-term memory on tumor-specific antigens, which makes them reliable candidates as a target for anti-tumor therapy. Memory T cells have two subsets: circulating memory T cells and tissue-resident memory T (Trm) cells. In gastrointestinal tissues, Trm cells reside in local tissues, survive for a long time, self-renew, and initiate a rapid response when encountering infection antigens and tumor antigens. At the same time, Trm cells are also considered to be the main population responding to PD-1 inhibitors, playing an important role in immune therapy (2, 3). Therefore, a systematic review of the role of Trm in gastrointestinal tumors will provide an important theoretical basis for better understanding how it plays a positive anti-tumor immune response and optimizes existing immunotherapy strategies.

2 Overview of tissue-resident memory T cells

2.1 Phenotype of tissue-resident memory T cells

Naive T cells can differentiate into memory T cells after being stimulated by antigens. Circulating memory T cells include central memory T cells (Tcm) and effector memory T cells, circulating from circulation, secondary lymphoid organs, and in some situations non-lymphoid tissues (4). Tissue-resident memory T cells were first found in the intestinal mucosa, but were once considered as a special subset of Tem cells (5). Gebhardt et al. later confirmed and officially named this type of memory T cell subset in the skin (6), and now tissue-resident memory T cells have been found in almost all human tissues, including lymph nodes (7). Tissue-resident memory T cells and circulating memory T cells have different phenotypes, molecular characteristics and functions (8) (Figure 1): Tcm is relatively static, and mainly exists in lymphatic tissues, highly expressing lymphoid homing receptor. Tcm can be activated when stimulated by antigens, and then proliferate and differentiate into other types of memory T cells (Figure 1). Compared to Tcm, Tem mainly exists in non-lymphoid tissues or tissues with inflammation. Mostly, Tcm differentiates into Tem under stimulation. Interestingly, it has been revealed that a small number of Tem cells can differentiate into Tcm cells to maintain stability and its durable effects in the absence of antigen stimulation (1). It used to be thought that Trm cells steadily reside in local tissues to realize rapid immune response to the antigens, with typical characteristics of low homing-related molecule expression and high expression of tissue-resident-associated molecules like CD69 and CD103 (6, 9, 10). Hartana et al. afterwards found a small number of Trm cells in the peripheral blood of healthy people (11),

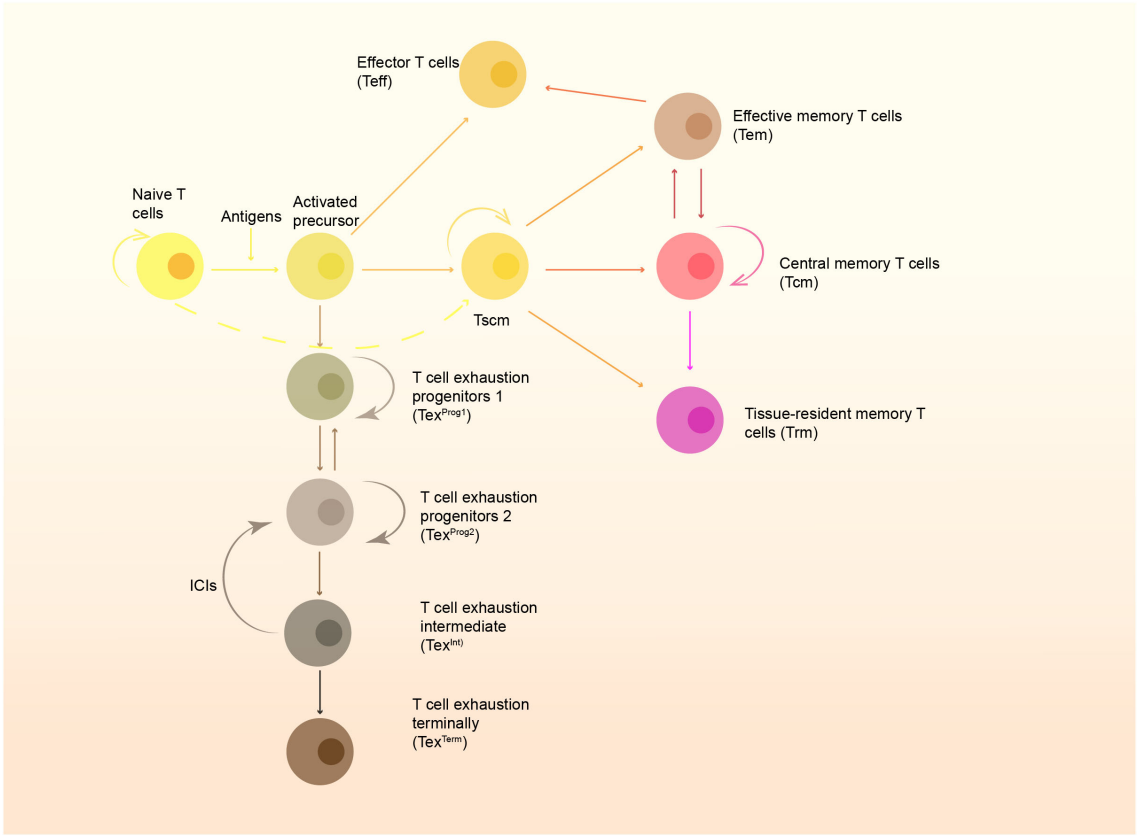

FIGURE 1
The formation of memory cells and the T cell exhaustion pathway. Naïve T cells are stimulated by antigens presented by APC and develop to active precursors, which further differentiate into effector T cells (Teff) and stem-like memory T cells (Tscm). Tscm can further develop to central memory T cells (Tcm), effector memory T cells (Tem) and tissue-resident memory T cells (Trm). Some of them can also become exhausted gradually, and restoration of function of these cells rely on immune checkpoint inhibitors (ICIs).

indicating that Trm cells might enter peripheral blood. Some Trm cells can upregulate the expression of molecules such as CD36 to move out of the tissues (12). Beura et al. (13) found that Trm cells in non-lymph node tissues can migrate to lymph nodes, thus increasing the accumulation of antigen-specific Trm cells in lymph nodes, especially in draining lymph nodes. Fonseca et al. (14) also found that the reactivated Trm can re-enter the circulating pool called "ex-Trm". And these ex-Trm cells retain strong affinity for the original tissue. Fonseca et al. pointed out that Trm cells have certain developmental plasticity and can regenerate Tcm cells and Tem cells, which allows outside-in immune responses. Behr et al. (15) proved this result and they also found that ex-Trm-derived cells showed a higher protective electrical potential than their non-ex-Trm-derived counterparts. Thus, Trm cells retain developmental plasticity and shape both local and systemic T cell responses.

The molecular characteristics of tissue-resident memory T cells generally include high expression of CD103, CD69, and CD49a, as well as low expression of CCR7 and S1PR1, among which the down-regulation of S1PR1 is considered as the precondition for tissue residency of Trm (16). T cells have been found to circulate into the blood in response to sphingosine-1-phosphate (S1P). However, CD69 play an antagoinistic role for S1PR1 (17) by binding to S1P interferes with the transmembrane region of S1PR1 and promoting S1PR1 internalization (18). Joint regulation of CD69 and other important transcriptional pathways (described below) eventually leads to the low expression and activity of S1PR1 in Trm, which can't respond to S1P. The synergistic effect of low CD62L and high CD69 expression is to prevent the lymphatic homing and migration of Trm cells, which is one of the critical factors for Trm to settle in tissues. Thus tissue-resident memory T cells can also be simply defined as $CD62L^{-}CD69^{+}$ T cells to distinguish them from circulating memory T cells. Similarly, low expression CD62L and CCR7 effectively prevent T cells from migrating through the vascular wall (8, 19–21).

In addition, CD103 and CD49a are considered key tissue residence molecules (20). CD103 can interact with E-cadherin on the surface of epithelial cells to increase the aggregation of Trm in tissues, and induces the response of tissue-resident memory T cells to chemokines (22). Although some tissue-resident memory T cells do not express CD103, molecules with similar effects to CD103 were found in these $CD103^{-}$ Trm cells: in liver, $CD103^{-}$Trm cells can adhere to the hepatic sinusoid epithelium by LFA-1, enabling tissue retention (23). In addition to helping T cells to reside in peripheral tissue, CD69 and CD103 played a significant role in the formation and survival of Trm (24). CD103 may also be related to lipid metabolism by inducing CD36, $CD103^{hi}$Trm often has a higher expression level of CD36 and up-regulation of lipid-related metabolic pathways than $CD103^{lo}$Trm (25). CD49a, the very late antigen-1(VLA-1), also known as integrin α1, can form a complex with CD49d that achieves adhesion to epithelial cells through its ligands, while this adhesion can allow Trm to migrate along the epithelial basement membrane. CD49a promotes the survival of Trm and is involved in the regulation of IL-15-induced production of granzyme and perforin to maintain the functional stability of Trm (20, 26, 27). Cytokines in the immune microenvironment, such as IL-2/IL-12/IL-15/IL-7, regulate CD62L and S1PR1 and play an essential role in the formation, survival, function maintenance, and regeneration of Trm in tissues (Figure 2).

With the development of sequencing technology, the heterogeneity of Trm has been revealed, which helps us better understand how Trm cells play the role in local tissues. As mentioned above, CD103 is essential for Trm residence and maintenance. $CD103^{+}$ Trm cells are the main force in gastrointestinal tissues to fight against infection and tumors, while $CD103^{-}$ Trm cells have a more unique function. For instance, in the intestine, $CD103^{+}CD69^{+}CD8^{+}$ Trm cells possess high ability to produce inflammatory cytokines, while $CD103^{-}CD69^{+}CD8^{+}$ Trm cells have a high expression of β2-integrin and are more able to produce granzyme (28). Besides, researchers have found that $CD103^{-}$ Trm can differentiate into $CD103^{+}$ Trm to mediate immune response towards secondary infections, instead of the primarily resident $CD103^{+}$ Trm (29, 30). Besides the different function, various subsets of Trm cells, including $CD103^{+}CD69^{+}$, $CD103^{-}CD69^{+}$ and $CD103^{-}CD69^{-}$ Trm cells, have shown great potential to proliferate. Further exploration

Transcription factors involved in Trm formation include high expression of Runx3, Hobit, Blimp1 and Notch, with low expression of T-bet, Eomes and Klf2. In addition, Trm also expresses pro-survival family members such as Bcl-2 and various anti-apoptotic factors (19, 21, 31). The expression of Runx3 is considered a key factor for the formation of Trm. Overexpression of Runx3 during thymic T cell development promotes the formation of $CD8^{+}$T cells and is also an important factor in the induction of CD103 (32). And effector T cells in tissues tend to have higher Runx3 expression (33). Runx3 can promote the expression of tissue-residency genes and molecules (CD69, Blimp-1, etc.) and suppress genes related to tissue egress and recirculation (T-bet, S1PR1, Klf2, etc.) (34, 35). Blimp-1, one of the downstream targets of Runx3, can also regulate the expression of S1PR1 and CD62L directly or indirectly through Klf2 and Sell, while Hobit, a homolog of Blimp-1, has a similar function (20, 21, 31, 36). Notch can also promote the expression of CD103 (37). In contrast, TCF-1, a transcription factor maintaining $CD8^{+}$ T cell stemness, can repress CD103 expression by directly suppressing the transcription and inhibiting TGF-β-induced CD103 expression, which restricts Trm development (38). Hobit may maintain Trm production in the gut and skin in the absence of Blimp-1 (36). The downstream targets of Notch are solute carriers of nutrients, including amino acids, indicating that Notch helps maintain the nutritional metabolism of Trm (39). In addition to regulating the formation of tissue-resident phenotypes, these transcription factors also control the cytotoxicity of Trm. Runx3 promotes the differentiation of cytotoxic T lymphocytes (CTLs) and inhibits terminal differentiation, ensuring the development, growth, and longevity of CTLs (34). At the same time, Runx3, together with Blimp-1, Hobit, T-bet and others, regulates the production of granzyme B and/or perforin through its complex regulatory pathway (40). It is worth noting that Hobit is superior to Blimp-1 in long-term expression of granzyme (41). Eomes was thought to suppress Trm cell formation, but a recent study revealed that Eomes was essential for Trm maintenance in the intestine but not the colon (42). Thus, various expression of transcriptional factors determines heterogeneity and existence of Trm cells, which can be altered in

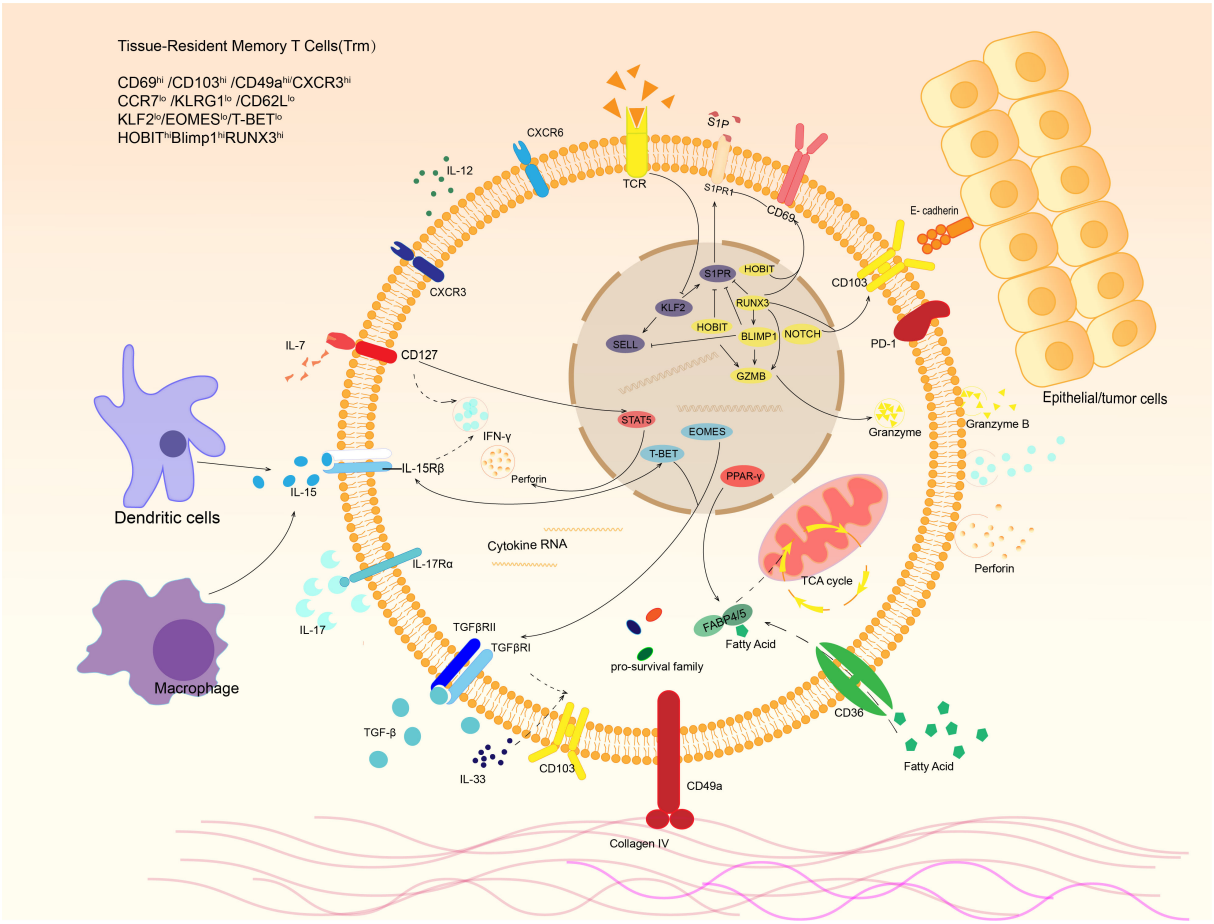

FIGURE 2
Phenotypes and signaling pathways of tissue-resident memory T cells. Trm cells express distinct phenotype under stimulation of various cytokines in tumor microenvironment. For example, dendritic cells and macrophages can release IL-15, which binds to IL-15 receptor and activates transcription factor T-bet, resulting in IFN-γ expression of Trm. In response to IL-7 in tumor microenvironment, STAT5 is activated and leads to IFN-γand perforin production. E-cadherin expressed by other cells and extracellular matrix like collagen IV are also able to bind the receptors expressed on Trm surface. After that, they release a variety of cytokines to kill targeted cells and regulate local immune microenvironment.

case of tumor or infection. Focusing on the alteration may help us better to understand the phenotype and function changes of Trm cells and provide more ideas to regulate these cells to play an anti-tumor role.

2.2 Anti-tumor effect of tissue-resident memory T cells and T cell exhaustion

Trm cells have been confirmed to monitor of local immunity and play an important role in infectious diseases (6, 19, 43–45) and autoimmune diseases (46, 47). The significant negative correlation between *ITGAE* (encoding CD103) and *CD69* gene expression and molecular markers of glioblastoma (48) suggests that $CD8^+$Trm cells may have an anti-tumor effect, as demonstrated by studies in other tumors (9, 44, 49, 50). At the same time, tissue-resident memory T cells are also a key target for the regulation of immune-checkpoint blockade (ICB) therapy (22, 51, 52). The anti-tumor effect of Trm is manifested in two aspects: 1. Trm mediates local immunity, and 2. It kills tumor cells by toxicity (53). Activated Trm can identify the tumor-associated antigens and secrete cytotoxic granular proteins, CCL3, CCL4, CCL5 and other chemokines, as well as pro-inflammatory cytokines such as interferon-γ (IFN-γ) and tumor necrosis factors (TNF) (53, 54). The anti-tumor effect of tissue-resident memory T cells is closely related to their phenotypic molecules (Table 1). The interaction between CD103 and cadherin protects the survival of Trm in tumor tissues, and also causes the bidirectional signal of T cell receptor (TCR) [24], and induces TCR-dependent tumor antigen-specific killing effect. The release of TNF-γ can promote the up-regulation of vascular adhesion molecule 1 (VCAM-1), recruit $CD8^+$ circulating memory T cells and B cells, and further induce and promote local immune response (22, 43). In the mouse melanoma model, the defect or inhibition of CD103 manifests as the immune system's imbalance in regulating tumor growth. Compared with the CD103 wild type mouse, the melanoma in the CD103 deficient mouse is large and grows faster (67). In addition, the cells with high CD103 expression are often accompanied by the expression of CD69 and PD1. $CD103^+$Trm also has higher cytotoxicity than $CD103^-$Trm (57, 58, 61). CD49a has a similar effect to CD103. After using CD49a inhibitors, the

mice in the experimental group also showed uncontrolled tumor growth (56).

The function of tissue-resident cells is regulated by other immune cells. Dendritic cells promote the differentiation and formation of tissue-resident memory T cells (68) and play a protective role in tumors. The interaction between $CXCR6^{+}$Trm and $CXCL16^{+}$APC is important for maintaining tumor immunity (69). However, some immune cells play a negative regulatory role, tumor-associated fibroblasts (CAFs) are essential in tumor microenvironment and have complex relationships with tumor cells and TILs. CAFs can inhibit Trm activity by upregulating the expression of PD-1 by cytokines, and increase the risk of lymphatic metastasis (70). In addition, Treg cells can inhibit Trm cell immune activity and promote tumor growth, and they have more significant infiltration in the tumor, especially tumor matrix (71, 72). These two immune cell subsets can work together with macrophage type 2 to form an immune barrier against anti-tumor immune response by Trm (72).

Trm has an excellent anti-tumor effect, but like other T cell subsets, it will gradually lose its immune activity and convert into exhausted T cells (Tex) when continuously stimulated by antigens and/or inflammatory factors. According to the expression of Ly108 and CD69, T cells are divided into four stages (Figure 1). The intermediate Tex subset (Tex^{Int}) will gradually lose its cytotoxicity and proliferation capacity. However, T cells at this stage can regain their cytotoxic effect after PD-1 blockade. Once the cells enter the terminally exhausted subset, T cells will no longer respond to immune checkpoint inhibitors (ICIs) (73). It is now generally accepted that exhausted T cells are characterized by low antigen-stimulated proliferation, high expression of multiple immune checkpoints and progressive loss of T-cell effector function. Thus, immune checkpoints are also known as exhausted-related molecules (74). Trm cells also express multiple immune checkpoints, such as PD-1, TIM-3, and CTLA-1, etc. Interestingly, although Trm cells have multiple immune checkpoint molecules, many studies have shown that their function is not exhausted (11, 75). On the contrary, the functional Trm is more powerful and metabolically active than Tex (64). But it is shown in multiple tumor models that Trm is a group of cells with the trend of exhaustion (9, 11, 53, 64, 75). Zheng et al. (76) performed single-cell sequencing on a variety of tumor-infiltrating T cells, including gastric cancer and esophageal cancer, and found that the exhausted T cells were mainly from effector memory T cells and tissue-resident T cells. Recent study has found that the exhaustion of $CD8^{+}$ T cells is accompanied by an increase in the number of Tc17 cells with poor cytolytic capacity (77).The scRNA-seq of gastric tumor also showed Tc17 exhaustion pathway originating from Trm (78). Another single-cell sequencing results showed that Trm cells could be divided into three subsets: Hobit-enriched $CD103^{hi}PD\text{-}1^{lo}$Trm, Granzyme K-enriched $CD103^{lo}PD\text{-}1^{hi}$ Trm, and $CD103^{hi}$ $PD\text{-}1^{hi}CTLA^{hi}LAG3^{hi}TIGIT^{hi}$ Trm, while the last subset is considered as exhaustion-related subtype (79). Milne et al. also identified subsets of memory T cells with resident gene expression characteristic of progenitor exhaustion T (Tpex) cell ($Id3^{hi}Blimp1^{lo}$) and terminal exhaustion (80), and this study indicates that there exists a complete developmental pathway to exhaustion in Trm. In general, Trm cells may keep their function with the expression of immune checkpoints, but they still can convert into exhausted T cells. The differentiation pathways and intrinsic mechanism remain unclear, and the exploration to the pending issue may provide novel strategies for anti-tumor therapy.

Dysfunction of T cells in the advanced tumor microenvironment is related to tumor immune escape. Once it happens, the number of T cells expressing either high-level or low-level cytotoxic granulosa proteins is significantly reduced and the exhausted-related molecules are significantly overexpressed in tumor microenvironment (TME) (57). Studies have pointed out that non-terminally Trm-Tex dynamic is related to tumor prognosis (63, 64, 76). And the population with high expression of cell cycle-related genes, though less, is likely to be related to the tumor-associated antigen (TAA) (81), and replenish effector Trm cells as they become exhausted (81, 82)

3 Tissue-resident memory T cells in gastrointestinal tumors

3.1 Tissue-resident memory T cells in gastric cancer

In normal gastric tissue, lamina propria mononuclear cells (LPMCs) have a tissue-resident phenotype, with more than 70% of LPMC $CD8^{+}$ T cells co-expressing CD103 and CD69, and nearly 20% expressing CD103 alone (83). $CD69^{+}CD103^{+}$ Trm also accounts for approximately 30% of TILs in the TME of gastric adenocarcinoma with high expression of PD-1, TIGIT, and CD39 (49). Like most solid tumors, Trm cells in gastric cancer have significant spatial heterogeneity. In gastric cancer tissues, more $GZMB^{-}$ Trm cells can be seen, and $CD103^{-}$ T cells infiltrate more in the tumor matrix, while $CD103^{+}$ Trm cells appear more excessively in the tumor epithelium. Various types of Trm are decreased in the tumor matrix with lower activity and function (51). Besides, the infiltration of $CD103^{+}CD8^{+}$ Trm cells in advanced gastric cancer is also less than in early gastric cancer (57).

It has been found that development of gastric cancer is associated with dysfunction or declined abundance of Trm (84–86). Trm cells in the tumor microenvironment ingest free fatty acid (FFA) as the main energy source mainly through CD36-FABP4/FABP5 related metabolic pathways (25). However, gastric cancer cells also have up-regulated CD36 and lipid metabolism (87). Aoki (88) and Pan (87) found high expression of CD36 may be associated with peritoneal metastasis of gastric cancer. Furthermore, this suggested that there might be a competitive relationship on lipid uptake between gastric cancer cells and Trm. Recently, Lin et al. (49) revealed that gastric cancer cells deprive Trm of fatty acids through more aggressive competitive uptake, which leads to Trm death. They further found that blocking PD-1/PD-L1 reduced lipid metabolism of gastric cancer cells, but enhanced the lipid uptake and lipid metabolism of Trm cells.

In recent years, tertiary lymphoid structure (TLS) has been found to be associated with the prognosis or development of tumors. TLS is associated with survival and clinical outcomes in

patients with immunotherapy for tumors and can serve as a potential therapeutic target for tumors (89, 90). And TLS is also associated with a better prognosis for gastric cancer. Interestingly, Mori et al. found that $CD103^+CD8^+$Trm cells were found in and around TLS, which could secrete high levels of cytolytic enzyme and IFN-γ, and IFN-γ was considered to have the function of promoting TLS formation. Consistently, patients with CD103 overexpression also tend to have more abundant TLS. Patients with $CD103^{hi}TLS^{hi}$ also had a better therapeutic response to nivolumab (86, 91).

In addition to the susceptibility and immune microenvironment changes caused by genetic susceptibility, pathogenic microbial infection, and microbiome alterations also play an important role in the occurrence and development of gastric cancer and affect the function of TILs. Gastric cancer is one of the few tumors related to infection, *Helicobacter pylori* (*H. pylori.*) and Epstein–Barr virus (EBV) are the main infection-related factor (92–94). *H. pylori* can inhibit the $CD8^+$ CTLs by myeloid-derived suppressor cells (MDSCs) and induce the up-regulated expression of PD-L1 of tumor epithelial cells and macrophages, thereby inducing the resistance of gastric cancer to ICB therapy against PD-1/PD-L1 (95, 96). Xu et al. have shown that the induction of Trm proliferation and differentiation can enhance the local immune response to *H. pylori* (97). A recent study has shown that CagA-specific $CD8^+$ Trm cells can infiltrate the gastric mucosa and control the *H. pylori.* infection (98). EBV infection can induce DNA demethylation of host cells, which results in expression of tumor suppressor genes, loss of tumor-related antigens, and over-expression of immune checkpoint like PD-L1 and PD-L2 and induces immune evade of Epstein–Barr virus-associated gastric cancer (EBVaGC) by PD-1/PD-L1 interactions between tumor cells and T cells (99, 100). The typical characteristics of the gastric cancer microbiota were the flora change and the decrease in microbial diversity. The mouse model showed that enhanced *Methylobacterium* in gastric cancer promoted tumor progression by reducing the infiltration of $TGF^-β^+CD8^+$ Trm and was related to the exhaustion of Trm (101). Similarly, Yang et al. (102) showed higher CXCL13 production in $CD8^+$ Trm, which contributed to TLS formation.

3.2 Tissue-resident memory T cells in colorectal cancer

In normal intestinal tissue, the proportion of $CD69^+CD103^+CD8^+$ T cells in $CD8^+$ T cells can even exceed 80% (28). However, they have significant functional differences in the lamina propria and epithelial layer. The tissue-resident memory T cells have active pathways that regulate cell survival and cytokine signal transduction in the lamina propria with higher expression of Runx3,NR4A2,ICOS and LITAF, while they show more obvious cytotoxic characteristics in the epithelial layer with a higher level of GZMM,LTB,GZMA and CXCR3 (103). These $CD69^+CD103^+$ Trm cells have been found to highly express CD161 and CD127 (IL-7R), which help maintain T-cell cytotoxicity. In addition, IL-7 can restore the activity of $CD8^+$ T cells by reducing the expression of PD-1 (104).

The immune microenvironment regulates the function of $CD8^+$ T cells and the formation of CD8+ Trm: TGF-β can inhibit the migration of CD8 T cells, which, together with IL-33, can promote T cell differentiation into Trm (105), TGF-β can induce the synthesis of CD103 and CD69 molecules in the maintenance phase of Trm cells (22, 106). Once TGF-β is blocked, the abundance of Trm cells can significantly decrease (62). Paradoxically, TGF-β has two sides to tumor immunity, and it can regulate the expression of tumor cell cycle-related proteins and inhibit cell cycle from exerting anti-tumor effects in the early stage of cancer. It becomes a spy for immune responses to advanced tumors. When the tumor enters the advanced stage, the tumor cells can secrete a large amount of TGF-β to damage T cell mitochondrial respiration and inhibit the production of IFN-γ, thereby reducing T cell activity and helping the tumor escape through the Treg cell pathway (107, 108). IL-7 appeared to inhibit the negative effects of TGF-β on suppressing Trm development (104). Intraepithelial lymphocytes (IELs) are activated by IL-15 (109), and IL-15 can mediate their proliferation and survival, and regulate the expression of IFN-γ (110, 111). IL-15 can also regulate the growth and apoptosis of colorectal cancer tumor cells, and low level of IL-15 is also associated with low-infiltrating lymphocytes in tumor microenvironment and poor prognosis of the colorectal cancer (112). Desboi et al. (113) found that IL-15 hyper-agonist receptor-linker -IL-15 (RLI) could limit tumor growth in the early stage of colorectal cancer and the combined use of PD-1 inhibitors had a higher activation rate of $CD8^+$ TILs in colorectal cancer compared with PD-1 inhibitors or RLI alone, but had no significant inhibition or $CD8^+$ TILs activation for advanced colorectal cancer, which was consistent with T cell exhaustion.

The prognosis of colorectal cancer (CRC) is also related to its subtypes. Microsatellite instability (MSI) is considered as one of the main carcinogenic pathways of colorectal cancer and can be used as a prognostic marker. According to the mismatch repair (MMR) and MSI, RCRs can be divided into high microsatellite instability RCRs (MSI-H)/mismatch repair system defective CRC (dMMR), low microsatellite instability RCRs (MSI-L) and microsatellite stability RCRs (MSS). Colorectal patients with MSS/MSS-L have a worse prognosis and respond to targeted PD-1/PD-L1 or CTLA-4, while the sensitivity to ICIs and prognosis of those with dMMR/MSI-H are significantly better (114–116). Compared with normal intestinal mucosa or MSS-RCR tissue, $CD8^+$ T cells have more significant enrichment in MMR-deficient CRC tissue (117, 118). Studies have found that $CD8^+$ Trm in colorectal cancer patients has specific demethylation of CD103 and CD39-related genes (65), $CD103^+CD39^+$ T cells have a strong MHC-dependent tumor killing ability, and the co-expression of CD103 and CD39 is also considered to be the key to T cell tumor-specific recognition characteristics and differentiation from bystander T cells, and can be used as an independent risk factor for the prognosis of colorectal cancer (65, 119).

CRC is associated with environmental factors and earlier onset age has been observed among these patients (120, 121). In most cases, the adenoma-carcinoma-metastasis process is experienced, which is associated with the accumulation of specific genetic events

of "APC-KRAS-TP53". Particular case was reported that the lung metastases in a patient with metastatic colorectal cancer disappeared or shrank after autologous isolation and culture of $CD8^+$ T cells that had a specific effect on the mutant KRAS gene, and were still in a clinically disease-free state four months after surgery (122), which indicated the effectiveness and broad prospect of Trm as an as a potential target of colorectal cancer adoptive cell therapy.

4 Application of tissue-resident memory T cells in gastrointestinal tumors

4.1 Prognostic value and ICIs response of tissue-resident memory T cells

Tissue-resident memory T cells are associated with the prognosis of a variety of tumors (Table 1). In general, a high proportion of $CD8^+$ Trm predicts better survival, and has better prognostic value than the total number of $CD8^+$ T cells. Further studies show that non-terminal tissue-resident memory T cells may be more important (63); and it has also been found in ovarian cancer that its immunogenicity is determined by fewer stem cell-like tissue-resident memory T cells (82). Tissue-resident memory T cells, perhaps the highest tumor reaction potential T cells, are important participants in the anti-tumor effects, and can respond to ICIs in the early stage (123, 124). PD-1 blockade can significantly proliferate tissue-resident memory T cells with an enhancement of anti-tumor effect (2), and it also promotes the migration of Tcm into the tumor microenvironment and differentiation into Trm (125). Single-cell sequencing analysis also showed significant up-regulation of tissue presence-related phenotypes after blocking PD-1 (9). Tumor microenvironment in patients with better ICIs responses tends to be more Trm-rich (55), and it has been proved that highly infiltrated tissue-resident memory T cells can be used as a marker of benign ICB therapeutic response in colorectal cancer (65, 66), breast cancer (9, 50), melanoma (55) and other tumors (60). In addition, tissue-resident memory T cells can be highly enriched in the tumor microenvironment after chemoradiotherapy (126) and are associated with a good prognosis for patients who receive doublet chemotherapy after surgery (59), suggesting that ICIs combined with adjuvant chemoradiotherapy can achieve better anti-tumor effects. In fact, Phase III clinical trials have shown that Nivolumab combined with neoadjuvant chemotherapy significantly improved the overall survival and progression-free survival of patients with gastric cancer (127).

4.2 Enhancing activity and T cell therapy of tissue-resident memory T cells

Given the excellent anti-tumor effect and potential prognostic value, it is worth exploring how to make better use of tissue-resident memory T cells for anti-tumor therapy. And it also implies a better anti-tumor environment in the gastric cancer microenvironment because of a lower proportion of terminal-exhausted $CD8^+$ T cells and a higher proportion of $CD8^+$ Trm in the gastric cancer microenvironment (76). Enhancing the proliferative capacity and cytotoxicity of Trm may be a better option for gastrointestinal tumor immunotherapy by the combination of 4-1BB co-stimulation or RLI with PD-1 blockade at this stage (57, 113).

$CD8^+$ T cells can be induced to express CD103 by reprogramming tumor-infiltrating DCs with β-glucan gel polysaccharide. $CD103^+CD8^+$ T cells generated in this way could control the growth of existing tumors (128). In addition, it has been reported that a patient with locally recurrent gastric cancer was relieved by injecting DCs into tumor for 30 months (129). HBV-specific tumor-resident T cells correlated with relaxation-free survival of hepatocellular carcinoma (63), considering the relationship between gastric cancer and infection factors, as well as the particularity of gastrointestinal flora, the induction of infection-derived specific tissue-resident memory T cells by vaccine may have exploratory significance for preventing the occurrence of gastrointestinal tumors or intervening in their development (130). Induction the formation of Trm *via* cancer vaccines is also conceivable (62, 131, 132)

Autologous tumor infiltrating lymphocytes adoptive therapy has observed objective regression or even complete remission of tumors in melanoma (133) and breast cancer (134) with objective tumor regression, or even complete remission. As an important subset of TILs, Trm may be able to undertake this role better. Anada and Matthewd's research showed that the expression of *Runx-3* promoted the formation of tissue-resident memory T cells, and they use melanin model revealed that the metastasis and localization of $CD8^+$ T with high expression of *Runx-3* in TME inhibited the growth of tumor (35). As mentioned above, a part of recyclable tissue-resident memory T cells does exist in the human body (14, 15), which indicate that constructing T cells by inducing or coercing the expression of genes related to tissue retention may be one of the feasible pathways for cell therapy.

Although adoptive T cell therapy has made great achievements and shown great potential, how to select more tumor antigen-specific T (Tas) cells or induce the expansion of Tas cells is still a challenge. The lack of tumor antigen specificity of CAR-T increases the potential risk of targeted tumor removal toxicity, and even serious side effects (135). As mentioned above, tissue-resident memory T cells in the gastrointestinal tumor microenvironment have a significant portion co-express CD39 and CD103 (49, 65), which is considered to be a marker of tumor antigen-specific response in solid tumors (119). In addition, the TCR of Tas cells in patients is a more personalized choice of TCR-T cell therapy. A transcriptomic profiles of neoantigen-reactive T cells from gastrointestinal tumors also revealed that most neoantigen-reactive cells co-express CXCL13 and GZMA (136). He et al. proved that CXCL13 is a unique marker of Tas cells and they found ENTPD1 (CD39) can be used as a surface marker of $CD8^+$ Tas cells. Moreover, TCR-T cells expressing TCR from Tas cells show significant therapeutic effects on autologous patient-derived

TABLE 1 Overview of Trm phenotypes and functions in various tumors.

Tumor	Phenotype	Inhibitory receptors	Value of Trm	Reference
Breast cancer	$CD103^+$	PD-1 CTLA-4	Trm genotype was correlated with better prognosis and up-regulated after PD-1 blockade	(9)
Melanoma	$CD103^+CD69^+$	PD-1 CTLA-4 2B4	The increase in the number of tumor-resident memory was related to an improved survival with immunotherapy	(55)
	$CD45a/VLA\text{-}1^+$	Undetected	Associated with better survival	(56)
Gastric cancer	$CD103^+$	PD-1	4-1BB co-stimulation can enhance the Trm regeneration mediated by PD-1 blockade; Low level of tumor infiltration Trm is correlated with low survival rate.	(57)
	$CD103^+$	PD-1	$CD103^+CD8^+$T cells have a better prognostic value; High infiltration was associated with better adjuvant chemotherapy.	(58)
		Undetected		(59)
Glioblastoma	$CD103^+CD69^+$	Undetected	prolonged survival	(48)
Esophageal squamous cell carcinoma	$CD103^+$	PD-1 TIM-3 TIGIT LAG-3	Positively correlated with the overall survival rate; Induced to effectively inhibit tumor after PD-1 blockade	(3)
Ovarian cancer	$CD103^+$	Undetected	Associated with a better prognosis.	(60)
Vaginal melanoma	$CD103^+CD8^+$	PD1 CTLA4	The highest tumor response potential, and proliferation with ICB therapy; Associated with prolonged survival	(2)
Lung cancer	$CD103^+$	PD-1 TIM-3 LAG-3 CTLA-4	Predictive of a better survival outcome	(61)
Head and neck cancer	$CD49a^+CD103^+$	PD-1 Tim-3	better overall survival; biomarker for the efficacy of cancer vaccine.	(62)
Hepatocellular carcinoma	$CD69^+CD103^+CD57^+$	PD-1 TIM-3 CD39	More effective anti-tumor effect and related to the relapse-free survival.	(63)
	$CD103^+$Trm, $CD8^+$Tex	PD-1 CTLA-4 LAG-3	Trm/Tex was associated with survival	(64)
Colorectal cancer	$CD39^+CD103^+$	PD-1 Tim-3	Predicting the response to ICB therapy and prognosis	(65)
		PD-1 CTLA4		(66)
urinary bladder cancer	$CD103^+CD69^+$	PD-1	potential new targets for cancer immunotherapy	(11)

xenograft (PDX) tumors from autologous patients (137). Therefore, rational utilization of the tissue-resident property of $CXCL13^+$ Trm may lead to more precise targeted tumor therapy. Since it is relatively difficult to extract Trm in local tissues, Trm in tumor draining lymph nodes would also be a good alternative. Trm cells have been proved to exist in not only non-lymphoid tissues but also lymphoid tissues, especially lymph node (7), and infection-associated antigen-specific $CD8^+$ Trm within the lymph nodes can be migrated from non-lymph node tissue (13). Recent studies also showed that tumor-specific $CD8^+$ Trm existed in draining lymph nodes and could prevent the spread of melanoma in the lymph nodes (138). Hence, the tumor-specific Trm located in lymph node can not only prevent tumor cells spreading, but also can be an alternative option for extraction and TCR repertoire recognition and following TCR-T transformation.

5 Concluding remarks

Immunotherapy for gastrointestinal tumors remains a worldwide challenge. Immunotherapy for cancer aims to identify and eliminate tumor cells by stimulating T cells with tumor-killing effects to reach the tumor microenvironment. Tumor-infiltrating tissue-resident T cells can be used as a potential target population of ICIs, and it is also a biomarker for the prognosis of gastrointestinal tumors and PD-1 blocking effect. The phenotype and function of tissue-resident memory T cells implicate their potential therapeutic value. First, Trm resides in peripheral non-lymphoid tissues, and the reoccurring immune response is much faster than that of circulating memory T cells, thus enabling Trm to participate in immune regulation of tumor more quickly. Second, $CD8^+$ Trm can secrete a variety of cytokines to promote tumor cell lysis and death,

and the related phenotypic molecules can also exercise a regulatory effect on tumor growth. Therefore, we judged that the tissue-resident memory T cells could be potential extraction targets for adoptive T cell therapy. However, as we have mentioned repeatedly above, T cell exhaustion is closely related to the function of Trm and immune escape of tumor and Tex^{Term} has lost its immune activity. Besides, tumor tissues also contain T cell populations without tumor immune function such as bystander T cells. Therefore, in order to better utilize Trm for anti-tumor, we need more details how Trm cells' functions are restricted by tumor and find out the cell populations with tumor antigen specificity and long-term stable cytotoxic effect among numerous subsets or produce effective targeted anti-tumor T cells by cell technology to intervene in the exhaustion of $CD8^+$ Trm by certain means and implement more accurate regulation for this crimp.

Author contributions

ML, XW: Writing - original draft. DC: Figure drawing. XS and WG: Conceptualization, Writing – review & editing, funding acquisition. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by National Natural Science Foundation of China (81970500 XS, 82172645 WG), Start-up funding for the introduction of talents in Nanjing Drum Tower Hospital (RC2022-015).

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.

Publisher's note

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